Keeping your Cleanroom “Clean”

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Factors

- Humans as the main source of contamination
- Cleaning the cleanroom
- Cleaning the equipment
People are the major source of contamination

- The average body surface area is about 1.75 m².
- Corresponds to about 2,000,000,000 cells.
- The outer layer of skin is replaced in < 24 hours.

Considerations for reducing particles & microbes

- Level of activity
- Handwashing and garbing
- Illness and allergy season
- Burns and rashes

Individuals with rashes, recent tattoos, oozing sores, conjunctivitis, or active respiratory infection must report these conditions to the designated person(s). The designated person is responsible for evaluating whether these individuals should be excluded from working in compounding areas. Proposed USP<797>

Personnel Preparation

- Proper personal hygiene
- No cosmetics
- No nail polish or artificial nails
  - Nails neatly trimmed
- Cover any jewelry that cannot be removed
- No earbuds or electronics
- Remove outer garments
- Corrective & protective eyewear must be wiped down.

Proposed USP; address exceptions in SOPs.
Cleaning the cleanroom

What products are used and reused?  
How often?  
Who cleans?

Table 7. Purpose of Cleaning, Disinfecting, and Sporicidal Agents

<table>
<thead>
<tr>
<th>Type of Agent</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleaning agent</td>
<td>An agent used for the removal of residues (e.g., dirt, debris, microbes, and residual drugs or chemicals) from surfaces.</td>
</tr>
<tr>
<td>Disinfectant</td>
<td>A chemical or physical agent used on inanimate surfaces and objects to destroy fungi, viruses, and bacteria.</td>
</tr>
<tr>
<td>Sporicidal agent</td>
<td>A chemical or physical agent that destroys bacterial and fungal spores when used at a sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.</td>
</tr>
</tbody>
</table>
Cleaning v Disinfection v Sporicide Application

- Disinfectants and sporicides are more effective after cleaning removes substances that could reduce effectiveness.
- Contact time matters.
- Products have different contact times for different microorganisms.
- Bleach is a sporicide and is cheap.
- Sporicides with detergent are expensive.

- Why 70% IPA?
  - Need water to effectively denature bacterial proteins; also dries more slowly, better contact time.

https://www.cdc.gov/infectioncontrol/guidelines/disinfection/

Proposed USP <797> Table 8. Minimum Frequency for Cleaning and Disinfecting Surfaces

<table>
<thead>
<tr>
<th>Site</th>
<th>Cleaning</th>
<th>Disinfecting</th>
<th>Applying Sporicidal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pass-through(s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work surface(s) outside the PEC</td>
<td>Daily</td>
<td>Daily&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Floor(s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinks (See Section 4.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wall(s), door(s), and door frame(s)</td>
<td>Monthly</td>
<td>Monthly&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Monthly</td>
</tr>
<tr>
<td>Ceiling(s)</td>
<td>Monthly</td>
<td>Monthly&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Storage shelving and bins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equipment outside the PEC(s)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Many disinfectants registered by the EPA are one-step cleaning and disinfecting agents, which means that the disinfectant has been formulated to be effective in the presence of light to moderate soiling without a separate cleaning step.

The EPA Reg. No. of a product can be more useful than its brand name.

- Alternative brand names have the same EPA Reg. No. as the primary product.
- EPA Reg. No. consists of 2 sets of numbers separated by a hyphen
  - First part is Registrant’s company
  - Second part is product number.
- Distributor products have 3-part EPA Reg. No.
  - First 2 parts match the primary registrant’s product number
  - Third part is the Distributor/Relabeler

For example a product labeled as EPA Reg. No. 12345-12 is the identical formulation as EPA Reg. No. 12345-12-2567.

Contact Times are Microorganism Specific

Example from product literature

<table>
<thead>
<tr>
<th>Fungicidal/Mold Killing</th>
<th>Contact Time</th>
<th>Bactericidal</th>
<th>Contact Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus niger (hard surface)</td>
<td>1 min.</td>
<td>Enterobacter aerogenes</td>
<td>2 min.</td>
</tr>
<tr>
<td>Aspergillus niger (porous surface)</td>
<td>10 min.</td>
<td>Listeria monocytogenes</td>
<td>2 min.</td>
</tr>
<tr>
<td>Candida albicans (hard surface)</td>
<td>1 min.</td>
<td>Pseudomonas aeruginosa</td>
<td>2 min.</td>
</tr>
<tr>
<td>Trichophyton mentagrophytes (athlete’s foot fungus) (hard surface)</td>
<td>1 min.</td>
<td>Salmonella typhimurium</td>
<td>2 min.</td>
</tr>
<tr>
<td>Sporicidal</td>
<td>Contact Time</td>
<td>Staphylococcus aureus</td>
<td>2 min.</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>3 min.</td>
<td>Vibrio cholerae</td>
<td>2 min.</td>
</tr>
<tr>
<td>Viricidal</td>
<td>Contact Time</td>
<td>Salmonella enterica</td>
<td>2 min.</td>
</tr>
<tr>
<td>Avian influenza virus A (H3N2)</td>
<td>2 min.</td>
<td>Acinetobacter baumannii</td>
<td>2 min.</td>
</tr>
<tr>
<td>Human coronavirus</td>
<td>2 min.</td>
<td>Campylobacter jejuni</td>
<td>2 min.</td>
</tr>
<tr>
<td>Respiratory syncytial virus (RSV)</td>
<td>2 min.</td>
<td>Community Acquired Methicillin Resistant - Staphylococcus aureus (CA-MRSA)</td>
<td>2 min.</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>2 min.</td>
<td>Streptococcus Pneumoniae Penicillin Resistant - (PRSP)</td>
<td>2 min.</td>
</tr>
<tr>
<td>Rotavirus (strain WA)</td>
<td>2 min.</td>
<td>Streptococcus pyogenes</td>
<td>2 min.</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>2 min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculocidal</td>
<td>Contact Time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycobacterium bovis</td>
<td>5 min.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Factors to consider when choosing cleaning products

Detergents:
• Should be non-foaming, neutral and non-ionic
• Should be compatible with the disinfectant
• Residue should not inactivate the disinfectant

Disinfectants:
• Should have a wide spectrum of activity
• Should have rapid action (Short Contact Time)
• Must be sterile
• Safe to use
• Useable at cleanroom temperatures
• Should not damage equipment
• Rotation of products is no longer required

Sadle, T.: Cleanroom Cleaning and Disinfection: Eight steps for Success 2012

Box 7-1. Procedures for Cleaning and Disinfecting the PEC

• Remove visible debris with Sterile Water for Injection or Irrigation using sterile, low-lint wipers.
• Using a low-lint wiper, apply a cleaning agent, followed by a disinfecting agent, or apply an EPA-registered (or equivalent) one-step disinfectant cleaner to equipment and all interior surfaces of the PEC.
• Ensure the contact time is achieved.
• Using a low-lint wiper, apply sterile 70% IPA to equipment and all interior surfaces in the PEC.
• Allow the surface to dry completely before beginning compounding.

Proposed USP<797>
The Cost of Clean?

- Cost of supplies, equipment and garb
- N95 respirators for cleaning
  - Should be professionally fitted to individual
- Sterile, disposable, “low-lint” wipes
- Labor Costs. Cleaning time takes away from compounding.
- Time is money - Cleaning products with quicker contact times are usually more costly.
- However,
  What is the cost of non-compliance?

What is the cost of non-compliance?

- 12 hour BUD
- Form 483 is posted online after FDA inspection
  - No response → FDA Warning Letter
  - Insufficient improvement → FDA Consent Decree
- State actions?
- Loss of reputation
- Loss of business
## A Comparison of 3 Sporicidal Agents

<table>
<thead>
<tr>
<th>Sporicidal Agent</th>
<th>Contact Time</th>
<th>Average Cost</th>
<th>Active Ingredients</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iradecon 32 oz. (Decon Labs)</td>
<td>5 min.</td>
<td>$39.41</td>
<td>0.525% Sodium Hypochlorite 99.475% “other”</td>
<td>Very Strong Bleach Smell</td>
</tr>
<tr>
<td>Clorox Healthcare Bleach Germicidal Cleaner 32 oz. (Clorox)</td>
<td>3 min.</td>
<td>$11.95</td>
<td>0.65 % Sodium Hypochlorite 99.35% “other”</td>
<td>Fruity Floral Bleach smell</td>
</tr>
<tr>
<td>Peridox 32 oz. (Contec)</td>
<td>3 min.</td>
<td>$42.04</td>
<td>Hydrogen Peroxide &amp; Peracetic Acid</td>
<td>Offensive Vinegar Smell. Company recommends Charcoal filtered Masks. ($36.00/8)</td>
</tr>
</tbody>
</table>

### Cleaning Supplies

- **Wipers, Sponges & Mop Heads**
  - Must be “low linting”
  - Must be disposable
  - If disposable, must be discarded after each cleaning activity
  - Dispose with minimal agitation away from work surfaces

- **Reusable Cleaning Tools (Mop Handles)**
  - Must be made of cleanable materials (e.g., non-wooden)
  - Must be cleaned before and after each use
  - Must be dedicated for use in each area
  - Must be stored in the area (do not remove, except for disposal)
WHO CLEANS?

- Environmental services?
- Pharmacy technicians?
- Outside cleaning company?
- Who trains and supervises?

Demonstration of proficiency is required for cleaning personnel.
Cleaning personnel must also be proficient in handwashing and garbing procedures. Per USP

THAT'S NOT IN MY JOB DESCRIPTION

Cleaning “from clean to dirty” USP<797> Section 7

Do What Your Mother Taught You

- PECs first
- Ceilings, then walls, windows, doors
- Using overlapping strokes
- Floors Last
- Start to finish in ISO 7 area first, then ISO 8
Cleanroom Tacky Rollers

• From one cleanroom vendor
  • The hand-held poly tacky roller is used for smooth surfaces. Polyurethane coated film provides an anti microbial agent. The tacky roller has perforated sheets and when each sheet is contaminated it is simply peeled off the roll to uncover a clean sheet. The refill simply slides on and off the core handle.

• From another cleanroom vendor
  • Cleans particles from cleanroom walls and other surfaces
  • Select peel-off adhesive sheets made of polyethylene film (for smooth surfaces) or polyethylene film/foam laminate (for textured surfaces)
  • Handle extensions allow a "reach" of up to 6 feet

• Controversy about residue from roller

No mention of tacky rollers in USP<797>

Cleaning the ceiling in ISO 7 room – Best Practices

Start at farthest corner from ISO 8 wall (cleanest)

Single pass all the way across

Frequency, method(s), and location(s) of cleaning must be established in written SOPs.

Training program is required.

Proposed USP<795>

No further guidance on methods is presented in USP<797>. 
First pass of cleaning

Second pass should overlap first pass

For full Contec video, https://youtu.be/gvAhBwdWDv0
Pattern of overlapping strokes

Same pattern for walls. Start from farthest wall, clean towards ISO 8.

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</thead>
<tbody>
<tr>
<td>PEC(s) and equipment inside the PEC(s)</td>
<td>Equipment and all interior surfaces <strong>daily</strong> and when surface contamination is known or suspected.</td>
<td>Equipment and all interior surfaces <strong>daily</strong> and when surface contamination is known or suspected. Apply sterile 70% IPA to the horizontal work surface at least <strong>every 30 minutes</strong>, but do not disrupt compounding</td>
<td>Monthly</td>
</tr>
<tr>
<td>Removable work tray of the PEC</td>
<td>Work surface of the tray <strong>daily</strong></td>
<td>Work surface of the tray <strong>daily</strong> All surfaces and the area underneath the work tray <strong>monthly</strong></td>
<td>Work surface of the tray <strong>monthly</strong> All surfaces and the area underneath the work tray <strong>monthly</strong></td>
</tr>
</tbody>
</table>
Procedures for cleaning and disinfecting the PEC

- **Pre-Clean**
  - Remove visible particles, debris or residue with Sterile Water for Injection OR Sterile Water for Irrigation
  - Use “low lint” wipes

- **Clean**
  - Apply cleaner (sterile) to low lint wipe outside of PEC
  - AVOID spraying (UConn recommendation)
  - Wipe from cleanest to dirtiest
  - Allow for proper contact time

- **Disinfect**
  - Using sterile 70% IPA, leaves no residue
  - Allow to dry completely

*Clean the PEC with a sporicidal agent monthly*

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Order of Wiping PEC (for a Horizontal LAFS)

- Start at the top in the back (cleanest).
- Wipe inside ceiling side-to-side from back to front
- Turn wipe to fresh surface
- Wipe bar
- Turn wipe to fresh surface; add more product if necessary
- On one side, start at the top in the back, wipe top-to-bottom using overlapping strokes
- Turn wipe to fresh surface; add more product if necessary
- Repeat on other side
- NEW WIPE for the surface
- Start in the back, wipe side-to-side from back to front

*Wipe filter surface at your own risk!*

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- *Not in USP*
- *UConn recommended best practice*
Tips for using wipes

- Wipe spills up immediately
- Clean regularly
- Fold sterile “non-linting” wipes in half or in quarters
  - in half= 4 sides, quarters=8 sides
- Best practice is to wipe in 1 direction with 10% overlap
- Use a damp wipe - not dry or too wet
- Fold the wipe first then apply cleaner
- Do not let the bottle of cleaner touch the sterile wipe

Meadows 2015 Seven deadly sins of cleanroom wiping and how to avoid them https://blog.gotopac.com/2015/01/22/the-seven-deadly-sins-of-cleanroom-wiping-and-how-to-avoid-them/

Questions to Consider

- Which should be cleaned first?
  - ISO 5 PEC or ISO 7 room containing it
  - Equipment in the ISO 5 PEC or the ISO 5 PEC
  - ISO 7 Ante-room or buffer room
- To minimize down time for cleaning:
  Is it acceptable to clean the ante-room and buffer room simultaneously?
- Is it acceptable for the ante-room to be cleaned the day after/before the buffer room?
Administrative Challenges

How well does your staff understand their role in reducing particle production?

How is this information conveyed?

Do your SOPs provide explanation to emphasize significance of human particle generation?

How rigorously does your staff adhere to the SOPs?

Does adherence trail off over time?

Do you have one or more natural leader(s) among your staff who dismiss the need for controls on particles and the role of humans?