Disinfectant Regulation, Technologies, Sterility and Validation

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Agenda

- Regulations
- Technologies
- Sterility
- Validation

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Disinfectant regulation

Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)

- **All germicidal products fall under the FIFRA as amended (1988) and administered by EPA**
- **FDA regulation as medical device per Food Quality Protection Act of 1996 if used to reprocess other medical devices or if used as a sterilant for medical devices**

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EPA requirements

- Environmental Protection Agency (EPA)
  - Safety, use, disposal
  - Efficacy
    - Association of Official Analytical Chemists (A.O.A.C.) Official Methods of Analysis

EPA classifications

- Sanitizer
- Disinfectant
- Sterilant

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Sanitizer defined

- **Proper use results in bacteria reduction of >99.9%**
  - **Used on precleaned surfaces**

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Disinfectant defined

- Proper use results in 100% kill of vegetative bacteria, target viruses and target fungi
  - May or may not require precleaning
    - Serum efficacy

Sterilant defined

- **Proper use results in 100% kill of all microorganisms, including bacterial spores**
  - **Always requires precleaning**

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Application conditions

- Effects on EPA claims
  - Concentration
  - Time
  - Temperature
  - Surface
  - Bioburden

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Agenda

- Regulations
- ➢Technologies
- Safety
- Application

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Chemical Types

- Phenolics
- Quats
- Sodium hypochlorite
- Chlorine dioxide
- Hydrogen peroxide
- Peracetic acid
- Peracetic acid/hydrogen peroxide blends
- Glutaraldehyde/formaldehyde
- Alcohols

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Disinfectant components

Component	Function in disinfectant
• Water	Solvent
• Antimicrobials	Kill, reduce microbes
• Oxidants	Oxidize, kill microbes
• Chelants	Tie up calcium, iron, stabilize oxidants, potentiate antimicrobial action
• Solvents	Solubilization and stabilization
• Bases	Alkalinity source
• Acids	Acidity source
• Surfactants	Wetting

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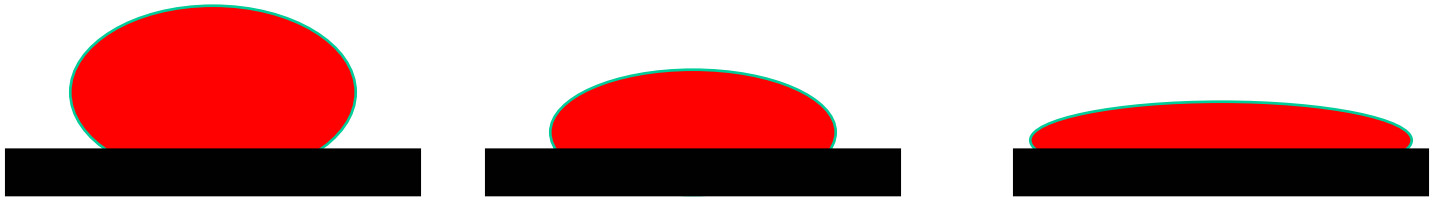
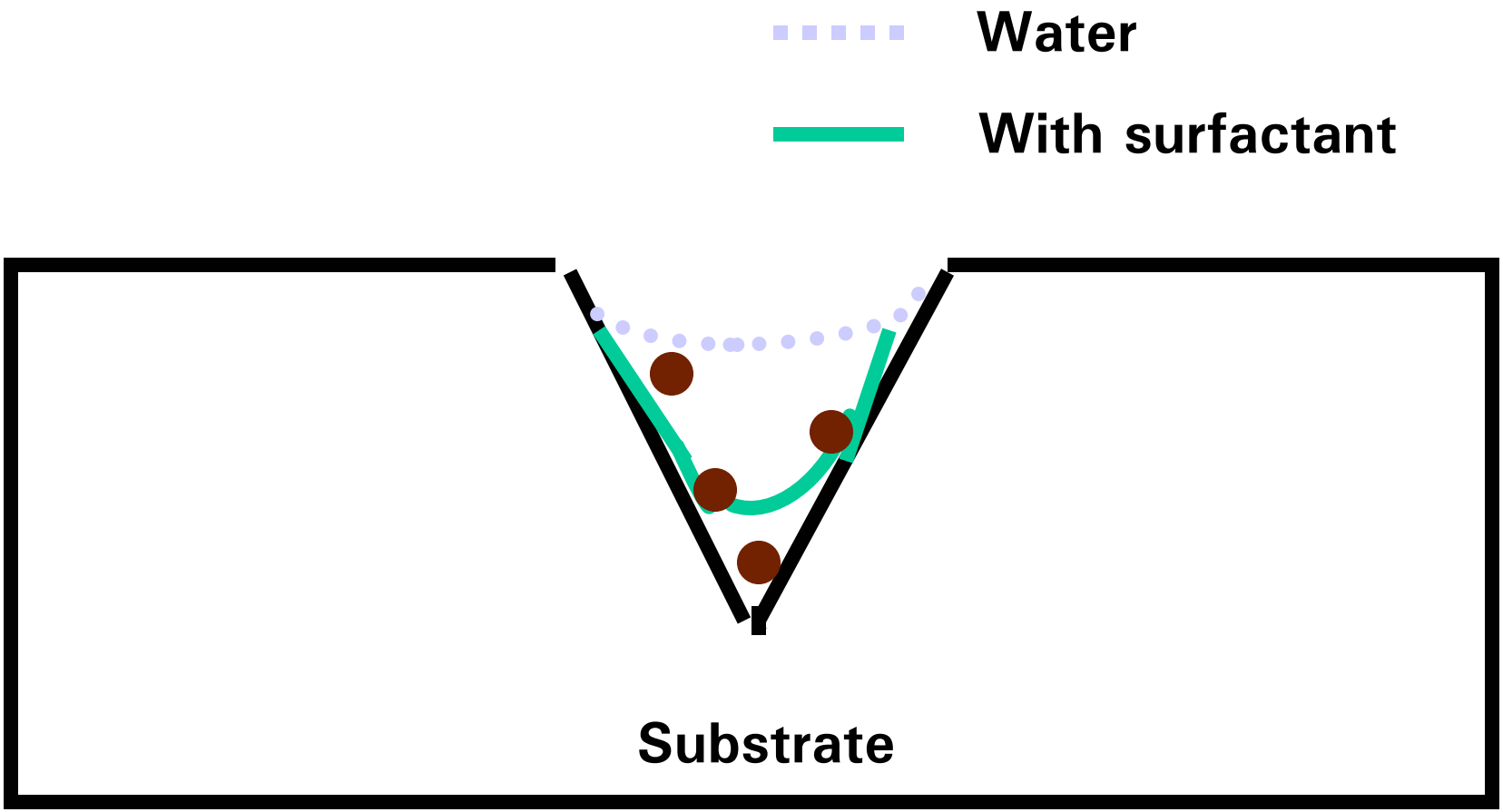
Effects of surfactants

- Influence of Surfactants on Wetting
  - Ability to displace particles
  - Penetrate soil and surface irregularities



No Surfactants Surfactant A Surfactant B

Access to microbes



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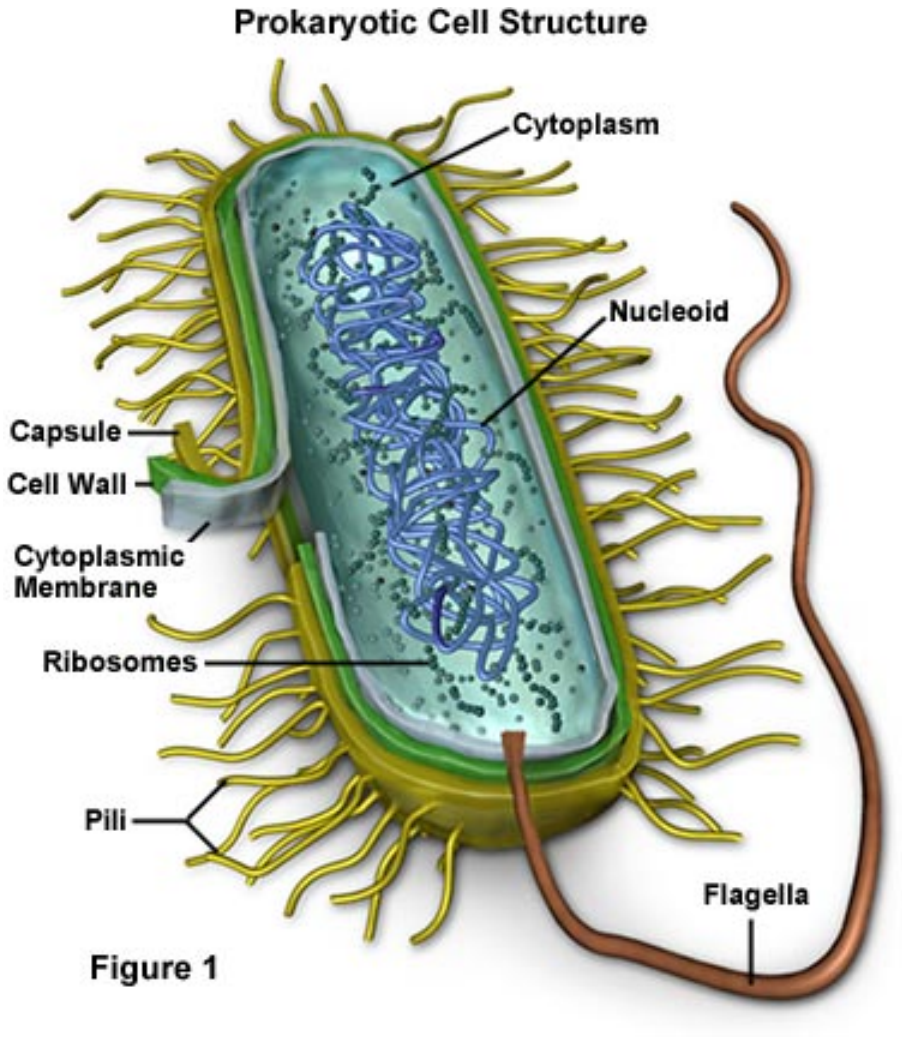
Killing Mechanisms

- **Bacterial spores**
  - **Spore coat penetration**
- **Vegetative bacteria**
  - **Cell wall disruption, cytoplasmic disruption**
- **Fungi**
  - **Cell wall disruption, cytoplasmic disruption**
- **Virus**
  - **Affect capsid, nucleic acids**

Prokaryotic Cell



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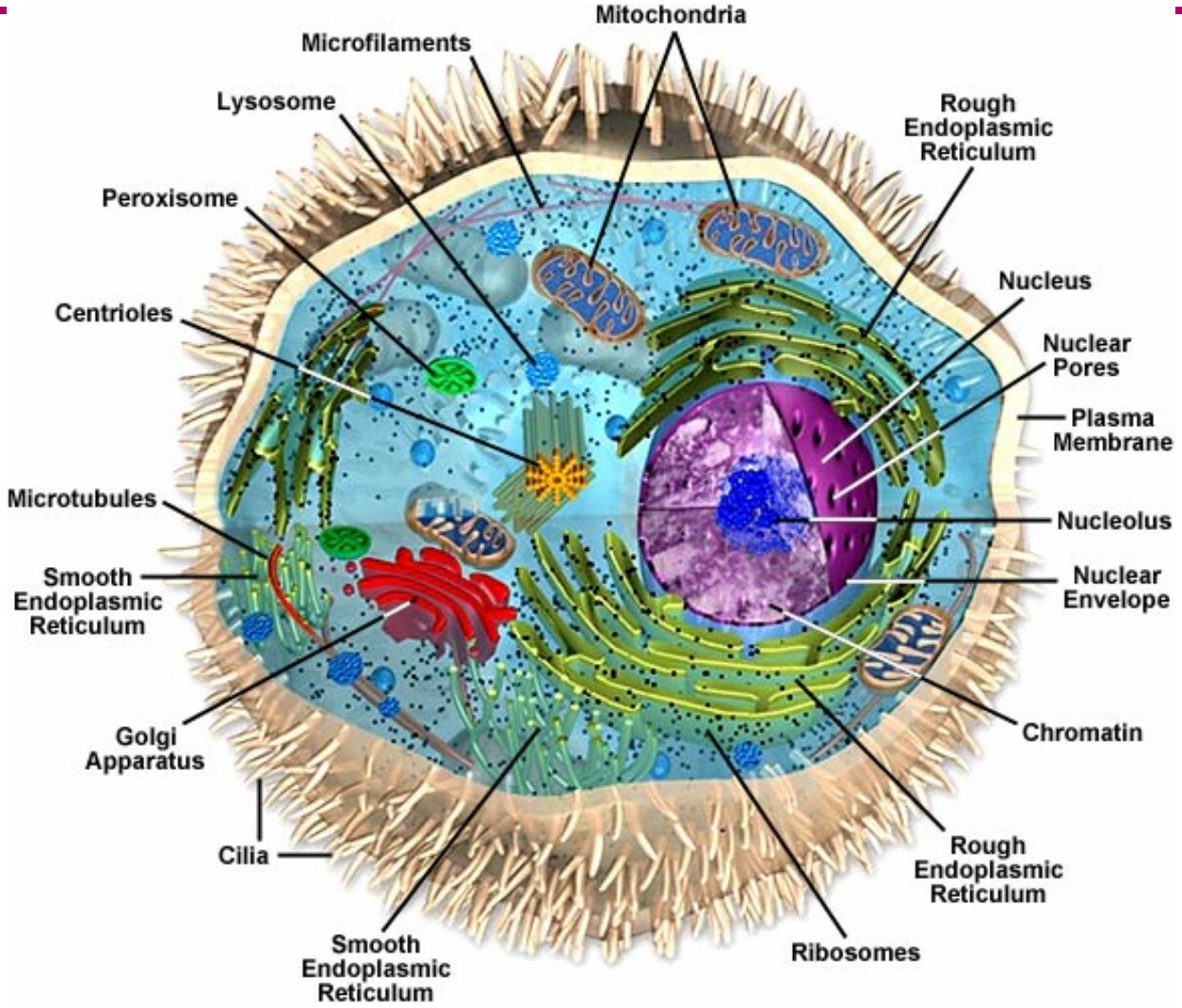
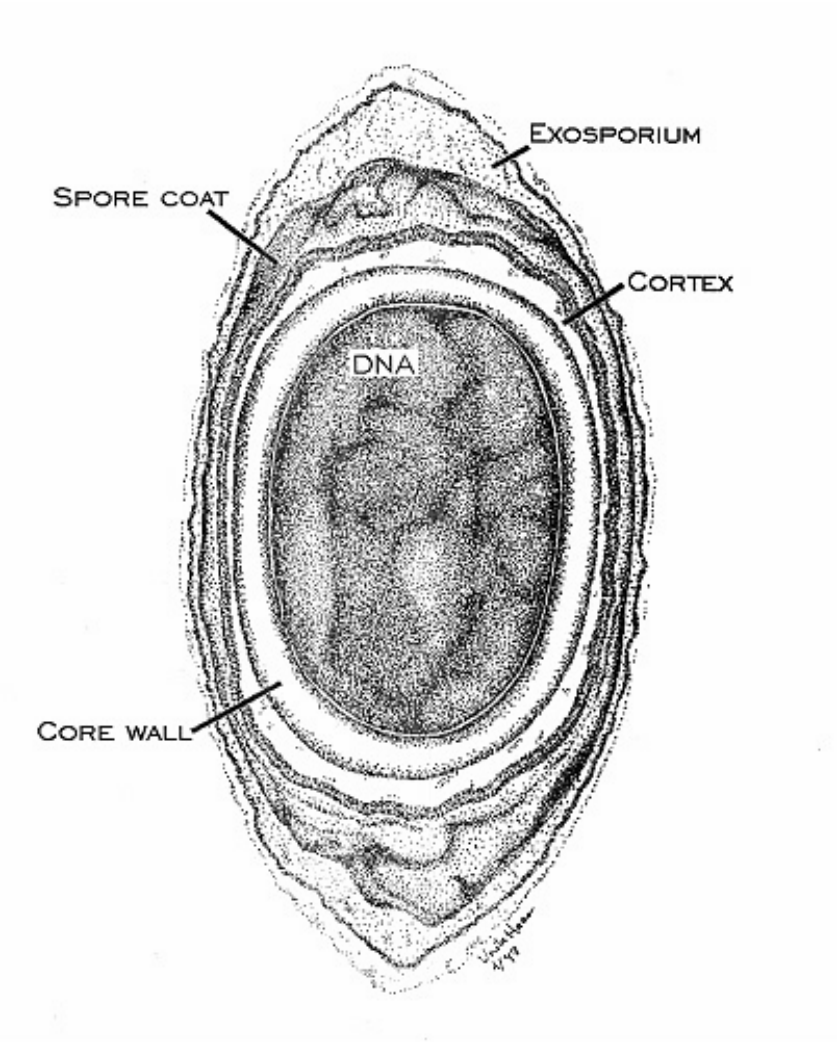
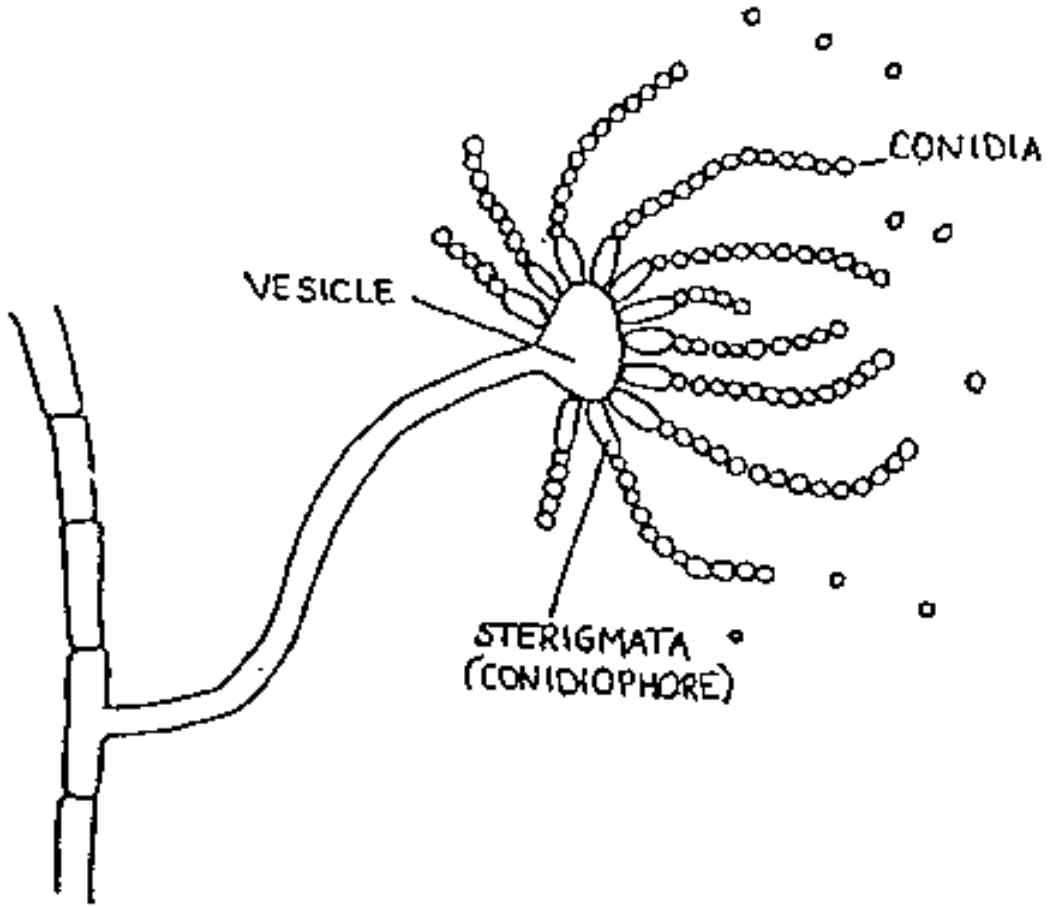
Eukaryotic Cell



Endospore



Aspergillus niger



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Phenolics - features

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

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Phenolics - limitations

- Not Sporicidal
- Disposal Issues
- Activity Affected by Other Chemical Agents

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Quats - features

- Broad spectrum activity
- EPA registered alkaline (and acidic)
- Nonionic surfactancy provides good cleaning

Quats - limitations

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

Hydrogen peroxide / peracetic acid blends - features

- Fast, broad spectrum activity, sporicidal
- Less corrosive than comparably effective oxidizers
- EPA registered
- Safer for personnel
- Self-sterilizing (sterility tested)

Hydrogen peroxide / peracetic acid blends - limitations

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

Alcohol - Features

- No residue
- Broad spectrum
- Evaporates readily

Alcohol - Limitations

- Not sporicidal
- Poor cleaner
- Flammable
- Limited contact time
- Not EPA registered
- VOC emissions

Agenda

- Regulations
- Technologies
- ➢Sterility
- Validation

Sterility

"Solutions used to sanitize and disinfect surfaces in the sterile core are not rendered sterile before being introduced and used in the sterile core." GMP TRENDS, Issue #483, March 1, 1997

Sterility

“Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilised. Disinfectants and detergents used in Grades A and B areas should be sterile prior to use.” Rules and Guidance for Pharmaceutical Manufacturers and Distributors, Annex 1, Section 38, 1997

Sterility

“Typically, disinfectants used in aseptic filling areas are diluted with Water for Injection and are prepared aseptically.”, <1072> Disinfectants and Antiseptics, Pharmacopeial Forum, Vol. 28 (1) [Jan.-Feb. 2002]

Sterility

"Upon preparation, disinfectants should be rendered sterile, and used for a limited time, as specified by written procedures." Sterile Drug Products Produced by Aseptic Processing – 2002 FDA Draft Concept Paper (Lines 1047-1048)

Sterility

- Purpose
  - To prevent introduction of foreign organisms into environment
- Sterilization practices
  - Filtration
    - 0.22 micron
    - PVDF, Teflon (PTFE)
  - Gamma irradiated concentrates
    - WFI dilution required

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Agenda

- Regulations
- Technologies
- Sterility
- ➢Validation

Validation of sanitizing agents

- Applies to non-critical (non product contact) processes
- Cleanroom sanitization procedures
- Not stipulated in cGMPs; however...

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Regulatory comments

"5142W...Deviations from GMPs included... validation deficiencies involving ...failure to adhere to the written cleaning procedure and assure the effectiveness of sanitization procedures" Warning Letter Bulletin - 4/21/97

Regulatory comments

"...Qualification to evaluate the effectiveness of the cleaning and disinfection for the ...Biohazard Hood has not been completed." GMP TRENDS, Issue #484, 3/15/97

Disinfectant validation components

- In vitro testing
  - Suspension testing
  - Carrier testing
- In situ testing
- Environmental monitoring
  - Data trending
  - Identification of organisms

Disinfectant validation procedural recommendations

- USP <1072>
- ISO /DIS 14698-3

In vitro options

- AOAC
  - Use-dilution Test
  - Sporicidal Activity of Disinfectants
  - Germicidal Spray Products as Disinfectants
- ASTM
  - Time Kill Method
  - Spray Slide
  - Sanitizer method
  - Wipe method

- Variations of all of the above

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Other in vitro options

- EN
  - 1276
  - 1650
  - 13704
  - 13697
- AFNOR
  - NFT 72-150 Suspension
  - NFT 72-190 Carrier Test
- DGHM Suspension Test
- TGA

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Key considerations In vitro

- Technique
  - Suspension vs. carrier
  - Substrates
  - Neutralization/dilution
  - Subculture techniques
- Microorganisms
- Efficacy requirements

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Suspension test

- Estimate the in vitro bactericidal activity of the disinfectant under precise experimental conditions including
  - Microbial strain
  - Preparation of inoculum
  - Volume of inoculum vs. disinfectant
  - Temperature
  - Disinfectant concentration and contact period
  - Interfering substances (i.e. inorganic, organic matter)

Carrier test

- Estimate the in vitro bactericidal efficacy when reproducing surface disinfection conditions including
  - Substrate
  - Application technique
    - Spray, immersion or wipe
  - Drying time
  - Surface area vs. inoculum
  - Interfering substances
- Issues
  - Recovery from surface
  - Surface condition

Substrates

- Traditional methods
  - Stainless steel disks or penicylinders
  - Watch glasses or glass slides
  - Porcelain penicylinders and silk suture loops
- Cleanroom disinfectant validations – representative materials, large surface areas
  - Stainless steel
  - Various plastics and elastomers
  - Bodycote aluminum wall
  - Epoxy-coated flooring
  - Polymeric flooring
  - Rubber or nitrile gloves

Neutralization

- Elimination of inhibitory residual disinfectant activity
  - Chemical neutralization – neutralizing the active
  - Dilution - generally not effective alone (alcohols)
  - Filtration – separating the active from the organism
- Issues
  - Antimicrobial activity of neutralizer (toxicity)
  - Mechanical separation causing damage to cells
- Validation of neutralization is required

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Chemical neutralizers

- Polysorbate 80 (Tween)
- Lecithin
- Letheen broth
- Sodium thiosulfate
- Catalase
- Glycine
- D/E neutralizer

Microorganisms

- **Microorganisms**

  "The Firm's sanitizing agents have not been validated with environmental microorganisms which have been observed to be part of the firm's environmental bioburden." GMP TRENDS, 11/15/93

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Microorganisms

- Environmental isolates must be considered
  - Broad spectrum
  - Most frequently occurring
  - High levels
  - Demonstrated decontamination difficulty
- USP challenge organisms may also be considered

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In situ data

Room	Media Type	Action Limits	Pre-Sanitization[a]	Range (#cfu/unit)[b]	Post-Sanitization[a]	Range (#cfu/unit)[b]
#1	Biotest	>2.5 cfu/ft^3	3 of 4	0.3[d]	0 of 4	0
	RODAC	>2 cfu/plate	2 of 8	0 to 1	0 of 8	0
	Settling	>2 cfu/plate	0 of 4	0	0 of 4	0
	Swabs	>2 positive	0 of 4	N/A[c]	0 of 4	N/A[c]
#2	Biotest	>2.5 cfu/ft^3	1 of 4	0.04[d]	0 of 4	0
	RODAC	>2 cfu/plate	2 of 9	0 to 1	0 of 9	0
	Settling	>2 cfu/plate	0 of 4	0	1 of 4	0 to 1
	Swabs	>2 positive	1 of 7	N/A[c]	0 of 7	N/A[c]

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- ✓Regulations
- ✓Technologies
- ✓Sterility
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