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

• 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
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).
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 vise versa during glove manipulation or normal operations.
  – Should be validated by the manufacturer.
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 affects 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.
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

Graphics courtesy of Germfree Laboratories
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

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

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