Current Industry Trends - Including Cleaning and Disinfection trends, Disinfectant Validation Trends, and Current Warning Letter Activity.

Jim Polarine Jr. MA.
Technical Service Manager
Steris Corp.
Agenda

• Current Industry Trends
  ➢ Cleaning and Disinfection
    – Disinfectant Validation
    – Current Warning Letters
Aspergillus niger

Courtesy Jim Polarine
Cleanroom Fungi

Courtesy Dan Klein
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) ref. Anne Marie Dixon
  - 600 square feet (56 square meters) in ISO-5 (Grade A & B)
  - 1,000 square feet in (93 square meters) ISO-6, 7, 8 (Grade C & D)
- Grid (Blueprint of the Room)
- Pull and lift
- Overlapping strokes (by 20%)
- Figure 8 (also called figure S) or Unidirectional mopping strokes
Controlled Areas

• 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.
### Class 100,000 Closed Processes – Recommendations
(solution prep, fermentation, purification, media prep, wash bays, raw material weigh area, stopper prep, packaging inspection)

<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>high-level disinfectant with surfactants</td>
<td>daily at shutdown, between process changeover</td>
<td>not necessary</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, mop</td>
<td>high-level disinfectant with surfactants followed with sporicide</td>
<td>monthly</td>
<td>not necessary</td>
</tr>
<tr>
<td>• general</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• doors, handles, high-traffic areas</td>
<td>mop</td>
<td>high-level disinfectant with surfactants</td>
<td>daily</td>
<td></td>
</tr>
<tr>
<td>Equipment</td>
<td>spray, wipe</td>
<td>high-level disinfectant with surfactants</td>
<td>daily during processing</td>
<td>as needed to remove residue buildup</td>
</tr>
<tr>
<td>• adjacent to access ports</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• surface upstream airflow path to process opening</td>
<td>spray, wipe</td>
<td>high-level disinfectant with surfactants</td>
<td>weekly</td>
<td></td>
</tr>
<tr>
<td>Other Surfaces</td>
<td>wipe</td>
<td>high-level disinfectant with surfactants</td>
<td>daily</td>
<td>not necessary</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>
## Class 10,000 - Outside Laminar Flow Hoods, Rooms, and Halls - Recommendations

<table>
<thead>
<tr>
<th>Surface</th>
<th>Method</th>
<th>Cleaning Agent</th>
<th>Frequency</th>
<th>Rinse</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Floors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• normal traffic paths</td>
<td>mop</td>
<td>high-level disinfectant with surfactants</td>
<td>daily after transfers</td>
<td>not necessary</td>
</tr>
<tr>
<td>• proximity to open process or transfer areas</td>
<td>mop</td>
<td>high-level disinfectant with surfactants followed by a sporicide</td>
<td>weekly or monthly, if necessary</td>
<td></td>
</tr>
<tr>
<td><strong>Walls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• general</td>
<td>wipe</td>
<td>high-level disinfectant with surfactants followed by a sporicide</td>
<td>weekly or monthly</td>
<td>not necessary</td>
</tr>
<tr>
<td>• door plate</td>
<td>mop</td>
<td>high-level disinfectant with surfactants</td>
<td>daily</td>
<td></td>
</tr>
<tr>
<td><strong>Equipment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• shelving</td>
<td>spray or wipe</td>
<td>high-level disinfectant with surfactants</td>
<td>before and after use</td>
<td>WFI rinse as necessary to address residue buildup</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>sporicide</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Furniture and Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• chair (wheels)</td>
<td>spray or wipe</td>
<td>high-level disinfectant with surfactants</td>
<td>daily</td>
<td>not necessary</td>
</tr>
</tbody>
</table>
## Class 100 – Laminar Flow Hoods and Aseptic Filling Suites – Recommendations

<table>
<thead>
<tr>
<th>Surface</th>
<th>Method</th>
<th>Cleaning Agent</th>
<th>Frequency</th>
<th>Rinse</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>External Hoods</strong></td>
<td>wipe</td>
<td>sterile high-level disinfectant with surfactants</td>
<td>daily</td>
<td>not necessary</td>
</tr>
<tr>
<td>• back, sides, top</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• door, sliding panel</td>
<td>wipe</td>
<td>sterile high-level disinfectant with surfactants</td>
<td>daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>sporicide</td>
<td>weekly or in response to microbial monitoring</td>
<td></td>
</tr>
<tr>
<td><strong>Inside Hood or Curtain</strong></td>
<td>wipe</td>
<td>sterile high-level disinfectant with surfactants</td>
<td>daily, preuse and postuse</td>
<td>WFI as necessary in product contact areas, or to address residue buildup</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><strong>• curtains</strong></td>
<td>wipe</td>
<td>sterile high-level disinfectant with surfactants</td>
<td>daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>sporicide</td>
<td>weekly or in response to microbial monitoring</td>
<td></td>
</tr>
<tr>
<td><strong>Adjacent Flooring and Walls</strong></td>
<td>mop</td>
<td>sterile high-level disinfectant with surfactants</td>
<td>daily, between lots and shifts</td>
<td>not necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sterile high-level disinfectant followed by a sporicide, as necessary</td>
<td>weekly or in response to microbial monitoring</td>
<td></td>
</tr>
</tbody>
</table>
Sporicidal Agent Application

✓ Rationale

✓ Spore control vs. chemical exposure

✓ Corrosivity and Irritation
Application Frequency

- Sporicidal agent
  - Rationale
    - Weekly
    - Monthly
    - Quarterly
  ✓ Should be written in SOP’s
New Mopping Systems

• The Mop King (http://www.am-king.com/mopking.htm)
• The Micron Swep (http://www.youtube.com/watch?v=qTWaYQlX2IY)
Agenda

• Current Industry Trends
  ➢ Cleaning and Disinfection
  ➢ Disinfectant Validation
  – Current Warning Letters
In Vitro Options for Testing

- **AOAC**
  - Use-dilution Test
  - Sporicidal Activity of Disinfectants
  - Germicidal Spray Products as Disinfectants
- **ASTM**
  - Time Kill Method
  - Spray Slide
  - Sanitizer method (E1153)
  - Wipe method
  - Quantitative Carrier Method (E2111 & E2197)
  - Biofilm Method (E1427)
  - Viral Testing (Suspension E1052)
  - Viral Testing (Carrier E1053)
  - Standard Guide for Evaluation of Cleanroom Disinfectants (E2614-08)
- Variations of all of the above
More In Vitro Options for Testing

- **EN**
  - 1276 (bacterial suspension test)
  - 1040 (bacterial suspension test)
  - 1650 (fungal suspension test)
  - 13704 (sporicidal suspension test)
  - **13697 (Carrier test)**
  - 14476 (Viral Testing)
  - 14348 (TB Testing)
- **AFNOR (France)**
  - NFT 72-150 Suspension
  - NFT 72-190 Carrier Test
- **DGHM Suspension Test (Carrier & Suspension Tests)**
- **TGA (Australia)**
Testing at Contract Labs & Industry

- European Testing is generally EN-13697 Hard Surface Testing Method
  - Log Reduction Values commonly used are from USP 35 <1072> (3 Log for Vegetative Bacteria and 2 Log for Bacterial and Fungal spores)
  - Some contract labs will conduct ASTM Methods E2111 or E2197
- Some companies develop their own coupon testing methods
- Some companies use Modified AOAC testing methods
- Costs at contract labs includes contact time, surface, and test conditions. Viral testing more expensive.

There are no currently harmonized disinfectant efficacy testing methods between the US and EU.
Key Variables with EN-13697

- Hard Water
- Soil Load (Albumin + Tryptone) or Skimmed Milk Clean vs. Dirty Soil Loads
- Contact time 5 Minutes
- The Organism (Some fungi and *Bacillus* are more resistant)
- Nature of the Surface being Tested
- Technique of Application (Immersion, Spray, Wiping)
Disinfectant Validation Studies

• The cost of a study can vary quite a bit depending on:
  – Who is conducting the study (Inside or outside microbiology lab)
  – The number of organisms tested
  – The contact times tested (many companies test more than one time point)
  – Number of substrates tested
  – Number of disinfectants or sporicides tested
  – The age of product they want to test (i.e., do they want to use product after 7 days)
  – The different test methods they want to use
  – Any other variables they may want to consider in their testing (soiled vs. clean conditions, etc.)
### Case Study on Substrates

Table 3. Efficacy (log reduction) of Low pH phenolic: (1:256 Dilution) against test microorganisms on representative surfaces

<table>
<thead>
<tr>
<th>Surface</th>
<th><em>Staphylococcus epidermidis</em></th>
<th><em>Pseudomonas aeruginosa</em></th>
<th><em>Corynebacterium glutamicum</em></th>
<th><em>Candida albicans</em></th>
<th><em>Aspergillus niger</em></th>
<th><em>Penicillium chrysogenum</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stainless Steel</td>
<td>6.62</td>
<td>&gt;6.10 (^b)</td>
<td>4.18</td>
<td>&gt;4.31 (^b)</td>
<td>&lt;3.00 (^c)</td>
<td>4.95</td>
</tr>
<tr>
<td>Glass</td>
<td>6.85</td>
<td>6.42</td>
<td>5.26</td>
<td>&gt;5.80 (^b)</td>
<td>2.98</td>
<td>5.11</td>
</tr>
<tr>
<td>Aluminum</td>
<td>6.35</td>
<td>5.69</td>
<td>5.14</td>
<td>&gt;3.93 (^b)</td>
<td>&lt;3.00 (^c)</td>
<td>3.48</td>
</tr>
<tr>
<td>Epoxy</td>
<td>4.36</td>
<td>4.45</td>
<td>4.48</td>
<td>3.19</td>
<td>&lt;3.00 (^c)</td>
<td>&lt;3.00 (^c)</td>
</tr>
<tr>
<td>Enamel</td>
<td>&gt;6.05(^b)</td>
<td>&gt;5.72(^b)</td>
<td>5.45</td>
<td>&gt;3.92 (^b)</td>
<td>&lt;3.00 (^c)</td>
<td>2.83</td>
</tr>
<tr>
<td>Acrylic</td>
<td>4.53</td>
<td>6.06</td>
<td>4.49</td>
<td>2.92</td>
<td>&lt;3.00 (^c)</td>
<td>&lt;3.0 (^c)</td>
</tr>
<tr>
<td>Miplan</td>
<td>4.36</td>
<td>3.87</td>
<td>4.29</td>
<td>4.37</td>
<td>&lt;3.00 (^c)</td>
<td>3.25</td>
</tr>
<tr>
<td>Vinyl</td>
<td>4.08</td>
<td>3.68</td>
<td>3.93</td>
<td>2.61</td>
<td>&lt;3.00 (^c)</td>
<td>2.1</td>
</tr>
<tr>
<td>Hardwood</td>
<td>5.18</td>
<td>&gt;4.54 (^b)</td>
<td>5.26</td>
<td>3.2</td>
<td>&lt;3.00 (^c)</td>
<td>2.59</td>
</tr>
<tr>
<td>Melamine Covered Wood</td>
<td>&gt;5.38 (^b)</td>
<td>&gt;5.64 (^b)</td>
<td>&gt;5.09 (^b)</td>
<td>&gt;5.12 (^b)</td>
<td>3.65</td>
<td>3.95</td>
</tr>
<tr>
<td>Plastic</td>
<td>&gt;5.73 (^b)</td>
<td>&gt;5.32 (^b)</td>
<td>&gt;5.05 (^b)</td>
<td>&gt;4.04 (^b)</td>
<td>&lt;3.00 (^c)</td>
<td>2.44</td>
</tr>
<tr>
<td>Plexiglas</td>
<td>&gt;5.90 (^b)</td>
<td>5.62</td>
<td>4.83</td>
<td>&gt;4.40 (^b)</td>
<td>&lt;3.00 (^c)</td>
<td>3.85</td>
</tr>
<tr>
<td>Print</td>
<td>5.85</td>
<td>5.86</td>
<td>5.74</td>
<td>4.51</td>
<td>&lt;3.00 (^c)</td>
<td>3.38</td>
</tr>
<tr>
<td>Chromium</td>
<td>6.55</td>
<td>5.95</td>
<td>6.63</td>
<td>4.08</td>
<td>&lt;3.00 (^c)</td>
<td>2.61</td>
</tr>
</tbody>
</table>

\(^a\) Disinfectant Efficacy = (Log MSP\(_{\text{positive control}}\) - Log MSP\(_{\text{test coupons}}\)), where MSP\(_{\text{positive control}}\) = Mean surviving population on positive control coupons; MSP\(_{\text{test coupon}}\) = Mean surviving population on test coupons after disinfectant treatment; \(^b\) Each of triplicate coupons showed no growth after disinfectant treatment; \(^c\) Each of triplicate coupons showed TNTC growth
Spore Testing

6% H₂O₂ vs. Spor-Klenz RTU
Standard Time Kill Study 13 Jun 2007
*B. subtilis* spores 19659  Baseline = 6.60 log₁₀

Ave. Log Reduction

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>1 min</th>
<th>3 min</th>
<th>5 min</th>
<th>10 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>6% Hydrogen Peroxide</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>SK RTU</td>
<td></td>
<td></td>
<td>6.50</td>
<td>6.50</td>
</tr>
</tbody>
</table>

STERIS Corporation
ATCC: Hydrogen Peroxide 6%

**Spore Forming Microorganisms**

Log Reduction ± SD

- A. niger
- B. subtilis

**Vegetative Microorganisms**

Log Reduction ± SD

- C. albicans
- P. aeruginosa
- S. aureus

CT = 9 min.

2 Log Reduction Target

3 Log Reduction Target
ATCC: H202/PAA RTU

Spore Forming Microorganisms

CT = 5 min.

Vegetative Microorganisms

2 Log Reduction Target

3 Log Reduction Target
Hard Surface Tests

Hard Surface Comparison
H2O2/PAA RTU
Bacillus subtilis ATCC 19659

Average Log Reduction

Glass  Stainless  Enamel  Epoxy  Miplan  Vinyl  Acrylic

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Efficacy Comparison with Fungi

Aspergillus niger ATCC 16404
Standard Time Kill

<table>
<thead>
<tr>
<th>Active</th>
<th>30 seconds</th>
<th>60 seconds</th>
<th>120 seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quat A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quat B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quat C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenol A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenol B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% Bleach</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70% Isopropanol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H2O2/ PAA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Agenda

• Current Industry Trends
  ➢ Cleaning and Disinfection
  ➢ Disinfectant Validation
  ➢ Current Warning Letters
Current Guidance on Disinfectants

- USP 35 General Chapter <1072>
- ISO /DIS 14698-parts1-3
- The Orange Guide 2009
- Aseptic Processing Guide 2004
- Current Industry Articles (Jose Martinez, Scott Sutton, Richard Prince)
- USP 35 <797>
- Several Industry Books (Seymour S. Block)
Current Warning Letter

• “Your firm has not established procedures designed to prevent microbiological contamination of drug products purporting to be sterile” Warning Letter February 22, 2012
“Your Disinfectant qualification for (b) (4) and (b) (4) bi-spore disinfectants documented that the log reduction criteria (Bacteria>4, Fungi>3) was not met when challenged with multiple organisms in variety of surfaces. After disinfection you recovered *Micrococcus luteus* on vinyl, (b) (4), stainless steel, glass and wall laminate and *Enterobacter cloacae, Rhodococcus* sp, *Burkholderia cepacia, Pseudomonas aeruginosa* on glass. However your procedures for routine cleaning of the aseptic manufacturing area continue to require the use of unqualified disinfectants during days (b) (4) through (b) (4) of your disinfection program” Warning Letter October 7, 2011.
“The materials that were tested in the Disinfectant Efficacy study were not representative of all the surfaces present in the Aseptic Processing Area.” “The stainless steel coupon tested did not represent these damaged surfaces” Warning Letter May 25, 2011
Current Warning Letter

• “Furthermore, we evaluated your environmental data from 2008 to 2010 and are concerned with the lack of comprehensive investigations when mold and bacteria were identified in your aseptic filling facility that exceeded action levels.”

Warning Letter February 10, 2011
Current Warning Letter

• “We note that the cGMP violations listed in this letter include similar violates to those cited in the previous February 2008 inspection including failure to adequately conduct disinfectant efficacy studies” Warning Letter July 14, 2011.
Current Warning Letter

• Specifically, no disinfectant validation was performed for your (b)(4) cleaning of vessels, surfaces, and other equipment used during the collagen impregnation process. Your firm’s laboratory simulation Disinfectant Efficacy Testing report, dated January 27, 2009 shows that the disinfectants used by your firm can remove microorganisms placed on carrier test coupons; however, no disinfectant validation study was conducted to demonstrate that your (b)(4) cleaning and sanitizing procedures are adequate in removing contaminants from actual Collagen processing equipment. Warning Letter August 11, 2010.
Current Warning Letter

• “The inspection documented mold contamination in the Class 100 production room and visible black mold on the wall” “Your firm did not establish a schedule for cleaning with an agent designed to kill spores, although mold continued to be found in the class 10,000 area.” Warning Letter October 29, 2010
483 Observation

• “During sanitization and sporicidal agent revalidation studies completed in .... two sporicidal agents routinely used by the firm failed to achieve corporate acceptance criteria of....for all challenge microorganisms used in testing. The sporicidal agents remained on the form’s approved sanitizing and sporicidal agents list for parenteral areas until.... The revalidation study completion dates and sporicidal agents failing to achieve the acceptance criteria are as follows.....”

• June 2008 GMP Trends
“Systematic facility cleaning for mold was not initiated in a timely manner. Systematic cleaning was initiated after several months of environmental excursions for mold throughout the manufacturing areas, including aseptic areas.” Warning Letter March 28, 2008.
483 Observation

•“There are no assurances that the currently used...disinfectant is effective against fungi and molds. Per protocol....the disinfectant effectiveness study for....the assay test method validation was for ....recovery rate. However, the data obtained during the performance qualification demonstrated that the minimum of....acceptance criteria established per protocol....was not consistently obtained during the positive control recovery studies.”

•January 2009 GMP Trends
•“Your responses indicate that you will conduct an additional study to evaluate the effectiveness of your disinfectants, as well as perform cleaning validation of the ___ laminar flow hood. Please be advised that the completion date of Q1/2008 for these activities appears excessive. We remind you that the failure to adequately evaluate your disinfectants is a repeat observation from our 2004 inspection. We recommend that you re-evaluate your proposed time frame for completion of both studies.” Warning Letter September 19, 2007
Warning Letter-Disinfection

Warning Letter-Disinfectants

•“There is no assurance that the disinfectant ____ is effective against mold, since it did not meet your established recovery rate acceptance criterion in the December 2001 “Disinfectant Validation and Efficacy Study of ____ by the Surface Test Method” study.” Warning Letter May 24, 2007.
• “There are no sanitizer/disinfectant efficacy studies using … against microorganisms isolated in the aseptic production area using comparable material found in the manufacturing area such as …..” GMP trends 6/15/2006
Regulatory Notes

• “Approximately 80% of all microorganisms’ growth in the…filling room, monobblend aseptic filtration, and trivalent formulation room excursions were not identified to the genus level.” GMP Trends 9/1/2005.
Warning Letter

•“Your firm does not ensure that a _____ system is employed, or that the disinfectant is rendered sterile prior to use.”

•However your response to our FDA-483 is inadequate because the following were not addressed: Effectiveness of _____ solution at the dilution used, and 2) effectiveness of __________

•throughout the shelf life (up to the expiry date).”

•Warning Letter March 2009.
Agenda

• Current Industry Trends
  ➢ Cleaning and Disinfection
  ➢ Disinfectant Validation
  ➢ Current Warning Letters