Cleanroom Best Practice:
Disinfectant Rotation and Residue Removal

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Introduction

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Aaron Mertens

- Technical Service Specialist
- STERIS Corporation | Life Sciences
- Mobile: 440-530-0060
- E-Mail: Aaron_Mertens@steris.com
- Web: www.sterislifesciences.com

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Cleanroom Best Practice: Disinfectant Rotation and Residue Removal in the Cleanroom

Objective:

To provide an overview of recommended practices for disinfectant use in the cleanroom environment.

Outline

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- Background
- Disinfectant Rotation
- Residue Removal

- Program Recommendations
- Regulatory and GMP expectations
- Industry Trends
- Technical Literature Resources

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Background

EPA Classification

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Three antimicrobial groups:

Sanitizer

Disinfectant

Sterilant

Sanitizer

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- Reduces but does not necessarily eliminate all microorganisms on a surface.
- Minimum 99.9% reduction of each test organism.
- Used on pre-cleaned surfaces

Disinfectant

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- Kill or inactivate disease producing microorganisms on inanimate objects
- Proper use results in 100% kill of vegetative bacteria, target viruses and target fungi
  - 4 Log reduction of bacteria
  - 3 Log reduction of viruses
  - 6 Log reduction of fungi
- May or may not require pre-cleaning

Steriliant

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- Proper use results in 100% kill of all microorganisms, including bacterial spores (*B. subtilis, C. sporogenes*)
- 6-7 Log reduction
- Always requires precleaning

Chemical Types

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- Alcohols
- Phenolics
- Quaternary Ammonium Chloride Compounds
- Peracetic acid / Hydrogen peroxide blends
- Sodium hypochlorite
- Chlorine dioxide
- Hydrogen peroxide
- Peracetic acid
- Ozone
- Biguanides
- Iodine Products
- Glutaraldehyde / Formaldehyde
- Sodium Hydroxide

Alcohols

Phenolics

Quaternary Ammonium Chloride Compounds

Peracetic acid / Hydrogen peroxide blends

Application Conditions

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Effects on EPA claims, activity of the biocide

- pH
- Temperature
- Time
- Concentration
- Surface Condition
- Bioburden
- Soil Levels
- Water Hardness

Alcohol

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- No residue
- Broad spectrum
- Evaporates readily
- Removes residue

Limitations:

- Poor cleaner
- Flammable
- Limited contact time
- Not EPA registered
- Not sporicidal
- VOC emissions
- IPA (TLV 200ppm)

Phenolics

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- TB effective and broad spectrum
- EPA registered
- Anionic / Neutral surfactants provide good cleaning ability
- Alkaline or acidic formulas available

Limitations:

- Not sporicidal
- Residues
- Activity affected by incompatible chemical agents

Quaternary Ammonium Chlorides

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- Broad spectrum activity
- EPA registered
- Cationic surfactancy provides excellent cleaning

Limitations:

- Not sporicidal
- Not always TB effective
- Activity affected by incompatible chemical agents

Sporicides (H_2O_2/ Peracetic acid blends)

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- Fast, broad spectrum activity, sporicidal
- Less corrosive than comparably effective oxidizers
- EPA registered
- Safer for personnel

Limitations:

- Corrosive to soft metals
- Pre cleaning required
- Temperature sensitive
- Pungent odor (vinegar)

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Disinfectant Rotation

Contamination Control

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STERIS:

Helping to deliver safe and effective drugs to the marketplace.

Maintenance of cleanroom bioburden, using sanitants, disinfectants and sporicides on surfaces in the environment.

Why do we rotate?

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Rotation of a disinfectant and a sporicide helps ensure bacterial spores do not take hold in manufacturing and aseptic areas.

Regulatory expectations (FDA, MHRA, EU)

USP 38 <1072>, PDA Technical Report

Why do we rotate?

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The development of microbial resistance to antibiotics is a well-described phenomenon. The development of microbial resistance to disinfectants is less likely, as disinfectants are more powerful biocidal agents than antibiotics and are applied in high concentrations against low populations of microorganisms usually not growing actively, so the selective pressure for the development of resistance is less profound.

United States Pharmacopeia 30, Chapter <1072>,
"Selection of a Disinfectant for Use in a Pharmaceutical Manufacturing Environment"

Key Issues – Rotation Science

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- No microbe develops resistance to disinfectants in the cleanroom – resistance to certain chemistries is an inherent trait of certain microbes (e.g. fungal and bacterial spores)
  - Cleanroom environments are usually not a ideal location for microbes to reproduce
  - Don’t argue science with Customers
- Microbes can develop resistance to antibiotics in the human body
  - Substantially larger number of microbes so increased chance for mutation
  - Human bodies are more complex systems so microbes can “hide”
  - Microbes thrive and reproduce in the body so are not under stress
- Rotation of chemicals ensures full spectrum of microbes are eliminated from the environment
  - This is the goal of any contamination control program

Key Issues - Rotation

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- Why do facilities rotate?
  - Good practice to ensure all microorganisms eliminated
  - Inspectors from FDA, MHRA, EMA, HPRA, ANSM, ANVISA, CFDA etc. expect it
  - Recommended by USP 39 <1072> Disinfectants and Antiseptics, Aseptic Processing Guide, Orange Guide, PDA TR No. 70 etc.
- Why is it important to rotate like or compatible chemicals?
  - Some disinfectants contain incompatible ingredients
    - For example, cationic (Quats) and anionic (Phenolics) surfactants cannot be mixed (they can form a sticky residue)

Rotation Guidance

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- PDA TR 70
  - *"Given this knowledge, the pharmaceutical and biotechnology **industries have moved away from the rotation of two disinfecting agents**. This formerly common practice led to high residue levels and subordinate efficacy performance. Today most firms use a system whereby a **disinfectant is rotated with a sporicide to more effectively reduce the bioburden** levels. The rotation of a disinfectant with a sporicide is **superior to the use of rotations of multiple disinfectants.**"*

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What is rotation?

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

Sterilant Application

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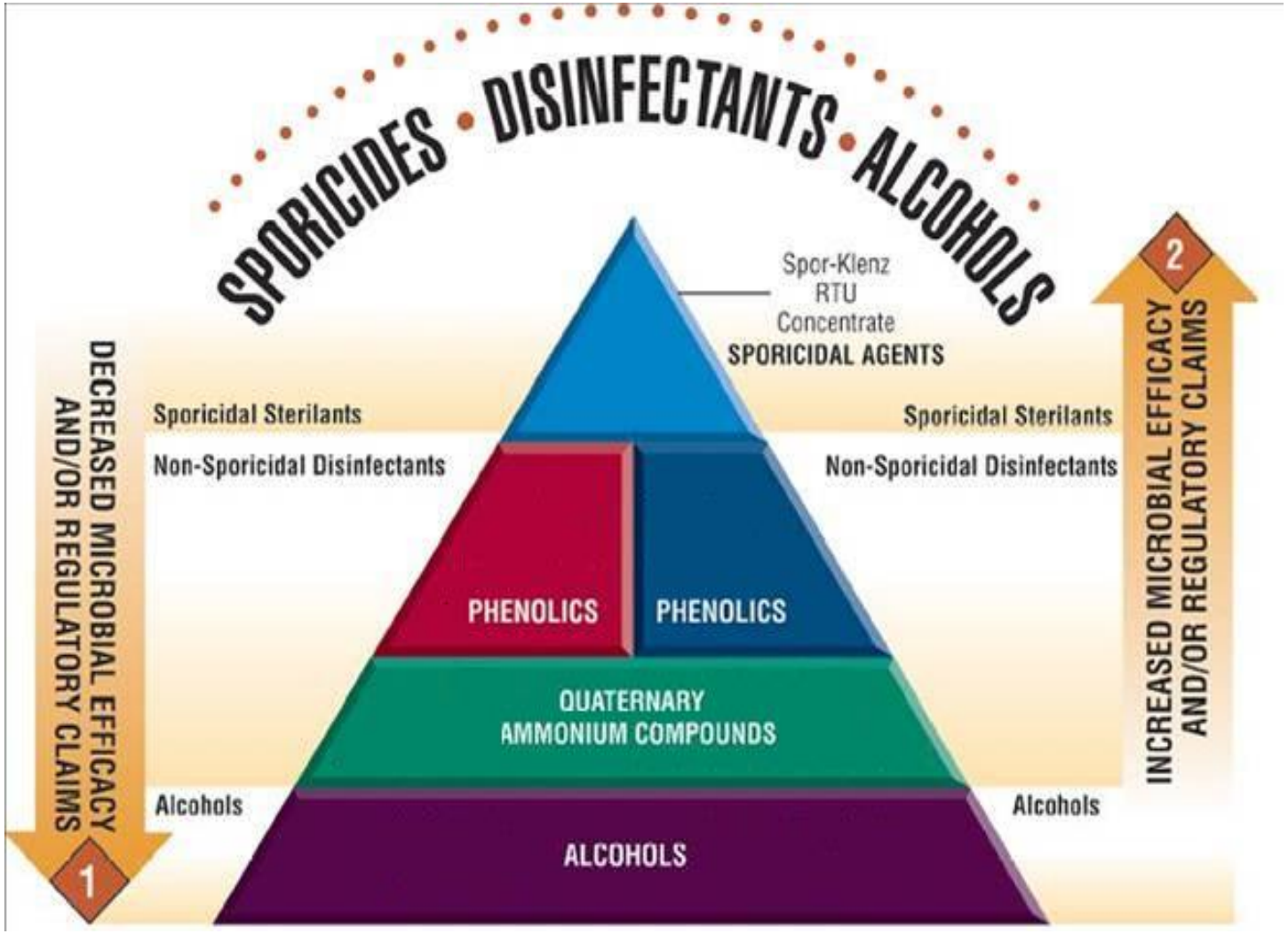
Frequency Rationale

- Spore control vs. chemical exposure
- Corrosivity and Irritation

Sporicidal agent

- Rationale (environmental monitoring)
- Weekly, monthly, quarterly
- Should be specified in SOP's



Warning Letter and 483 Summary: Rotation

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- The focus has been on Sporicides as part of rotation
- The focus has been on contact time for Sporicides
- The focus has been on frequency of Sporicides

FDA WL 1/17/17

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"no use of sporicidal disinfectant on surfaces inside aseptic filling room **(b)(4)**, although your environmental monitoring detected spore-forming organisms there; and"

FDA Warning Letter 1/17/17.

FDA WL 12/23/16

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"Our inspection found multiple deficient practices at your facility that pose a significant microbiological contamination risk. For example, your cleaning and disinfection program lacked use of a sporicidal agent. Significantly, the microbe identified in the sterility failures is a spore-former. In addition, our inspection identified poor facility maintenance. This included leaking pipes in the cleanroom ceiling, chipped and cracked floors in the batch tank room, and blue and black particulates as well as dust on tanks next to the ingredient charging ports."

FDA WL 12/23/16

FDA WL 3/10/16

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"For example, in your response to our observation regarding the contact dwell time for **(b)(4)**, your firm amended its cleaning and disinfection policy to include a **(b)(4)** requiring a **(b)(4)** contact dwell time. However, the manufacturer recommends that "**(b)(4)**" for use as a sporicide, and you did not provide documentation to justify this reduced dwell time." FDA WL 3/10/16

Recent FDA 483

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"Specifically, you do not successfully control for spore-forming organisms. Our review of your environmental monitoring records indicates that you have had 48 actions or alerts with several different species identified for both personnel and ISO 5 monitoring. Species include, but not limited to, *Bacillus simplex*, *Bacillus circulans*, *Bacillus niabensis*, *Bacillus amyloliquefaciens* and *Bacillus cereus*.

(GMP Trends 3/1/16)

FDA 483

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"Specifically, your firm does not adequately rotate solutions and use appropriate wipes for cleaning and disinfecting your ISO 5 laminar flow hoods and ISO 7 clean rooms. Your firm has used non-sterile wipes (Item ….. non-woven wipes) to clean and disinfect the ISO 5 hoods and ISO 7 Clean rooms throughout the year. Also, your firm has used sterile ….. throughout the year according to cleaning logs dated ….. Your firm has not rotated solutions to account for sporicidal agents."

(GMP Trends April 1, 2015)

PDA Technical Report No. 70

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"All rotation systems should be evaluated via the use of area classification, environmental monitoring data, and/or risk assessment."

Section 10, 11 Pages 36 and 38

Cleaning and Disinfection: Rotation

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- PDA TR No. 70

  "Given this knowledge, the pharmaceutical and biotechnology **industries have moved away from the rotation of two disinfecting agents**. This formerly common practice led to high residue levels and subordinate efficacy performance. Today most firms use a system whereby a **disinfectant is rotated with a sporicide to more effectively reduce the bioburden** levels. The rotation of a disinfectant with a sporicide is **superior to the use of rotations of multiple disinfectants.**" Section 11 Page 38

Sterilant Usage in Rotation

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- Existing facility and program: disinfectant and sporicidal usage is adjusted based on changing risk factors but more so environmental trending data.
- New facility program: disinfectant and sporicide is based on a risk based model. The model includes risk of product contamination due to its exposure to the environment, personnel, the manufacturing process, and environmental monitoring data.

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Residue Removal

Residue Removal

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Maintain surfaces in the cleanroom periodically using a rinsing agent to remove residue from the surfaces.

The presence of residue may:

- impact disinfectant effectiveness
- hide microbial contamination
- contaminate environment and/or product
- be an aesthetic issue
- create a particulate issue

Rinsing Strategy

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Where does the residue come from?

- Customer product, process residue
- Disinfectants, sporicides, sanitizers

Existing cleanrooms that may have never had a rinsing program

Implementing a rinsing program in a new cleanroom environment

How to identify residue

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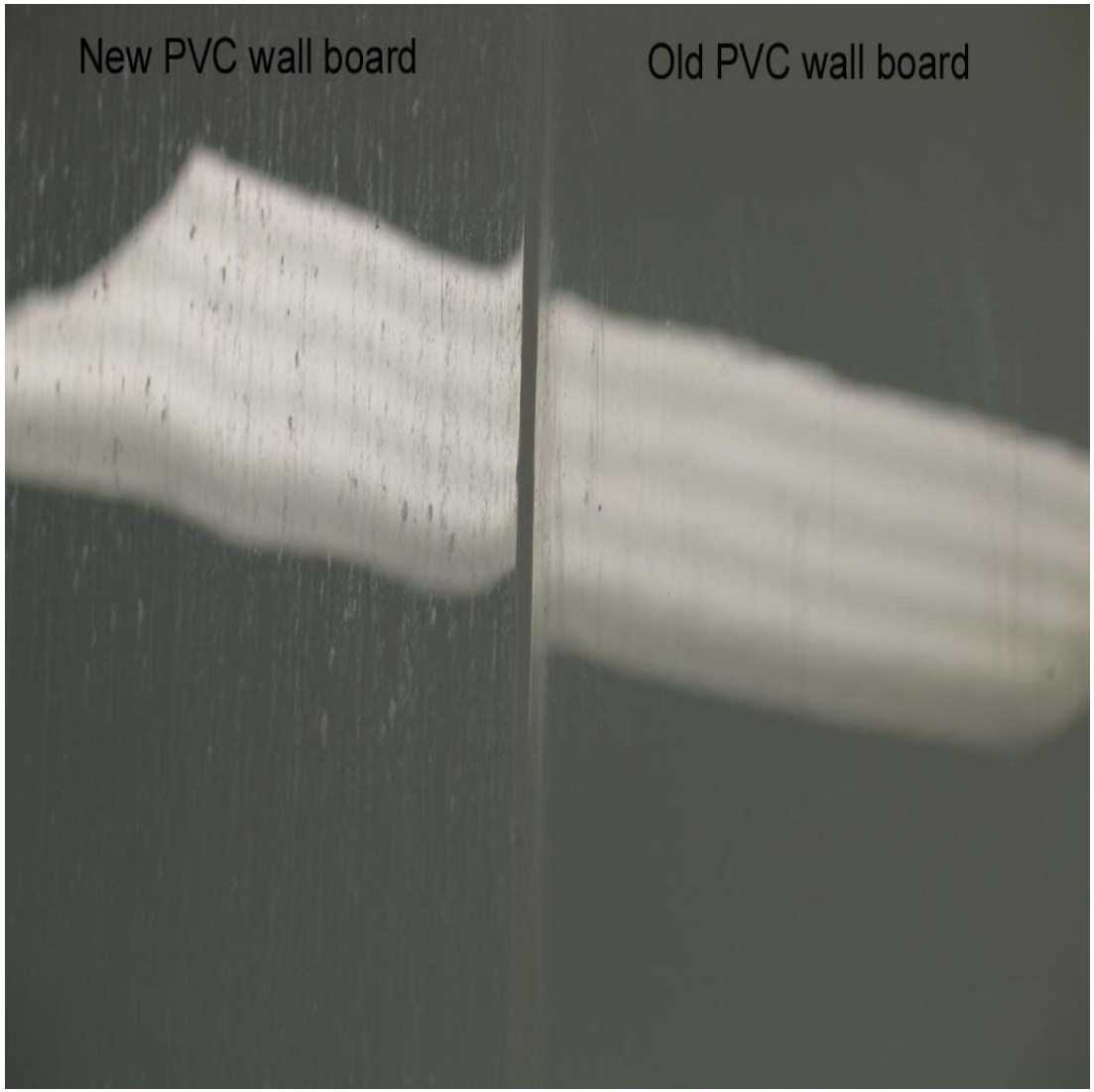
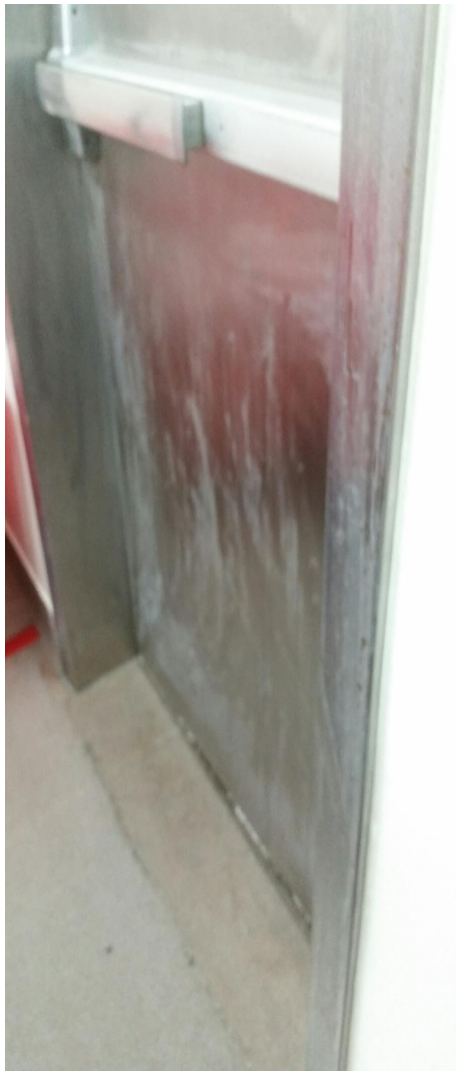
Visual inspection

What does it look like?

How do residues appear on typical cleanroom surfaces such as epoxy, vinyl and stainless steel?





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Residues on Substrates:

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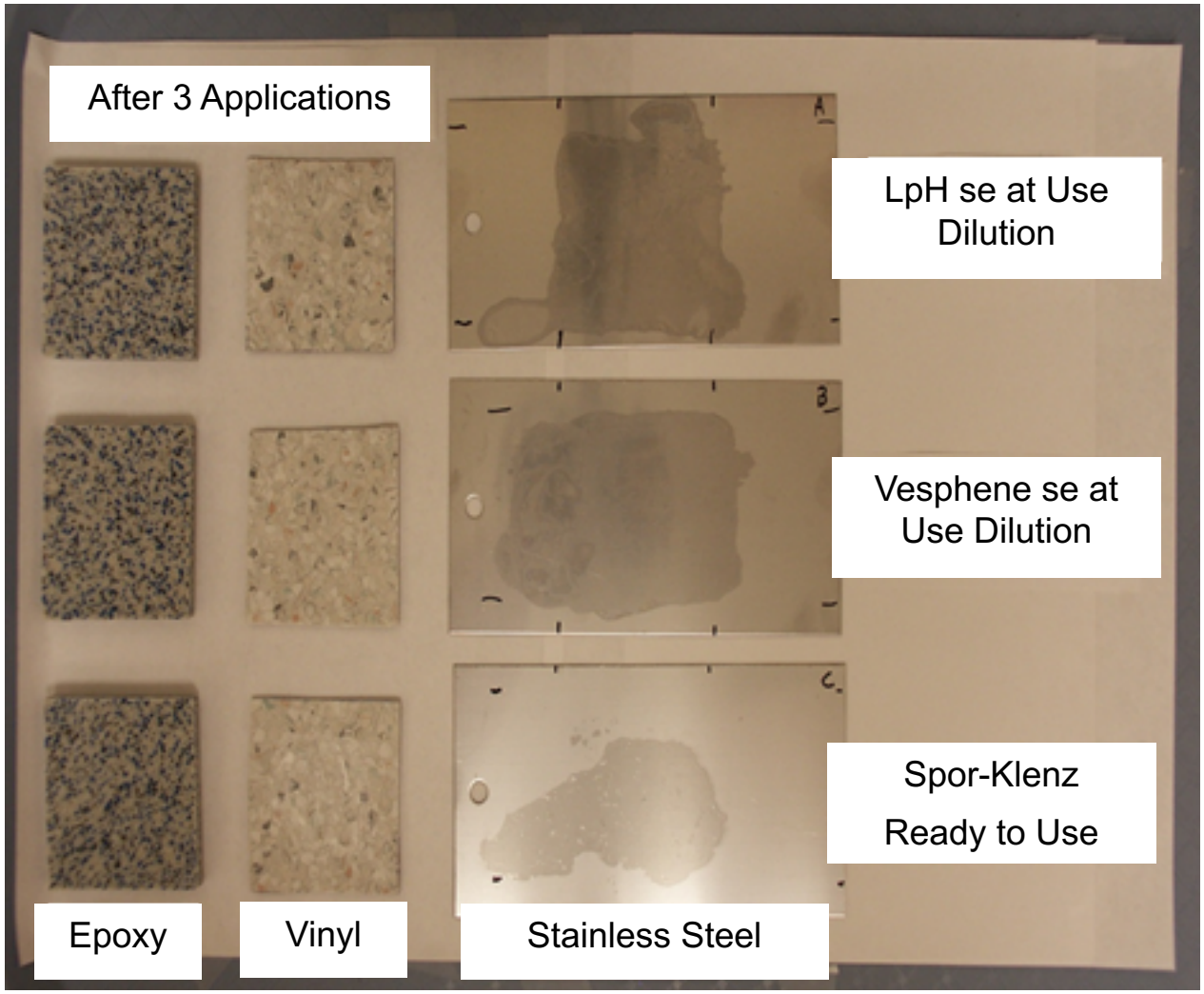

Surface Types and Topography

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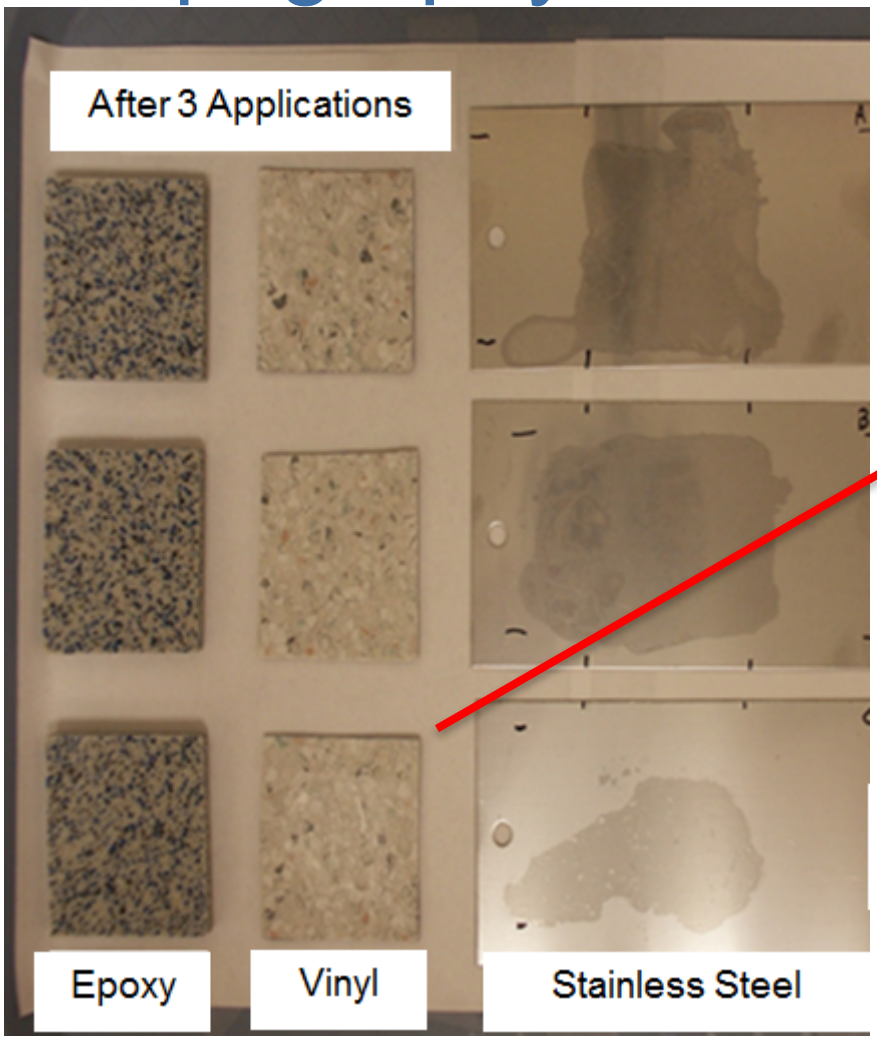

Residue Warning Letter 2/27/13

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- Your firm does not always keep laminar flow hoo[illegible] filter sur[illegible]ved whi[illegible] filte[illegible] incl[illegible]

Takeaways
1) Visual residues are not acceptable
2) White particles are not acceptable
3) Residual removal strategies will address this warning letter

- I observed white particles on the floor of the clean room…approximately two to three millimeters square.

USP 39 <1072>

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- Disinfectants
  - typically removed with 70% alcohol wipes.
- Disinfectant residual removal
  - monitor for effectiveness as a precaution against potential product contamination

PDA TR No. 70

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"Irregular or porous surfaces trap residues and other contaminants and make the surface more difficult to clean and disinfect. Development of appropriate cleaning systems is critical to successfully preparing a surface for disinfection. Cleaning operations should routinely occur and frequencies should be based on area classification, usage, risk and visible cleanliness. A good cleaning agent is formulated to contain an effective surfactant system that will support the water in its efforts to release particles, residues and other foreign materials. Procedurally, strict cleaning (without the use of a sanitizer, disinfectant or sporicide) should be conducted on a routine basis as defined by written procedures."

Recommendations

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- "Routinely" remove residue
- Questions:
  - When (or how often) do you rinse?
  - What disinfectants do you use?
  - Do you use automated cleaning equipment?
    - How is the equipment being maintained?
  - Is there equipment with moving parts present?
  - Do you have any visible residue?
  - Do you have any sticky, tacky or slippery floor issues?

Rinsing Frequency

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Guidance USP 39 <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)

Recommendations

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- Routine rinsing (residue removal)
  - Water For Injection
    - Concern: potential source for contamination
  - 70% Isopropanol, 70% Ethanol
    - Concerns: flammability , volatile organic carbon fumes (i.e., air permit issue), or personnel exposure (i.e., Short Term Exposure Limits, STEL)
  - 3% H_2O_2
  - Sterile detergents
    - Concern: will leave a residue too (and may not be required)

Recommendations

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- Heavy Residue Removal
  - May require laboratory evaluation
  - Details of contamination program and current rinsing program required & critical
  - Formulated cleaner / detergent may be required
  - Rinse with WFI to remove possible residue from detergent
  - Once cleanroom surface has been returned to a “clean state”, implement the routine rinsing procedure as maintenance

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Summary

Contamination Control Program Recommendation

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Rotation: Disinfectant and Sterilant Program

- Disinfectant - Phenol or Quat
- Sporicide

- Frequency established using risk based approach and adjusted based on environmental trending data

Rinsing Program:

- WFI or 70% Alcohol on a routine basis (cleaners can be used for buildup removal)
- Frequency based on surface aesthetics

Resources

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Disinfectant Rotation:

- Technical Tip 420-200-4002, “A Rational Approach to Alternating (Rotating) Disinfectants in Pharmaceutical, Biotech and Medical Device Cleanrooms”

Residue Removal:

- Technical Tip 420-200-4038, “Residue Removal Recommendations for Hard-Surface Germicidal Agents used in Critical Environments”
- Case History 420-500-4001, “Cleaning Floors in Cleanrooms with ProKlenz NpH Neutral Detergent”

General Disinfection:

- Technical Tip 420-200-4001, “Product Property Charts for STERIS Sanitizers/Disinfectants and Sterilants”
- Technical Tip 420-200-4014, “Disinfectant Application Guidelines for Cleanrooms and Controlled Environments”
- Technical Tip 420-200-4021, “Survey of Disinfectant Usage in Parenteral Facilities”

References

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- USP 39 <1072> Disinfectants and Antiseptics
- PDA Cleaning and Disinfection TR No. 70 (2015)
- Annex 1 (2008) and MHRA Orange Guide (2016)
- FDA Aseptic Processing Guide (2004)
- FDA, MHRA, HPRA, CFDA, ANSM, ANVISA, & EMA Expectations
- Industry Articles (Ex. Scott Sutton, Jose Martinez, Richard Prince, Rebecca Smith, Tim Sandle)
- The CDC Handbook - A Guide to Cleaning & Disinfecting Cleanrooms (Tim Sandle 2016)
- A Guide to Disinfectants and their use in the Pharmaceutical Industry (Pharmig 2006)
- USP 39 <1116> Microbiological Control and Monitoring of Aseptic Processing Environments
- PIC/S Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments (2014)
- WHO Annex 6
- PHSS Technical Monograph #20 “Bio-contamination characterization, control, monitoring and deviation management in controlled/GMP classified areas
- USP 39 <797> Pharmaceutical Compounding-Sterile Preparations

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Thank you!

- Audience
- PDA Southern California Chapter
- Stacey Betts – Local Account Manager

Current Rotation Practices

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"The need for the rotation of disinfectants in a pharmaceutical cleanroom sanitization program is not supportable from a scientific basis. The assumptions that proponents of the practice assert as facts, e.g. generation of resistant organisms, greater efficacy of alternating agents, are not supported by the literature. However, **even when using a validated disinfectant as part of a well-managed cleanroom sanitization program, periodic use of a sporicide is a prudent**—even an essential—component of the sanitization program. It is needed to address the occasional appearance of spore-forming organisms in the environmental monitoring program and therefore ensure the cleanest possible environment for manufacturing."

Sutton, SVW. Disinfectant Rotation - a Microbiologist's View. *Controlled Environments*. July 2005. p 12

Current Rotation Practices

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"The need for rotation of disinfectants in a pharmaceutical clean room sanitization program is unsupportable from a scientific basis. The assumptions that proponents of the practice assert as facts (generation of resistant organisms, greater efficacy of alternating agents) are not supported in the literature. **However, even when using a validated disinfectant as part of a well-managed clean room sanitization program, periodic use of a sporicide is a prudent, even an essential component of the sanitization program. It is needed to address the occasional appearance of spore-forming organisms in the environmental monitoring program, and hence ensure the cleanest possible environment for manufacturing**."

Disinfection and Decontamination: Principles, Applications, and Related Issues. "Disinfectant Rotation in a Cleaning Disinfection Program for Clean Rooms and Controlled Environments", Scott V. W. Sutton 2008 Taylor Francis Group LLC.

Current Rotation Practices

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" **Rotation of a common disinfectant and a sporicidal helps ensure that bacterial spores do not take hold in manufacturing and aseptic** areas. But the rotation of common disinfectants such as those based on phenol- derivatives, aldehydes, and oxidizing agents has no scientific basis."

Martinez, JE. The rotation of disinfectants principle: true or false? *Pharmaceutical Technology* (2009), p 69.

Current Rotation Practices

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- "It is clear that using a sporicide is highly important, but agents that have sporicidal activity tend to be harsh and unacceptable for everyday use. **For this reason it is recommended that a sporicide is used in rotation with another effective disinfectant that is more suitable for regular use**."

Smith, RJ. Rotational Cleaning – Is it necessary? *Cleanroom Technology*, Jan 2014. p 67

Cleaning and Disinfection: Rotation

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"Where **disinfectants** are used, **more than one type should be employed**. Monitoring should be undertaken regularly in order to detect the development of resistant strains."

MHRA - Rules and Guidance for Pharmaceutical Manufacturers and Distributors. 2015 (p. 85)

Tim Sandle: The CDC Handbook

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"Within Europe the **rotation of two disinfectants with differing modes of activity is a regulatory expectation. The frequency of rotation needs to be defined by the user and supporting data can be supplied through field trials**".

CDC Handbook: A Guide to Cleaning and Disinfecting Cleanrooms. Pages178 and 180, 2012.

Tim Sandle: Rotation

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"When using disinfectants with different modes of activity more often one of the selected disinfectants is sporicidal. With regard to the frequency of rotation this tends to based on the environmental monitoring data. Given that environmental monitoring data should be reviewed for trends on a regular basis this allows the frequency of cleaning and disinfection to be based on risk."

La Vague "Selecting of Cleanroom Disinfectants" # 42 June 2014.

Tim Sandle: Recent Article

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"**Thus in selecting disinfectants many pharmaceutical manufacturers will opt to have two 'in-use' disinfectants and sometimes to have a third disinfectant as a reserve in case a major contamination incident arises**, such as a bioburden contamination build up, which appears resistant or difficult to eliminate using the routinely used disinfectants. The reserve disinfectant will often be more powerful and sporicidal, such as an oxidizing agent, the routine use of which is restricted because of likely damage to the equipment and premises. Typically the two primary disinfectants are rotated."

Pharmaceutical Facility Sanitization: Best Practices Considered. Tim Sandle American Pharmaceutical Review, March 31, 2016.