We will Learn

- What isolators are and why they were developed
- The difference between a RABS and an isolator
- The fundamental types of isolators
- The basics of isolator design and how materials are aseptically transferred to the isolator interior
- How isolators are decontaminated
Cleanroom contamination

• People are the greatest source of bio-contamination in the manufacture of sterile products.
• Separation of the people from the aseptic zone is the best method for controlling contamination.
• Physical barrier segregation is the method of choice
The aseptic integrity spectrum

- Open Bench
- Traditional Cleanroom
- RABS
- Isolators

Increased sterility assurance

Increasing system integrity

Advanced aseptic processing
Characterising The Technologies
Traditional cleanroom – characteristics

- Grade B/ISO7 Room scale critical environment contains operators
- Critical **Grade A/ISO5 Aseptic process Core** located in the **Grade B/ISO7 room**
- Operators open equipment from surrounding Grade B/ISO7 room to load the process and intervene using defined SOPs. High reliance on operator garments
- Bio-decontamination...
  - Topical disinfection of surfaces
  - Room fumigation in some cases (rare these days)
- Separation between operators and aseptic process core
  - Polycarbonate doors
  - Screens
  - Curtains
Traditional cleanroom – principles

Conventional Clean Room

- HEPA Filters
- Class 100 (ISO 5)
- Filling Mechanism
- Nozzle
- Vial
- Conveyor

Grade B Room

Grade A Zone
Open cleanroom – examples
Open cleanroom – examples
Traditional cleanroom – is it acceptable today?

• The traditional open cleanroom practice of 30 years ago is now under great pressure – examples:
  • Lack of sterilisation of stopper hoppers, bowl feeders and placers
  • Requirement to achieve Grade A continuity in the handling of change parts and components such as stoppers – requirement to mimic the protection afforded by the isolator or RABS
• My personal opinion is that the “open Cleanroom” approach is no longer acceptable practice = NOT cGMP
The minimum acceptable practice today

- Rigid screens separate personnel from the aseptic process.
- Highly controlled access to the machine enclosure.
Minimum open cleanroom – principles (limited access)

Grade B Room

Grade A Zone

HVAC - Fans

HEPA Filters

3-6" From HEPAS

Class 10,000 (ISO 7)

Class 100 (ISO 5)

Filling Mechanism

Conveyor

Nozzle

Vial

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The “RABS” restricted access barrier system
Definitions (ISPE)

- A barrier system is:
  - “A system of physical partitions that affords Grade A protection by partially separating its interior from the surrounding environment utilizing airflow.”

- Restricted Access Barrier System (RABS) is:
  - “An aseptic processing system that provides an enclosed, but not closed, environment meeting Grade A conditions utilizing a rigid-wall enclosure and air overspill to separate its interior from the surrounding environment.”
RABS types

Active RABS

Positive Pressure
Grade A

Room Grade B

Passive RABS

Room Grade B

Grade A
RABS – characteristics

• The Grade B/ISO7 Room scale critical environment contains operators
• Critical Grade A/ISO5 Aseptic process Core sits in Grade B/ISO7 room
• Operators use glove ports for intervention, and closed component handling from the surrounding Grade B/ISO7 room
• Bio-decontamination...generally as open room
  – Topical disinfection of surfaces
  – Room fumigation in some cases (rare these days)
• Separation between operators and Grade A/ISO5 Aseptic process core
  – Polycarbonate doors
  – Screens

With glove ports and transfer ports for components
RABS – principles

In passive RABS resistance to airflow can cause lateral flows.

Locally increased UDAF zone to protect door opening for very limited interventions.

Passive RABS

Grade B

Class 10,000 (ISO 7)

Class 100 (ISO 5)

Filling Mechanism

Grade A

Conveyor

Nozzle

vial

Grade B Room

HVAC

HEPA Filters
RABS – principles

Active RABS

Grade A

Grade B
Room

Class 100
(ISO 5)

Class 10,000
(ISO 7)

Nozzle

Conveyor

HVAC

HEPA Filters

Filling
Mechanism

Locally increased UDAF zone to protect door opening for very limited interventions
RABS – examples
The “closed RABS” “gassable RABS” restricted access barrier system
Closed RABS – principles

This variation has the ability to close a valve to allow a closed system gassing, fumigation or bio-decontamination or surface sterilisation.

Grade B
Class 10,000 (ISO 7)
Closed RABS – principles

Grade B
Class 10,000 (ISO 7)

Grade A
Class 100 (ISO 5)
Filling Mechanism

This variation has the ability to close a valve to allow a closed system gassing, fumigation or bio-decontamination or surface sterilisation.
The “Isolator”
US FDA’s view of (aseptic processing) isolators

- A well-designed positive pressure isolator, supported by adequate procedures for its maintenance, monitoring, and control, offers tangible advantages over traditional aseptic processing, including fewer opportunities for microbial contamination during processing.
Definitions (ISPE)

- An (aseptic) isolator is defined as
  - “A decontaminated unit meeting Grade A conditions that provides uncompromised, continuous, isolation of its interior from the surrounding environment.”
Isolator – characteristics

- Small contained enclosure excludes process operators
- Critical **Grade A Aseptic process Core** sits in **Grade C or D “at rest” room**
- Operators only open equipment when off-line. Human access via glove ports, and closed process loading
- Bio-decontamination…
  - Topical disinfection of surfaces inside isolator
  - or more often ...... Internal Isolator aerosol or vapour sanitisation
- Separation between operators and aseptic process core
  - Isolator shell
  - Windows
  - Glove ports
  - Transfer ports sterilised change-parts & components
Isolator – principles

Grade C or min Grade D

Isolator

Grade A

HEPA Filters

Filling Mechanism

Nozzle

Vial

Conveyor

Air Return

Class 100
(ISO 5)

Air Return

Class 100,000
(ISO 8)
Isolator – examples
Isolator – examples
1989 – ampoule filling isolator with softwall isolator

Photo Courtesy of Bosch Packaging –www.boschpackaging.com
Half suit (SS/polycarbonate isolator)

www.pharmsystems.com/LabServices/LabFacility...
Isolator transfer operations

- The mechanisms chosen for the various transfer operations are crucial to protect the aseptic processing core.
- A direct interface with the autoclave, de-pyrogenation tunnel, and/or sterilizing transfer device, is the most secure approach.
- The transfer mechanism should be capable of protecting the interior from bio-contamination. The major consideration is the ability to sterilize or surface bio-decontaminate the contents of the transfer device before allowing access to the controlled workspace.
Isolator “rapid transfer ports”

- A common technique for passing items into the enclosure is via a rapid transfer port (RTP).
- In this case, items are sterilized in a canister which is designed to be docked onto the transfer door of the enclosure without transferring contamination from outside to inside.
- The docking process seals the outer face of the transfer door to the lid of the canister in an air tight manner. Air tightness is ensured by the use of multiple-lip seal gaskets.
Rapid transfer ports

Step 1: Attach Transfer Canister or Bag Assembly

Step 2: Dry Heat Sterilize Isolator Port/Transfer Canister Interface

Step 3: Open isolator port

Step 4: Close protective collar and transfer product

Courtesy Central Research Laboratories - [www.skan.ch/Rtp.pdf](http://www.skan.ch/Rtp.pdf)
Isolator technology – some other important considerations

• Glove Systems and Gauntlets
• Leak Detection
• Bio-decontamination method
• Airflow Modeling
• Vapour and Material Compatibility
• Environmental Monitoring
Gloves – the weak point?

- Monitoring should be carried out routinely and should include frequent leak testing of the isolator and glove/sleeve system. EU Annex 1
- The integrity of gloves, half-suits, and seams should receive daily attention and be addressed by a comprehensive preventative maintenance program. FDA Aseptic guide
Isolator glove leak tests

- Methods
  - Pressure decay test (most common)
  - Oxygen diffusion test
- Frequency
  - Before batch or campaign
Enclosure leak test methods

- Quantified
  - Pressure decay test
  - Leakage rate test – Maintaining a constant pressure with a known flow rate
- Detective work – finding leaks
  - Tracer gas
  - Smoke
  - Ultrasonics
Isolator bio-decontamination

- Cleaning of enclosure should be carried out before decontamination
- It should be noted that only surface bio-decontamination is accomplished by the various treatments that may be used.
- Surfaces must be exposed sufficiently to the agent in order to achieve isolator bio-decontamination.
The design of the interior and content of an isolator should allow for its frequent decontamination.

When an isolator is used for multiple days between decontamination cycles, the frequency adopted should be justified. (ultimately validated by process media simulations)

This frequency, established during validation studies, should be re-evaluated and increased if production data indicate deterioration of the microbiological quality of the isolator environment.
Decontamination cycles

- Cycles should be developed with an appropriate margin of over-kill to provide confidence in robustness of the decontamination processes.
- Normally, a four- to six-log reduction can be justified depending on the application.
- The specific BI spore concentration and resistance used and the selection of BI placement sites should be justified.
- The uniform distribution of a defined concentration of decontaminating agent should also be evaluated as part of these studies.
How are isolators bio-decontaminated?

- Most common bio-decontamination agent is vaporized hydrogen peroxide used as a vapour-in-air mixture although other materials are available. Recently aerosolized H2O2 has been introduced.
- Operation must be conducted at controlled temperature and relative humidity (≈30%)
- Catalytic converters to remove breakdown products of hydrogen peroxide at the end of a bio-decontamination cycle with H2O2
Typical vapour $\text{H}_2\text{O}_2$ cycle*

- **Dehumidification** – Reduction of relative humidity
- **Condition** – Rapid increase to desired hydrogen peroxide vapor concentration
- **Biodecontamination** – Maintenance of desired hydrogen peroxide vapor concentration
- **Aeration** – Rapid reduction of hydrogen peroxide vapor

*Cycle used by STERIS VHP® M1000 Modular Continuous Biodecontamination System – [www.steris.com](http://www.steris.com)
Typical bio-decontamination cycle

STERIS VHP® M1000 Modular Continuous Biodecontamination System – www.steris.com
Environmental monitoring

- The expectation is to follow cleanroom practice as defined in the GMPs.
- The greatest challenge is the transfer of microbiological media INTO and OUT of the isolator during processing.
  - The micro monitoring ensures acceptable microbiological quality of:
    - Air
    - Surfaces
    - Gloves (or half-suits)
- Airborne particle monitoring is required to evaluate particle levels within the isolator during processing.
Learned

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- What distinguishes a RABS from an isolator
- The fundamental types of isolators
- The basics of isolator design and how materials are aseptically transferred to the isolator interior
- How isolator surfaces are decontaminated
- Environmental monitoring follows cleanroom practice
Thank you for your time. Questions?

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