



CETA Compounding Isolator Testing Guide

CAG-002-2006

Revised December 8, 2008

1.0 Overview:

The purpose of this document is to establish an industry-based minimum set of testing criteria appropriate for all Compounding Isolators used pursuant to USP Chapter 797 ¹. Compounding Isolators consist of Compounding Aseptic Isolators used for compounding sterile preparations and Compounding Aseptic Containment Isolators used for compounding sterile hazardous drug preparations in pharmacy applications. While this document gives general guidance or referenced guidance through relevant industry documents, it is not the intention to set the specific acceptance criteria. It is the manufacturer's responsibility to determine exact testing procedures consistent with these guidelines and assign appropriate values pertaining to acceptance criteria that is consistent with user requirements. This guide has also been established to create a uniform approach for field certifiers to allow consistent and repeatable testing at all facilities.

1.01 General Responsibilities:

The criteria outlined are intended to describe currently accepted practice. Responsibility for test performance lies with the manufacturer during design and production, and field certifiers at the installation site. INFORMATIONAL NOTES are inserted to aid users of this guide by providing a format or general reference for the information desired. The engineering and design concepts employed are up to the individual manufacturer's discretion. The general assumptions in determining the minimum criteria for Compounding Aseptic and Compounding Aseptic Containment Isolators covered in this document are:

- used for compounding sterile preparations
- used in either a classified or unclassified space
- use of "open" design, using pass-through chamber systems to transfer material in and out
- may be either positive or negative pressure depending on the hazard of the drugs
- no expectation of end user employing gaseous decontamination of the Compounding Isolator

An isolator certified by the manufacturer as meeting the criteria established in CETA CAG-002-2006 shall post the following on the front of the cabinet in a location readily visible to the user:

1. Notice of pass or failure of the Preparation Ingress and Egress Test (2.09).
2. Whether or not designed for use with volatile hazardous drug compounds, toxic, flammable or explosive materials.
3. Indication of the results of the Recovery Time Determination Test (2.07).

NOTE: Instructions for material transfer should be developed by individual user/ facility, based on their SOPs taking into account purge and recovery times listed by the isolator manufacturer.

- a. Purge time for the pass through
- b. Purge time after materials are entered into the isolator

An isolator field certified to the statement "in accordance to CETA CAG-002-2006" shall have the following information posted on the front of the cabinet in a location readily visible to the user:

1. Information to be completed by testing technician:
 - A. Date tested
 - B. Reference report number
 - C. Due for retest date (month and year)
 - D. Tested by:
 - 1) Name printed
 - 2) Signature

- **Critical Area**
An ISO Class 5 environment.
- **Critical Site:**
A location that includes any component or fluid pathway surfaces (e.g. vial septa, injection ports, beakers) or openings (e.g. opened ampule, needle hubs) exposed and at risk of direct contact with air (e.g. ambient room or HEPA filtered), moisture (e.g. oral and mucosal secretions), or touch contamination. Risk of microbial particulate contamination of the critical site increases with the size of the openings and exposure time.
- **Critical Work Zone:**
The defined specific localized area starting 6" (15.2 cm) below the IV bar including horizontal and vertical space within the work area where aseptic manipulations are performed.
- **Design Acceptance Test:**
A manufacturer test performed to verify that the design meets intended criteria. Must be successfully completed on at least 2 units of each model and size upon introduction and modification of that design.
- **Direct Compounding Area (DCA)**
A critical area within the ISO Class 5 primary engineering control (PEC) where critical sites are exposed to unidirectional HEPA-filtered air, also known as first air.
- **HEPA (high-efficiency particulate air) Filter**³
An extended-medium, dry-type filter in a rigid frame when tested at rated airflow having a minimum particle collection efficiency of 99.97% for 0.3- μ m mass median diameter particles of DOP when tested in accordance with MIL-STD-282⁴.
- **Main Chamber:**
The primary chamber containing the work area, critical work zone, and means for manipulation of the preparation. This includes plenums and areas covered with diffusers.
- **Pass-through Chamber:**
The chamber designed to separate the surrounding ambient space from the main chamber while facilitating the movement of materials between the two areas.
- **Particle Elevation:**
Airborne room particles elevation to enable certain tests. This elevation may be accomplished through the use of aerosol generator, theatrical smoke generator, or other smoke sources that provide suitable particle size and quantity
- **Primary Engineering Control (PEC)**
A device or room that provides an ISO Class 5 environment for the exposure of critical sites when compounding CSPs. Such devices include, but may not be limited to, laminar airflow workbenches (LAFWs), biological safety cabinets (BSCs), compounding aseptic isolators (CAIs) and compounding aseptic containment isolators (CACIs).
- **Surrogate Manipulation:**
A manipulation of a preparation that involves the use of substituted materials that closely resemble actual materials used in sterile compounding to provide a similar impact upon the environment tested and to resemble actual operational conditions during testing
- **Unidirectional Airflow:**
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.

- **Volatile**
A gas, vapor, or micro-aerosol potentially generated during the pharmacy compounding process that can pass through a High Efficiency Particulate Air (HEPA) filter.
- **Work Area**
The horizontal and vertical space within the isolator from wall to wall and from the base or floor to the top within the main chamber. This excludes plenums and areas covered with diffusers.

1.04 Safety Concerns

Testing in accordance with this document may involve hazardous materials, equipment and operations. It is the responsibility of the user to consult and establish appropriate safety and health practices and to determine the applicability of regulatory limitations prior to use of this document.

2.00 Compounding Isolator Tests:

The following tests are offered to establish that the Compounding Isolator design is appropriate for the task, that test methods are repeatable and accurately reproducible in the field, to provide detailed guidance for the field certifier through a specific field test documentation and / or through a designated section of the product owner's manual, and to set appropriate acceptance values.

The manufacturer shall be responsible for identifying special accommodations, or ancillary equipment that may be needed for accurately field testing the Compounding Isolator design. These may include, but are not limited to the methods, sources, or devices to provide accurate and repeatable testing such as:

- correcting for impact of operating pressures where applicable
- provision of ports to support the use of diagnostic equipment
- supplementary equipment, materials, products to facilitate tests
- providing and updating performance information as necessary
- For turbulent flow isolators, provide chamber volume needed to calculate air changes.

INFORMATIONAL NOTE:

Metric equivalents (SI) are provided in parentheses () behind English measurement values throughout this document as an aid or cross-reference.

2.01 Airflow Test:

Purpose:

This test verifies the appropriate airflow parameters are met for the manufacturer's design intent.

Apparatus:

- A calibrated thermal anemometer with an accuracy of ± 3.0 fpm (0.015 m/s) or $\pm 3\%$ of the indicated velocity, whichever is greater.

Procedure:

Main Chamber:

Measure the air velocity in the Compounding Isolator using equally spaced points in the horizontal plane that produces the most repeatable readings.

INFORMATIONAL NOTE:

As an example, the horizontal plane would be set at X inches (cm) below the filter diffuser using a X inch (cm) grid.

An example of uniformity ranges may be a) +/- Y % of the average or +/- X fpm (m/s), whichever is greater, or b) +/- Y % of the average velocity.

Procedure – All Compounding Isolators:

Pass-through Chamber

In a purged pass-through chamber, the manufacturer shall develop a repeatable method of determining airflow volume or velocity to achieve the stated purge objective.

1. For unidirectional purged pass-through, measure the air velocity at multiple points across the pass-through using equal points in a plane that produces the most repeatable readings or determine an alternate repeatable method to determine that the specified purge objective is met.
2. For non-unidirectional purged pass-through, the manufacturer will determine the optimum location and method that produces the most repeatable readings or determine an alternate repeatable method to determine that the specified purge objective is met

INFORMATIONAL NOTE A: *Airflow velocity and / or volume and chamber pressurization will interact with each other. Both tests should be verified before recording final airflow and pressure values.*

INFORMATIONAL NOTE B: *Ideally the manufacturer's recommended pass-through purge time should relate to and specify an acceptable level of airborne particulate at conclusion of the purge time. For example, a purge time of X seconds or minutes should result in airborne particle levels consistent with ISO Class Y at 0.1 μm and larger size particulate classification ⁵ within the pass-through chamber.*

Acceptance Criteria:

- The manufacturer will determine the appropriate acceptance criteria for the particular design. **Unidirectional Airflow Compounding Isolator** velocity criteria shall be expressed in terms of a range of velocities in feet per minute (fpm) (meters per second (m/s)) along with a velocity uniformity designator. For example, a statement would be presented as *the average velocity shall fall between ___fpm (m/s) and ___fpm (m/s) and ___% uniformity from the average*

INFORMATIONAL NOTE: *Airflow velocity and / or volume and chamber pressurization will interact with each other. Both tests should be verified before recording final airflow and pressure values.*

2.02 Chamber Pressure Test:

Purpose:

This test is performed to determine that pass-through and main chamber pressures are adequate to aid in providing Compounding Isolator separation between the main chamber and ambient spaces.

Apparatus:

- A calibrated mechanical or electronic differential pressure indicating device.

INFORMATIONAL NOTE: Differential pressure indicating devices should have a fast reaction or update capability (time constant) of less than 1 second in order to detect momentary or large changes in differential pressure.

Procedure:

1. Utilize the factory installed test port or sealed access location to main and pass-through chambers.
2. Attach test instrument tubing into chamber and allow pressure levels to stabilize.

Test 1:

- Record pressure level of main chamber with outer and inner pass-through doors closed and isolator gloves / gauntlets extended into Compounding Isolator.
- Fully open outer pass-through door. Document any change to the pressure.
- Confirm that the pressure does not change from positive to negative or from negative to positive.
- Close outer pass-through door. Document any change to the pressure.

Test 2:

- Record pressure level of main chamber with outer and inner pass-through doors closed and isolator gloves / gauntlets extended into isolator.
- Using Compounding Isolator glove, fully open inner door. Document the change to the pressure.
- Confirm that the main chamber pressure does not change from positive to negative or from negative to positive.
- Close inner door. Determine if pressure level returns to original levels.

Test 3a:

- Record pressure level of Compounding Aseptic Isolator main chamber with outer and inner pass-through doors closed and isolator gloves / gauntlets extended into isolator.
- Insert hands into gloves and pull back from isolator to simulate operator hand removal. An example of a reasonable pull back time is no greater than 3 seconds from fully extended to fully extracted (gloves at a point even with the view panel)
- Determine the change in pressure and verify that the pressure does not change from positive to negative.

Test 3b:

- Record pressure level of Compounding Aseptic Containment Isolator main chamber with outer and inner pass-through doors closed and isolator gloves / gauntlets extended outside isolator.
- Insert hands into gloves and push into main chamber to simulate operator hand insertion.
- Determine the change in pressure and verify that the pressure does not change from negative to positive.

Acceptance:

- Compounding Isolator operating pressure range shall be determined by the manufacturer.
- The pressure shall not change from positive to negative or from negative to positive during any manipulations.

2.03 Site Installation Assessment Tests:

Purpose:

These tests are performed to verify:

- The airflow or pressure setpoint(s) where an audible and/or visual alarm will activate to signify unfavorable operating conditions within the compounding isolator and/or the remote exhaust blower.
- Functional pass-through door interlock operation.
- Proper canopy or exhaust connection performance.

Apparatus:

- A calibrated thermal anemometer with an accuracy of ± 3.0 fpm (0.015 m/s) or $\pm 3\%$ of the indicated velocity, whichever is greater.
- A calibrated mechanical or electronic differential pressure indicating device.
- Alarm adjustment/alignment tool.
- A source of visible smoke - such as a chemical smoke tube.

Procedure:**Test 1: Airflow or Pressure Alarm Test:**

- Verify the alarm setpoint(s) using the compounding isolator or alarm manufacturer's performance verification procedures.
- Adjust as necessary.
- Return isolator to certification setpoint.

Test 2: Door Interlock Verification Test:

- Verify the inner and outer door interlock system operates as per manufacturer's design criteria.

Test 3a: Exhaust System Performance – Canopy Connections:

- Using a visible smoke source, verify negative pressure at the gap.
- Measure the duct static pressure between the air gap and any duct-mounted balancing dampers.

Test 3b: Exhaust System Performance – Hard ducted connections:

- Measure the duct static pressure between the isolator discharge point and any duct-mounted balancing dampers.

Acceptance:**Airflow or Pressure Alarm Test**

- The setpoint(s) shall be determined by the manufacturer as appropriate for operator safety, product sterility and/or containment.

Door Interlock Verification Test

- Determined by the manufacturer.

Exhaust System Performance

- No smoke shall escape into the room once it enters the exhaust system

2.04 Gauntlet Breach Air Velocity Test:**Purpose:**

This test is performed on containment Compounding Isolators to assure some level of operator protection in the event of a significant glove or gauntlet integrity failure.

Apparatus:

- A calibrated thermal anemometer with an accuracy of ± 3.0 fpm (0.015 m/s) or 3% of the indicated velocity, whichever is greater.

Procedure:

1. Determine that all other operating parameters have been met.
2. Remove one gauntlet from chamber view screen.
3. Measure velocity at the geometric center of the opening. A minimum of 3 samples at a minimum of 1 location shall be taken.
4. Record results.

Acceptance:

- The velocity shall be determined by the manufacturer as appropriate for operator safety.

INFORMATIONAL NOTE: *Published sources show various ranges of airflow velocities that pertain to gloveboxes and other containment devices.*

These sources include:

- NSF/ANSI Standard 49 (75 to 100 lfpm) (0.38 to 0.51 lm/s)⁶
- ANSI/AIHA Z9.5-2003 (≥ 100 lfpm) (0.51 lm/s)⁷

2.05 HEPA Filter Integrity Test:**Purpose:**

This test determines the integrity of the all HEPA filters, filter housings, and filter mounting frames. The cabinet shall be operated at operational airflow for this test.

Apparatus:

- A calibrated Aerosol Photometer capable of indicating 100% upstream concentration with an aerosol of between 10 and 90 μg per liter of polydispersed dioctylphthalate (DOP or DEHS) CAS# 117-81-7, polyalphaolefin (PAO) CAS# 68649-12-7 or an equivalent fluid. Unit must have a threshold sensitivity of at least 10^{-3} micrograms per liter and be capable of measuring concentrations over a range of 10^5 times the threshold sensitivity. The sampling rate shall be 1 CFM (28.3 lpm) ($\pm 10\%$) with an inlet probe having sufficient area (1.7 square inches) (11.0 cm^2) as to maintain a probe inlet velocity of 90 fpm (0.46 m/s) or slightly higher.
- Laskin Nozzle aerosol generator or equivalent.

Procedure:**Main and Pass-through Chamber HEPA filters:**

1. Turn on the Compounding Isolator blowers and lights.
2. Remove the HEPA filter diffuser screen(s) if present and where possible.
3. Introduce the aerosol in a manner that will create a well mixed aerosol upstream of the filter.
4. If a specific introduction location is needed to achieve a well mixed aerosol, that location should be documented by the device manufacturer.
5. Sample or calculate the upstream challenge and verify that a 10-90 μg per liter has been introduced.
6. Adjust the photometer to 100% based on the challenge levels used.
7. With the nozzle of the probe held not more than 1.0 inch (2.5 cm) from the area being tested, scan the entire downstream side of the HEPA filter(s), the perimeter of each filter pack and mounting frame by passing the photometer probe in slightly overlapping strokes at a traverse rate of not more than 2 inches (5.1 cm) per second when using a rectangular probe.
8. For filters that cannot be scanned, the manufacturer shall develop a test procedure that allows for probe testing at a location where adequate mixing and safety to the certifier can be achieved.

INFORMATIONAL NOTE: *The manufacturer shall verify both temporal and spatial uniformity of challenge as outlined in IEST-RP-CC034⁸.*

Acceptance Criteria:

For filters that can be scanned:

- Sustained aerosol penetration shall not exceed 0.01% of the upstream concentration.

For filters that cannot be scanned:

- Sustained aerosol penetration shall not exceed 0.005% of the upstream concentration.

Filter patch size shall not exceed 3% of the effective filter area of the side being patched. The maximum width of any one patch shall not exceed 1.5 inches (3.8 cm).

2.06 Particle Containment Integrity and Enclosure Leak Test:

Purpose:

This test is performed on Compounding Aseptic Containment Isolators only. This test can aid in determining the particle integrity of the cabinet construction joints, seams, access panels and seals, glove ports and entry/exit points into the main chamber or where elevated particle levels have been detected at or near the work surface and where other potential leak sources have been eliminated (e.g. damaged HEPA filters, damaged glove/gauntlet, etc.).

NOTE: A suitable alternative test method to 2.06 is the AGS-G001–2007 Guideline for Gloveboxes⁹ section # 9.6.2 Leak Detection. Acceptance criteria is less than or equal to 0.5% of the device volume per hour.

Apparatus:

- A calibrated discrete particle counter with a particle size discrimination capability of 0.5 µm.

Procedure –Compounding Aseptic Containment Isolators:

1. The isolator shall be operated at operational airflow.
2. Verify the background count in the testing room is at least 3,520,000 particles per cubic meter (ppcm) or 100,000 particles per cubic foot (ppcf). If the count is too low, elevate the background levels using an aerosol generator or smoke generator.
3. Scan interior of main chamber within 1 inch (2.5 cm) of surfaces using a scan rate of no more than 2 inches (5.1 cm) per second.
4. Areas of interest include:
 - a) all welded or gasketed seams
 - b) side glass gasket/seams
 - c) pass-through chamber door seals
 - d) glove ports perimeters and gloves
 - e) front view screen gasket seals
 - f) trash or sharps exit ports/chutes
 - g) lights installed inside the main chamber
 - h) any penetrations into the main chamber

Acceptance:

- Any detected leaks do not exceed ISO class 5 conditions of 3,520 particles per cubic meter (ppcm) at 0.5µm size particles and larger when the probe is held stationary within 1” (2.5 cm) of the leak.

INFORMATIONAL NOTE:

Elevating operating pressures during this test may aid in locating leak sources.

This test is most effective when performed in uncontrolled environments (>3,520,000ppcm or >100,000ppcf).

2.07 Recovery Time Determination Test:

Purpose:

This test is performed to determine the amount of time it takes the main chamber to recover to ISO Class 5 particle levels after an event such as an open door or a surge of process generated contamination.

Apparatus:

- Laskin Nozzle aerosol generator or equivalent.
- A calibrated discrete particle counter with a particle size discrimination capability of 0.5 µm and variable sample times.
- Time keeping device capable of reading in minutes and seconds.
- Particle sample probe cover.

Procedure:

1. Set the particle counter sample time to 6 second sample periods with a 14 second hold time in “Concentration” mode to report in particles per cubic meter or foot.
2. With the Compounding Isolator running, measure particle levels at the center of the work-surface of the main chamber.
3. Collect multiple samples to determine average baseline particle levels using 6 second samples.
4. Three consecutive baseline particle level samples should be established and noted.
5. Turn off particle counter sample pump and cover the particle counter sampling probe.
6. Turn off Compounding Isolator and fill the chamber with particulate using a Laskin nozzle generator set at 1 Laskin nozzle at 20 psi (138 kPa) for five seconds per cubic foot (per 0.028 cubic meter) of chamber interior space.
7. Turn on the Compounding Isolator and start timer.
8. To prevent sampling above the particle counter’s coincidence loss rate or damaging the device, wait until the smoke is visibly cleared from the chamber and remove particle counter probe cover and begin sampling.
9. Maintained particle levels are achieved when three consecutive counts are at or below the originally determined baseline particle level.
10. Total recovery time is considered from Compounding Isolator blower turn-on time to the first particle count where maintained particle levels were achieved.

Acceptance criteria:

- The manufacturer will determine the appropriate acceptance criteria for their particular design. Recovery time will be expressed in minutes and seconds to recover to baseline from excursion.

2.08 Airflow Smoke Pattern Test:**Purpose:**

This test determines that the airflow within the compounding chamber conforms to the manufacturer’s design criteria.

- Airflow within the Direct Compounding Area is downward with no dead spots or refluxing in the Critical Site, that ambient air does not enter the chamber other than through the supply HEPA filter, and that once the air enters the Direct Compounding Area, it is removed to the returns without reentry.

Apparatus:

- A source of visible smoke that is generally neutrally buoyant

INFORMATIONAL NOTE: *Chemical smoke tubes or glycol-based smoke generators are examples of acceptable smoke sources.*

Procedure:

1. Pass the smoke along the work area beginning 1 inch (2.5 cm) from all main chamber walls and view screens at a height determined to authenticate the purpose of test.
2. Pass smoke over gloves, gauntlets, IV bars, interior lights, or other extruding features that may be installed within the main chamber.

3. For Compounding Aseptic Containment Isolators, pay particular attention to all penetrations, pass-through door, trash disposal tubes and gloves where turbulence may occur or may indicate significant penetration of the Compounding Isolator.

Acceptance criteria:

- The smoke shall show smooth downflow with a minimum of dead spots or reflux (upward flow) at obstructions and across the critical work zone and it is removed to the returns without reentry.

2.09 Preparation Ingress and Egress Test:

Purpose:

This test is performed to determine if the Compounding Isolator pass-through system is capable of supporting material transfer while maintaining the designated cleanliness classification during the transfer.

Apparatus:

- A calibrated discrete particle counter with a particle size discrimination capability of 0.5 μm .
- Aerosol generator or smoke tubes.
- Empty perforated transfer tray.
- Time keeping device capable of reading in seconds.

Procedure:

1. Verify the background count in the testing room is at least 3,532,000 particles per cubic meter (ppcm) (100,000 particles per cubic foot (ppcf)).
2. If the count is too low, elevate the background levels using an aerosol generator or smoke generator.
3. Place the particle counter probe in the Main Chamber approximately 6 to 8 inches (15.2 to 20.3 cm) off the isolator floor surface, approximately 2 inches (5.1 cm) outside the normally used path of the inner pass-through chamber door swing and within the area that would be affected by the airflow caused by the movement of the door. Probe placement should be so that the operator's arms will not pass directly over the probe when removing material from the pass-through.
4. Verify the particle counts meet ISO Class 5 levels before beginning the test cycle.
5. Set the particle counter for a one minute count with no more than a one second hold time.
6. Open the outside pass-through door.
7. Place a perforated empty transfer tray into the pass-through and close the outer door.
8. Wait for the manufacturer's recommended purge time or start the purge cycle.
9. After completion of the purge cycle, open the inside pass-through door and move the transfer tray from the pass-through to the work area.
10. Close the inside pass-through door.
11. Document the particle counts during the transfer process and for a period of one minute after the transfer.

Acceptance Criteria:

- The particle counts shall not exceed the ISO Class 5 @ 0.5 μm and larger class limit at any time during this test.

2.10 Particle Count Tests:

Purpose:

This is a two part test and is performed to verify that the Compounding Isolator main chamber operates within ISO class 5 conditions at 0.5 μm and larger during Static (At-Rest) and Dynamic Operating (Operational) conditions to determine that air within the isolator and the immediate proximity of exposed sterilized preparation operations would be of appropriate particle quality during compounding operations. Air shall be sampled in a manner that characterizes the true level of extrinsic particle contamination to which the product is exposed. Classified pass-through chambers shall be tested in the Static (At Rest) state.

Apparatus:

- A calibrated discrete particle counter with a particle size discrimination capability of 0.5 μm .
- Clean surrogate materials and transfer tray

2.10A Procedure- Static Particle Level:

1. Sample ports compatible with particle counting equipment should be used to facilitate accurate and repeatable testing.
2. Determine particle locations per ISO 14644-1:1999. Note that a reasonable sample plan is one that addresses the entire work surface and may result in more than minimum sample locations allowed by ISO 14644-1:1999. An example of a reasonable plan for the Main Chamber is one where the locations are in each of the four corners (6" (15.2 cm) from interior walls) and one at the geometric center of the work-area. A reasonable sample plan for the Pass-through would be one location at the geometric center with a minimum of 3 samples.
3. Determine that particle sampling tube has been appropriately purged of particles.
4. Perform the particle counter background noise count rate (zero count) test prior to sampling.
5. The Compounding Isolator should be empty, clean, and safe for access when tested.
6. Position the particle counter isokinetic probe at the 1st location to sample the air as it reaches the clean zone, the probe height being typically no more than 12" (30.5 cm) above the work surface.
7. Operate the Compounding Isolator for a period of time appropriate for the design to clean up the work area.
8. Sample the assigned locations within the space.
9. Note the particle levels at the specified locations.

2.10B Procedure- Dynamic Operating Test (Monitoring):

1. Sample ports compatible with particle counting equipment should be used to facilitate accurate and repeatable testing.
2. Determine that particle sampling tube has been appropriately purged of particles.
3. Perform the particle counter background noise count rate (zero count) test prior to sampling.
4. Compounding Isolator should contain all of the cleaned surrogate compounding components that would support surrogate manipulation operation during the test.
5. Particle counter isokinetic probe location(s) should be placed near the direct compounding area where there is most potential risk to the exposed sterile preparation, containers, and closures. The particle counting probe should be placed in an orientation demonstrated to obtain a meaningful sample.
 - a. Position the particle counter isokinetic probe within the airflow not more than 12 inches (30.5 cm) away from the location of the Critical Site within the Direct Compounding Area.
6. Purge the compounding isolator as specified in the operating procedures prior to conducting the particle count survey. If not specified in the operating procedures, allow the isolator to purge for 5 minutes.
7. To simulate actual preparation, perform surrogate manipulation using both gloves during particle testing to determine whether activity affects particle levels at the sample point.
8. Document the particle levels.

Acceptance Criteria:

- ISO 14644-1:1999 Class 5 at 0.5 µm and larger At Rest and Operational.

INFORMATIONAL NOTE:

- *Generally, conditions are met when none of the individual counts exceed the class limit or equivalent of 3,520 particles per cubic meter (ppcm) at 0.5µm size particles and larger.*
- *Where between 2 and 9 locations are sampled, a statistical analysis of the upper 95% confidence level (UCL) must confirm that sample levels fall within the acceptance criteria per ISO 14644-1:1999*

INFORMATIONAL NOTE:

When selecting a Discrete Particle Counter (DPC), the instrument should have the ability of displaying and recording the count and size of discrete particles in air with a size discrimination capability to detect the total particle concentration in the appropriate particle size ranges for the class under consideration. ⁵

2.11A Volatile Hazardous Drug Containment Test -Total Exhaust Compounding Isolator:**Purpose:**

This test ¹⁰ is to verify that Compounding Aseptic Containment Isolator properly connected to building exhaust provides worker protection from the escape of volatilized hazardous drugs during all aspects of compounding operations.

Apparatus:

- A calibrated Infrared Portable Ambient Air Analyzer, Electron Capture Device, or equivalent. Instrument shall be a continuous reading instrument for the tracer gas of choice. Range of detection shall be at least from 0.01 ppm (parts per million) to 100 ppm. The accuracy of the instrument shall be $\pm 10\%$ of the reading for concentrations above 0.1 ppm and $\pm 25\%$ for concentrations between 0.01 ppm and 0.1 ppm. The repeatability of the instrument shall be $\pm 1\%$ of the reading at 50 ppm tracer gas concentration. The response time shall not exceed 10 seconds for 90% indication of actual concentration. The instrument shall not exhaust more than 50 lpm (liters per minute). The detectors shall be calibrated with a known concentration of tracer gas within 24 hours preceding a test. The method for calibration shall be those furnished or specified by the detector manufacturer and shall use the tracer gas that was selected as a standard. The analyzer shall have a strip chart recorder or data logger.
- Tracer Gas – Sulfur Hexafluoride (SF₆), (or a gas of similar molecular weight and stability, supplied from a cylinder capable of maintaining 30 psig (207 kPa) at the test release rate for at least one hour). The tracer gas release rate shall be 4.0 lpm. The tracer gas shall be commercial grade or reagent grade. Since the detection instrument is calibrated by the actual tracer gas, a 100% pure gas is not required. Low-grade mixtures are inappropriate since they significantly reduce the limit of detection for the test.
- Tracer Gas Ejector System - The tracer gas is piped to the ejector. The trace gas passes through a critical orifice, entrains air through the holes in the side of the ejector tube, and is distributed through a wire mesh outlet diffuser.
- Critical Orifice - the flow rate of the tracer gas is determined by the upstream pressure and size of the orifice. The size for the orifice using sulfur hexafluoride as tracer gas, at a flow rate of 4.0 lpm and a nominal upstream pressure of 30 psig (207 kPa) is 0.025 inches (0.635 mm). The orifice size and pressure will give the approximate flow rate of tracer gas; however, the actual flow rate must be measured. Convert the measured value to standard conditions: 70°F (21.1°C) at one atmosphere. The ejector system release rate shall be calibrated within 24 hours preceding a test and each time the orifice plate is changed.
- Flow meter - capability of reading 4 lpm, accuracy of $\pm 3\%$ of full scale or better calibrated per manufacturer's specifications.
- Pressure Gauge - capability of reading 30 psig (207 kPa), accuracy of $\pm 2\%$ of full scale calibrated per manufacturer's specifications.
- Surrogate materials and transfer tray.

INFORMATIONAL NOTE: For compounding of volatile drugs, Compounding Aseptic Containment Isolators which use negative pressure plenums and ducts are preferred. For those compounding isolators with positive pressure plenums or ducts, the seam leak test of step #6 should also be performed along all duct connections and plenum seams.

Procedure:

1. Place surrogate materials into main chamber via pass-through chamber.
2. Record room background levels of SF₆ (or tracer gas).
3. Activate SF₆ gas flow and verify 4 LPM flow rate through ejector within isolator.
4. Perform surrogate manipulations.
5. Upon conclusion of surrogate manipulation, stop SF₆ gas flow and place surrogate materials in pass-through chamber.
6. Seal inner door and follow established purge time.
7. Upon completion of established purge time, open exterior pass-through door and retrieve surrogate preparation.
8. Tester takes SF₆ samples at the least favorable position within 1” (2.5 cm) of exterior pass-through chamber door based on Isolator design (i.e. measure just below door on static pass-through or measure just above door on integral vertical flow pass-through).
9. Remove materials from pass-through chamber.
10. Document results.

Acceptance Criteria:

- Tracer gas concentration level shall not exceed 0.01 ppm at any time during these tests.

2.11B Volatile Hazardous Drug Containment Test-Partial-Recirculating Compounding Isolator:

Purpose:

This test¹⁰ is to verify that the partial-recirculating Compounding Aseptic Containment Isolator that is properly connected to building exhaust system provides personnel protection from the escape of volatilized hazardous drugs during all aspects of compounding operations. Due to its design, any volatiles released in the workzone will partially recirculate and partially exhaust from the building.

Apparatus:

- A calibrated Infrared Portable Ambient Air Analyzer, Electron Capture Device, or equivalent. Instrument shall be a continuous reading instrument for the tracer gas of choice. Range of detection shall be at least from 0.01 ppm (parts per million) to 100 ppm. The accuracy of the instrument shall be ± 10% of the reading for concentrations above 0.1 ppm and ± 25% for concentrations between 0.01 ppm and 0.1 ppm. The repeatability of the instrument shall be ± 1% of the reading at 50 ppm tracer gas concentration. The response time shall not exceed 10 seconds for 90% indication of actual concentration. The instrument shall not exhaust more than 50 lpm (liters per minute). The detectors shall be calibrated with a known concentration of tracer gas within 24 hours preceding a test. The method for calibration shall be those furnished or specified by the detector manufacturer and shall use the tracer gas that was selected as a standard. The analyzer shall have a strip chart recorder or data logger.
- Tracer Gas – Sulfur Hexafluoride (SF₆), (or a gas of similar molecular weight and stability, supplied from a cylinder capable of maintaining 30 psig (207 kPa) at the test release rate for at least one hour). The tracer gas release rate shall be 4.0 lpm. The tracer gas shall be commercial grade or reagent grade. Since the detection instrument is calibrated by the actual tracer gas, a 100% pure gas is not required. Low-grade mixtures are inappropriate since they significantly reduce the limit of detection for the test.

- Tracer Gas Ejector System - The tracer gas is piped to the ejector. The trace gas passes through a critical orifice, entrains air through the holes in the side of the ejector tube, and is distributed through a wire mesh outlet diffuser.
- Critical Orifice - the flow rate of the tracer gas is determined by the upstream pressure and size of the orifice. The size for the orifice using sulfur hexafluoride as tracer gas, at a flow rate of 4.0 lpm and a nominal upstream pressure of 30 psig (207 kPa) is 0.025 inches (0.635 mm). The orifice size and pressure will give the approximate flow rate of tracer gas; however, the actual flow rate must be measured. Convert the measured value to standard conditions: 70°F (21.1°C) at one atmosphere. The ejector system release rate shall be calibrated within 24 hours preceding a test and each time the orifice plate is changed.
- Flow meter - capability of reading 4 lpm, accuracy of $\pm 3\%$ of full scale or better calibrated per manufacturer's specifications.
- Pressure Gauge - capability of reading 30 psig (207 kPa), accuracy of $\pm 2\%$ of full scale calibrated per manufacturer's specifications.
- 60 mL syringe filled with tracer gas Sulfur Hexafluoride (SF₆) (or a gas of similar molecular weight and stability) and placed within a sealed plastic bag.

Procedures:

1. Place sealed plastic bag containing SF₆ gas-filled 60 mL syringe in main chamber.
2. Record room background levels of SF₆.
3. Perform surrogate manipulation by opening bag and releasing 60 mL of tracer gas into workzone. Start timer upon release of tracer gas. Place syringe back into bag and seal. Place sealed bag into pass-through chamber, then open outer pass-through door and remove bag.
4. Operator places analyzer detector in least favorable position within 1" (2.5 cm) of exterior pass-through chamber door based on Isolator design. (i.e. measure just below door on static pass-through or measure just above door on integral vertical flow pass-through).

NOTE: Either a main chamber or pass-through chamber purge or delay time may be required to meet acceptance criteria. Repeat Phase 2 with adequate purge or delay time until acceptance criteria is met.

Acceptance Criteria:

- SF₆ concentration level shall not exceed 0.01 ppm at any time during these tests.

INFORMATIONAL NOTE:

With the test results, a risk analysis can be performed for the hazardous drug preparation process equating amount of volatiles generated by the hazardous drug compounding process to purge time required for the safe removal of compounded materials.

To assure personnel protection, the test uses a known quantity of volatile tracer gas (SF₆), released into the main chamber airstream, while monitoring the material transfer process for tracer gas just outside the external interchange door. The test is designed to determine the volatile purge time based on the known release volume.

The NIOSH Alert: Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings (2004)¹¹ recommends against the use of recirculating cabinets for the manipulation of volatile hazardous drugs. This test procedure should not be misconstrued as an endorsement of recirculating isolators with volatile drugs.

2.12 Hazardous Particle Containment Test:

Purpose: This test is to verify that Compounding Aseptic Containment Isolator provides worker protection from the escape of hazardous drug particles during all aspects of compounding operations.

NOTE: This test is not required if Section 2.11A or 11B is successfully completed.

Apparatus:

- A calibrated discrete particle counter with a particle size discrimination capability of 0.5 μm .
- A calibrated aerosol photometer capable of indicating 100% upstream concentration with an aerosol of between 10 and 90 μg per liter of polydispersed dioctylphthalate (DOP), polyalphaolefin (PAO) or an equivalent fluid. Unit must have a threshold sensitivity of at least 10^{-3} micrograms per liter and be capable of measuring concentrations over a range of 10^5 times the threshold sensitivity. The sampling rate shall be 1 CFM (28.3 lpm) ($\pm 10\%$) with an inlet probe having sufficient area (1.7 square inches) (11.0 cm^2) as to maintain a probe inlet velocity of 90 fpm (0.46 m/s) or slightly higher.
- Laskin Nozzle aerosol generator or equivalent.
- Aerosol diffuser (shown in Figure 1 below)
- Particle diluter.
- Time keeping device capable of reading in minutes and seconds.
- Cleaned preparation transfer tray and safe surrogate compounding manipulation materials.



Figure 1

INFORMATIONAL NOTE:

The aerosol diffuser is used to reduce turbulence caused by the aerosol generator within the isolator chamber.

The diffuser should be centered between the glove ports and centered between the back wall and the view screen.

Procedure:

Operational test – material transfer test:

1. This test should be performed in a controlled atmosphere such as a cleanroom. The interior of isolator main and pass-through chambers should be clean.
2. Place the aerosol diffuser in the isolator main chamber and connect to the aerosol generator.
3. Operate the isolator normally.
4. Place cleaned preparations transfer tray and safe surrogate materials via the pass-through into the main chamber.
5. Activate aerosol supply.
6. Perform surrogate manipulations.

7. Upon conclusion of surrogate manipulations, stop aerosol generator.
8. Place surrogate materials and tray into pass-through chamber and follow established purge time using time keeping device to verify.
9. With the particle counter (with installed particle diluter), and photometer test probes, 2.5" (6.4 cm) directly under the center of the door swing of the exterior pass-through door, monitor particle levels, remove materials and transfer tray from pass-through chamber via exterior door.
10. Record the particle counts at 0.5 μm and larger (calculate actual particle levels based upon diluter rating) and photometer readings as the materials are removed from the pass-through chamber and for a period of 30 seconds after the door is closed. Verify that arm movement in opening the door does not create a particle stream.

INFORMATIONAL NOTE: To avoid the impact of arm movement creating a particle stream when opening the door, a non-shedding remote handle or door handle actuator should be considered.

Acceptance Criteria:

- No elevation in particle level during completion of transfer process.

2.13 Pass-through Particle Purge Time Determination Test:

Purpose:

This test is to determine the appropriate purge cycle time to be used after placing materials in the pass-through prior to transferring them into or out of the main chamber.

Apparatus:

- A calibrated discrete particle counter with a particle size discrimination capability of 0.5 μm .
- A source of visible smoke that is generally neutrally buoyant or aerosol particulate detectable by the particle counter. Source is to be determined by the manufacturer.

Procedure for non-unidirectional "Purge" and static pass-through designs:

1. Place the particle counter probe at the geometric center of the pass-through work surface at a height of 6" (15.2 cm).
2. Place a transfer basket on the pass-through work surface.
3. Measure the ambient particle count concentration in the pass-through.

NOTE: If the ambient count at 0.5 μm and larger is not above the equivalent of 3,520,000 ppcm, elevate the counts using smoke or particulate source to achieve at least this level.

4. Initiate purge and particle count cycles simultaneously.
5. Three second particle count samples in concentration mode (normalized to particles per cubic meter) with a one second delay to be taken until counts are at manufacturer's recommended levels for material transfer into the main chamber. This will usually be less than the equivalent of 3,520 ppcm at 0.5 μm and larger particle sizes.
6. Document the time required to get to the manufacturer's recommended levels. This time period will be communicated to the end user in the owner's manual.

Procedure for “constant operation” unidirectional and non-unidirectional pass-through designs:

1. Establish a background room ambient particle concentration at least equivalent to 3,520,000 ppcm at 0.5 μm and larger. Document the background count.
2. Place the particle counter probe at the geometric center of the pass-through work surface at a height of 6” (15.2 cm).
3. Open the outer pass-through door and place a transfer basket on the pass-through work surface.
4. Initiate particle count cycle immediately after closing the outer pass-through door.
5. Three second particle count samples in concentration mode (normalized to particles per cubic meter) with a one second delay to be taken until counts are at manufacturer’s recommended levels for material transfer into the main chamber. This will usually be less than the equivalent of 3,520 ppcm at 0.5 μm and larger particle sizes.
6. Document the time required to get to the manufacturer’s recommended levels. This time period will be communicated to the end user in the owner’s manual.

Acceptance Criteria:

- The maximum acceptable purge time shall be determined by the manufacturer and confirmed using this procedure.

3.0 Reference Material:

¹ USP 32-NF27: United States Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852, www.usp.org.

² CAG-001-2005 (*revised 12/08/2008*): Applications Guide for the use of Compounding Isolators in Compounding Sterile Preparations in Healthcare Facilities, Controlled Environment Testing Association, 1500 Sunday Drive, Suite 102, Raleigh, NC 27607, www.cetainternational.org.

³ IEST-RP-CC001.4: HEPA and ULPA Filters, Institute of Environmental Sciences and Technology, 5005 Newport Drive, Suite 506, Rolling Meadows, IL 60008, USA, www.iest.org

⁴ MIL-STD-282: MIL/QQ (Military Standard) Standardization Document Order Desk, 700 Robbins Ave, Bldg 4, Section D, Philadelphia, PA 19111-5094, <http://dodssp.daps.dla.mil>.

⁵ ISO 14644-1:1999: Cleanrooms and associated controlled environments-Classification of air cleanliness, International Organization for Standardization, Case Postale 56, CH-1211 Geneve 20, Switzerland, www.iest.org.

⁶ NSF/ANSI 49-2008: Class II (laminar flow) Biosafety Cabinetry, NSF International, P.O. Box 130140, Ann Arbor, MI 48113-0140, www.nsf.org.

⁷ ANSI/AIHA Z9.5-2003: American Industrial Hygiene Association, 2700 Prosperity Ave., Suite 250, Fairfax, VA 22031, www.aiha.org

⁸ IEST-RP-CC034.2: HEPA and ULPA Filter Leak Tests, Institute of Environmental Sciences and Technology, 5005 Newport Drive, Suite 506, Rolling Meadows, IL 60008, USA, www.iest.org.

⁹ AGS-G001 – 2007, 2nd Edition: Guideline for Gloveboxes, American Glovebox Society, P.O. Box 9099, Santa Rosa, CA 95405, www.gloveboxsociety.org.

¹⁰ ANSI/ASHRAE 110-1995: Method of Testing Performance of Laboratory Fume Hoods, American Society of Heating, Refrigerating and Air-Conditioning Engineers, Inc. 1791 Tullie Circle, NE, Atlanta, GA 30329, www.ashrae.org.

¹¹ NIOSH Alert for Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings, Department of Health and Human Services, CDC, NIOSH, NIOSH – Publications dissemination, 4676 Columbia Parkway, Cincinnati, OH 45226-1998, www.cdc.gov/niosh.

APPENDIX:

The following is an example of surrogate compounding procedures used during Dynamic Particle Counting procedures (2.10B).

Supplies:

- 2 x 10 mL syringe with needle
 - 1 x 20 mL Sterile Water for Injection (SWFI) vial
 - 1 x 100 mL bag of Dextrose 5% Water (D5W/NS) or 0.9% Sodium Chloride
 - 4 Sterile Alcohol wipes
 - Isopropyl Alcohol (IPA) or equivalent disinfectant
 - 1 blank label (to be affixed to the bag prior to placing into pass-through)
- 1) All supplies introduced into the isolator environment for immediate compounding, are to be picked from the warehouse or inventory area. All products will be removed from their master cartons (non-laminated or corrugated cardboard), or non-plastic over wrap prior to leaving the warehouse or inventory area.
 - 2) After inspection, the products and/or supplies are transferred into the isolator pass-through in plastic bin or tote.
 - 3) The operator will insert hands into glove ports of the isolator, seat hands in gloves; disinfect the gloves with an appropriate disinfectant (IPA).
 - 4) The operator will disinfect the interior surfaces of the primary compounding chamber with an appropriate disinfectant and allow the surfaces to dry after establishing that it is safe to do so where flammable materials are used.
 - 5) The operator will open the interior pass-through door, retrieve the bin/tote, close the pass-through door and place the bin/tote in corner of isolator, gather supplies out of bin/tote, and place immediately in front of the operator.
 - a. Open one syringe by separating the two halves of the packaging, by slowly peeling the paper half, from the plastic outer wrap, laying the syringe onto the work surface (place packaging in the bin/tote).
 - b. Remove the cap of the SWFI vial and disinfect with IPA pad (place pad and packaging in bin/tote after use).
 - c. Pick up the syringe with the free dominant hand.
 - d. Utilizing just the pinkie finger of the non-dominant hand, dislodge the needle cap, and pierce the septum of the vial and withdraw 3 mL of SWFI.
 - e. Remove needle for vial and transfer the SWFI from the syringe into the 100 mL bag of D5W/NS.
 - f. Repeat the transfer from the vial into the bag for a total of 5 injections.
 - 6) Upon completion of transfers, place 100 mL bag onto the work surface.
 - 7) Place the syringe and vial of SWFI in the bin/tote.
 - 8) Peel back label and label 100 mL bag with blank label.
 - 9) Place the labeled bag and label backing into the bin/tote.
 - 10) Pick up the bin/tote and open inner pass-through door and place bin/tote into pass-through.
 - 11) Disinfect the interior surfaces of the isolator with the appropriate disinfecting agent.
 - 12) Place cleaning wipes and waste in the pass-through or trash disposal port.
 - 13) Operator will remove hands from glove ports and retrieve bin/tote from pass-through via the outer pass-through door.