EU GMP Annex 1 Requirements on Aseptic Processing

PDA Parenteral Drug Association

PDA TRAINING

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Annex 1- EU-PIC/s-WHO

EUROPEAN COMMISSION

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The Rules Governing Medicinal Products in the European Union
Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use

Annex 1

Manufacture of Sterile Medicinal Products

GUIDELINES

The Rules Governing Medicinal Products in the European Union
Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use

2.1 The manufacture of sterile products is subject to special requirements in order to minimize risks of microbial, particulate and endotoxin/pyrogen contamination. The following key areas should be considered:

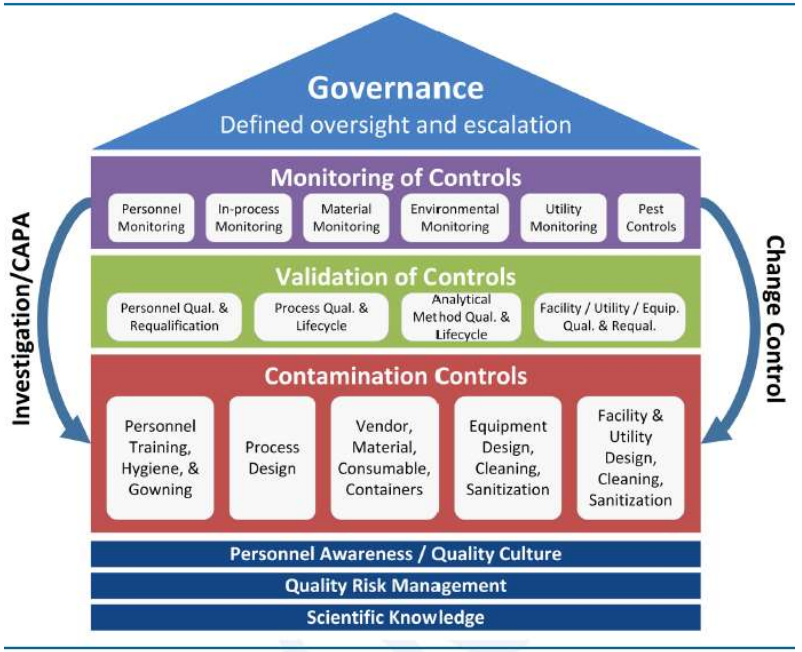
i. Facility, equipment and process should be appropriately designed, qualified and/or validated and where applicable, subjected to ongoing verification according to the relevant sections of the Good Manufacturing Practices (GMP) guidelines. The use of appropriate technologies (e.g. Restricted Access Barriers Systems (RABS), isolators, robotic systems, rapid/alternative methods and continuous monitoring systems) should be considered to increase the protection of the product from potential extraneous sources of endotoxin/pyrogen, particulate and microbial contamination such as personnel, materials and the surrounding environment, and assist in the rapid detection of potential contaminants in the environment and the product.

4.3 Restricted Access Barrier Systems (RABS) or isolators are beneficial in assuring required conditions and minimizing microbial contamination associated with direct human interventions in the critical zone. Their use should be considered in the CCS. Any alternative approaches to the use of RABS or isolators should be justified.

Implementation of Annex 1

- Quality Risk Management QRM and Contamination Control Strategy CCS implementation
- Investigate the most critical steps for your sterile product. Where do you have open sterile Container, Filling path, Stopper Transfers until your Container is closed
- Investigate the transfers from C to A or B to A. Are they validated? Do they provide appropriate Transfer Technologies
- Investigate your current manual interventions. Can they be eliminated or automated.
- Does an upgrade of your installation to a RABS is possible or better replace to an Isolator?
- Implementation “The House of Control” for the CCS

Quality Risk Management QRM and Contamination Control Strategy CCS



- Source: PDA TR 90

Implementation of Annex 1

Contamination Control according Annex 1 starts from inside out.

Barrier

- RABS/cRABS or Isolator
- Europe and Noth America are Isolator focused based on Information from the FDA during ISPE and PDA Conferences
- PDA Survey from 2018, 50% Conventional Installations and 50% Barrier of new installation
- ISPE Survey from 2022 20% Conventional and 80% Barrier.

Barrier

Conventional Aseptic Processing
⟶ Highest risk of human intervention

RABS «Restricted Access Barrier System»
⟶ Reduced risk of human intervention

Isolators
⟶ Lowest risk of human intervention

Facilities

NO !! BARRIER!!

BARRIER

BARRIER

Barrier

RABS «Restricted Access Barrier System»

- Reduced risk of human intervention

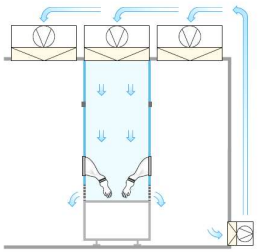
RABS “ Restricted Access Barrier System”

- Operator have access to critical areas
- Barrier but doors can be opened
- Grade B environment.
- Intensive Training and Monitoring
- Definition of RABS

Barrier

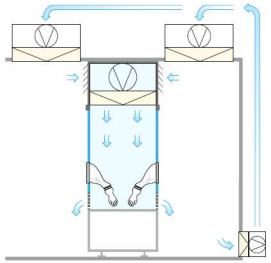
Passive Open RABS

- (Passive) Airflow from HEPA ceiling
- Air overspill into the Room
- Physical barrier with aerodynamic air flow
- Outside Grade B (Iso 7) / Inside Grade A (Iso 5)
- Sporicidal gassing only together with clean room
- Doors open able in production
- No toxic products possible



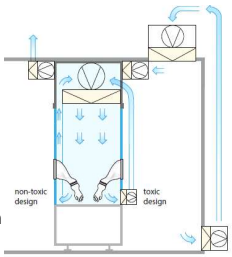
Active Open RABS

- Active Airflow with own HEPA ceiling
- Air overspill into the Room
- Physical barrier with aerodynamic air flow
- Outside Grade B (Iso 7) / Inside Grade A (Iso 5)
- Sporicidal gassing only together with clean room
- Doors open able in production
- No toxic products possible



Closed RABS

- Active airflow with air return
- No air overspill into room
- Physical barrier
- Positive or negative pressure, with intake/exhaust air systems
- Outside Grade B (Iso 7) / Inside Grade A (Iso 5)
- Sporicidal gassing in closed RABS possible independent of cleanroom
- Doors open not possible during production
- Toxic products possible



Definitions

Passive open RABS on a syringe line

Definitions

Active open RABS on Freeze Dryer

Closed RABS Example

Barrier

Isolators

- ⟶ Lowest risk of human intervention

Isolators

- ⟶ Operator have no direct access to critical areas
- ⟶ Validated and accepted decontamination system using vaporized or nebulized H2O2
- ⟶ Reduced Clean Room requirements outside of the Isolator (ISO 7/8 Grade C/D)
- ⟶ Less Gowning of the Operator
- ⟶ Open and Closed Isolator

Barrier

Open Isolator

Closed Isolator

SKAN

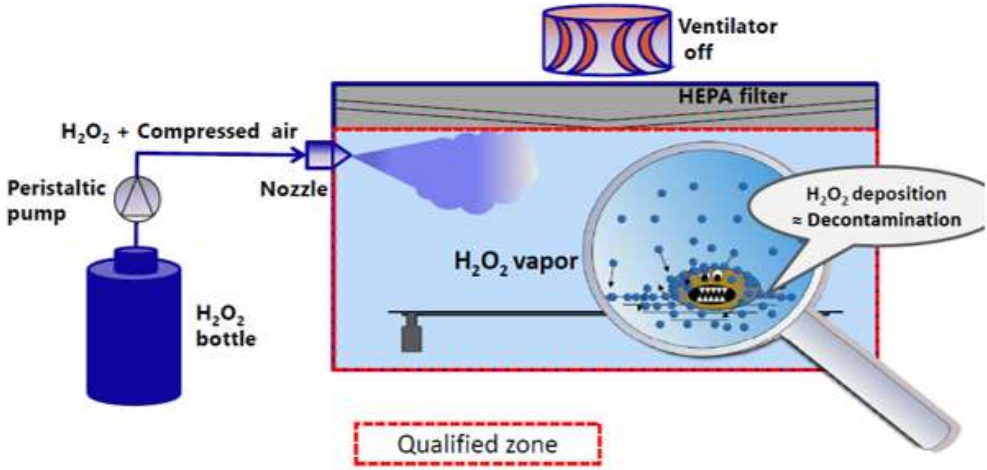
Decontamination

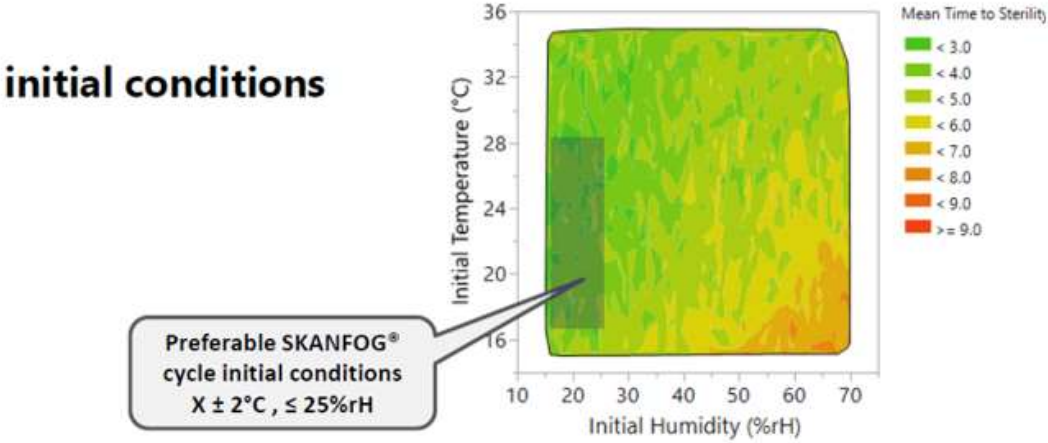
- Isolators

4.22 Decontamination methods (cleaning and bio-decontamination, and where applicable inactivation for biological materials) should be appropriately defined and controlled. The cleaning process prior to the bio-decontamination step is essential; any residues that remain may inhibit the effectiveness of the decontamination process. Evidence should also be available to demonstrate that the cleaning and bio-decontamination agents used do not have adverse impact on the product produced within the RABS or isolator.

i. For isolators

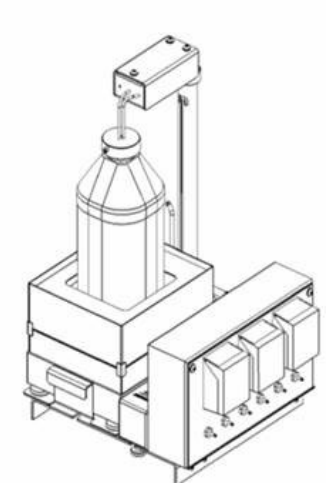
The bio-decontamination process of the interior should be automated, validated and controlled within defined cycle parameters and should include a sporicidal agent in a suitable form (e.g. gaseous or vaporized form). Gloves should be appropriately extended with fingers separated to ensure contact with the agent. Methods used (cleaning and sporicidal bio-decontamination) should render the interior surfaces and critical zone of the isolator free from viable microorganisms.



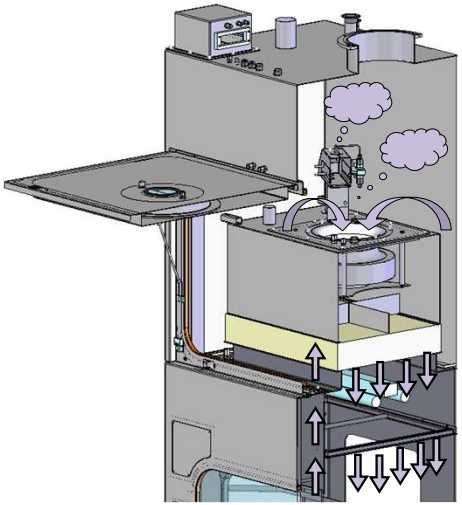


Decontamination

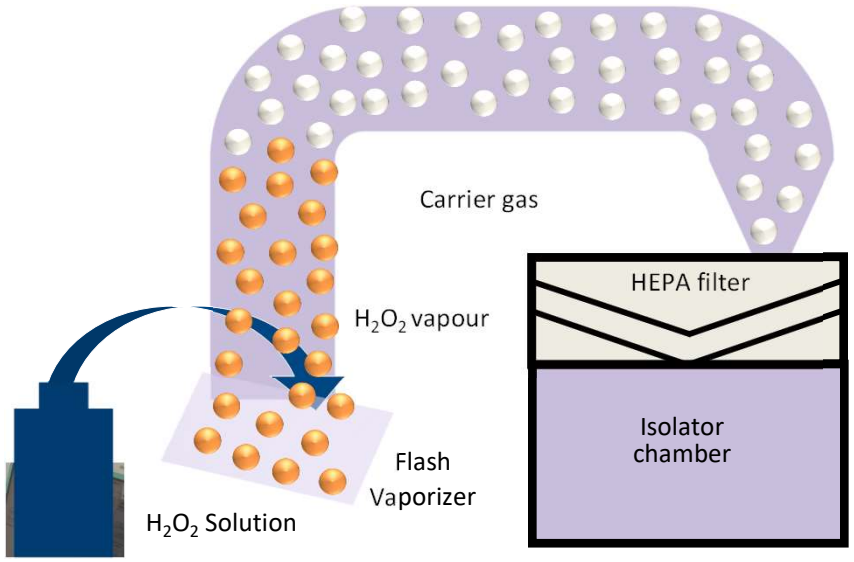
⟶ Dosing unit



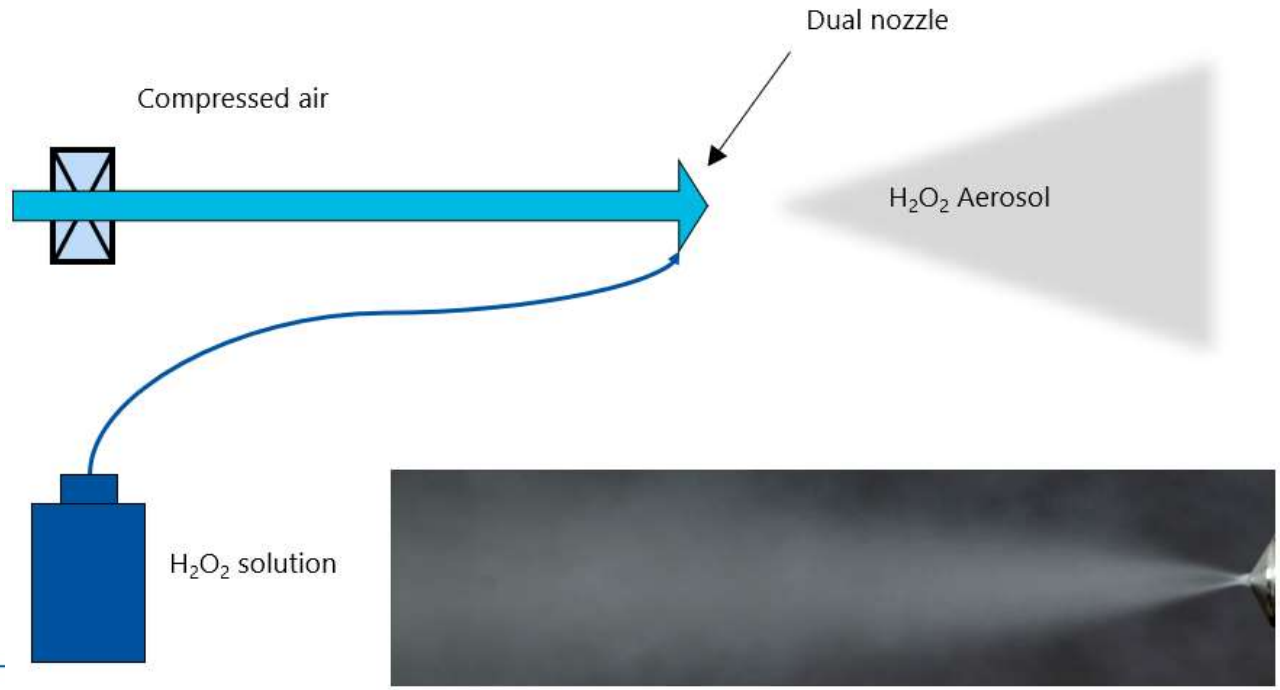
⟶ Vaporizer plate



Decontamination

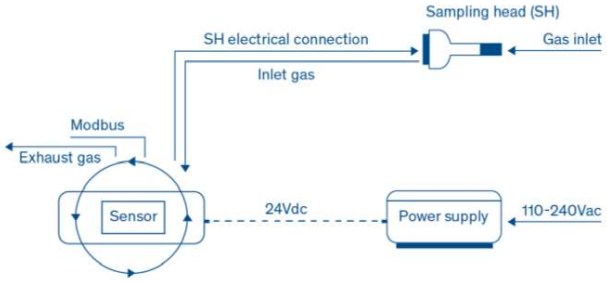


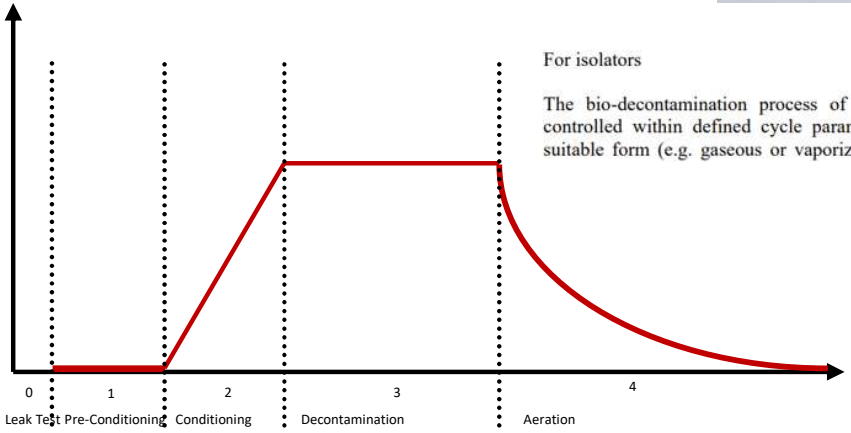
Decontamination



Decontamination

Decontamination effect

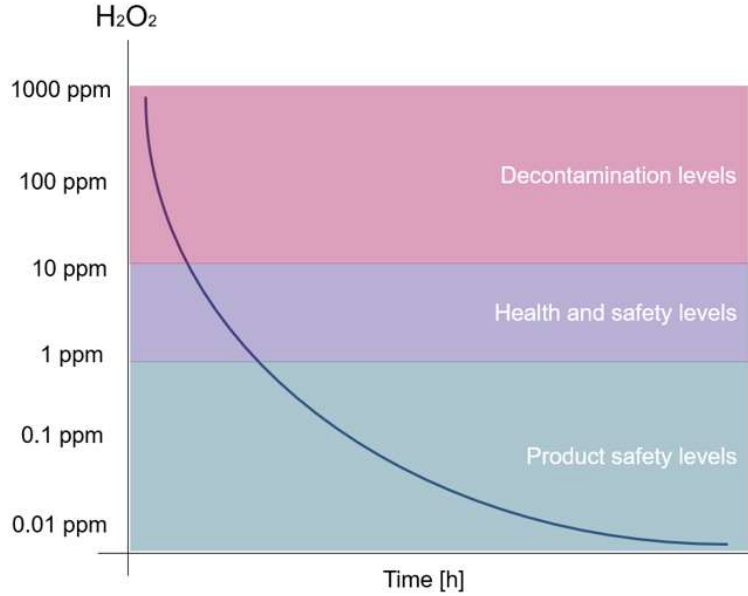




Cycle phases

For isolators

The bio-decontamination process of the interior should be automated, validated and controlled within defined cycle parameters and should include a sporicidal agent in a suitable form (e.g. gaseous or vaporized form). Gloves should be appropriately extended



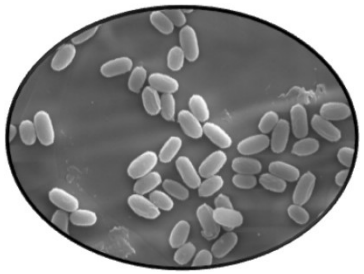
Decontamination SKAN - Optaria verification in the Isolator Chamber. High Concentration measure for the aseptic surface decontamination and low concentration measure for the product safety.

PEOPLE SCIENCE AND REGULATION®

BI`s

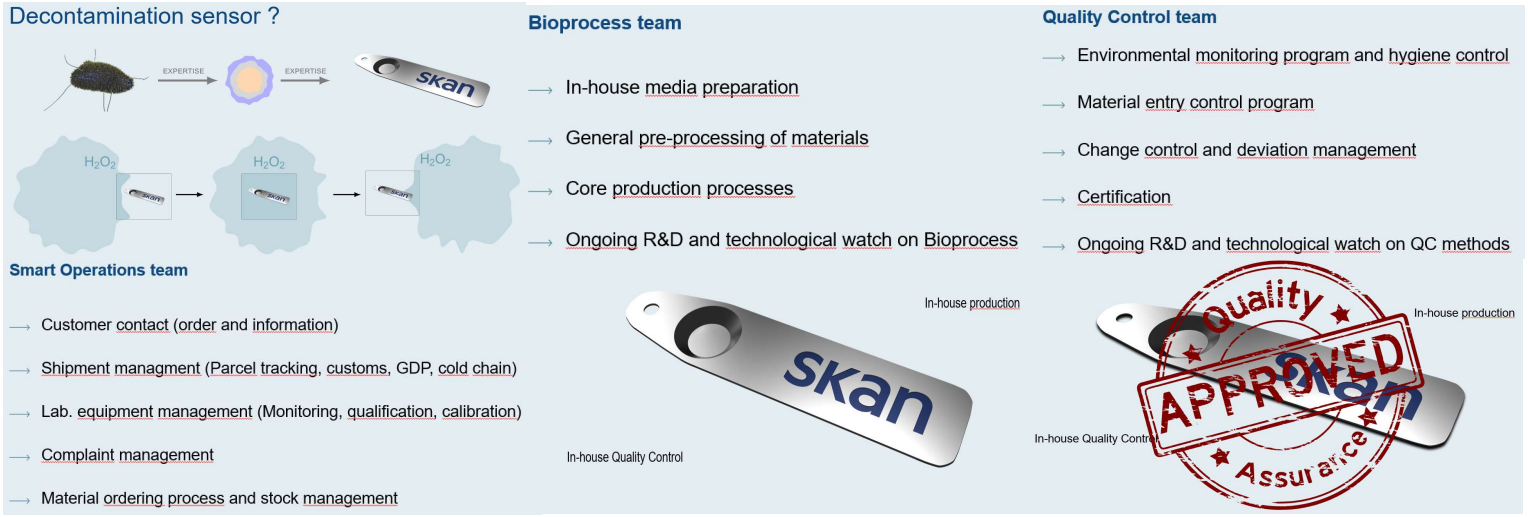
Proof of Surface Decontamination with Biological Indicators

8.43 The reliability of BIs is important. Suppliers should be qualified and transportation and storage conditions should be controlled in order that BI quality is not compromised. Prior to use of a new batch/lot of BIs, the population, purity and identity of the indicator organism of the batch/lot should be verified. For other critical parameters, e.g. D-value, Z-value, the batch certificate provided by the qualified supplier can normally be used.



BI`s

Proof of Surface Decontamination with Biological Indicators



Gloves

4.21 The materials used for glove systems (for both isolators and RABS), should be demonstrated to have appropriate mechanical and chemical resistance. The frequency of glove replacement should be defined within the CCS.

i. Isolators:

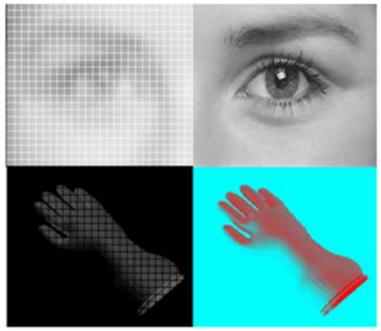
a. For isolators, leak testing of the glove system should be performed using a methodology demonstrated to be suitable for the task and criticality. The testing should be performed at defined intervals. Generally glove integrity testing should be performed at a minimum frequency of the beginning and end of each batch or campaign. Additional glove integrity testing may be necessary depending on the validated campaign length.
Glove integrity monitoring should include a visual inspection associated with each use and following any manipulation that may affect the integrity of the system.
For manual aseptic processing activities where single unit or small batch sizes are produced, the frequency of integrity verification may be based on other criteria, such as the beginning and end of each manufacturing session.

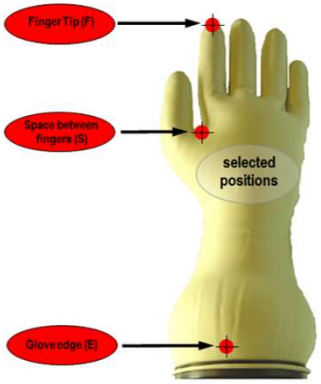
b. Integrity / leak testing of isolator systems should be performed at defined intervals.

Isolator Glove Test

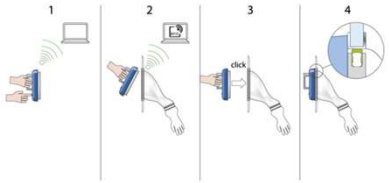
Gloves

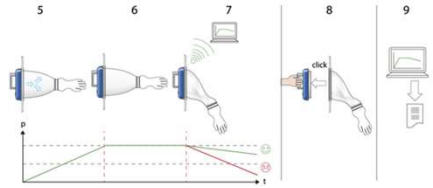
Visual Test

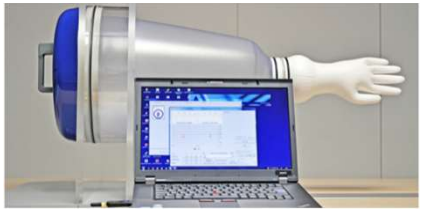




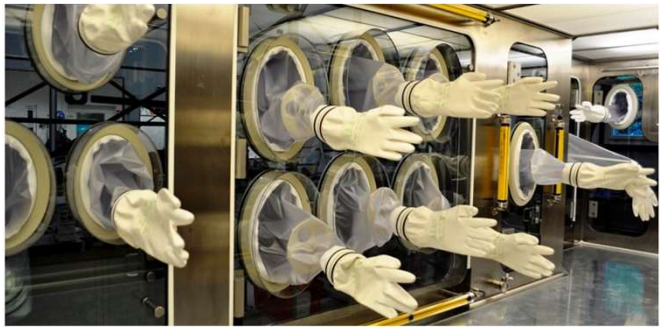
Physical Test

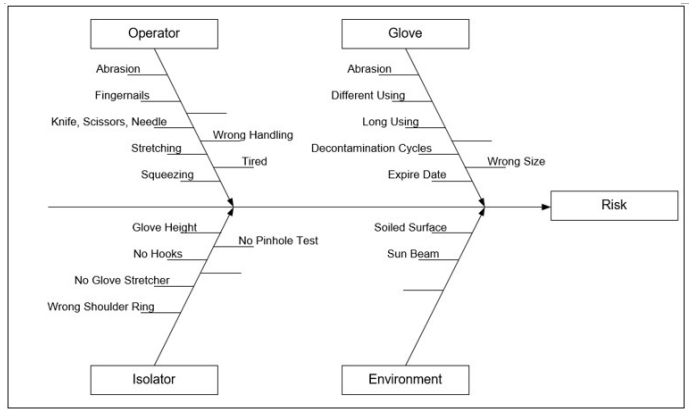






Glove Quality Risk Management





Material Transfers

- E-Beam, Material Airlocks, RTPs

4.10 The transfer of equipment and materials into and out of the cleanrooms and critical zones is one of the greatest potential sources of contamination. Any activities with the potential to compromise the cleanliness of cleanrooms or the critical zone should be assessed and if they cannot be eliminated, appropriate controls should be implemented.

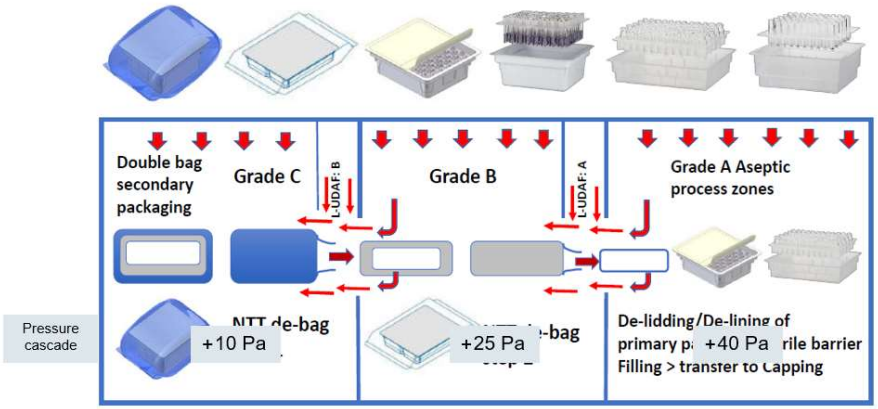
8.47 Where materials, equipment, components and ancillary items are sterilised in sealed packaging and then transferred into grade A, this should be done using appropriate validated methods (for example, airlocks or pass-through hatches) with accompanying disinfection of the exterior of the sealed packaging. The use of rapid transfer port technology should also be considered. These methods should be demonstrated to effectively control the potential risk of contamination of the grade A and grade B areas and, likewise, the disinfection procedure should be demonstrated to be effective in reducing any contamination on the packaging to acceptable levels for entry of the item into the grade B and grade A areas.

Material Transfers

8.46 Where required, materials, equipment and components should be sterilised by validated methods appropriate to the specific material. Suitable protection after sterilisation should be provided to prevent recontamination. If sterilised items are not used immediately after sterilisation, these should be stored using appropriately sealed packaging and a maximum hold time should be established. Where justified, components that have been packaged with multiple sterile packaging layers need not be stored in a cleanroom if the integrity and configuration of the sterile pack allows the items to be readily disinfected during transfer by operators into grade A (e.g. by the use of multiple sterile coverings that can be removed at each transfer from lower to higher grade). Where protection is achieved by containment in sealed packaging, this packaging process should be undertaken prior to sterilisation.

8.47 Where materials, equipment, components and ancillary items are sterilised in sealed packaging and then transferred into grade A, this should be done using appropriate validated methods (for example, airlocks or pass-through hatches) with accompanying disinfection of the exterior of the sealed packaging. The use of rapid transfer port technology should also be considered. These methods should be demonstrated to effectively control the potential risk of contamination of the grade A and grade B areas and, likewise, the disinfection procedure should be demonstrated to be effective in reducing any contamination on the packaging to acceptable levels for entry of the item into the grade B and grade A areas.

8.48 Where materials, equipment, components and ancillary items are sterilised in sealed packaging or containers, the packaging should be qualified for minimizing the risk of particulate, microbial, endotoxin/pyrogen or chemical contamination, and for compatibility with the selected sterilisation method. The packaging sealing process should be validated. The validation should consider the integrity of the sterile protective barrier system, the maximum hold time before sterilisation and the maximum shelf life assigned to the sterilised items. The integrity of the sterile protective barrier system for each of the sterilised items should be checked prior to use.



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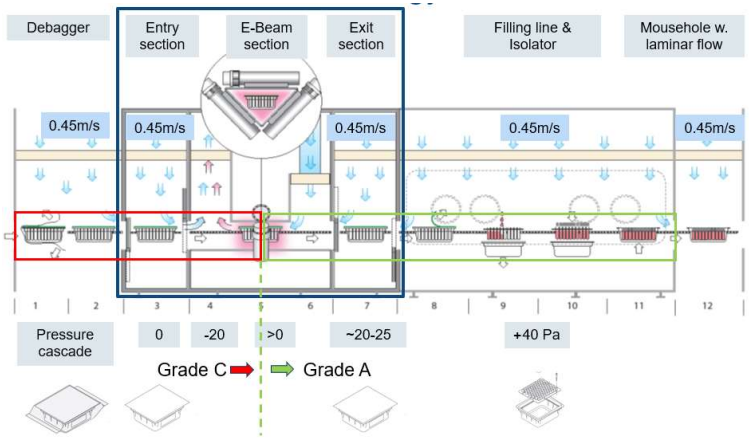
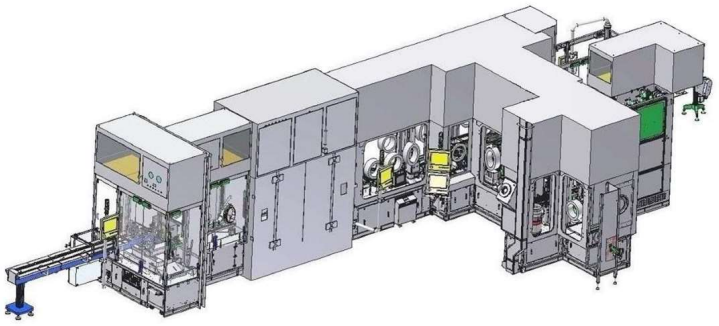
Material Transfers

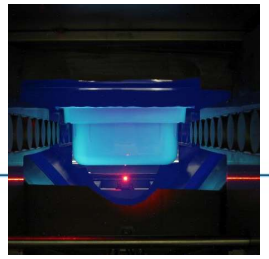


Basel '23 ebeam

ebeam

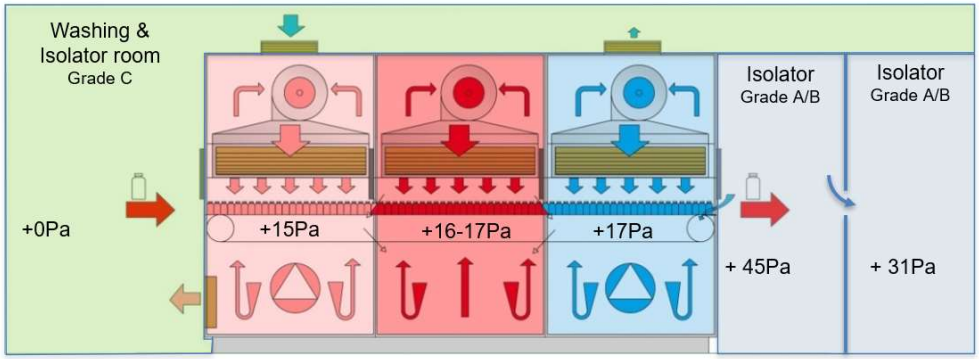


Basel '23 ebeam



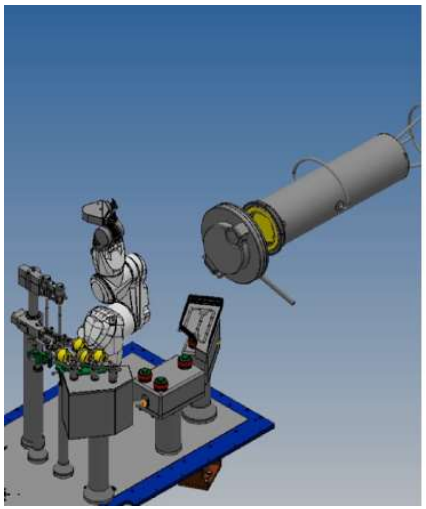
Material Transfers

- H2O2 Airlock



- Dry Heat Tunnel

Material Transfers



- Rapid Transfer Port

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- AT Sterile Connector

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Cleaning

- Cleaning before Decontamination

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5.4 The cleaning process should be validated to be able to:

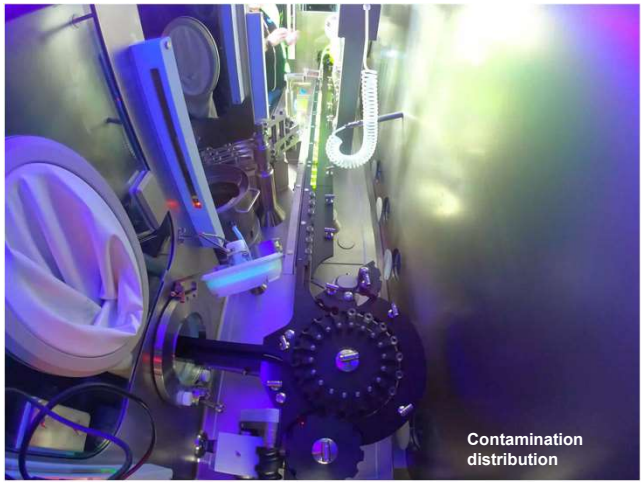
i. Remove any residue or debris that would detrimentally impact the effectiveness of the disinfecting agent used.
ii. Minimize chemical, microbial and particulate contamination of the product during the process and prior to disinfection.

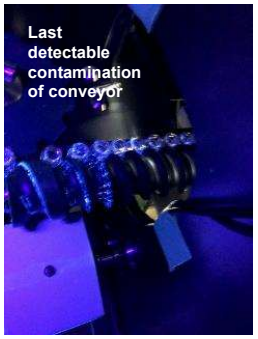
Table 1 Proposed EH&S and GMP surface limits for non-product contact surfaces and air limits inside of isolators

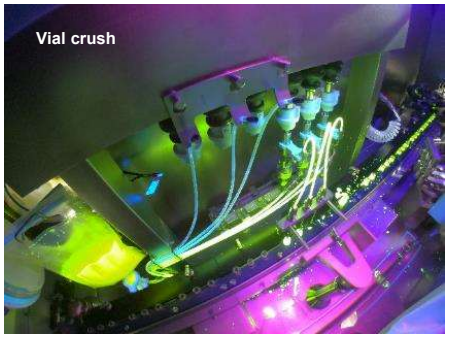
Occupational Exposure Bands (OEBs) Acceptable worker exposure (µg/m³) *(8-hour time-weighted average). The acceptable exposure is the conservative end of the OEB.*	Limit for surface with no direct product contact inside the isolator (µg/dm²) *Acceptable based on GMP and occupational health criteria.*	Limit for "public" surface with uncontrolled possibility of unprotected hand contact (µg/dm²) *Driven by occupational health criteria only.*	Limit for airborne API inside of isolator after cleaning at product changeover (µg/m³) *Driven by GMP criteria only.* **
OEB 1: range 1000-5000 ug/m³ Exposure limit: 1000 ug/m³	Visually clean	Visually clean	10000
OEB 2: range 100-1000 ug/m³ Exposure limit: 100 ug/m³	Visually clean	100	1000
OEB 3: range 10-100 ug/m³ Exposure limit: 10 ug/m³	100	10	100
OEB 4: range 1-10 ug/m³ Exposure limit: 1 ug/m³	10	1	10
OEB 5: range 0.1-1 ug/m³ Exposure limit: 0.1 ug/m³	1	0.1	1
OEB 6: range less than 01 ug/m³ Exposure limit: 0.01 ug/m³ or lower	0.1 or lower	0.01 or lower	0.1 or lower

** This limit is safe under the assumption that as a maximum, the total API burden of the previous product suspended in 1 m³ of air inside the isolator would go into one single therapeutic dose of the following products. Please also consider above that for simplification reasons the PDE/OEL ratio of 10 was assumed in regard to cross-contamination. Be aware that this needs to be justified for each product and product sequence due to difference in adjustment factors and administration route.

Cleaning



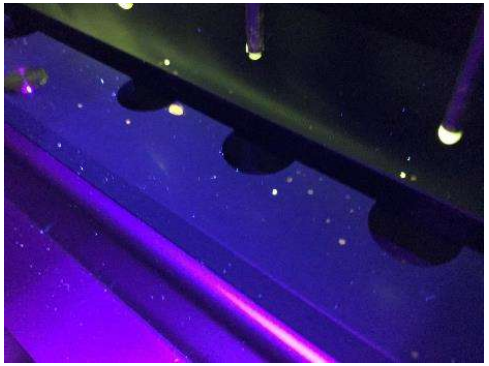




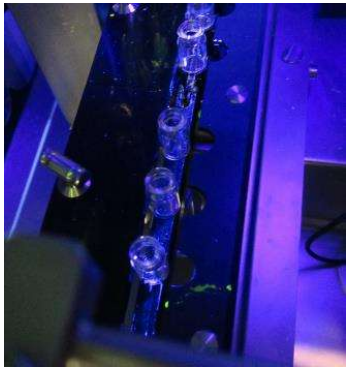
- Simulation of filling with worst case parameters (highest speed and volume)
- Simulation of worst case scenarios – vial break, contamination distribution, spillage in FIPA, splashes on RTP ports, etc.
- Delineation of practical contamination level risk sub-areas
- Characterization of distributions patterns

Cleaning

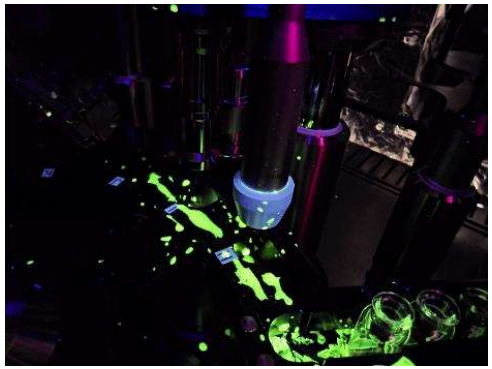
Contamination spread



Filling



Mechanical transfer



Vials crush

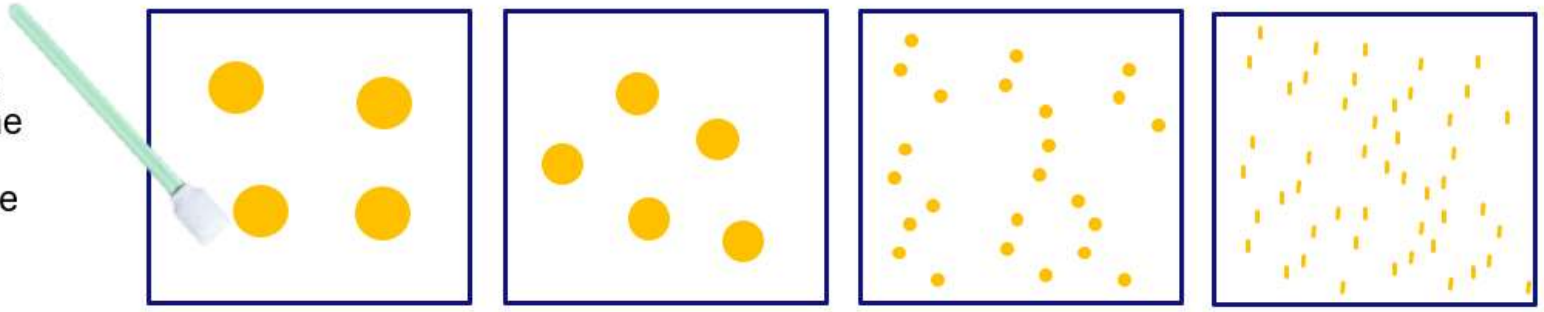
Cleaning

Coupons → Spike surrogate → Testing recovery technique → Sample preparation → Sample analysis → Recovery rate

Beside the chemistry of the soils, **recovery rates** are heavily **impacted** by the **type & geometry of the material,**




the **contamination distribution** and the type of **recovery tools** adopted in the cleaning studies



Recovery rate

Cleaning

- Different APIs ≠ VRL limits
- Different materials ≠ VRL limits
- Different matrixes ≠ VRL limits
- Different patterns ≠ VRL limits

API	API + Component 1	API + Component 2

ug/dm²	API - 1	API - 2
313		
625		
1250		
2500		
5000		

Cleaning

CLEAN IP

CLEAN Indicators & Prints

- SKAN contamination dosing printer technology is designed to help our customer to establish suitable contamination control strategies.
- No more random and uncontrolled spiking studies where the pattern distribution is left to chance.
- By using our SKAN patented printing approach you will be able to reliably and accurately deposit contamination patterns on your manufacturing and surrogate materials.

CLEAN IP

CLEAN Indicators & Prints

Your challenge

- Development and test of a suitable cleaning strategy
- Identify for different materials the visual threshold when your API or residues becomes visible
- Check residual contamination after the cleaning process

Indirect Product Contact Parts

5.5 For aseptic processes, direct and indirect product contact parts should be sterilised. Direct product contact parts are those that the product passes through, such as filling needles or pumps. Indirect product contact parts are equipment parts that do not contact the product, but may come into contact with other sterilised surfaces, the sterility of which is critical to the overall product sterility (e.g. sterilised items such as stopper bowls and guides, and sterilised components).

Line Set Up - Stopper Transfers

- Stopper Bowl and Stopper transfer Design to meet Annex 1 requirements
  - Does the assembly of the stopper transfer parts support aseptic assembly and reduce the risk of contamination?
  - The design shall allow to install all components without touching critical surfaces and avoid working above critical surfaces
  - Covers should remain until the critical items are installed and the containment is closed

Source: Steris

Stopper Transfers examples

- Stopper Transfer with stopper Bowl

- Stopper Transfer with sorting plate

Robotics

2.1 The manufacture of sterile products is subject to special requirements in order to minimize risks of microbial, particulate and endotoxin/pyrogen contamination. The following key areas should be considered:

i. Facility, equipment and process should be appropriately designed, qualified and/or validated and where applicable, subjected to ongoing verification according to the relevant sections of the Good Manufacturing Practices (GMP) guidelines. The use of appropriate technologies (e.g. Restricted Access Barriers Systems (RABS), isolators, robotic systems, rapid/alternative methods and continuous monitoring systems) should be considered to increase the protection of the product from potential extraneous sources of endotoxin/pyrogen, particulate and microbial contamination such as personnel, materials and the surrounding environment, and assist in the rapid detection of potential contaminants in the environment and the product.

8.9 Where possible, the use of equipment such as RABS, isolators or other systems, should be considered in order to reduce the need for critical interventions into grade A and to minimize the risk of contamination. Robotics and automation of processes can also be considered to eliminate direct human critical interventions (e.g. dry heat tunnel, automated lyophilizer loading, sterilisation in place).

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