Barrier Technologies, RABS and Isolators, Glove Integrity, Robotics, Decontamination

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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

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Annex 1

Manufacture of Sterile Medicinal Products

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.

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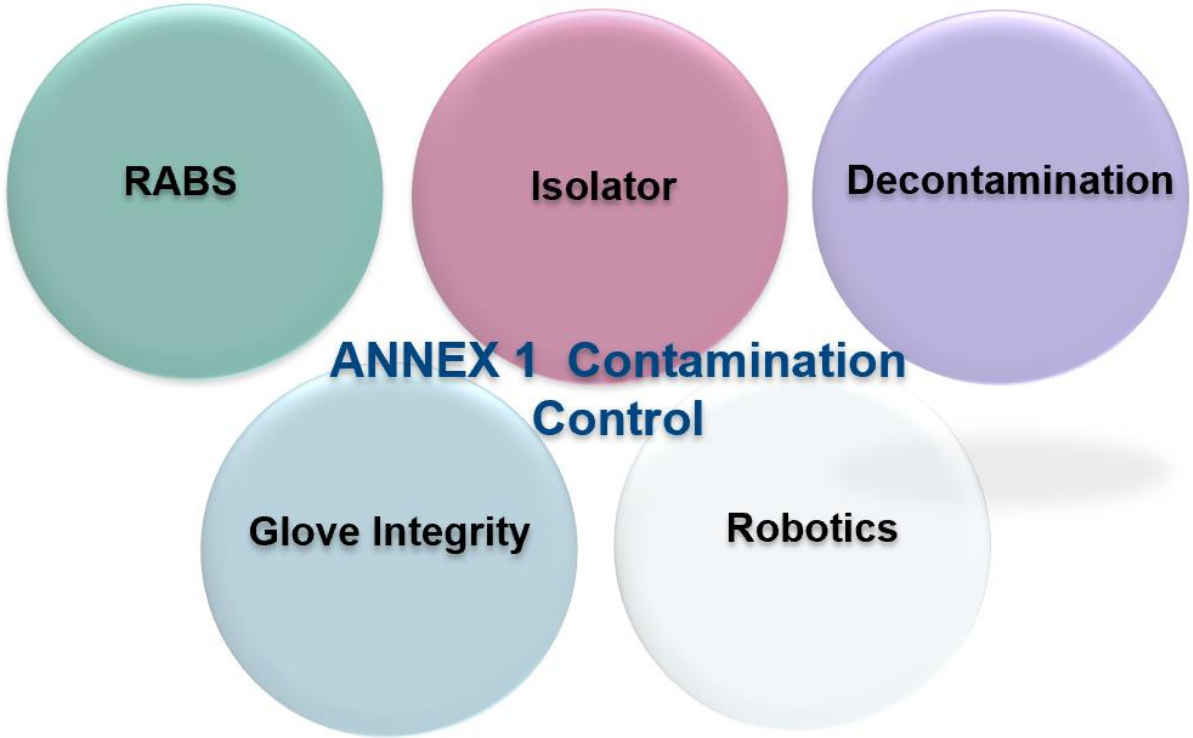
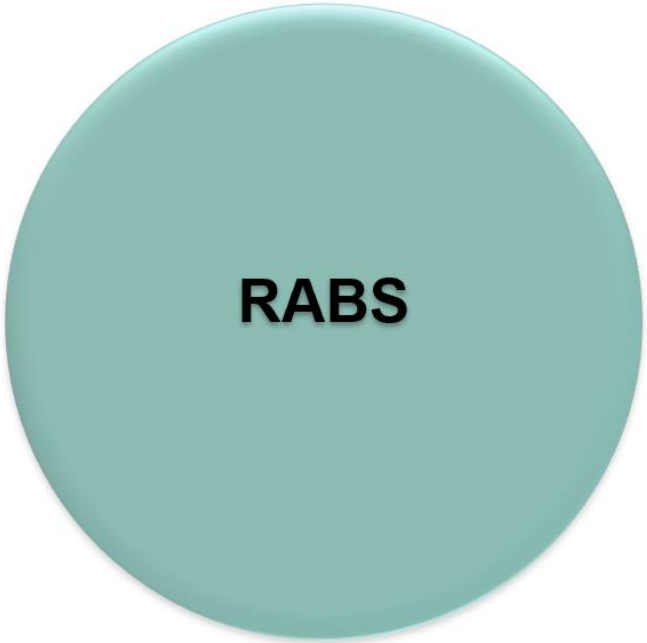
Conventional Aseptic Processing
⟶ Highest risk of human intervention

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

Isolators
⟶ Lowest risk of human intervention

Facilities


RABS
Isolator
Decontamination
ANNEX 1 Contamination Control
Glove Integrity
Robotics


RABS

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RABS «Restricted Access Barrier System»

- Reduced risk of human intervention

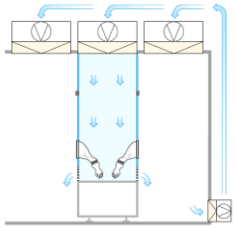
RABS " Restricted Access Barrier System"

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

Different RABS Technologies

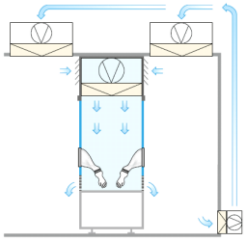
Passive Open RABS

- (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



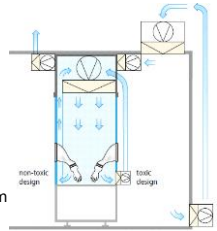
Active Open RABS

- 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


Isolator

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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

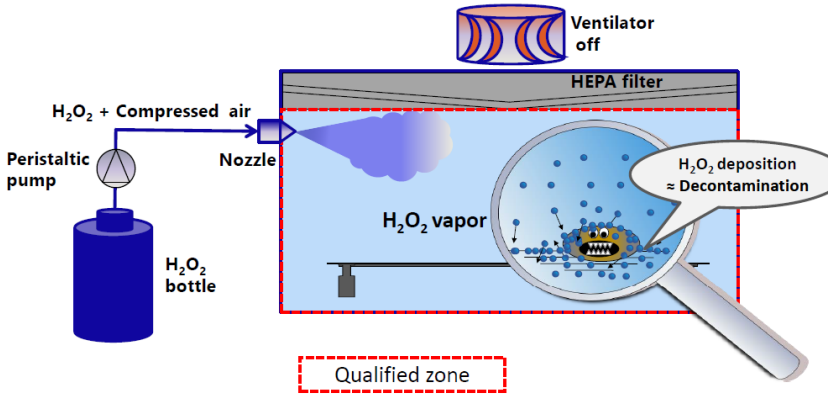
Different Isolator Technologies

Open Isolator

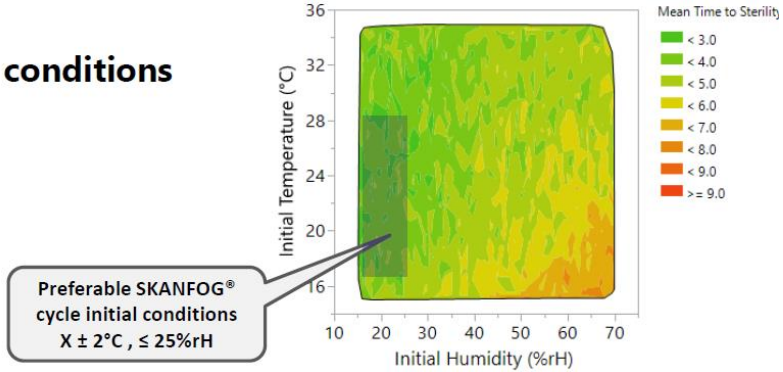
Closed Isolator


Decontamination

Contamination Control Strategy



initial conditions



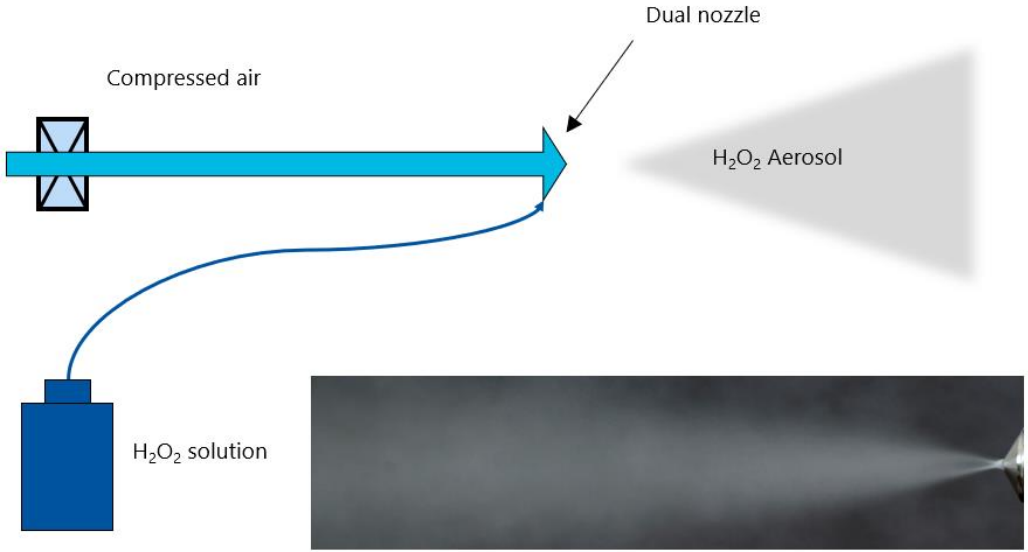
4.22 Decontamination methods (cleaning and bio-decontamination, and where applicable inactivation for biological materials) should be appropriately defined and controlled. The cleaning process prior to the bio-decontamination step is essential; any residues that remain may inhibit the effectiveness of 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.

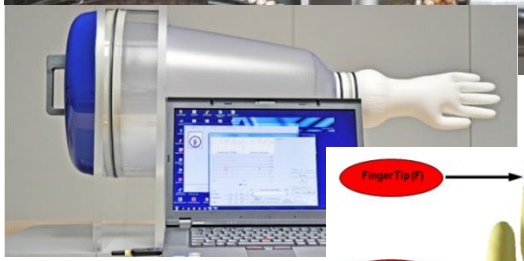
Contamination Control Strategy

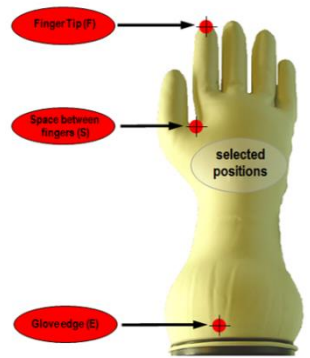
Surface Decontamination with atomized H_2O_2




Glove Integrity

Contamination Control Strategy





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.

Robotics

Aseptic Fill and Finish

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Annex 1

Manufacture of Sterile Medicinal Products

s fully automated
h

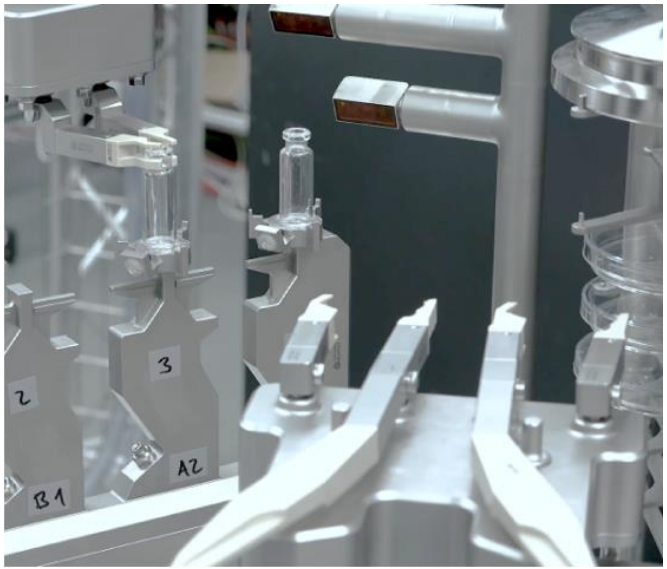
2.1 The manufacture of sterile products is subject to special requirements in order to minimize risks of microbial, particulate and endotoxin/pyrogen contamination. The following key areas should be considered:

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.

Gloveless fully automated Fill&Finish

- Design according to GMP (Annex 1 Draft)
- Design according BPOG/Biophorum URS for Gloveless Fill & Finish
- Holistic Contamination Control Strategy
- Aseptic line concept and line set up without human interventions
- Fully Track and Trace incl. Lyophilization
- Smart & intelligent use of robotics
- Smart & intelligent use of transfers as for Tubs, Stoppers etc.
- First air concept
- Fully automated line setup
- Validated transfers
- Intelligent sorting of stoppers and caps
- Designed for high potent products or products with a high BioSafety Level
- CLEAN Design for Surface and Air – Performance in the SKAN CLEAN Lab

Aseptic Fill and Finish



4.4 For the manufacture of sterile products, there are four grades of cleanroom/zone.

Grade A: The critical zone for high-risk operations (e.g. aseptic processing line, filling zone, stopper bowl, open primary packaging or for making aseptic connections under the protection of first air). Normally, such conditions are provided by a localised airflow protection, such as unidirectional airflow workstations within RABS or isolators. The maintenance of unidirectional airflow should be demonstrated and qualified across the whole of the grade A area. Direct intervention (e.g. without the protection of barrier and glove port technology) into the grade A area by operators should be minimized by premises, equipment, process and procedural design.

4.19 The design of the technology and processes used should ensure appropriate conditions are maintained in the critical zone to protect the exposed product during operations.

i. Isolators:

a. The design of open isolators should ensure grade A conditions with first air protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing.
b. The design of closed isolators should ensure grade A conditions with adequate protection for exposed products during processing. Airflow may not be fully unidirectional in closed isolators where simple operations are conducted. However, any turbulent airflow should not increase risk of contamination of the exposed product. Where processing lines are included in closed isolators, grade A conditions should be ensured with first air protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing
c. Negative pressure isolators should only be used when containment of the product is considered essential (e.g. radiopharmaceutical products) and specialized risk control measures should be applied to ensure the critical zone is not compromised.

First Air – Refers to filtered air that has not been interrupted prior to contacting exposed product and product contact surfaces with the potential to add contamination to the air prior to reaching the critical zone.

For the Breakout Session

- What should be improved on Barriers like Isolators?
- What would you expect in the future for Surface Decontamination and Glove Testing?
- Where do you see Robotics current and in the future, Learning about the design and control of Robotic Isolators (Do your firm consider Robotic Isolator)? (Question from Rick Friedman FDA)

Thank You

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