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Current Industry Trends -Including Cleaning and Disinfection trends, Disinfectant Validation Trends, and Current Warning Letter Activity.

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Agenda

- Current Industry Trends
  - ➢ Cleaning and Disinfection
  - – Disinfectant Validation
  - – Current Warning Letters

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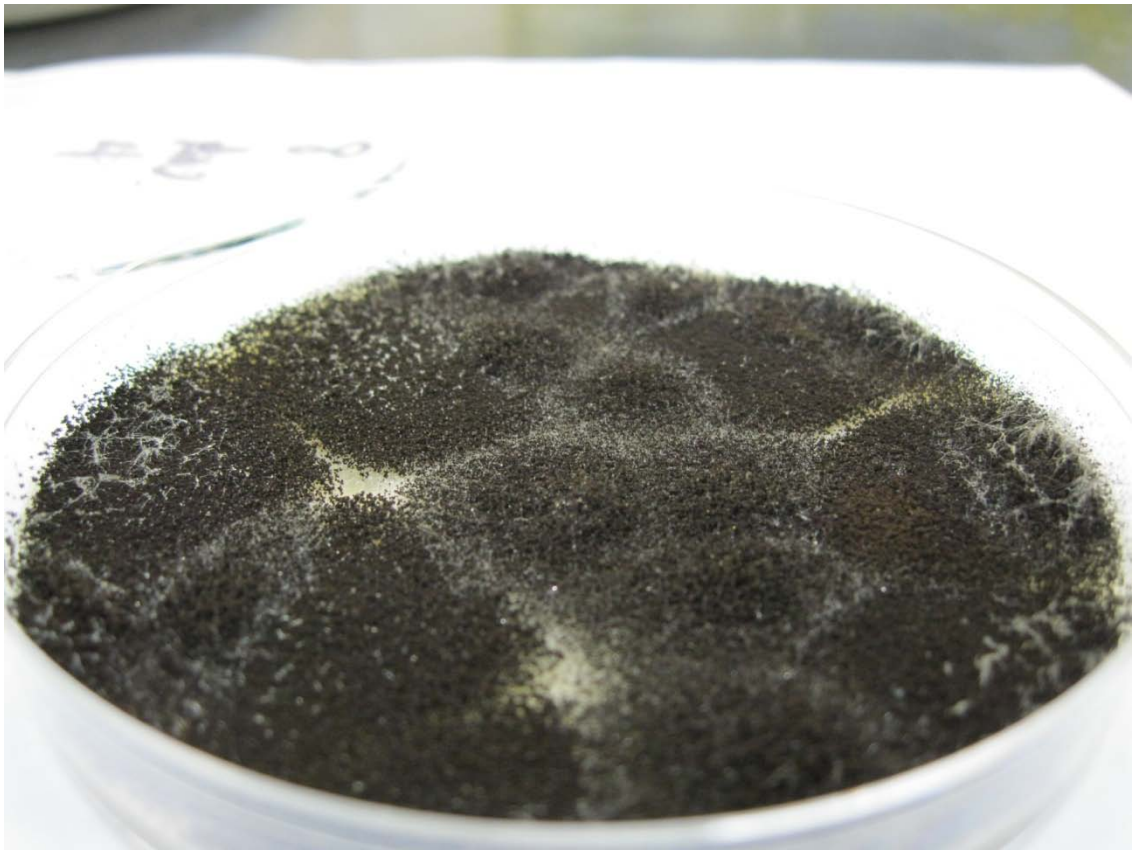
Aspergillus niger

Courtesy Jim Polarine



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Cleanroom Fungi

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Courtesy Dan Klein

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Application Techniques

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- 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

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Controlled Areas

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- 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.

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Class 100000 - D

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Class 100,000 Closed Processes – Recommendations

(solution prep, fermentation, purification, media prep, wash bays, raw material weigh area, stopper prep, packaging inspection)

Surface	Method	Cleaning Agent	Frequency	Rinse
Floors • around drains • foot traffic paths • spill areas • access ports	mop	high-level disinfectant with surfactants	daily at shutdown, between process changeover	not necessary
Walls, Ceilings • general	wipe, mop	high-level disinfectant with surfactants followed with sporicide	monthly	not necessary
• doors, handles, high-traffic areas	mop	high-level disinfectant with surfactants	daily	
Equipment • adjacent to access ports	spray, wipe	high-level disinfectant with surfactants	daily during processing	as needed to remove residue buildup
• surface upstream airflow path to process opening	spray, wipe		weekly	
Other Surfaces • sinks • benches • trash containers	wipe	high-level disinfectant with surfactants	daily	not necessary

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Class 10000 - C

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Class 10,000 – Outside Laminar Flow Hoods, Rooms, and Halls – Recommendations

Surface	Method	Cleaning Agent	Frequency	Rinse
Floors • normal traffic paths	mop	high-level disinfectant with surfactants	daily after transfers	not necessary
• proximity to open process or transfer areas		high-level disinfectant with surfactants followed by a sporicide	weekly or monthly, if necessary	
Walls • general	wipe	high-level disinfectant with surfactants followed by a sporicide, if necessary	weekly or monthly	not necessary
• door plate	mop	high-level disinfectant with surfactants	daily	
Equipment • shelving • portable tanks • processing items	spray or wipe	high-level disinfectant with surfactants	before and after use	WFI rinse as necessary to address residue buildup
• carts (wheels)		sporicide		
Furniture and Other	spray or wipe	high-level disinfectant with surfactants	daily	not necessary
• chair (wheels)		sporicide		

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Class 100 - A & B

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Class 100 – Laminar Flow Hoods and Aseptic Filling Suites – Recommendations

Surface	Method	Cleaning Agent	Frequency	Rinse
External Hoods • back, sides, top	wipe	sterile high-level disinfectant with surfactants	daily	not necessary
• door, sliding panel	wipe	sterile high-level disinfectant with surfactants	daily	
		sporicide	weekly or in response to microbial monitoring	
Inside Hood or Curtain • work surface • sidewalls • apparatus/critical surfaces	wipe	sterile high-level disinfectant with surfactants	daily, preuse and postuse	WFI as necessary in product contact areas, or to address residue buildup
		sporicide	weekly or in response to microbial monitoring	
• curtains	wipe	sterile high-level disinfectant with surfactants	daily	
		sporicide	weekly or in response to microbial monitoring	
Adjacent Flooring and Walls	mop	sterile high-level disinfectant with surfactants	daily, between lots and shifts	not necessary
		sterile high-level disinfectant with surfactants followed by a sporicide, as necessary	weekly or in response to microbial monitoring	

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Sporicidal Agent Application

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- ✓ Rationale
  - ✓ Spore control vs. chemical exposure
    - ✓ Corrosivity and Irritation

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Application Frequency

- Sporicidal agent
  - Rationale
    - Weekly
    - Monthly
    - Quarterly
      - ✓Should be written in SOP's

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Commonly Used Equipment

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Courtesy Micronova Mfg.

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New Mopping Systems

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

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In Vitro Options for Testing

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- AOAC
  - Use-dilution Test
  - Sporicidal Activity of Disinfectants
  - Germicidal Spray Products as Disinfectants
- ASTM
  - Time Kill Method
  - Spray Slide
  - Sanitizer method (E1153)
  - Wipe method
  - Quantitative Carrier Method (E2111 & E2197)
  - Biofilm Method (E1427)
  - Viral Testing (Suspension E1052)
  - Viral Testing (Carrier E1053)
  - Standard Guide for Evaluation of Cleanroom Disinfectants (E2614-08)
- Variations of all of the above

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More In Vitro Options for Testing

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- EN
  - 1276 (bacterial suspension test)
  - 1040 (bacterial suspension test)
  - 1650 (fungal suspension test)
  - 13704 (sporicidal suspension test)
  - 13697 (Carrier test)
  - 14476 (Viral Testing)
  - 14348 (TB Testing)
- AFNOR (France)
  - NFT 72-150 Suspension
  - NFT 72-190 Carrier Test
- DGHM Suspension Test (Carrier & Suspension Tests)
- TGA (Australia)

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Testing at Contract Labs & Industry

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- European Testing is generally EN-13697 Hard Surface Testing Method
  - Log Reduction Values commonly used are from USP 35 <1072> (3 Log for Vegetative Bacteria and 2 Log for Bacterial and Fungal spores)
  - Some contract labs will conduct ASTM Methods E2111 or E2197
  - Some companies develop their own coupon testing methods
  - Some companies use Modified AOAC testing methods
  - Costs at contract labs includes contact time, surface, and test conditions. Viral testing more expensive.

There are no currently harmonized disinfectant efficacy testing methods between the US and EU.

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Key Variables with EN-13697

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- Hard Water
- Soil Load (Albumin + Tryptone) or Skimmed Milk Clean vs. Dirty Soil Loads
- Contact time 5 Minutes
- The Organism (Some fungi and *Bacillus* are more resistant)
- Nature of the Surface being Tested
- Technique of Application (Immersion, Spray, Wiping)

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Disinfectant Validation Studies

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- The cost of a study can vary quite a bit depending on:
  - Who is conducting the study (Inside or outside microbiology lab)
  - The number of organisms tested
  - The contact times tested (many companies test more than one time point)
  - Number of substrates tested
  - Number of disinfectants or sporicides tested
  - The age of product they want to test (i.e., do they want to use product after 7 days)
  - The different test methods they want to use
  - Any other variables they may want to consider in their testing (soiled vs. clean conditions, etc.)

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Case Study on Substrates

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Table 3. Efficacy (log reduction) of Low pH phenolic: (1:256 Dilution) against test microorganisms on representative surfaces

Surface	*Staphylococcus epidermidis*	*Pseudomonas aeruginosa*	*Corynebacterium glutamicum*	*Candida albicans*	*Aspergillus niger*	*Penicillium chrysogenum*
Stainless Steel	6.62	>6.10 [b]	4.18	>4.31 [b]	<3.00 [c]	4.95
Glass	6.85	6.42	5.26	>5.80 [b]	2.98	5.11
Aluminum	6.35	5.69	5.14	>3.93 [b]	<3.00 [c]	3.48
Epoxy	4.36	4.45	4.48	3.19	<3.00 [c]	<3.00 [c]
Enamel	>6.05 [b]	>5.72 [b]	5.45	>3.92 [b]	<3.00 [c]	2.83
Acrylic	4.53	6.06	4.49	2.92	<3.00 [c]	<3.0 [c]
Miplan	4.36	3.87	4.29	4.37	<3.00 [c]	3.25
Vinyl	4.08	3.68	3.93	2.61	<3.00 [c]	2.1
Hardwood	5.18	>4.54 [b]	5.26	3.2	<3.00 [c]	2.59
Melamine Covered Wood	>5.38 [b]	>5.64 [b]	>5.09 [b]	>5.12 [b]	3.65	3.95
Plastic	>5.73 [b]	>5.32 [b]	>5.05 [b]	>4.04 [b]	<3.00 [c]	2.44
Plexiglas	>5.90 [b]	5.62	4.83	>4.40 [b]	<3.00 [c]	3.85
Print	5.85	5.86	5.74	4.51	<3.00 [c]	3.38
Chromium	6.55	5.95	6.63	4.08	<3.00 [c]	2.61

[a] Disinfectant Efficacy = (Log $MSP_{(positive\ control)}$ - Log $MSP_{(test\ coupons)}$), where $MSP_{(Positive\ Control)}$= Mean surviving population on positive control coupons; $MSP_{(test\ coupon)}$ = Mean surviving population on test coupons after disinfectant treatment; [b] Each of triplicate coupons showed no growth after disinfectant treatment; [c] Each of triplicate coupons showed TNTC growth

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Spore Testing

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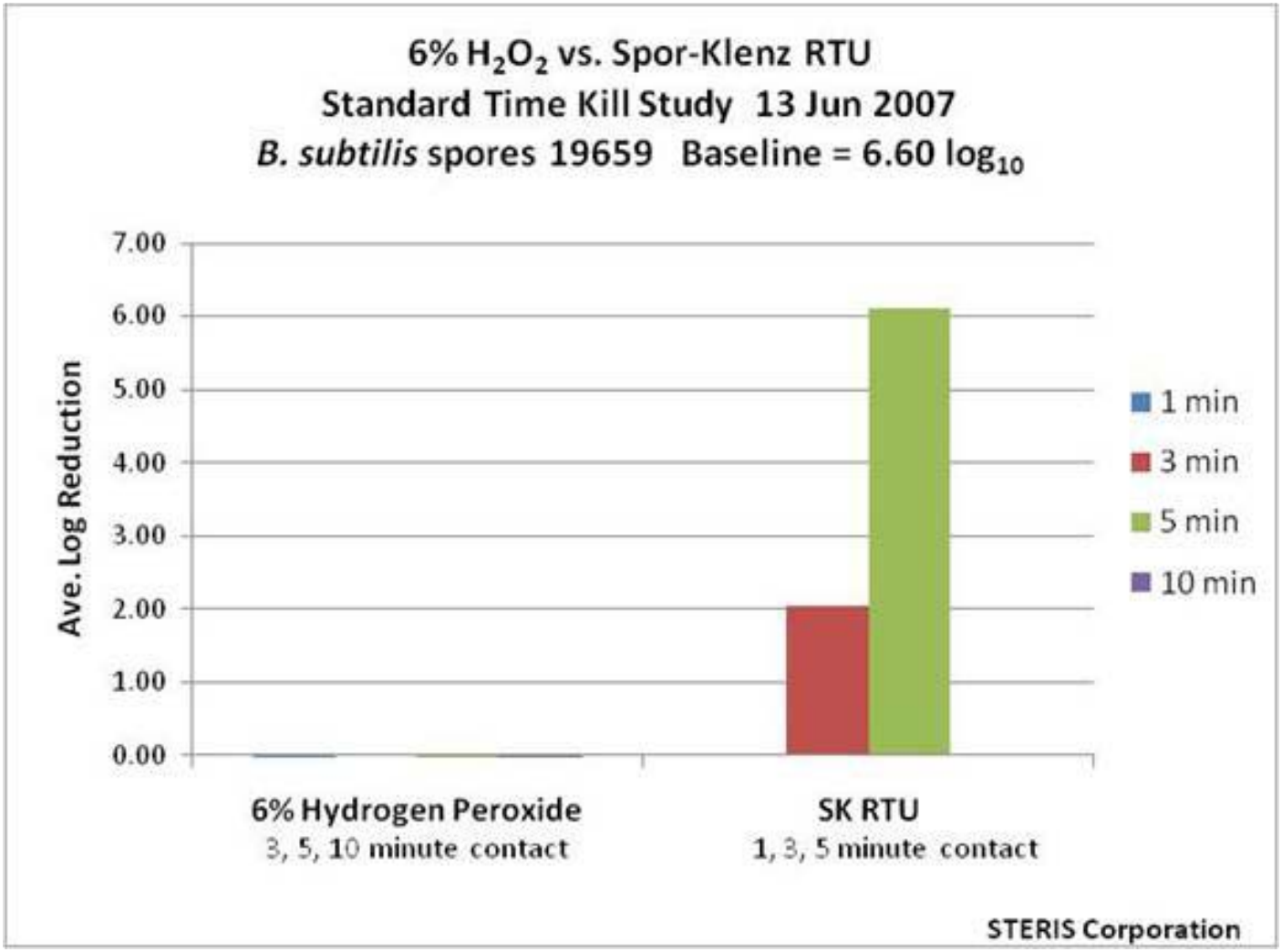

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ATCC: Hydrogen Peroxide 6%

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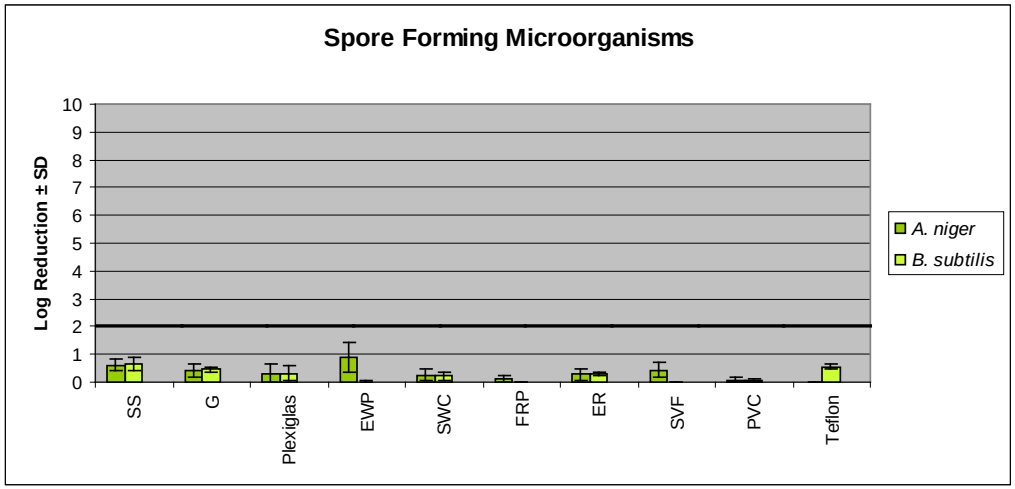
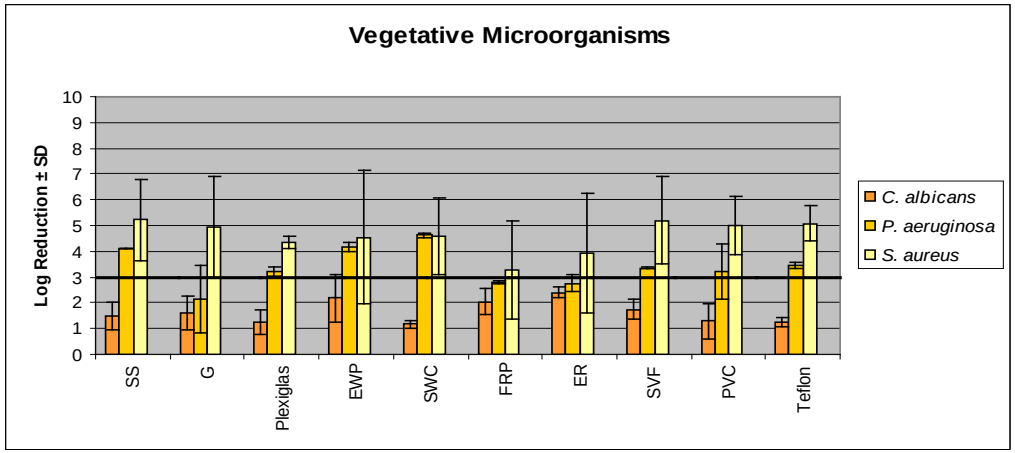


CT = 9 min.

2 Log Reduction Target



3 Log Reduction Target

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ATCC: H202/PAA RTU

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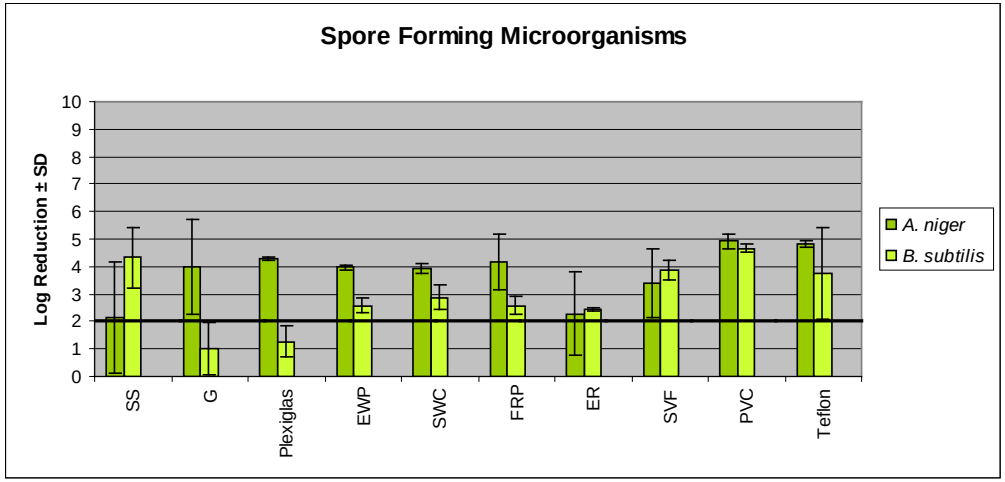
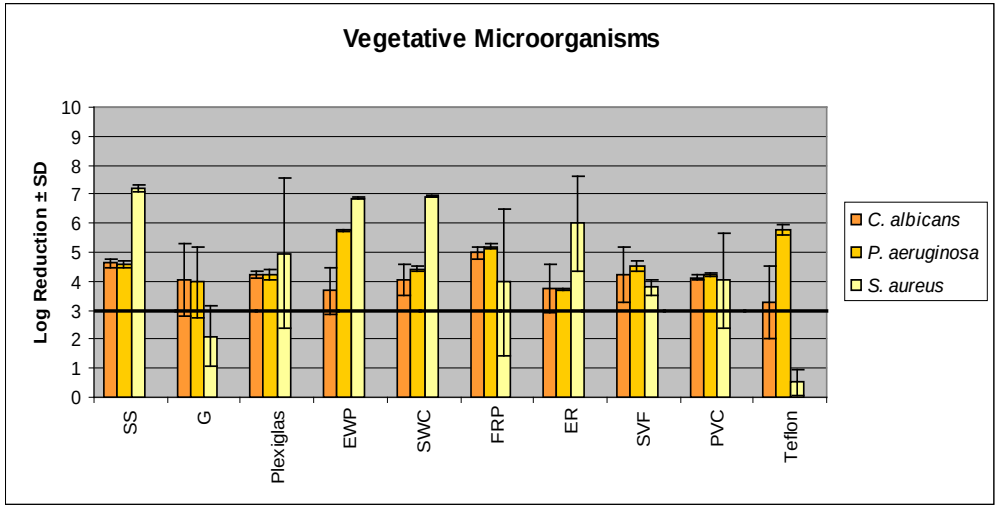


CT = 5 min.

2 Log Reduction Target



3 Log Reduction Target

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Hard Surface Tests

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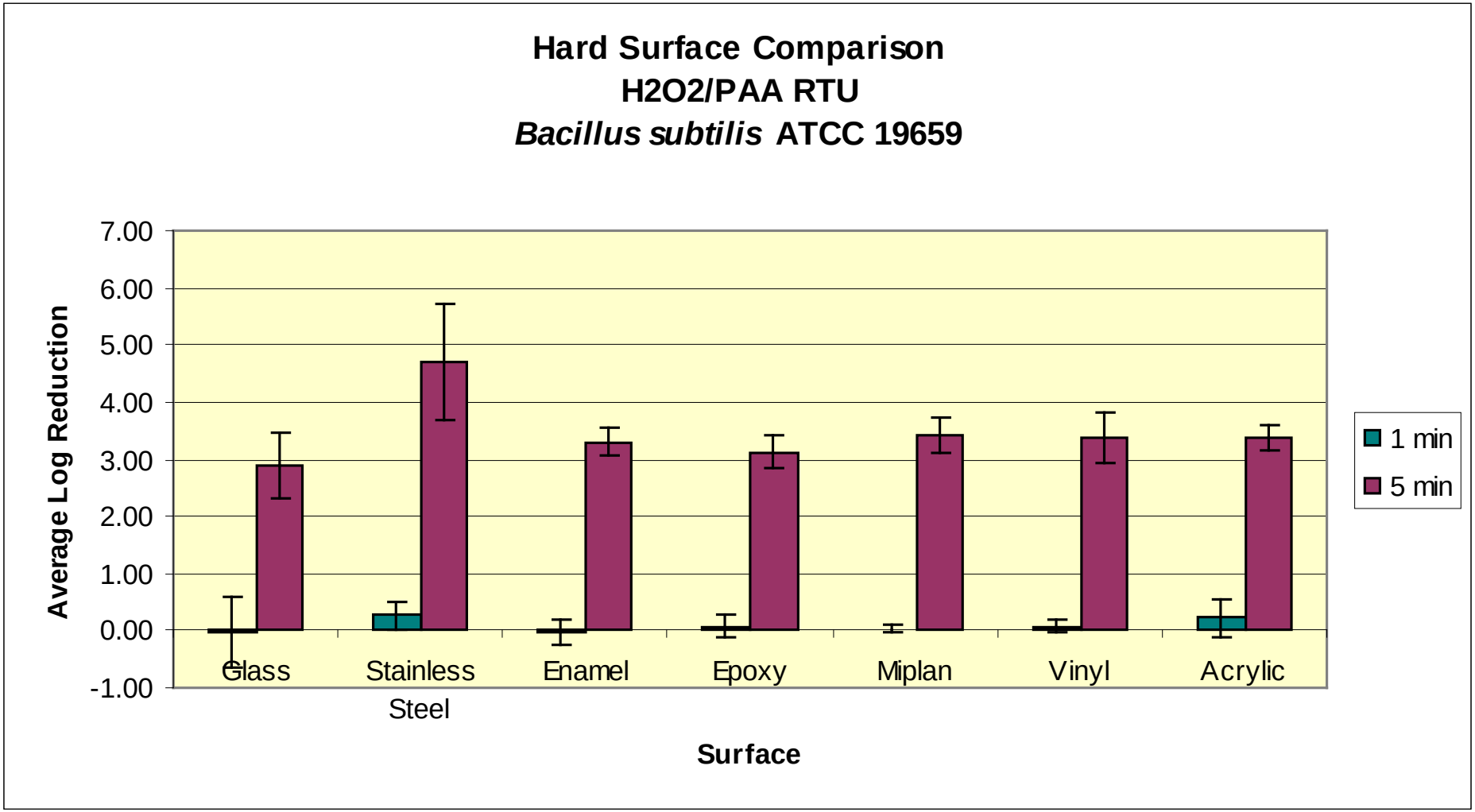

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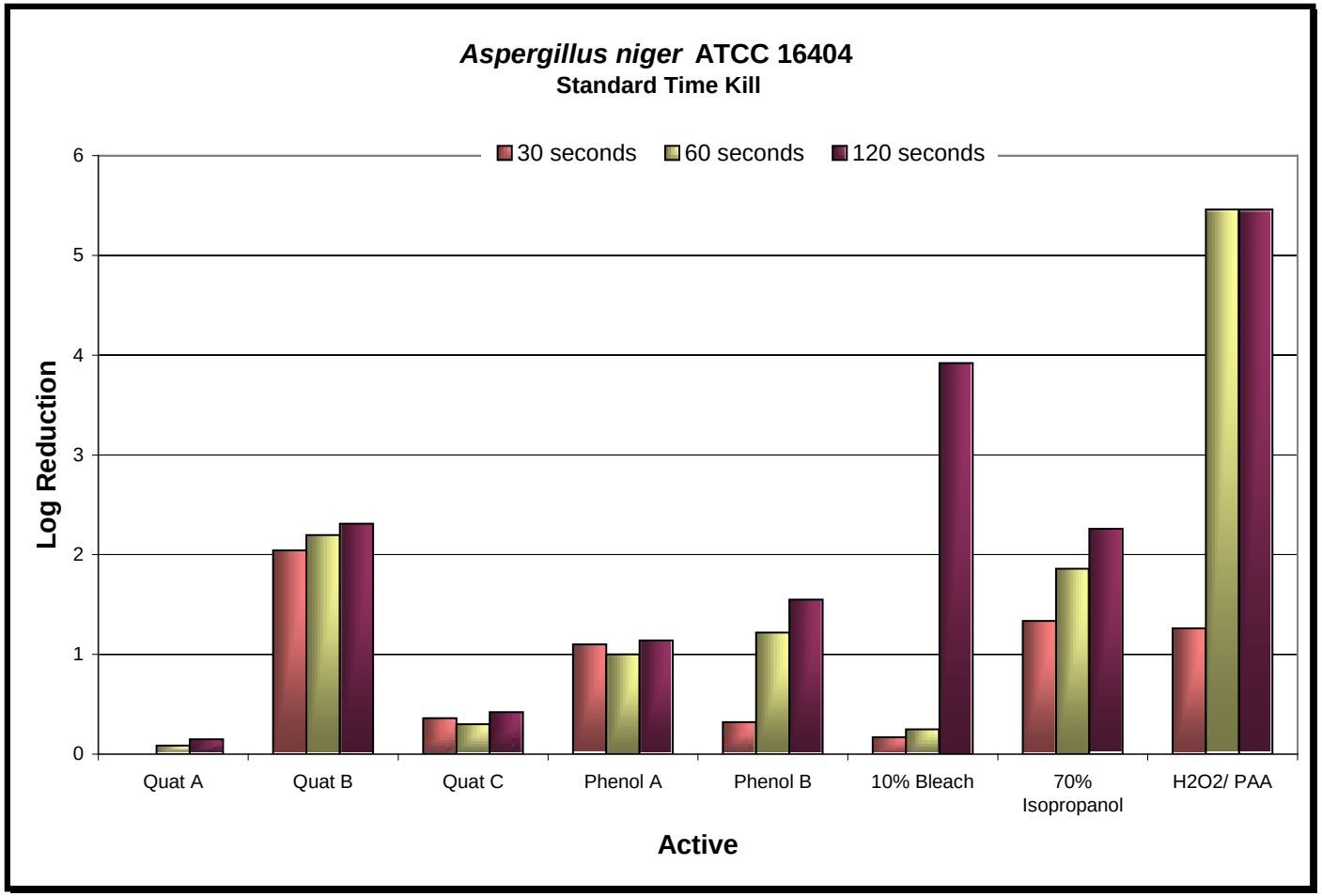
Efficacy Comparison with Fungi



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Current Guidance on Disinfectants

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- USP 35 General Chapter <1072>
- ISO /DIS 14698-parts1-3
- The Orange Guide 2009
- Aseptic Processing Guide 2004
- Current Industry Articles (Jose Martinez, Scott Sutton, Richard Prince)
- USP 35 <797>
- Several Industry Books (Seymour S. Block)

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Current Warning Letter

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- “Your firm has not established procedures designed to prevent microbiological contamination of drug products purporting to be sterile” Warning Letter February 22, 2012

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Current Warning Letter

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"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.

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Current Warning Letters

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"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

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Current Warning Letter

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- “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

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Current Warning Letter

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- “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.

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Current Warning Letter

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- Specifically, no disinfectant validation was performed for your **(b)(4)** cleaning of vessels, surfaces, and other equipment used during the collagen impregnation process. Your firm's laboratory simulation Disinfectant Efficacy Testing report, dated January 27, 2009 shows that the disinfectants used by your firm can remove microorganisms placed on carrier test coupons; however, no disinfectant validation study was conducted to demonstrate that your **(b)(4)** cleaning and sanitizing procedures are adequate in removing contaminates from actual Collagen processing equipment. Warning Letter August 11, 2010.

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Current Warning Letter

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- “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

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483 Observation

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- "During sanitization and sporicidal agent revalidation studies completed in …. two sporicidal agents routinely used by the firm failed to achieve corporate acceptance criteria of….for all challenge microorganisms used in testing. The sporicidal agents remained on the form's approved sanitizing and sporicidal agents list for parenteral areas until…. The revalidation study completion dates and sporicidal agents failing to achieve the acceptance criteria are as follows….."
- June 2008 GMP Trends

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Warning Letter

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- “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.

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483 Observation

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- "There are no assurances that the currently used…disinfectant is effective against fungi and molds. Per protocol….the disinfectant effectiveness study for….the assay test method validation was for ….recovery rate. However, the data obtained during the performance qualification demonstrated that the minimum of….acceptance criteria established per protocol….was not consistently obtained during the positive control recovery studies."
- January 2009 GMP Trends

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Warning Letter-Disinfectants

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- "Your responses indicate that you will conduct an additional study to evaluate the effectiveness of your disinfectants, as well as perform cleaning validation of the ___ laminar flow hood. Please be advised that the completion date of Q1/2008 for these activities appears excessive. We remind you that the failure to adequately evaluate your disinfectants is a repeat observation from our 2004 inspection. We recommend that you re-evaluate your proposed time frame for completion of both studies." Warning Letter September 19, 2007

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Warning Letter-Disinfection

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- "The November 2003 disinfectant effectiveness validation study of ___ used to disinfect your facility, did not meet your established ___ log reduction acceptance criterion for ____ set forth in your validation study protocol." Warning Letter May 24, 2007.

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Warning Letter-Disinfectants

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- "There is no assurance that the disinfectant ____ is effective against mold, since it did not meet your established recovery rate acceptance criterion in the December 2001 "Disinfectant Validation and Efficacy Study of ___ by the Surface Test Method" study." Warning Letter May 24, 2007.

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483 Observation

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- “There are no sanitizer/disinfectant efficacy studies using … against microorganisms isolated in the aseptic production area using comparable material found in the manufacturing area such as …..” GMP trends 6/15/2006

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Regulatory Notes

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- "Approximately 80% of all microorganisms' growth in the…filling room, monoblend aseptic filtration, and trivalent formulation room excursions were not identified to the genus level." GMP Trends 9/1/2005.

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Warning Letter

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- "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.

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Questions & Answers

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