

The Five W's of Isolators and Complying with USP Chapter <797>

Presented by

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Disclaimer

“Although I am a member of the USP Compounding Expert Committee, I am speaking today in my individual capacity and not as a member of the Committee or as a USP representative.

The views and opinions presented are entirely my own. They do not necessarily reflect the views of USP, nor should they be construed as an official explanation or interpretation of <797>.”

“You can avoid reality, but you cannot avoid the consequences of avoiding reality.”

Ayn Rand (1905-1982)

Objectives

- After this session, you will be able to:
 - Describe the components of a Compounding Aseptic Isolator (CAI)
 - Distinguish the types of CAIs commonly used in sterile compounding including hazardous and non-hazardous applications
 - Explain the facility and operating requirements necessary when using an isolator as outlined in USP <797>

Background - References

- **NIOSH Alert** - www.cdc.gov/niosh
Preventing Occupational Exposure to Antineoplastic and other Hazardous Drugs in Health Care Settings
- **United States Pharmacopeia** - www.usp.org
USP 32 /NF27 Chapter <797> Pharmaceutical Compounding-Sterile Preparations (current version USP 34/NF 29)
- **Controlled Environment Testing Association (CETA)**
www.cetainternational.org
 - CAG-001-2005: *Applications Guide for the use of Compounding Isolators in Compounding Sterile Preparations in Healthcare Facilities*
 - CAG-002-2006: *Isolator Testing Guide*

Engineering Controls

- Engineering controls that are used in sterile compounding use airflow through High Efficiency Particulate Air (HEPA) filters to create air of the desired Cleanliness Classification:
 - **ISO Class 5** (direct compounding area inside of a primary engineering control such as a CAI)
 - **ISO Class 7** (buffer area or ante area adjacent to negative pressure ISO Class 7 hazardous buffer area)
 - **ISO Class 8** (ante area adjacent to non hazardous buffer area)

Primary Engineering Controls (PECs)



**Laminar Air Flow Workbench
(LAFW)**



**Biological Safety Cabinet
(BSC)**

Primary Engineering Controls (PECs)



**Compounding Aseptic Isolator
(CAI)**



**Compounding Aseptic Containment Isolator
(CACI)**

CAI Design Characteristics

- **Prerequisite Features of CAIs**
 - Supplied with minimum type C or J HEPA filtered air
 - May discharge unfiltered air into the room
 - Note the following about CACIs:
 - May discharge HEPA filtered air to the room **only** in the **absence** of volatile HDs
 - When used with volatile HDs, then CACI air must be discharged through a HEPA to outside the building
 - Must maintain containment during compounding operations and material transfer

CAI Design Characteristics

(continued)

- **Prerequisite Features of CAIs**
 - Must maintain ISO Class 5 during dynamic operating conditions
 - Must be designed to allow for safe and effective ***disinfection***
 - Access to the CSP is through gloves
 - Ingress and egress through closed (RTP) or open systems (PTs) that protect the work area from the outside environment

Previous USP positions

- “a well-designed positive pressure barrier isolator...may offer an acceptable alternative to the use of conventional LAFWs in clean rooms for aseptic processing...it is preferred, but not necessary, to locate barrier isolators within [an ISO Class 8] buffer air quality area.”
 - **USP Chapter <797> Compounded Sterile Preparations-January 2004**
- “Barrier isolators are located, operated, and used according to manufacturers’ recommendations”
 - **Proposed revisions to USP Chapter <797> Compounding Sterile Preparations - Pre 2006**

Historical positions: Isolators for sterile compounding

- In 1998, the New Jersey Board of Pharmacy permitted the use of “barrier isolators” as an alternative to primary and secondary engineering controls.
- USP and NIOSH developed standards for dealing with sterile compounding and hazardous drugs at roughly the same time:
 - Both initially introduced language in 2004
 - Both showed early and heavy influence of industry

Historical positions: Isolators for sterile compounding

- Both eventually acted to counter misunderstandings
- NIOSH was first to realize more guidance was needed to help end users through confusing manufacturer’s jargon
 - NIOSH’s 2004 release had helpful language
 - USP’s 2004 release **too trusting**; they introduced improved language in 2008
- The term “barrier isolator” was omitted from the NIOSH Alert because it was subject to a variety of interpretations, especially as they pertain to hazard containment and aseptic processing.

Definitions: Isolator (2004 NIOSH Alert)

- A device that is sealed or is supplied with air through a microbially retentive filtration system (HEPA minimum) and may be reproducibly decontaminated.
- When **closed**, an isolator uses only decontaminated interfaces (when necessary) or rapid transfer ports (RTPs) for material transfer.
- When **open**, it allows for the ingress/egress of materials through defined openings that have been designed and validated to preclude the transfer of contaminants or unfiltered air to adjacent environment.
- An isolator can be used for aseptic processing, for containment of potent compounds, or for simultaneous asepsis and containment.
- Some isolator designs allow operations within the isolator to be conducted through attached rubber gloves without compromising asepsis and/or containment.

NIOSH Definitions

- **Aseptic isolator:**
 - A ventilated isolator designed to exclude external contamination from entering the critical zone inside the isolator.
- **Containment isolator:**
 - A ventilated isolator designed to prevent the toxic materials processed inside it from escaping to the surrounding environment.
- **Aseptic containment isolator:**
 - A ventilated isolator designed to meet the requirements of both an aseptic isolator and a containment isolator.

Compounding Aseptic Isolator (CAI)

- 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 (CACI)

- A **CACI** designed to provide *worker protection* from exposure to undesirable levels of airborne drug throughout the compounding and material transfer processes and to provide an aseptic environment for compounding sterile preparations.



Compounding Aseptic Containment Isolator

- Air exchange with the surrounding environment should not occur unless the air is first passed through a microbial retentive filter (HEPA minimum) system capable of containing airborne concentrations of the physical size and state of the drug being compounded.
- Where *volatile drugs* are prepared, the exhaust air from the isolator *should be appropriately removed by properly designed building ventilation.*
- Unlike BSCs, there is no current NSF equivalent



Current USP Chapter <797> Position

“CAIs must be placed in an ISO class 7 buffer area UNLESS they meet ***all*** of the following conditions:

1. The isolator shall provide isolation from the room and maintain ISO Class 5 during dynamic operating conditions, including transferring ingredients, components, and devices into and out of the isolator and during preparation of CSPs.
2. Particle counts sampled approximately 6 to 12 inches upstream of the critical exposure site shall maintain ISO Class 5 levels during compounding operations.
3. Not more than 3,520 ppcm shall be counted during material transfer, with the particle counter probe located as near to the transfer door as possible without obstructing the transfer.

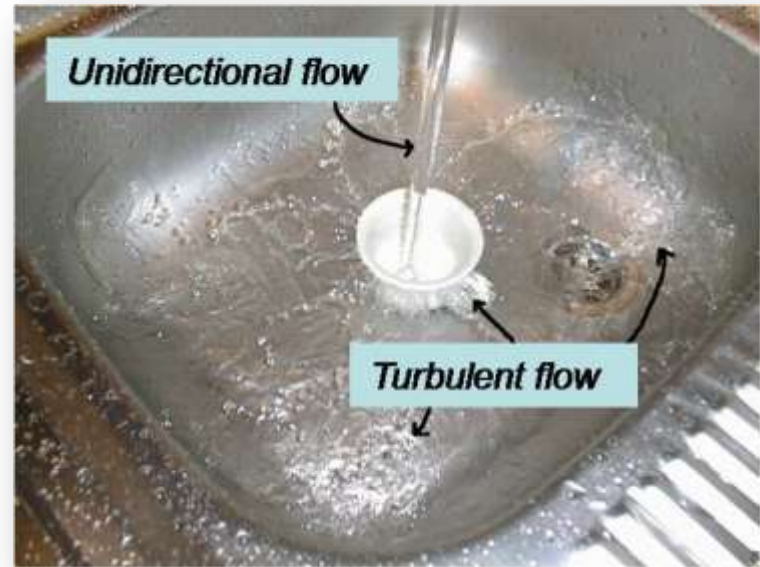
(Sample procedures are detailed in CETA Applications Guide CAG-002-2006 section 2.09)

It is incumbent on the compounding personnel to obtain documentation from the manufacturer that the CAI will meet this standard when located in worse than ISO Class 7 environments.

Current USP Chapter <797> Position

Turbulent flow isolators are not in compliance with USP <797>

- “The airflow in the primary engineering control (PEC) ***shall be unidirectional*** (laminar flow) and because of the particle collection efficiency of the filter, the ***“first air”*** at the face of the filter is, for the purposes of aseptic compounding, free from airborne particulate contamination.”



Current USP Chapter <797> Position

Turbulent flow isolators are not in compliance with USP <797>

- “Proper design and control prevents turbulence and stagnant air in the critical area. In situ air-pattern analysis via smoke studies should be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic (working) conditions.”

Peters GF, McKeon MR, Weiss WT. Potentials for Airborne Contamination in Turbulent and Unidirectional Airflow Compounding Aseptic Isolators. Am. J. Health-Syst. Pharm. 2007; 64:622-631.

Current USP Chapter <797> Position

- Recovery time shall be documented and internal procedures developed to ensure adequate recovery time is allowed.
 - After transferring material into and out of the isolator
 - Before and during compounding operations
- Follow certification procedures such as those outlined in:
 - CAG-003-2006 shall be performed by a qualified individual no less than every 6 months
 - CAG-003 refers to CAG-002 for isolator test procedures

If the PEC is a CAI or CACI that does *not* meet the requirements above or is a LAFW or BSC *not* located in an ISO Class 7 area, then *only low risk, 12 hour beyond use dating (BUD) preparations can be prepared inside.*

Full Enclosure

- Myth: “An isolator is a magic box, because we work through a physical barrier, there will be no contamination.”
- Reality: The full enclosure MUST be accompanied by proper airflow and effective decontamination and disinfection to yield an effective sterile compounding environment



www.hyview.com

Decontamination/Disinfection

- Transfer of material into and out of the isolator is one of the greatest potential sources of contamination. Routes include bags, boxes, paper and markers.
- Research has shown that:
 - 60% of consumables are contaminated with bacteria
 - 40% of consumables are contaminated with bacterial spores
- Spraying alone is not enough:

Organism	Spray	Spray + Wipe
Aspergillus Niger	84%	98.5%
Bacillus subtilis	27%	94%

M. G. Cockcroft, D. Hepworth, J. C. Rhodes, P. Addison, A. M. Beaney. "Validation of Liquid Transfer Disinfection Techniques for Transfer of Components Into Hospital Pharmacy Cleanrooms," Hospital Pharmacist (September, 2001).

Contaminated Material

Table 1: Sample testing of items routinely used in isolators

Item	% contaminated	% Bacillus (spores)
Syringe package	60.0	40.0
Swab package	66.7	16.6
Needle package	60.0	20.0
Sharps bin	57.1	42.9

M. G. Cockcroft, D. Hepworth, J. C. Rhodes, P. Addison, A. M. Beaney. "Validation of Liquid Transfer Disinfection Techniques for Transfer of Components Into Hospital Pharmacy Cleanrooms," Hospital Pharmacist (September, 2001).

Decontamination / Disinfection

- The isolator design should facilitate physical disinfection of all work surfaces. Interior seams should be shaped and sized to facilitate easy cleaning.
- All interior surfaces should be easily reached through the gloves to accommodate cleaning.
- If the interior is designed in a manner that does not permit easy physical disinfection of all surfaces, an alternative gaseous decontamination process must be developed and validated.



Decontamination / Disinfection

- Most isolators are difficult to disinfect because of the limitations of working through gloves.
 - Many aftermarket products are available to make this task easier.
 - Time should be factored into the process to allow for adequate daily disinfection as well as work surface disinfection between processes.



Gowning

- Compounding personnel are expected to wear the same garb 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 is not required.
 - Some manufacturers recommend hair net, gown and gloves when loading the ante chamber
- Consideration must be given to touch contamination and particulate transfer during the material loading process.

Sampling and Monitoring

All environmental sampling

(particle counts and viable air sampling)

AND

Personnel/work practice monitoring

(surface and gloved fingertip sampling, aseptic media fills)

are required

regardless of primary engineering control used!

(LAFW, CAI and CACI)

Glove Systems

- Manipulations within a barrier isolator are conducted through a glove/sleeve (gauntlet) assembly.
- Two types of glove/sleeve assemblies are available:
 - **One-Part:** Glove and sleeve are single, unbroken unit
 - **Two-Part:**
 - Glove and sleeve are separate and are connected at the sleeve (gauntlet) by some type of seal system.
 - The two-part system allows for the relatively simple change-out of gloves.
 - Most of the isolator systems sold to the US market are provided with a two-part assembly.

Glove Systems

(continued)

- It is common practice to use a double glove system to minimize the possibility of a tear or leak to compromise the environment within the isolator.
- An ordinary latex glove can be worn underneath if desired.
- Don sterile gloves over the tops of the isolator glove. Re-sanitize the sterile gloves frequently during compounding.
- Glove life will be affected by the cleaning agents, solvents, and process materials.



**An example of a “push-through”
easy change glove system by
Innovative Technology, Inc. that
is user friendly.**

Glove Systems

(continued)

- Gloves and gauntlets should be inspected daily for pinholes as well as breaches at seams, gaskets and seals.
- A regular replacement program should be established so gloves are replaced before a breach of integrity occurs.



Glove Systems

(continued)

- The sequence to the right is one example of the many glove change systems available.
- Be sure to try the system provided by each isolator manufacturer for your application.
- Glove systems are often interchangeable so you should be able to pick the system you like best.

1.



2.



3.



4.



5.



6.



7.

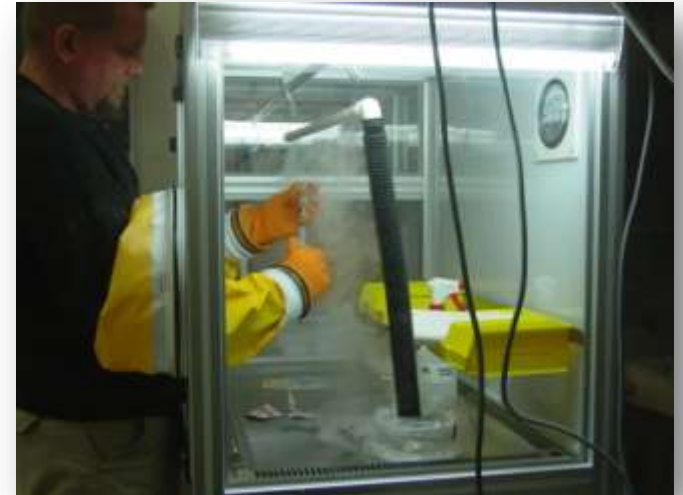


Just remember to don sterile gloves over the gauntlet gloves before compounding.

Operational Considerations

- Unidirectional airflow isolators are designed to use the concept of “first air” to aid aseptic technique.
 - Material Staging
 - Control Cross Contamination
- Material Transfer Considerations
 - HEPA Filter Purge time
 - Transfer chamber
 - Compounding chamber

Isolators are NOT magic boxes!



Operational Considerations

- 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?
 - How will trash and sharps disposal occur? 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

(continued)

- Process flow
 - How will materials be staged?
 - How will materials be transferred in and out of the isolator?
 - Will support personnel pass additional materials in or will the compounding technician/pharmacist have to de-glove and re-glove between processes?
- Pharmacist review
 - Is the isolator set up to permit the pharmacist to review the compounding process?
- Ergonomics
 - Most isolators can be equipped with height adjustment capabilities to facilitate different size workers.
 - Issues with externally vented cabinets

Summary

- Isolators are NOT “magic boxes” that eliminate concern for proper disinfection and aseptic technique.
- They are simply contamination control tools to reduce the likelihood of contamination but do not replace work practice controls related to aseptic technique.
- Material transfer, production processes, and disinfection must be planned and the proper isolator design matched to the operation.
- All USP Chapter <797> personnel training, cleaning, and environmental sampling requirements need to be performed when using an isolator

Acknowledgement

Jim Wagner, Controlled Environment Consulting
for his generosity in providing with me with
slides to make this webinar accurate and
current as it relates to the use of CAIs and
CACIs and complying with USP Chapter <797>

Closing Thought

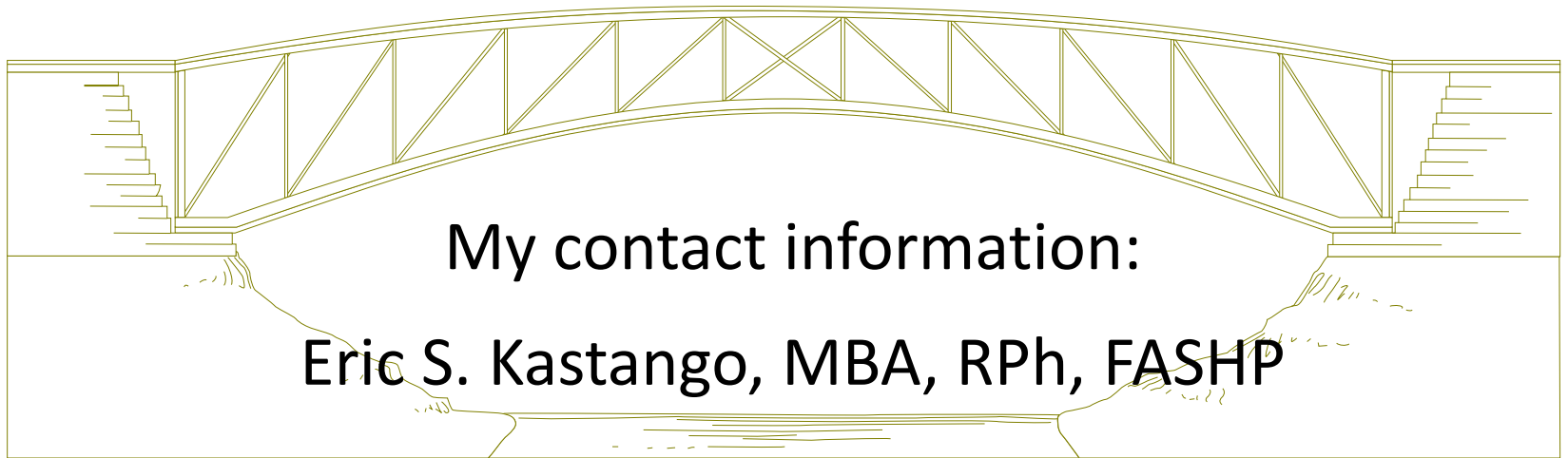
Pedantry and mastery are opposite attitudes toward rules.

To apply a rule to the letter, rigidly, unquestioningly, in cases where it fits and in cases where it does not fit, is pedantry ...

To apply a rule with natural ease, with judgment, noticing the cases where it fits, and without ever letting the words of the rule obscure the purpose of the action or the opportunities of the situation, is mastery.

George Polya, mathematician (1887-1985)

Thank you



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