Requalification MIC family of Isolators

Requalification of the MIC family of Isolators to FDA Guidance for industry – Sterile Drug Products Produced by Aseptic Processing 2004Appendix1: Aseptic Processing Isolators Closed System Isolator.

Revalidation Company	Contact Phone Number	Date of Inspection	Re-inspection Date

Technician Name (print)	Technician Signature

Model	Serial Number	Facility Name	Location	Contact Person
MIC Single				
MIC Dual				
MIC - EDU				

Index Requalification Protocol

1.0 General

1.1 Purpose:

5 The original validation included the following: 1. Glove integrity; 2. Design Airflow; 3. Pressure Differential; 5. Transfer of Materials (Viable Environmental Evaluation); and 6.Clean Air Classifications. It is important to note that for pharmacy applications the components used in compounding are not sterile on the outside of the packages and containers.

The purpose of the requalification is to verify that the MIC is operating in accordance with the validation documentation and in compliance with guidance presented in FDA Guidance for industry – Sterile Drug Products Produced by Aseptic Processing 2004 Appendix 1: Aseptic Processing Isolators for *closed system isolators*. A series of criteria will be evaluated to show that the specific design of the MIC isolators meet the definition of a closed system isolator.

1.2 General Description

The MIC family of isolators is designed to provide an aseptic environment in which aseptic operations can occur. The isolators are designed with a standard chamber configuration of 40" wide by 24" deep and 26" high for the single. The MIC dial has two chambers joined to provide two chambers on the same base. The MIC EDU configuration is 40" wide by 27" deep and 34" high. The MIC single and MIC dual use the same chamber configuration and evaluation of the single chamber represents both isolator configurations.

The original validation was conducted on a "worse case" configuration of a negative pressure environment inside the isolator. The MIC family of isolators demonstrates the following properties demonstrating compliance to FDA guidance for closed system isolators: Glove Integrity: Design Airflow; Materials of Construction; Pressure Differential; Transfer of Materials; Clean Air Classifications; Gas Tight Construction

1.3 Definitions:

Asepsis – A state of control attained by using an aseptic work area and performing activities in a manner that precludes microbiological contamination of the exposed sterile product [1]

Component – Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in the final drug product.[1]

Dynamic – Conditions relating to a clean area classification under conditions of normal operation.[1]

HEPA filter – High efficiency particulate air filter with a minimum 0.3 micron particle retaining efficiency of 99.97 percent of airborne particles 0.3 micrometers (µm) in diameter..[1]

ISO Class 5 – Is the maximum concentration limit (particles /m^3 of air at 0.5 microns defined by ISO standard 14644-1:1999(E) classification of air cleanliness. 14644-2000(E) describes specifications for testing for continued compliance to ISO 14644-1:1999(E). ISO14644-3:2005(E) describes test methods for compliance to ISO14644-1:1999(E).

Isolator – A decontamination unit, supplied with Class 100 (ISO 5) or higher air quality, that provides uncompromised, continuous isolation of the interior from the external environment.[1]

Closed System Isolator – Employ connections with auxiliary equipment for material transfer. Turbulent flow can be acceptable within closed isolators, which are normally compact in size and do not house processing lines. In most sound designs air showers over the critical area once and then is systematically exhausted from the enclosure. The air handling system should be capable of maintaining the requisite environmental conditions within the isolator.[1]

Inches of water column Measurement of pressure is denoted as "Inwc" or w.c

Material CERTS - Documents defining the chemical composition of materials

Re-Qualification – Ensuring that the isolator is still in the qualified state as determined by validation and a practical assessment within a defined time period [2]

Sterility Assurance Level (SAL) is a term used in microbiology to describe the probability of a single unit being non-sterile after it has been subjected to the decontamination process. **SAL** is also used to describe the killing efficacy of a decontamination process.

Unidirectional flow – An airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed to reproducibly sweep particles away from the critical processing or testing area.[1]

Validation – Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.[1]

Worse Case – A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, that pose the greatest chance of process or product failure. [1]

(1) Source Glossary FDA Guidance for industry – Sterile Drug Products Produced by Aseptic Processing 2004
(2) GMP News 02/10/2013

2.0 Glove and Sleeve Integrity

2.1. Objective

2.2 Methodology

Visual inspection supported by method used in the factory verification of the system using methods outlined in section 12.0 Gas Tight Construction will verify the glove sleeve integrity. After completion of evaluation used in 12.0 transfer data to the results section under "ammonia leak test".

The MIC owner's manual contains recommendations as to visual inspection and frequency of glove change.

2.3 Test equipment, support materials and instruments required:

None visual inspection

2.4 Acceptance Criteria

No leaks detected

2.5 Results

Item	Leaks (Yes/ No)	Initials
Right glove and sleeve		
Left glove and sleeve		

3.0 Viable Environmental Evaluation of Isolator

3.1 Objective

The objective of this test is the evaluation of airborne microorganisms if present in both in the ISO class 5 environment and the room area surrounding the controlled environment. Monitoring should occur during normal operations to allow for collection of meaningful data. This protocol is intended to provide for monitoring of viable airborne particulate and should be supplemented with surface and fingertip monitoring programs.

3.2 Methodology

Viable airborne sampling is to occur on a semiannual basis within both the ISO class 5 compounding environment and the surrounding controlled environment. The sampling is conducted with a viable airborne collection device. The recommended volume is 1000 liters of air. There are a number of collection devices available. The device is to be calibrated per manufacturer's recommendations.

The isolator's interior samples are to be taken at the center of the compounding zone (approximately 20 inches from the side wall and twelve inches from the back wall and center of the airlock door and approximately 12 inches from the side wall). This site encompasses the critical zone of the isolator. The outside location is on top of the airlock if possible.

Testing Instructions:

1. Remove the outside wrap of the sampling plates in the airlock of the MIC and spray. Close the outer door and wait 45 seconds.

2. Open inner door and remove sampling plates from the airlock into the MIC.

3. Place the sampler in the airlock and spray down with sterile alcohol. Close the outer door. Wait 45 seconds.

4. Open inner door and remove the sampler from the airlock. Spray down with alcohol.

5. Before beginning manipulations pick up spray bottle and spray down the sampler and the gloves and sleeves of the chamber. Allow 45 seconds for the alcohol contact time.

6. The inside and outside sample times should be based on collecting 1000 liters of air.

7. Tape for securing the plate lids should not be brought into the MIC until after the sampling is complete and the lid is in place on the sample plate so as to not contaminate the sample.

8. After any handling of materials spray down gloves.

9. Samples are to be kept cold after collect and during transport. Samples are to be submitted to a certified testing lab for analysis. (Results from the laboratory may take up to 10 days and will be forwarded on a separate report to pharmacy management.)

3.2.3 Test equipment, support materials and instruments required:

1. Viable air sampler collection device
   Manufacturer: _____ Model: _____ Calibration Date: _____

2. TSA Media Growth plates
   Lot Number: _____ Expiration Date: _____

3. Sterile alcohol for decontamination of sampling head and outer wrap of plates

4. Labels for identification of samples
   a. Two inside samples
   b. One external sample
   c. Two control samples (one positive and one negative)

5. Return shipper with ice packs if using an outside testing facility

3.2.4 Acceptance Criteria

Recommended Action Levels Microbial Contamination*
Based on (cfu per cubic meter [1000 liters] of air per plate)

Classification Air Sample
ISO Class 5 > 1
ISO Class 7 > 10
ISO Class 8 or worse > 100
Source: Guidance for Industry–Sterile Drug Products Produced by Aseptic Processing–Current Good Manufacturing Practice–US HHS, FDA September 2004.

3.2.5 Results

Samples collected, packaged and ready for shipment	Meets acceptance criteria Yes/No	Initials/Date:

4.0 Air Flow Design

Airflow studies should be conducted under dynamic conditions (e.g., in-situ smoke study) to initially qualify the HVAC/HEPA unit *and* when any changes are made to the HVAC/HEPA unit or the critical area that might affect airflow. Any indication of poor air control (e.g., non-laminar, turbulent) should be corrected before use.

• HEPA periodic testing/recertification should be performed at least twice a year to ensure that appropriate air flow and quality is maintained. These tests should include: integrity testing of the HEPA filters, particle counts, and air velocity checks.

Supplies required;

a. Two 10ml syringes
b. One 10 ml vial (water for injection)
c. One 50 ml bag of solution

Instructions:

1. Remove any outer wraps
2. Place materials in transfer basket
4. Place basket with materials into transfer chamber and spray the transfer chamber
5. Insert hands into gloves of the isolator
7. Open transfer chamber door and move basket into the chamber
8. Place basket towards the rear of manipulation area
9. Turn on particle counter and commence evaluation
10. Remove materials from basket
11. Commence transfer via syringe of ten ml from the vial into the solution bag
12. The transfer into the bag completes evaluation turn off particle counter

Note: Consult with pharmacy if they prefer a different sequence of operations
During the activity turn on particle counter and verify that counts in the first minute meet ISO class 5 criteria of less than 3520 particles of 0.5 micron per cubic meter

4.1 Visualization Test

Introduce a single smoke stream at the left most point of the left gloveport. Video record the smoke moving in a single direction and from left to right across the critical area.
A video of the validation smoke test is included on the CD Documentation disc.

4.2 Particles removed from Critical Preparation Area

4.2.1 Objective

To verify that the air flow is removing particles from the critical preparation area by moving in a single direction, in a robust and uniform manner, and at sufficient speed to reproducibly sweep particles away from the critical processing or compounding area. The airflow is from left to right across the critical area when facing the isolator. The critical area is defined as between the outer edge of the glove ports and three inches in from the front and back wall of the isolator.

4.2.2 Methodology - Simulate activity in the critical zone by the following steps:

Place particle counting probe at the following locations;

1. Six inches from back wall and six inches from the left wall
2. Twelve inches from back wall and six inches from the left wall
3. Eighteen inches form back wall and six inches from the left wall

Repeat the test two times.

4.2.3 Test equipment, support materials and instruments required:
Calibrated particle counter

4.2.4 Acceptance Criteria

Removing particulate from critical zone at a speed to reproducibly sweep particles away from the critical processing or testing area The difference between the particle count number after the count has stabilize and one minute later is less than 3520 particles of 0.5 micron.

4.3 Integrity Testing of the HEPA Filters

4.3.1 Objective

Verify HEPA filter integrity via a challenge test of supply HEPA filter

4.3.2 Methodology- Introduce the aerosol challenge:

1. Determine supply air volume.
2. Calculate the upstream concentration.
3. Introduce the challenge upstream of the supply HEPA filter.
4. Recommended Test Method – Full access for a direct scan of HEPA filter.
5. Leak rate greater than 0.01% of the upstream aerosol concentration is considered a leak.
6. If applicable, repair any leaks.

4.3.3 Test Equipment

Thermo anemometer, aerosol generator, and aerosol photometer

4.3.4 Acceptance Criteria

Leak rates greater than 0.01% (direct filter scan) of the upstream aerosol concentration are not acceptable. A leak rate greater than 0.01% is considered a leak. (reference ISO 14644-3:2005, Annex B, B.6)
Note 1: Portions of the test methods have been adopted from IEST-RP-CC034.
Note 2: Some MIC isolators may be set up where access for a direct filter scan is not possible. In these cases, it is acceptable to probe the membrane that separates the chamber from the filter duct.

4.5 Results

Air flow design evaluation	Meets acceptance criteria Yes/No	Initials/Date:
Removes particles from critical zone of isolator		
Integrity test of inlet HEPA filter		

via aerosol challenge test		

5.0 Pressure Differential Verification

5.1 Objective

To verify that the MIC chamber will maintain a set level of pressure. The MIC chambers are regulated by flow control valves and can be set to either a positive or negative pressure. The pressures will fluxuate during normal operation because the MIC chamber is gas tight. The volume of the chamber is impacted by movement of the sleeves required during activities occurring in the chamber. The purpose of this verification is to determine that a state of control is maintained by the MIC chamber within a range of +0.2 to + 0.4 for positive pressure units and -0.2 to -0.4 for negative pressure units.

5.2 Methodology

Select a setting of the pressure differential gauge and observe for a period of **two minutes** to determine that the pressure differential is stable and does not change. Conduct for the following pressure setting: +0.2; +0.4; -0.2 and -0.4 inches water column.

5.3 Test equipment, support materials and instruments required:

None - visual verification of pressure gauge

5.4 Acceptance Criteria

The pressure differential gauge maintains the preset pressure level with +/- range of 0.20 and 0.04 WC

5.5 Results - Pressure Differential Verification

Actual Results Acceptable	**Yes**	**No**	**Initial / Date**	**Date**

6.0 Clean Air Classification as ISO Class 5 Verification

6.1 Objective

6.1.1 Verify that the MIC chamber meets ISO Class 5 air quality during dynamitic operation based on testing locations described in 9.2.1.

6.1.2 Verify the classification of the surrounding environment in which the MIC is being placed.

6.2 Methodology.

6.2.1 The following test locations are to be used:

A. Six to twelve inches below the left HEPA filter

B. Place particle counter probe six inches off the left wall of the isolator and 9" above the isolator floor with the probe opening facing toward the critical area The three floor locations are: six inches, twelve inches and eighteen inches from back wall.

C. Take two readings at each location.

7.2.2 Verify the classification of the surrounding environment in which the MIC is located. Place non-viable collection horn on top of the decontamination chamber. **Take three readings**.

6.3 Test equipment, support materials and instruments required

Calibrated particle counter and calibration CERT for particle counter

6.4 Acceptance Criteria

6.4.1 The particle counts recorded during the evaluation conducted in 9.2.1 do not exceed ISO class 5.

6.4.2 It is acceptable for the MIC to be placed in an ISO 8 or ISO 9 environment. If the environment is ISO Class 9 the particle counts should not exceed 10,000,000 particles size of 0.5 micro per cubic meter of air. Counts are to be taken in dynamic conditions. Record data and attach particle counter print strips if available from both 9.4.1 and 9.4.2 to document.

6.5 Results – Clean Air Classification as ISO Class 5 Verification - Dynamic conditions*

Test	Run 1	Run 2	Run 3	Particle Counter Information. Name model and serial number	Calibration Date	Initials/Date:
A						
B						
C						
Room						

	Actual Results Acceptable	Yes	No	Initial / Date

7.0 Gas Tight Construction – Optional Test

7.1 Objective:

The gas tight construction verification is to determine that the MIC is gas tight.

7.2 Methodology

Verify integrity of the isolator, by placing an ammonia source inside the chamber of the isolator and with a pH sensitive cloth check each potential leak source by placing the pH sensitive cloth over the outside of the isolator surfaces listed below. The isolator is to be under positive pressure during testing with a target level of 0.20 to 0.40 inches of w.c.. Required to perform the test is an ammonia source inside the isolator with test strips of pH sensitive cloth outside of the isolator.

7.3 Test equipment, support materials and instruments required

Ammonia source – Lab Chem, Inc. 50% V/V

Test cloth – Precision Laboratories Ammonia Leak Detector Cloth

7.4 Instructions:

1. Place the ammonia inside the isolator. Do not open container until it is in the isolator. Pour a small amount into open dish (a sharps container lid will work).

Place several small strips inside the isolator to verify that the cloth will turn color.

CAUTION: The ammonia has an intense odor and breathing should be avoided.

2. Turn on the blower and allow it to reach the maximum pressure.

3 .Remove the Ph sensitive cloth from package outside the isolator and teat into strips. Begin testing the points the points outlined in the results section.

4. After test is complete pour remaining ammonia back into original container before removing from isolator.

The Test strips are a bright yellow but when exposed to ammonia will turn a blue color. The greater the leak to brighter the color change to blue. Very small leaks can appear a green color.

7.5 Acceptance Criteria

Test strips maintain original color and do not turn blue.

7.6 Results.

Test Point	Initial (Pass/ Fail)	Retest* (Pass/ Fail)	Initials
All door seals			
Panel seals			
Filter housing seals (lids and connection to isolator			
Blower housing			
Ductwork connection from blower to filter housing			
Window seals			
Glove ports			
Trash and sharps ports			

* If a test point fails corrective action should be taken to fix the leak and then retest point

Summary Requalification Report

Requalification Company	Phone Number	Date	Re-inspection Date

Technician Name (print)	Technician Signature

Model	Serial Number	Facility Name	Location	Contact Person

2.0Glove and Sleeve Integrity -Results – Glove / Sleeve Integrity Testing

Actual Results Acceptable	Yes	No	Initial / Date

3.0 Viable Environmental Evaluation

Actual Results Acceptable	Yes	No	Initial / Date

4.0 Air Flow Design

Actual Results Acceptable	Yes	No	Initial	Date

5.0 Pressure Differential Verification

Actual Results Acceptable	Yes	No	Initial	Date

6.0 Clean Air Classification as ISO Class 5 Verification- Results – Dynamic conditions*

Test	Run 1 Count	Run 2 Count	Run 3 Count	Particle Counter Information. Name model and serial number	Calibration Date	Initials/Date:
A						
B						
C						
Room						

	Actual Results Acceptable	Yes	No	Initial / Date

7.0 Gas Tight Construction – Results

Actual Results Acceptable	Yes	No	Initial / Date

Unit Passes Requalification: _____ Date of next Requalification: _____