

Compounding Aseptic Isolators (CAI)

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Disclaimer

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Objectives

- After this session, you will be able to:
 - Describe the components of a Compounding Aseptic Isolator (CAIs) including their effect how you operate in the isolator
 - Differentiate the types of CAIs commonly used in sterile compounding including hazardous and non-hazardous applications
 - Explain the facility requirements outlined in USP <797> when using an isolator
 - Apply appropriate certification criteria to CAIs

Background - References

- Controlled Environment Testing Association (CETA)

www.cetainternational.org

1. [CAG-001-2005:“Applications Guide for the use of Compounding Isolators in Compounding Sterile Preparations in Healthcare Facilities”](#)
2. [CAG-002-2006:“Isolator Testing Guide”](#)

- United States Pharmacopeia

www.usp.org

1. [USP 32 /NF27 Chapter <797> Pharmaceutical Compounding-Sterile Preparations](#)

- NIOSH Alert

www.cdc.gov/niosh

1. [Preventing occupational exposure to Antineoplastic and other hazardous drugs in health care settings](#)

Definition

Compounding Aseptic Isolator

A form of isolator *specifically designed for compounding* pharmaceutical ingredients or preparations. It is designed to *maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes*. Air exchange into the isolator from the surrounding environment should not occur unless the air has first passed through a microbial retentive filter (HEPA minimum).



Definition

Compounding Aseptic Containment Isolator

A **CAI** designed to provide *worker protection* and to provide an aseptic environment. Where *volatile drugs* are prepared, the exhaust air from the isolator *should be appropriately removed by properly designed building ventilation.*



CAI Features

- Design parameters:
 - Full enclosure of the drug compounding process.
 - Intentional use of air pressure relationships
 - Positive vs. negative
 - Capture velocities adequate to remove aerosolized drug product near its point of generation.
 - Unidirectional Airflow
 - HEPA filters for sterility and containment.
 - Material transfer processes that allow material transfer without contamination to product or environment
 - External venting for vaporized hazardous drugs

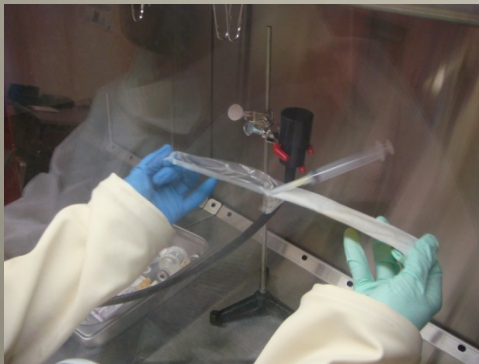


Full Enclosure



“An isolator is a magic box, because we work through a physical barrier, there will be no contamination”

Disproven early thought on isolators

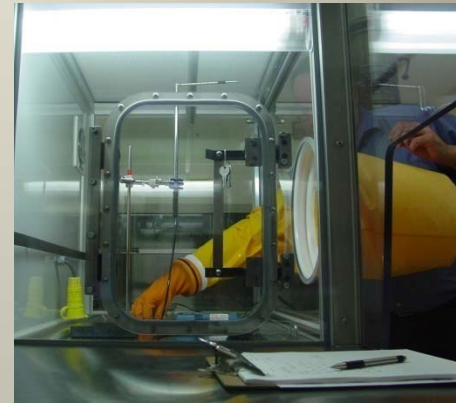


Reality is that the full enclosure **MUST** be accompanied by proper airflow and other factors to yield an effective sterile compounding environment

Pressurization

- **Compounding Aseptic Isolators**
 - Net displacement of air is out of isolator
 - Positive pressure of at least 0.1" water gauge
- **Compounding Aseptic Containment Isolators**
 - Net displacement of air is into the isolator
 - Negative pressure of at least 0.1" water gauge
 - Potential for contamination to product if cabinet leaks
- **Pressure Stability**
 - The pressure should not change state from positive to negative or vice versa during glove manipulation or normal operations.
 - Should be validated by the manufacturer.

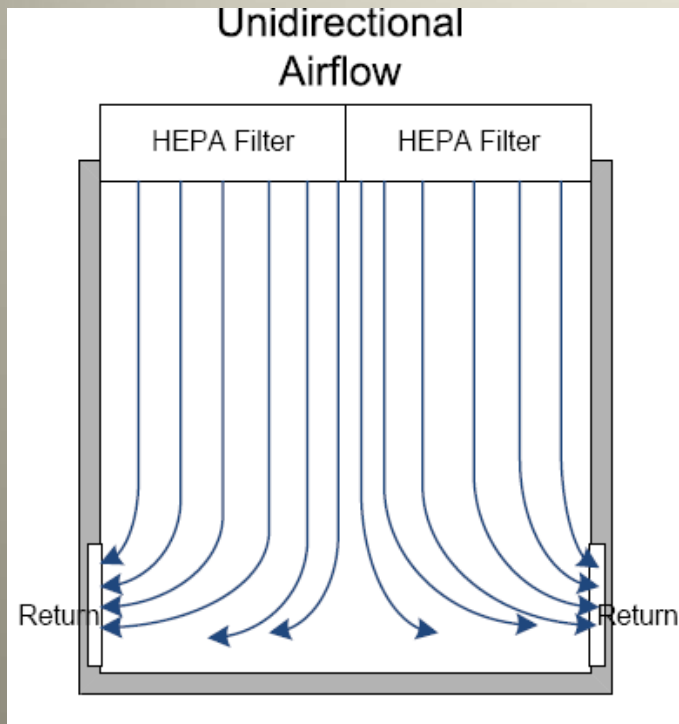
Positive pressure isolator



Negative pressure isolator

Airflow Definitions

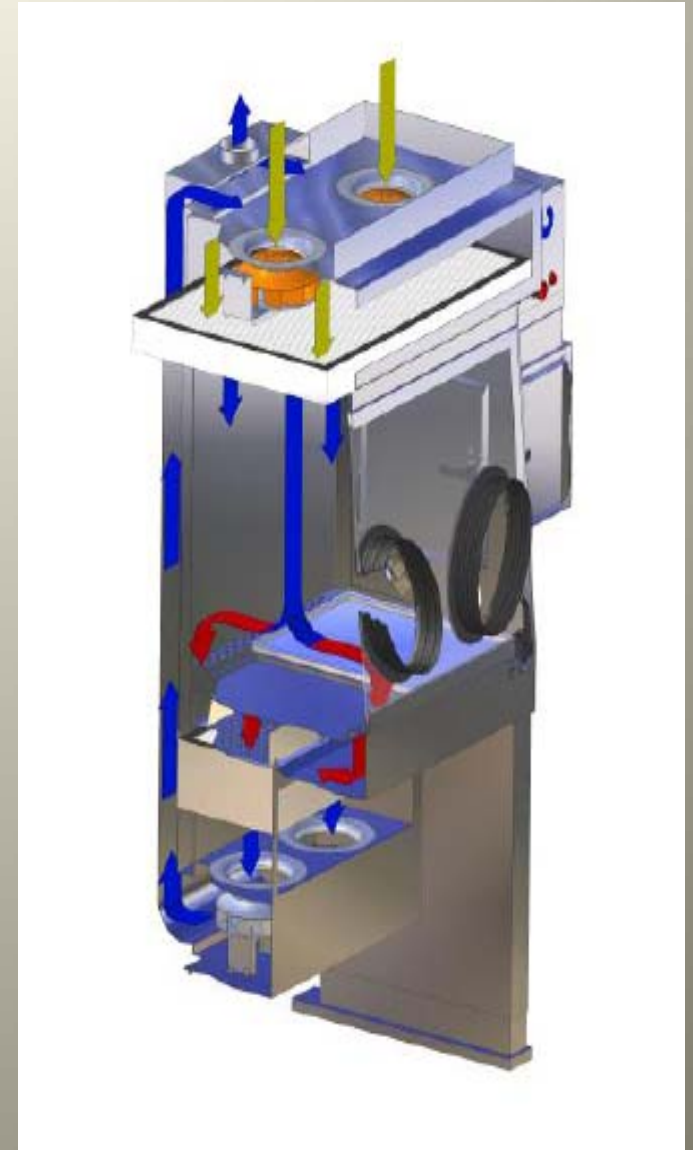
- Unidirectional flow
- Flow control to eliminate particles from critical work sites
- HEPA-filtered air should be supplied in critical areas at a velocity sufficient to sweep particles away from the compounding area and maintain unidirectional airflow during operations.
- Laminar vs. Unidirectional



Airflow

- ***Unidirectional Airflow:***
 - Provides the work zone with a continuous supply of filtered air. This mass airflow effect serves to sweep contaminants past and away from the preparation and out of the isolator environment.
 - The rate of contamination removal is very high since the HEPA filtered air moves through the work zone as a continuous “piston”.

Schematic courtesy of
Germfree Laboratories



First Air



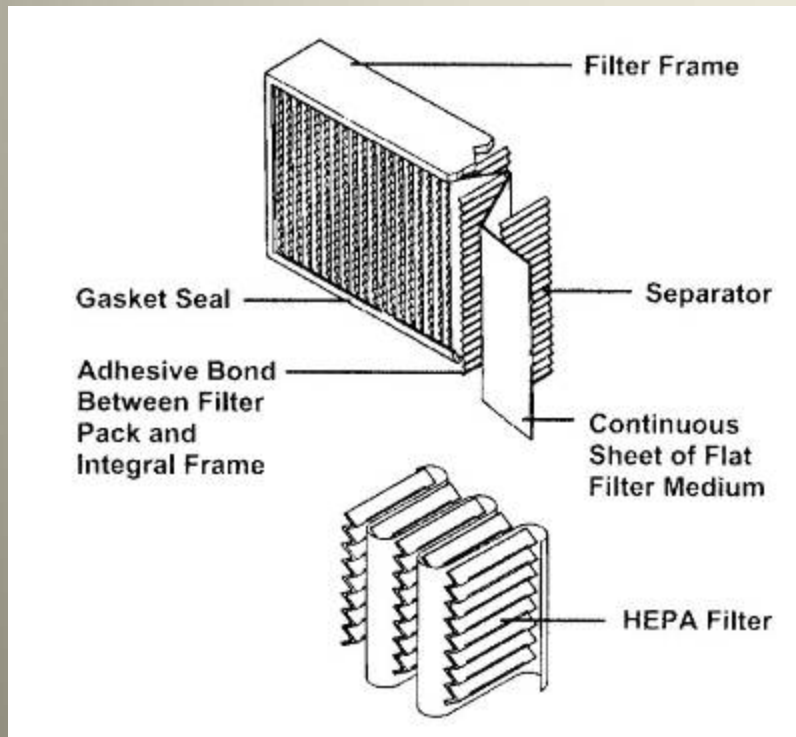
Improper hand placement disrupts first air

First Air



Proper hand placement takes advantage of first air

HEPA Filters



- The HEPA filter is a particulate filter, retaining airborne particles and microorganisms, while allowing gases to pass freely through.
- HEPA filters retain particulate matter by multiple mechanisms working together.
- IEST-RP-CC001.4 Performance Levels:
- Type C Filter:
Tested for overall penetration and have been leak tested. The minimum filter efficiency of the encapsulated filter type is 99.99% on thermally generated 0.3 μm particles.
- Type K Filter:
Tested for overall penetration per IEST-RP-007 and has been leak tested. The minimum efficiency is 99.995% at either 0.1-0.2 μm or 0.2-0.3 μm particle size range.

Pass-through systems

- Material transfer is one of the greatest potential sources of contamination.
- Three types of pass-through systems
 - **Static Air**
 - **Dilution Airflow**
 - **Unidirectional Airflow**
- For placement outside of a cleanroom, the isolator ***must isolate***.



Static pass-through



Dilution airflow pass-through



Unidirectional flow Pass-through

Isolator Placement

- USP Chapter <797> states:
 - CAIs must be placed in an ISO class 7 cleanroom **UNLESS** they meet all of the following conditions:
 - The isolator must isolate
 - Maintain ISO Class 5 during dynamic operating conditions
 - Maintain ISO Class 5 during material transfer
 - Isolator performance must be validated
 - CETA CAG-002-2006
 - Most unidirectional isolators with purged pass-through systems will easily meet the USP criteria.

Isolator Placement

- The room should
 - Accommodate hand washing and appropriate gowning
 - Be adequately sized to support the operation
 - Material storage
 - Support operations
 - Cleaning, replacement gloves, sleeves, etc.
 - Be appropriate for hazard level of drugs being compounded

Decontamination / Disinfection

- Design should facilitate physical disinfection of all work surfaces.
 - Interior seams shaped and sized to facilitate easy cleaning.
 - Interior surfaces easily reached through gloves.
 - Aftermarket products available
- Limitations of disinfecting through gloves.
 - Aftermarket products.
 - Allow adequate time
 - Daily disinfections
 - Disinfections between processes
 - Glove replacements



Decontamination / Disinfection

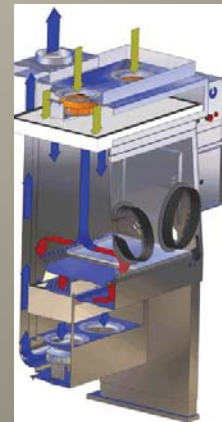
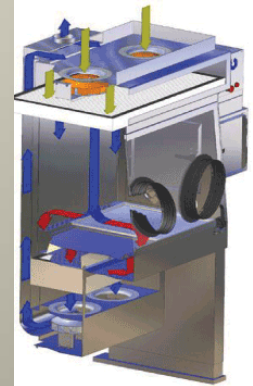
- Gaseous Decontamination
 - Required in cGMP
 - Typically not required for compounding.
- Compounding applications where adequate particulate contamination is not provided.
 - Turbulent flow, static pass-through
 - Vaporous Hydrogen Peroxide (VHP)
 - Chlorine Dioxide (CD)

Hazardous Drug applications

- Compounding Aseptic Containment Isolators
 - Minimum 0.10" Negative pressure
 - HEPA Filters contain particles not vapors or fumes
 - Internal recirculation
 - External venting
 - 100% exhaust
 - Roof top exhaust motor
 - Building re-entrainment
 - Exhaust stack
- Hazardous drug storage – isolator placement
 - 12 ACPH
 - 0.01" negative pressure
 - Separate from other inventory

Air Recirculation

- **Non-recirculating positive pressure**
 - Recirculating positive pressure little different in terms of usage
- **Recirculating negative pressure**
 - Limited by potential recirculation of volatile drugs
- **Non-recirculating negative pressure**
 - Most complicated installation
 - Least limitations



Glove systems

- Physical barrier between work and worker
 - Must facilitate frequent glove change
 - CAIs for US market are provided with a two-part glove assembly.
 - Consider double glove
 - USP requires use of sterile gloves
 - Glove change frequency
 - Experience
 - Cleaning agents
 - Solvents and process materials
 - Glove quality
 - NIOSH recommends 30 minutes for hazardous drugs
 - Gloves should be inspected regularly



Traditional glove change process



Picture provided by Innovative Technology, Inc.

Gowning

- Operators are expected to wear the same garbing when using an isolator as described for a cleanroom operation **unless** the manufacturer provides written documentation based on validated environmental testing that any component(s) of PPE or personnel cleansing are not required.
 - Consideration must be give to touch contamination and particulate transfer during the material loading process.

Operational Considerations

- The considerations that need to be addressed when setting up an operation around an isolator include the following:
 - Isolator disinfection/decontamination
 - What processes are to be employed?
 - What equipment is needed to support the process?
 - Trash
 - Will the outer wrap be removed in the pass-through or in the main compounding chamber?
 - Some isolators are equipped with trash and sharps disposal accommodations.
 - Glove replacement
 - How often and by whom?
 - Is the isolator set up to accommodate easy glove replacement?

Operational Considerations (cont.)

- The considerations that need to be addressed when setting up an operation around an isolator include the following:
 - Process flow
 - How will materials be staged?
 - How will materials be transferred in and out of the isolator?
 - Will support personnel pass materials or will the compounding technician/pharmacist have to de-glove and re-glove between processes?
 - Pharmacist review
 - Is the isolator set up to accommodate the pharmacist review process?
 - Ergonomics
 - Most isolators not vented outside the building can be equipped with height adjustment capabilities to facilitate different size workers.

Isolator Certification

- CAls used for sterile compounding should be certified every 6 months to the procedures outlined in CETA CAG-002-2006.

Procedure	Manufacturer	Field Test
2.01 Airflow Test	X	X
2.02 Chamber Pressure Test	X	X
2.03 Site Installation Assessment Tests	D	X
2.04 Gauntlet Breach Air Velocity Test	D	O
2.05 HEPA Filter Integrity Test	X	X
2.06 Particle Containment Integrity and Enclosure Leak Test	X	O
2.07 Recovery Time Determination Test	D	O
2.08 Airflow Smoke Pattern Test	X	X
2.09 Preparation Ingress and Egress Test	D	X
2.10 Particle Count Tests	X	X
2.11 Volatile Hazardous Drug Containment Tests	D	O
2.12 Hazardous Particle Containment Test	D	O
2.13 Pass-through Particle Purge Time Determination Test	D	O

X = Mandatory

O = Optional

D = Design criteria qualification

Summary

- Unlike the common myth promoted by some isolator manufacturers, isolators are NOT “magic boxes” that eliminate all concern for proper aseptic technique.
- They are simply contamination control tools intended to augment well thought out operations.
- Material transfer, production processes, and disinfection must be planned and the proper isolator design matched to your operation.