潔淨室與潔淨空氣設備(Isolator或RABS)去汙染(Decontamination)程序的開發與確效

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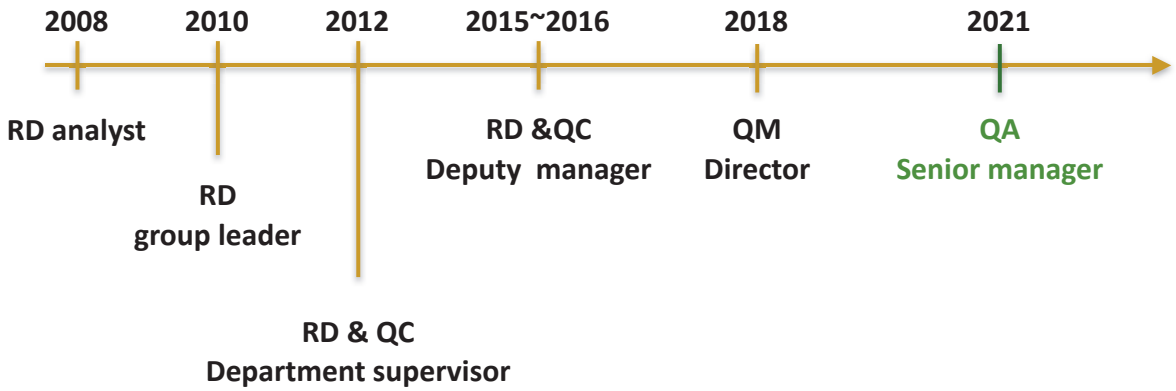
報告日期　：2021.11.01

110TPDA04029

Self introduction



Injection product

WARNING LETTER

Customceutical Compounding

MARCS-CMS 610092 — AUGUST 25, 2020

1. The investigators observed poor practices during aseptic processing, including a technician failing to sanitize materials prior to placing them into the ISO 5 classified area. In addition, personnel engaged in aseptic processing exposed facial skin within the ISO 5 classified area.

4. Your firm used non-sterile cleaning wipes inside the ISO 5 aseptic processing area.

5. Personnel failed to adequately sanitize equipment held in your laminar flow hood. In addition, personnel did not allow adequate disinfectant contact time to achieve sporicidal effect.

Hawaii Health Systems Corporation dba Kona Community Hospital Pharmacy

MARCS-CMS 611130 — FEBRUARY 01, 2021

4. Your firm used a non-sterile disinfectant within the ISO 5 aseptic processing area.

WARNING LETTER

Infuscience, Inc. dba Bioscrip Infusion Services

MARCS-CMS 609526 — DECEMBER 21, 2020

6. Materials or supplies were not disinfected prior to entering the ISO 5 classified aseptic processing areas from the ISO 7 classified areas.

7. Disinfectant contact time and coverage of the item intended to be disinfected were inconsistent with the manufacturer's and firm's instructions and there was no assurance that adequate levels of disinfection were achieved.

WARNING LETTER

Family Pharmacy of Statesville, Inc.

MARCS-CMS 611664 – NOVEMBER 06, 2020

1. Your firm did not use a sporicidal agent in the ISO 5 areas.

2. Your firm re-used bottles containing **(b)(4)**, for use in the ISO 5 area, without assurance that the bottles remained sterile after multiple uses. In addition, commercially purchased sterile wipes, for use in the ISO 5 area, were stored in a manner which increases the potential for contamination to be introduced onto the wipes.

Agenda

- Definition of decontamination
- The considerations prior to decontamination
- The methodology of decontamination
- Design & Development of Decontamination Process for Cleanroom (Grade B) Decontamination
- Design & Development of Decontamination Process for Clean Air Equipment (Isolator & RABS of Grade A)
- Validation of Decontamination Process.
- Conclusion

Definition of Decontamination

Decontamination – The overall process of removal or reduction of any contaminants (chemical, waste, residue or microorganisms) from an area, object, or person. The method of decontamination used (e.g. cleaning, disinfection, sterilization) should be chosen and validated to achieve a level of cleanliness appropriate to the intended use of the item decontaminated.

~ 2020 PIC/S 2nd draft annex I

Decontamination is a broadly defined term used to describe a variety of processes that reduce microbial populations without an expectation for total kill.[1] It is not a substitute for sterilization; a sterilization process should be used wherever possible. A variety of chemical agents and methods are used that vary depending upon the application. Decontamination is used for bioburden reduction of materials, equipment, and environments in support of sterile product manufacture:

- For materials and surfaces that cannot be sterilized
- For materials and surfaces that do not require sterilization

[1] Sterilization is preferred over decontamination and should be utilized wherever possible, consistent with minimization of handling post-sterilization.

~ USP41 <1211>Sterility Assurance

Decontamination

A process that is designed to remove soil (including microorganisms) and may consist of cleaning and/or disinfection.

~ PDA technical report 51

Definition of Decontamination

Clean

⇓

Disinfection

Decontamination

Decontamination of controlled environments and non-product contact surfaces

- In conventional cleanrooms, including restricted access barrier systems (RABS), this is predominantly a manual process performed after cleaning of the room/production line
- Decontamination of items upon transition into an environment of higher classification
- Isolators commonly use an automated process
- Periodic decontamination of operator gloves during processing

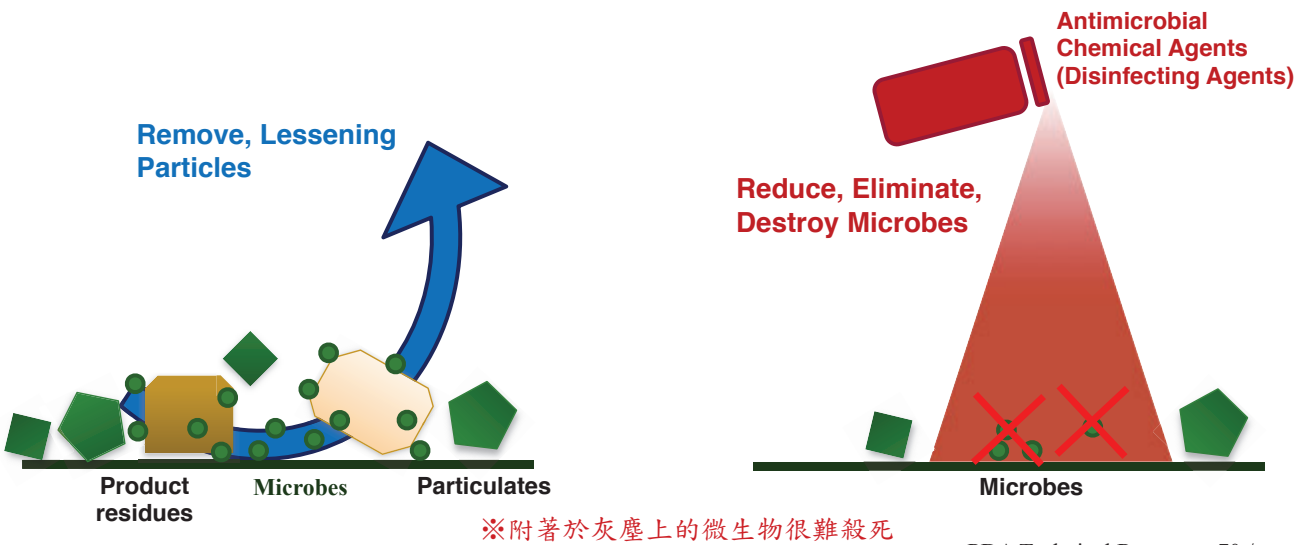
Decontamination of product contact surfaces

- Large equipment (e.g., stopper bowls) can be manually sanitized on a frequent basis in addition to sterilization to avoid the extensive manipulation required for their installation post-sterilization[2]
- Re-decontamination of sterilized equipment after aseptic assembly or intervention
- Periodic decontamination of previously sterilized utensils prior to interventions

~ USP41 <1211>Sterility Assurance

The considerations prior to decontamination

Clean → Disinfection



※附著於灰塵上的微生物很難殺死

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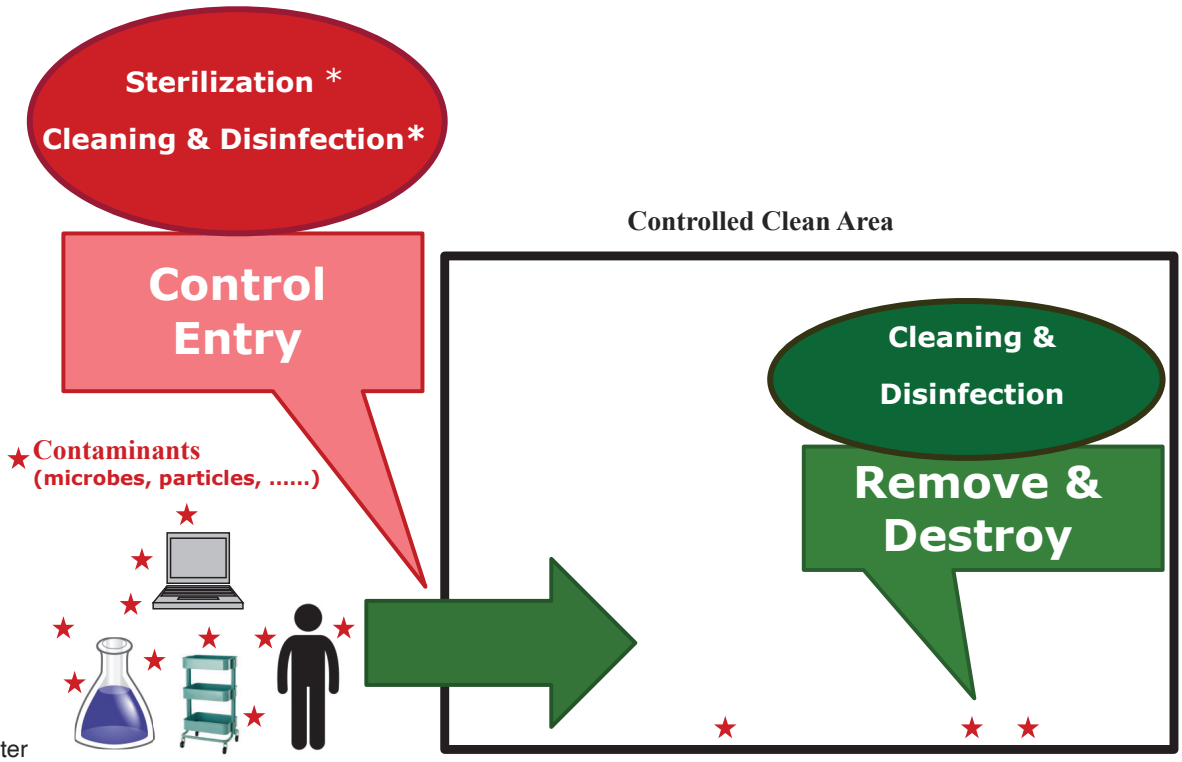
"Control of the Environment"



Air
Water
Personnel
Components(stoppers, vials, plungers…)
Instruments
Reagents
Tools
……

*Grade A/B: Sterilization if possible

Grade C/D: Cleaning & Disinfection when acceptable

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The methodology of decontamination
- Clean
- Disinfection

Application Methods

Spraying:
- Produce the best wetting of surfaces: Lager droplets
- Lack mechanical actions: Not clean the surface

Mopping:
- Mechanical action: remove residues, viable and non-viable contamination
- Not uniform wetting as spraying
- Not sufficient to provide the required amount of disinfectant agent contact time.

Wiping:
- As Mopping
- Smaller surfaces: door handle, return vents, equipment, carts and pass-through area.

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Application Methods

Fogging or Gassing:

- Excellent results but does require longer of time to ensure adequate distribution of the agent and sufficient surface contact time.
- Fogging: Fine droplet; Gassing: gas form
- No mechanical force: Not clean the surface
- Safety consideration
- Chemical agents commonly used gassing or fogging of clean rooms include the following:
  - Paraformaldehyde
  - Peracetic acid/ hydrogen peroxide
  - Phenols
  - Bleach (dilute solution of sodium hypochlorite, also called "liquid bleach".)
  - Quaternary ammonia
  - Vapor phase hydrogen peroxide (VHPH)
  - Gaseous chlorine dioxide
  - Ozone

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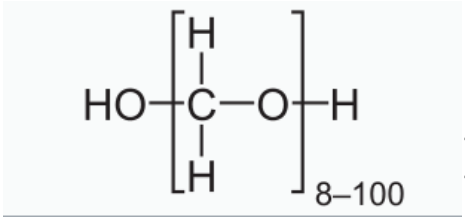
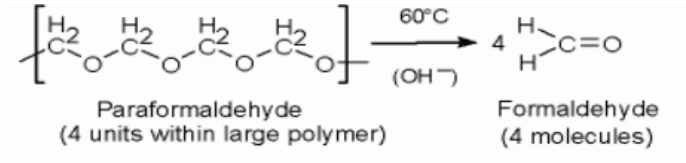
Gassing - Paraformaldehyde

- Large-scale clean room decontamination methodology for many years
- Heating of paraformaldehyde to release formaldehyde gas
  - Portable fans are set up prior to the creation of the gas
- The utmost safety concern-a potential carcinogen



Paraformaldehyde:
the polymerization product of formaldehyde with a typical degree of polymerization of 8–100 units.



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Ozone Gas

- Gassing small or large scale operations
- Ozone is made by adding high voltage to oxygen
- High concentration of ozone gas (200 ppm or more, relative humidity of 80% or more)
- Safety concerns
- Residues that are left behind on product-contact surfaces are also a significant concern and must be evaluated.

Ozone is very reactive and because most pharmaceutical products are susceptible to ozone attack, product quality may be affected.

Gaseous Chlorine Dioxide

- Similar to paraformaldehyde or VPHP rather than wet droplet fogging, as it is a gas product
- Corrosion, residual and safety

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Wet Droplet Fogging

- Generation or vaporization of small liquid droplets from a chemical agent that is placed into an air steam by a generator that is linked to a fogging device.
- Droplets usually range in size from 10.0 to 25 .0 microns.
  - Dry Fog is a very fine fog with an average mean droplet diameter of 10 µm or less.
- Portable fans are used to circulate the droplets throughout the room
- Efficacy is based on the fogging time and the chemical agent used.
  - Peracetic acid and hydrogen peroxide, sodium hypochlorides, phenols, and quaternary ammoniums are normally used
- Lightly coat all surfaces with a thin but constant layer of chemical agent for an extended period.
- Once inhalation concerns are acceptable, end users could enter areas and dry any surfaces that are not completely dried.
- Depending on the chemical agent used, corrosion and residual can be controlled. However, with overuse and without manual cleaning procedures, residues can build up over time and corrosion can occur.

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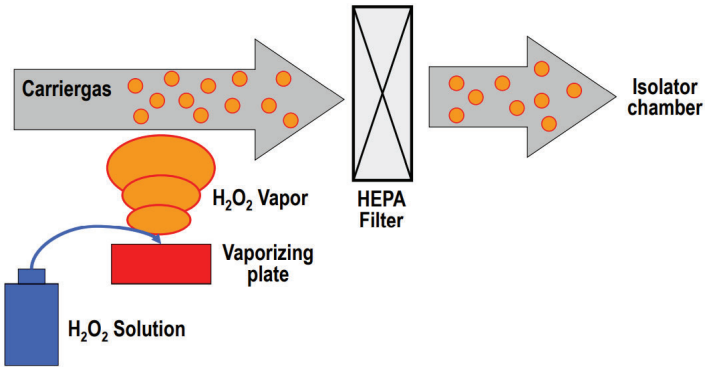
Vaporized Phased Hydrogen Peroxide (VPHP)

- Noncarcinogenic
- $H_2O_2 \rightarrow H_2O + O_2$
- Vaporized 35% hydrogen peroxide (250-1200 ppm) in to manufacturing areas through portable or fixed distribution systems but not a cleaning step
- Considered a disinfection step rather than a sterilization process
- Leaks to the external environment and clearance time should be tested and assessed properly to assure safety
- Conclusive studies proving validation of the system are specific to the operation and the setup where it will be used. Each area should be assessed for effectiveness in its own validation study



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Types of Disinfecting Agents

Agents	Vegetative Micro-organisms	Bacterial, fungal spores	Ingredients	Example
Sanitizer	√ (+)	X	Alcohols	70%EtOH 70%IPA (better than EtOH)
			H_2O_2	<3%
Disinfectant	√ (++)	X	phenols	LpH
			Quaternary ammonium	ABQ -50 Tego 2000
			H_2O_2	3%-5%
Sporicide	√ (+++)	√	Sodium hypochlorite	bleach
			Peracetic acid	Minncare Cold Sterilant
			Ozone	8% by weight
			H_2O_2	≥6%

PDA Technical Report no.70 page.05 & 18,
USP<1072> page.03

“Resistance”

Antibiotics

Disinfecting Agents

??

圖案來源：網路下載

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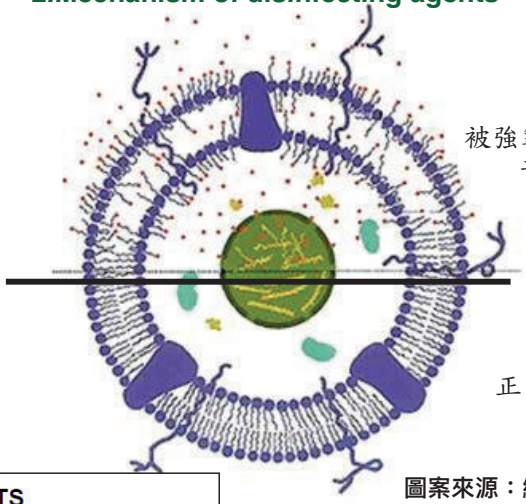
“Resistance”

Resistance to Disinfecting Agents in Aseptic Manufacturing Facilities

免煩惱!!

1.High concentration v.s. Low population

2.Mechanism of disinfecting agents

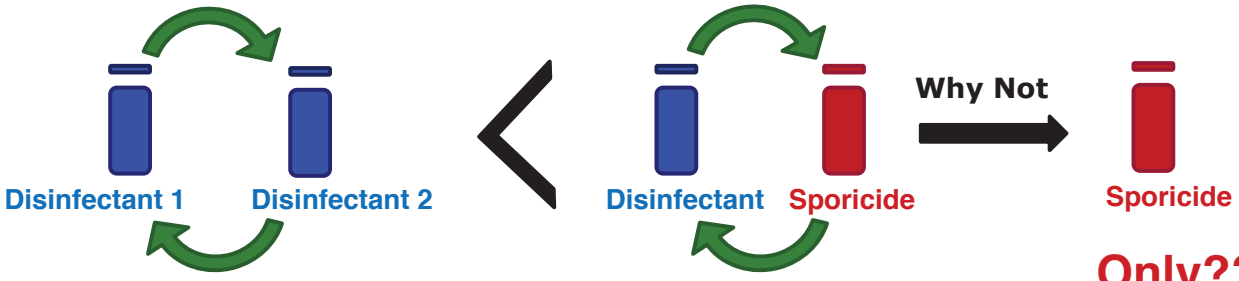


圖案來源：網路下載

MICROBIAL RESISTANCE TO DISINFECTANTS

The development of microbial resistance to antibiotics is a well-described phenomenon. The development of microbial resistance to disinfectants is less likely to occur at significant levels, as disinfectants are more powerful biocidal agents than antibiotics. In addition, they are normally applied in high concentrations against low populations of microorganisms usually not growing actively, so the selective pressure for the development of resistance is less profound. However, the most frequently isolated

USP<1072> page.06



Only??

SANITATION

61. The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written programme. Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the development of resistant strains.

PIC/S GMP annex I 2021

Disinfection

4.36 The disinfection of cleanrooms is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programme. For disinfection to be effective, prior cleaning to remove surface contamination should be performed. More than one type of disinfecting agent should be employed to ensure that where they have different modes of action and their combined usage is effective against all bacteria and fungi. Disinfection should include the periodic use of a sporicidal agent. Monitoring should be undertaken regularly in order to assess the effectiveness of the disinfection program and to detect changes in types of microbial flora (e.g. organisms resistant to the disinfection regime currently in use). Cleaning programs should effectively remove disinfectant residues.

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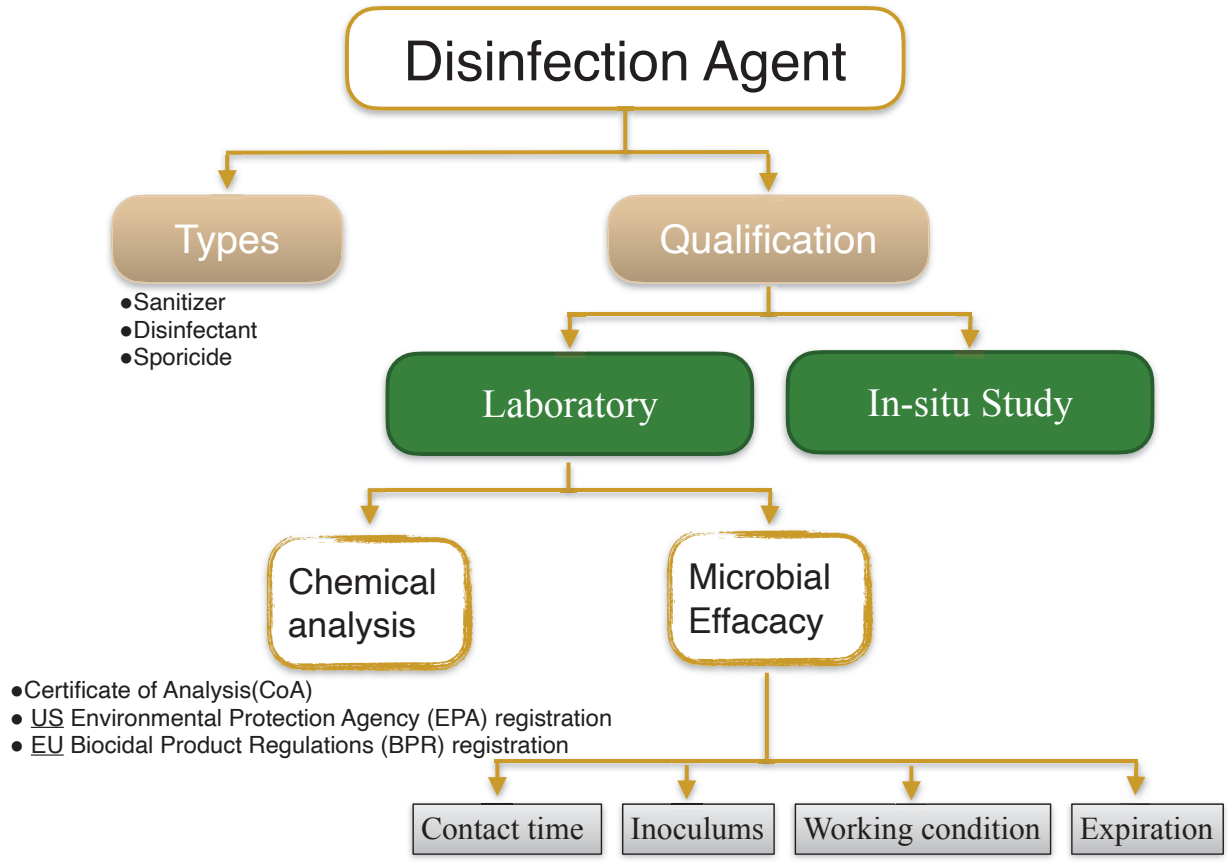

Contact time | Inoculums

Agents	Contact time	Minimum Reduction	
		PDA TR70	USP<1072>
Sanitizer	Sufficient (Max 90 sec) but **< 120 sec**	>1 Log	Vegetative: ≥ 3 Log
Disinfectant	Sufficient (1-5min) but **< 10min**	>1 Log	Vegetative: ≥ 3 Log
Sporicide	Sufficient (1-5min) but **< 10min**	>1 Log	Vegetative: ≥ 3 Log Spore: ≥ 2 Log

Contact Time!!

PDA Technical Report no.70 /page.10,14,18,24,31

USP<1072> page.07

Working condition

- Nature of disinfected surface
- Residue wipe down
- Inoculums
- Concentration
- pH
- Temperature ……etc.

◆**Corrosion: Rust or pitting**
Metal surfaces + Chlorine-containing products / IPA對壓克力板有輕微腐蝕性

◆**Chemical incompatibility with the surface: Melting, softening, immediate discoloring**
Softer, lower-grade metal + Peracetic acid/ H_2O_2

◆**Drying:**
Vinyl, Plexiglas, Kydex, Mipolam, epoxy + Peracetic acid/ H_2O_2 / Alcohols

◆**Discoloring or staining:**
Phenols/ Iodine

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Disinfection Agent		殘留特性, 使用後需以70% IPA 擦拭
Sanitizer	Alcohols (EtOH, IPA)	不殘留，不需後續擦拭
Disinfectant	phenols	殘留，建議擦拭
	Quaternary ammonium	殘留，建議擦拭
Sporicide	Sodium hypochlorite	殘留，建議擦拭
	Peracetic acid	殘留，建議擦拭
	H_2O_2 (≥6%)	不殘留，不需後續擦拭

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Expiration

1.Disinfecting agents

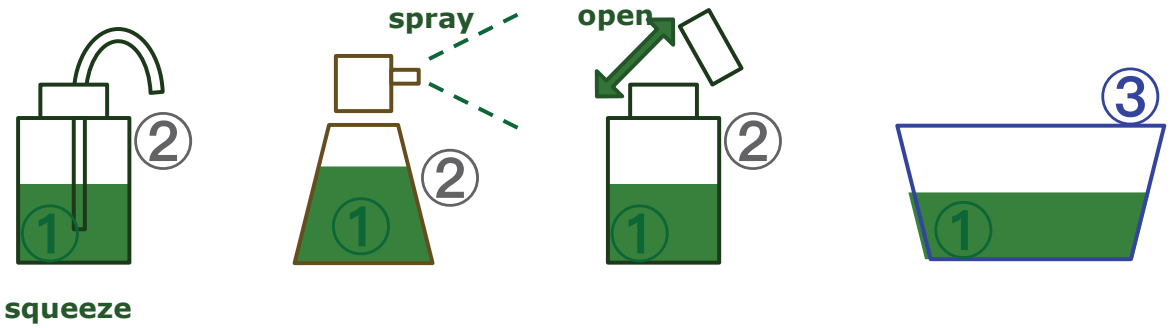
A. Not Opened: Manufacturer's expiration date
B. Opened, diluted: in-house study.

2.Container

A. Bioburden level

3.Open bucket

A. Discard the contents upon completion of the cleaning operation



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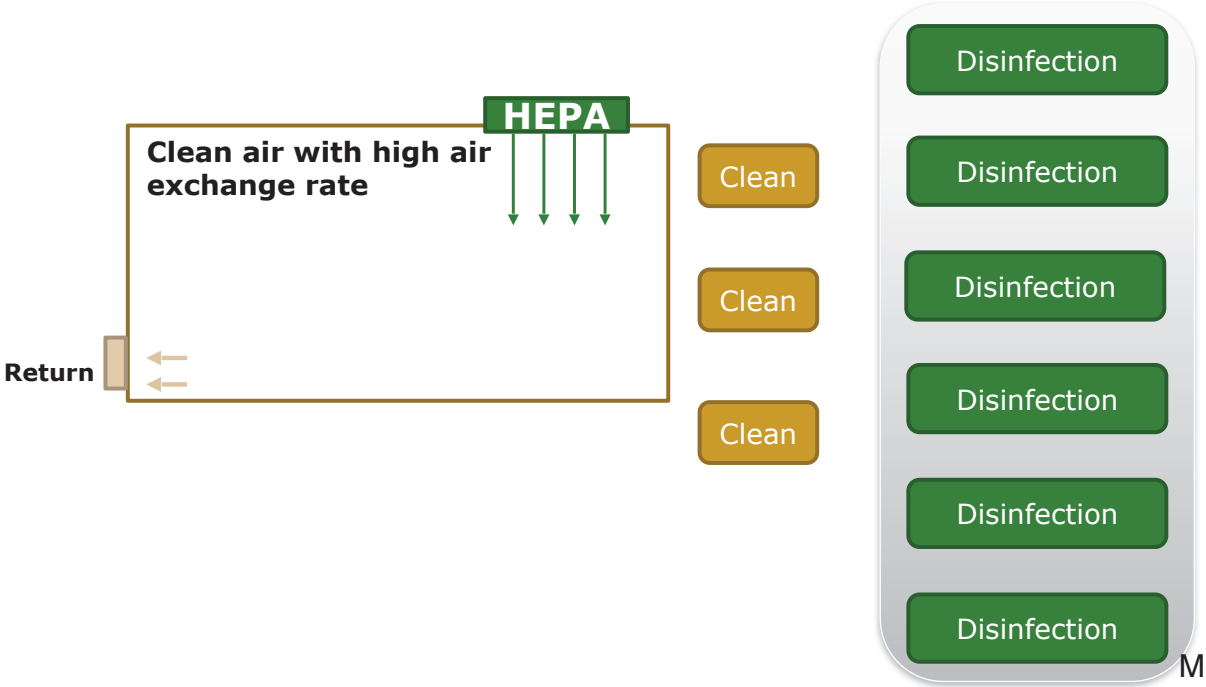
Design & Development of Decontamination Process for Cleanroom (Grade B) Decontamination

Decontamination procedures in grade B cleanroom

- An established frequency
- An adverse trends and/or a return from a shutdown
- Routine disinfection conducted without a prior cleaning step



More frequently!!

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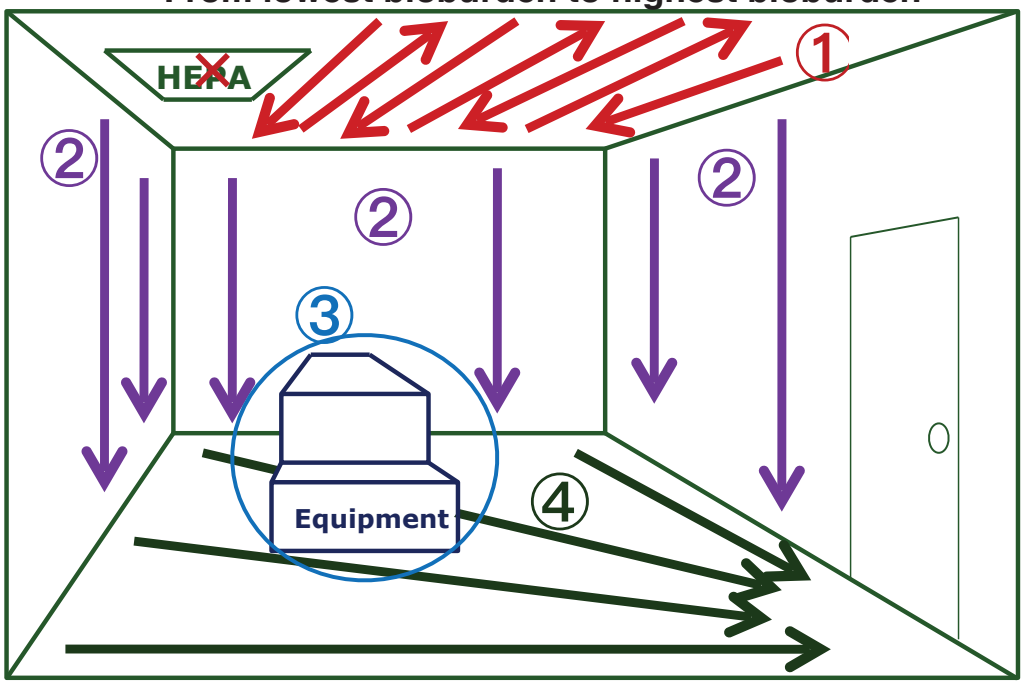
Decontamination of Grade B cleanroom

From lowest bioburden to highest bioburden



Ceilings(not HEPA filters)→ Walls → Equipments → Floors

(Agents may degrade filter matrix) (Top to Bottom) (Further to closer to the exit)

1. Cleaning agent (high surfactant based product)
Ceilings (Not HEPA filters)→ Wall → Equipment → Floor in a succession from the furthest point to the closest point to the room exit.

2. Squeegee: Remove the excess the liquid and contaminants
Ceilings (Not HEPA filters) → Wall → Floor in a succession from the furthest point to the closest point to the room exit.

3 Sterile dry mop/wipe/HEPA-filtered wet vacuum
Lift the dirtied liquid from the area

4. Mop/spray/wipe: wet the surfaces sufficiently with sterile disinfecting agent.
Ceilings (Not HEPA filters) → Wall → Floor in a succession from the furthest point to the closest point to the room exit.

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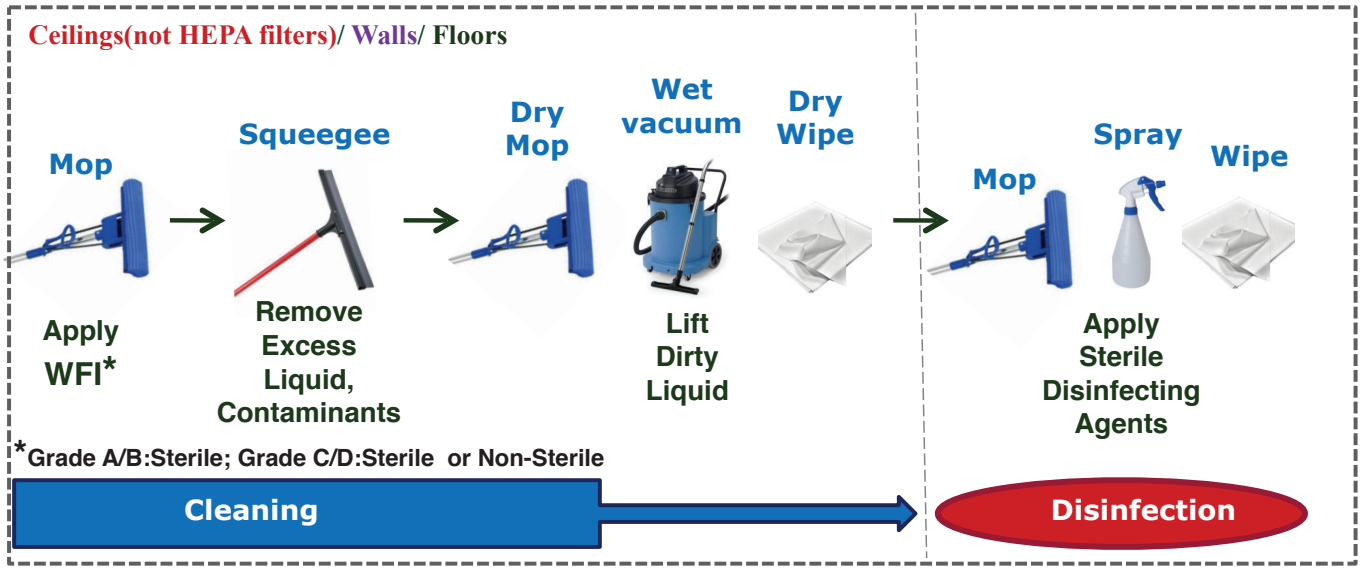

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Decontamination of Materials

Curtains

- Material substrates: most vinyl
- Difficult but critical activity: soft surface, rougher
- Clean: high-surfactant-based cleaning product or 70% IPA + mechanical force(wiping or mopping).
- Disinfectant/Sporicide: H_2O_2 or peracetic acid (normally a minimum of five minutes)
- Greater frequency than wall surface since they may come in contact with personnel more frequently.

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Decontamination of Equipment Surfaces

Non-product-contact Equipment Surfaces

- Critical location (close to product-contact surfaces): do not leave the residue that may be transferred inadvertently to a product-contact-surface.
  - ✓ Chemical agent, fibers from wipes…
  - ✓ Preclean for any product spills, broken glass, torn stoppers, damaged caps and other foreign matter before attempting disinfection.

Work Surface

- Work tables ,carts and setup areas: near product or components that come in contact with product.
- Frequency of cleaning is normally daily but should be based on usage.

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Decontamination of Equipment Surfaces

Nonstructural Clean Room and Hard-to-Clean Surfaces

- Routinely clean and disinfection and the frequency should be based on environmental monitoring results and/or a risk-based analysis.
- The surface is visibly free from particulate and residue.

Routine Nonstructural Surfaces	Hard-to-Clean Surfaces
Tanks	Tops of doors
Carts	Tracks
Countertops	Conveyers
Racks	Phones
Packaged supplies on racks	Equipment feet and legs
Storage bins	Underside of tanks, carts, and equipment
Stairs	Wheels
Exterior of tubing or pipes	Incubators, refrigerators, and cold rooms
Work surfaces	
Non-product-contact surfaces	
Non-product-equipment	
Monitors, samplers, gauges	
Tools (sterilization may be required)	

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Hold Times For Cleaned Areas, Non-Product-Contact Equipment, and Utensils

Cleaned Area or facility

Studies should be based on viable and nonviable sampling performed after cleaning and disinfection and at or beyond the maximum time allowed between cleaning and sanitization.

- Include the normal level of non-production activities.

Non-product-contact equipment and utensils

Those materials should be stored in a manner that ensures integrity is maintained for the established hold times.

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Return From a Shutdown

A shutdown is a planned or required stoppage of operations that is likely to compromise the environmental conditions in the classified area.

- Regularly scheduled activities: preventive maintenance…
- Unscheduled activities: unexpected power outages…

Bring the area or facility back to a state of control in accordance with the area's environmental classification.

Clean → *Disinfection* → *Monitoring data*

Decontamination process should be supported with *in-situ data*

Viable and Non-viable

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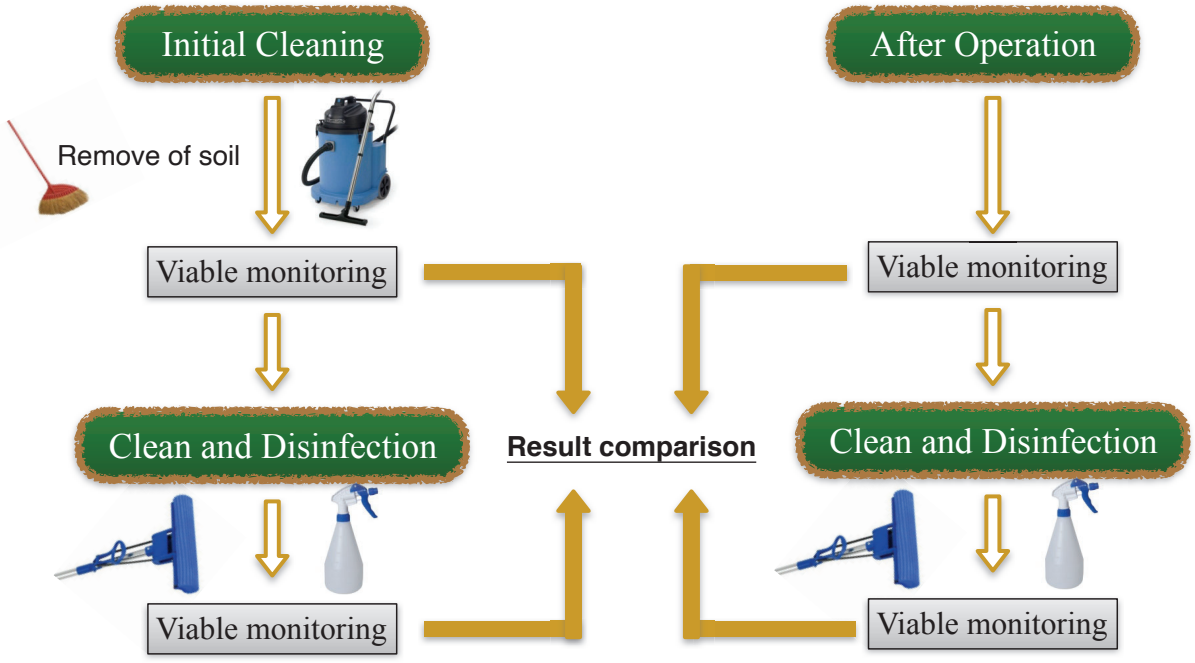
In-Situ Study

Start-up of a Facility or Area
(Open/after shutdown/area modification/idle)

During Routine operation



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Design & Development of Decontamination Process for Clean Air Equipment (Isolator & RABS of Grade A)

Points to Consider for the Aseptic Processing of Sterile Pharmaceutical Products in Isolators (PTC-isolator)

Q: What are the special considerations for cleaning and disinfecting isolator interiors (nonproduct contact surfaces) prior to decontamination?

Recommendation

The qualification or validation of the cleaning and disinfecting of nonproduct contact surfaces should be based on risk assessment. The cleanliness of nonproduct contact surfaces should be visually verified, at the least.

Cleaning process

1. Process and product requirement
2. The design of the isolator interior
3. The surfaces to be cleaned

a. Location of surface within the isolator
b. Activities performed at given location
c. Material surface quality and cleanability
d. Effect of product or foreign material residue (including cleaning material residue) on decontamination process

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Disinfection process

- A disinfection process may establish a baseline prior to the decontamination of the isolator interior.

The definition of the required level of inactivation in terms of BIs.

Lower levels of log reduction may be acceptable in areas

Critical Area (Aseptic processing)

minimum of 6-log reduction BI

Temperature mapping, chemical indicator mapping, vapor distribution, and BI mapping are among the methodologies used for determining worst case location.

PDA TR.51/page 30

The decontamination process may depend on the level of bioburden

- Normal bioburden, common practice to apply at least the ISO 8 limit “in operation” for open and closed isolators with gloves.

  Note: *Current FDA guidance recommends a background environment of no less than ISO 8 in operation; current EU GMP Annex 1 recommends ISO 8 at rest (Grade D).*

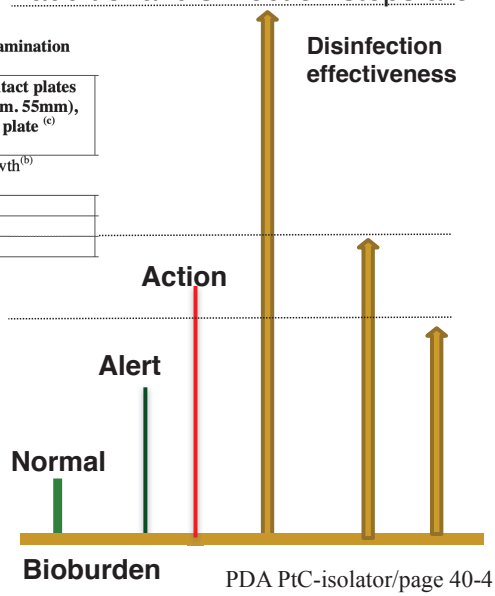
- Hold time prior disinfection (under the protection of the HEPA- different consideration from the normal operation in the isolator)
- Hold time after disinfection
- The bioburden is higher than the disinfection effectiveness →additional disinfection steps are required.

Table E: Comparison of regulatory

FDA		In-operation (particles per cubic meter)	Active air action			
ISO	USP	0.5 µm	Limits			µm
ISO 5	100	3,520	1	A	3,520	20
ISO 6	1,000	35,200	7	N/A		
ISO 7	10,000	352,000	10	B	352,000	2,900
ISO 8	100,000	3,520,000	100	C	3,520,000	29,000
N/A	N/A	N/A	N/A	D	N/A	N/A

Table 7: Maximum action limits for viable particle **contamination**

Grade	Air sample cfu/m^3	Settle plates (diam. 90 mm) cfu/4 hours [a]	Contact plates (diam. 55mm), cfu/ plate [c]
A	No growth[b]		
B	10	5	5
C	100	50	25
D	200	100	50



PDA PtC-isolator/page 40-41

The design of the isolator interior should be adequate for the cleaning and disinfection process.

- Materials of construction of the isolator interior should be cleanable and resistant to cleaning and disinfectant chemicals, treatment, and process
- Surfaces should be smooth and nonporous
- Surfaces should drain properly and not pool or accumulate liquids
- Critical spaces (areas, surfaces, or environments that, if microbiologically or chemically contaminated, pose a risk of contamination to product or product contact surfaces) should be accessible to the cleaning procedure
- Areas within the isolator that expose product or generate or harbor foreign material should be limited

PDA PtC-isolator/page 41

Q: What are the current options for isolator interior decontamination?

Hydrogen peroxide
Peracetic acid → **Peroxygen compound (powerful oxidizing agent)**

$$O_2^- + H_2O_2 \rightarrow OH^\bullet + OH^- + O_2$$

The presence of free radicals results in the oxidation of proteins, DNA, and other components within the spore leading to its inactivation.

Decontamination agents are typically dispersed in two basic states: gaseous and vapor phase. VHP decontamination is an extremely potent, complex process due to its biphasic nature [both liquid and vapor (gas) phases are typically present in the chamber].

PDA PtC-isolator/page 43

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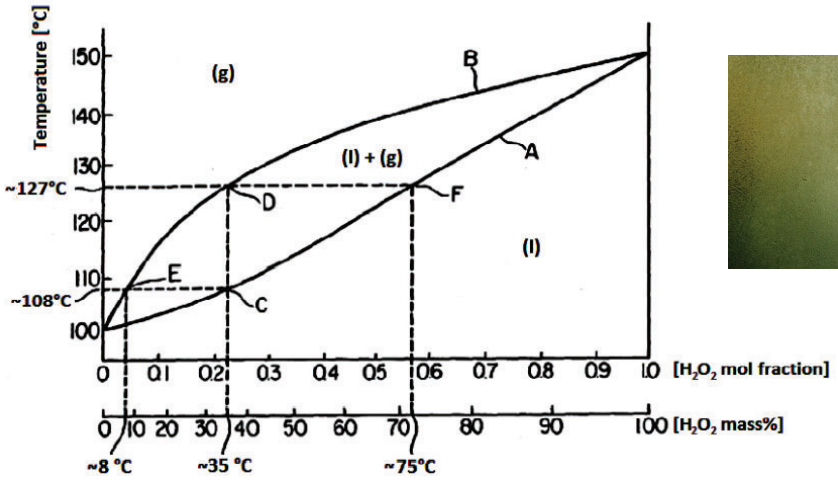
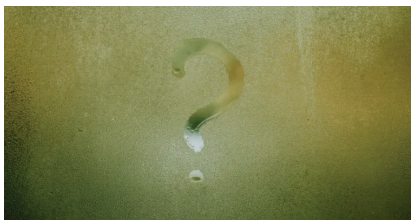
The phase equilibrium is extremely sensitive to minor differences in temperature, VHP, and water concentration, making it virtually impossible to know the exact process physical parameters at any given time and location

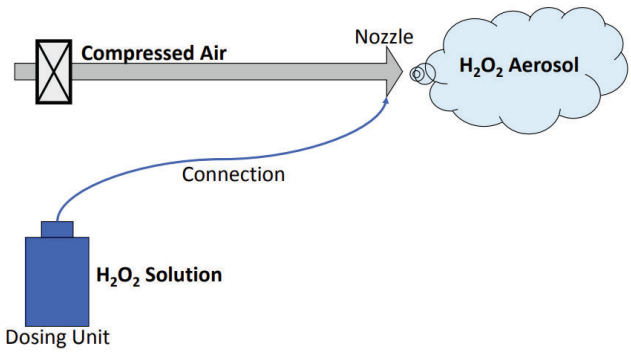




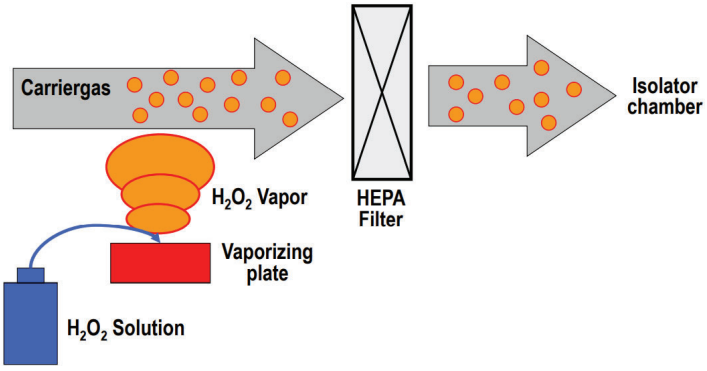
Isobaric equilibrium liquid-vapor (T,x,y diagram) for the real mixture of hydrogen peroxide and water (Hatanaka & Schibauchi, 1989)

Two main approaches for VHP vapor generation used in the industry

Fogging



Hare hot plate vaporization



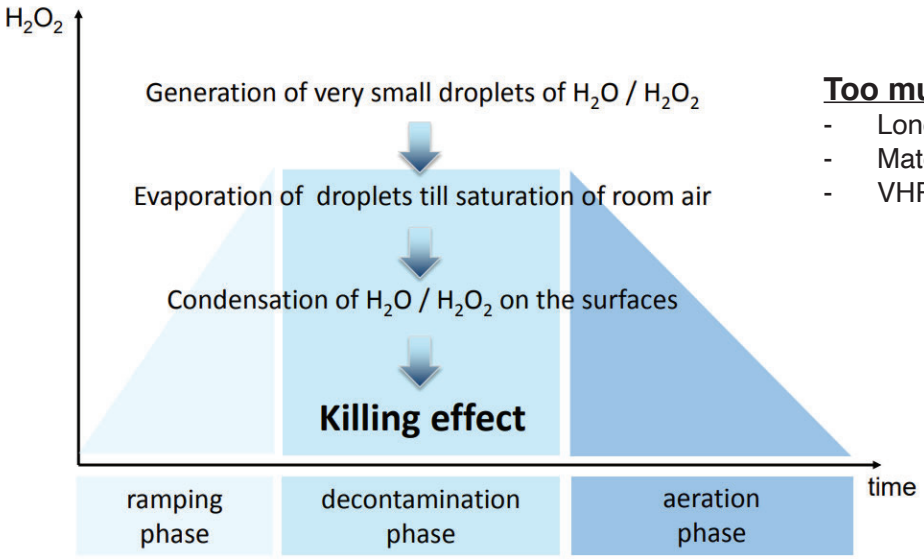
Depending on the generated droplet size, fog is termed “dry” or “wet” by the industry

- Wet: droplet sizes larger than approximately 15–20 µm
- Dry: a droplet size below 15 µm

Hot plate vaporizers should be operated to ensure flash vaporization of injected VHP.
An operating temperature too low or liquid dosing too high may result in VHP boiling that will affect the efficacy and may even lead to explosion!

Although pure hydrogen peroxide solutions are not usually explosive at atmospheric pressure, equilibrium vapor concentrations of hydrogen peroxide above 26 mol per cent (40 weight per cent) become explosive in a temperature range below the boiling point of the liquid.

The generally accepted understanding is that increasing the saturation of the VHP atmosphere increases the efficacy, because a large amount of liquid VHP is deposited on the surfaces.



Too much deposited VHP

- Long aeration duration
- Material compatibility
- VHP ingress concerns

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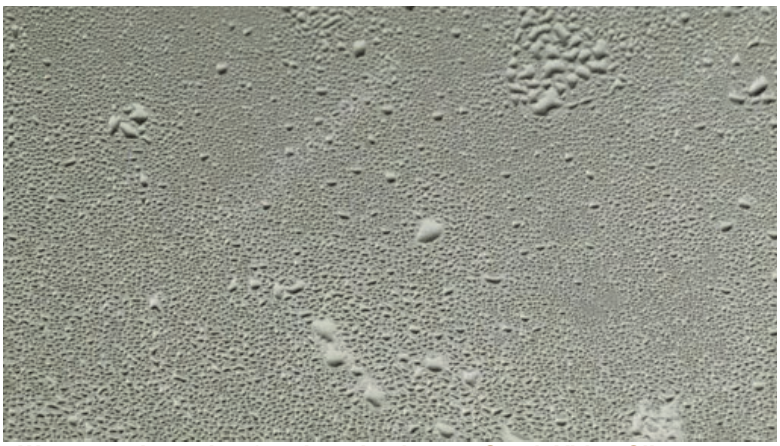
Q: Should empty isolator mapping of temperature and humidity be performed as part of decontamination qualification studies?

Temperature mapping of isolators or decontamination chambers should be consistent with the requirements for decontamination.
→ Influence the amount of localized condensation



Water condensation forming, timelapse - Stock Video Clip - K007/9302 - Science Photo Library

The hottest areas, typically closest to the vapor inlet and any operating equipment, are potentially "worst case" because of reduced condensation.

It is important to maintain near-constant room conditions to minimize process variability during the individual VHP process and between multiple VHP cycles over time

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Q: What conditions and configurations should be considered during decontamination cycle development and validation?

Avoid any materials potentially touching

Decontamination Process

- Environmental conditions (temperature, humidity range, and variation)
- Fan or blower speed (fixed or variable) or isolators without a fan
- Decontamination agent concentration, dose levels, and rates of application

Load Configuration

- Minimum and maximum loads
- Load placement and orientation
- Characteristics of load materials
- Exposure of material and load surfaces
- Extension of gloves
- Position of doors and openings

Material Properties

- Compatibility of materials with the decontamination agent or process
- Substances or materials on a surface that could adversely affect the decontamination process or outcome
- Porosity of materials
- Stacking or placement of materials
- Wrapping or folding of wrapping materials that occlude surfaces from decontamination

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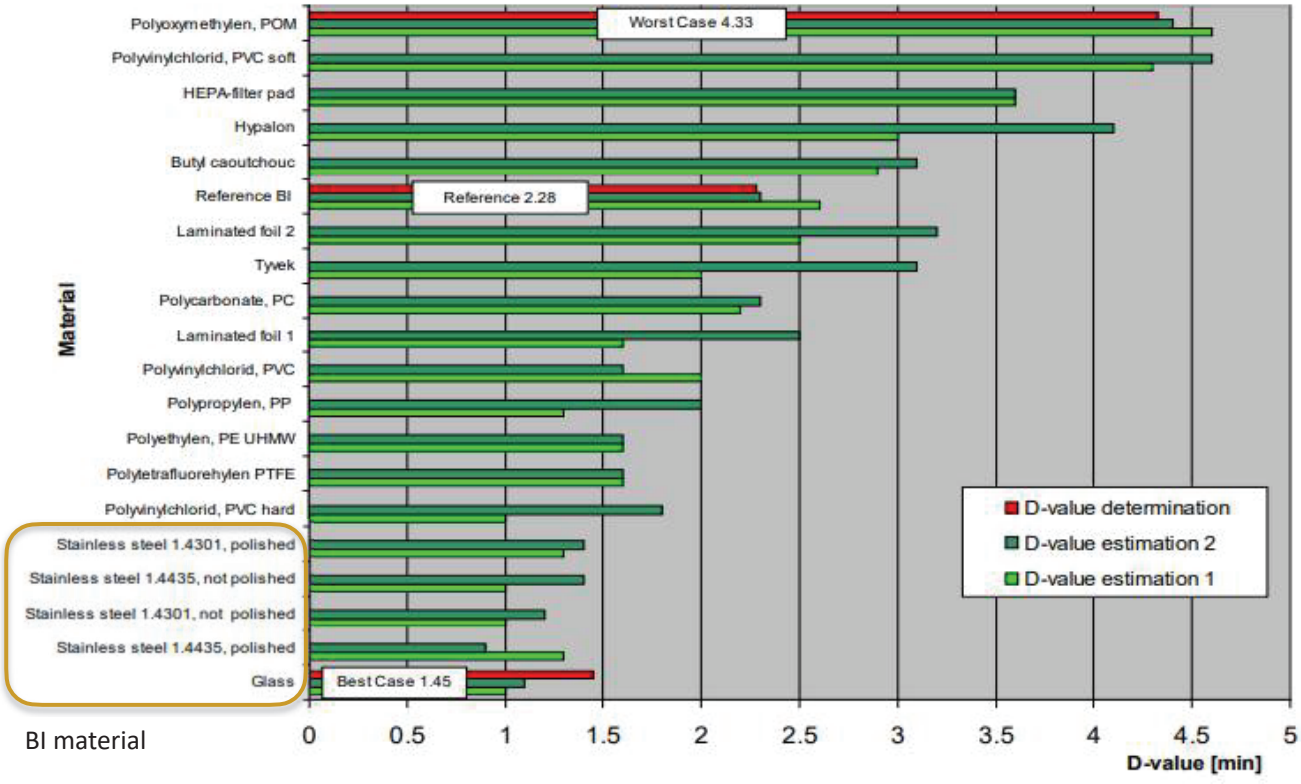
D-value on different materials



BI material

Q: What are the key differences between cycle development and cycle qualification?

Cycle development

- Involve the adjustments of conditions, parameters and setting.

Cycle qualification

- Documented evidence of the reliability and effectiveness
- Testing and monitoring is designed to confirm that the cycle is performing to specifications.
- For a production cycle, an **overage** of decontaminating agent and/or exposure time is typically included
- Decontamination cycles for critical areas used in aseptic processing are commonly validated to a 6 log reduction of the biological indicator.

The potential impact and the likelihood of impact of cycle variables and conditions that may affect the performance of the cycle, including:

- Isolator loading configurations, placement, orientation, and loading of materials and equipment within the isolator (e.g., orientation, packaging, number of items)
- Biological indicator selection and placement
- Chemical indication selection and placement (Mapping for worst case location)
- Process parameters for qualification cycle and for production cycle
- Decontamination agent concentration, dose, and application rate
- Effect of decontamination agent and cycle on isolator interior, material, and equipment surfaces
- Process parameters for aeration and decontamination agent removal
- Effectiveness of decontamination agent
- Interference of the decontamination cycle effectiveness as a result of contact with the isolator interior, equipment, or material surfaces
- Systems and instrumentation in place to control the decontamination cycle
- Automation programs
- Air circulation fan and blower placement, configuration, and speeds
- Distribution of the decontamination agent throughout the isolator
- Temperature and humidity distribution throughout the isolator
- Bioburden within the isolator or on the surfaces within the isolator that require decontamination

Q: Which BI should be used for cycle development and cycle qualification? What are the requirements for such a BI (e.g., spore count, D-value)?

Process	Selected Organism	ATCC Derivation
Peracetic acid Hydrogen peroxide	*Geobacillus stearothermophilus*	7953 or 12980 (Ph. Eur.)

- BI should be a suitably qualified organism (e.g., *Geobacillus stearothermophilus)* with not less than 10^6 spores/carrier.
- Microbial count recovery of incoming biological indicator control should be between 50% and 300%.
- BIs should be handled and stored at temperatures and humidity conditions as specified by the vendor prior to use.
- Carrier should be made of a material that is also commonly used in the isolator, typically stainless steel.
- BI should consist of a monolayer of spores to guarantee direct contact of the VHP to the spores on the carrier.
- The consistency of BIs within one BI batch should be checked prior to use (e.g., by determining the survival-kill window).
- BI should be packed in a material permeable for H_2O_2 and easy to handle in the lab.
- D-value of the BI should be known and should be comparable from one validation to the next in order to make validations comparable and in order to see any shift in the efficacy of the VHP decontamination efficacy.

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Two sources of variability in validation of decontamination cycle:

A. The inherent variability of the BI
B. Variability that may arise from the decontamination cycle setup and procedure.

Qualification of BI

Enumeration **Resistance studies.**

PDA TR.51/page 28

Enumeration

The determination is the efficient removal of the spores from the carrier

USP <55> Biological indicators-Resistance performance test

Mechanically disrupt to achieve a homogeneous suspension of the spores

Ultrasonic energy

- The number and output power of the transducers fitted in the ultrasonic bath
- Ultrasonic frequency and the use of single or swept frequency
- Damping effects of equipment placed in the bath (e.g., plastic-coated racks should not be used as they absorb ultrasonic energy).
- Use of glass containers to maximize transmission of ultrasonic energy to the contents of the bottle or tubes
- Spacing of bottles containing the BIs in the bath. Bottles should be placed in standardized positions and should not touch each other.
- Specification for the container. Height of the base of the bottle in the bath will determine the position of the BI with respect to nodes and internodes of the ultrasonic waves and determine the intensity of the exposure of the BI to ultrasonic energy. This effect may be reduced in baths that employ a “frequency sweep” mode of operation.
- The addition of a surfactant to water in the bath

The independent spore count should be between 50% and 300% of the manufacturer’s stated value.

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System D-Value Determination

The system D-value is an essential part of the quality control program aimed at determining batch-to-batch variation in BIs’ resistance.

- Usually determined in a routine place in the isolator, not a hard-to-reach surface

The test method used to determine the system D-value should reflect as closely as possible actual sporicidal vapor phase process conditions present during routine production. The system D-value is unique to the specified generator/enclosure combination.

*vapor concentrations, temperature of air/surfaces, humidity, same chamber and gas generator positions

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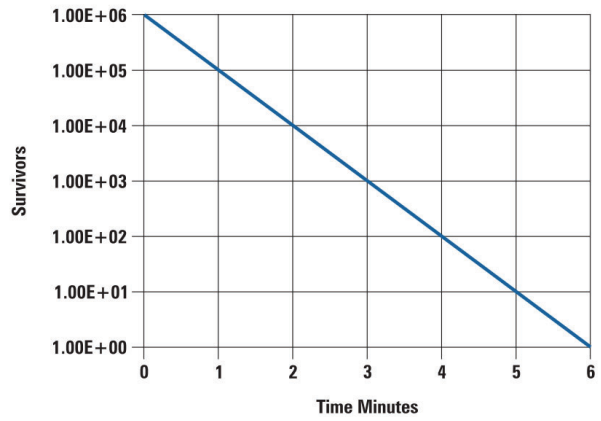
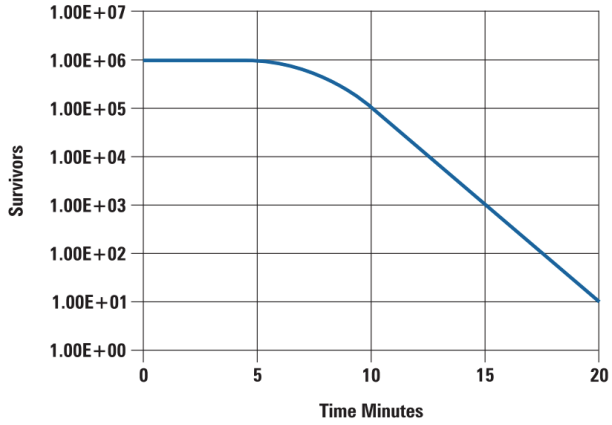
Figure 3.5-1 Idealized Plot of Death Kinetics



It has been shown experimentally that, the rate at which the spores are killed is logarithmic, when they are exposed to steady state sterilization conditions

D -Value
x minutes → reduce 10 factor
2x minutes → reduce 100 factor

Figure 3.5-2 Typical Survivor Curve



Changes in the rate of lethality experienced by the target microorganisms will result in deviations from the ideal straight line log survivor time plot.

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Worst case location determination studies should be conducted prior to BI lethality studies. The following are examples of lethality studies:

- **Kill or no Kill of BIs**
  - simplest form of biological indicator challenge.

- **Timed Removal of BIs Throughout the Cycle**
  - Various types of death kinetics studies are based on BIs' timed removal.
  - A fractional cycle approach involves the timed removal of BIs throughout the cycle, defining the BIs' lethality point. . Once the lethality point has been established, a safety margin appropriate to the process may then be determined

- **BIs with Different Numbers of Spores**
  - BIs carrying different numbers of spores are available commercially (e.g., 3 log/4 log/6 log) to determine lethality.

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Q: How should multiple BIs be used and evaluated during VHP decontamination cycle development and validation?

Recommendation

The exposure of multiple, usually three, BIs at given locations may be used to evaluate and qualify the effectiveness of the decontamination cycle.

BI location and placement

- Locations that will provide the best opportunity for identification of difficult to decontaminate surfaces.
  - Risk assessment of the isolator, including the configuration of the isolator, the composition and positioning of nonproduct contact surfaces that may impact the effectiveness of the cycle, and the condition and distribution of decontamination agent.
- Where difficult-to-decontaminate surfaces or locations are identified, placement of multiple (usually triplicate) BIs at individual locations during cycle development and qualification may provide information about the efficacy of the decontamination cycle.

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The failure to deactivate one or more of the BIs at a given location should be investigated. The outcome of the investigation should indicate whether the growth is due to the cycle failure or to a BI-related issue.
The investigation should consider conditions that may adversely affect the decontamination cycle, such as:

- Confirmation of indicator organism growth
- BI lot or batch variation
- BI D-value, population, and resistance
- BI preparation and handling
- BI spore clumping or occlusion (rogue spores)
- Review of handling, incubation, and recovery methods
- BI placement configuration and location
- Insufficient exposure to the decontamination agent
- Decontamination cycle parameters
- Decontamination agent concentration
- Decontamination agent application or injection
- Control and monitoring instrumentations and sensors
- Temperature or humidity changes
- Condition, bioburden, and cleanliness of the isolator interior
- Effect of decontamination agent retention

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Q: What effect could oil-based HEPA-filter integrity agents have on the isolator decontamination cycle?

HEPA-filter testing is critical to ensure efficacy of the decontamination process, but it is also important to consider any potential contamination that could be introduced in the system by the procedures used to test the filters.

Any residue from HEPA-filter test- ing that might be trapped on filters or surfaces can be removed and that any remaining residue will not compromise subsequent decontamination cycles.

- oil-based material to test the filters, ensure that the filter does not retain any of the mate- rial, because it could interact with the VHP in the system and negatively impact the efficacy of the decontamination process

> If the challenge aerosol is oil (DOP, PAO,) it will be captured and absorbed into the filter medium, and the filter needs to be permitted to "dry out" for some time after testing let the oil evaporate and pass through as a vapor. - ISPE HVAC

- HEPA-filter testing would, ideally, occur before requalification cycles.

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Q: Should each load be qualified during the decontamination cycle qualification?

The variability of the load within the isolator should be minimized and controlled.
→ a risk-based approach should be used to qualify the decontamination of these loads.

The requalification process should align with the original validation strategy. If the approach includes qualifying each presentation within the isolator, the requalification should mimic that approach.

- Rotating loads, where all loads are qualified over time. This approach is supported by data collection and risk-based principles. That is only possible with data and strong monitoring processes to ensure control of the process.
- Bracketing strategies (e.g., minimum and maximum loads) may also be employed with proper assessment.

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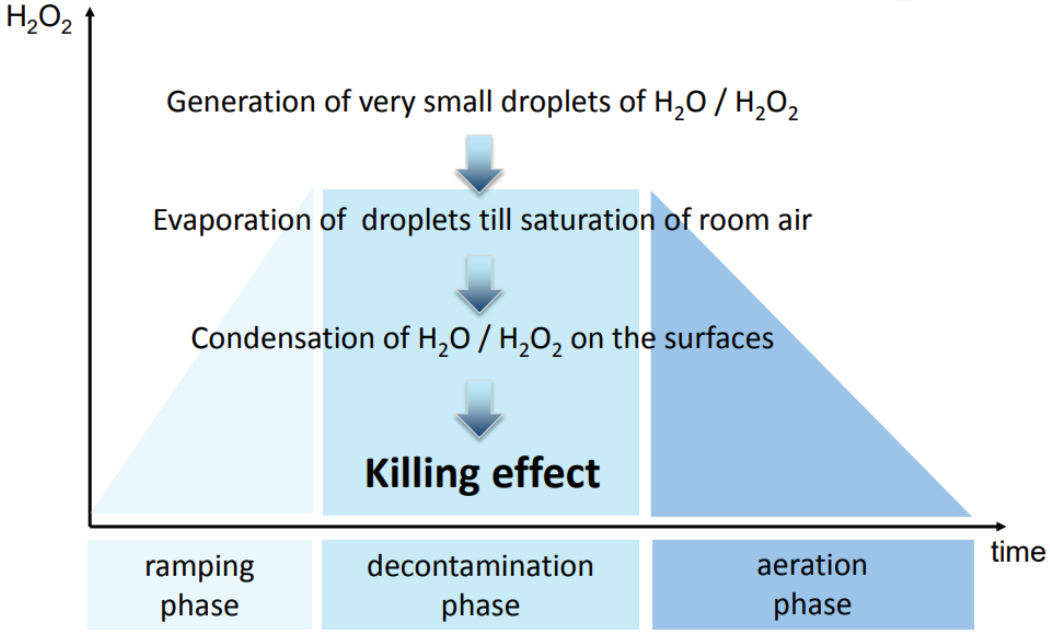
Validation of Decontamination Process.

Validation of the decontamination process



Temperature Humidity Disinfectant- expiry Injection flow and time	Dwell flow, pressure and time BI inacitivation Loading pattern	Residual H_2O_2

Documentation of final worst case of condition and configuration

Conclusion

Frequency For Cleaning And Disinfection

Several approaches

1. <u>Area classification</u> Most stringent cleaning and disinfection frequency for the most stringent area classification	Grade A: clean and disinfect daily Grade C: clean and disinfect weekly Grade D: clean and disinfect monthly
2. <u>Environmental Monitoring Data</u> Potential fluctuations in the levels and types of bioburden recovered as revealed by daily or periodic data trending and review.	Reduce established cleaning frequencies based on sustained satisfactory area performance.

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Frequency For Cleaning And Disinfection

Several approaches

3. Risk-based Model
   The risk of product exposure to the environment and personnel and the type of manufacturing conducted in the classified area.

a. Within an aseptic manufacturing boundary (Grade D → grade C) : More frequently
b. Manufacturing areas that are immediately adjacent and contiguous (via airlocks) with open aseptic processing areas (for example, Grade C and adjacent Grade A)
c. Areas that support microbial growth include locations for charging of powdered media and/ or ingredients to vessels.
d. The age of the building or a difficult-to-clean layout
e. Microbial air or surface action level excursions, power and/ or HEPA filter failures, or periodic facility shutdowns.

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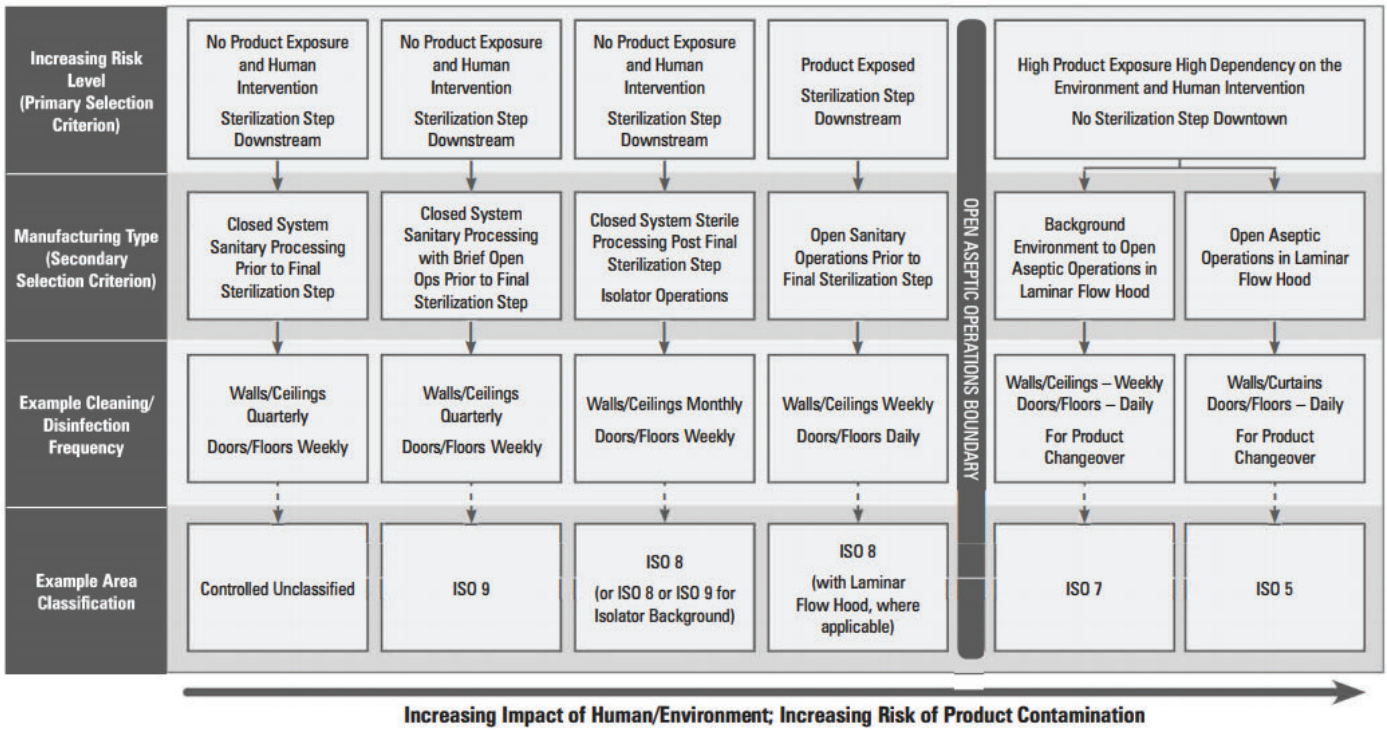
Example risk-based approach for selection of routine cleaning and disinfection frequencies for classified manufacturing areas



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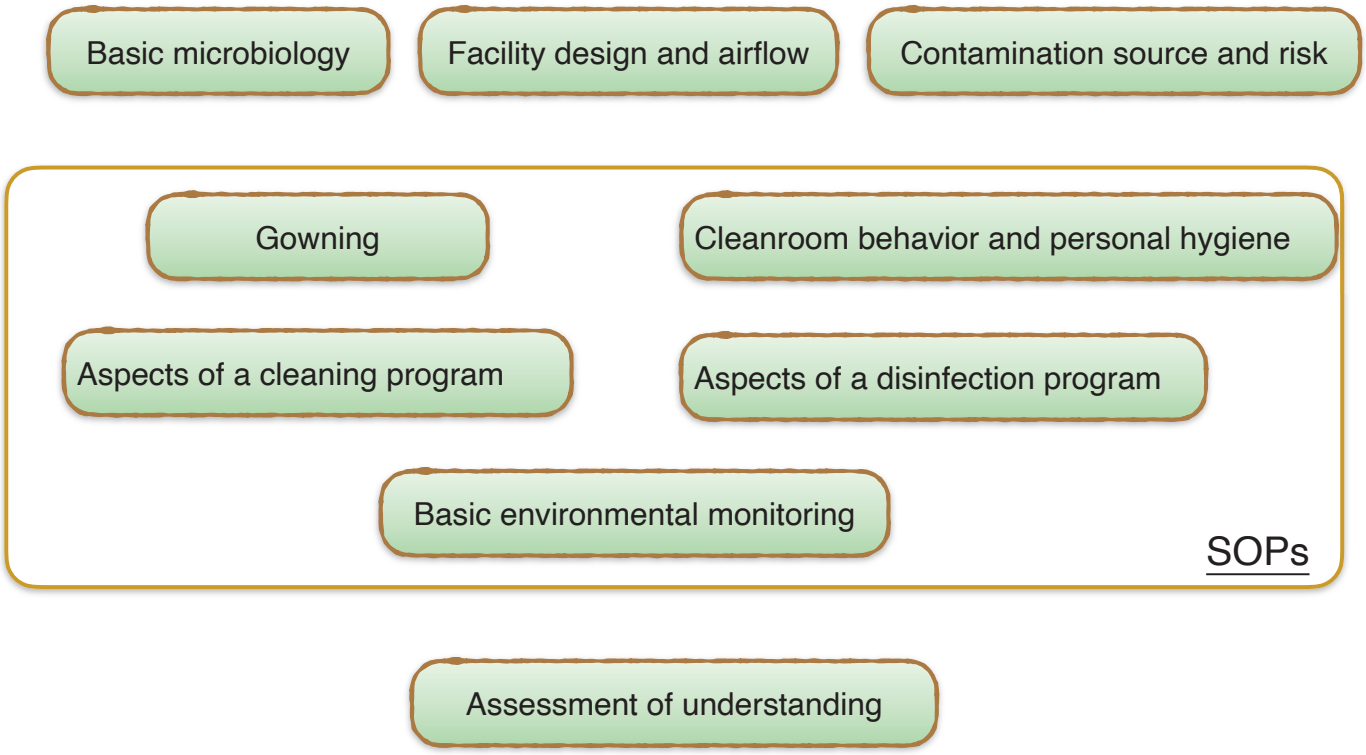
Environmental Monitoring data review

When to adjust the strategy of the decontamination?

1. OOT
2. Normal Flora change
   - Gram-positive cocci and small non-spore-forming gram-positive rods: Personnel
   - Gram-positive rods and fungi: external environment (air and soil) , which can include the facility's interstitial spaces
   - Gram-negative rods: water or liquid related

Training



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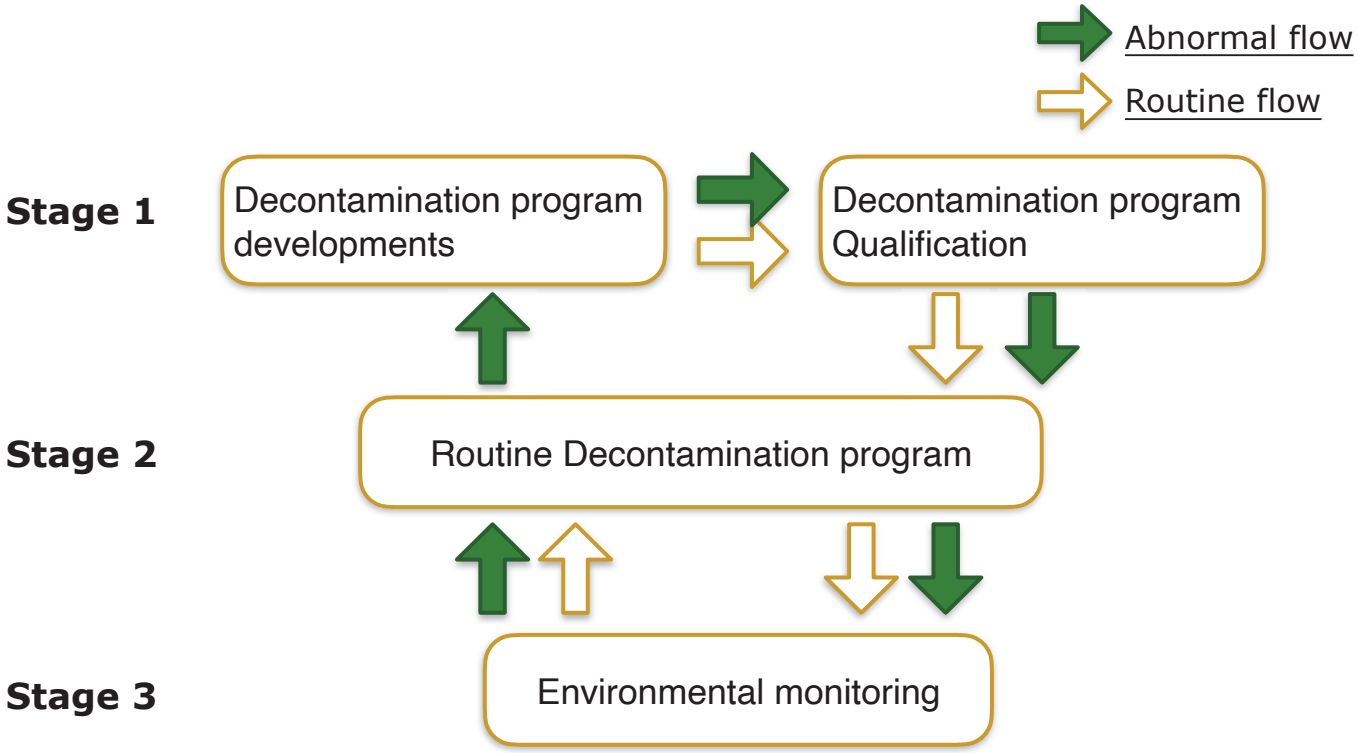
Decontamination Lifecycle management



Reference

- Technical Report No. 70 Fundamentals of Cleaning and Disinfection Programs for Aseptic Manufacturing Facilities
- Technical Report No. 51 Biological Indicators for Gas and Vapor-Phase Decontamination Processes: Specification, Manufacture, Control and Use
- USP41 <1211>Sterility Assurance
- 2020 PIC/S 2nd draft annex I
- PDA Points to Consider for the Aseptic Processing of Sterile Pharmaceutical Products in Isolators
- PharmTech_NA_Jan2020_wm page 53-57

Thanks for Your Attention

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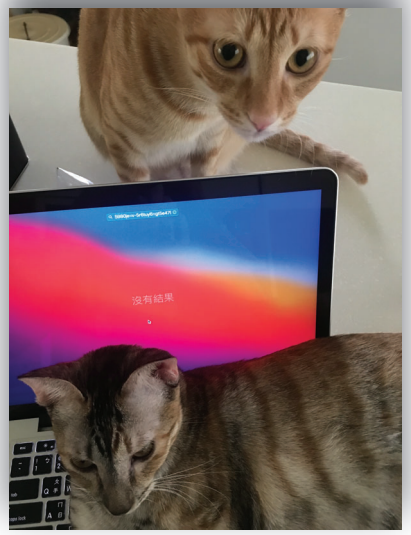

Q & A