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Contamination Control Basics Risk and Resolution

Parenteral Drug Association West Coast Chapter
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Ziva Abraham is the President and Founder of Microrite, Inc., a California based consulting firm providing consulting and training services to pharmaceuticals, biotechnology, medical devices and in vitro diagnostics in the areas of quality assurance, quality control, microbiology, and validation.

Ziva has over 35 years of academic, research, clinical and industrial experience in microbiology, and quality assurance. Ziva has received her Master's Degree in microbiology with a focus on Mycology and has conducted research on developing microbial Insecticides using entomogenous bacteria and fungi towards her Ph.D. degree.

Her career also includes founding and managing clinical laboratories for Maccabi Medical in Israel. She has trained personnel from various industries in microbiology techniques and methods. She uses her extensive experience to teach why assessing risk of microbial contamination should be in the forefront of any company that has products for human/veterinary use.

Her experience in clinical laboratories has provided her with the framework to understand the effects of microbial contamination in products from a patient safety perspective.

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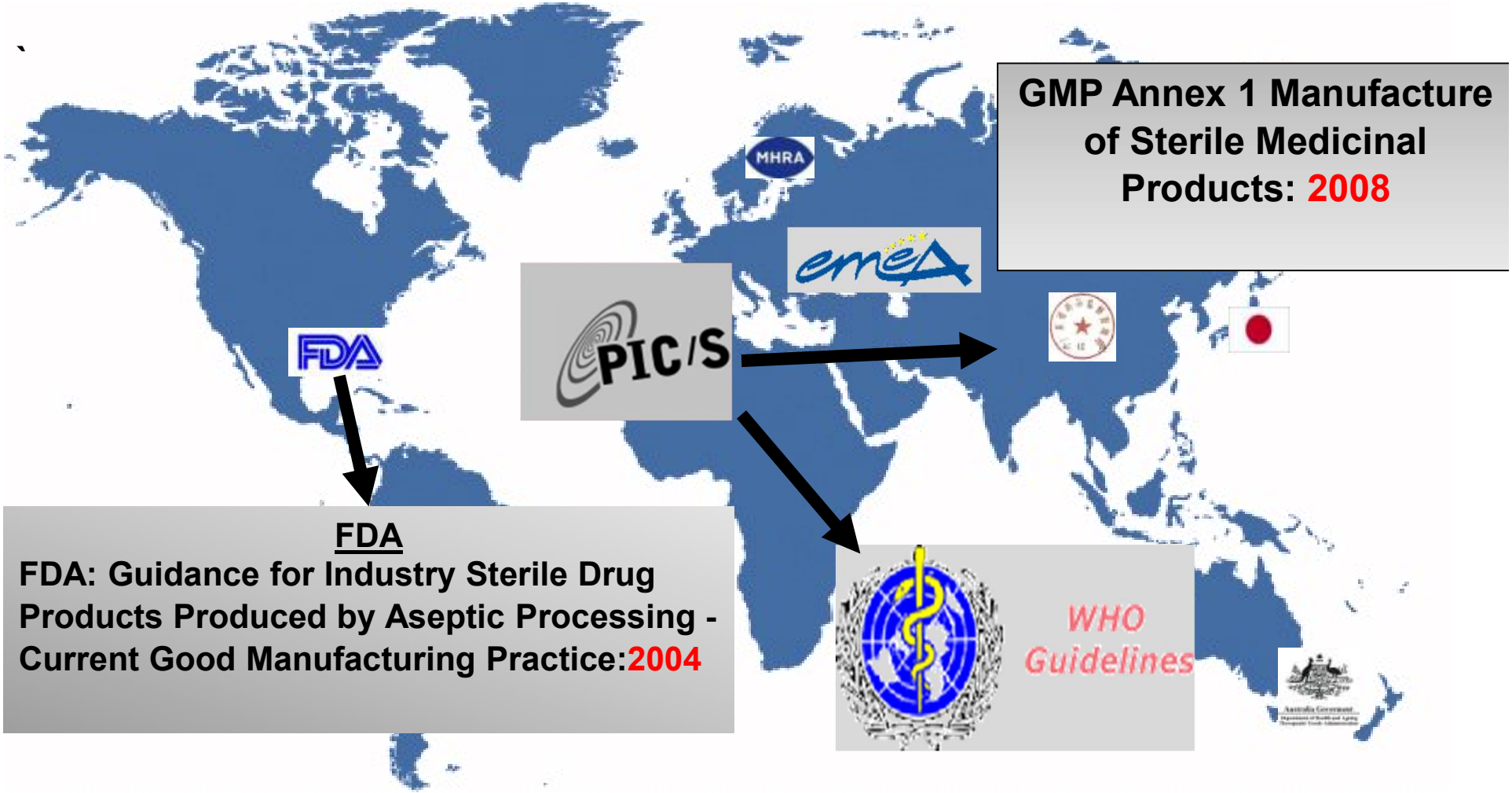
What will be discussed

- Cleanroom and barrier system flaws that lead to contamination events
- Human borne contamination due to gown choice and management
- Myths related to disinfection and cleaning
- Equipment contamination issues-understand the gaps
- Process related contamination
- Common errors in environmental monitoring
- Common causes of release testing failures

Contamination Control is NOT a Paper Exercise!

It is a Mindset !!

Current Regulatory Thinking



GMP Annex 1 Manufacture of Sterile Medicinal Products: 2008

FDA

FDA: Guidance for Industry Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice:2004

The Mindset for Controlling Contamination

Contamination Control CANNOT be attained unless:

- Product requirements are set per patient risk
- Knowing the real risk not perceived risk

- Having the right knowledge base to assess these risks
- Designing the facility, process and testing from a risk perspective

Cleanroom and Barrier System Flaws that lead to Contamination Events

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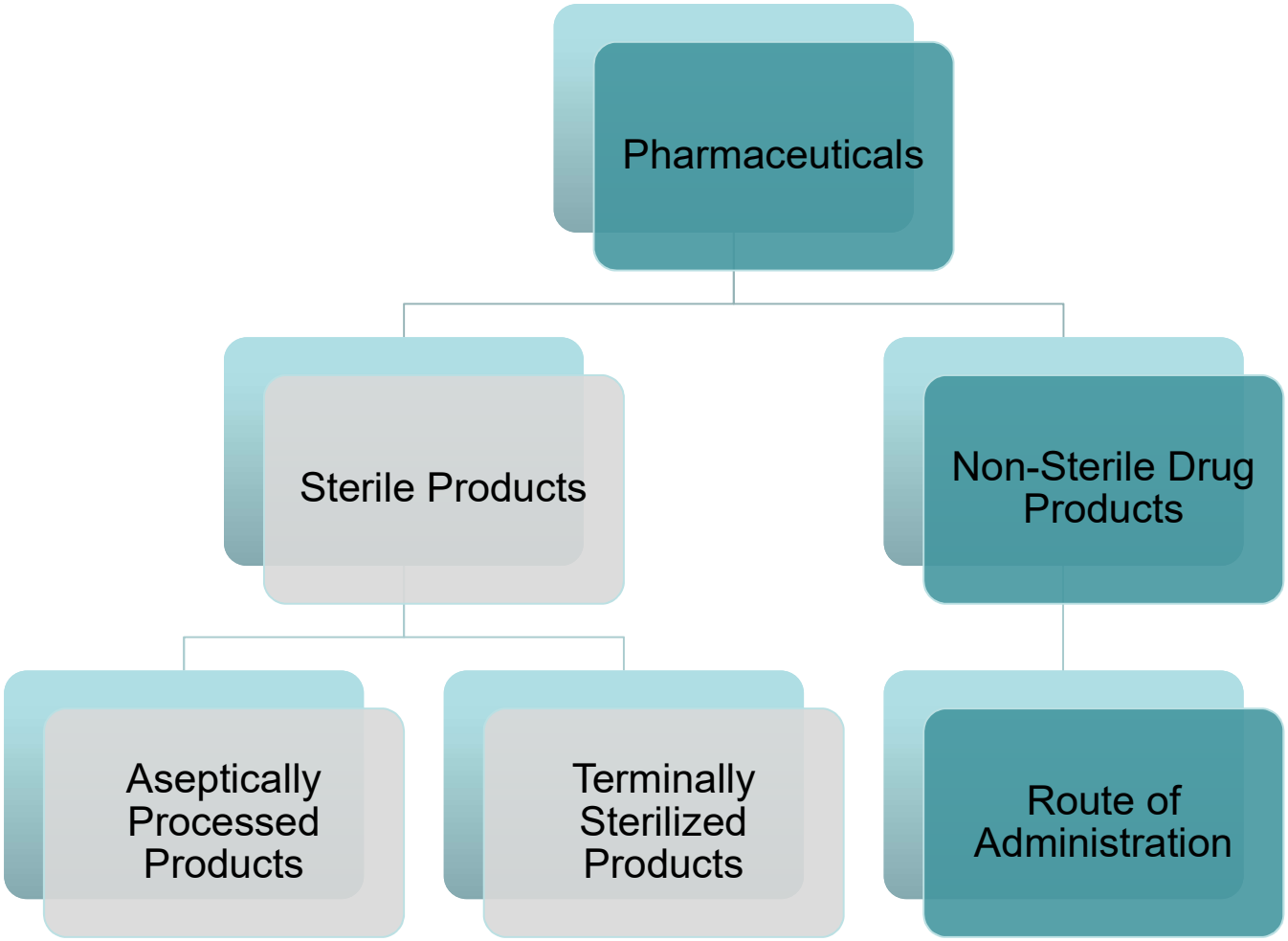
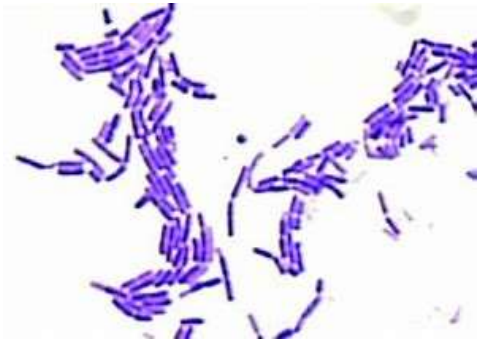
Risk Assessment??

"We've considered every potential risk except the risks of avoiding all risks."

Contamination risk varies depending upon product



Risk in Terminally Sterilized Products



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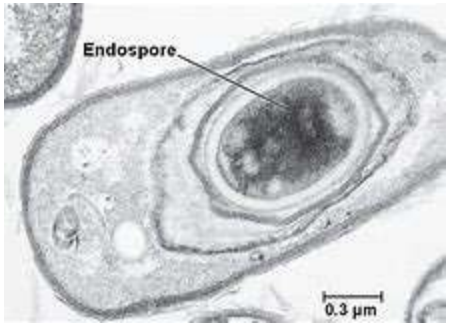
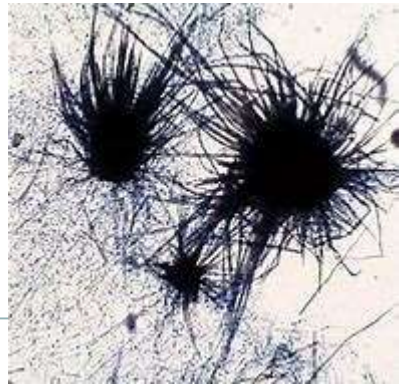


Terminally Sterilized Products

Should Meet Pre-Sterilization Bioburden

What if the organisms are difficult to sterilize



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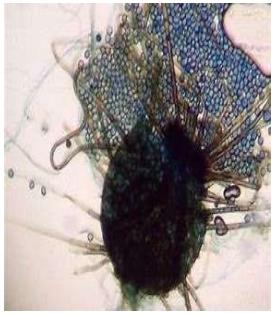

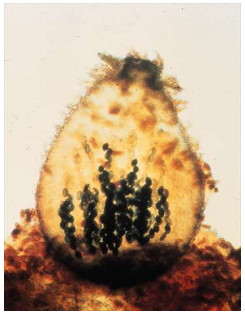

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Risk in Sterile and Non-Sterile Products

Sterile	Nasal and Inhalation	Eye	Auricular	Cutaneous	OSD
All microorganims are objectionable	*Pseudomonas and S. aureus* are tested for microbial limits, however there are many other bacteria and mold that are objectionable. Fungal pneumonia is very prevalent in immunocompromised patients Nasal and lung infections can lead to blood and systemic infections	*Staphylococcus aureus Pseudomonas aeruginosa* are tested for microbial limits test, however fungal keratitis cases have been wide spread from time to time	*Staphylococcus aureus Pseudomonas aeruginosa* are tested for microbial limits test, however other bacteria and fungi have been known pathogens Ear infections can spread to orofacial cavity	*Staphylococcus aureus Pseudomonas aeruginosa* are tested for microbial limits test, however fungal cutaneous infections and bioflim formation on wound is very prevalent. Any contaminated open wound can cause sepsis and systemic infections	Tested for E. coli for microbial limits test, however *B.cereus* causes alimentary canal infections

Specified organisms tested per USP<1111> are minimum requirements. There are many other organisms that can harm the patient. Microbial identification and knowing the predominance of microorganisms in the environment as well as product is very important

Warning Letter

"Your facility design may represent an additional contamination risk to the products you manufacture."

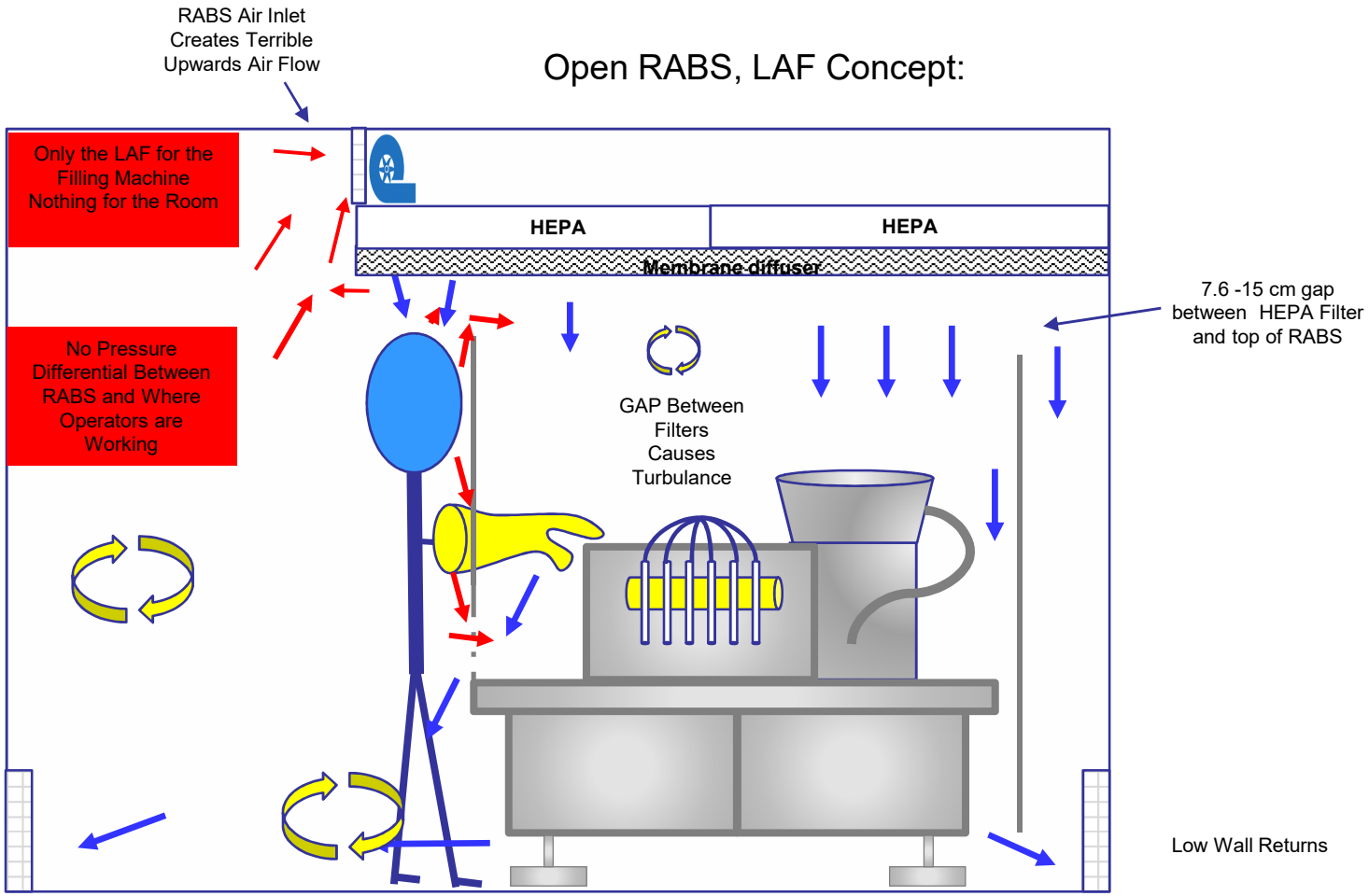
"Furthermore, data falsification and manipulation, and your reliance on incomplete records to release product to the market, are repeat violations."

- Facility was in operation for making sterile drugs for **multiple sponsors**
- Deficiencies in aseptic processing (aseptic practices & Cleanroom/Barrier Design)
- Multiple Sponsor Audits **ALWAYS PASSED**
- Had LOADS of Risk Assessments, Validations and QRM documents
- All Media Fills passed and no excursions!
- FDA suspected EM data integrity due to the poor aseptic practices observed and the sub-par cleanroom/barrier system design and integration
- An Army of consultants were hired to close CAPAs but none of the consultants ever walked the facility or entered into the cleanrooms

Root Cause:

Cleanroom and Barrier System integration was flawed which led to continuous excursions and Media Fill failures, however due to the amount of business, management……

What Is Wrong with the Picture?



Warning Letter

"The repeated serious violations at your facility demonstrate that your facility's oversight and control over the manufacture of drugs is inadequate."

"In particular, our warning letters discuss the history of recurring serious defects in your marketed **(b)(4)** products, including but not limited to non-sterile **(b)(4)** with visible contamination, **(b)(4)**, and other evidence of lost integrity, and most recently quality issues relating to assay, impurities, and **(b)(4)**. These issues have been exacerbated by the lack of prompt identification and appropriate remediation, and FDA intervention has generally been necessary for your firm to adequately investigate and remove the defective products from distribution."


A6-05/L6/H01-05


Poor Cleanroom/Barrier Integration Limits the HEPA Filtered Air Delivered into the Grade B Support Area
THIS IS an OUTDATED Approach to Contamination Control
Grade A Air Inlet to LAF
Grade B Air Supply
Cleanroom Curtains? It's 2019

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The Celling Return Phenomenon

Pass throughs are critical

Draft Annex 1

Pass through hatches without active filtered air supply should be avoided.

If necessary, provisions and procedures should be in place to avoid any risk of contamination (e.g. by the incoming material or by **entering air).**

AFV/Smoke Studies is the MOST Misunderstood CR Test

Smoke Studies are Often Approached as a Rubber Stamp Test

Often Conducted Under the **Assumption** That They Will Pass Because Other Cleanroom Tests Have Passed;

- Air Volume and Air Velocity
- Particle Count
- Differential Pressure
- Filter Integrity

This approach coupled with other factors contribute to Smoke/AFV Study Errors that Lead to

- Contamination of products
- Failed media fills
- Environmental monitoring excursions
- Recalls
- Warning Letters
- Risk to patient-sterility test passing does not mean that the entire batch is contamination free

FDA 483 Observation

Inadequate Cleanroom Design and Smoke Study Deficiencies

Your stopper hopper leans diagonally over the top of the filling line during stopper loading operations, thereby blocking first air over open, exposed sterile vials.
In addition to this inadequate design, your smoke studies performed for your ISO 5 areas also lacked simulation of multiple critical interventions that occur during aseptic manufacturing operations.

Thorough smoke studies are essential to evaluate the effects of such interventions on unidirectional airflow and to ensure design modifications are made wherever necessary.

The ISO 5 area is critical because sterile product is exposed and therefore vulnerable to contamination. Your aseptic filling process should be designed, and operations executed, to prevent contamination hazards to your sterile product. The flawed design of the filling line and execution of the aseptic operations promote influx of contamination into the critical filling areas.

Thorough

Minimal

483 Regarding Smoke Study for EM

- During the airflow analysis (smoke study) of aseptic connections on your (b)(4) equipment inside the laminar air flow (LAF) ISO-5 area, our investigator identified air flow disturbances and turbulence. Under dynamic conditions, air did not sufficiently sweep across and away from sterile connections, so the sterility of any product processed under these conditions could be compromised.

- Furthermore, in our review of the smoke study, we identified multiple aseptic technique breaches during aseptic connection of the (b)(4) equipment. Your equipment design and aseptic processing operator competencies appear to contribute to the lack of unidirectionality.

- Aseptic processing equipment should provide for appropriate ergonomics that enable operators to reproducibly conduct aseptic manipulations. In addition, it is critical that your aseptic processing operators have the knowledge and skills to practice strict aseptic techniques. Even operations that have been successfully qualified can be compromised by poor operational, maintenance, or personnel practices.

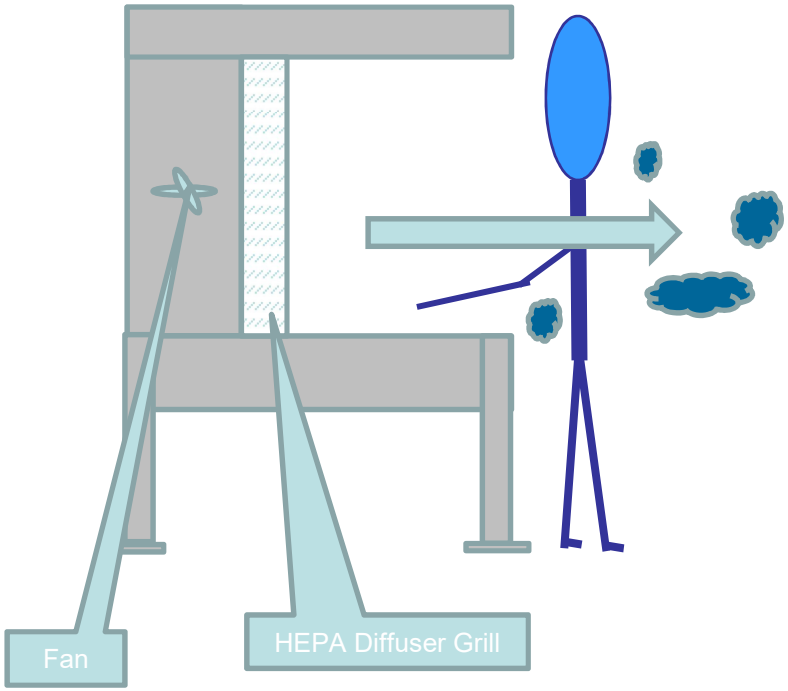
Myths Related to Smoke Studies

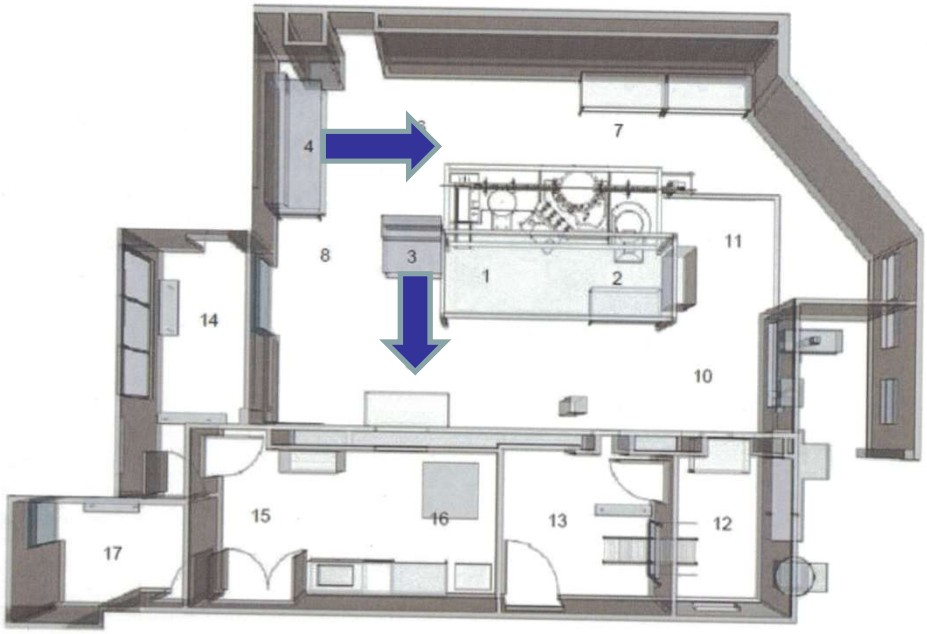
- What is the purpose of smoke studies?
- Have it on file?
- Or map airflows and prevent contamination?
- Airflows cannot be mapped using heavy medium that is not buoyant!
- In-situ air pattern analysis is to ensure that there is no ingress of contamination from less controlled area or over personnel
- That air from operations such as cappers, robotic arms, etc. does not flow over open product
- That eddy currents do not become reservoirs for contamination
- L&R method

Case Study: Sterile manufacturer failing media fills and sterility tests

- Open product under the dead space?
- Smoke study passing
- Filling needles in eddy currents
- How can this be cleaned?

Horizontal Flow Benches





Horizontal Flow Benches Critical for Aseptic Operations =POOR CONTAMINATION CONTROL

- Lower Pressure Area is created in by the obstacle. This creates a Reversal of Air Flow that can create a Channel or Reservoir for Contamination
- Once a Person is in front of the opening, air flow reversal can contaminate products.

Case Study

CMO utilizing passive RABS

Mold Recovered during Sterility Test

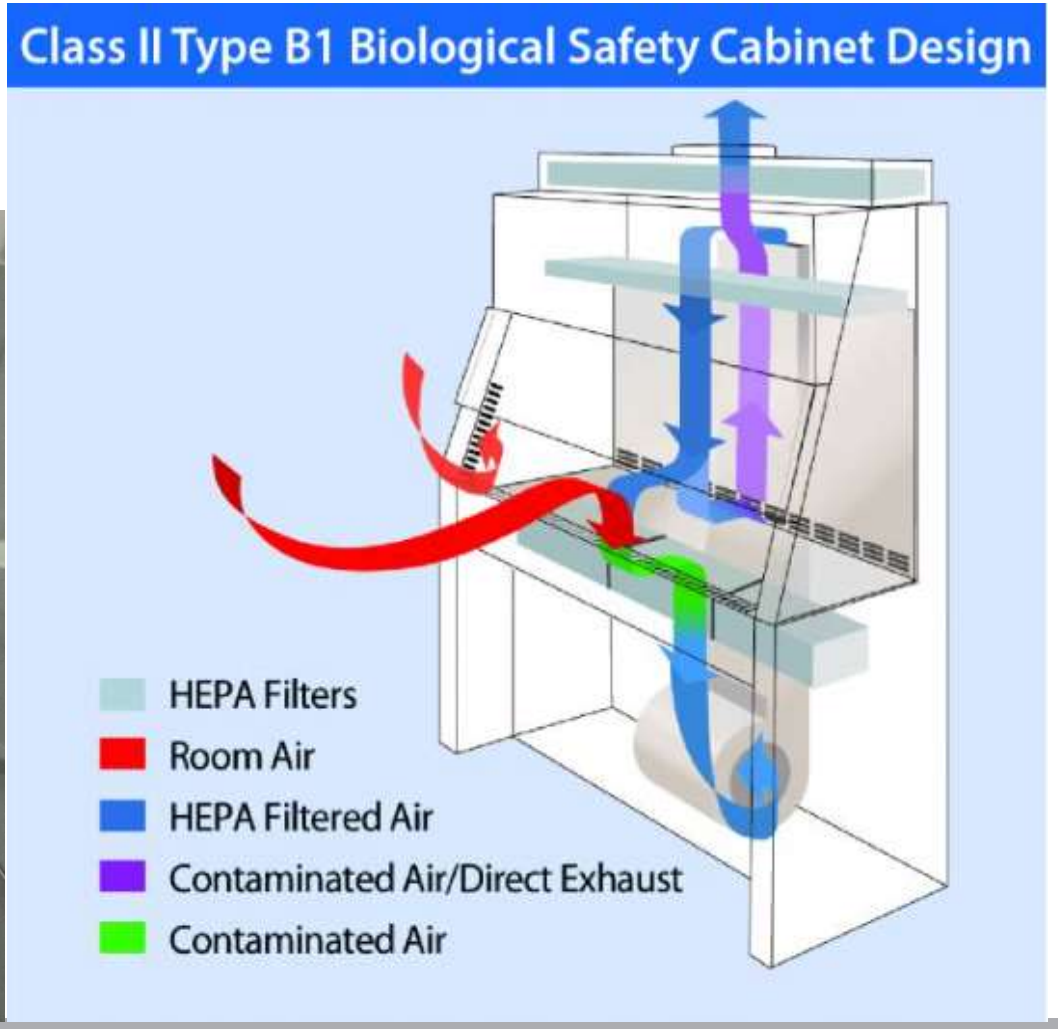
- Entire Room ISO Class 5 with Passive RABS
- 1000 Air Changes Per Hour for the RABS
- Continuous Microbial Sampling System (desiccated plates) no excursions detected
- Recovery Study on plates performed in horizontal LFH **APPLES to ORANGES**
- Non- Sterile RABS gloves used, and disinfected by bleach wipe-down

More is not always better!

Biological Safety Cabinets

What is important?

- Placement
- Certification
- Cleaning…

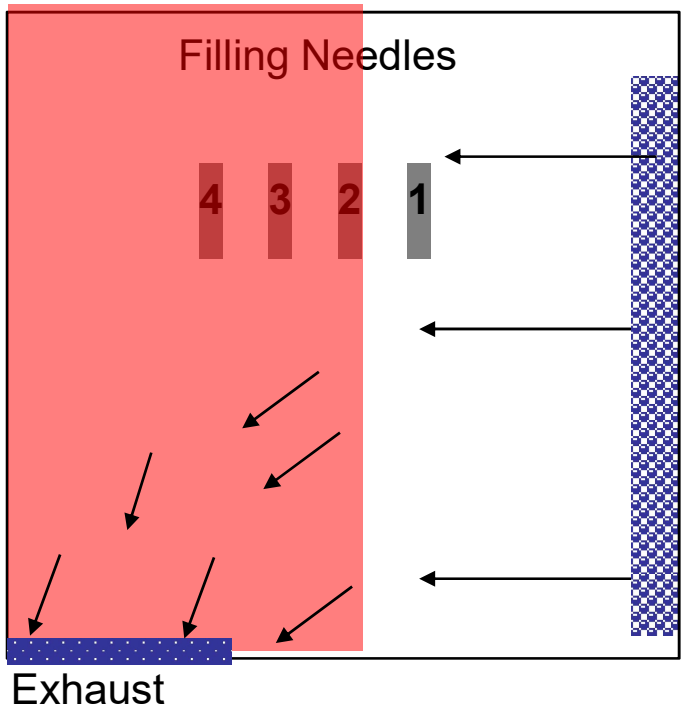


Isolators are not Magic!!

[1]MHRA's view on sterilization of direct and indirect contact items in an Isolator:

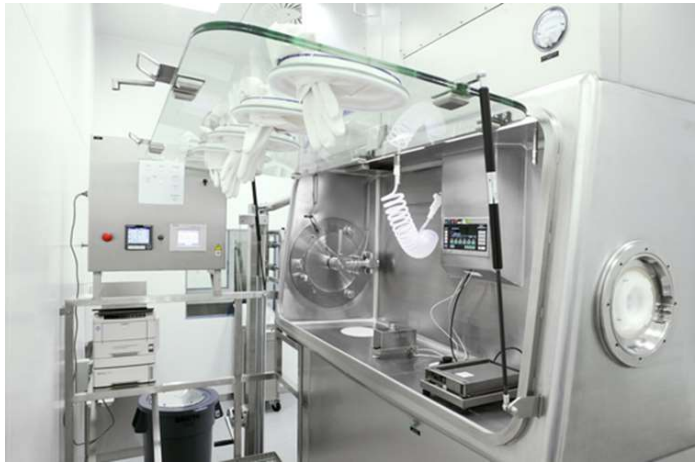
VHP is considered too fragile of a sterilization method due a number of issues seen with biological indicators failing the process due to clumping of spores at a microscopic level

[1] **https://mhrainspectorate.blog.gov.uk/2018/04/20/vhp-vapour-hydrogen-peroxide-fragility/**

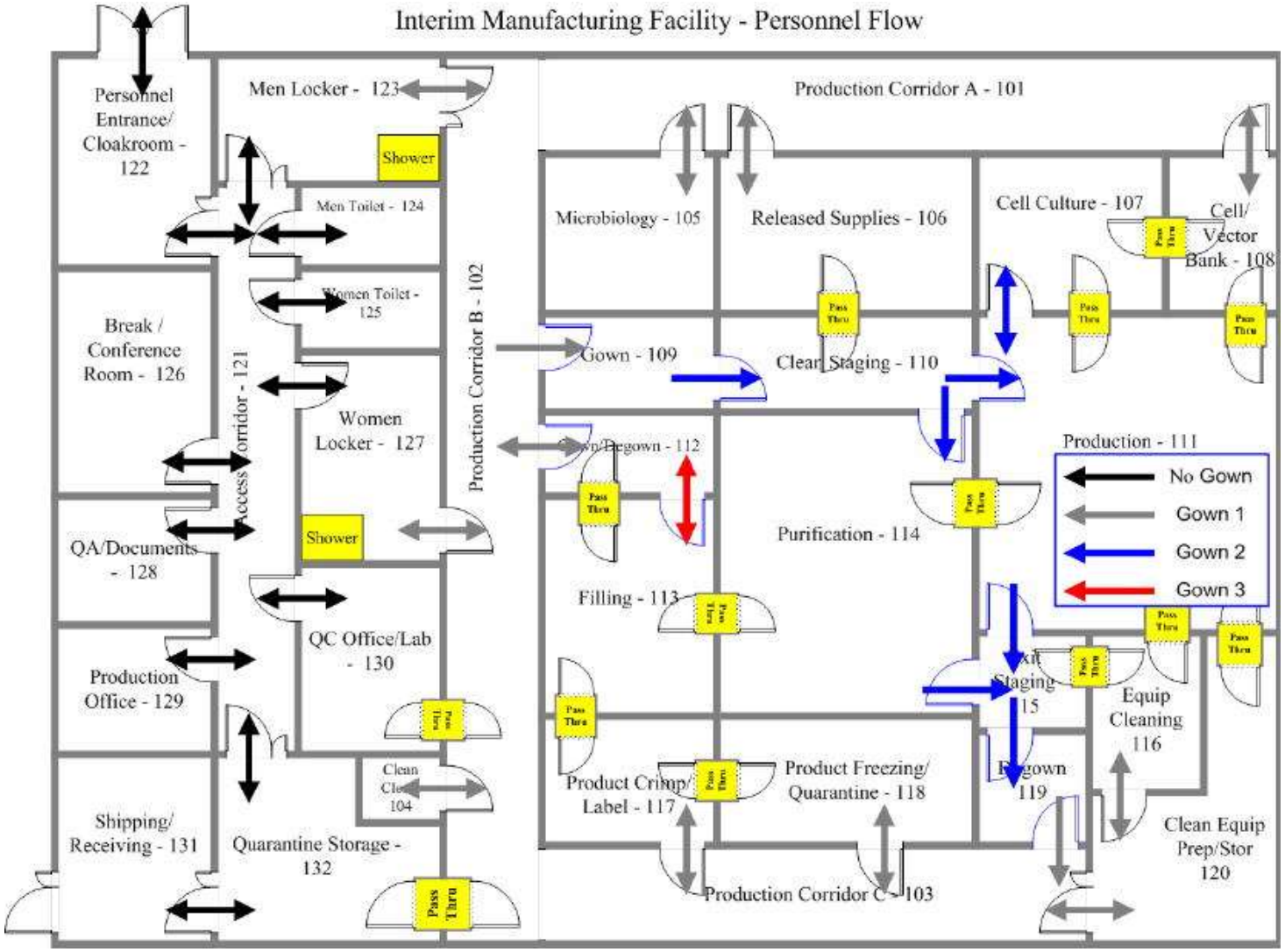


First Air is Only Delivered to Filling Needle 1

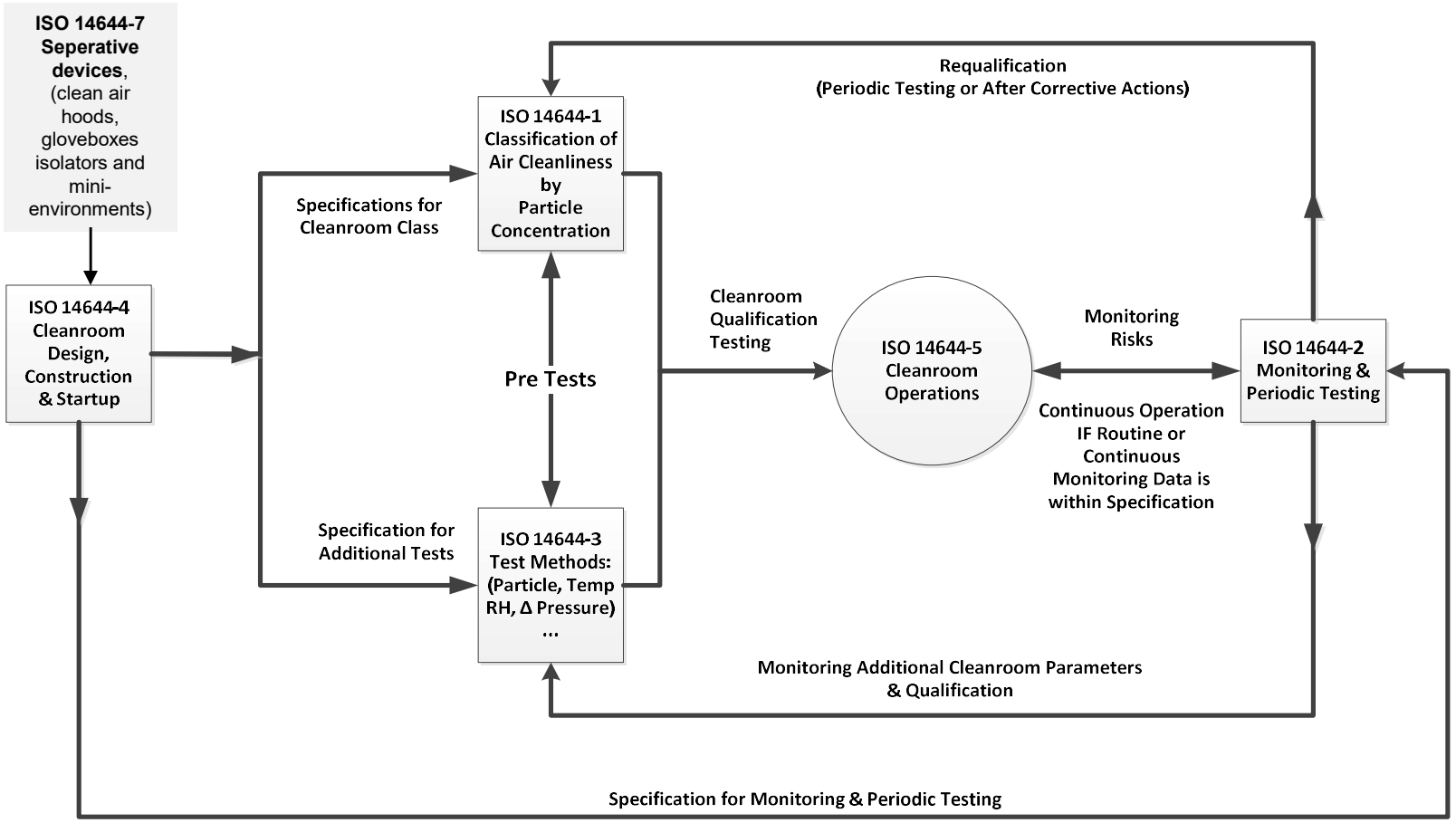
HEPA Filter



Personnel, Material and Waste Flows



ISO Doctrine of Contamination Control



Human Borne Contamination due to Gown Choice and Management Gaps

Case Study 483s

Aseptic garments worn in the filling area were also non-integral.

We observed 7 of **(b)(4)** sterile gowns with tears or holes;
8 of **(b)(4)** had loose threads.

We observed 2 of **(b)(4)** sterile hoods with tears or holes;
12 of **(b)(4)** had loose threads.

We observed 8 of **(b)(4)** sterile booties with tears or holes;
11 of **(b)(4)** had loose threads.

Procedure PDN/013/R8 **"Handling of Aseptic Area Garments" required production personnel to examine the garments for tears, holes, and loose threads, but our investigator found that these checks were not being performed**.

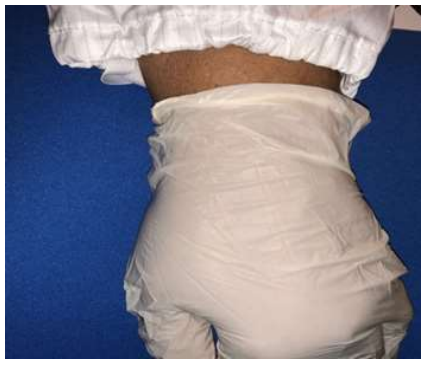
Non-integral **(b)(4)** gloves were used in Suites **(b)(4)** and **(b)(4)** for conducting aseptic processing operations.

For example, on February 12, 2015, we found that 15 of **(b)(4)** gloves in Suite **(b)(4)**, and 4 of **(b)(4)** gloves from Suite **(b)(4)**, were non-integral.

Gowns

Cleanroom garments themselves can become a source of contamination

- Number of laundry cycles without testing for particle generation as well as loss of filtration efficacy
- Garments shedding particles from normal, excessive or abusive wear
- Residues remaining from after cleaning or decontamination treatment
- Particles that penetrate the cleanroom clothing through the fabric, openings or seams
- Fibers released in cleanroom with low abrasion resistance of the clothing fabric
- Wrong detergents used



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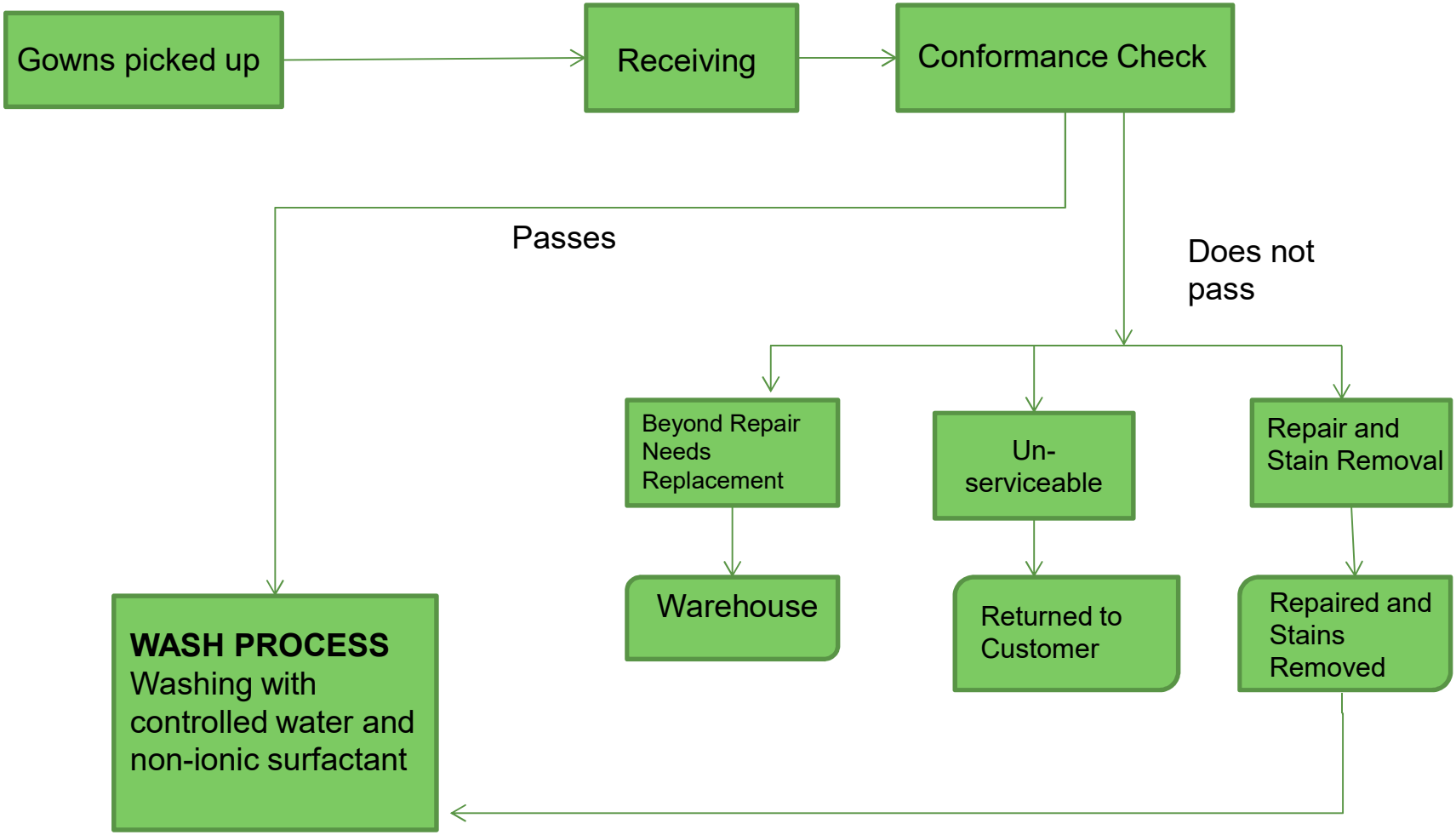
Laundered Gown Supplier Audit



Some Gowning Errors and Training Deficiencies

- Wrong gowning sequence
- Tacky mats not used correctly
- Stepping on tacky mats after wearing shoe covers
- Hanging gowns incorrectly
- Degowning in clean side of the gown room-the cleanroom door phenomenon
- Materials pass through the gowning airlock
- Gowns stored in lockers with reusable shoe covers
- Gown laundered by regular laundry service
- Scrubs worn throughout the facility including break rooms
- Dedicated shoes not cleaned
- Dedicated shoes stored in the same lockers as non-dedicated shoes
- Gowns stored in cardboard boxes

Cleaning Disinfection and Disinfectant Qualification

FDA 483 Observation

Cleaning Operations

Your cleaning program is deficient. While operator entries in sanitization records state that all required sanitization steps were completed in cleanrooms, many steps were actually skipped, and various pieces of equipment were not sanitized.

Your operators did not ensure the mop makes proper contact with the floor. Mops were not wetted frequently to ensure adequate coverage. For example, an operator cleaned the walls surrounding Line AH for several minutes without rewetting the mop.

In your response, you stated that you have performed targeted training on sanitization procedures. Further, you note that your disinfectant efficacy program demonstrates the ability of your agents to reduce bioburden. Your response is inadequate. You are not consistently following your validated procedures.

Although you acknowledge that all disinfection activities had not been completed, you have not determined the scope of these poor practices observed at your facility, including identifying employees involved and how long this has been occurring. You did not extend your investigation to determine if complete disinfection activities and proper documentation practices were followed.

Cleaning is a Science and should be treated as such!

Cleaning Operations

The disinfectant used to clean the interior of the ISO 5 **(b)(4)** is non-sterile.
The wipes used to clean the interior of the ISO 5 **(b)(4)** are not used in a manner that maintains sterility. The wipes are purchased sterile and are not individually wrapped. But the bulk package is opened and stored in an unclassified room.

Operators placed sterile wipes on a ledge below the filling line and later used the same wipes to clean the interior of the ISO 5 filling area cabinet doors and part of the filling area machine where open sterile vials were exposed.

Your firm used non-sterile wipes as part of your disinfection program for the aseptic processing areas.

The wipes used to clean the interior of the ISO 5 **(b)(4)** are not used in a manner that maintains sterility. The wipes are purchased sterile and are not individually wrapped. But the bulk package is opened and stored in an unclassified room.

Knowledge Gap

Phenolics	Do not kill spores, fungal or bacterial, bactericidal and virucidal claims, leaves residue Examples: Vesphene, LpHse
QACs	Do not kill spores, fungal or bacterial, bactericidal and virucidal claims, leaves residue Example: Intercept
Bleach	Kills spores, very unstable, available chlorine may vary depending upon time on shelf
H202	3% kills vegetative bacteria, greater than 6% sporicidal, safe enough to use for food industry

Knowledge Gap

PAA Chemistries	Mixture of peracetic acid and H2O2 forms a potent sporicidal agent
Aldehydes	Formaldehyde and Gluteraldehyde potent sporicides, highly carcinogenic
Alcohol	Sanitizer, 30% water required to seep through cell wall barrier and disrupt cell contents, some bacteria may use it as carbon source (pseudomonads)

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What organisms are tested for label claim?

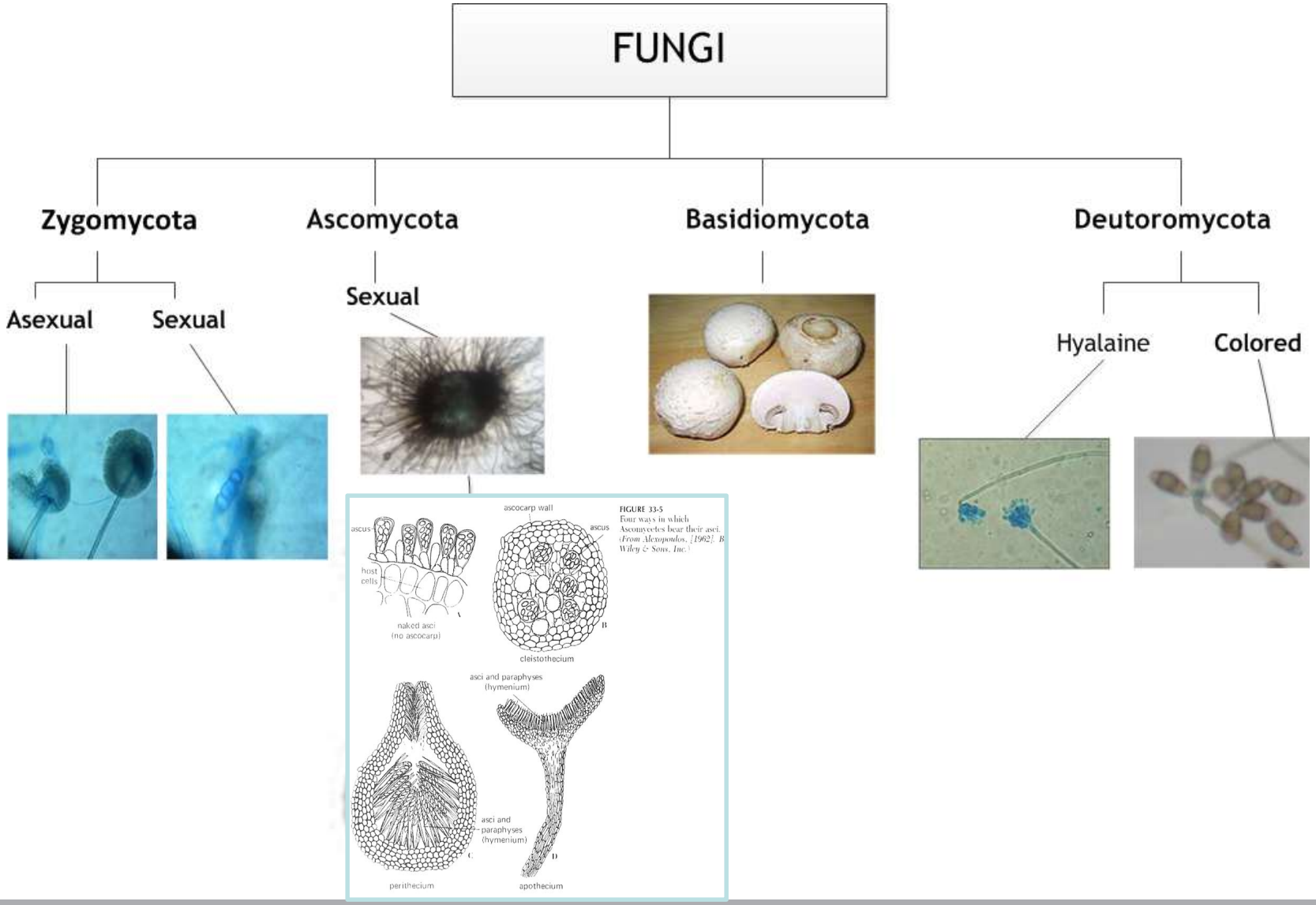
T. mentagrophytes for fungicidal claim
EU methods require a mold *A.niger* and a yeast *C. albicans*

AOAC for bacterial is *S. cholerasuis*, *S. aureus* and *P. aeruginosa* also common for many different regions and agencies

AOAC for sporicidal is an aerobic *B. subtilis* and an anaerobic *C. sporogenes*

Why label claims can be misleading and Aspergillus is not the toughest spore to kill

Fungi Found in Cleanrooms



A=Compatible, no significant effects noted
B=Material exhibited some minor reactions
C=Significant reaction-material still some performance qualities
NR=Exposure to product results in material failure

Material Compatibility

Material	Effect of		
	Minncare concentrate	3% Minncare Solution	1% Minncare Solution
Non Porous Materials			
ABS	B	A	A
Acrylic	A	A	A
C-PVC	A	A	A
Polyoxymethylene	A	A	A
Polyphenylene Oxide/Polystyrene	A	A	A
Polyamide	C	B	A
Plexiglass	A	A	A
Polycarbonate	A	A	A
Polyethylene	A	A	A
High-Density Polyethylene	A	A	A
UHMW Polyethylene	A	A	A
Polypropylene	A	A	A
Polysulfone	A	A	A
Polyurethane	NR	B	A
PVC (rigid)	A	A	A
Polyvinylidene Fluoride	A	A	A
Polytetrafluoroethylene	A	A	A
Anodized Aluminum	B	B	B
Copper	NR	NR	NR
Brass	NR	NR	NR
Stainless Steel	A	A	A
Elastomers and Epoxys			
Buna-N	NR	B	B
EPDM	NR	A	A
Ethylene Propylene (EPR)	B	A	A
Latex	NR	B	B
2-Chlorobutadiene	NR	NR	NR
Silicone	A	A	A
Vinylidene Fluoride	B	B	A
Epoxy Adhesive	NR	B	A
Epoxy Paint	NR	NR	NR

Material Compatibility

Case Study

Client found *Chaetomium globosum* on a belt in the filling line

They performed DE study; however the fungus could not be killed at routine or extended contact time

Client decided to increase the concentration of sporicidal agent from 1:100 to 1:50 dilution

End result: walls were eaten up, floors with pits

Panic: Sporicide is not good for the facility, stopped using the sporicidal agent and ……

Chemical Compatibility Overlooked

Cellulose and Bleach interaction
Cellulose and H2O2 interaction

Bleach (sodium hypochlorite) definitely reacts with cellulose.
It was the first treatment used to bleach wood and paper to make it turn white.

The problem with this is the efficacy against organisms will be used quickly and lost, bleach with a higher pH will react slower but also takes longer to kill microbes.

This happens with H2O2 as well, but with the addition of peracetic acid the ability to power through organics remains high.

Case Study:
Bleach used for disinfection of a stem cell facility, however cotton string mops were used

- Contamination prevailed until they changed from cotton mops to polyester mops

Chemical Compatibility Overlooked

Bleach and QAC interaction

Chemical Reactions from Mixing Bleach and Ammonia
Mixing bleach and ammonia is extremely dangerous, since toxic vapors will be produced.

The primary toxic chemical formed by the reaction is chloramine vapor, with a potential for hydrazine formation.

Case Study:
Invitro Diagnostic facility with major contamination issues

- Routine Disinfection Program was:
  - Cleaning with Quaternary Ammonium compound with follow-up disinfection with bleach
  - This program yielded no improvement in contamination control while leaving sticky floors and sticky work surfaces

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QAC Recalls

Infections Associated with Contaminated Antiseptic Products.

Product and Mechanism of Contamination	Clinical Outcome	Responsible Organism*
Iodophor, including povidone-iodine and poloxamer-iodine		
Intrinsic contamination	Peritonitis, replacement of dialysis catheter, pseudoperitonitis, pseudobacteremia, and infection at dialysis catheter insertion site	*Burkholderia cepacia* and *Pseudomonas aeruginosa*
Extrinsic contamination	None reported	—
Alcohol product		
Intrinsic contamination	Pseudobacteremia	*Bacillus cereus*
Extrinsic contamination	Bacteremia	*Burkholderia cepacia*
Chlorhexidine gluconate alone or with cetrimide		
Intrinsic contamination	None confirmed	—
Extrinsic contamination	Death, bacteremia, removal of indwelling central venous catheter in patients with cancer, replacement of dialysis catheter, pseudobacteremia, wound infection, and colonization	*Burkholderia cepacia*, *Achromobacter xylosoxidans*, *Ralstonia pickettii*, and *Serratia marcescens*
Quaternary ammonium compound, including benzalkonium chloride and benzethonium chloride		
Intrinsic contamination	None confirmed	—
Extrinsic contamination	Death, bacteremia, septic arthritis requiring prolonged antibiotic therapy (occasionally necessitating surgery), and injection-site infection	*Burkholderia cepacia* and *Mycobacterium abscessus*

* Responsible organisms are listed only for cases in which genetic-fingerprinting methods have confirmed the source of contamination. Contamination of antiseptic drug products may occur either during manufacturing (intrinsic contamination) or during manipulations by the end user (extrinsic contamination).

DE studies are subjective

Common DE Study Errors

- Dilutions not verified
- Dilution errors lead to erroneous results
- Analyst errors in dilution
- Recovery not adequate
- Neutralization not adequate
- Variability in recovery

DE study is to evaluate the chemical efficacy of the agent on hard surfaces using specific microorganisms

It is NOT validation of the cleaning procedure.

Case Study

- Concentrated and RTU Sporicide was sent for testing to a contract laboratory
- RTU showed efficacy on vegetative bacteria, spore formers as well and monilaceous fungi
- Concentrated Sporicide failed all the above

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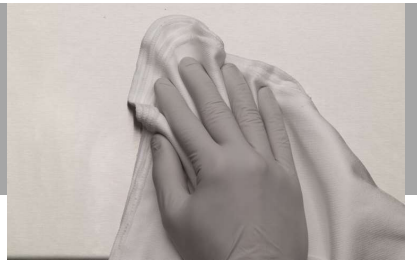


Cleaning Supplies and Materials

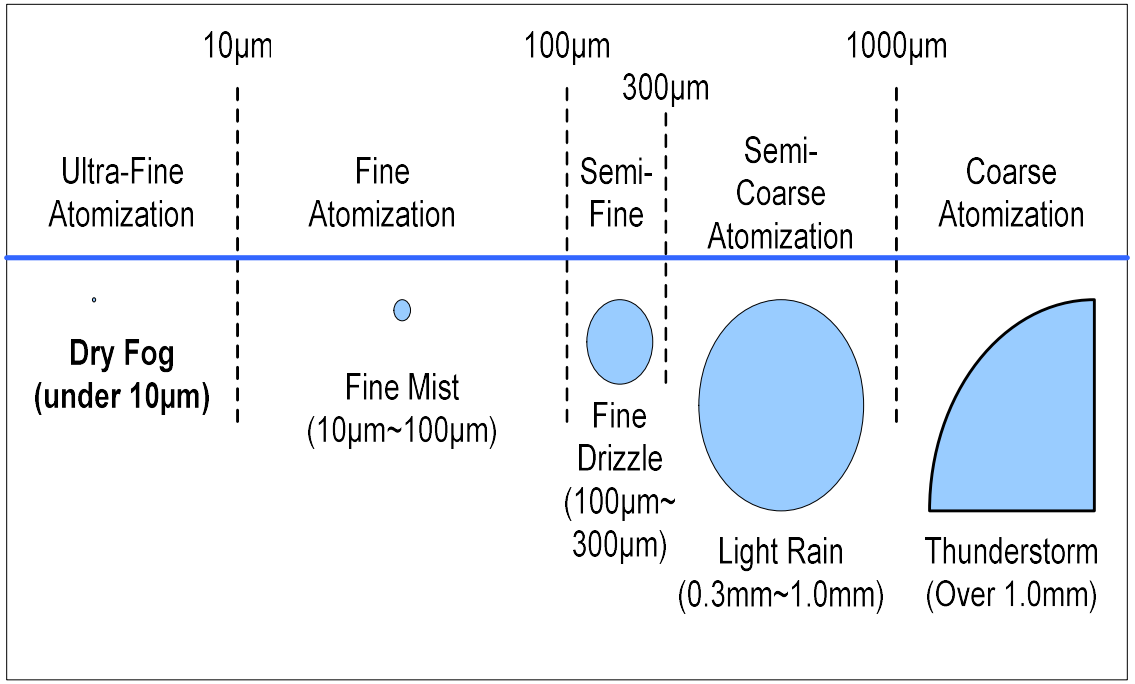
Physical Removal

- Absorb disinfectant
- Apply without soaking
- Reach nooks and crannies
- High retention capacity
- Break surface tension
- Low release of collected dirt and debris
- Not cellulose based when using bleach or hydrogen peroxide

Courtesy of Benchmark: 8-10x load capacity vs traditional polyester

Fogging

Does fogging help reduce risk?



- Sporicidal performance
- Distribution
- Coverage

Equipment Contamination Issues
Understand the Gaps

Risk Based Approach to Qualification/Validation

User Requirement Specifications

- Whether the intended validation effort is for equipment, cleanroom, processes or software, a User Requirement Speciation (URS) should be well written
- This facilitates a starting point and traceability to ensure that basic functions are established
- These basic functions will be used later for assessing risks
- Software validation typically also has a Functional Requirement Specifications (FRS) that follows the URS in a logical, traceable way. The FRS shows the way the software post-configuration will meet the requirements of the URS.

Risk Based Approach to Qualification/Validation

Risk can be detected early if the sequence of verification is adequate:

Cleanroom/Facility	Equipment
URS-User Requirement Specifications	URS-User Requirement Specifications
Design Verification by CFD	DQ- Design Qualification
Commissioning	FAT-Factory Acceptance Criteria
IQ-Installation Qualification	SAT-Site Acceptance Test
Static AFV	IQ-Installation Qualification
OQ-Operational Qualification	OQ-Operational Qualification
In-situ Air pattern analysis	PQ-Performance Qualification
Performance qualification	

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Traditional vs Risk Based

Traditional	Risk-Based Approach
(Product) User Requirements not Formally Documented	Process Requirements Documented, Approved
Protocols Developed from “Templates”	Risk Assessments: Determine Critical Aspects of Design
IQ/OQ Protocols “Preapproved” before risk assessment	Engineering Testing (“Commissioning”) Verification
Commissioning not Leveraged	All Documents with Technical Merit Used as Evidence of Fitness for Use
Engineering and “Validation” Personnel Often Distinct	Emphasis on Meeting Process Requirements
Emphasis on Documents – Not System Performance	

Equipment related contamination

Microbial Aspect of Cleaning Validation

- What is the function of the equipment?
- What are the performance requirements?
- What can cause failures?
  - Design
  - Cleaning
  - Sterilization
  - Testing
  - **Location**
  - **Cleanliness of location**
  - Aseptic connections
  - **Airflow around aseptic connections**
  - Personnel practices during aseptic connection
  - Hold times

Common Errors in Equipment and Components Cleaning

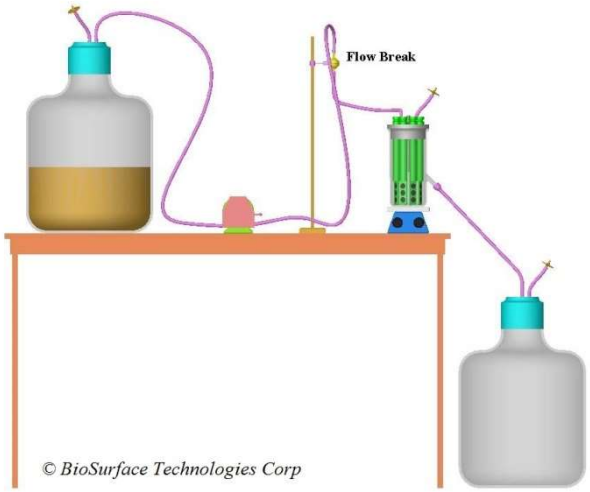
- Critical components of the microbial reduction/elimination plan not well thought through
- Strategy not well defined for addressing microbial contamination of parts and components
- Impact of raw materials, intermediates and APIs not understood
- Effect of microbial load from materials, environment and personnel not known
- Type of microbes hard to sterilize not considered
- Load of micro-organisms hard to sterilize not considered
- Biofilm formation not considered during developing cleaning validation
- Type of contamination vs choice of cleaning agent
- Method for testing may not be adequate

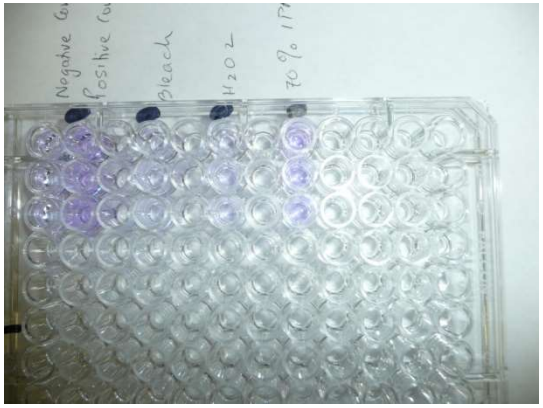
Cleaning Validation

- It is practically impossible to prove that production equipment is “clean” at the level of 100%
- Cleaning validation provides a means of proving that the contamination levels have been
  - reduced below contamination acceptance limits
- The cleaning validation program should involve a rational monitoring program to maintain a validated state
- Cleaning validation activity should cover :
  - active residue identification
  - active residue detection
  - method selection
  - sampling method selection
  - the establishment of residue acceptance criteria
  - methods validation
  - recovery studies
  - identification of equipment parts in direct contact with the product
- The good preparation and proper implementation of cleaning validation tools (matrices and tables) is a determinant factor in the success of a cleaning validation program

Cleaning validation can be simulated

Performing studies before changing cleaning procedures for equipment with biofilm





Process Related Contamination

Process Risk Assessment

Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes.

Aseptic behavior is described in AAI43 Aseptic Technique procedure, revision 32, dated 4.9.18. A. During the inspection, our investigators observed poor aseptic processing techniques that were previously videotaped at your facility
Operators were seen reaching over open vials during interventions. These vials were not removed from the line. Interventions are not executed using the closest door available. During the review of the video, we observed interventions on the far side of the filling area being executed from the near side of the filling area.
The addition of rubber stoppers is not performed aseptically. Stopper bag is held over the head of the operator and dangled through the XXX.
The bag touches the inside of the hopper and is shook to empty the stoppers bag. Smoke studies show the operator touching the inside of the hopper with his glove during addition.
The outer bag was removed up to 20 minutes prior to addition.
The inner bag was handled multiple times during this period.
Operators were seen touching their gowning. In one case the operator touched their lower leg/shoe, then proceeded to touch a stopper bag.
Fallen vials were not removed and instead replaced onto the line.

Process Risk Assessment

Though the aseptic filling process is validated using media fills, sterile filtration, equipment cleaning, equipment and component sterilization are validated, there are aspects that are difficult to validate due to variability. These include but are not limited to:

- Material transfer
- Disinfection and sanitization
- Gowning
- Aseptic technique
- Aseptic assembly

Even if media fill passes, there is no guarantee that interventions are risk free

This is the reason why all interventions (routine and non-routine) should be addressed during dynamic smoke studies and media fills

Process Risk Assessment

Filling Risk

- Vertical Laminar Flow-No barrier
- Vertical Laminar Flow-curtains
- Vertical Laminar Flow-hard enclosure
- Horizontal Laminar flow
- RABs
- Isolator
- Blow Fill Seal

Process Risk Assessment

Aseptic Filling Risk Assessment

- Risk in well designed and validated RABs is mainly due to interventions

Common errors:

- Gowning not adequate
- Gloves too short
- Settle plates at wrong locations
- Cleaning of RABs not adequate
- Monitoring equipment-continuous vs hand held

According to Reinmuller and Ljungqvist a gowned operator may release as many as 10,000 CFU/hr.

Crucial to identify airflow issues, RABS configuration BEFORE blaming the operator

Contamination Risk Assessment

System	Reliance on Personnel	Risk	Reasons
Filling in Passive RABS	Validation, Cleaning, Maintenance	High	Design issues, no pressure differential between Grade A and grade B environment
Filling in Active RABS	Validation, Cleaning, Maintenance	Moderate	Improved design, pressure differential (10-15 Pa) and airflow
Filling in BSCs	Certification, qualification, cleaning, location, level, maintenance	Moderate	Room design, airflows, proximity to other activities
Filling in Isolators	Qualification, validated VHP cycle, Transfer of materials, maintenance (gloves gaskets, etc.)	Low	If design is adequate and isolators adequately decontaminated with sterility assurance of transferred materials

Contamination Risk Assessment

System	Reliance on Personnel	Risk	Reasons
Filling in Curtained areas	Cleaning, qualification, support areas	Very high	Flexible, swing, hard to clean, personnel in contact with unclean curtains, curtain material not validated for disinfection efficacy
BFS	Same as isolator	Moderate	Same as isolator

Process Risk Assessment

Container Risk Assessment

- Sterilization of container closures
- Container design
  - Ampule/vial
  - Size of container
  - Size of opening
  - Syringe
  - Multi chamber
- Container feed
  - Oven fed
  - Tunnel fed
  - Any other method of feed

Process Risk Assessment

Lyophilization Risk

- Manual loading
- Automatic loading
- No trays

Transfer to Lyophilizer

- Trays on cart
- Trays on LF cart
- Conveyer

Sterilization

- Sanitization only
- Sterilization of chamber
- Sterilization of chamber and condenser

Process Risk Assessment

Routine interventions; e.g. replenishing of components or monitoring activity

- Time taken for non-routine intervention cannot be estimated; such as stopper jams, fallen or broken vials
- Defective seals
- Leaks
- Mechanical failures where manual work is required
- Such interventions should be considered during airflow studies (smoke studies) and media fills

Process Risk Assessment

High Risk

- Containers with large openings
- Slow filling speed
- RABS or BSCs

Low Risk

- Isolators
- Automation
- Small containers
- High speed filling

Common Errors in Environmental Monitoring

483 Regarding Risk Based Monitoring

"Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

You have inadequate scientific justification for your environmental monitoring sampling plans in manufacturing areas for aseptically-filled injectable drug products. This includes the locations of viable airborne particulate sampling, settle plates, and contact surface monitoring."

483 Regarding Risk Based Monitoring

"Your EM data for the filling areas did not specify the sampling location of the RABS (b)(4) used during filling and (b)(4) operations. SOP QCD/MIC/034-10 *Procedure of Surface Monitoring by Swab* does not require sampling from predetermined (b)(4) locations identified as critical risk points of your filling and (b)(4) operations. Instead, the procedure permits individual operators to determine the location to be sampled. Additionally, you only collected a (b)(4) swab sample from (b)(4), and failed to sample other (b)(4) used in daily aseptic operations."

Aerobic and Anaerobic Monitoring

Product risk due to aerobes as well as anaerobes should be understood

GAP: Sterility samples are screened for anaerobes, however anaerobic monitoring of the sterility test environment is not performed

- Though obligate anaerobes may not be present in the environment, facultative anaerobes are prevalent and may not grow aerobically but may show up during sterility testing
- Media and incubation should be adequate for recovering environmental organisms, process organisms
- Media should be adequate for neutralizing disinfectants and cleaning agents
- Some gases may get contaminated with anaerobes

Inspectors Expectations/Draft GMP (PIC/S and EU) Annex 1:

Environmental Monitoring as Addressed in Draft Annex 1:

Particle counters should be qualified (including sampling tubing). **Portable particle counters with a short length of sample tubing should be used for qualification purposes**.

Case Study: Inspector's Comment Particle Sample Tubing

Regulatory Thinking on Particle Sample Tubing:

GMP Annex 1: Clause 11

Cleanroom and clean air device monitoring

- "The system selected must be appropriate for the particle size considered.
- Where remote sampling systems are used, the length of tubing and the radii of any bends in the tubing must be considered in the context of particle losses in the tubing."

PIC/S Recommendation: "GMP Annex 1 Revision 2008, Interpretation of Most Important Changes for the Manufacture of Sterile Medicinal Products" January 2010

- "Recommendation: This section addresses concerns especially for the sedimentation of 5 µm particles in remote systems **(as a rough example, s-shaped bent tubing of 1.5 m length can already absorb about 30% of the 5 µm particles.)"**
- "The company must qualify their particle sampler and sampling system for both particle sizes, 0.5 µm and 5 µm."

Case Study: Inspector's Comment Particle Sample Tubing

Sample Tubing for NV Particle Counting:

ISO 14644-1:2015 for Particles >5 micron, no greater than 1 meter

[1] Bend Radius (>15cm)

[1] ASTM F50-12:2015 Standard Practice for Continuous Sizing and Counting of Airborne Particles in Dust-Controlled Areas and Clean Rooms Using Instruments Capable of Detecting Single Sub-Micrometre and Larger Particles

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483 Regarding non-viable monitoring

"No representative non-viable particle (NVP) monitoring data supports your current ISO-5 classification for the product path from the (b)(4) to the (b)(4), which transfers product to the (b)(4) during aseptic processing of finished drug products.

During our inspection, **we documented that your NVP probes are placed (b)(4) surface instead of near the working area**. Placing the probe (b)(4) instead of near the working area means **you are unable to detect NVPs where sterile drugs are exposed during aseptic processing.**

Additionally, transferring (b)(4) vials from the filling suite to the (b)(4) can take up to (b)(4). This **extended exposure time** may increase contamination hazards. However, your firm lacks adequate environmental monitoring of this part of the operation. **It is essential that your sampling plan include areas where (b)(4) and product are exposed to the environment,** and at greater risk of contamination."

ISO 14698-1 Properties of an Air Sampler

Air Sampler ability to capture organisms (via particle Impaction) for incubation and counting.

Physical Efficiency:

The ability of the air sampler to collect various sizes of particles. Regardless whether the particle is a micro-organism, carries a microorganism, or is an inanimate particle. This is the slit or hole size, the sample air velocity and the distance between the plate and inlet jet.

Biological Efficiency:

The efficiency in collecting microbe-carrying particles. Biological efficiency will be lower than physical efficiency for a number of reasons, such as the survival of the micro-organisms during collection and the ability of the collection medium to support their growth.

Trends

Through EM trends, regulators want to know:

- That the facility is running in a state of control
- Facility bioburden is consistently within established limits
- There are no major contamination episodes
- Organisms prevalent in the environment are not objectionable via the mode of administration
- Trends are adequately documented and reviewed on a frequent basis
- If there are adverse trends observed, they are investigated and product risk assessed

Quality Control

Assessing Risk During Testing

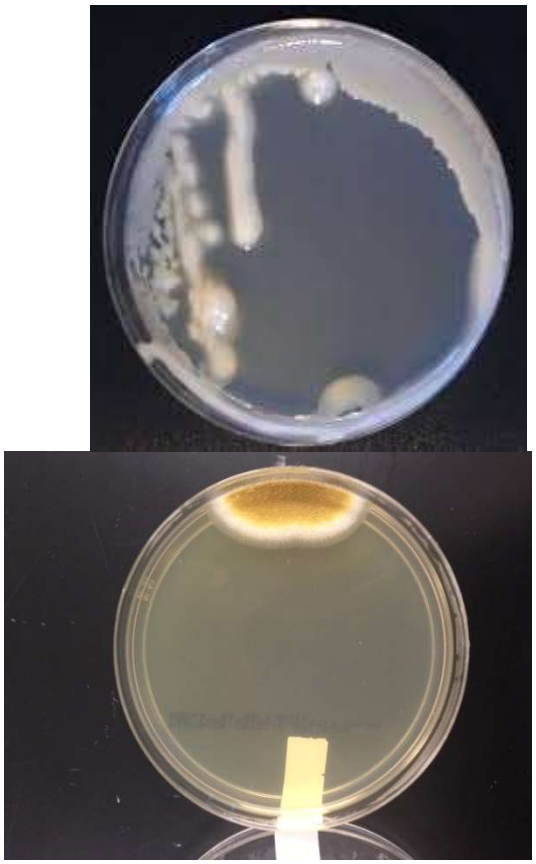
Common laboratory errors that lead to false positive of negative results

- Laboratory design and operations
- Separation of clean and dirty operations
- Cleaning and disinfection
- Flow of materials and personnel
- Technique
- Storage of cultures
- Validation of test method
- Testing for more organisms than required by compendia
- Reading errors
- Review expertise
- Training

Quality Control of Media is Critical

Common causes for erroneous results :

- Discoloration or hemolysis
- Storage location
- Integrity of packaging
- Broken or cracked petri dishes
- Quality and accuracy of labeling
- Condensation in petri dishes
- Retracted medium
- Dried and cracked media
- Sloped or uneven filling of pe
- Contamination
- Gel strength
- Pitted surface or large bubbl
- Presence of leakage….



Case Study: Dried out Media/Data Integrity

- **Risk assessment has been misused to justify a decision, hide issues but not to assess real risk**
  - The intent of QRM is to make data-driven and scientifically sound decisions **Proactively** not **retroactively!**
  - Many companies who are cited for failures or data integrity have a QRM system and have assessed risk with loads of paperwork

Case Study:

- Company cited for **dried-out media**. However just prior to the citation they had performed a study/risk- assessment to prove there was no risk in using the dried-out media.
- They used their "**own select challenge organisms**" (specifically chosen to survive the low moisture content of the compromised media).
- The study was performed before an upcoming and anticipated regulatory inspection.
- Data integrity issues were related to no growth in the EM plates during media fills and production filling.

Differentiate between

Regulation: A rule or order issued by an executive authority or regulatory agency of a government and having the force of law

Standard: In essence, a standard is an agreed way of doing something

Compendia: A collection of concise but detailed information about a particular subject, especially in a book or other publication

Guidance: Advice or information aimed at resolving a problem or difficulty, especially as given by someone in authority

Publication: To publish is to make content available to the general public

Usually applied to text, images, or other audio-visual content on any traditional medium, including paper (newspapers, magazines, catalogs, etc.)

AND THEN THERE IS HERESAY…

If you have any questions regarding the content of this presentation, please feel to contact me at zabraham@microrite.com