LEARNING OBJECTIVES

- Understand the basis of Chemical selection, use and application
- Detail the proper order of cleaning
- List appropriate application methods
- Describe the Importance of Cleaning and Disinfection
Topics Covered

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

USP 42 <1072> Disinfectants and Antiseptics:

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

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

“The purpose of the cleaning and disinfection program is not only to control microbial contamination but also to serve as a corrective action for the loss of control for viable excursions contamination. While the destruction of viable cells are an integral part of the cleaning and disinfection program, the use of disinfection as a singular focus without efforts to control contamination from entering the area is without technical merit. Environmental monitoring (EM) evaluates the efficacy of controls on the manufacturing environment. It is through control of bioburden levels entering the area, along with cleaning and disinfection, that acceptable viable control of the manufacturing or appropriate testing environment is achieved. “
5.31 The disinfection of clean areas is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programme (for disinfection to be effective, cleaning to remove surface contamination must be performed first). More than one type of disinfecting agent should be employed, and should include the periodic use of a sporicidal agent. Disinfectants should be shown to be effective for the duration of their in use shelf-life taking into consideration appropriate contact time and the manner in which they are utilized. Monitoring should be undertaken regularly in order to show the effectiveness of the disinfection program and to detect the development of resistant and/or spore forming strains. Cleaning programs should be effective in the removal of disinfectant residues.

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

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

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

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

FDA WL 2/11/19.

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2019/ucm631353.htm
• Specifically, your firm failed to use sterile cleaning agents in the routine cleaning of ISO 5 LAFW and BSC hoods and the nuclear and pain medicine ISO 7 clean rooms. Examples of non-sterile cleaning agents include, but are not limited to the following:
  • (b) ___ does not appear to be high enough to be sporicidal (made with non-sterile water).

[Link](https://www.fda.gov/media/129281/download)
Recent FDA 483 (5/16/2019)

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

https://www.fda.gov/media/128970/download
Recent FDA WL: Cleaning and Disinfection

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

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

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

FDA WL 9/14/18

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm622651.htm
Recent WL on Cleaning and Disinfection

“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

“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

Cleanroom Behavior

“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

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
  – Sterilant (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

• Disinfectant
  – Proper use results in 100% kill of vegetative bacteria, target viruses and target fungi
  – May or may not require pre-cleaning
    • Serum efficacy - 5% BSA and EN methods differ example: skimmed milk as a soil load
Cleaning and Disinfection: Product Selection

• Sterilant
  – Proper use results in 100% kill of all microorganisms, including bacterial endospores (*B. subtilis*, *C. sporogenes*)
  – Always requires pre-cleaning
    • Water quality is important
Increased Microbial Efficacy and/or Regulatory Claims

Sporicides

Disinfectants

Alcohols

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.
Review - Microflora in Cleanrooms (U.K.)

- Tim Sandle
- 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.)

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

- Gram-positive sporing rods, 13%
- Gram-positive non-spore forming rods, 3%
- Gram-negative rods, 2%
- Fungi, 1%
- Gram-positive cocci, 81%
### Review - Microflora in Cleanrooms (U.K.)

<table>
<thead>
<tr>
<th>Genus</th>
<th>A/B (6729)</th>
<th>C/D (2500)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Micrococci (and related)</strong></td>
<td>38%</td>
<td>40%</td>
</tr>
<tr>
<td><strong>Staphylococci</strong></td>
<td>21%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Bacillus (and related)</strong></td>
<td>13%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Pseudomonas (and related)</strong></td>
<td>&lt;1%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Corynebacterium (and related)</strong></td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Rhodococci</strong></td>
<td>&lt;1%</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td>N/A</td>
<td>3%</td>
</tr>
</tbody>
</table>
Microorganism Resistance Hierarchy

Staphylococcus haemolyticus

Courtesy Grace Thornhill
Aspergillus Spores

Fungal Conidiospores
Cleanroom Fungi

Aspergillus

Courtesy Dan Klein
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Aspergillus Spores

Courtesy Bruce Ritts
Aspergillus brasiliensis

Courtesy Bruce Ritts
SEM: Pseudomonas 5,000X magnification
Bacillus Subtilis

Courtesy Bruce Ritts
Biofilms

Courtesy Dan Klein

Legionella
Chemistries & Frequency
Cleaning and Disinfection

Control microbial contamination
  • Destruction of viable cells

Corrective action for loss of control
  • Viable and non-viable excursions

Disinfection used in conjunction with contamination control program
  • Prevent contamination from entering the room
Cleaning and Disinfection

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

• Post construction and after worst case events either a triple cleaning or a double cleaning with a neutral or acidic cleaner would be recommended.
## Disinfectant Components

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

• Influence of Surfactants on Wetting
  – Ability to displace particles
  – Penetrate soil and surface irregularities
  – Better contact
Wetting Surface Tension and Penetration

- Disinfectant with no surfactant
- Disinfectant with surfactant

Microorganism or Soil

Substrate

Good coverage with Surfactant
Contamination Control

• Control what enters your environment
  – Viable and non-viable
• Begin with items transferred into facility
  – Components, carts, personnel, tanks, tools, etc.
  – Defined entrance procedures
• Good control leads to less
  – Excursions
  – Investigations
  – Down time
All items cleaned, sterilized or disinfected

*Highest level of decon possible*

Sterilization OR Automatic Disinfection (VHP) OR Manual Disinfection
Chemical types

- Disinfectants and sanitizers
  - Phenolics
  - Quats
  - Alcohols
  - Hydrogen Peroxide 3%

- Sterilants and sporicides (potentially)
  - Sodium hypochlorite
  - Chlorine dioxide
  - Hydrogen peroxide 6%
  - Peracetic acid
  - Peracetic acid/hydrogen peroxide blends
  - Glutaraldehyde/formaldehyde
  - Ozone
  - Nitrogen Dioxide
  - Vaporized Peracetic Acid and VHP®
Factors in Performance

- Temperature
- Contact time
- Concentration
- Surface
- Presence of organic matter
- Water Quality (hardness)
Phenolics - Features & Limitations

• Features
  – TB effective and broad spectrum
  – EPA registered
  – Anionic / Neutral surfactants provide good cleaning ability
  – Alkaline or acidic formulas available

• Limitations:
  – Not sporicidal
  – Residues
  – Activity affected by incompatible chemical agents
Quats - Features & Limitations

• Features
  – Broad spectrum activity
  – EPA registered alkaline (and acidic)
  – Cationic surfactancy provides excellent cleaning

• Limitations:
  – Not sporicidal
  – Not always TB effective
  – Activity affected by incompatible chemical agents
H₂O₂/PAA RTU

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

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

• Features
  – Broad spectrum activity (including spores)
  – Effective in the presence of organic material
  – Decomposition products are non-hazardous
  – Solution or vapor effective

• Limitations
  – Unstable at higher temperatures
  – Irritant
  – Corrosive to soft metals
Bleach - Features & Limitations

• Features
  – High level of disinfectant efficacy
  – Sporicidal at 800ppm - 5,000ppm

• Limitations:
  – Pre-cleaning required
  – Temperature and light sensitive
  – May only be a disinfectant, not a sterilant
  – Safety concern with chlorine gas
  – Corrosive to eyes and skin
  – Corrosive to soft metals and stainless steel
  – May produce THM in presence of organic material
  – Generally not EPA registered

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Sodium Hypochlorite

\[
\text{OCI}^- + \text{H}_2\text{O} \rightleftharpoons \text{HOCl} + \text{OH}^- 
\]

<table>
<thead>
<tr>
<th>Hypochlorite Ion</th>
<th>Hypochlorous Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>% Hypochlorous acid</td>
</tr>
<tr>
<td>4.0</td>
<td>Almost 100</td>
</tr>
<tr>
<td>5.0</td>
<td>99.6</td>
</tr>
<tr>
<td>6.0</td>
<td>95.8</td>
</tr>
<tr>
<td>7.0</td>
<td>69.7</td>
</tr>
<tr>
<td>8.0</td>
<td>18.7</td>
</tr>
<tr>
<td>9.0</td>
<td>2.2</td>
</tr>
<tr>
<td>10.0</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Reference: Holweida (1928)
Chlorine Dioxide - Features

- High level disinfectant efficacy
- Efficacy against non-enveloped viruses (MVM)
- EPA Registered
Chlorine Dioxide - Limitations

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

• Features
  – Broad spectrum activity (including spores)
  – Non-corrosive
  – May be used in fogging applications

• Limits
  – Requires activation
  – Unstable and inactivated by organic material
  – Requires long contact time
  – Safety (toxicity)
  – May have to neutralize residues
Halogens - Features & Benefits

- **Features**
  - Broad spectrum disinfectant
  - Stable and less irritating
  - Non-corrosive

- **Benefits**
  - Not sporicidal (unless higher concentration validated)
  - Safety
  - Possible Staining
  - Mainly used as antiseptics
Alcohol Features & Limitations

• Features
  – No residue & Evaporates readily
  – Broad spectrum
  – Excellent at removing residues

• Limitations
  – Not sporicidal
  – Poor cleaner
  – Flammable
  – Limited contact time
  – Not EPA registered
  – Volatile Organic Carbons (VOC) emissions
  – Isopropyl Alcohol (IPA) (Threshold Limit Value (TLV) 200ppm)
Isopropyl Alcohol (IPA) - Aerosol, Trigger Spray, Squeeze Bottles
70% IPA Efficacy Against Molds

Fungicidal Activity of 70% Isopropyl Alcohol using Time Kill Method

Log Reduction

Organism

A. niger 16404
A. fumigatus 28282
A. fumigatus 96918
T. mentagagrophes 9533
S. chartarum 16275
P. notatum 10108

30 sec
60 sec
Cleaning Supplies

Tank/Vessel
• If interior sterile, only address exterior

Special attention to wheels
• Increased contact time
• Manual wiping

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

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

Mop heads/Sponges – Sterilized

Other equipment
- Mops, buckets, squeegees, carts
- Sterilized (disinfected at a minimum)
Manufacturing Components & Supplies

Sterile components used in process

- Packaged in container that can be sanitized
Disinfectant Application

Spraying
- More wetting, no cleaning

Mopping
- Mechanical action cleaning, less wetting

Wiping
- For smaller surfaces, less wetting

Fogging/Gassing
- Excellent efficacy, high residues, no cleaning
Application Techniques

- 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)
- Grid (Blueprint of the Room)
- Pull and lift
- Overlapping strokes (by 20%)
- Figure 8 (also called figure S) or Unidirectional overlapping mopping strokes

Two Bucket System

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

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

Illustration of Pull-lift Technique

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.

Bucket Systems
• **Mop King Jr.**
  
  • [http://www.am-king.com/mopkingjr.htm](http://www.am-king.com/mopkingjr.htm)

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

AmKing Technologies, Bedford, NH
MicronSwep system by Vileda Professional and Micronclean (www.micronswep.com)
CE Duo
Features and Benefits

• Combines microfiber and foam technologies
  You get disinfection and removal in the same tool. 99.99% reduction in surface bacteria without disinfectant.

• Two sided cleaning tool
  Doubles the floor space cleaned with each bucket dip.

• Only mop system that will clean floors, walls and ceilings
  Eliminates the cost and inefficiency of maintaining multiple systems.

• Lightest and most ergonomic tool on the market
  Reduces fatigue and potential for muscle strains.

Courtesy of Vileda Professional
1. Both utilize FHP’s proprietary foam technology
2. Outer Material: adhesive free lamination of Vileda’s polyester or microfiber

*Courtesy of Vileda Professional*
Bucket Trolley

- **Electro Polished Stable Stainless Steel Chassis**: Contamination free surface with smooth weldings, easy to wipe clean. Wide chassis for excellent stability when wringing.
- **Detachable Pushbar**: Airtight and easy to put on/off for sterilization.
- **Handle Holders**: New innovative handle holders avoiding any dirt traps or issues when sterilizing. Ultimate fixation of handles through extra pin wire support.
- **Color Coded Buckets and Bins**: Single or double bucket options. Buckets and bins incl. color coded clips to customize to your needs.
- **Frame Holders**: Two handle holders – one designed for flat mops and one for Roll-O-Matic sponge mops.
- **Cleanroom castors**: Exclusively designed for Vileda Professional with emphasis on comfort, reduction in noise while in use and ability to be autoclaved. Each trolley comes with set of four two brake castors.

Pre-Prepared Trolley

- **Working Station**: Top shelf with fixed position for 1 pre-box or 2 x 6L buckets. Innovative drawer shelf construction for easy access to our cleanroom mops.
- **Bin Bag Holder**: 70L bin bag holder to dispose of used mops. 70L bin bag size avoids slipping of bags during use and contributes to the operators' ergonomics.
- **Storage area**: Store your prebox and ability to place 25L longish bucket.

Courtesy Vileda Professional
**Compact CE Bucket Dolly**

- **Double Bucket Dolly**
  - **2x CE 22L Bucket**
    - 2x solid and stable polypropylene plastic bucket (1x blue + 1x red)
    - 100% autoclavable
  - **Ergonomic Designed Polymer Bail**
    - Very ergonomic designed polypropylene plastic bail
  - **CE Bucket Sieve**
    - Electropolished stainless steel sieve in unique design with special hole pattern, integrated bucket splash guard and additional handle support (keeps the handle hands-free straight!)
  - **CE Double Bucket Chassis**
    - Electropolished stainless steel chassis in unique design that prevents the buckets from toppling over
  - **4x Ø75 mm Stainless Steel Swivel Castors**
    - 100% autoclavable castors
    - Fixed stainless steel screw/nut connection on the chassis
    - 2 castors with brake – 2 w/o brake

*Courtesy of Vileda Professional*
Broken Glass and Broken Ampules

Courtesy of Vileda Professional

**CE Sweeper and Pan**
- Sweep up broken glass in your cleanroom quickly and easily
- No need to change gloves when an item is dropped on the floor
- Keeps workers from touching the floor within the controlled environment
- Can be sprayed or wiped down with common disinfectants
- Stands up easily for storage or can be hung
- Adjustable bag holder for different size collection bags

<table>
<thead>
<tr>
<th>Case Code</th>
<th>Description</th>
<th>Size</th>
<th>Case</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>119908</td>
<td>CE Sweeper</td>
<td>35.4 x 7.8 x 19 in</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>119914</td>
<td>CE Sweeper Pan</td>
<td>30.7 x 12.2 x 6.8 in</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>
Two & Three Bucket Systems

Courtesy of Perfex Corp.

Courtesy of Micronova Mfg.
Commonly Used Equipment

Courtesy Micronova Mfg.
Latest Equipment

Isolator Tool

Courtesy of Micronova Mfg.

Lyo Tool
Cleaning and Disinfection: Techniques

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

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

- Rinsability
- Residues
- Stability
- Compatibility
- Efficacy
Cleaning and Disinfection Best Practices

How often to clean???

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

• Sporicidal agent
  – Rationale
    • Weekly
    • Monthly
    • Quarterly

• Should be written in SOP’s
  – Extraordinary Cleaning
  – Used Based on Risk
  – Fungal and Bacterial Spore Outbreaks
CNC (Controlled Not Classified)

Area Cleaning Frequency

- Hallways and Floors ---Mop daily ---Rinse as needed
- Walls and Ceilings---Mop monthly—Rinse as needed
- Equipment (carts, racks, trash receptacles, etc.)---Wipe weekly---Rinse as needed
- Rinsing is based on visual observation and safety
Grade D (ISO 8 at rest)

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

A sporidical agent must be used quarterly, semi-annually or as needed in response to microbial monitoring. 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)

<table>
<thead>
<tr>
<th>Surface</th>
<th>Method</th>
<th>Cleaning Agent</th>
<th>Frequency</th>
<th>Rinse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Floors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Normal Traffic Paths</td>
<td>Mop</td>
<td>Disinfectant with surfactant</td>
<td>Daily after transfers</td>
<td></td>
</tr>
<tr>
<td>• Proximity to Open Process or Transfer Areas</td>
<td>Mop</td>
<td>Disinfectant with surfactant followed by a sporicide</td>
<td>Weekly or monthly, if necessary</td>
<td></td>
</tr>
<tr>
<td>Walls</td>
<td>Wipe or Mop</td>
<td>Disinfectant with surfactant followed by a sporicide, if necessary</td>
<td>Weekly or monthly</td>
<td></td>
</tr>
<tr>
<td>• General</td>
<td>Wipe or Mop</td>
<td>Disinfectant with surfactant</td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td>• Door Plate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equipment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Shelving</td>
<td>Spray or Wipe</td>
<td>Disinfectant with surfactant</td>
<td>Before and after use</td>
<td></td>
</tr>
<tr>
<td>• Portable Tanks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Processing Items</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Carts (wheels)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Surfaces</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Furniture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Chair (wheels)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Surfaces</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Furniture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Chair (wheels)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As needed to remove residue buildup.
Grade A (ISO 4.8) or B (ISO 5 at rest, ISO 7 in operation)

<table>
<thead>
<tr>
<th>Surface</th>
<th>Method</th>
<th>Cleaning Agent</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>External Hoods</td>
<td>Wipe</td>
<td>Sterile disinfectant with surfactant</td>
<td>Daily</td>
</tr>
<tr>
<td>• Back, Sides, Top</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Door, Sliding Panel</td>
<td>Wipe</td>
<td>Sterile disinfectant with surfactant</td>
<td>Daily</td>
</tr>
<tr>
<td>Inside Hood or Curtain</td>
<td>Wipe</td>
<td>Sterile disinfectant with surfactant</td>
<td>Daily, preuse and postuse</td>
</tr>
<tr>
<td>• Work Surface</td>
<td></td>
<td>Sterile Sporicide</td>
<td></td>
</tr>
<tr>
<td>• Sidewalls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Apparatus/Critical Surfaces</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curtains</td>
<td>Wipe or Mop</td>
<td>Sterile disinfectant with surfactant</td>
<td>Weekly or in response to microbial monitoring</td>
</tr>
<tr>
<td>Adjacent Flooring and Walls</td>
<td>Mop</td>
<td>Sterile disinfectant with surfactant followed</td>
<td>Weekly or in response to microbial monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>by a sterile sporicide, as necessary</td>
<td></td>
</tr>
</tbody>
</table>
# Recommended Frequency

<table>
<thead>
<tr>
<th>Controlled Area</th>
<th>Daily</th>
<th>Weekly</th>
<th>Monthly</th>
<th>Yearly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Floors</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceilings</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Walls</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Fixtures/Equipment</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

## 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

<table>
<thead>
<tr>
<th>Cleaning Agents</th>
<th>Daily (Scheduled working days)</th>
<th>Weekly (Every 7 days ± 3 days)</th>
<th>Monthly (Every 28 days ± 10 days)</th>
<th>Semi-Annual (Every 180 days ± 30 days)</th>
<th>Annual (Every 365 days ± 30 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LpH Or Vespelhite</td>
<td>70% IPA</td>
<td>LpH Or Vespelhite or 70% IPA</td>
<td>LpH Or Vespelhite</td>
<td>LpH Or Vespelhite</td>
</tr>
<tr>
<td>Surfaces</td>
<td>Floors</td>
<td>High contact areas</td>
<td>Floors</td>
<td>Walls</td>
<td>Floors</td>
</tr>
</tbody>
</table>

**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 117: D D M M M A
- Gowning Room 122: D D M M M A

**ISO Class 7 Rooms**
- **Clean Corridor Room 109**: D D W M M A
- Fill Room 115: D D W M M A

**ISO Class 5 Laminar Flow Hood**
- Laminar Flow Hood Room 115: Clean before and after each use and weekly (7 days ±3 days) if not in use during the week
- Unclassified Rooms: Packaging Room W M S A

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

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

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

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

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)
“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
Cleaning and Disinfection: Rotation

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

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

Article 315
Item 1: "these areas should be cleaned and sanitized frequently in accordance with a specific program approved by Quality Assurance."

Item 2 says “the areas should be monitored regularly to detect the emergence of resistance microorganisms”.
Cleaning and Disinfection: Disinfectant Rotation

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

Cleaning and Disinfection: Resistance & Rotation

- PDA TR No. 70 2015

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

Cleaning and Disinfection: Rotation

- USP 42 <1072> Disinfectants and Antiseptics
- Annex 1 (Draft 2018) and MHRA Orange Guide (2016)
- FDA, MHRA, HPRA, CFDA, ANSM, ANVISA, CFDA, FDAHA, Swissmedic, & EMA Expectations
- Industry Articles (Ex. Scott Sutton, Jose Martinez, Richard Prince, Rebecca Smith, Crystal Booth, Jeanne Moldenhauer)
- PDA Cleaning and Disinfection TR No. 70 (2015)
- PDA TR #69 on Biofilms (2015)
- USP 42 <1116> Microbiological Control and Monitoring of Aseptic Processing Environments
- WHO Annex 6
- PHSS Technical Monograph #20 “Bio-contamination characterization, control, monitoring and deviation management in controlled/GMP classified areas
Cleaning and Disinfection: Rinsing

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.
- Dr. Sharon Thoma's view on residues
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
  - Cleaners: Acidic, Basic or Neutral (low concentrations)
  - Periodic rinsing based on aesthetics and safety

- **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...
Surface Types and Topography

- Sticky mats
- Drains
- Edges and corners
Surface Conditions Effect Performance

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

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