USP <797>/<800>

Cleanroom Design & Environmental Monitoring

A presentation for HealthTrust Members
November 14, 2018

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Disclosures

- The presenter has no financial relationships with any commercial interests pertinent to this presentation.
- This program may contain the mention of drugs or brands presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand or drug.

Objectives

The Pharmacist learning objectives:

- Discuss the requirements for environmental controls in sterile compounding environments.
- Recall the required tests to prove compliance with USP <797> & <800>.
- Plan corrective actions for non-compliance issues often found in sterile compounding clean areas.

Objectives

The Pharmacist Technician learning objectives:

- Define the environmental controls required to maintain sterility in USP <797> compliant cleanrooms.
- Recall principles of Environmental Monitoring and Personnel Monitoring as it relates to USP <797>.

What is USP <797>?

- An enforceable chapter of the U.S. Pharmacopeia—National Formulary
- Defines “best practices” and standards for sterile compounding nationally

USP <797> Purpose

The intentions behind the requirements of USP <797>:

- Patient Safety—health violations can cause serious injury to patients
- Drug Sterility—assure that medication does not become contaminated during preparation

Who does it apply to?

USP <797> applies to:

- All persons who perform sterile compounding
- All places where sterile compounding is performed

What is USP <800>?

- An enforceable chapter of the U.S. Pharmacopeia—National Formulary
- A “companion” chapter that covers both sterile and non-sterile compounding of hazardous drugs (HDs)
- USP <797> still applies for sterile compounding generally
- Chapter <800> becomes official Dec. 1, 2019

Enforcement

Who is empowered to enforce USP <797>?

- FDA
- State Pharmacy Boards (for approved states)
- State Departments of Public Health
- The Joint Commission (formerly JCAHO)
- Centers for Medicare and Medicaid Services (CMS)

Why Comply?

- Regulation—FDA, Regulations in some states
- Accreditation—Joint Commission
- Best Practices—Proof against liability
- Marketing—Competitive Advantage
- Out-of-State Compounds

Lead up to USP <797>

- **1938**: Federal Food, Drug and Cosmetic Act
  - Establishes USP-NF as standard practices for pharmacies, chapters <1> through <999> enforceable by FDA
- **1960's-1970's**: Publicized incidents of patient injury/death related to sterile compounding
- **1990's**: USP <1206> established as recommended (non-enforceable) sterile compounding guidelines

Lead up to USP <797>, *continued*

- **2000's**: Several incidents linked to compounding
  - 2001: Walnut Creek, CA; 40 patients exposed to tainted medication, 4 developed meningitis, 2 deaths
  - 2002: North Carolina; 5 patients infected by tainted medication, 1 death, recall from 11 states
  - 2005: Washington, D.C.; two patients blinded following cataract surgery involving bacterially contaminated medicine
- **2004**: USP <797> published, establishing standards for sterile compounding
- **2008**: Chapter is updated with stricter standards. This is the current version.

New England Compounding Center

Why the push for USP <797> compliance?

- **September 2012**: regulators investigated the NECC in Framingham, Massachusetts, in connection with a multi-state meningitis outbreak
  - 20 States received tainted steroid injections that were compounded at NECC
  - A total of 753 cases of fungal infections linked to the drug, the majority being meningitis and/or spinal infections
  - 64 associated deaths

Source: Data collected from CDC website as of 30 OCT 2015 (last update)

USP <797> Terms

- **CSPs -** Compounded Sterile Preparations
- **PEC** - Primary Engineering Control
- **SEC** - Secondary Engineering Control
- **Buffer Room** - Area where PEC is located
- **Ante Room -** Transitional area adjacent to Buffer
- **Hazardous Drugs** (HDs) - Exposure to these drugs can cause cancer, developmental or reproductive toxicity or organ damage

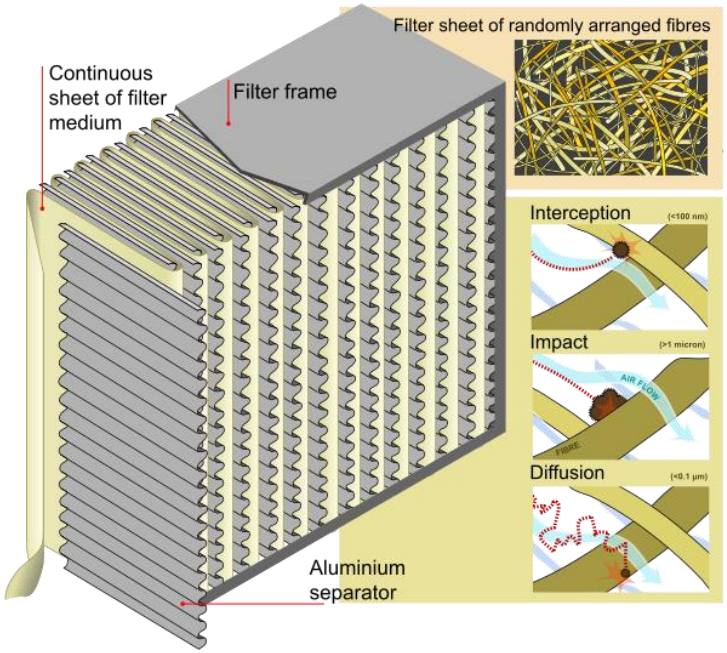
General Concepts

Basic cleanroom concepts as they relate to a USP <797> environment:

- HEPA filtration
- Control over airborne particulate
- Unidirectional airflow
- Room isolation

HEPA Filters

- **HEPA** (High-Efficiency Particulate Air) Filters are 99.97% efficient at removing particles at 0.3µm.
- Adequate ventilation helps to dilute particulate and other potential contaminants in the cleanroom air.
- HEPA filters are used in both PECs and SECs.



Airborne Particulate

Particulate is a major source of contamination in cleanroom environments.

- Consists of dust, fibers, shed skin cells, microbes & other microscopic airborne debris
- Vector for microorganisms
- Can interfere with potency of CSPs
- Can trigger immune response from patients

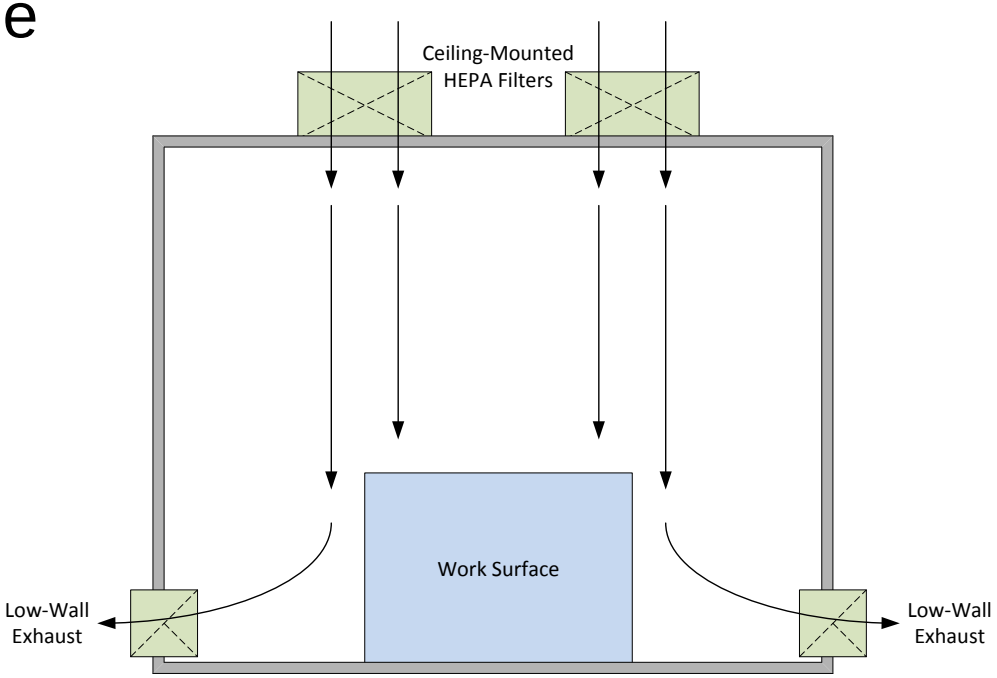
ISO Classifications

ISO Class	USP <797> Area	≥ 0.5 µm	
		particles/ft^3	particles/m^3
5	PEC	100	3,520
6	N/A	1,000	35,200
7	Buffer	10,000	352,000
8	Ante	100,000	3,520,000

[3]Per ISO 14644-1 – Cleanrooms and Associated Controlled Environments

Unidirectional Airflow

- HEPA-filtered air must be introduced at the ceiling for ISO class 7 areas
- Air should be exhausted through low-wall returns
- Ensures continuous dilution of contaminants in air & prevents refluxing/dead spaces



Room Isolation

Positive room pressure keeps the cleanroom environment isolated from uncontrolled air elsewhere in the facility.

Prevents dirt, particulate & other airborne contaminants from entering the cleanroom through doorways, ceiling tiles or other cracks/crevices.

PEC Requirements

A **PEC** is:

"A device or room that provides an ISO class 5 environment for the exposure of critical sites when compounding CSPs."

Some examples:

- Laminar Airflow Workbenches (LAFWs), also called Unidirectional Flow Devices (UFDs)
- Biological Safety Cabinets (BSC)
- Compounding Aseptic Isolators (CAIs), usually positively pressured
- Compounding Aseptic Containment Isolators (CACIs), always negatively pressured

PEC Examples

BSC

(Vertical Airflow)

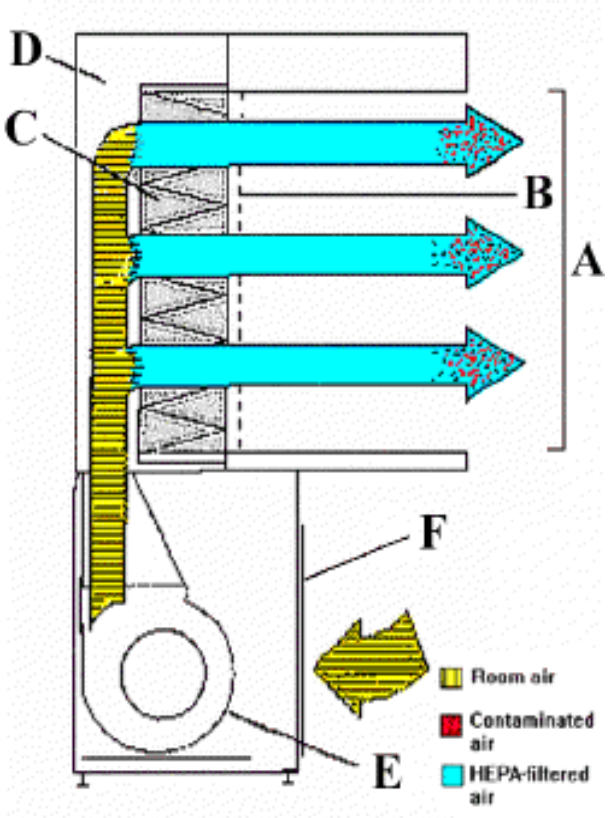
LAFW

(Horizontal Airflow)

Isolator - CAI

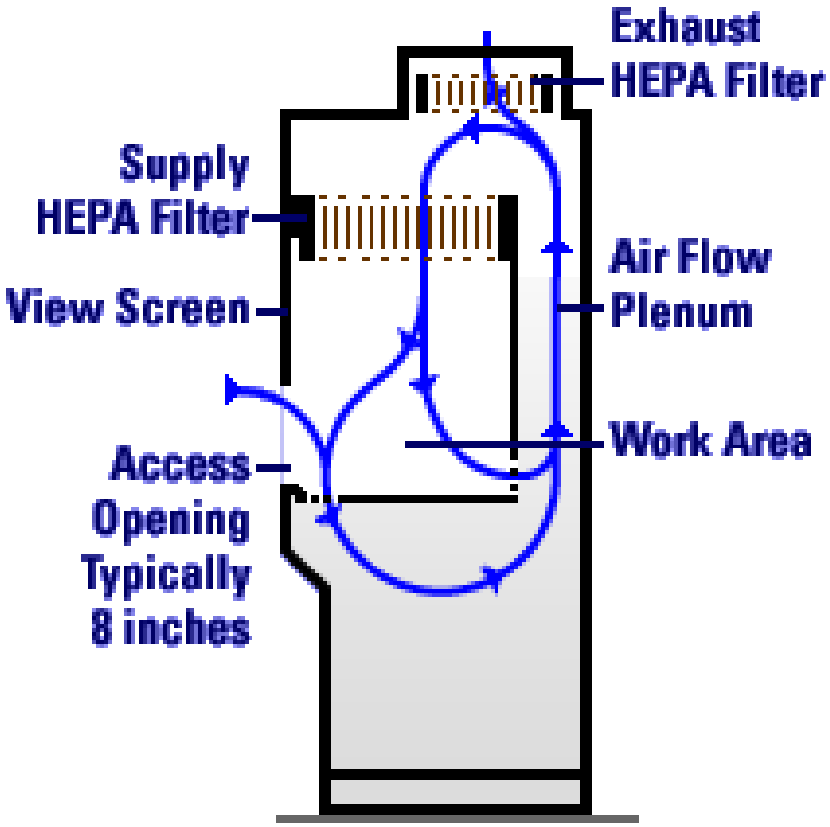
Laminar Airflow Workbench

- HEPA filtered air flows over the workspace
- Airflow is unidirectional across workspace
- Recirculated air contributes to room air changes
- Only suitable for non-hazardous compounding



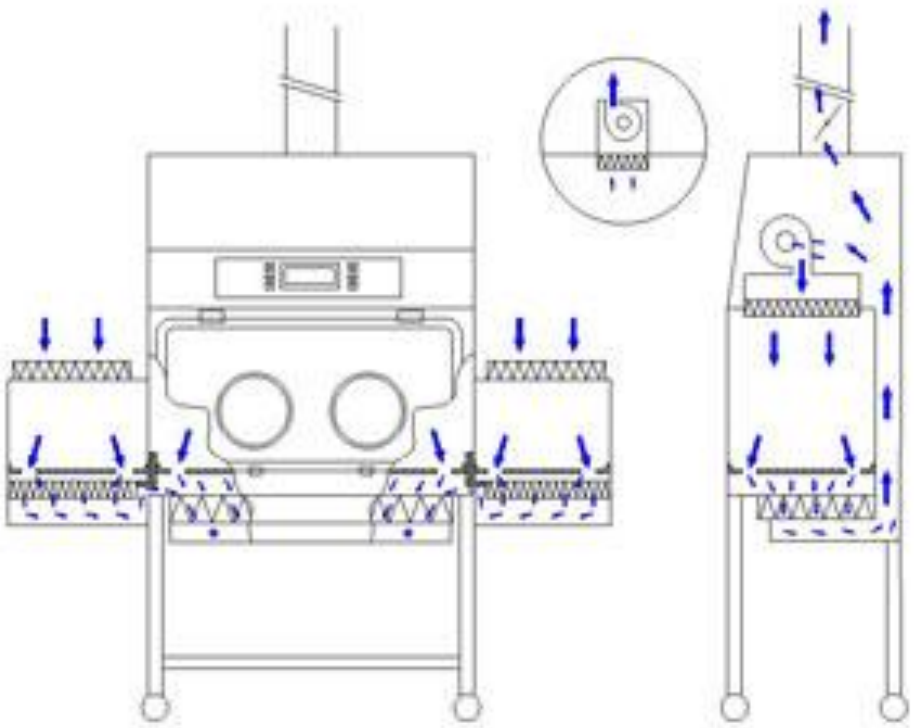
Biological Safety Cabinets

- Offers both contamination control and worker protection
- Airflow from room does not enter work area
- Airflow from work area does not vent into room
- HEPA filtered unidirectional supply air
- HEPA filtered exhaust air



Compounding Isolators

- Isolated from surrounding environment (i.e., no mixture with ambient room air)
- HEPA filtered, unidirectional airflow over work surface
- CACIs provide worker protection (allow for hazardous compounds)
- CAIs do not (non-hazardous compounds only)



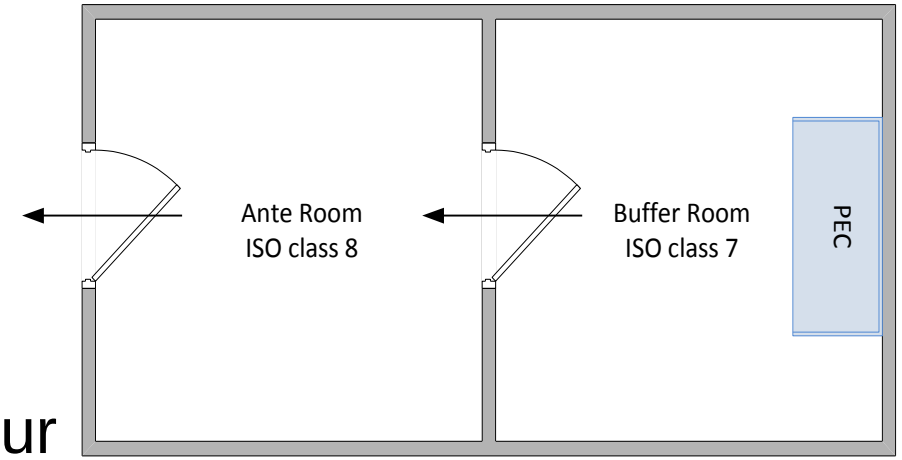
PEC Recap

PEC Type	Product Sterility	Hazard Containment
LAFW	Yes	No
BSC	Yes	Yes
CAI	Yes	No
CACI	Yes	Yes

Non-hazardous Compounding Environmental Requirements

Standard Requirements:

- ISO class 7 Buffer Room
- ISO class 8 Ante Room
- At least 0.02 “w.c. (Inches of Water Column) positive pressure to the outside
- At least 30 air changes/hour of HEPA-filtered air



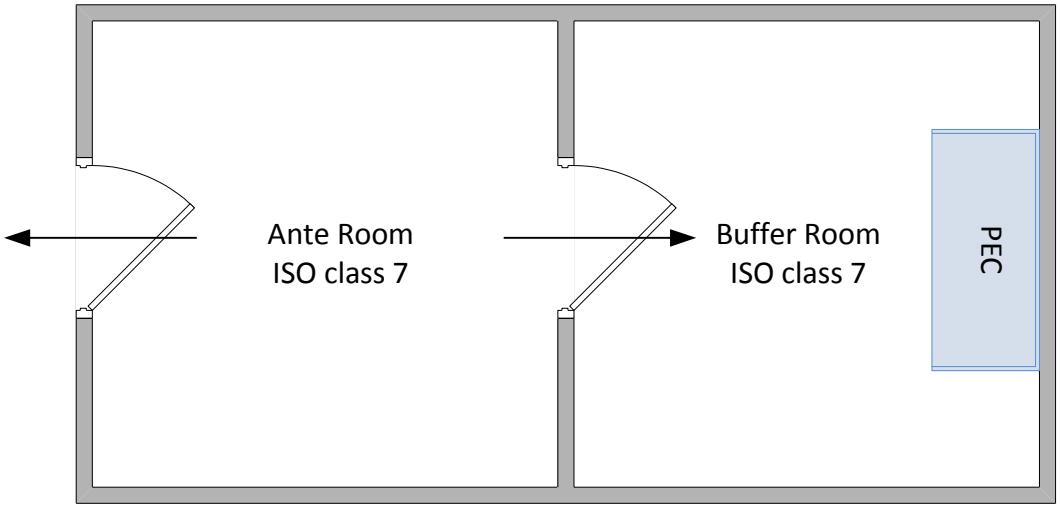
Hazardous Compounding Environmental Requirements

Same requirements as non-hazardous, with the following exceptions:

- The PEC must provide hazard containment (i.e., biological safety cabinet or negative-pressure isolator).
- The PEC should be 100% vented to the outside through HEPA filtration.
- The room must have at least 0.01”w.c. *negative* pressure to the outside.
  - Note: Hazardous & non-hazardous compounding are not compliant in same area.
- Requires an ISO class 7 buffer AND ante area.

Hazardous Compounding Environmental Requirements

Hazardous Compounding Pharmacy



New USP <800>

USP <800> Hazardous Drugs—Handling in healthcare settings changes include:

- Addressing both sterile & non-sterile compounding of HDs
- Unambiguously stating the need for a **dedicated room**
- Antineoplastic HDs must be stored in a **negatively pressured room**
- Buffer area must have between 0.01 and 0.03 “w.c. negative pressure
- Specific instructions for **protective gowning**
- Guidelines for cleaning/decontamination of HD spills/residue

New USP <800>, *continued*

USP <800> Hazardous Drugs—Handling in healthcare settings changes include:

- 12-hour BUD rule applies to hazardous compounding
- Hoods must be 100% vented to the outside through HEPA filtration
- Note: the USP <800> committee has removed a requirement for buffer & ante room exhaust to also be HEPA filtered
- HD residue sampling recommended to form a baseline, & then at least every six months

HD Residue Sampling

NIOSH warns that hazardous drugs can cause acute & chronic human health effects, including cancer.

USP <797> recommends **sampling for hazardous drug residue** every six months.

- Common drugs for sampling: Cyclophosphamide, Ifosfamide, Methotrexate, Fluorouracil
- While the literature has not selected any acceptance limits for hazardous drug residue, Cyclophosphamide levels of 1.0 ng/cm^2 have been found to result in human uptake.

HD Residue Sampling

USP <797> recommends sampling:

- PEC workspaces
- Countertops where finished CSPs are placed
- Areas adjacent to PEC, including floors
- Patient administration areas

12-hour Beyond-use Date

USP <797> allows an exception to the rule of placing the PEC in an ISO class 7 Buffer area if:

- CSPs are to be administered within 12 hours of compounding, or per physician's orders, whichever sooner
- CSPs meet the definition of "low-risk" per USP <797>
- The PEC is not located near potential contamination (e.g., doors, windows, flow-of-traffic, food prep, etc.)

12-hour Beyond-use Date, *continued*

Pros:

- No requirements for buffer/ante area ISO classification, HEPA filtration or room pressure for non-haz rooms
  - Haz rooms still require negative pressure and ≥12 AC/H
- May be suitable for older facilities not designed to meet the standard USP <797> specs

Cons:

- Expensive
- Scheduling challenges

Isolator Considerations

USP <797> allows an exception to the rule of placing the PEC in an ISO class 7 Buffer area if:

- The PEC is an isolator (CAI or CACI) that provides isolation from the room & meets ISO class 5 during normal operations, compounding & material transfer.
- The pharmacy determines the recovery time of the unit & establishes internal procedures to maintain ISO class 5 during material transfer & compounding operations.

Isolator Considerations

Pros:

- No requirements for buffer/ante area ISO classification, HEPA filtration or room pressure for non-haz rooms
  - Haz rooms still require negative pressure and ≥12 AC/H
- Useable with all risk-levels of compounding

Cons:

- Expensive
- Reduced production/worker comfort

Isolator Examples

CAI

CACI

Required Tests

USP <797> requires the following tests to demonstrate compliance:

- Certification of PEC
- Non-viable Airborne Particle Counting
- Certification of HEPA Filters
- Room Air Exchange Rates
- Room Differential Pressures
- Viable Airborne & Viable Surface Sampling
- HD Residue Sampling (recommended)

Certification of PEC

Primary Engineering Controls are required to be certified to the appropriate industry standards at least semi-annually.

This includes, but may not be limited to:

- Verification of airflow velocity & direction in accordance with manufacturer's specifications and/or intended use
- Tested to ISO class 5 within the workspace
- Leak testing of HEPA filters
- Must be performed by a qualified individual

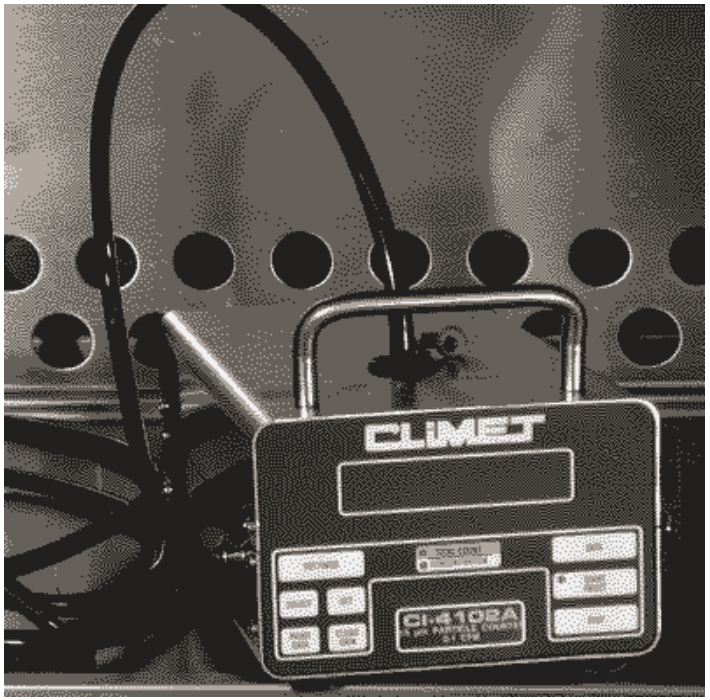
Particle Counting

Particle Counting:

- Is intended to detect non-viable (i.e., non-living) particulate matter that could contaminate CSPs
- Is also a good way to measure the effectiveness of environmental controls
- Is performed semi-annually, or whenever the room/equipment are modified, moved or repaired

Particle Counting, *continued*

- Tested according to ISO 14644—Cleanrooms & Associated Controlled Environments
- USP <797> determines which ISO classifications apply to what areas



ISO Classifications

ISO Class	USP <797> Area	≥ 0.5 µm	
		particles/ft^3	particles/m^3
5	PEC	100	3,520
6	N/A	1,000	35,200
7	Buffer	10,000	352,000
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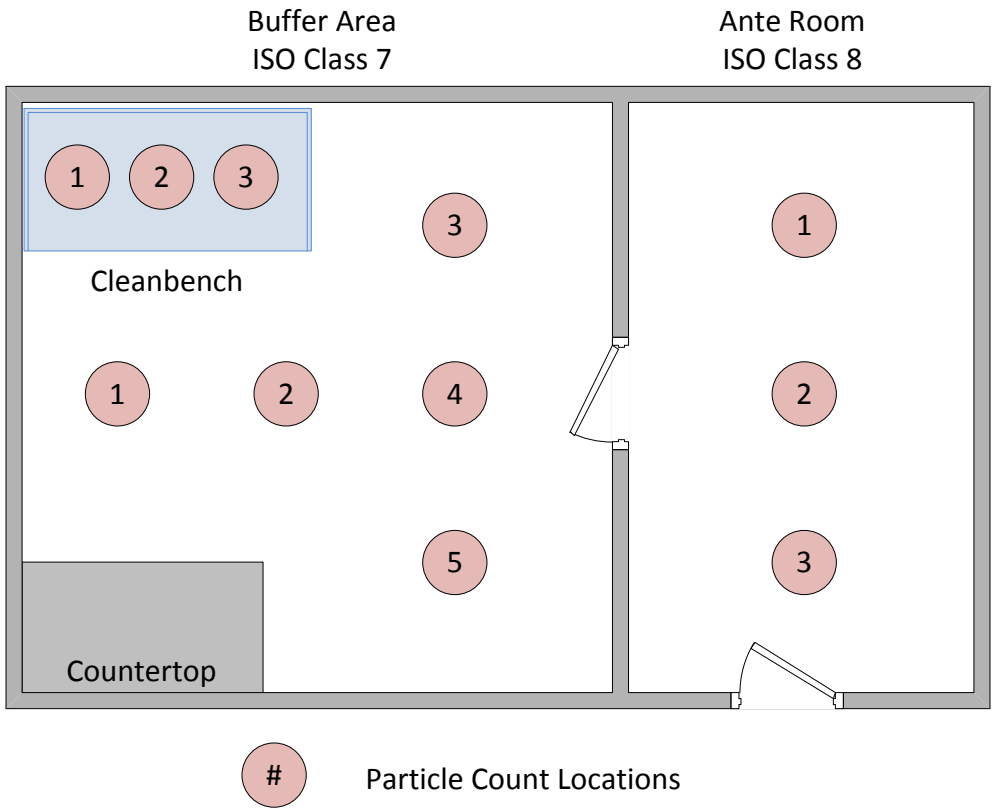
[3]Source: Per ISO 14644-1 – Cleanrooms and Associated Controlled Environments

Particle Counting



What causes high particle counts?

Airborne particulate can be generated by several sources:

- Construction/building materials
- Humans
- Operations elsewhere in the facility
- Cardboard/packaging

What can be done to prevent high particle counts?

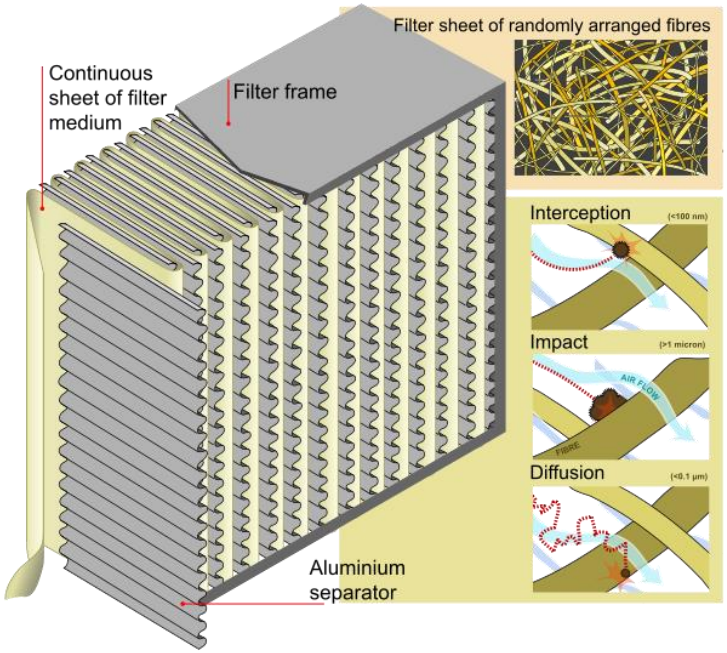
- HEPA-filtration & unidirectional airflow
- Good room isolation & pressurization
- Good gowning practices
- Proper storage of materials
- Restrict traffic through critical areas
- Clean the area regularly to remove dust/debris

For areas that cannot meet ISO class 7:

- Use of an Isolator or low-risk compounding with a 12-hour beyond-use-date

HEPA Filters

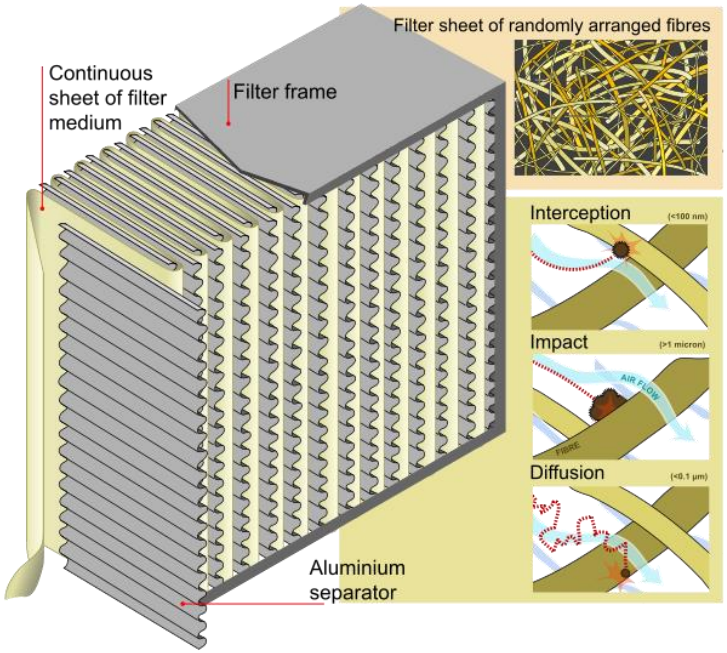
- HEPA-filtered air must be introduced at the ceiling for ISO class 7 areas.
- HEPA filters are to be leak tested in accordance with IEST-RP-CC001 as part of semi-annual testing.



HEPA Filters, *continued*

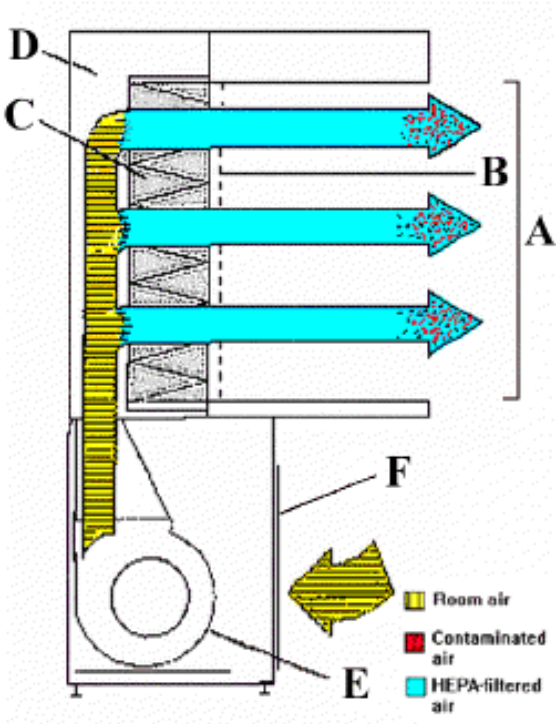
Note: Make sure HEPA filters are readily testable prior to a technician showing up on-site.

Depending on HVAC system, filter may require an aerosol injection port to allow for leak testing.



Room Air Exchange Rate

- ISO class 7 Buffer & Ante Areas require sufficient HEPA-filtered airflow to provide ≥30 air changes per hour (ACPH) for the room.
- Room HEPAs only need to provide ≥15 AC/H if recirculated air (e.g., HEPA-filtered air from the PEC) can make up the difference.

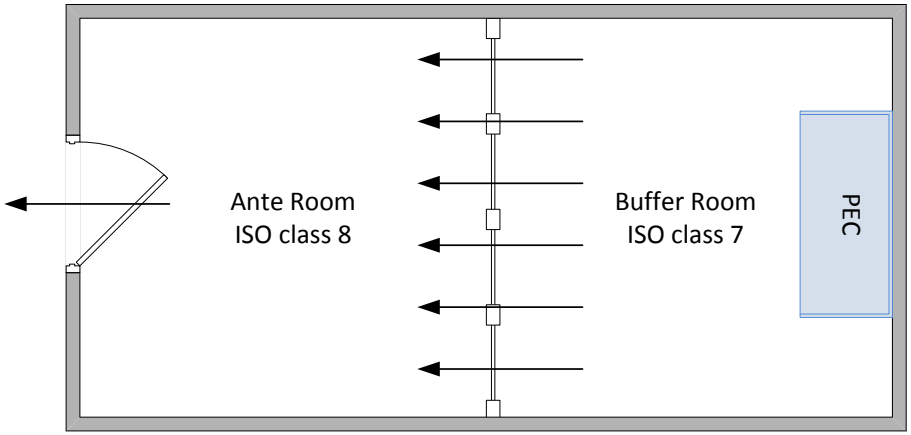


Room Pressurization

- Non-hazardous buffer & ante areas require at least 0.02 “w.c. of *positive* air pressure to the exterior. (i.e., the net flow is out of the room)
- For hazardous buffer areas, between 0.01 & 0.03 “w.c. *negative* air pressure is required.

Displacement Airflow

For non-hazardous ante and buffer areas that are not physically separate, the pressure requirement may be substituted with >40 fpm consistent airflow across the line of demarcation.



Note: This option will be removed in the next version of <797>.

Viable Sampling

Viable Sampling is intended to detect living contaminants for both hazardous and non-hazardous areas such as:

- Bacteria and other microorganisms
- Fungal growth

Appropriate areas for Viable Sampling:

- Within the PEC's direct compounding area
- Devices (e.g., computers & printers), objects (e.g., carts) & work surfaces (e.g., countertops & shelves) within the Buffer & Ante Rooms

Viable Sampling, *continued*

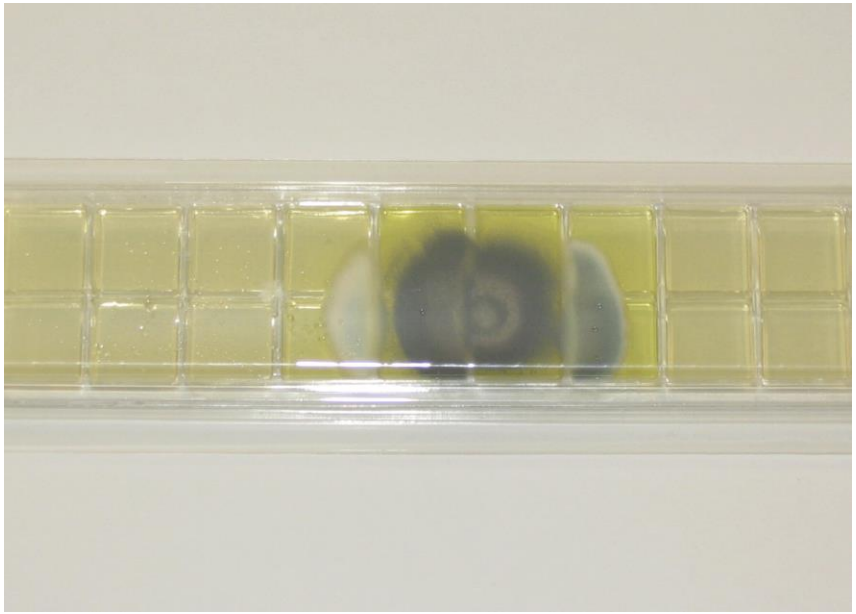
Media Selection:

- Sampling requires a general-purpose medium that supports the growth of bacteria
  - e.g., Soybean-Casein Digest Medium (a.k.a., Tryptic Soy Agar)
- High-risk compounding areas require the use of fungal-selective media
  - e.g., Malt Extract Agar or Sabouraud Dextrose Agar

Viable Sampling, *continued*

Airborne Viable Sampling:

- Impaction method is required, using quantitative air samplers
- Passive settling method *not* compliant
- 400L – 1000L samples; minimum 1000L in ISO class 5 zones
- Samples collected on agar plates



Viable Sampling, *continued*

Surface Viable Sampling:

- Samples collected on agar contact plates
- “Touch & roll” method
- Clean surface immediately after sampling to remove residue

Viable Sampling, *continued*

Media Incubation:

- TSA media incubated at 30–35 degrees Celsius for 48 to 72 hours
- Fungal-selective media incubated at 26–30 degrees Celsius for 5–7 days
- Colony forming units enumerated
- USP <797> requires that all air samples demonstrating growth be identified to at least the genus level

Viable Sampling, *continued*

ISO Class	USP <797> Area	Airborne Criteria CFUs/m^3	Surface Criteria CFUs/plate
5	PEC	≤ 1	≤ 3
7	Buffer	≤ 10	≤ 5
8 or worse	Ante	≤ 100	≤ 100

Viable Sampling, *continued*

Fingertip/Glove Sampling:

- Samples collected from the tips of fingers & thumbs on sterile gloves using agar plates
- Used to demonstrate proper gloving & hand hygiene practices
- USP <797> requires that this be tested three times as part of the initial qualification for compounding CSPs
- Incubated at 30-35°C for three days
- Zero CFUs allowed for initial qualification
- Re-qualification is annual, with <3 CFUs allowed

What causes viable growth?

There are **several, typical sources** for viable contamination:

- Human-borne: including organisms carried by skin, breath, mucous, clothing, etc. This is the most common source of contamination for the typical cleanroom.
- Airborne: carried in from the outside or elsewhere in the facility
- Water-borne: can be caused by splashes near sink

What can be done to prevent viable growth?

Utilize good cleanroom techniques:

- Isolate & pressurize the room to keep out external sources of contamination
- Use HEPA filtration to dilute contaminants in air
- Regularly clean critical surfaces with approved disinfectants (e.g., 70% IPA)
- Use good gowning practices to prevent human-borne contamination

What are the corrective actions for viable growth?

Following are a recommended battery of corrective actions when viable samples come back high:

- Verify that no unusual circumstances would have affected the environmental controls
- Review gowning requirements with personnel
- Clean affected area with disinfectant and retest
- Consider identification of organisms (USP <797> requires identification to at least genus level)

  Note: may be done concurrently with retesting

USP <797> Update Draft

The USP published a second draft for public comment on July 27, 2018. Comments are welcome until Nov. 30, 2018.

USP <800> and the new <797> are both planned to come into effect on Dec. 1, 2019, to ensure no overlap of conflicting language.

USP <797> Update Draft

Current proposals for change include:

- General clarification & improvement of layout
- Risk categories simplified as Category 1 or Category 2
- Monthly viable surface sampling
- Fungal-selective media not addressed
- New surface sampling criteria

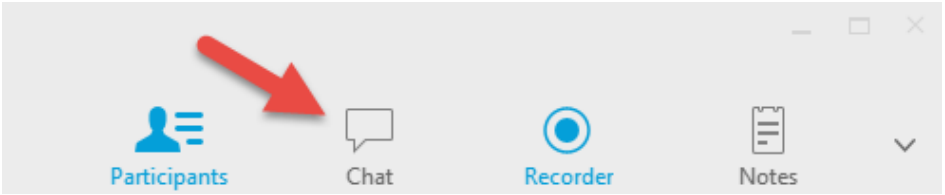
USP <797> Update Draft

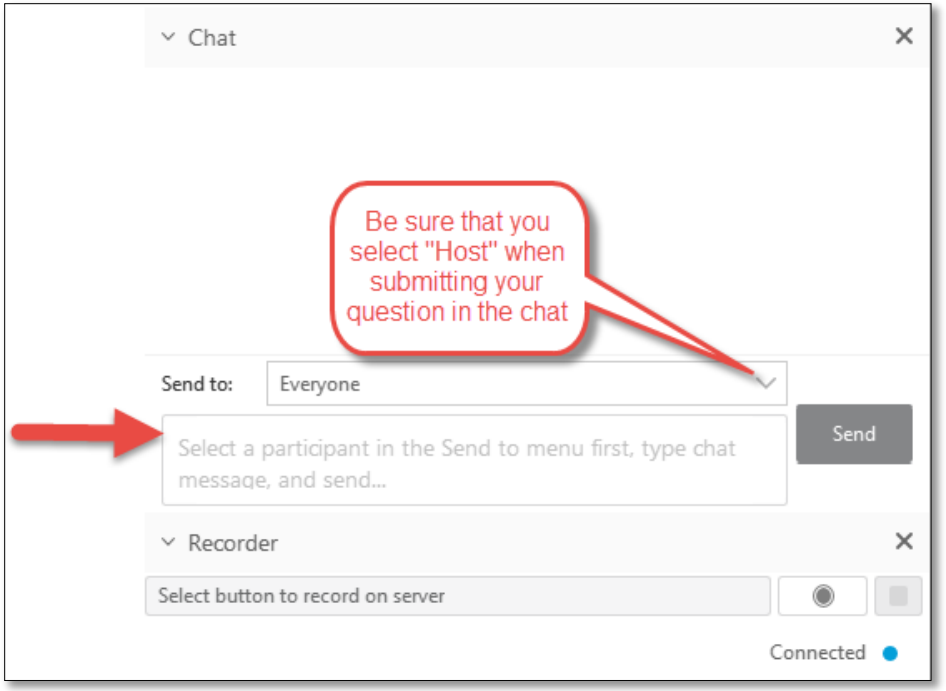
Current proposals for change include:

- Dynamic smoke studies required as part of semi-annual certification
- CAIs and CACIs re-categorized as Restricted-Access Barrier System (RABS), which require ISO class 7 buffer areas to quality for Category 2

Questions?

To ask the presenter a question, simply type it into the “chat” box within the WebEx tool bar.





Thank you for attending!

Presented by

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