ENGINEERING PHARMACEUTICAL INNOVATION

Sterility Test Isolator – Design, Construction and Examples

By

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WALKER BARRIER SYSTEMS

Formerly CPS Barrier

Why Use Isolators for Sterility Testing ?

- **The use of barrier isolator technology for sterility testing of pharmaceuticals and medical devices has clearly demonstrated the ability to significantly decease and even eliminate the incidence of “false positive” results. The superior testing results have not only increased laboratory testing confidence but have also decreased overall operation costs**

False Positives

- **Impact**
  - Costs $40K - $500K/year
    - Delays Product Release – Increased Quarantine Time
      - Investigation Required
        - Cost & Time of Investigation
          - Destroy "Good" Product
            - Lost Sales $

Courtesy: Millipore Corporation

Design Considerations

- Amount/Size Products to be Tested ?
- Size of Isolator System ?
- Configuration of System ?
- Rigid or Flexible Wall Construction ?
- Method of Decontamination (Manual or Automatic) ?
- Material Compatibility ?
- Uni-Directional or Turbulent Air Flow ?
- Manipulation-Range of Motion ?
- Transfer of Equipment and Material ?
- Illumination of Enclosure ?

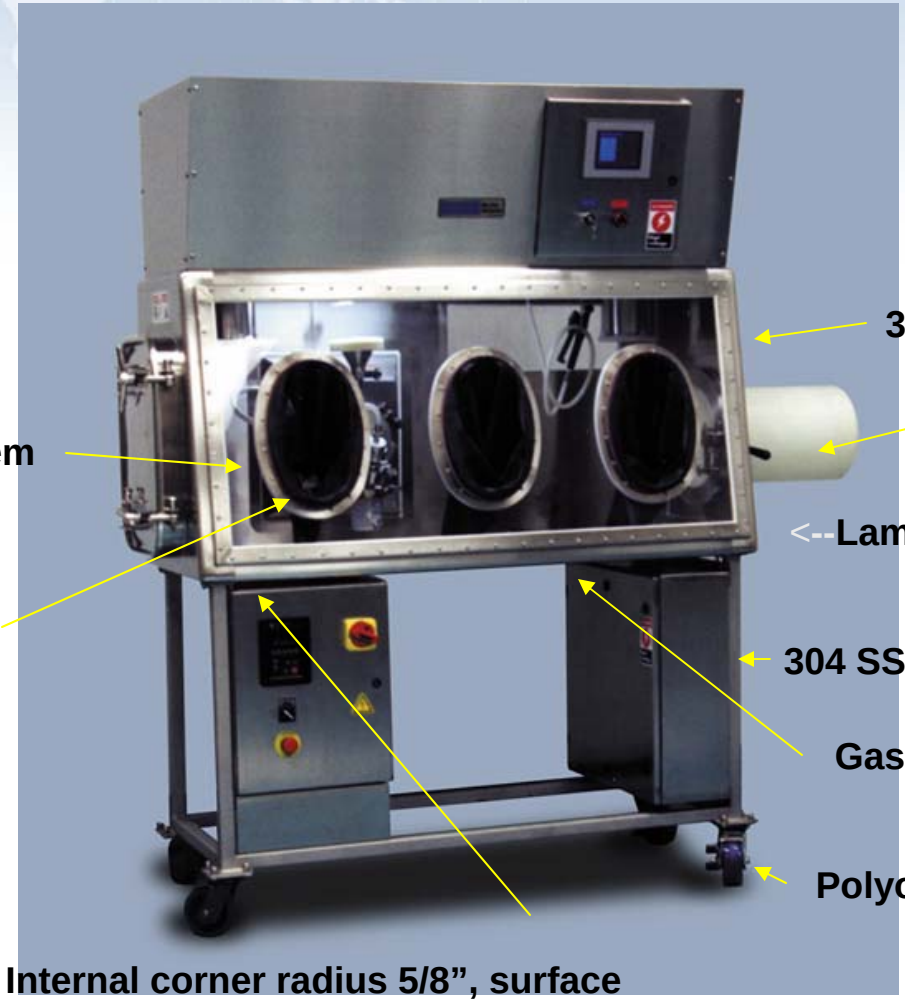
Mock Up Construction

- **Mock ups are an important part of isolator design.**
- **Construction is of wood and often uses actual components.**
- **Operators can perform ergonomic studies before final design.**

Mock Up Construction

It is important to involve the end user in the mock up evaluation

Rigid Wall Isolator Materials of Construction



316L SS Shell

RTP Alpha - SS & Polypropylene

<--Laminated safety glass

Glove Ports - Ultem

Gloves - Hypalon, Butyl, Neoprene, Viton

304 SS Frame

Gaskets - FDA silicone or EPDM

Polyolefin Casters

Internal corner radius 5/8", surface finish <22 Ra

Gloves & Gloveports

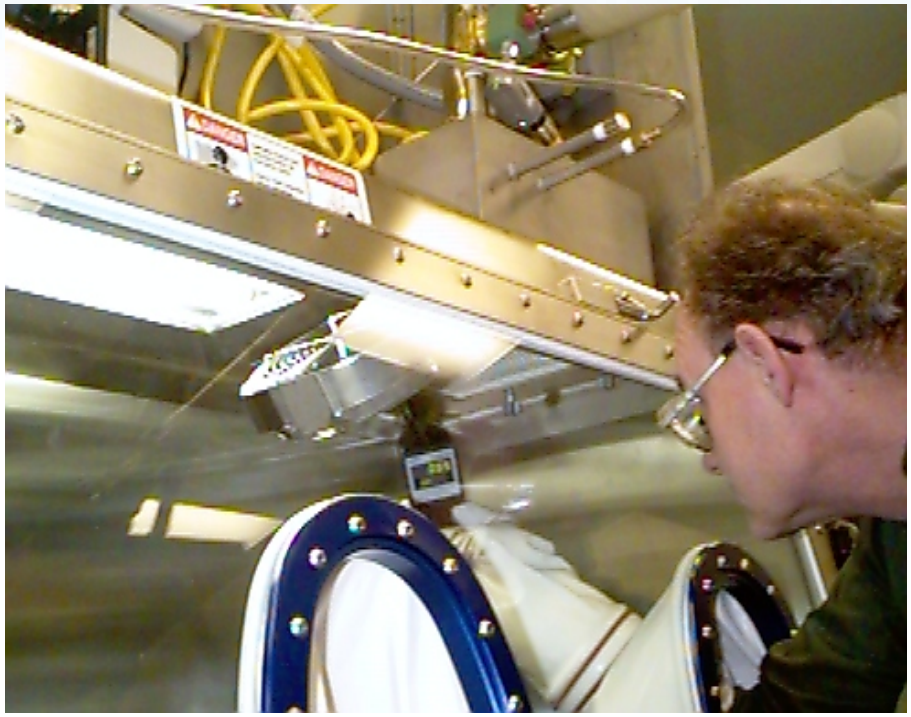
- **Ultem Molded Gloveports and retainers**
- **Gloves made of Hypalon, Neoprene, or Butyl**
- **Gloves designed with a double o-ring groove to allow safe glove change-out**

Flexible Wall Isolator Materials of Construction

Sterility Test Isolator Design and Construction

- Air Handling Systems:
  - HEPA filters are required.
  - Meets Class 100 conditions at rest.
  - Constant air over pressure required.
  - No requirement for air velocity or air changes exist.
  - Airflow can be turbulent or uni-directional

HEPA Filters



- HEPA Filters
  - Inlet and Outlet HEPA filters are provided at 99.97% efficiency for 0.3 micron particles
  - Variable speed blower with pressure controller provides constant positive pressure

Transfer Ports and Doors

- Steam Sterilizer Interface
  - Isolators are attached to exit door of pass through sterilizer to allow direct transfer of media, supplies, etc. into the isolator system.
- RTP Systems
  - RTP's allow 2 isolators to be connected and move supplies aseptically from one isolator to the other.

Interface Isolators

Entry Side of Sterilizer

- Materials enter sterilizer.
- Sterilizer door closed and cycle initiated.
- Sterilized material leave sterilizer though exit door into isolator.

RTP Use

Sterility Test System with Transfer Isolator and Work Station Isolator.

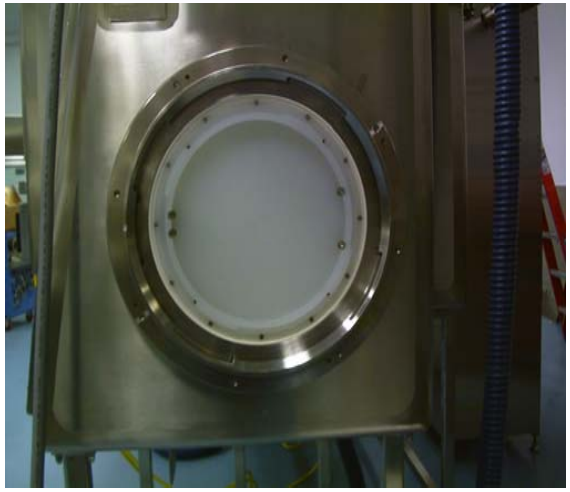
350mm RTP beta flange on transfer isolator is docked to 350mm RTP alpha flange on work station isolator.

Test materials and product are transferred from the transfer to work station isolator for sterility testing without breaking integrity of either isolator.

RTP Docking Sequence

The use of the RTP system allows for contained transfer of sterile or hazardous materials from within and/or out of the isolator without breaking containment.

1. RTP Alpha flange exterior mounted on end panel of an isolator.



2. RTP Beta Flange on a Polypropylene Container

RTP Docking Sequence

3. RTP Beta Container Approaches Alpha Flange on Isolator

4. RTP Beta Container Tabs are Docked with Slots in Alpha Flange

RTP Docking Sequence

5. RTP Beta Container is Rotated 60^0 using Handles.

<6. Via Glove Ports or Half-Suit, the Docked RTP Door Assembly is Opened within the Isolator.

7. View Inside RTP Container from within Isolator

Controls Systems Examples

Single Loop Control

- **Pressure Control by Red Lion single loop controller.**
- **Other control logic controlled by Allen Bradley Pico Controller.**
- **Audible and visual pressure alarms**
- **Selector switch for the following modes:**
  - **Run**
  - **Sterilize**
  - **Aerate**
  - **Stop**

PLC

- **Allen Bradley Micrologix PLC with PanelView+ 600 Touchscreen.**
- **Automatic Control of Decontamination Cycle. Pass Word Protect Screens Include:**
  - **Run**
  - **Sterilize**
  - **Aerate**
  - **Stop**
  - **Maintenance**
  - **Alarms**

Sterility Test Isolator System Automatic Decontamination

Isolator PLC system communicates directly with hydrogen peroxide generator.

Automatic valves require no operator intervention.

System can be automatically decontaminated overnight.

Sterility Test Isolator Systems

Sterility Test System with Transfer Isolator and Work Station Isolator.
Features Include:

- **350mm RTP System**
- **Optional PLC with Automatic Valves**
- **Large, Locking Caters**
- **Positive Pressure Ventilation/Filtration System**
- **Distribution Fans**
- **316L Stainless Steel & Glass Construction**

Transfer Isolator

- Transfer of Aseptic Product Samples
- Features Include:
  - Large, Locking Casters
  - 350mm RTP Beta Flange
  - Hatchback Window
  - Positive Pressure Ventilation/Filtration System
  - Distribution Fans
  - 316L Stainless Steel & Glass Construction
  - SS Wire Rack Shelves
  - Optional Lift Stand
  - Optional Glove Extenders

Large Sterility Test Isolator System

System includes:

- Dual Half-suit Work Station Isolator
- 3 glove Transfer Isolator
- 350mm RTP's
- Positive Pressure, Ventilation/Filtration System
- 316L Stainless Steel & Glass Construction
- PLC with automatic valves

Large Sterility Test Isolator System with Autoclave Interface

System includes:

- Autoclave Interface Isolator with half-suit
- Dual Half-suit Work Station Isolator
- 3 glove Transfer Isolator
- 350mm RTP's
- Positive Pressure Ventialtion/Filtration System
- 316L Stainless Steel & Glass Construction
- PLC with automatic valves

New Isolator Designs Used in Sterility Testing

Glove Sterility Testing Isolator

Glove Sterility Test Isolator

- **Available in 3,4 and 6 glove sizes**
- **Stainless steel and glass construction with oversize blower and valves allow for rapid decontamination.**
- **Ability to decontaminate and test in the same day.**
- **No RTP required.**
- **No validation of “sterility" maintenance required.**

6 Glove Sterility Test Isolator with Integrated VHP M100

Sterility Test Isolator

- **Stainless steel and glass construction with oversize blower and valves allow for rapid decontamination.**
- **Ability to decontaminate and test in the same day.**
- **No RTP required.**
- **No validation of “sterility" maintenance required.**

•Integrated VHP generator and Millipore system

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6 Glove Sterility Test Isolator with Integrated VHP M100 – Cycle Development

- The isolator was setup as follows:
  - A NIR sensor for monitoring VHP concentration was located in the center of the isolator.
  - 16 biological indicators and 12 chemical indicators were placed inside the isolator for each cycle. The biological indicator was a 10^6 population of Geo*bacillus stearothermophilus* inoculated on stainless steel,
  - The indicators were retrieved as soon as the concentration reached 1 ppm. The aeration time was documented.
  - The chemical indicators were observed for even color change.

Cycle Development Study courtesy of Steris Corporation

1.RESULTS:

Cycle	Injection rate (g/min.)	Time	Concentration	Aeration time	Total Cycle Time
Cycle 1	6.2	15	1.9 mg/L*	102	130
Cycle 2	5.5	20	2.0 mg/L*	100	130
Cycle 3	5.0	20	2.0 mg/L	76	110

* Condensation was observed.

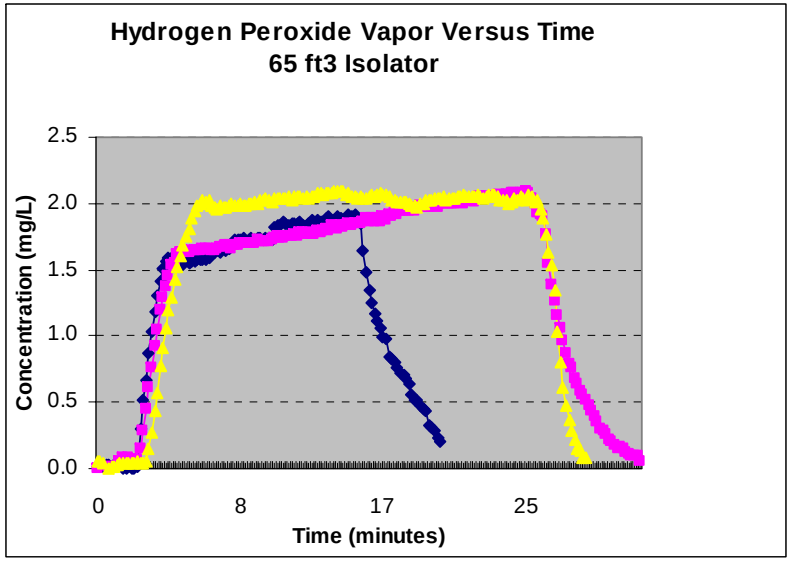
1.Biological/ Chemical Indicator Data:

1.Cycle 1: 0/12 locations and 0/16 indicators were positive; even color change among all chemical indicators.

2.Cycle 2: 0/12 locations and 0/16 indicators were positive; even color change among all chemical indicators.

3.Cycle 3: 0/12 locations and 0/16 indicators were positive; even color change among all chemical indicators.

2.Positive controls were positive for growth; negative controls were negative for growth.



CONCLUSION:

•All 3 test cycles resulted in complete kill of all biological indicators. The third cycle using lower injection rates resulted in the fastest total cycle time of less than 2 hours. Condensation of the hydrogen peroxide seemed to have contributed to increased aeration times.

6 Glove UAF Sterility Test Isolator

•Glove extenders –used during decon cycle

•UAF blower and filter x2

Sterility Test Isolator

- **Positive pressure isolator with recirculating Uni-directional airflow (note: there is no requirement by regulatory agencies for UAF in sterility test isolators)**

•Storage shelves and diffuser screen

Half-Suit Isolator

Half-Suit Sterility Test Isolator

- **Stainless steel and glass construction with oversize blower and valves allow for rapid decontamination.**
- **Ability to decontaminate and test in the same day.**
- **No RTP required.**
- **No validation of “sterility" maintenance required.**

Sterility Test Isolator Location

- Classified room not required.
- Limit access to non essential staff.
- Provide adequate space around isolators for maintenance, staging and moving of transfer isolators.
- Temperature and RH control of room is important, but no environmental monitoring of room is required.
- Uniform temperature conditions in room required so not to effect isolator sterilization methods.

Barrier Isolator Benefits

- Virtually No Sterility False Positives
- Ability to maintain sterility of equipment over a period of time
- No gowning required
- Less expensive to operate versus clean room

Barrier Designs

Flexible Wall Isolators

Advantages

- Lower Cost
- Easily Assembled/Disassembled
- Lightweight
- Good Visibility
- Good Flexibility for Glove Ports

Disadvantages

- Difficult to Leak Test
- Subject to Punctures
- Canopies Need Replacing
- Limited Resistance to Chemicals
- Adsorption and Permeation of Hydrogen Peroxide

Barrier Designs

Rigid Wall Isolators

Advantages

- High Resistance to Chemicals
- More Easily Leak Tested
- Durable
- No Adsorption/Permeation of Hydrogen Peroxide
- Better Aesthetic Appearance

Disadvantages

- More Expensive
- Longer Assembly/Disassembly
- Need Additional Lighting
- Less Flexibility for Glove Ports
- Heavier Weight

Using Isolators for Sterility Testing results in:

Happy Quality Control Team

Extremely Happy Management

Aseptic Isolator Examples

Miscellaneous Aseptic Isolators

Horizontal Uni-directional Flow Powder Addition Isolator

Horizontal Uni-directional Flow Combo Isolator. Used for drum lid removal, cone placement and drum separation.

Formulation and Sampling Isolator.

M&O Perry Vial Fill Machine Isolator

Full front and rear return ducts for maximum UAF

M&O Perry Vial Filler. Features include:

- Fully welded floor and columns
- Uni-directional airflow
- Hatchback windows for internal access
- 316L SS & glass construction
- RTP system for vial, stoppers, caps and sterile liquid transfer

Groninger High Speed Syringe Fill Machine Isolator

Inside the “U” of the fill machine. 6 up fill heads. SS RTP container for introduction of sterile fill head parts.

Plunger bowl and product exit opening. Blanked off for VHP. Light curtains for operator safety.

Groninger High Speed Syringe Filler. Features include:

- Integrated VHP-M1000
- uni-directional airflow,
- 31 glove ports in hatchback windows
- integrated at customer site
- 316L SS & glass construction

Aseptic Barrier Systems

Flexicon Fill Machine Isolator Features include:

- 316L SS and glass construction
- Positive pressure system with uni-directional airflow
- Negative pressure breach system
- Spray wand and drain system
- Entry and exit RTP flanges for batch process
- H_2O_2 Injection nozzle
- Particle monitoring ports

Robotic Syringe Fill Machine Isolator with:

- Positive pressure
- Uni-directional airflow
- H_2O_2 decontamination connections
- PLC with automated valves
- RTP system
- Multiple glove ports
- Reduced number of moving parts

Aseptic/Containment Barrier Systems

RadioPharmaceutical Liquid Filling Interface Isolator.

Features include:

- Integrated Base on Filler
- 350mm RTP for Component Entry
- Manipulators
- Uni -Directional Ventilation/Filtration System
- 1.25” thick 316L Stainless Steel & Lead Glass Construction
- Customer Nuclear Exhaust

Thank You!

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BARRIER SYSTEMS

Engineer's RISK vs REWARD

- RISK: Public Humiliation and the death of thousands of innocent people
- REWARD: A certificate of appreciation in a handsome plastic frame

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