Disinfection Processes

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Technical Service Manager
Steris Corp.

Agenda

• Current Industry Trends
  ➢ Cleaning and Disinfection
    – Current Warning Letters & Industry Guidance
### VALIDATION – Microorganism Selection

#### Microorganisms and Examples

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>More Resistant</td>
<td></td>
</tr>
<tr>
<td>Bacteria</td>
<td>Bacillus, Geobacillus, Clostridium</td>
</tr>
<tr>
<td>Protozoa</td>
<td>Cryptosporidium</td>
</tr>
<tr>
<td>Helminth Eggs</td>
<td>Ascaris, Enterobius</td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>Mycobacterium leprae, M. avium, M. chelonae</td>
</tr>
<tr>
<td>Small, Non-Enveloped Viruses</td>
<td>Poliovirus, Parvoviruses, Papilloma viruses</td>
</tr>
<tr>
<td>Prion</td>
<td>Gaussia, Acanthamoeba</td>
</tr>
<tr>
<td>Fungi</td>
<td>Aspergillus, Penicillium</td>
</tr>
<tr>
<td>Gram-negative bacteria</td>
<td>Pseudomonas, Providencia, Eschericsta</td>
</tr>
<tr>
<td>Vegetative Fungi and Algae</td>
<td>Aspergillus, Fischyphoton, Candida, Colormycetes</td>
</tr>
<tr>
<td>Vegetative Helminths and Protozoa</td>
<td>Ascaris, Cryptosporidium, Giardia</td>
</tr>
<tr>
<td>Large, non-enveloped viruses</td>
<td>Adenoviruses, Reoviruses</td>
</tr>
<tr>
<td>Gram positive bacteria</td>
<td>Staphylococci, Streptococci, Pseudomonas</td>
</tr>
<tr>
<td>Enveloped viruses</td>
<td>HIV, Hepatitis B virus, Herpes, Simplex virus</td>
</tr>
</tbody>
</table>

#### Bacillus cereus / sphaericus

#### Bacillus subtilis / G. stearothermophilus

#### Clostridium spp

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### Contamination Control

#### Microbial Resistance to Stress

- **Least Resistant**
  - Spores
  - TB
  - Bacteria
  - Enveloped Viruses

- **Most Resistant**
  - Sporicides
    - Low pH Phenolics
    - High pH Phenolics
    - Quaternary Ammoniums

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### Classifications

- **Sterilants**
  - $\text{H}_2\text{O}_2$/PAA, NaOCl
- **Disinfectants**
  - Phenols and Quats
- **Sanitizers**
  - 70% IPA, ETOH

### 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>Solvents</td>
<td>Solubilization and stabilization</td>
</tr>
<tr>
<td>Antimicrobials</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</td>
</tr>
<tr>
<td>Oxidants, oxidants,</td>
<td>Potentiate antimicrobial action</td>
</tr>
<tr>
<td>Bases</td>
<td>Alkalinity source (NaOH, KOH)</td>
</tr>
<tr>
<td>Acids</td>
<td>Acidity source (HCl, Phosphoric Acid)</td>
</tr>
<tr>
<td>Surfactants</td>
<td>Emulsification, Wetting</td>
</tr>
</tbody>
</table>

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Effect of Surfactants

- Influence of Surfactants on Wetting
  - Ability to displace particles
  - Penetrate soil and surface irregularities
  - Better contact

Access to microbes

Water

With surfactant

Substrate
Molds common to cleanrooms and coldrooms

- *Aspergillus* species
- *Penicillium* species
- Stachy bottrus
- *Candida albicans*
- Cladosporium
- Mucor
- Scopulariopsis
- Trychophyton

Bacterial Spores in Operations

- *Bacillus subtilis*
- *Bacillus cereus*
- *Bacillus pumilus*
- *Bacillus licheniformis*
- *Bacillus sphaericus*
- *Bacillus thuringiensis*
- *Paenibacillus polymyxa*
- Geobacillus
- Clostridium difficile
Aspergillus niger

Courtesy Jim Polarine

Cleanroom Fungi

Courtesy Dan Klein
New Mopping Systems

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

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
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


Two and Three Bucket Systems

Courtesy Perfex Corp.

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• Surfaces
  – Floors
  – Walls
  – Isolators
  – Lyophilisers
  – Cabinets
  – Tanks
  – Curtains/Softwalls

Courtesy Micronova Mfg.

• Adaptable
• Resistant
• Dedicated

Courtesy Micronova Mfg.
Mop Heads for Cleanrooms

- Disinfectant applicator
- Choice of widths
- Universal
  - Floors/Walls
  - Large/small areas

Spills and Leaks

Courtesy of Micronova Mfg.

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Commonly Used Equipment

Sprayers and Foamers

Acid Sprayer
- Compatible with oxidizers, phenolics, quats, and other acids

Cart
- Carts designed for 5 gal pail

Sanitation Sprayer
- Sprayer Attachment
- Has rinse cycle

Foam Master
- Plant Air powered
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 100000 - D

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</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>- railings</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 10000 - C

### 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>Floors</td>
<td>mop</td>
<td>high-level disinfectant with surfactants</td>
<td>daily after transfers</td>
<td>not necessary</td>
</tr>
<tr>
<td>• traffic paths</td>
<td></td>
<td>high-level disinfectant with surfactants</td>
<td>weekly or monthly, if necessary</td>
<td></td>
</tr>
<tr>
<td>• proximity to open</td>
<td></td>
<td>high-level disinfectant with surfactants</td>
<td>weekly or monthly, if necessary</td>
<td></td>
</tr>
<tr>
<td>• process or transfer</td>
<td></td>
<td>high-level disinfectant with surfactants</td>
<td>weekly or monthly, if necessary</td>
<td></td>
</tr>
<tr>
<td>• areas</td>
<td></td>
<td>high-level disinfectant with surfactants</td>
<td>weekly or monthly, if necessary</td>
<td></td>
</tr>
<tr>
<td>Walls</td>
<td>wpe</td>
<td>high-level disinfectant with surfactants</td>
<td>daily</td>
<td>not necessary</td>
</tr>
<tr>
<td>• general</td>
<td></td>
<td>high-level disinfectant with surfactants</td>
<td>daily</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>not necessary</td>
</tr>
<tr>
<td>Equipment</td>
<td></td>
<td>high-level disinfectant with surfactants</td>
<td>daily</td>
<td>not necessary</td>
</tr>
<tr>
<td>• shelving</td>
<td></td>
<td>high-level disinfectant with surfactants</td>
<td>daily</td>
<td>not necessary</td>
</tr>
<tr>
<td>• portable tanks</td>
<td></td>
<td>high-level disinfectant with surfactants</td>
<td>daily</td>
<td>not necessary</td>
</tr>
<tr>
<td>• processing areas</td>
<td></td>
<td>high-level disinfectant with surfactants</td>
<td>daily</td>
<td>not necessary</td>
</tr>
<tr>
<td>• cabinets (shelves)</td>
<td></td>
<td>high-level disinfectant with surfactants</td>
<td>daily</td>
<td>not necessary</td>
</tr>
<tr>
<td>Furniture and Other</td>
<td></td>
<td>high-level disinfectant with surfactants</td>
<td>daily</td>
<td>not necessary</td>
</tr>
<tr>
<td>• chair (shelves)</td>
<td></td>
<td>high-level disinfectant with surfactants</td>
<td>daily</td>
<td>not necessary</td>
</tr>
</tbody>
</table>

## Class 100 - A & B

### 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>External Hoods</td>
<td>wpe</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>sterile high level disinfectant with surfactants</td>
<td>daily</td>
<td>not necessary</td>
</tr>
<tr>
<td>• door, cleaning pantry</td>
<td></td>
<td>sterile high level disinfectant with surfactants</td>
<td>daily</td>
<td>not necessary</td>
</tr>
<tr>
<td>Inside Hood or Curtain</td>
<td></td>
<td>sterile high level disinfectant with surfactants</td>
<td>daily</td>
<td>not necessary</td>
</tr>
<tr>
<td>• wall surfaces</td>
<td></td>
<td>sterile high level disinfectant with surfactants</td>
<td>daily</td>
<td>not necessary</td>
</tr>
<tr>
<td>• apparatus/critical surfaces</td>
<td></td>
<td>sterile high level disinfectant with surfactants</td>
<td>daily</td>
<td>not necessary</td>
</tr>
<tr>
<td>• curtains</td>
<td>wpe</td>
<td>sterile high level disinfectant with surfactants</td>
<td>daily</td>
<td>not necessary</td>
</tr>
<tr>
<td>Adjacent Flooring and Walls</td>
<td>mop</td>
<td>sterile high level disinfectant with surfactants</td>
<td>daily</td>
<td>not necessary</td>
</tr>
</tbody>
</table>

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Sporicidal Agent Application

✓ Rationale

✓ Spore control vs. chemical exposure

✓ Corrosivity and Irritation

Application Frequency

☐ Sporidal agent
  ☐ Rationale
    ☐ Weekly
    ☐ Monthly
    ☐ Quarterly
  ✓ Should be written in SOP’s
Alternative Technique

- Foaming
- VHP
- Spraying (also known as fogging)
  - Aerosolizes disinfectant
- Fumigation
  - Vaporizes disinfectant
- Full immersion
  - Disinfectant soak

Hydrogen Peroxide Vapor

- Sporicidal at Low Concentrations
  - (Typically 1-2 mg/l at 25°C)
- Non-Toxic Residues

2H₂O₂ → 2H₂O + O₂

Cold Sterilization Process

4-80°C
Room Decontamination

Walk-In Refrigerator Type
Construction

Oklahoma Medical Research Foundation, Oklahoma City, OK

Fogger / Dynafogger

✓ Room Size
✓ Effectiveness
✓ Material Compatibility
✓ Contact Time
✓ Re-entry Time

Courtesy of Microclean-
What is Rotation?

- Alternation of antimicrobial actives
  - Two disinfectants in sequence, regular rotation, with sterilant as needed
  - One disinfectant daily, with sterilant weekly or monthly

Rotation Guidance

- USP 35 <1072>
- Conner & Eckman Studies
- FDA, MHRA, IMB, French and Japanese, & EMA Expectations
- Industry Articles (Ex. Scott Sutton, Jose Martinez, Richard Prince)
- USP 35 <797>
Residues on Substrates:

Surface Type and Topography

Photos provided by Brook Meadows
Rinsing Frequency

- **Rinsing**

- **Guidance USP 35 <1072**
  - 70% IPA or Water for Injection
  - Cleaners (Acidic, Neutral, Basic)
  - As needed to control residue
    - Aesthetic
    - Safety Risk (Sticky, Tacky, Slippery)
    - Particulate Issues
    - Functional
    - Microbial Issue (Hiding Microbes & Food Sources)
    - Product risk (Flaking of residues into filled products)

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**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>Staphylococcus epidermidis</th>
<th>Pseudomonas aeruginosa</th>
<th>Corynebacterium glutamicum</th>
<th>Candida albicans</th>
<th>Aspergillus niger</th>
<th>Penicillium chrysogenum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stainless Steel</td>
<td>6.62</td>
<td>6.10</td>
<td>4.18</td>
<td>4.31</td>
<td>&lt;3.00</td>
<td>4.95</td>
</tr>
<tr>
<td>Glass</td>
<td>8.85</td>
<td>6.42</td>
<td>5.26</td>
<td>5.80</td>
<td>2.98</td>
<td>5.11</td>
</tr>
<tr>
<td>Aluminum</td>
<td>8.35</td>
<td>6.69</td>
<td>5.14</td>
<td>3.93</td>
<td>&lt;3.00</td>
<td>3.48</td>
</tr>
<tr>
<td>Epoxy</td>
<td>4.38</td>
<td>4.45</td>
<td>4.48</td>
<td>3.19</td>
<td>&lt;3.00</td>
<td>&lt;3.00</td>
</tr>
<tr>
<td>Enamel</td>
<td>&gt;6.05</td>
<td>&gt;5.72</td>
<td>5.45</td>
<td>&gt;3.00</td>
<td>&lt;3.00</td>
<td>&lt;3.00</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</td>
<td>&gt;3.00</td>
</tr>
<tr>
<td>Mylar</td>
<td>4.36</td>
<td>3.87</td>
<td>4.29</td>
<td>3.37</td>
<td>&lt;3.00</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</td>
<td>2.1</td>
</tr>
<tr>
<td>Hardwood</td>
<td>5.18</td>
<td>4.54</td>
<td>5.26</td>
<td>3.2</td>
<td>&lt;3.00</td>
<td>2.99</td>
</tr>
<tr>
<td>Melamine Covered Wood</td>
<td>&gt;5.94</td>
<td>&gt;5.41</td>
<td>&gt;5.09</td>
<td>&gt;4.94</td>
<td>&lt;3.00</td>
<td>&gt;3.00</td>
</tr>
<tr>
<td>Plastic</td>
<td>&gt;5.94</td>
<td>&gt;5.32</td>
<td>&gt;5.09</td>
<td>&gt;4.04</td>
<td>&lt;3.00</td>
<td>&lt;3.00</td>
</tr>
<tr>
<td>Plexiglas</td>
<td>&gt;5.94</td>
<td>5.62</td>
<td>4.83</td>
<td>&gt;4.40</td>
<td>&lt;3.00</td>
<td>3.85</td>
</tr>
<tr>
<td>Porcelain</td>
<td>5.85</td>
<td>5.86</td>
<td>5.74</td>
<td>4.61</td>
<td>&lt;3.00</td>
<td>3.38</td>
</tr>
<tr>
<td>Chromium</td>
<td>6.55</td>
<td>5.96</td>
<td>6.63</td>
<td>4.08</td>
<td>&lt;3.00</td>
<td>2.61</td>
</tr>
</tbody>
</table>

* Disinfectant Efficacy = (Log MSP_{positive control} - Log MSP_{test coupons})
* Where MSP_{positive control} = Mean surviving population on positive control coupons; MSP_{test coupons} = Mean surviving population on test coupons after disinfectant treatment; * Each of triplicate coupons showed no growth after disinfectant treatment; * Each of triplicate coupons showed TNTC growth.
Spore Testing

ATCC: Hydrogen Peroxide 6%

CT = 9 min.

2 Log Reduction Target

3 Log Reduction Target
ATCC: H202/PAA RTU

CT = 5 min.

2 Log Reduction Target

3 Log Reduction Target

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Hard Surface Tests

Hard Surface Comparison
H2O2/PAA RTU
Bacillus subtilis ATCC 19659

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Efficacy Comparison with Fungi

Aspergillus niger ATCC 16404
Standard Time Kill

<table>
<thead>
<tr>
<th>Time</th>
<th>Quat A</th>
<th>Quat B</th>
<th>Quat C</th>
<th>Phenol A</th>
<th>Phenol B</th>
<th>10% Bleach</th>
<th>75% Isopropanol</th>
<th>H2O2/PAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 seconds</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 seconds</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>120 seconds</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Agenda

- Current Industry Trends
  - Cleaning and Disinfection
  - Current Warning Letters & Industry Guidance
Current Guidance on Disinfectants

- USP 35 General Chapter <1072>
- ISO /DIS 14698-parts1-3
- The Orange Guide 2007
- Aseptic Processing Guide 2004
- Current Industry Articles (Jose Martinez, Scott Sutton, Richard Prince)
- USP 35 <797>
- Several Industry Books (Seymour S. Block)

483 Observation

- “The records do not include specific documentation on the time employed in the cleaning and disinfection of the separate areas in order to make a better assessment about the procedures executed and if they are consistently followed.”

March 1, 2012
483 Observation

• “The firm enlisted the services of a contract firm to conduct cleaning and disinfection and inspection reports lacked adequate scientific justification and/or rationale documentation to support conclusions or actions to handle OOS results.” March 15, 2012

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
Current Warning Letter

“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.

Current Warning Letters

“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

• “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

Warning Letter

• “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.
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.

Questions & Answers