Residue removal in Cleanroom Environments

Contamination Control Solutions
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Technical Service Manager

• STERIS Life Sciences – 4 years
• 24 years experience
  – R&D: Immunoassay Development & Monoclonal Antibody development
  – Biopharma: Upstream and Downstream processing, Technical Transfer, Compliance, Validation
  – Solid Dose: Extended release manufacturing

• B.S. in Biochemistry from the University of Missouri, St. Louis.
Overview of Recommended Practices for Residue Removal in the Cleanroom

• Regulatory and GMP expectations
• Residues found in the Cleanroom
  – Conditions leading to residues
  – Typical components of disinfectants & what they look like in appearance
  – Residue types on various substrates
• Residue Removal
  – Program Recommendations
Regulatory and GMP Expectations

• Pharmaceutical Inspection Convention (PIC/S)
  – Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments

• Food and Drug Association (FDA) Guidance for Industry 2004
  – Sterile Drug Products Produced by Aseptic Processing – current Good Manufacturing Practices)

• USP 38 General Chapter <1072>
  – Disinfectants and Antiseptics
  – Lists contamination of pharma products by disinfectant
Regulatory and GMP Expectations

- Parenteral Drug Association (PDA)
  - Technical Report 70, Fundamentals of Cleaning and Disinfection Programs for Aseptic Manufacturing Facilities
    - Mentions residue removal as important for inspection readiness
    - Discusses types of cleaning agents
    - Defines what is meant by “cleaning” and why necessary
    - Describes how to assess frequency
    - Section concerning reducing corrosion and deterioration of surfaces
Regulatory and GMP Expectations

• 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”
  – “I observed splatters of rust and white colored residue…”
Why Residues are a concern

• Efficacy concerns:
  – Residues inhibiting Biocides
  – Do residues support harbor microbial growth?
  – Do residues inhibit preceding actives (rotational chemistries)?

• Functional Issues:
  – Sticky or opaque surfaces due to residues

• Aesthetic Issues:
  – Surfaces do not look “clean”

• Safety Issues:
  – Transfer (direct and indirect) from surfaces to manufactured drug products or medical devices
  – Personnel safety (slippery, tacky, sticky, etc.)
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Where does the residue come from?

- Existing cleanrooms which lack rinsing program

This is a problem? Why? We clean the door all the time...
Where does the residue come from?

- Compatibility issues
  - Different agents in rotation program
  - Surface substrates

- Poor cleaning practices
- Drug product/process spills
Where does the residue come from?

A 1996 train derailment in Weyauwega spilled 9,000 gallons of sodium hydroxide; the town was evacuated for 17 days.
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## Disinfectant Components

<table>
<thead>
<tr>
<th>Component</th>
<th>Residue Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>Water spots</td>
</tr>
<tr>
<td>Surfactant</td>
<td>Very faint yellow to clear, gelatinous and sticky White solid beads.</td>
</tr>
<tr>
<td>Chelants</td>
<td>White or pinkish grey solid</td>
</tr>
<tr>
<td>Solvent</td>
<td>No residue visible</td>
</tr>
<tr>
<td>Bases</td>
<td>White to tan crystals</td>
</tr>
<tr>
<td>Acids</td>
<td>Clear glaze with points of precipitates</td>
</tr>
<tr>
<td>Builders</td>
<td>White powder</td>
</tr>
</tbody>
</table>
| Antimicrobials | White to yellow  
Brown, pinkish tan  
Clear, gelatinous, sticky glaze                  |
| Oxidant     | Water spots                                                                         
No residue visible to white to tan powder or crystals from additives                  |
| Dyes        | Red, yellow, blue, color residues                                                   |
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Surface Type and Condition

- Visually smooth surfaces can be irregular
- Glass and stainless steel typically the least challenging
- Older or damaged surfaces can be more challenging
Residues on Substrates:

New PVC wall board  Old PVC wall board
Residues on Substrates:

Desco Quartz Epoxy flooring system, 1.5 years, floors daily with phenolics and 1/month application of sporicidal agent
Residues on Substrates:

After 3 applications:

- Low pH phenolic disinfectant at use dilution
- High pH phenolic disinfectant at use dilution
- Sporicidal agent at use dilution
Residues on Substrates:
Residues on Substrates: Lab testing

• Objective:
  – Test 4 flooring samples to determine what conditions prevent staining
    • Disinfectants/drug product were applied to each of the floor systems

1 – Drug product air dried followed by phenolic disinfectant at use-dilution, air dried
2 – Drug product mixed with phenolic disinfectant at use-dilution then air dried
3 – Drug product mixed with phenolic concentrate, then air dried
4 – Drug product only, air dried
Residues on Substrates: Lab testing

• Results:
  – Oxidative detergent required to clean the surface
    • 1-3%, ambient, 1 minute scrub, rinse
  – Cleaning agents left surface tacky
  – After cycles of 3 applications of residues/cleaning, 2 of the 4 floor samples showed yellow stains
  – Drug product mixed with concentrated cleaner was more difficult to remove

• Take home:
  – Evaluate residue interaction with disinfectant
  – Careful use of concentrated disinfectants
  – Evaluate “cleaning” capability of rinse agent chosen
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Program Recommendations

• Incorporate rinse/cleaning into cleaning and disinfection program
  – Nondestructive mechanical action to remove contaminants and residue
  – In addition to sanitizers, disinfectants or sporicides
Program Recommendations

• How often to clean???
  – Environmental cleaning frequency determined by:
    • ISO Classification of area
    • Activity level in area or use
    • Environmental monitoring feedback
    • Type of process being performed & equipment used
    • Substrates
    • Visual observation
Program Recommendations: Rinsing Options

• Guidance USP 38 <1072>
  – 70% IPA or Water for Injection
  – Cleaners (Acidic, Neutral, Basic)

• PDA tech report 70
  – Water, organic solvent, commodity chemical
diluted in water and formulated detergent diluted in
water.
  – Ideal cleaning agent formulated with surfactant
system to release particles, residues and other
foreign materials.
Use of water (WFI)

• Advantages
  – Safest to use
  – Leaves no additional residues

• Disadvantages
  – May be less effective in removing residues
  – Leaves surface wet with (perhaps) no antimicrobial residues to inhibit growth while wet
Use of 70% IPA

• Advantages:
  – May be more effective in dissolving residues
  – Leaves no additional residue
  – Provides antimicrobial activity
  – Leaves surface dry

• Disadvantages
  – Flammability
  – Personnel exposure (i.e. Short Term Exposure Limits – STEL)
  – Not desirable in areas in which TOC or particulate monitoring is being conducted
Use of a Formulated Cleaner

• Advantages
  – May be more effective in dissolving or emulsifying residues
  – Relatively safe

• Disadvantages
  – Will leave a residue itself
  – Issues with proper dilution
Program Recommendations: Rinsing Options

• Heavy Residue Removal
  – May require laboratory evaluation
  – Details of contamination program and current rinsing program required & critical
  – Formulated detergent or another detergent may be required
  – Once cleanroom surface has been returned to a “clean state”, implement the routine rinsing procedure as maintenance
## Program Recommendations: Rinsing Options

<table>
<thead>
<tr>
<th>Cleaning Agent</th>
<th>Percent Residue Remaining on Stainless Steel Coupon After Removal Techniques of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immersion:</td>
</tr>
<tr>
<td>Acidic Cleaner</td>
<td>12.3</td>
</tr>
<tr>
<td>Alkaline Cleaner</td>
<td>3.8</td>
</tr>
<tr>
<td>Neutral Cleaner</td>
<td>1.7</td>
</tr>
<tr>
<td>IPA, 70%</td>
<td>10.2</td>
</tr>
<tr>
<td>Direct Q Water</td>
<td>7.8</td>
</tr>
<tr>
<td>Average %</td>
<td>7.2</td>
</tr>
</tbody>
</table>

**Note:** Process cleaners will leave a residue and may need to be rinsed after use
Contamination Control
Program Recommendation

• Build up on Vinyl, Epoxy or Terrazzo Floors
  – WFI
  – Acidic, Basic, or Neutral Cleaners
• Build up on Stainless Steel & Equipment
  – 70% IPA
  – WFI
• Build up of phenolics on Lexan or Vinyl Curtains
  – 70% IPA
  – Acidic Cleaners
Contamination Control Program Recommendation

• For clean rooms we still recommend
  – Disinfectant Rotation
    • Phenols or Quats on monthly basis (never a phenol and a quat)
  – Sterilant use routinely based on environmental data
  – Rinsing on a routine basis
    • Not necessarily daily, but SOPs should include weekly/monthly rinsing with IPA or water
  – Evaluate cleanability of heavy residues
References

- USP 38 <1072> Disinfectants and Antiseptics
- FDA, MHRA, HPRA, CFDA, French and Japanese, & EMA Expectations
- Industry Articles (Ex. Scott Sutton, Jose Martinez, Richard Prince, Rebecca Smith)
- PDA Cleaning and Disinfection TR70 (2015)
- USP 38 <1116> Microbiological Control and Monitoring of Aseptic Processing Environments
Thank you for your attention!
Contact Information

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