PDA Technical Report No. 70
Fundamentals of Cleaning and Disinfection Programs for Aseptic Manufacturing Facilities

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Sr. Technical Services Manager
PDA Missouri Valley Chapter
October 3, 2016
# PDA Task Force Members

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<thead>
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</tr>
</thead>
<tbody>
<tr>
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</tr>
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</tr>
</tbody>
</table>
Contents of PDA TR No. 70

• The PDA Task Force worked for 6 years
• There are 26 sections in the TR and 8 Appendix Sections
• Extensive Bibliography
• Several editing sessions and approval from SAB and PDA’s Board of Directors
• 70 Pages in Length
Goals of the TR

• Define Industry Best Practice
• Provide a Comprehensive Document
• Current Industry Reference
• Teach and Educate
Current References

- USP 39 <1072> Disinfectants and Antiseptics
- FDA, MHRA, HPRA, CFDA, ANSM, ANVISA, & EMA Expectations
- Industry Articles (Ex. Scott Sutton, Jose Martinez, Richard Prince, Rebecca Smith)
- PDA Cleaning and Disinfection TR #70 (2015)
- PDA TR #69 on Biofilms (2015)
- ISO 14644 (parts 1-12) ISO 14698 (parts 1-3)
- USP 39 <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
PDA TR No. 70 Key Points

• Terminology and Definitions
• Regulatory Inspections
• Disinfectant Validation
• Cleaning and Disinfection Frequency
• Resistance and Rotation
• Shut Down
• Conducting Investigations
Terminology

• 50 definitions
• Some Key terms:
  – Adverse Event
  – Aseptic Processing Area
  – Contaminant
  – Transfer Disinfection
  – Validation
  – Penicylinder
  – Isolate
  – HEPA
  – Pyrogen
Cleaning and Disinfection: Product Selection

• EPA Classifications
  – Sanitizer
  – Disinfectant
  – Sterilizer (Sporicide)
Cleaning and Disinfection: Product Selection

• Sanitizer
  – Proper use results in bacteria reduction of >99.9%
  – 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
  – 4 log reduction of bacteria
  – 3 log reduction of viruses
  – 6 log reduction of 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 spores (*B. subtilis*, *C. sporogenes*)
    • 6-7 log reduction
  – Always requires pre-cleaning
    • Water quality is important
SURFACE DISINFECTANTS & ALCOHOLS

1. PRODUCTS AT THE BASE 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.

1. INCREASED MICROBIAL EFFICACY AND/OR REGULATORY CLAIMS.

Sterilants

SPORICIDES

PHENOLIC DISINFECTANTS

QUATERNARY AMMONIUM DISINFECTANTS

ALCOHOLS

Non-Sporicidal Disinfectants

Non-Sporicidal Disinfectants

Alcohols

Alcohols
PDA TR No. 70 Key Points

• Terminology and Definitions
• Regulatory Inspections
• Disinfectant Validation
• Cleaning and Disinfection Frequency
• Resistance and Rotation
• Shut Down
• Conducting Investigations
Recent FDA Focus

- Disinfectant Validation
- Equipment Control
- Shut Down
- CAPA Investigations
- Mold and Bacillus Control
- Use of Sterile Products in ISO-5
- Smoke Studies
“Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm’s operations as are necessary to prevent contamination or mix-ups during the course of the following procedure: (CFR) 21CFR 211.42 (v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions
“In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents, and disinfectants where used.”
“Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products.”
PDA TR No. 70 Key Points

• Terminology and Definitions
• Regulatory Inspections
• Disinfectant Validation
• Cleaning and Disinfection Frequency
• Resistance and Rotation
• Shut Down
• Conducting Investigations
Specifically,

a. Despite your firm’s use of sporicidal disinfectants, a variety of spore forming bacteria are routinely recovered from your environmental and personnel monitoring within the aseptic processing areas.

b. Non-sterile disinfectants are routinely used by your employees during cleaning of aseptic processing area, including the critical work area and buffer room. For example, the technician was observed disinfecting the interior walls, followed by the aseptic processing work surfaces using the same mop head.

c. Your firm has not conducted disinfectant efficacy studies to demonstrate that the disinfectants and application methods (e.g. spray, wipe, mop, aerosol, etc.) used to clean the walls, ceilings, work surfaces and other items in the work areas can sufficiently reduce bioburden.

GMP Trends July 15, 2016
Disinfectant Validation

• Suspension Studies
• Neutralizers
• Coupon Studies
• In Use Expiry Testing
Neutralizers

Table 5.2.1-1

<table>
<thead>
<tr>
<th>Antimicrobial Chemical Agent</th>
<th>Neutralizing Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohols</td>
<td>Dilution or Polysorbate 80</td>
</tr>
<tr>
<td>Sodium Hypochlorite</td>
<td>Sodium Thiosulfate</td>
</tr>
<tr>
<td>Quaternary Ammonium Compounds</td>
<td>Polysorbate 80 and Lecithin</td>
</tr>
<tr>
<td>Phenolic Compounds</td>
<td>Dilution or Polysorbate 80 and Lecithin</td>
</tr>
<tr>
<td>Hydrogen Peroxide/Peracetic Acid and Hydrogen Peroxide</td>
<td>Catalase</td>
</tr>
<tr>
<td>Antimicrobial Chemical Agent</td>
<td>Organism Type</td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Sanitizer</td>
<td>Non-spore formers</td>
</tr>
<tr>
<td>Disinfectant/Sporicide</td>
<td>Non-spore formers</td>
</tr>
<tr>
<td>Disinfectant/Sporicide</td>
<td>Mycoplasma</td>
</tr>
<tr>
<td>Sporicide</td>
<td>Mold Spores</td>
</tr>
<tr>
<td>Sporicide</td>
<td>Bacterial Spores</td>
</tr>
</tbody>
</table>
Efficacy of Sporicides

Efficacy of Aseptic Products in a Time Kill Study
*A. brasiliensis* ATCC 16404  Baseline 5.28 log$_{10}$

- Spor-Klenz RTU
- 0.525% NaOCl in WFI
- 6% H2O2 in WFI

Efficacy of Aseptic Products in a Time Kill Study
*B. subtilis* ATCC 19659  Baseline = 6.48 log$_{10}$

- Spor-Klenz RTU
- 0.525% NaOCl in WFI
- 6% H2O2 in WFI
PDA TR No. 70 Key Points

- Terminology and Definitions
- Regulatory Inspections
- Disinfectant Validation
- Cleaning and Disinfection Frequency
- Resistance and Rotation
- Shut Down
- Conducting Investigations
Example of Risk-Based Approach for Cleaning & Disinfection Frequency

<table>
<thead>
<tr>
<th>Increasing Risk Level (Primary Selection Criterion)</th>
<th>No Product Exposure and Human Interaction</th>
<th>No Product Exposure and Human Interaction</th>
<th>No Product Exposure and Human Interaction</th>
<th>Product Exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterilization Step Downstream</td>
<td>Sterilization Step Downstream</td>
<td>Sterilization Step Downstream</td>
<td>Sterilization Step Downstream</td>
<td>Sterilization Step Downstream</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Manufacturing Type (Secondary Selection Criterion)</th>
<th>Closed System Sanitary Processing</th>
<th>Closed System Sanitary Processing</th>
<th>Closed System Sterile Processing</th>
<th>Open Sanitary Operations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to Final Sterilization Step</td>
<td>Sterile Processing</td>
<td>Post Final Sterilization Step</td>
<td>Operations Prior to Final</td>
<td>Operations in LFH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example Cleaning/Disinfection Frequency</th>
<th>Walls/Ceiling Cleanly Doors/Floors Weekly</th>
<th>Walls/Ceiling Cleanly Doors/Floors Weekly</th>
<th>Walls/Ceiling Mostly Doors/Floors Weekly</th>
<th>Walls/Ceiling Weekly Doors/Floors Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ISO 8 (or ISO 8 or ISO 9 for Isolator Background)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example Area Classification</th>
<th>Controlled Unclassified</th>
<th>ISO 9</th>
<th>ISO 8 (or ISO 8 or ISO 9 for Isolator Background)</th>
<th>ISO 8 (w/ LFH, where applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Increasing Impact of Human/Environment; Increasing Risk of Product Contamination
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

- pH
- Temperature
- Contact time
- Concentration
- Surface
- Presence of organic matter
- Water Quality (hardness)
Application Frequency

• Sporicidal agent
  – Rationale
    • Weekly
    • Monthly
    • Quarterly

• Should be written in SOP’s
  – Extraordinary Cleaning
  – Fungal and Bacterial Spore Outbreaks
## 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>Wipe</td>
<td>Disinfectant with surfactant</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>• Benches</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 sporicidal 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>Mop</td>
<td>Disinfectant with surfactant</td>
<td>Daily after transfers</td>
<td></td>
</tr>
<tr>
<td>• Normal Traffic Paths</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Proximity to Open Process or Transfer Areas</td>
<td></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</td>
<td>Weekly or monthly</td>
<td>As needed to remove residue buildup</td>
</tr>
<tr>
<td>• General</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Door Plate</td>
<td></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>Before and after use</td>
<td></td>
</tr>
<tr>
<td>• Shelving</td>
<td></td>
<td></td>
<td></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>Spray or Wipe</td>
<td>Disinfectant with surfactant</td>
<td>Daily</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>Sporicide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Sterile WFI or 70% IPA as needed to remove residue buildup.
## 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>X</td>
<td></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>

<table>
<thead>
<tr>
<th>Class 100,000 (ISO 8)</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>X</td>
<td></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>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class 10,000 (ISO 7)</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>X</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>X</td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Class 100 (ISO 5)</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>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walls</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixtures/Equipment</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## 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 30 days ± 10 days)</th>
<th>Semi-Annual (Every 189 days ± 30 days)</th>
<th>Annual (Every 365 days ± 30 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LpH Or Vesphene</td>
<td>70% IPA</td>
<td>LpH Or Vesphene</td>
<td>LpH, Vesphene or * 70% IPA</td>
<td>SporKlenz</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 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**
- Fill Room 1 Room 115

### 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.
PDA TR No. 70 Key Points

• Terminology and Definitions
• Regulatory Inspections
• Disinfectant Validation
• Cleaning and Disinfection Frequency
• Resistance and Rotation
• Shut Down
• Conducting Investigations
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 39 <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.”
Cleaning and Disinfection: Rotation

- Martinez, JE. The rotation of disinfectants principle: true or false? Pharmaceutical Technology (2009), p 69
  - “Rotation of a common disinfectant and a sporicidal helps ensure that bacterial spores do not take hold in manufacturing and aseptic areas. But the rotation of common disinfectants such as those based on phenol-derivatives, aldehydes, and oxidizing agents has no scientific basis.”
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.”
Cleaning and Disinfection: Rotation

- 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.”
Cleaning and Disinfection: Rotation

- USP 39 <1072> Disinfectants and Antiseptics
- FDA, MHRA, HPRA, CFDA, ANSM, ANVISA, & EMA Expectations
- Industry Articles (Ex. Scott Sutton, Jose Martinez, Richard Prince, Rebecca Smith)
- PDA Cleaning and Disinfection TR #70 (2015)
- PDA TR #69 on Biofilms (2015)
- USP 39 <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.
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)
This is a problem? Why? We clean the door all the time...
Surface Types and Topography

- Sticky mats
- Drains
- Edges and corners
Cleaning and Disinfection: Techniques

• Cleanest to dirtiest area
• Top to bottom and back to front
• Most critical to least critical surface
• Clean the farthest corner of the room towards the exit that will be used to leave the room.
• Rooms divided by demarcation with two “classifications”
  – Clean to the stricter classification
• Mops and buckets: ISO level dedicate
• Double glove when cleaning floor drains
Change out frequency of use-dilution buckets

• Based on industry survey, IEST working group
• Every 600 ft²/ 55.74 m² (ISO 5,6)
• Every 1000 ft²/ 92.90 m² (ISO 7,8)
• Assume 4 gal (2 gal per bucket) when calculating volume needed for a given area
• e.g. for a 10,000 ft² room (ISO 7), will need 40 gal

Floor Drains

• Floor drains are needed in some areas, but they could become a significant contamination source
• Drains may be extremely difficult to keep clean due to the potential formation of biofilm
• May require oxidative chemistries on less rugged materials
• How do you do this without damaging the drains?
Drain Cleaning

“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.
Mop Heads

- Resistant
- Lint-free
- Various
  - string
  - Sponge
- Sterile and non-sterile

Ref: Micronova Mfg.
Buckets

- Adaptable
- Resistant
- Dedicated

Ref. Micronova Mfg.
Wipes

- Various materials:
  - Nylon
  - Polyester
  - Rayon
  - PVA
  - Microfiber
  - Latex
- Sterile and non-sterile

Ref. Micronova Mfg.
Newer Mopping 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
Newer Mopping Systems

MicronSwep system by Vileda Professional and Micronclean
(www.micronswee.com)
# Cleaning and Disinfection: Equipment supplies

<table>
<thead>
<tr>
<th>FISHER #</th>
<th>CATEGORY</th>
<th>MFG #</th>
<th>DESCRIPTION</th>
<th>CS QTY</th>
<th>qty</th>
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<td>Tool</td>
<td>SSA-2P</td>
<td>Acme Adapter; Female locking screw</td>
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<td>2</td>
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<tr>
<td>19121801</td>
<td>Bucket</td>
<td>C-7</td>
<td>Double Bucket System</td>
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<td>19035365</td>
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<td>Slimline Wringer</td>
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<td>12&quot; Handle</td>
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<td>ITC6-911IR</td>
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<td>NC#</td>
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<td>JZMZSM11-14S</td>
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<td>19035241</td>
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<td>18000403</td>
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<td>Handle 60&quot; Plastic</td>
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<td>Handle</td>
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<td>Handle 40&quot;-72&quot; Handle Plastic</td>
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<td>19041814B</td>
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<td>QDNS-18</td>
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<td>1</td>
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<tr>
<td>19041803B</td>
<td>Tool</td>
<td>RS-18</td>
<td>18&quot; Rubber Squeeggie Blade</td>
<td>12</td>
<td>1</td>
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</tbody>
</table>
Cleaning and Disinfection: Techniques

- **Pharma Pump up sprayer**
  - Compatible with SporKlenz, LpH and Vesphene
  - 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
PDA TR No. 70 Key Points

• Terminology and Definitions
• Regulatory Inspections
• Disinfectant Validation
• Cleaning and Disinfection Frequency
• Resistance and Rotation
• Shut Down
• Conducting Investigations
Triple Clean

• No unified definition

• PDA TR No. 70: “Facilities should strongly consider having special start-up cleaning and disinfection programs in place following “shutdowns” or when significant construction is performed.”

• 2X Disinfectant and 1X Sporicide
## In Situ Data-Case Study

<table>
<thead>
<tr>
<th>Room</th>
<th>Media Type</th>
<th>Action Limits</th>
<th>Pre-Sanitization&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Range (&lt;sup&gt;b&lt;/sup&gt;cfu/unit)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Post-Sanitization&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Range (&lt;sup&gt;b&lt;/sup&gt;cfu/unit)&lt;sup&gt;b&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>#1</td>
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<td>&gt;2.5 cfu/ft&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>0.3&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>0 of 4</td>
<td>0</td>
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<tr>
<td></td>
<td>Swabs</td>
<td>&gt;2 positive</td>
<td>0 of 4</td>
<td>N/A&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0 of 4</td>
<td>N/A&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
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<td>0 to 1</td>
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<tr>
<td></td>
<td>Swabs</td>
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<td>N/A&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0 of 7</td>
<td>N/A&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Case Study: Construction Event

- Worst Case Events
- 9X Clean [1X Sporicide + 2X Phenolic repeated on days 1,2,3]
- Fogging
- Chlorine Dioxide, Ozone, or Fumigation
- VHP®
- Triple Clean
  - Defined 3X Disinfectants and Sporicide (Different Definitions)
  - EM frequency (Static and Dynamic)
  - Release of the room
## Triple Clean in a Cleanroom

<table>
<thead>
<tr>
<th>Sample</th>
<th>Action Limit</th>
<th>Pre Triple Clean</th>
<th>Post Triple Clean</th>
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</thead>
<tbody>
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<td>RODAC</td>
<td>2 cfu/plate</td>
<td>3 cfu/plate</td>
<td>&lt;1 cfu/plate</td>
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<td>RODAC</td>
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<td>31 cfu/plate</td>
<td>&lt;1 cfu/plate</td>
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<tr>
<td>RODAC</td>
<td>2 cfu/plate</td>
<td>3 cfu/plate</td>
<td>&lt;1 cfu/plate</td>
</tr>
</tbody>
</table>

Results from an ISO-8 Cleanroom (554ft² room)
Cleaning and Disinfection Efficacy - *In situ* study
Time 0

Red = Spore formers  Green = Other
After 1X Cleaning - No Sporicide
After 2X Cleaning – No Sporicide
After 3X Cleaning - No Sporicide
After Sporicide
PDA TR No. 70 Key Points

• Terminology and Definitions
• Regulatory Inspections
• Disinfectant Validation
• Cleaning and Disinfection Frequency
• Resistance and Rotation
• Shut Down
• Conducting Investigations
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
Summary Slide

- Terminology and Definitions
- Regulatory Inspections
- Disinfectant Validation
- Cleaning and Disinfection Frequency
- Resistance and Rotation
- Shut Down
- Conducting Investigations
Thank you for your attention!

jim_polarine@steris.com