Designing an effective cleaning procedure for medical devices through laboratory studies

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Agenda

• Medical device categories
• Regulatory approach
• Residues
• Critical factors affecting cleaning
• Laboratory evaluation and case studies
• Cleanliness criteria
• References
Scope

- To discuss laboratory studies that led to the design of a successful cleaning procedure to be incorporated in the medical device manufacturing process.

- To review critical parameters and cleanliness acceptance criteria to ensure that medical devices are successfully cleaned.
Medical Device Categories
for cleaning/decontamination purposes*

Non-critical:
- Non invasive, normally contact intact skin
  - Mostly skin contact
  - Ex: beds, monitoring instruments
  - Cleanliness is less critical. Microbial control

Semi-critical:
- Non invasive, normally contact mucous membranes
- High-level disinfection is required
- Endoscopes, breathing circuits
- Others: in-vitro testing kits

Critical:

- Usually in contact with blood and open skin.
- Sterilization is required
- Implantable and semi-implantable
  - Metal parts, ceramic and assorted polymers
  - Ex: hip or knee implants, artificial organs, repairing tissues, surgical instruments, wound dressings
- Combination
  - It has both drug and med device claims

Medical Device – Life Cycle

Common Stages

- Conception and development
- Manufacture
- Packaging and Labeling
- Advertising
- Sales
- Use
- Disposal
Regulatory Approach to Cleaning for Medical Devices

- CFR Title 21, 820.70 Med Devices
- FDA Guide to Inspections of Med Device Manufacturers
- FDA Guidance
  - QSIT (Quality Systems Inspectional Technique)
- GHTF (Global Harmonization Task Force)
“Your firm failed to validate the sonication cleaning process to remove a substance affixed to the porous-coating area of implant products such as hip, shoulder, ankle, and knee products. In addition, you currently do not monitor the temperature or time of the sonication cleaning processes.” Warning Letter (October 2009)
## Residues Associated to the Manufacturing of Medical Devices

<table>
<thead>
<tr>
<th>Water Soluble</th>
<th>Water Insoluble</th>
<th>Volatile</th>
<th>Bioburden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detergents</td>
<td>Lubricants</td>
<td>Degreasers</td>
<td>Bacteria</td>
</tr>
<tr>
<td>Acids</td>
<td>Cutting Oils</td>
<td>Solvents</td>
<td>Viruses</td>
</tr>
<tr>
<td>Coolants</td>
<td>Greases</td>
<td></td>
<td>Spores</td>
</tr>
<tr>
<td>Hand lotions</td>
<td>Buffing Compounds</td>
<td></td>
<td>Endotoxins</td>
</tr>
<tr>
<td></td>
<td>Debris, dust</td>
<td></td>
<td>Prions</td>
</tr>
<tr>
<td></td>
<td>Ceramics</td>
<td></td>
<td>Biofilms</td>
</tr>
<tr>
<td></td>
<td>Polishing media</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Factors Affecting Cleaning of Medical Devices

CLEANER

RESIDUE  SURFACE
Parameters Affecting Cleaning of Medical Devices

- Time
- Action
- Concentration
- Chemistry
- Compatibility
- Temperature
Parameters Affecting Cleaning of Medical Devices

**Time:**
- Dirty hold time
- Cleaning times
  - Prewash
  - Wash
  - Rinse
  - Drying
- Cleaning solution change-out time
Parameters Affecting Cleaning of Medical Devices

**Action:**

- Related to force on the surface
- Helps to dislodge residues
- Uniformity to assure effectiveness
- Limited in spray balls
  - Distribution device, not an impingement device
Parameters Affecting Cleaning of Medical Devices

Chemistry:

- Selection of agent(s)
- Justified rationale
- Broad Spectrum
- Quality assurance
- Safety and disposal
Parameters Affecting Cleaning of Medical Devices

Concentration:

- Higher generally better
- Inverse relationship with time and temperature
- Materials compatibility issues
- Neutralization issue
- Safety in handling
Parameters Affecting Cleaning of Medical Devices

Compatibility:

• Relates to the material of constructions of the device
• Chemical resistance of substrates with cleaner
• Depends on cleaning parameters
Parameters Affecting Cleaning of Medical Devices

Temperature:
• Higher generally better
  – Exceptions
• Critical for wax and oil residues
  – Must approach melting point for emulsification
• Strong influence on mechanisms
• Control throughout process
Laboratory Evaluation
Determining Critical Cleaning Parameters

Cleaning Parameters:
• Time (wash, rinse, etc)
• Action
• Cleaning Agent
• Cleaner Concentration
• Temperature
• Material Compatibility
• Water Quality
Advantages of Laboratory Evaluation

- Accelerates cleaning SOP development
- Allows you to focus on scale-up engineering issues
- Provides valuable documentation for SOP development report
- Provide justification for regulatory audits
- Saves time and money
Manufacturer of Needles:

- Description: Technology transferred from another site. Manufacturing process included various cleaning steps. Last cleaning step before passivation was not being successful. Cleaning solution was dirty after one or two uses.

- Challenges: Cleaning steps are not being monitored. Several products were used but no clear rationale whatsoever. Final wash solution change out was based on visual appearance.

- Cleaning Process: Needles samples from each step were visually observed. Samples of all processing agents including were provided to assess their cleanability.
Laboratory Evaluation
Case Study #1

Solvent Wash
1. 20%v/v Aqueous Cleaner
2. Ethanol Rinse

Add 2 Coolants

Solvent Wash
1. Add 2 Buffing Compounds
2. Alcohol/Quat Wash
3. Citric Acid Rinse
4. Add 2 Polishing Compounds
5. Then Wash Again…

1. Two products for organic removal
2. Acid Treatment
Laboratory Evaluation
Case Study #1

• Experimental: Stainless steels coupons were coated according to each processing step and then cleaned by agitated immersion. Goal was to demonstrate that all soils could be successfully cleaned with one cleaner.

<table>
<thead>
<tr>
<th>PROCESSING SOILS</th>
<th>CLEANER</th>
<th>CONC.</th>
<th>TIME/TEMPERATURE</th>
<th>VISUAL OBSERVATION</th>
<th>WATER BREAK-FREE</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPS Liquid</td>
<td>Aqueous Alkaline</td>
<td>5% v/v</td>
<td>30 min / 60°C</td>
<td>Visually Clean</td>
<td>Yes</td>
</tr>
<tr>
<td>LPS Cream</td>
<td>Aqueous Alkaline plus Detergent Booster</td>
<td>1% v/v + 1% v/v</td>
<td>30 min / 60°C</td>
<td>Visually Clean</td>
<td>Yes</td>
</tr>
<tr>
<td>Macson</td>
<td>Aqueous Alkaline Cleaner</td>
<td>3% v/v</td>
<td>60 min / 60°C</td>
<td>Visually Clean</td>
<td>No</td>
</tr>
<tr>
<td>ProCut</td>
<td>Aqueous Alkaline Cleaner</td>
<td>5% v/v</td>
<td>60 min / 40°C</td>
<td>Visually Clean</td>
<td>No</td>
</tr>
<tr>
<td>Hangsterfer’s</td>
<td>Aqueous Alkaline Cleaner</td>
<td>5% v/v</td>
<td>60 min / amb</td>
<td>Visually Clean</td>
<td>No</td>
</tr>
<tr>
<td>Cimtech</td>
<td>Aqueous Alkaline Cleaner plus Detergent Booster</td>
<td>2% v/v + 2% v/v</td>
<td>60 min / 40°C</td>
<td>Visually Clean</td>
<td>No</td>
</tr>
</tbody>
</table>
Needles prior to final wash treatment with 5% Aqueous Alkaline Cleaner 60°C.

Needles after treatment with 5% Aqueous Alkaline Cleaner at 60°C for 60 minutes, no rusting or damages were observed.
Manufacturer of Orthopedic Implants:

- Description: New manufacturing process for the site. Customer wanted best evaluation possible to successfully clean all processing soils from the implants.
- Challenges: Implants are made of titanium parts.
- Cleaning Process: Samples of a processing agent including implants and a titanium cylinder were provided to assess compatibility and cleanability.
1st Part: to assess compatibility of grade 2 titanium with a commonly used Aqueous Alkaline Cleaner under extreme conditions.

<table>
<thead>
<tr>
<th>Part Description</th>
<th>Cleaning Process</th>
<th>Visual Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A metal cylinder marked “5” at its base</td>
<td>Ultrasonic washer, 40 kHz: Aqueous Alkaline Cleaner, 4 % v/v 80 °C, 8 hours</td>
<td>Color changed from silver metal to shiny bright blue</td>
</tr>
<tr>
<td>A metal cylinder marked “5” at its base base</td>
<td>Ultrasonic washer, 40 kHz: Aqueous Alkaline Cleaner, 50 % v/v 80 °C, 8 hours</td>
<td>Color changed from silver metal to dull dark gray</td>
</tr>
<tr>
<td>Two orthopedic implants</td>
<td>Ultrasonic washer, 40 kHz: Aqueous Alkaline Cleaner, 4 % v/v 80 °C, 8 hours</td>
<td>Color changed from silver metal to shiny bright blue</td>
</tr>
<tr>
<td>Two orthopedic implants</td>
<td>Ultrasonic washer, 40 kHz: Aqueous Alkaline Cleaner, 50 % v/v 80 °C, 8 hours</td>
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</tr>
</tbody>
</table>
## Laboratory Evaluation

**Case Study #2**

- **2nd Part:** Stainless steel coupons were coated with cutting oil emulsion and air dried for 100 hours. The residue was effectively removed by **ultrasonic wash** at 40 kHz using either set of cleaning parameters.

<table>
<thead>
<tr>
<th>CLEANER</th>
<th>CONC.</th>
<th>TIME/TEMPERATURE</th>
<th>VISUAL OBSERVATION</th>
<th>WATER BREAK-FREE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqueous Alkaline Cleaner + Detergent Booster</td>
<td>1 % v/v + 1 % v/v</td>
<td>10 min/60 °C</td>
<td>Visually clean</td>
<td>YES</td>
</tr>
<tr>
<td>Aqueous Alkaline Cleaner with Corrosion inhibitors + Detergent Booster</td>
<td>1 % v/v + 1 % v/v</td>
<td>20 min/60 °C</td>
<td>Visually clean</td>
<td>YES</td>
</tr>
<tr>
<td>Aqueous Alkaline Cleaner + Detergent Booster</td>
<td>1 % v/v + 1 % v/v</td>
<td>5 min/60 °C</td>
<td>Trace residue left</td>
<td>Not tested</td>
</tr>
<tr>
<td>Aqueous Alkaline Cleaner with Corrosion inhibitors + Detergent Booster</td>
<td>1 % v/v + 1 % v/v</td>
<td>15 min/60 °C</td>
<td>Trace residue left</td>
<td>Not tested</td>
</tr>
</tbody>
</table>
Laboratory Evaluation
Case Study #2

• 2nd Part continuation:

✓ A titanium cylinder and two implants parts were dipped in the Cutting Oil Emulsion and then air-dried at ambient temperature for 100 hours.
✓ The cylinder and implants were cleaned by ultrasonic wash at 40 kHz using a 1 % v/v solution of Aqueous Alkaline Cleaner plus 1 % v/v of Detergent Additive at 60 °C for 10 minutes. The cleaned parts looked clean and shiny. No evidence of corrosion was visually detected.
Manufacturer of Orthopedic Implants:

- Description: Manufacturing process utilizes two buffing compounds and one grease. Customer currently has an ultrasonic cleaning procedure using 4% v/v of an aqueous Alkaline Cleaner at 70°C for 5 minutes.
- Challenges: Customer wants to evaluate if these parameters are also effective for cleaning these compounds.
- Cleaning Process: Samples of compounds were provided to assess cleanability using two cleaning methods.
**1st Part of Evaluation:**

- The initial testing was done on SS coupons.
- Using ultrasonic wash was not effective for the buffing compounds. These were effectively removed from stainless steel coupons using spray wash.
- The grease compound was effectively removed from stainless steel coupons by spray wash, and by ultrasonic wash.
2nd Part of Evaluation:

- Dirty knee-joints sent by customer were effectively cleaned by ultrasonic wash and by spray wash using 4% v/v CIP 100.
- Several factors: cobalt chrome vs stainless steel; polished surfaces vs milled surfaces; very low amount of residue on joints vs heavy amount of residue on coupons.
Why surface cleanliness should be monitored?

• To ensure that it meets pre-established quality attributes.
• In many circumstances cleanliness is solely based on monitoring the cleaning parameters.
  ✓ this approach has its limitations
• Cleanliness check is recommended if is deemed critical to the subsequent step.
Cleaning Acceptance Criteria for Medical Devices

What must be considered?

- Evaluation of the performance of an existing cleaning process.
  - How does cleanliness correlate to the success of the subsequent operation?
  - How does cleanliness correlate to the final product non-conformance rate?

- Optimization of a new cleaning procedure during implementation.
  - Is the new cleaning process more efficient than the one being replaced?
Cleaning Acceptance Criteria for Medical Devices

Selecting a Testing Method:

- Type of contaminants to be monitored
- Type of sampling
  - direct
  - extraction
  - destructive
- Type of substrate being checked
- Limit of detection, accuracy, and precision
- Speed of measurement, acquisition, and cost
Examples of Commonly Used Test Methods:

- TOC
- Particle Count, USP <788>
- Non-volatile residue (gravimetric), ASTM
- Conductivity, USP <645>
- UV/Vis
- Biocompatibility, ANSI/AAMI 10993
- Bioburden, USP <61>
- Endotoxin, USP <85>
Establishing Residue Limits:
- Must be scientifically sound, achievable and verifiable
- Usually expressed in mg/cm² or mg/device
- Evaluate through risk assessment:
  - Using data from current cleaning capability
  - Using data from controlled experiments
Some Suggested References:

- ANSI/AAMI 10993: Biological Evaluation of Medical Devices Series
Questions