Debates and Challenges in Disinfectant Testing

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Science & Solutions for Life

Debate Regarding Coupon Testing

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- Pros for not testing
  - Reduce testing and resources costs significantly
  - Have one centralized coupon study as a reference

- Cons for not testing
  - There are in fact more resistant strains of bacterial spores such as *Bacillus cereus* that do not conform
  - There are some surface interactions that do not conform

End-User Disinfectant Validation Components

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- *In vitro* testing
  - Suspension testing (also called Time Kill Study)
  - Carrier Testing (also called Coupon Testing)
- *In situ* testing
- Environmental monitoring
  - Data trending (6-12 months, reviewed monthly)
  - Identification of organisms (mold, yeast, and bacteria)

Disinfectant Qualification Procedure Recommendations

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- USP 40 <1072> Disinfectants and Antiseptics
  - Suspension tests
  - Surface Challenge tests
- ASTM E2614-15: Guide for Evaluation of Cleanroom Disinfectants
- ISO 14698 (parts1-3)
  - Surface evaluation, focus on cleaning
- PDA Technical Report No. 70 (2015): Fundamentals of Cleaning and Disinfection Programs for Aseptic Manufacturing

What End-User knows?

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What the Vendor tells you

- Chemical makeup
- Recommended prep method (use-dilution)
- Efficacy using EPA required methods
  - Tested against ATCC organisms
- Usually 10 minute contact time

What End-User needs to know

- How the disinfectant performs:
  - in THEIR facility
  - prepared by THEIR procedures
  - on THEIR surfaces
  - with THEIR contact time
  - against THEIR resident microbes
  - applied by THEIR methods/procedures

Qualification and Validation

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- **Validation** typically refers to a process (FDA) – generally applies to the disinfection process used at a facility
  - Involves 3 steps – *In vitro* testing, *in situ* testing and environmental testing/trending
- **Qualification** – documented evidence that the disinfectants used in the disinfection process at a facility are effective against facility specific environmental isolates on facility specific surfaces.
  - Qualification typically involves coupon studies (*in vitro*) with in-house environmental isolates from the facility on facility specific surfaces
  - In-house isolates should include yeast, bacteria, spore forming bacteria and mold, and possibly viruses

End-User Disinfectant Validation Components

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- *In vitro* testing (Disinfectant Qualification)
  - Suspension testing (also called Time Kill Study)
  - Carrier Testing (also called Coupon Testing)
- *In situ* testing
  - Demonstrates effectiveness of products and application procedures in the “real world”
  - Includes statistical comparison before and after implementation of disinfectant
- Environmental monitoring
  - Demonstrates continued effectiveness of biocides and application procedures
  - Data trending (6-12 months, reviewed monthly)

Testing Protocols for Product Registration

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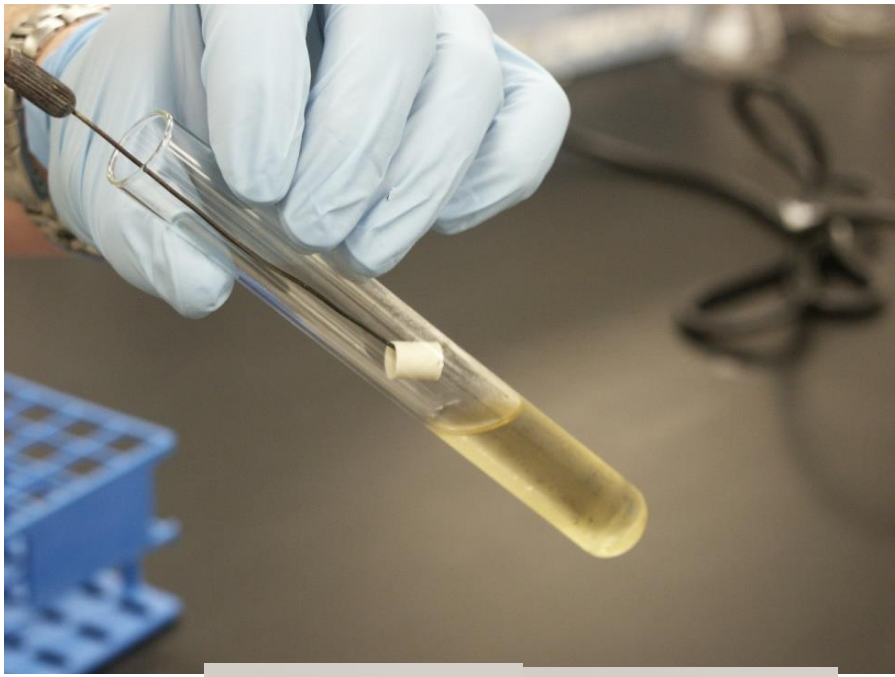
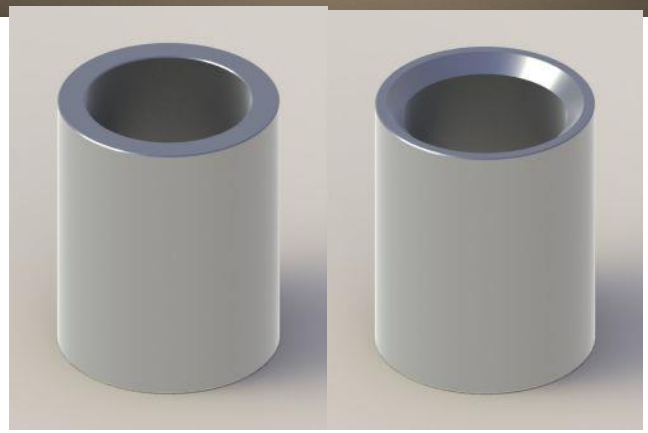
United States

- Typically AOAC Intl. methods
  - Primarily qualitative
  - Primarily use ring carriers
- Pass/Fail criteria differ for bacteria, TB, fungi and spores

Europe

- Methods divided into 3 tiers
- Primarily quantitative
  - Phase 1
    - Basic suspension tests
  - Phase 2
    - Simulation studies
    - Use hard surfaces
  - Phase 3
    - Tests under practical conditions





Courtesy Dan Klein

In Vitro Options for Testing

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- AOAC
  - Use-dilution Test Methods (955.14, 955.15, 964.02)
  - Sporicidal Activity of Disinfectants (966.04)
  - 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 (E2614-15)
- Variations of all of the above

More *In Vitro* Options

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- EN
  - 1276 (bacterial suspension test)
  - 1040 (bacterial suspension test)
  - 1650 (fungal suspension test)
  - 13704 (sporicidal suspension test)
  - **13697(2015) (Carrier test)**
  - 14476 (Viral Testing)
  - 14348 (TB Testing)
  - 14885 (2015)
  - 16777 (Viral Hard Surface test)

- AFNOR (France)
  - NFT 72-150 Suspension
  - NFT 72-190 Carrier Test
- VAH (DGHM) (Germany, Carrier & Suspension Tests)
- TGA (Australia)

EN 13697- 2015 Revision

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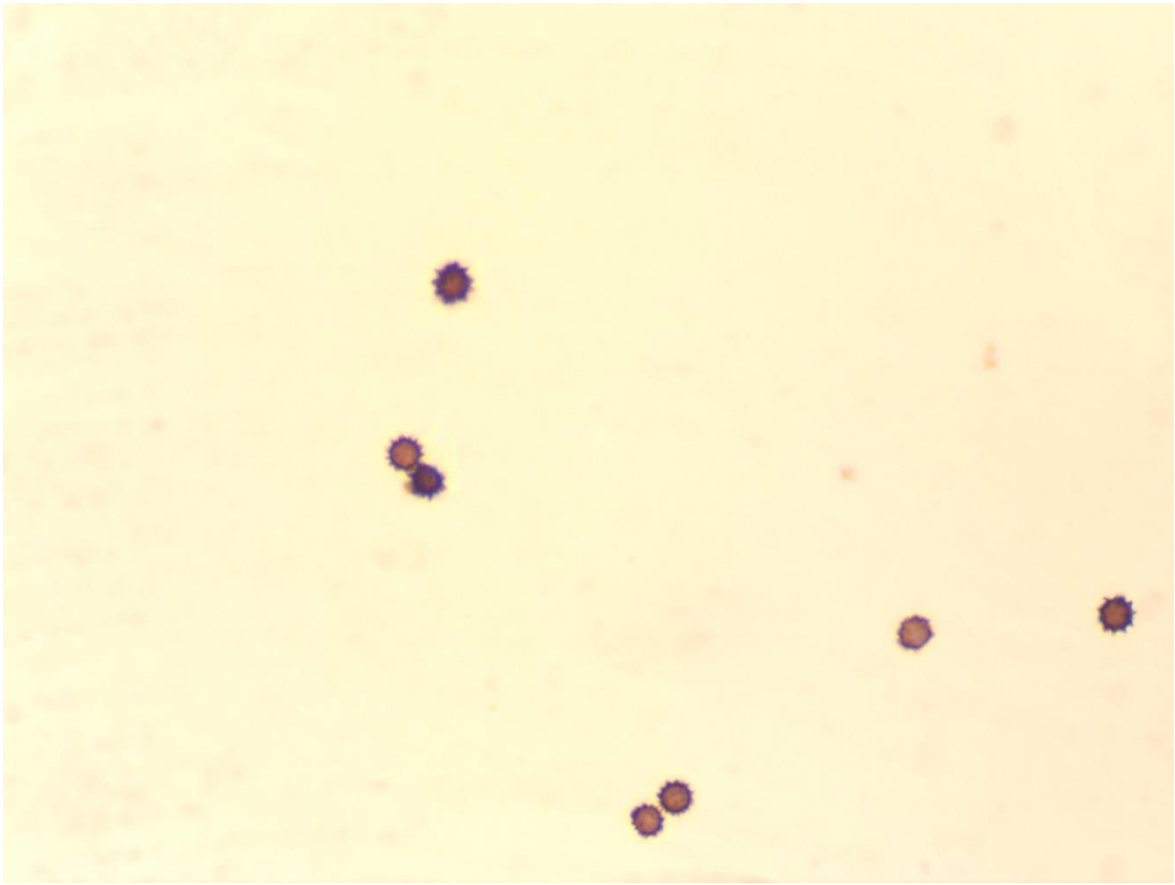
- Added a requirement for 75% spiny spores *A. brasiliensis* ATCC 16404
- Added skim milk interfering substance as obligatory for *P. aeruginosa*
  - May mitigate desiccation lethality for other G- bacillus
- Changed method verification acceptance criteria

Spiny Spores



Courtesy Dave Shields

Coupon Size

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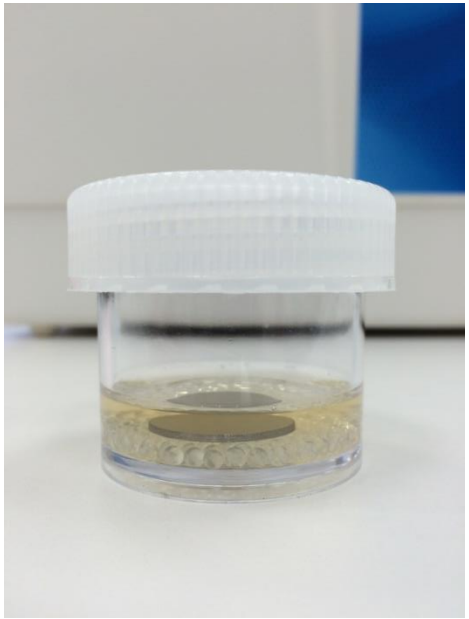
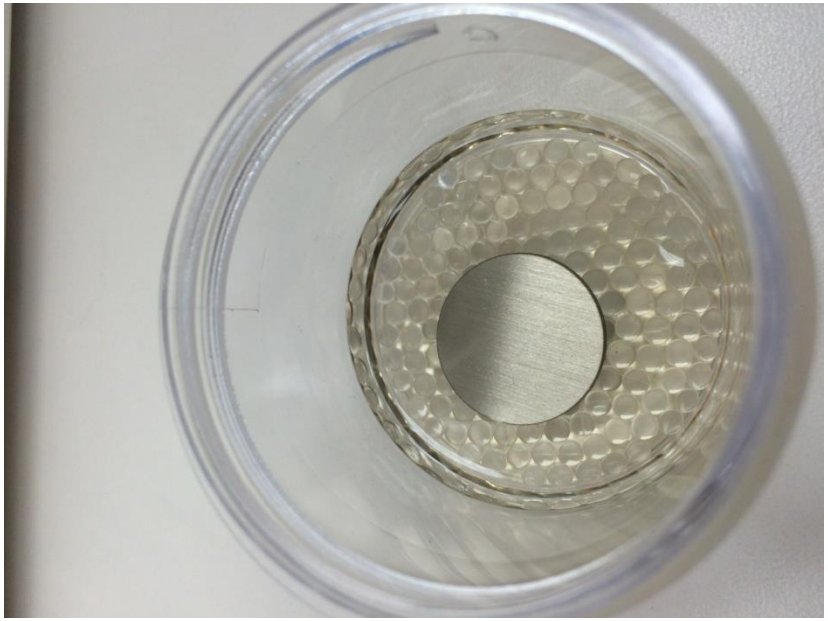
- USP <1072> Calls for 2” x 2” coupons-no other operatic details specified
- PDA TR #70 3.5 cm X 3.5 cm
- ASTM E2197 Calls for 1 cm disc
- EN 13697 Calls for 2 cm disc
- Larger coupons can limit possible recovery methods
- Having scientifically sound method, more important than arbitrary size

EN 13697

- Being a prescriptive test method allows for consistency across European facilities
- Video

Courtesy Dave Shields





In Vitro Carrier Comparison

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EN 13697

Inoculum

Test Product

Courtesy Dave Shields

In Vitro Carrier Comparison

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ASTM E 2197

Inoculum

Test Product

Courtesy Dave Shields

USP 40 <1072> 2”x2” Coupons?

- USP 40 <1072> does not provide specific guidance on recovery methods
- Established reference methods that specify recovery methods, utilize smaller coupons
- Using larger coupons can negatively impact some recovery methods
- The volume of inoculum and test product used in prescriptive reference methods obviates the need for larger coupons

USP 40 <1072> 2”x2”

- Necessary?

Courtesy Dave Shields

Key Considerations for *In Vitro* Testing

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- Use-dilution / expiration
- Temperature (hot WFI drops, use in cold room?)
- Substrates
- Technique
  - Suspension v. carrier
  - Neutralization/dilution
  - Subculture techniques
- Microorganisms
- Efficacy requirements

Substrates for Carrier Testing

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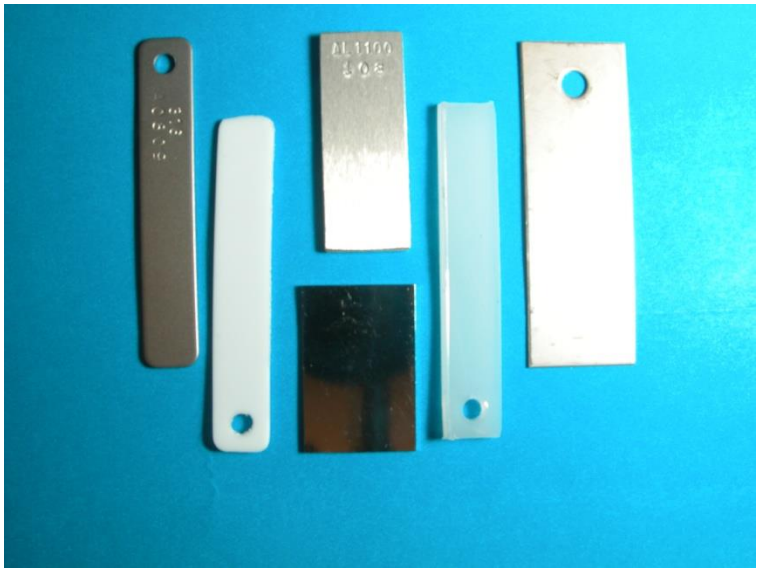
- Traditional methods (AOAC and ASTM)
  - Stainless steel disks, penicylinders or coupons
  - Watch glasses or glass slides
  - Porcelain penicylinders and silk suture loops
- Cleanroom disinfectant qualifications – representative materials
  - Stainless steel (416, 316, 316L, 306, 304)
  - Various plastics and elastomers
  - Lexan curtains
  - Kydex (thermoplastic alloy used for ceilings and walls)
  - Bodycote aluminum wall
  - Epoxy-coated flooring
  - Polymeric flooring
  - MMA Flooring
  - Vinyl Flooring
  - Terrazo Flooring
  - Acyrlic and Grout
  - Saniflex
  - Paints & Sealants
  - Gaskets (EPDM, Teflon)
  - Rubber or Nitrile gloves



Courtesy Dan Klein

Suspension Testing

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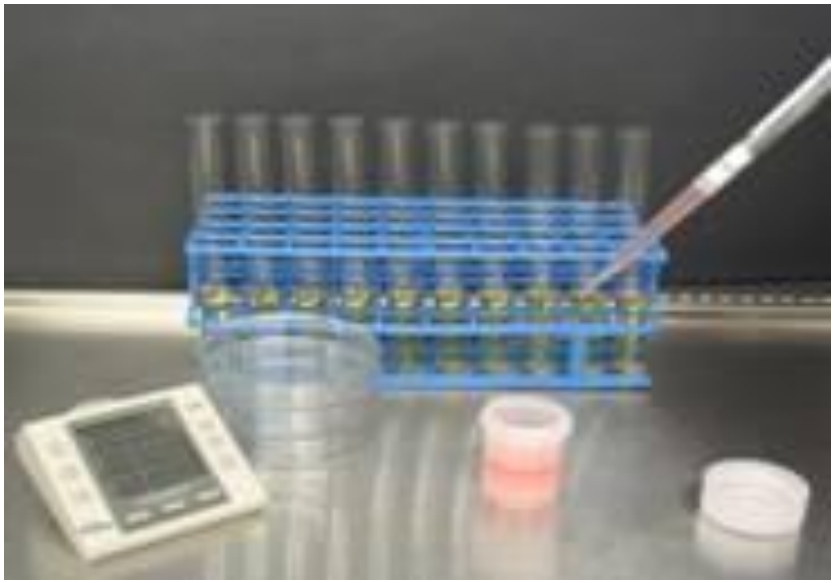
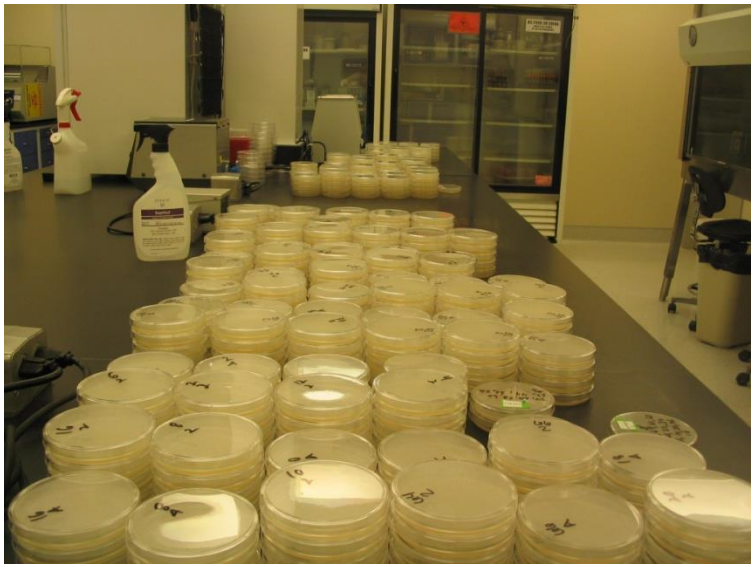
- Often called “Time Kill” study
- Estimates the *in vitro* activity of the biocide
- Often used for preliminary evaluation of several different biocides
- Not required, but useful screening tool





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Carrier Testing

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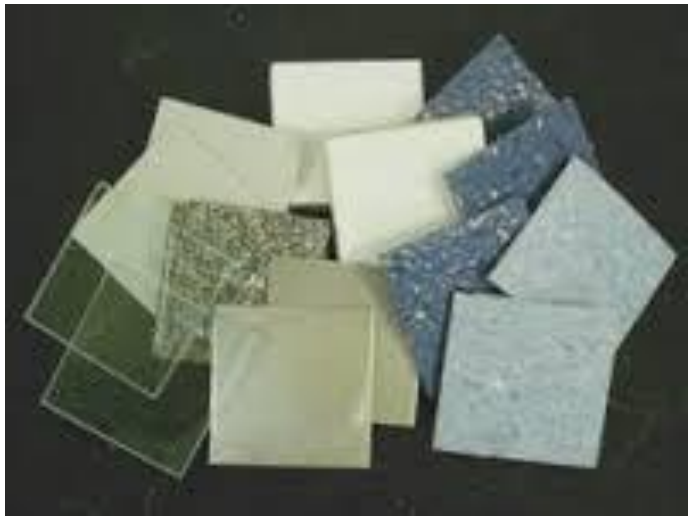
- Simulates practical conditions of disinfectant use and application
- Test organisms are dried on coupons made of varied substrates
- End-user required to perform carrier tests to qualify disinfectants



Courtesy Dan Klein

Neutralization Methods

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- Elimination of inhibitory residual disinfectant activity
  - Chemical neutralization of the active
  - Dilution - generally not effective alone (ex. alcohols)
  - Filtration + Rinsing – separating the active from the organism
- Issues
  - Antimicrobial activity of neutralizer (toxicity)
    - Thioglycollate, thiosulfate, and sodium sulfite can be toxic
  - If ineffective, contact time is inaccurate
- Validation of neutralization is required

Common Chemical Neutralizers

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Neutralizer	Biocide Class
Bisulfate	Gluteraldehyde
Catalase	Hydrogen Peroxide
Glycine	Aldehydes
Lecithin	Quats, Phenolics, Bis-biguanides
Letheen	Quats
Mg+2 or Ca+2 ions	EDTA
Polysorbate (Tween)	Quats, Phenolics, Iodine
Sodium Thiosulfate	Sodium Hypochlorite, Iodine

PDA TR No. 70 Neutralizers

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Table 5.2.1-1

Antimicrobial Chemical Agent	Neutralizing Agent
Alcohols	Dilution or Polysorbate 80
Sodium Hypochlorite	Sodium Thiosulfate
Quaternary Ammonium Compounds	Polysorbate 80 and Lecithin
Phenolic Compounds	Dilution or Polysorbate 80 and Lecithin
Hydrogen Peroxide/Peracetic Acid and Hydrogen Peroxide	Catalase

Neutralizing Broths

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Ingredient	AOAC	DEB	LET	NIH	TAT	TPL
Beef extract	5.0		5.0			
Casitone				15.0		
Cystine				0.5		
Dextrose		10.0		5.5		2.5
Lecithin		7.0	0.7		5.0	0.7
Peptamin	10.0		10.0			
Polysorbate 20					43.2	
Polysorbate 80		5.0	5.0			15.0
Sodium bisulfite		2.5				
Sodium chloride	5.0		5.0	2.5		
Sodium thioglycollate		1.0		0.5		
Sodium thiosulfate		6.0				
Soytone						3.0
Tryptone		5.0			20.0	17.0
Yeast extract		2.5		5.0		

Sutton, SW et al. 2002. Validation of Microbial Recovery From Disinfectants. PDA J Pharma. Sci. Technol. 56(5):255-266.

Microorganism Selection

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- Environmental isolates **must** be considered
  - Broad spectrum
  - Most frequently occurring
  - High levels in the environment
  - Demonstrated decontamination difficulty at the facility
  - “Worst Case”
- USP (ATCC or USDA) challenge organisms may also be considered but environmental isolates are the most critical

Microorganism Selection

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	Microorganism	Examples
More Resistant	Prions	Scrapie, Creutzfeld-Jacob disease, Chronic wasting disease
	Bacterial Spores	*Bacillus, Geobacillus, Clostridium*
	Protozoal Oocysts	*Cryptosporidium*
	Helminth Eggs	*Ascaris, Enterobius*
	Mycobacteria	*Mycobacterium tuberculosis, M. terrae, M. chelonae*
	Small, Non-Enveloped Viruses	Poliovirus, Parvoviruses, Papilloma viruses
	Protozoal Cysts	*Giardia, Acanthamoeba*
	Fungal Spores	*Aspergillus, Penicillium*
	Gram negative bacteria	*Pseudomonas, Providencia, Escherichia*
	Vegetative Fungi and Algae	*Aspergillus, Trichophyton, Candida, Chlamydomonas*
	Vegetative Helminths and Protozoa	*Ascaris, Cryptosporidium, Giardia*
	Large, non-enveloped viruses	Adenoviruses, Rotaviruses
	Gram positive bacteria	*Staphylococcus, Streptococcus, Enterococcus*
Less Resistant	Enveloped viruses	HIV, Hepatitis B virus, Herpes Simplex virus

Bacillus cereus / sphaericus

Bacillus subtilis / G. stearothermophilus

***Clostridium* spp.**

From McDonnell, "Antisepsis, Disinfection, and Sterilization: Types, Action, and Resistance" 2007, ASM Press

General Efficacy Recommendations

- Suspension acceptance criteria
  - 4-5 log reduction

- Carrier acceptance criteria USP 40 <1072>
  - 2 log reduction bacterial spores
  - 3 log reduction vegetative bacteria
    - Fungal spores do not have a defined log reduction

  - PDA TR No. 70
    - 1-5min disinfectant and sporicide >1 log reduction
    - 90sec sanitizer >1 log reduction

PDA TR No. 70 Table 5.2.2-1

Antimicrobial Chemical Agent	Organism Type	Suggested Contact Time	Suggested Minimum Reduction
Sanitizer	Non-spore formers	max. 90 sec	>1 Log
Disinfectant/Sporicide	Non-spore formers	1 - 5 min	>1 Log
Disinfectant/Sporicide	Mycoplasma	1 - 5 min	>1 Log
Sporicide	Mold Spores	1 - 5 min	>1 Log
Sporicide	Bacterial Spores	1 - 5 min	>1 Log

In Situ Testing

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- "…a statistical comparison of the frequency of isolation and the numbers of microorganisms isolated prior to and after the implementation of a new disinfectant." USP 40 General Informational Chapter <1072>

- "The effectiveness of these sanitization procedures should be measured by their ability to ensure that potential contaminants are adequately removed from surfaces (i.e., via obtaining samples before and after sanitization)." Sterile Drug Products Produced by Aseptic Processing – September, 2004 FDA

In Situ Protocols

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- Use actual cleaning procedure SOPs (update prior to study)
- “Worst case” conditions
- Compare environmental data before and after procedures
  - Should include data from more than one cleaning event
- Preparation and storage of disinfectants
  - Dilution accuracy is critical
    - SOP development before validation
  - Monitor and control storage of dilution
    - Expiry dating
  - Filter to remove microorganisms if necessary (ISO Class 5)
    - Filter validation (Compatibility and Bubble Point Testing)

In Situ Testing Frequency

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- New Cleanroom
- At Shut Down
- After Construction
- After a Power Failure
- After a Big Contamination Event
- After a Worst Case Event (Natural Disaster)

Part 3: Environmental Monitoring & Data Trending (recalculate monthly)

Environmental Monitoring Guidance

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- EU Annex 1 (2008) and MHRA Orange Guide (2015)
- ISO-14644 parts 1-12
- FDA Aseptic Processing Guide (2004)
- PDA TR No. 13 (2014)
- USP 40 <1116> (for Grades A, B,C,D)
- USP 40 <1115> (for Non-Sterile manufacturing)
- USP 40 <797> and USP 40 <800>

Case Study: Construction Event

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- Worst Case Events
- 9X Clean [1X Sporicide + 2X Phenolic repeated on days 1,2,3]
- Fogging
- VHP®
- Triple Clean
  - Defined 3X Disinfectants and Sporicide (Different Definitions)
  - EM frequency (Static and Dynamic)
  - Release of the room

Cleaning and Disinfection Efficacy - *In situ* study

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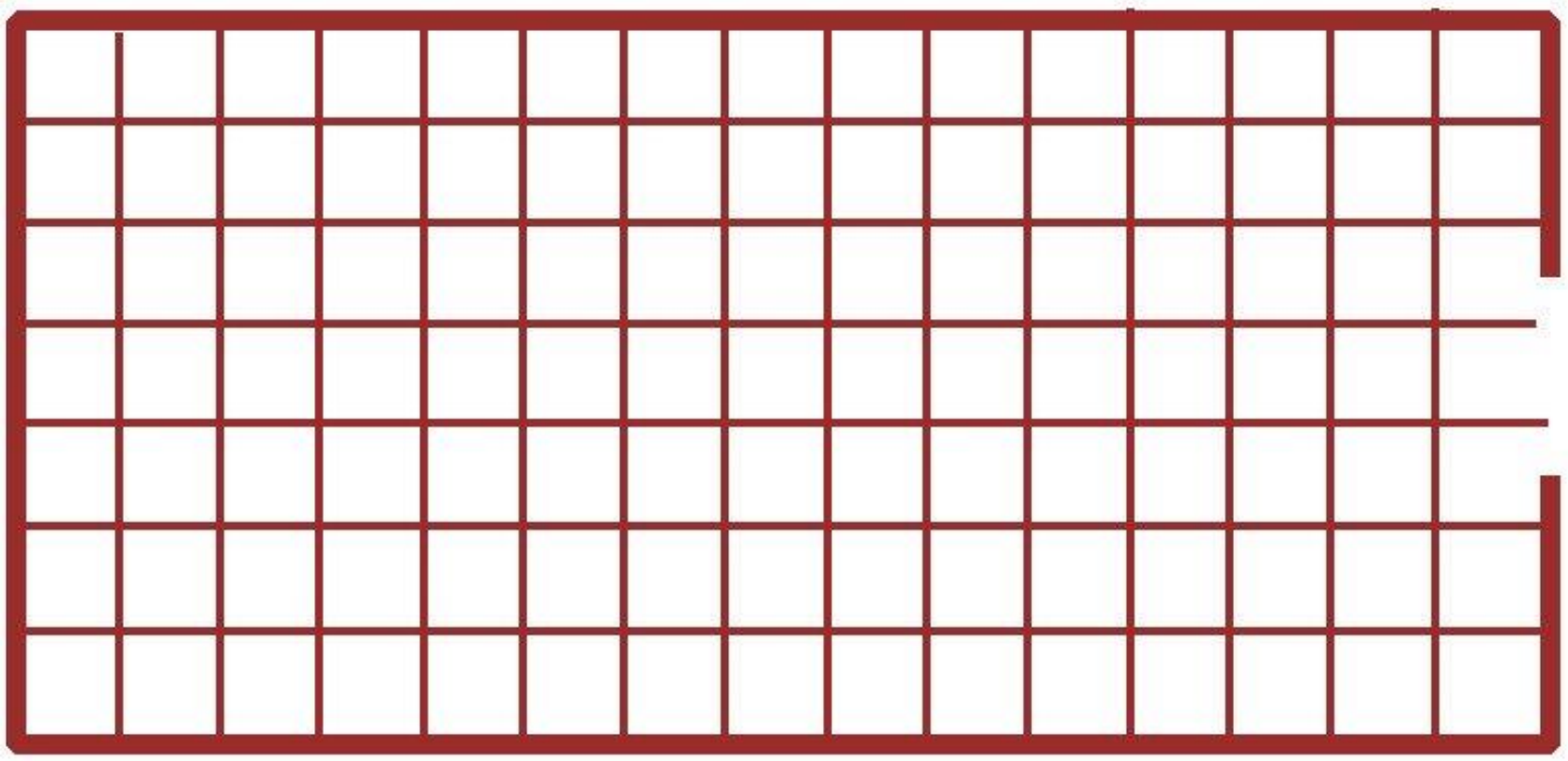

Time 0

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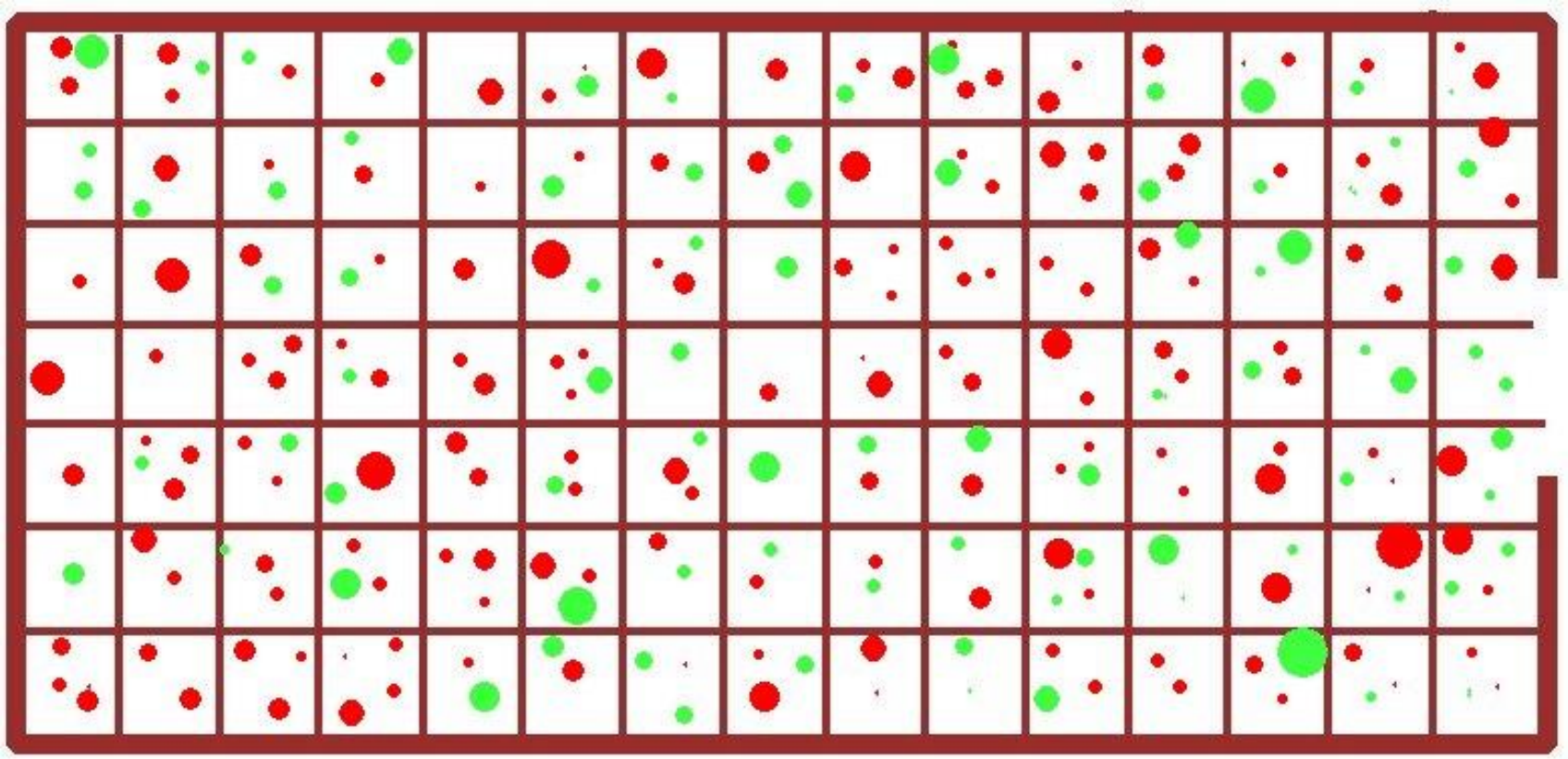
Red = Spore formers Green = Other



After 1X Cleaning - No Sporicide

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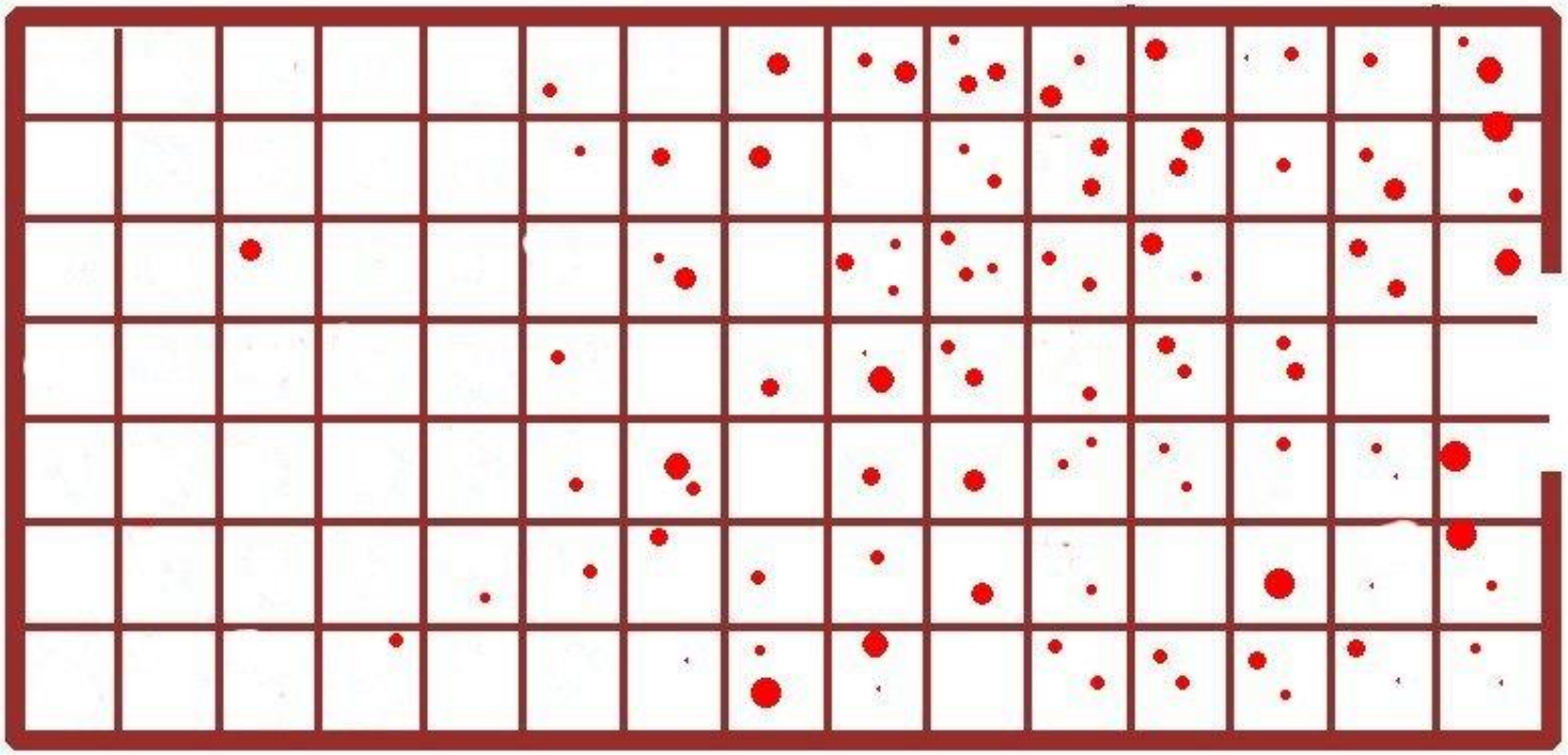
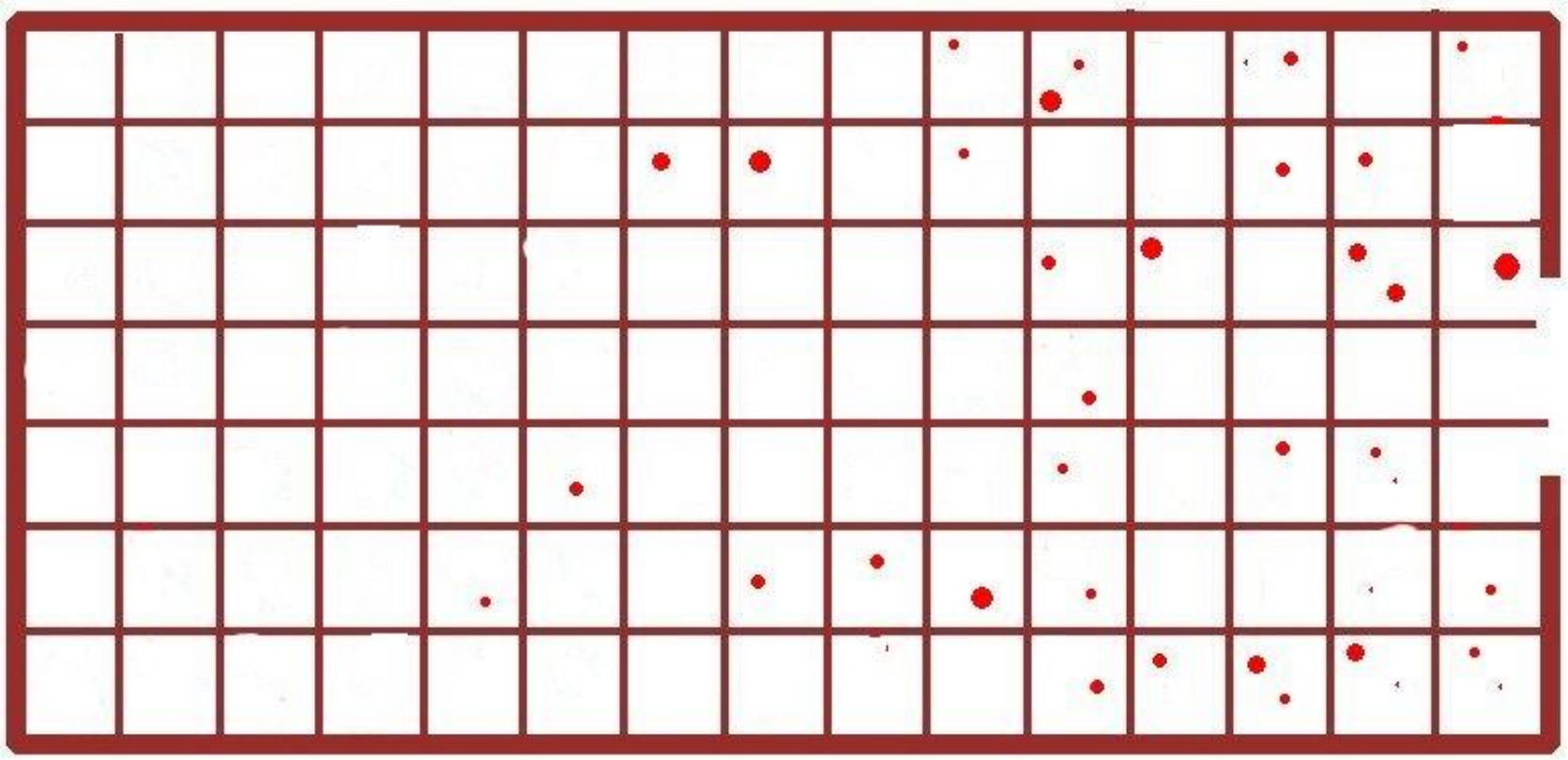
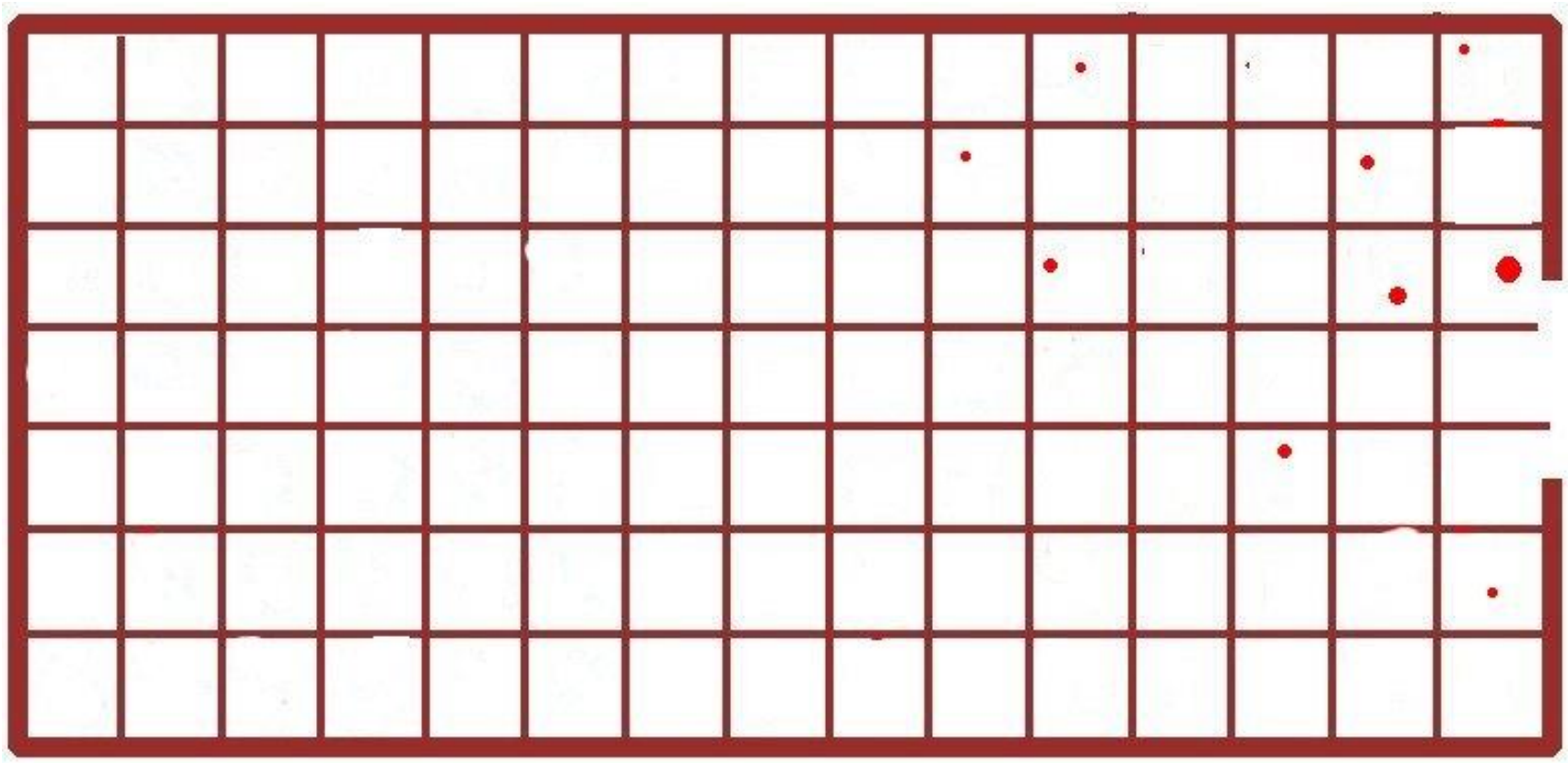


After 2X Cleaning – No Sporicide



After 3X Cleaning - No Sporicide



After Sporicide

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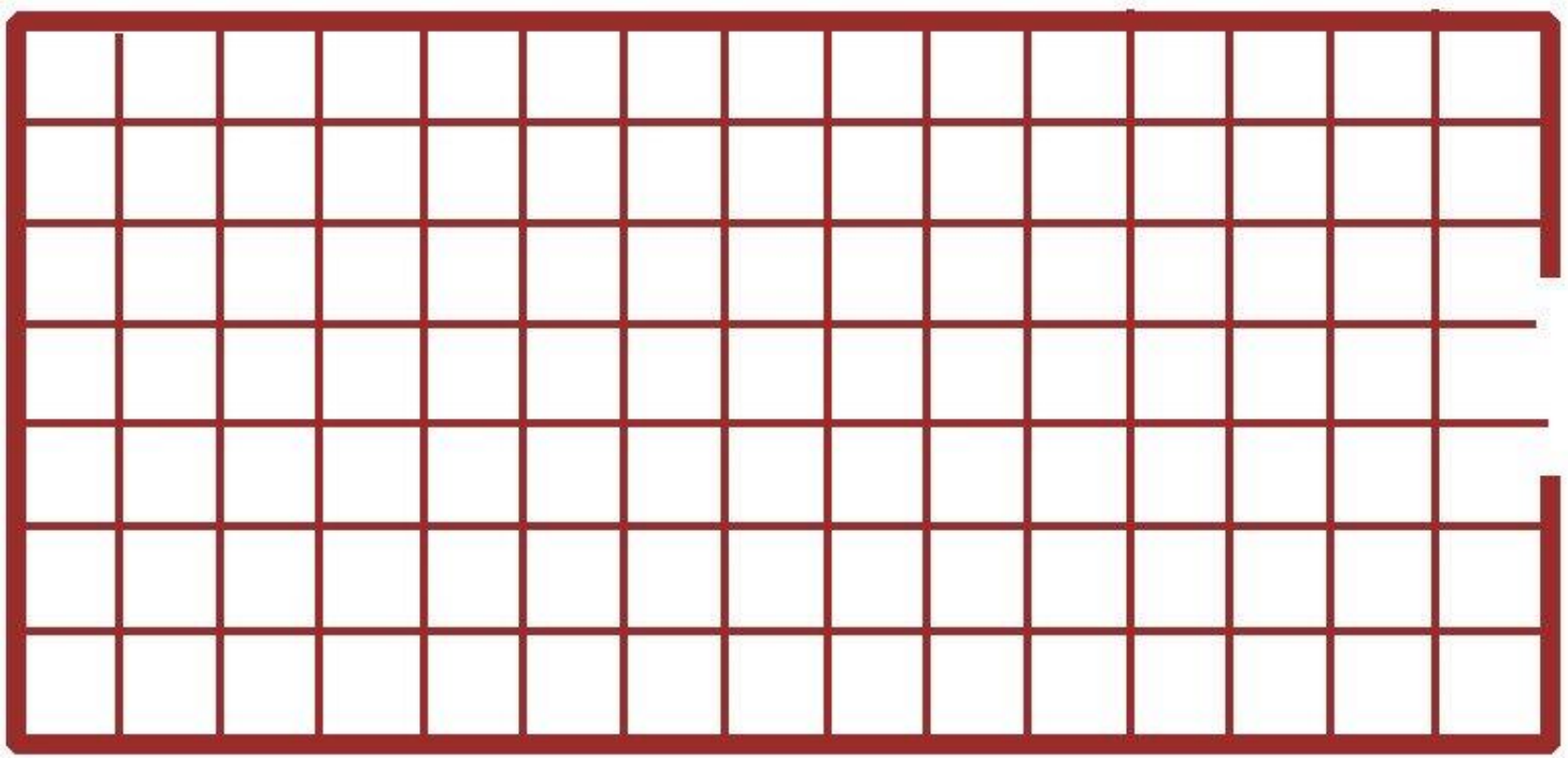


Most Common Causes for Failures in Efficacy Testing

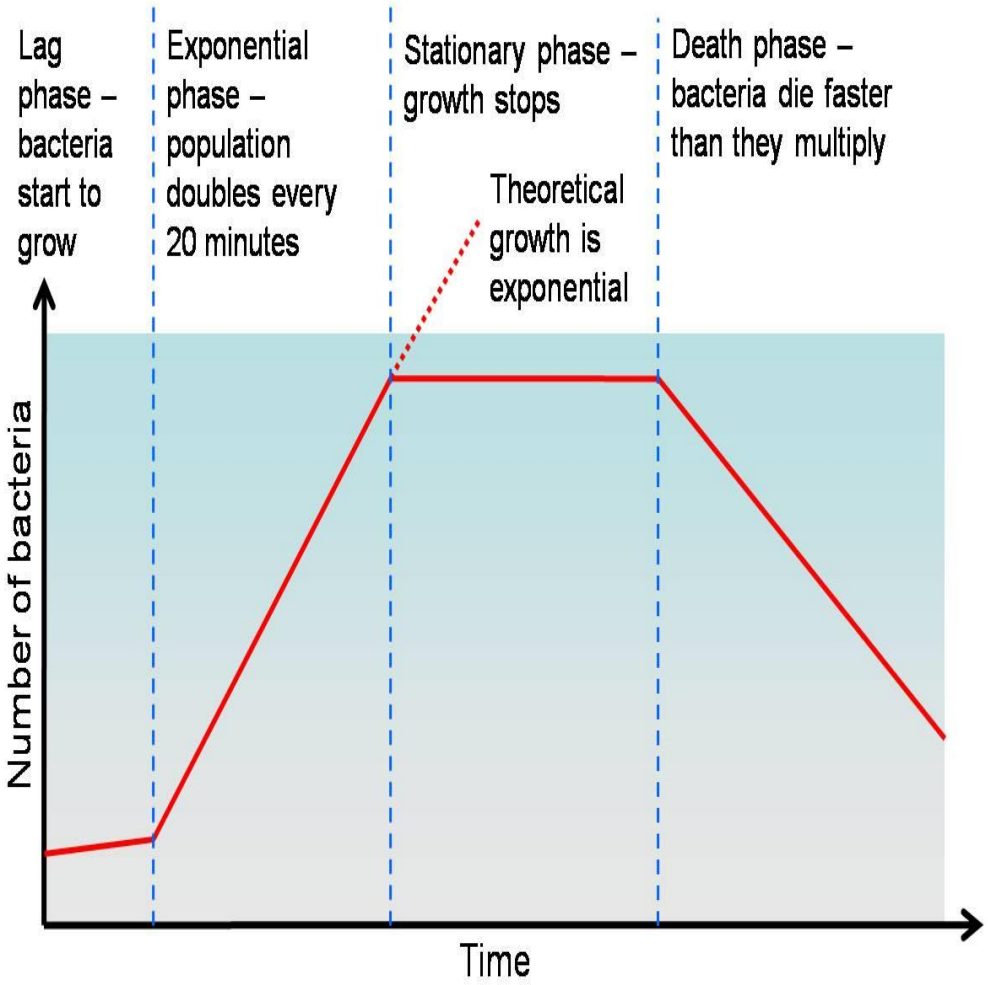
General	• Testing biocide against inappropriate microbes • Using inappropriate methods • Inadequate planning • Insufficient contact time
Neutralization	• Inadequate neutralization • Neutralizer toxicity
Inoculum	• Poor viability of inoculum suspensions • Fungal and bacterial spore suspensions prepared incorrectly
Surfaces	• Porous surfaces • Coupons not amenable to steam sterilization • Uneven inoculation or product coverage due to curvature or surface tension
Recovery	• Lethality after drying (e.g. *P. aeruginosa)* • Setting artificially high log reduction targets • Final plates are not countable • Recovery method not validated

In Vitro Testing - Issues Contributing to Test Failures

- Recovery issues post-drying (*P. aeruginosa*)
- Inoculum prep (e.g. fungal spores)
- Coupon prep (autoclaving – peeling Saniflex)
- Improper dilution of Concentrate
- Inappropriate biocide for organism type
- Insufficient contact time – should match SOP / check vendor label
- US vs. EU requirements

Inoculum Preparation - Viability

- Prepare inoculum suspensions from 18-24 hr cultures
- Titer (cfu/mL) and viability must be verified at the end of every test day



Inoculum Preparation - Fungal Spores

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- Use fungal spore suspensions for testing
- Hyphae/mycelia can prevent disinfectant from contacting and penetrating spore

	Microorganism	Examples
More Resistant	Prions	Scrapie, Creutzfeld-Jacob disease, Chronic wasting disease
	Bacterial Spores	*Bacillus, Geobacillus, Clostridium*
	Protozoal Oocysts	*Cryptosporidium*
	Helminth Eggs	*Ascaris, Enterobius*
	Mycobacteria	*Mycobacterium tuberculosis, M. terrae, M. chelonae*
	Small, Non-Enveloped Viruses	Poliovirus, Parvoviruses, Papilloma viruses
	Protozoal Cysts	*Giardia, Acanthamoeba*
	Fungal Spores	*Aspergillus, Penicillium*
	Gram negative bacteria	*Pseudomonas, Providencia, Escherichia*
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	Vegetative Helminths and Protozoa	*Ascaris, Cryptosporidium, Giardia*
	Large, non-enveloped viruses	Adenoviruses, Rotaviruses
	Gram positive bacteria	*Staphylococcus, Streptococcus, Enterococcus*
Less Resistant	Enveloped viruses	HIV, Hepatitis B virus, Herpes Simplex virus

Inoculum Preparation Fungal Spores

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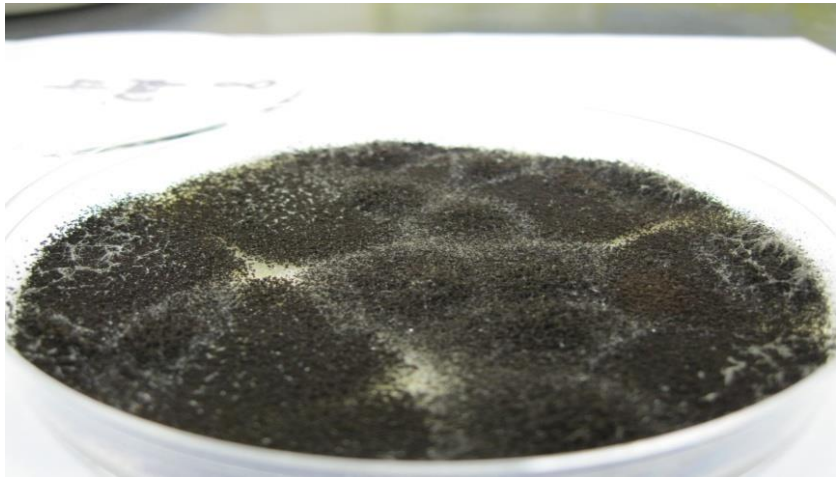
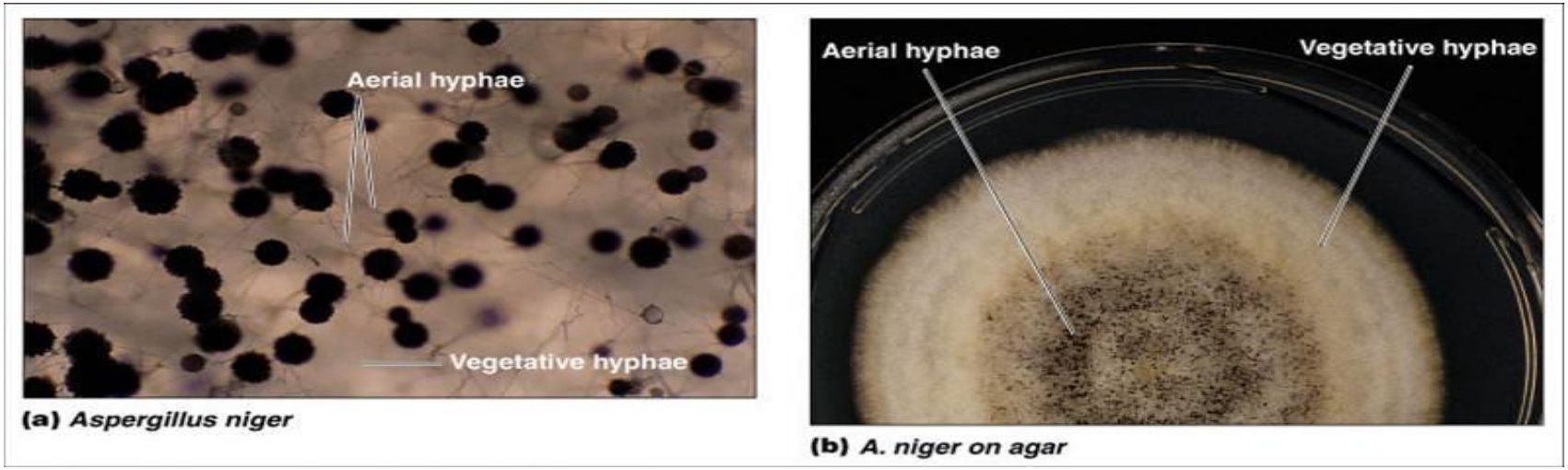
Cultures need to be incubated for a sufficient length of time before harvesting spores

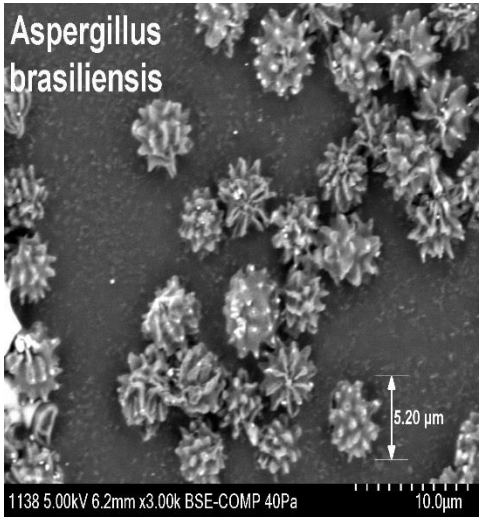


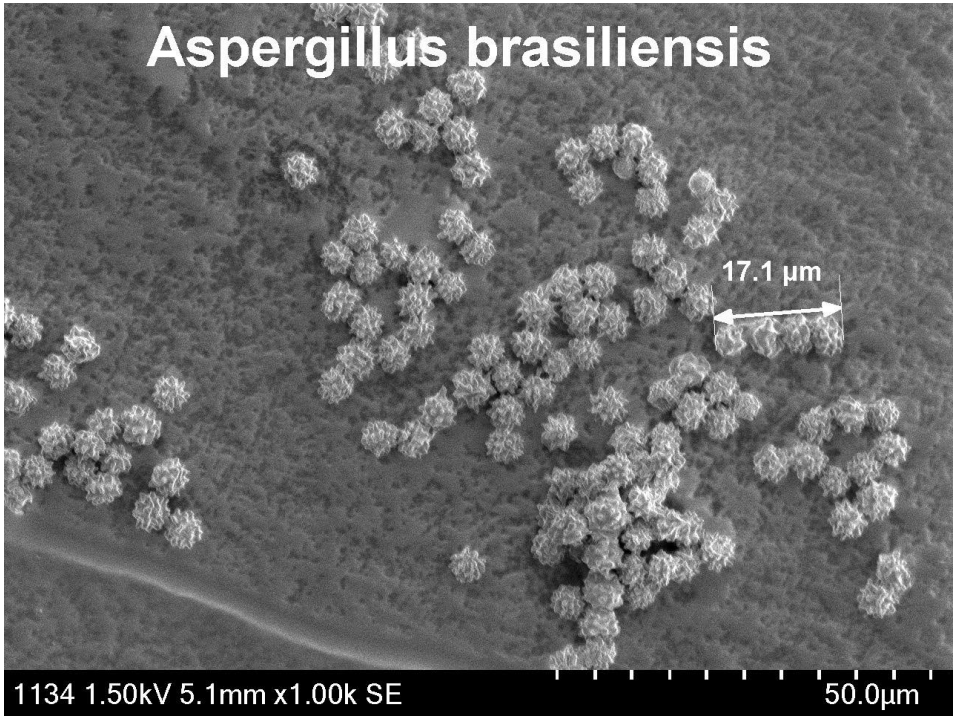


Courtesy Dan Klein

Aspergillus brasiliensis

Courtesy Bruce Ritts





Aspergillus Spores

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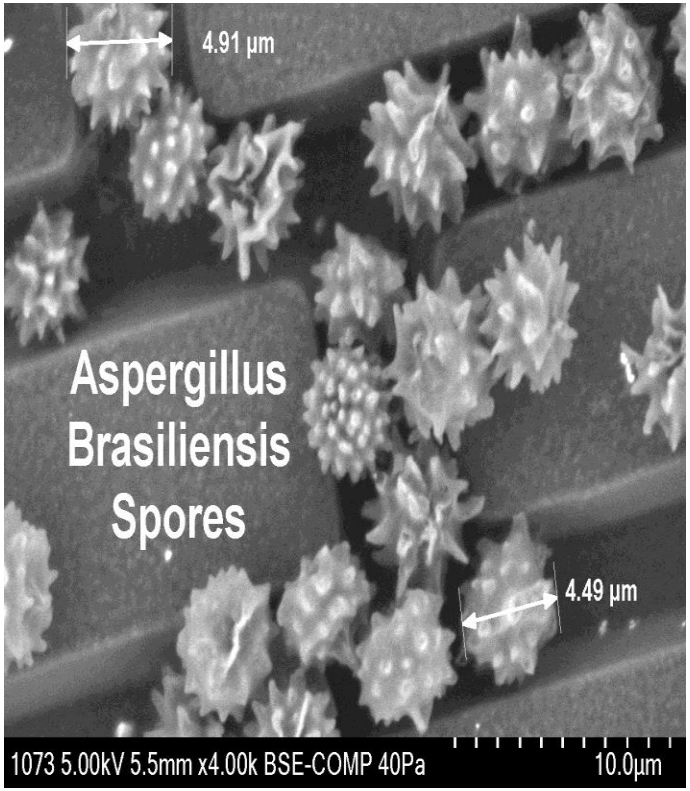
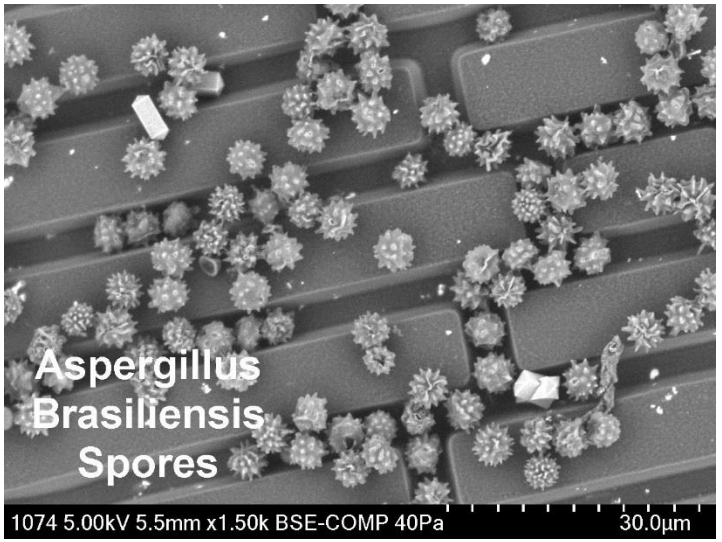
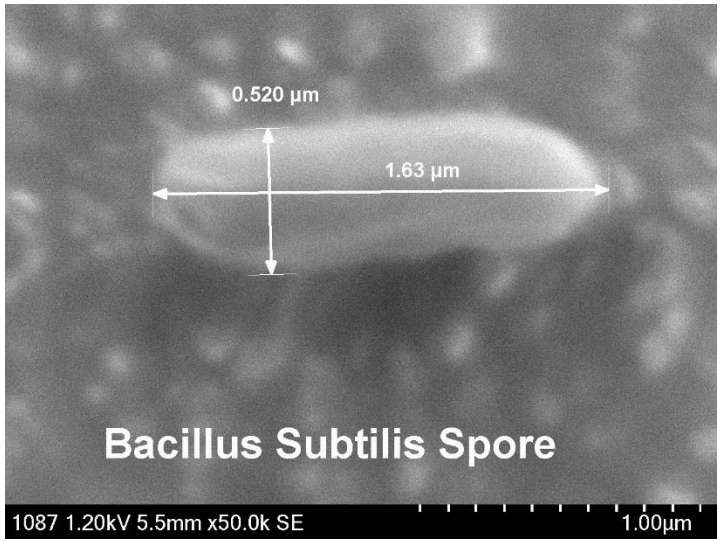


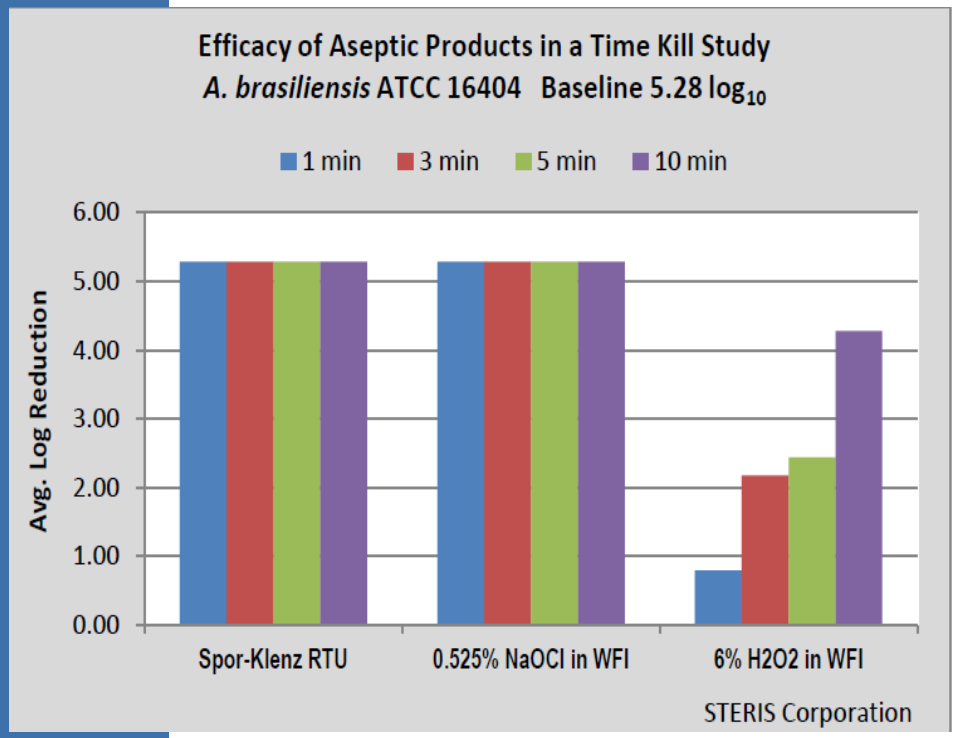


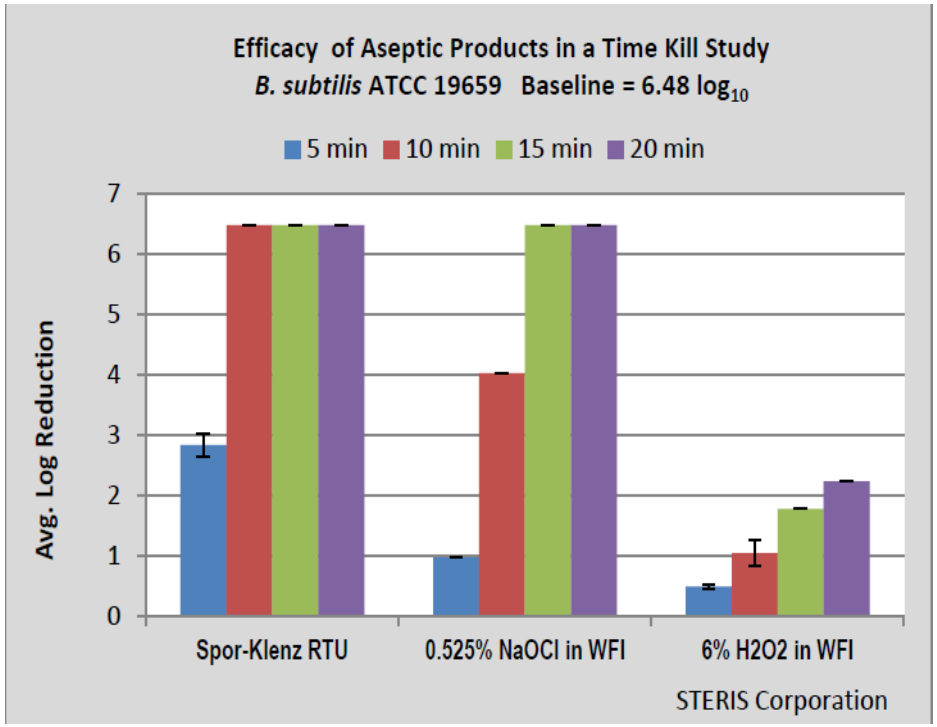
Bacterial Endospores



Courtesy Bruce Ritts

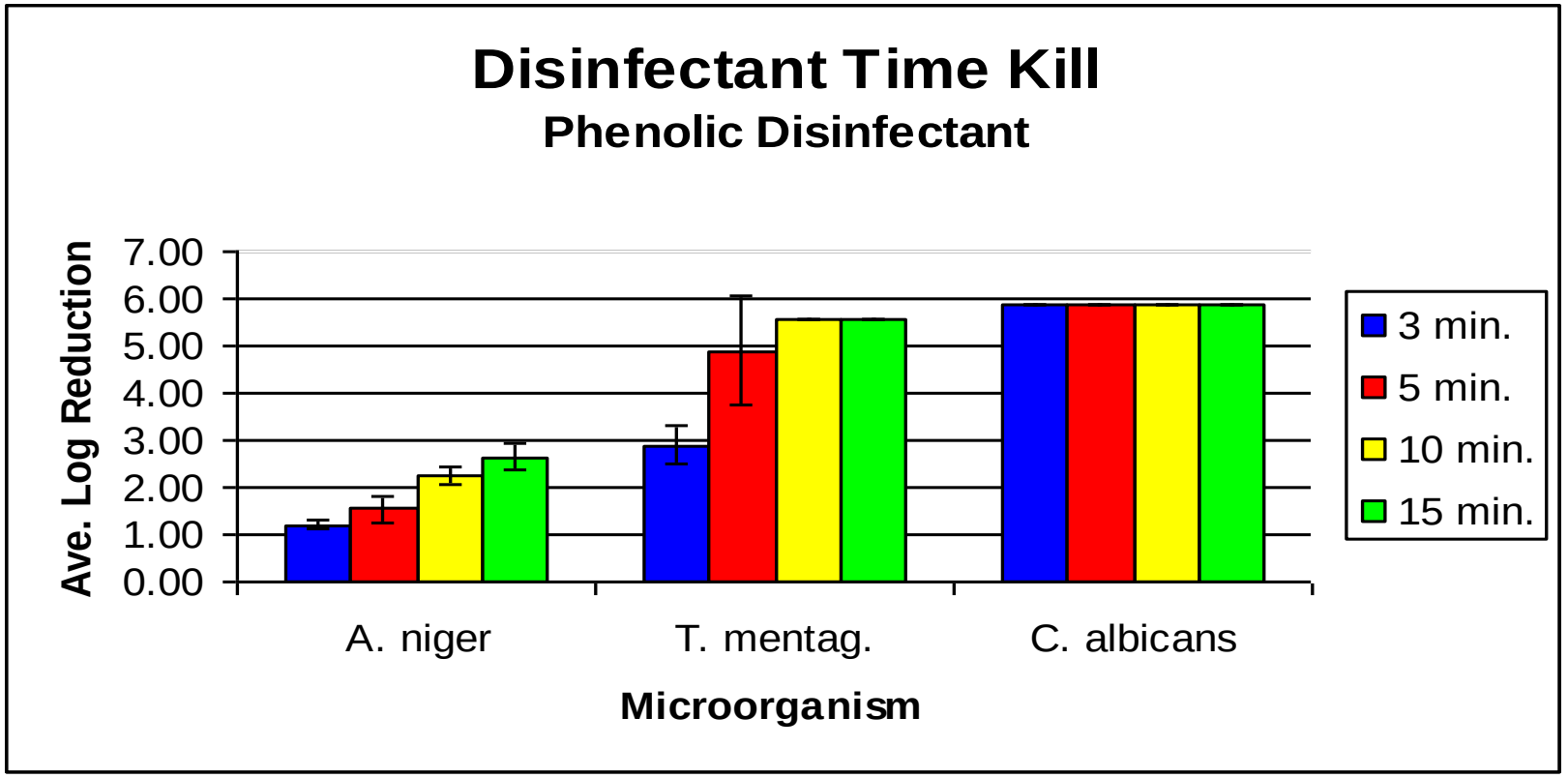
Efficacy of Sporicides





Testing Against Fungal Spores

- *Trichophyton mentagrophytes* is US EPA standard (easily killed)
- Cleanroom users test *Aspergillus brasiliensis* (typically the most difficult to kill mold)



Case Study on Substrates

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

Surface	*Staphylococcus epidermidis*	*Pseudomonas aeruginosa*	*Corynebacterium glutamicum*	*Candida albicans*	*Aspergillus brasiliensis*	*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]
Mipolam	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
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

Spore Testing

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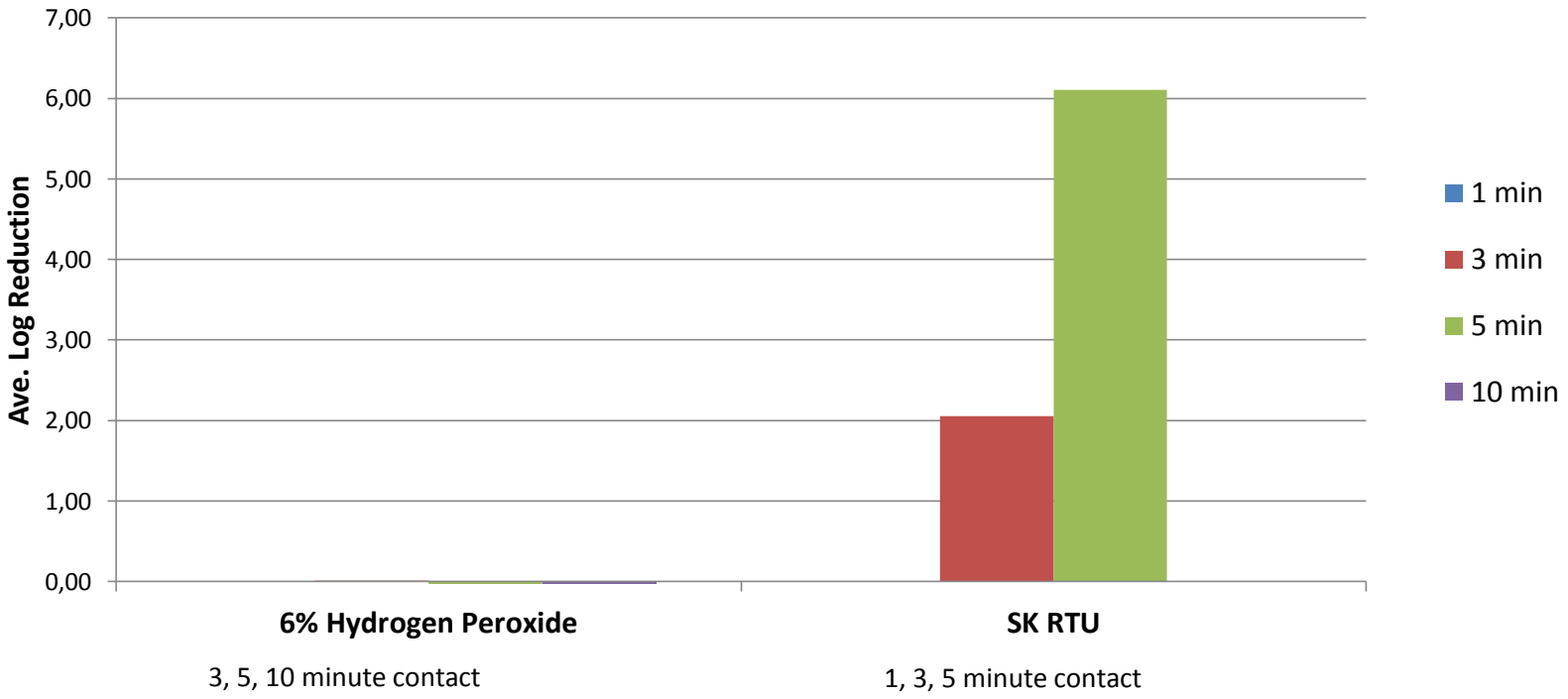
6% H_2O_2 vs. Spor-Klenz RTU
Standard Time Kill Study 13 Jun 2007
***B. subtilis* spores 19659 Baseline = 6.60 log_{10}**



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70% IPA Efficacy against Molds

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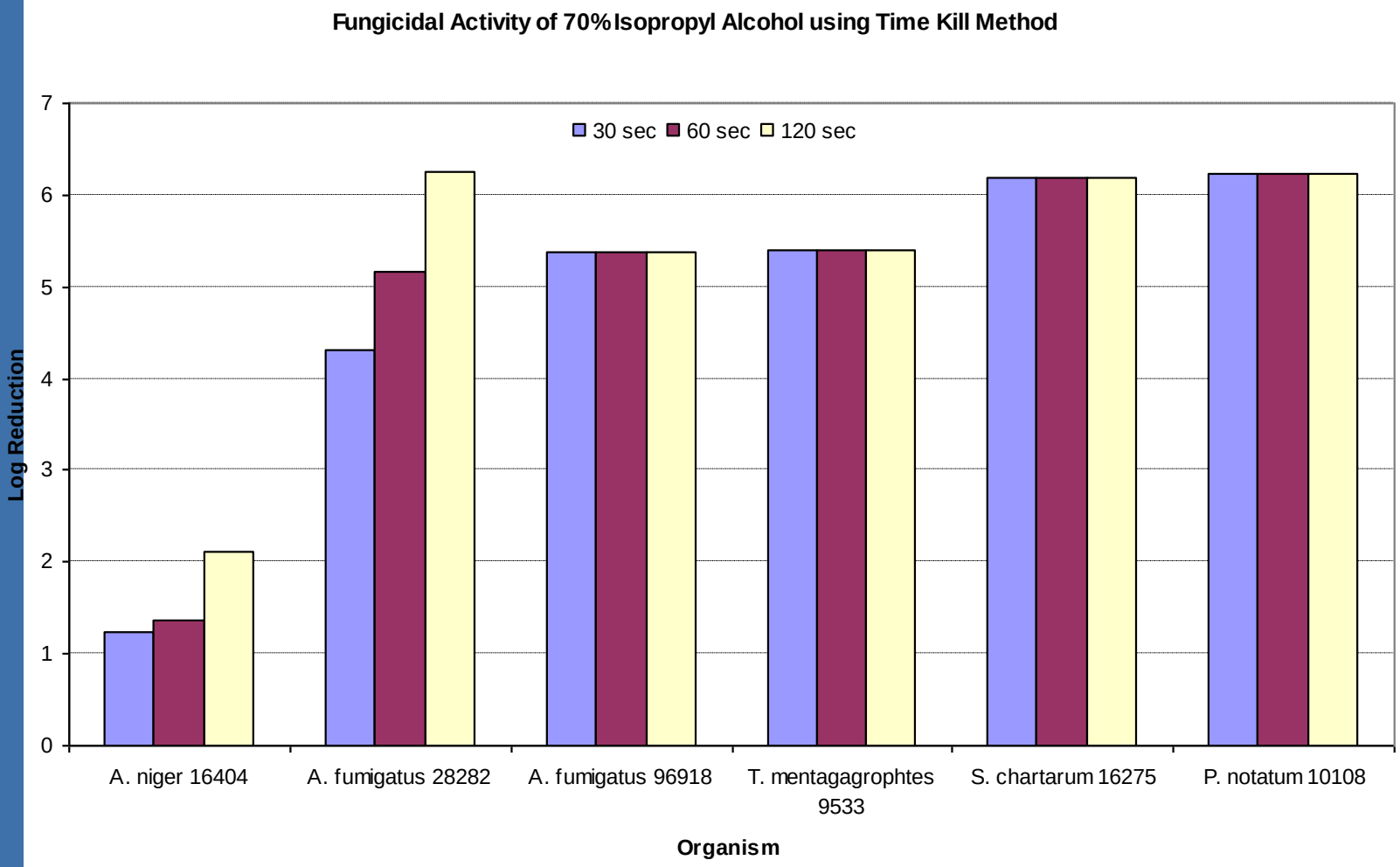

H2O2/PAA RTU against Molds

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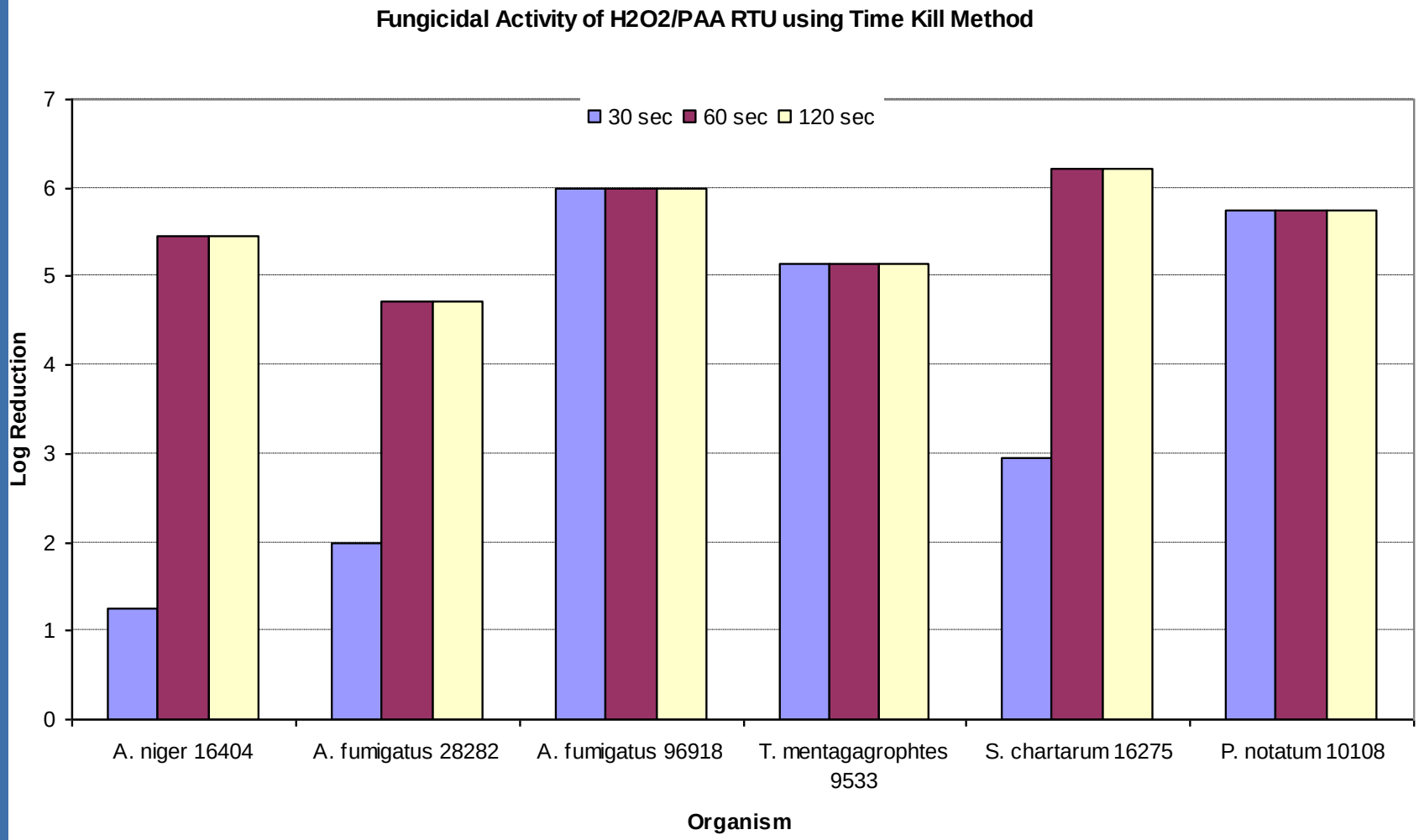
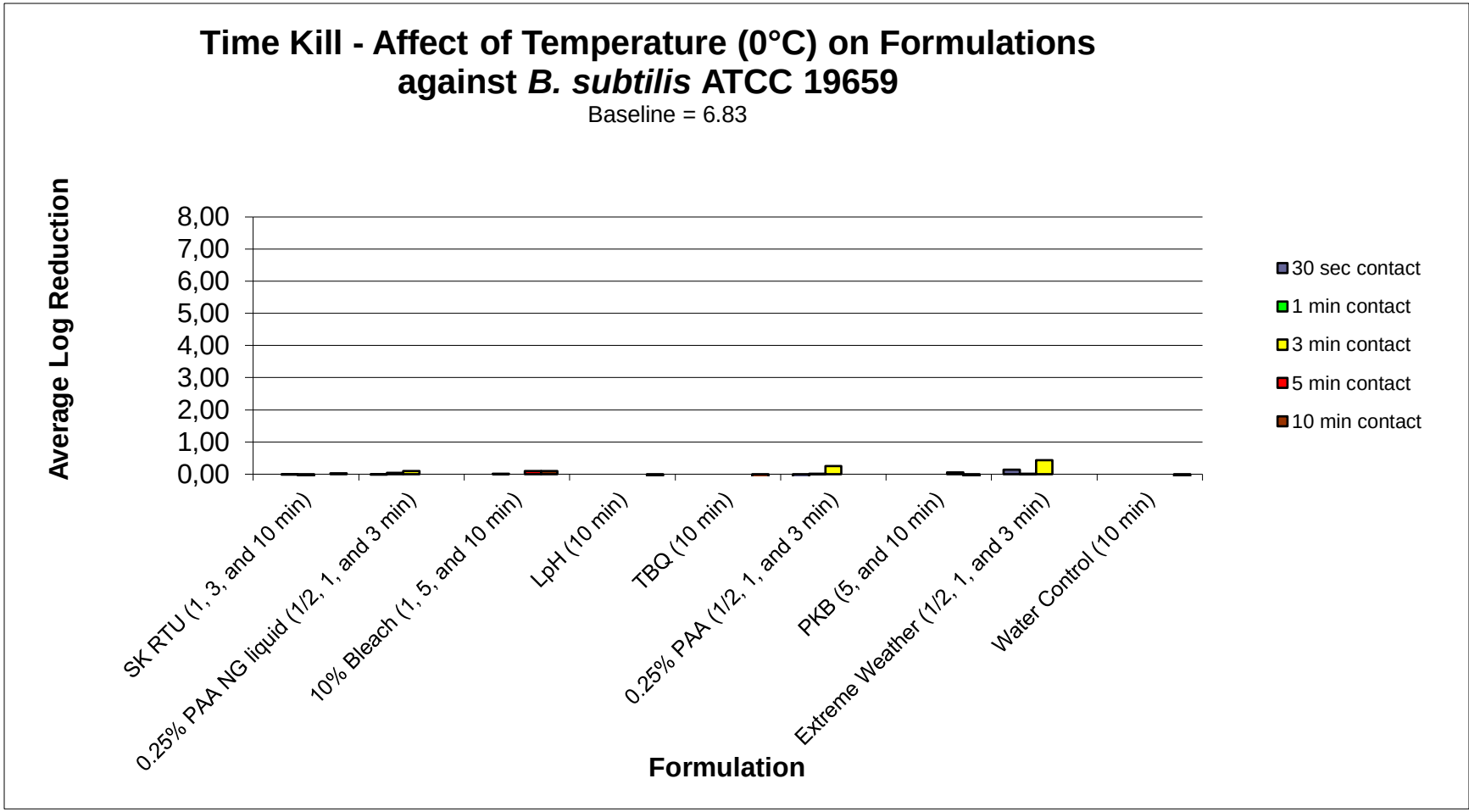
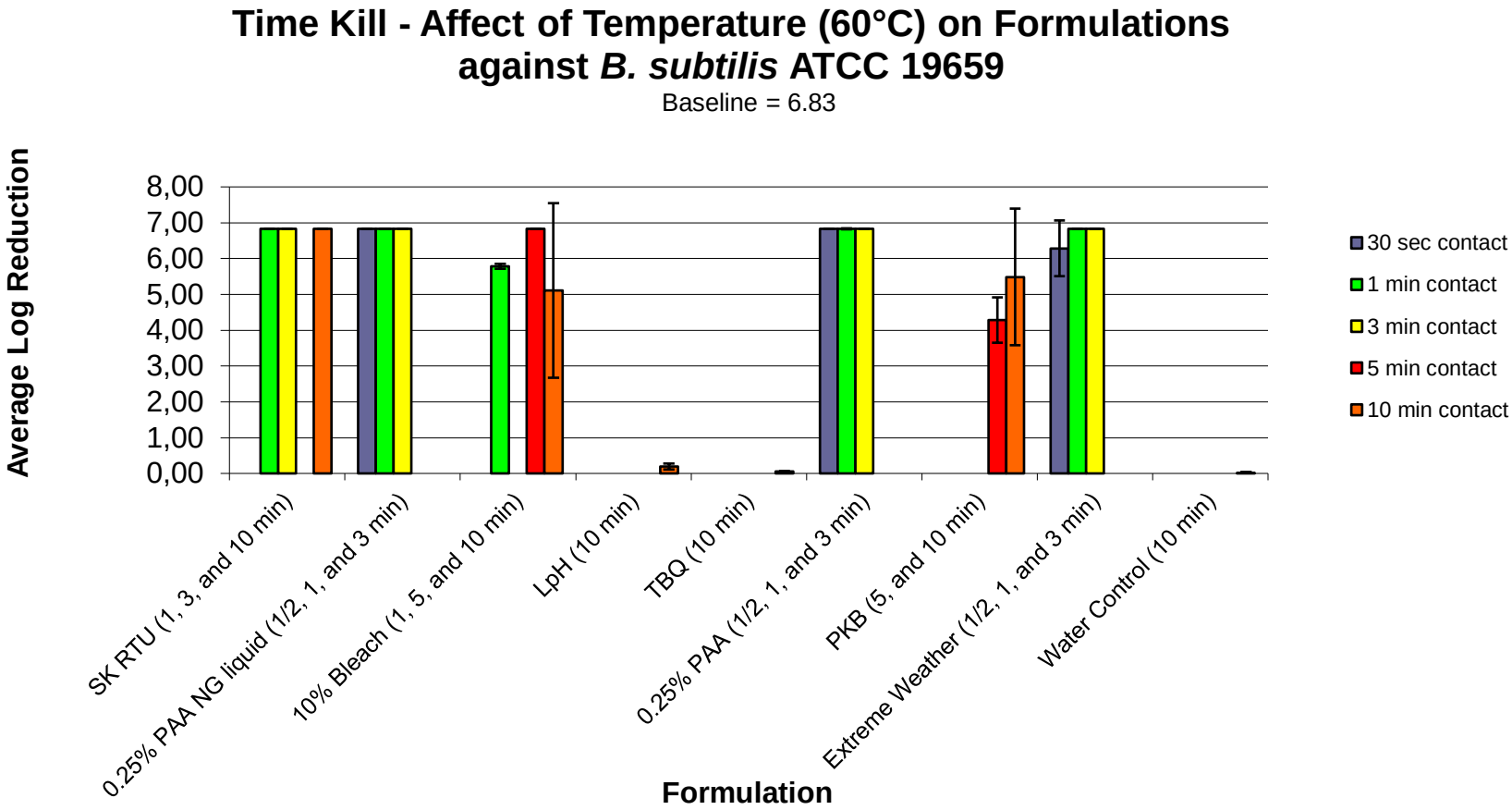


Temperature = 0°C



Temperature = 60°C



Surface/Coupon Issues

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- Surface type and condition can have a huge impact on efficacy
- Preparation of surfaces prior to testing
  - Autoclaving may not be acceptable for some surfaces
  - Residues must be removed
- Some surfaces pose a challenge during qualification studies:
  - Peeling after sterilization
  - Surface tension

Surface Preparation

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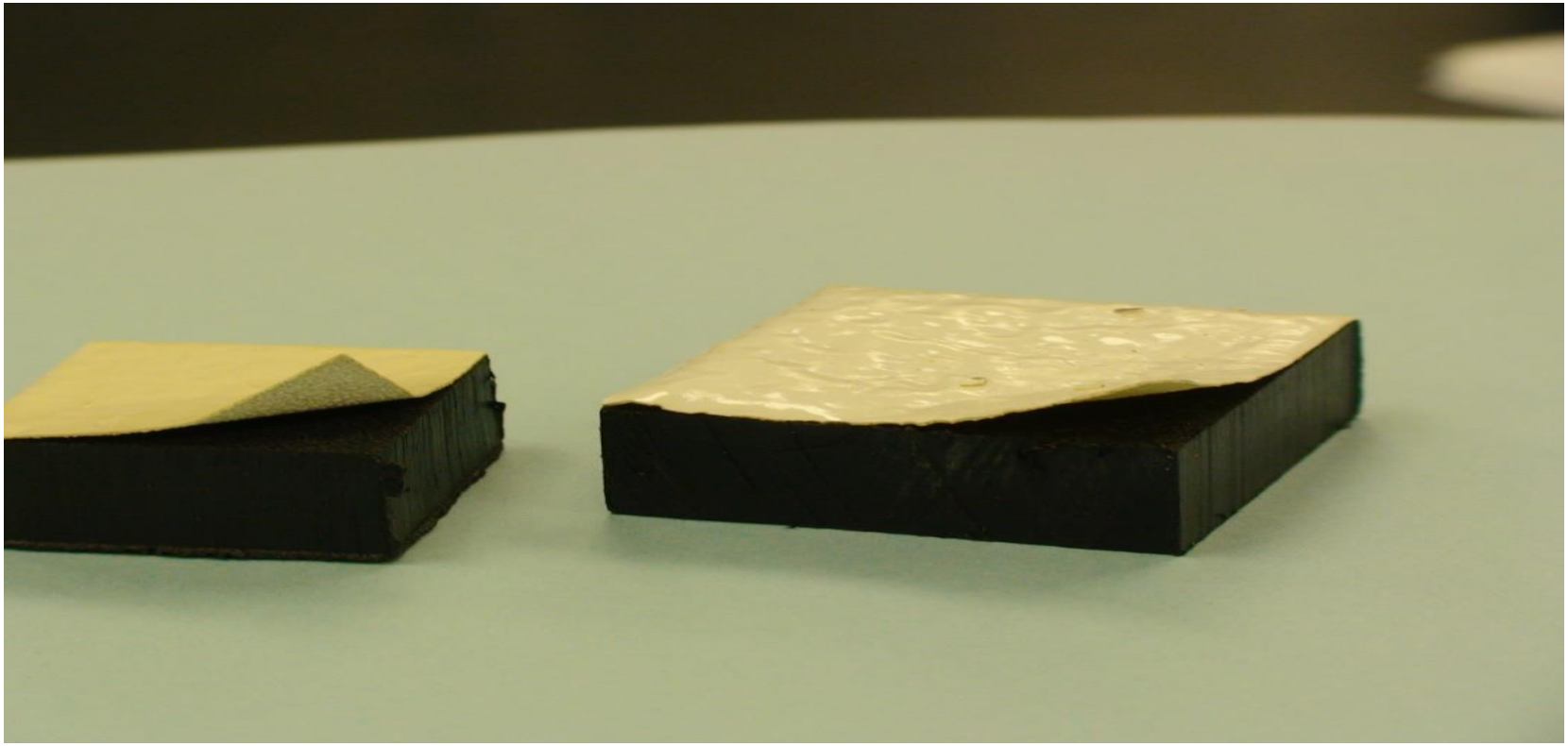
Autoclaving may not be acceptable for some surfaces (Saniflex)



Courtesy Dan Klein

Surface Tension Issue

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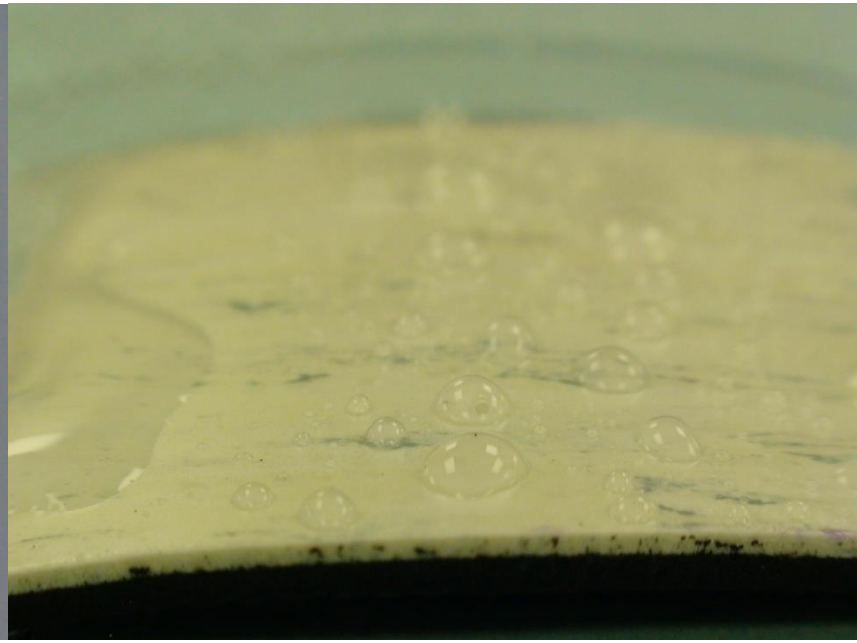

Courtesy Dan Klein

Coupon Issues

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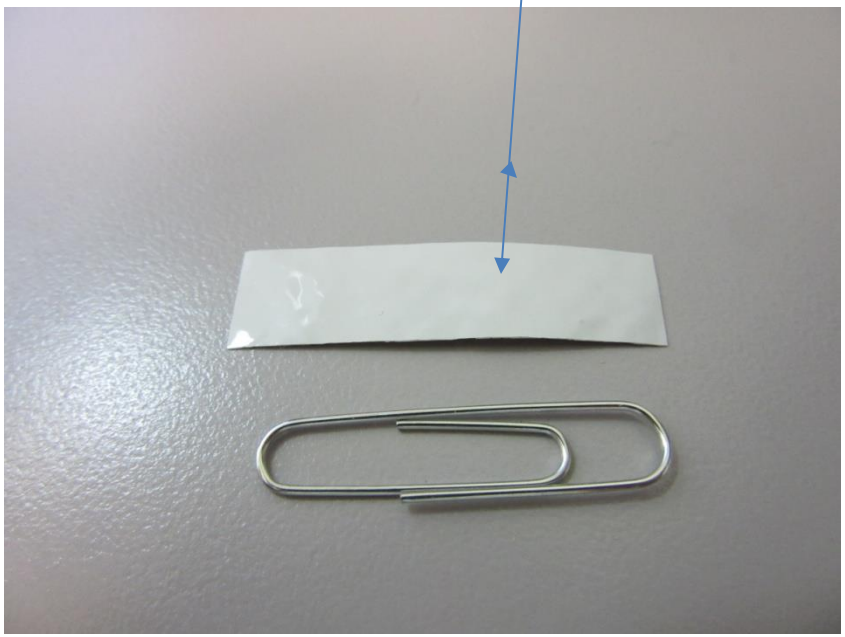
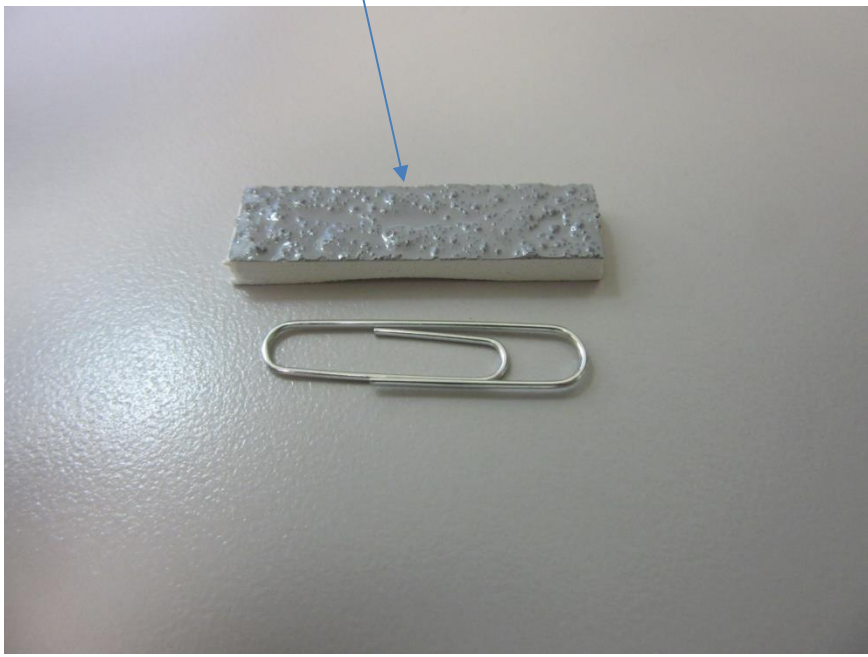
Painted Surfaces

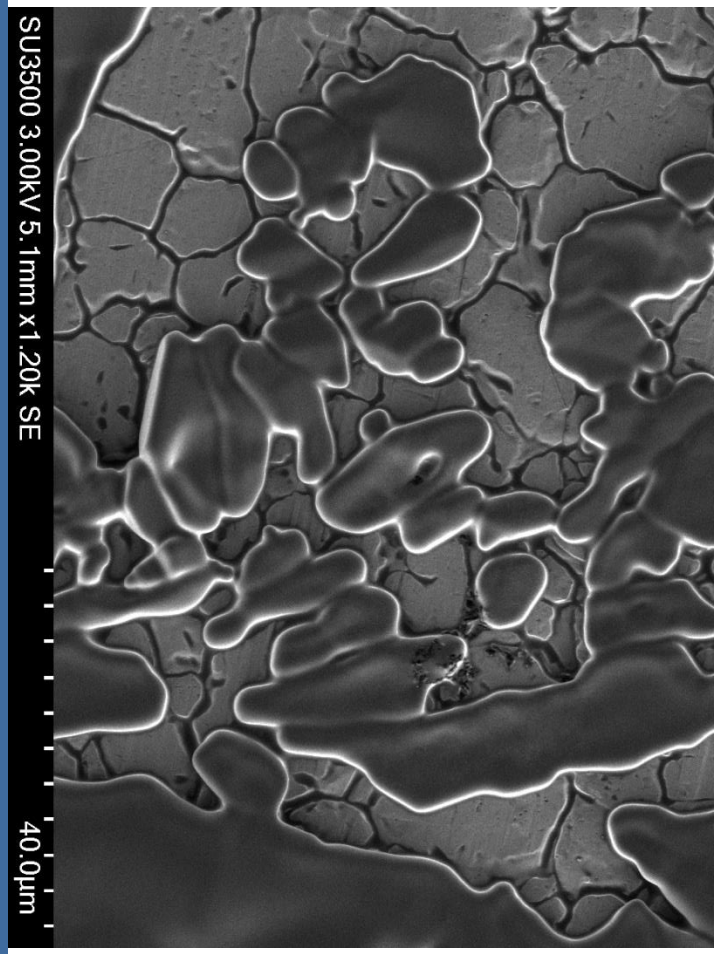
Courtesy Dan Klein

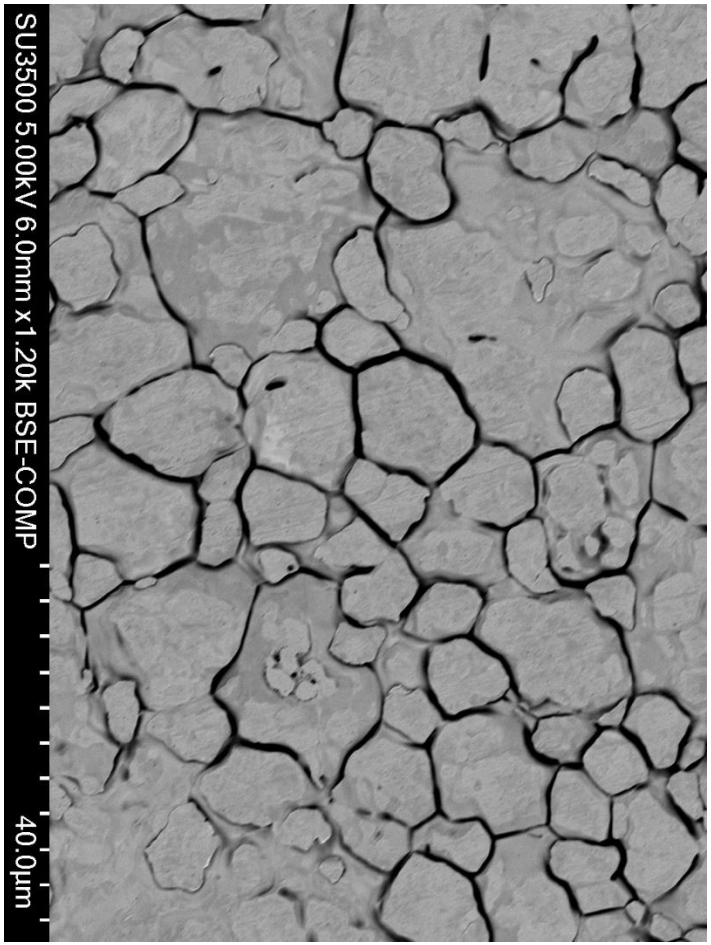


Surface Roughness



Surface Conditions Effect Performance

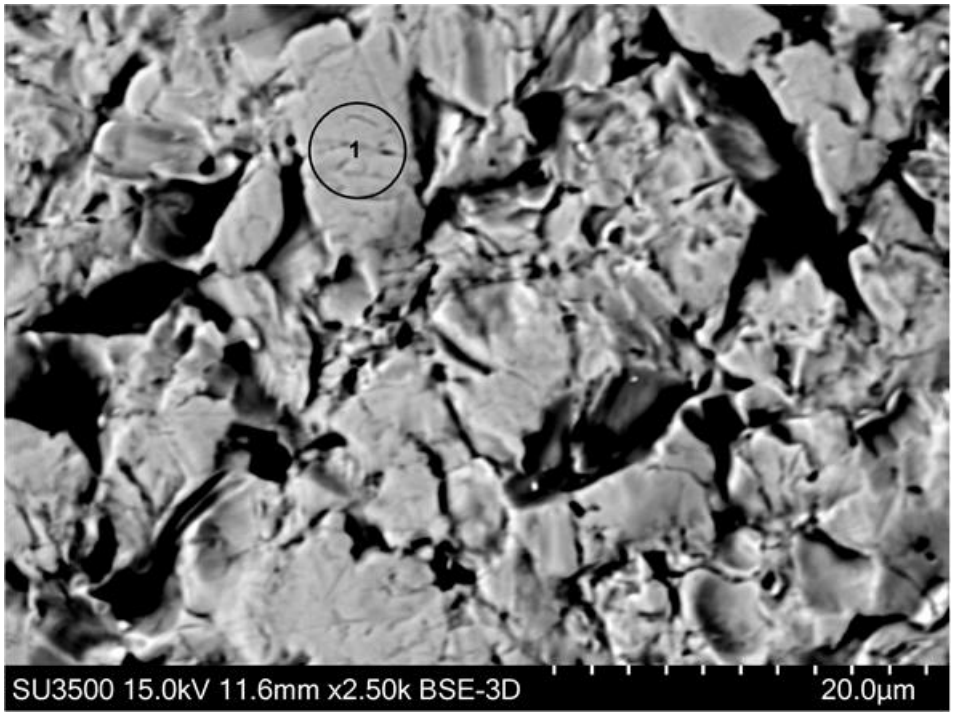




Courtesy Bruce Ritts

Surface Type and Condition

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



Courtesy Bruce Ritts

Surface Type and Condition

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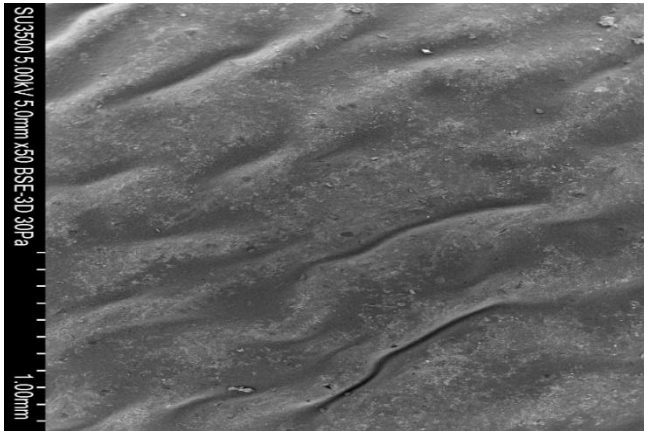

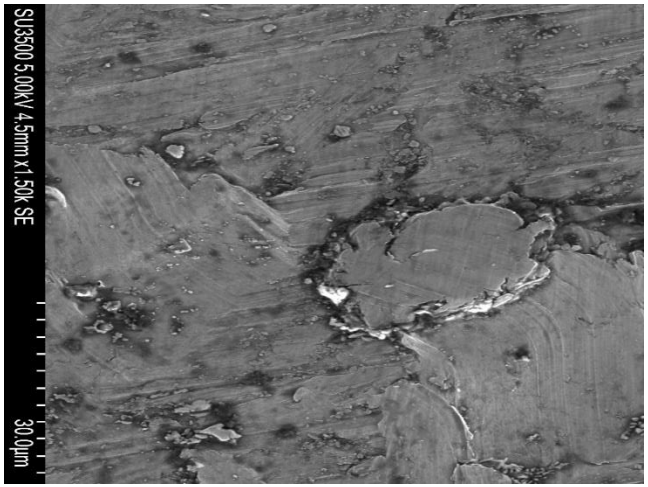

Recovery Method Issues

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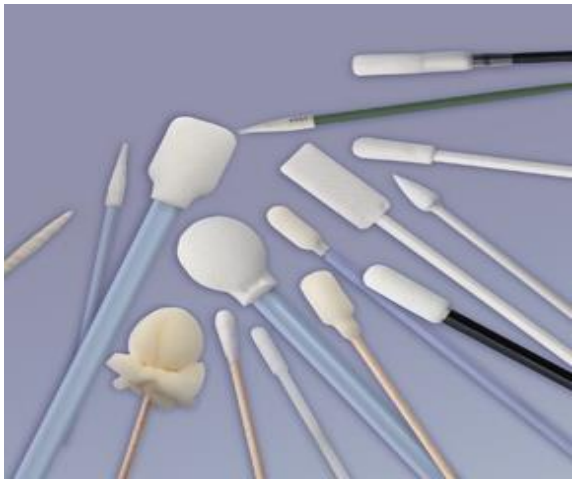
- Typical surface recovery methods
  - Contact plates (rarely used)
  - Swabs
  - Direct inoculation of coupons into neutralizing media
    - Requires sterile coupons
    - May include manual or automated dislodging
    - Stomacher bags



- Recovery method must be verified
- Final plates must be countable to calculate log reduction

Requalification

- Review annually to assess risk/ whether changes have occurred
- If new bioburden appears at high levels or inherently resistant organisms
- Re-evaluate every five years to determine if any repeat testing is needed due to testing deficiencies

Disinfectant Qualification Study Tips

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- AOAC methods are inappropriate for this testing (but some procedures such as inoculum prep, etc. can be of value)
- EN-13697, ASTM E2197, and PDA TR 70 offer valuable insight into quantitative surface testing
- Up-front planning is extremely important
- Combining physical removal and chemical kill in one study is not recommended
- Consistency is crucial to a positive outcome
- Reading the product labels to understand product claims and limitations is necessary
- Incorporate expiry dating specified in internal SOPs into the study
  - USP 40 <1072> “Diluted disinfectants must have an assigned expiration dating justified by acceptance studies.”

Summary

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- Disinfectant Testing
  - Vendor (AOAC for EPA registration)
  - End-user (USP 40 <1072>, ASTM, or EN methods)
  - Use of in-house isolates + surfaces crucial

Guidance documents

- USP 40 <1072> Disinfectants and Antiseptics
- USP 40 <1116> Microbiological Control and Monitoring of Aseptic Processing Environments
- USP 40 <1115> Bioburden Control of Nonsterile Drug Substances and Products
- Annex 1 EU GMPs (2008) and MHRA Orange Guide (2015)
- A Guide to Disinfectants and their use in the Pharmaceutical Industry (Pharmig 2006)
- FDA Aseptic Processing Guide (2004)
- New PDA Technical Report #70 on Cleaning and Disinfection (2015)
- 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
- FDA Guideline 21CFR Part 820
- FDA guideline the 21 CFR part 820

Debates and Challenges in Disinfectant Testing

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Thank you for your attention!

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