The Role of Healthcare Engineers in USP 797 & 800 Compliance

Presented By : Tony LaMacchia & Jim Lewandowski

Class 1 Air

WHEN THOSE UNDER YOUR CARE REQUIRE THE CLEANEST AIR.

Tony LaMacchia & Jim Lewandowski of Class 1 Air, Inc.

- We have more than 20 years of experience in cleanroom design, compliance testing and certification to ISO 14644.
- CETA National Board of Testing Accredited.
- Registered Cleanroom Certification Professional for Sterile Compounding Facilities.
- National Sanitation Foundation NSF Accredited for Biological Safety Cabinet Testing.
- Consultants for USP 797 & USP 800: performing gap analysis, performance evaluation, design, development and review of facility plans.
- Develop User Requirement Specifications - consulting prior to design to meet the intent of the standard.
- Performed risk assessments and investigation of failures due to microbial contamination.
- Consulted on more than 100 sterile compounding facilities.

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Crossing Paths: History of Industry Related Organizations

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Learning and Performance Objectives

At the end of this session, you will be able to:

- Recall the history of regulations and guidance to understand today's sterile compounding facility requirements.
- Apply the appropriate standards and guidance to the sterile compounding facility.

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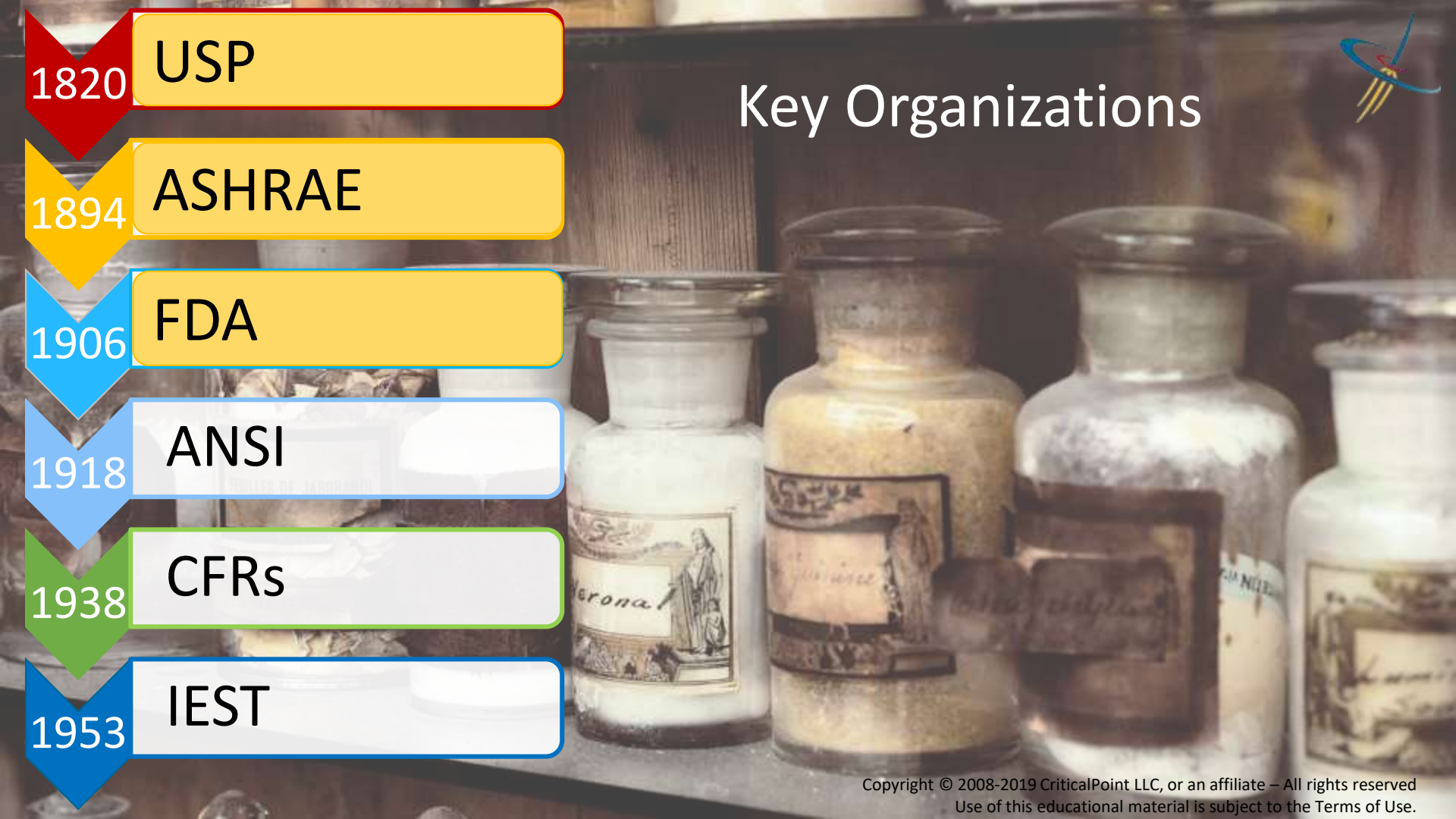
Key Organizations

- 1820 USP
- 1894 ASHRAE
- 1906 FDA
- 1918 ANSI
- 1938 CFRs
- 1953 IEST



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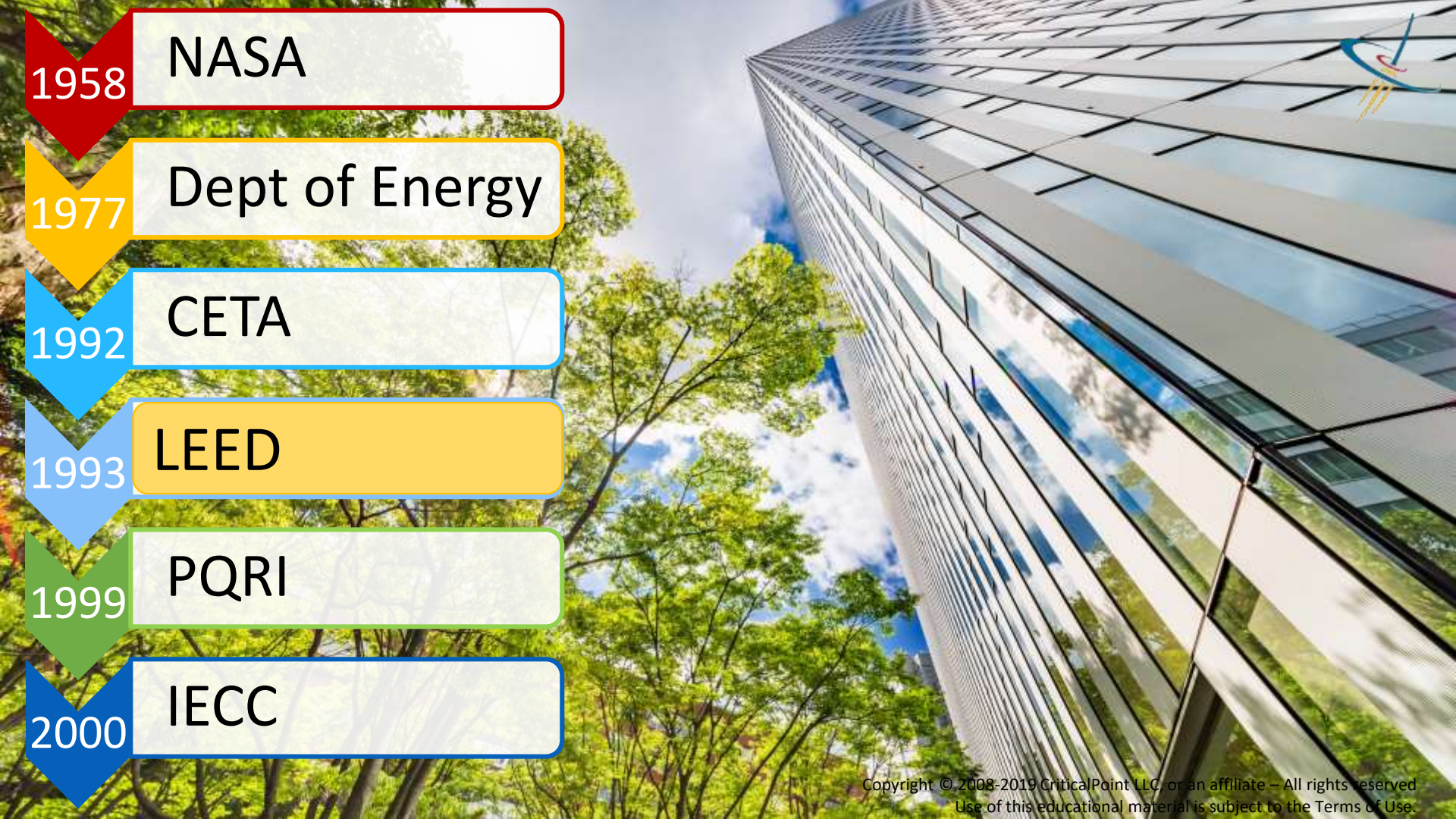

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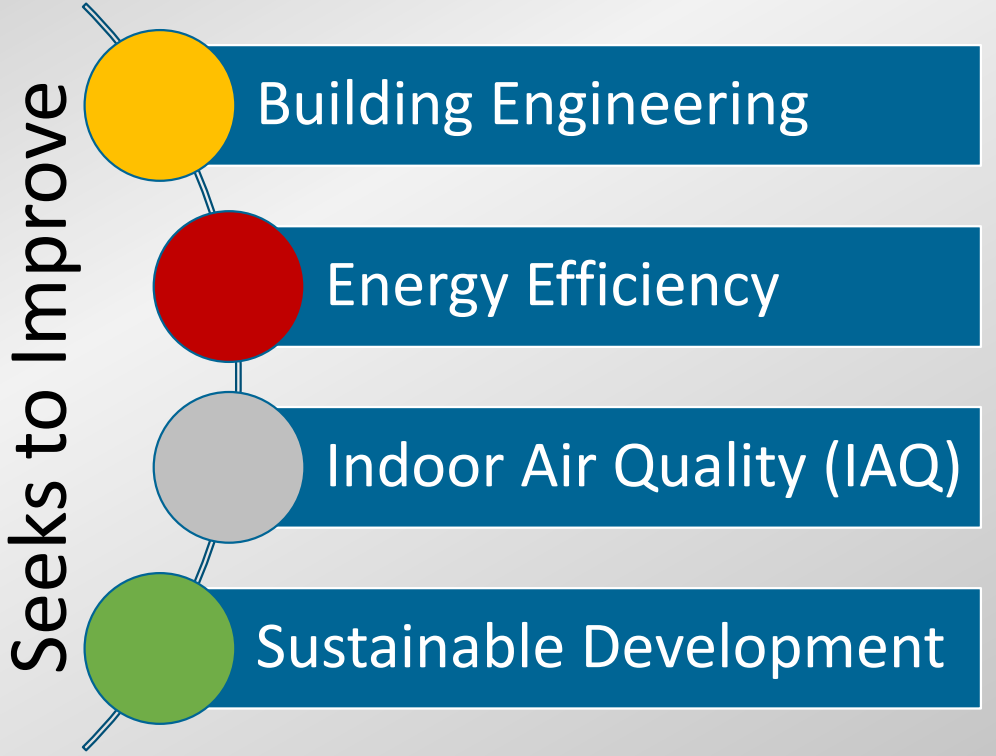
Overview of ASHRAE

- American Society of Heating, Refrigerating and Air-Conditioning Engineers
- Global association
- Develops and publishes technical standards



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Standard 55 - ASHRAE

Thermal Environment Conditions for Human Occupancy

- Focuses on realistic temperature and humidity ranges for a building space that provide comfort for the occupants
- Determined by…
  - Predicted mean vote (PMV) or an adaptive model and by determining a predicted percentage of the dissatisfied (PPD)
  - Other considerations like seasons, people's dress and what they may use to feel individually comfortable

The formulas to develop PMV and PPD in case studies are based on the general healthy adult population.

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What is the definition of acceptable IAQ?

"Air in which there are no known contaminants at harmful concentrations as determined by cognizant authorities and with which a substantial majority (80% or more) of the people exposed do not express dissatisfaction."

- ASHRAE S.62.1

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Standard 62.1 - ASHRAE

Ventilation for Acceptable IAQ

- 3 common methods
  1. Ventilation Rate Procedure (VRP)
  2. Indoor Air Quality Procedure (IAQP)
  3. Natural Ventilation Method (NVM)
- Can be used together or alone, goal is to achieve both optimal air quality and HVAC cost reduction

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Cleaner Air Technologies

- Minimum Efficiency Reporting Value (MERV) filters
- Reduced efficiency-HEPA filters called ASHRAE filters
- These can lessen the efficiency of the HVAC system, but improved design of these filters reduces pressure drops in the HVAC system, resulting in reduced overall energy consumption
- Most hospitals today are supplied by some sort of HEPA filtration.

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Putting It All Together

- As part of Standard 62.1, outside environment contaminates and biological levels are evaluated and investigated to determine acceptable ventilation and IAQ.
- The goal of is too achieve ***comfort*** not ***health quality***, while still minimizing adverse health effects.
- This standard has been code enforceable since 2001 and its concepts/requirements must be designed into a space within LEED technology.

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Standard 189.1 - ASHRAE

The Design of High Performance "Green Buildings"

- Net Zero Buildings produce as much energy as it uses, reducing energy costs to near "zero"
- Constructing solar energy to substitute energy use or other renewable resources to substitute energy
- "Replacing" what is used by adding live plants in and on buildings

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Overview of LEED

- Leadership in Energy and Environmental Design
- Voluntary Green Building Certification Program
- Sets environmentally responsible systems for design, construction, operation and maintenance
- Provides various accreditations for industry professionals

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Goals of LEED

Cost savings

Reduce energy consumption

Reduce water usage

Reduce impact on the environment

Efficiency by design and construction

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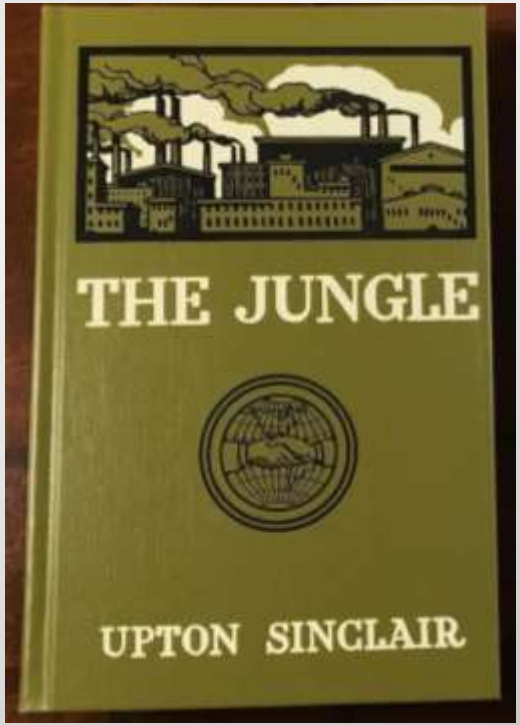
Overview of the FDA

- Food and Drug Administration formed from the Pure Food and Drug Act
  - Still applies as an enforcement for the standard of strength, quality or purity of a product
- Ensures that products available to the public are honestly, accurately and informatively represented
- Provides information to health industries by releasing ***guidelines***



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Overview of U.S. Pharmacopeia (USP)

- Founded because of lack of uniformity in medical practices
- 1888 the 1st National Formulary (NF) was published to standardize compounded drugs
- Non-profit organization recognized as an international standard
- The Food and Drug Act mandates that all drugs meet strength, quality and purity stipulated in the USP-NF

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USP Chapters <797> and <800>

- Design and engineering controls are a critical piece of the bigger sterile compounding puzzle
  - Contain some specific criteria for design parameters
  - General information on fit and finish
  - Some aspects are left up to the pharmacy, such as the location of the sink (2018 Proposed Version of <797>)
- Secondary Engineering Controls (SEC) are built using other normative references such as IEST, ISO, and ANSI.

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USP's Relationships

FDA	• No role in enforcing the USP standards • Liaisons to USP Expert Committees
State Boards of Pharmacy	• Responsibility of enforcing USP Chapter <797> and <800>
Accrediting bodies	• Reference USP Chapters

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What do Air Change Rates accomplish?

- Ventilation of Volatile Organic Compounds (VOCs)
- Hazardous and Biological Containment
- Dilution of Carbon Monoxide (CO), Carbon Dioxide (CO2)
- Particulate control via filtration

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Approximate Ventilation Design

General Environment	ACPH
Business Office	6 to 8
Laboratory	6 to 12
Restaurant Dining	8 to 10
Computer Rooms	10 to 12
Gas Station Restrooms	10 to 12
Operating Rooms	15 to 25
Parking Garages	15 to 30

Table adapted from ASHRAE 62.1-2001 and 2016

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USP Design (2018 Proposed Revisions)

USP Environment	Air Changes per Hour
ISO 7	≥ 30 (15 minimum from HVAC)
ISO 8	≥ 20 (15 minimum from HVAC)
C-SCA	≥ 12 (exhaust)
HD Storage	≥ 12 (exhaust)
SCA	No requirement

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Cleanroom Suite Energy Concerns

- Use and “waste” large amounts of energy
- MUST be within operating conditions as designed
- New energy models for spatial designs cannot work due to the nature of the design and what the state of control requires

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What's Best for Patients and Personnel

- The sterile compounding pharmacy and its operating budget require more attention to ensure safety.
  - Patient = USP <797>
  - Personnel = USP <800>
- Both chapters are enforceable including the engineering control design specifications.
- General facility areas can follow new energy technology, but pharmacy must follow USP Chapters <797> and <800> for design compliance.

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Today…

2004
- January 1, USP <797> first published
- NIOSH Alert published

2008
- USP Chapter <797> revised, new standard effective June 2008

2011
- 1st CriticalPoint <797> Compliance Survey, annually thereafter

2012
- CDC & CMS recognize USP <797>
- NECC tragedy 78 deaths, 778 affected

2013
- The Drug Quality and Security Act becomes law – 503A/503B

2014
- FDA Guidance to 503B Pharmacies

2017
- Several pharmacists sentenced to prison
- USP 800 is delayed until Dec 1, 2019

2018
- FDA issues updated Guidance for 503B

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Evidence of Damage: Pew Charitable Trusts (continued)


THE PEW CHARITABLE TRUSTS

SEARCH

MENU

The Pew Charitable Trusts / Research & Analysis / National Assessment of State Oversight of Sterile Drug Compounding

REPORT

National Assessment of State Oversight of Sterile Drug Compounding

DOWNLOADS

February 23, 2016 | Drug Safety Project

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Evidence of Damage: Pew Charitable Trusts (continued)

- In 2015 Pew published the National Assessment of State Oversight of Sterile Drug Compounding
  - The Pew Trusts found that only 30% of states (13 of 43 that responded) require sterile compounding pharmacies to report serious adverse events.
  - Contamination of sterile preparations was the *most common compounding error*, though others were the result of pharmacists' and technicians' miscalculations and mistakes in filling prescriptions.

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NECC Summary

New England Compounding Center (NECC) Meningitis Outbreak (updated)	
Date	September 21, 2012 to present since patients are still suffering
Location	USA (20 States)
Cause	Fungal meningitis contamination of steroid medication
Injuries	778 total case count; 384 meningitis and spinal infection; 7 stroke; 325 paraspinal/spinal infection; 33 peripheral joint infection; 2 spinal and peripheral joint; some patients recovering from the meningitis are falling ill again. sufferers of the new infection are now coping with epidural abscesses and infections near the injection site.
Deaths	78
Judicial	Cadden sentenced to 9 years, Chin sentenced to 8 years Court requires restitution from both

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Year	State	Description of Adverse Event
2012	MA	Some 753 patients had fungal meningitis/other infections after receiving steroid injections contaminated with fungus. 68 died.
2013	TN	26 patients reported adverse events, including skin abscesses, after receiving injections of contaminated compounded methylprednisolone acetate.
2013	TX	15 patients developed bacterial bloodstream infections (2 died) after receiving infusions of compounded CaGluc contaminated with bacteria.
2013	GA	5 patients had endophthalmitis after receiving ophthalmic injections of repackaged Avastin.
2013	TX	6 patients had AEs, including fever/“flu-like” symptoms, after receiving injections of compounded methyl cobalamin.
2014	FL	At least 37 patients had serious AEs after receiving intravitreal inj. of repackaged Avastin (bevacizumab) or Lucentis (ranibizumab).

Adapted from: "Toward Better-Quality Compounded Drugs- An Update from the FDA," by Woodcock, Janet, and Dohm, Julie, 2017, *New England Journal of Medicine*, 377, 2511.

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Year	State	Description of Adverse Event
2014	Several	FDA received reports of AEs associated with CSPs that should have contained L-citrulline but contained different active ingredient. Sub potent L-citrulline in persons with certain urea-cycle defects can lead to high ammonia levels, which is serious and potentially life-threatening.
2014	IN	Several neonates experienced over sedation after receiving super potent compounded midazolam.
2014	TX	1 patient had severe flushing, stinging, & dizziness after infusion of compounded Mg SO_4. Patient's blood had ⬆ levels of magnesium.
2015	FL	FDA received several reports of AEs possibly associated with compounded vitamin D3 capsules that were approximately 300% more potent than expected.
2015	TX	A patient died after using a compounded topical anesthetic cream. A court heard evidence that the cause of death was ketamine and cyclobenzaprine toxicity.

Adapted from: "Toward Better-Quality Compounded Drugs- An Update from the FDA," by Woodcock, Janet, and Dohm, Julie, 2017, *New England Journal of Medicine*, 377, 2511.

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Year	State	Description of Adverse Event
2015	AL	5 patients who received betamethasone sodium phosphate and betamethasone acetate developed redness at the injection site, swelling, and pain. 3 hospitalized and blood cultures positive for staphylococcus aureus.
2016	IN	3 infants had serious AEs after receiving compounded morphine sulfate that was nearly 2500% more potent as it should have been.
2016	SD	7 patients had thyrotoxicosis after receiving super potent compounded oral liothyronine products. Three (3) hospitalized in an ICU.
2017	TX	At least 43 patients had AEs including vision loss after receiving compounded steroid-and-antibiotic eye injections.
2017	CA	2 patients had hypersensitivity reactions, and 1 died, after receiving an IV medication prepared with a compounded curcumin product.

Adapted from: "Toward Better-Quality Compounded Drugs- An Update from the FDA," by Woodcock, Janet, and Dohm, Julie, 2017, *New England Journal of Medicine*, 377, 2511.

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Deaths irrelevant?

Really?

Evidence of dozens of deaths 'irrelevant' for meningitis jury, defendants argue

GLOBE STAFF/FILE

In this 2012 photo, federal agents are seen in NECC offices in Framingham.

By Maria Cramer | GLOBE STAFF MAY 01, 2018

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What went wrong? …a failure of leadership

- Inadequate, ineffective, and corrupt oversight
- Education, competency and proficiency
  - Untrained employees
  - Lack of competency and proficiency evaluation systems
- Poor/incomplete investigations and remediation
- Improper use of sterilizing equipment
- Lack of SOPs

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Insanitary Conditions at Compounding Facilities

- FDA published this draft guidance initially in August 2016; latest revision September 2018
- Applies to both 503A and 503B
- A drug is deemed to be adulterated “if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health.”
- Drug products prepared, packed, or held under insanitary conditions could become contaminated and cause serious adverse events, including death.

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FDA Actions 2012 to 2018

- 34 draft and final guidance on compliance policies
- 4 regulations addressing products that can/cannot be compounded
- 2 draft memorandum of understanding (MOU) with the states addressing certain distributions of compounded drugs
- Almost 500 inspections of 503A and 503B facilities between passage of DQSA and the end of fiscal year 2017
- More than 150 recalls of compounded drugs
- More than 180 warning letters issued
- 70+ referral letters to state regulatory authorities for follow up

Examining Implementation of The Compounding Quality Act. Testimony of Scott Gottlieb, M.D., Commissioner of Food and Drugs Before the Subcommittee On Health, House Committee On Energy And Commerce. January 30, 2018 https://www.fda.gov/NewsEvents/Testimony/ucm594297.htm

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USP Chapters Timeline

Note: The current version of General Chapters <795> and <797> published in USP-NF are official.

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Key Takeaways

- The ***easy way*** is using USP chapters on compounding!
- Illinois requires compliance; Wisconsin's regulations were meant to "align with" 797
- Pharmacy keeps choosing the hard way by not complying with these MINIMUM standards!
- If pharmacy does not comply, the FDA will force a path down a much harder road!

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Engineering and Facility Terminology versus Pharmacy Terminology

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Learning and Performance Objectives

At the conclusion of this session, you will be able to:

- Identify the terms that are shared and recognize the similarities and differences in the meaning of those terms.
- Explain why a pharmacy cleanroom needs more air changes per hour (ACPH) than other locations in the hospital.
- Discuss why USP cannot and should not rely on new energy conservation technologies.
- Describe why the EPA does not supersede the FDA for patient healthcare safety.

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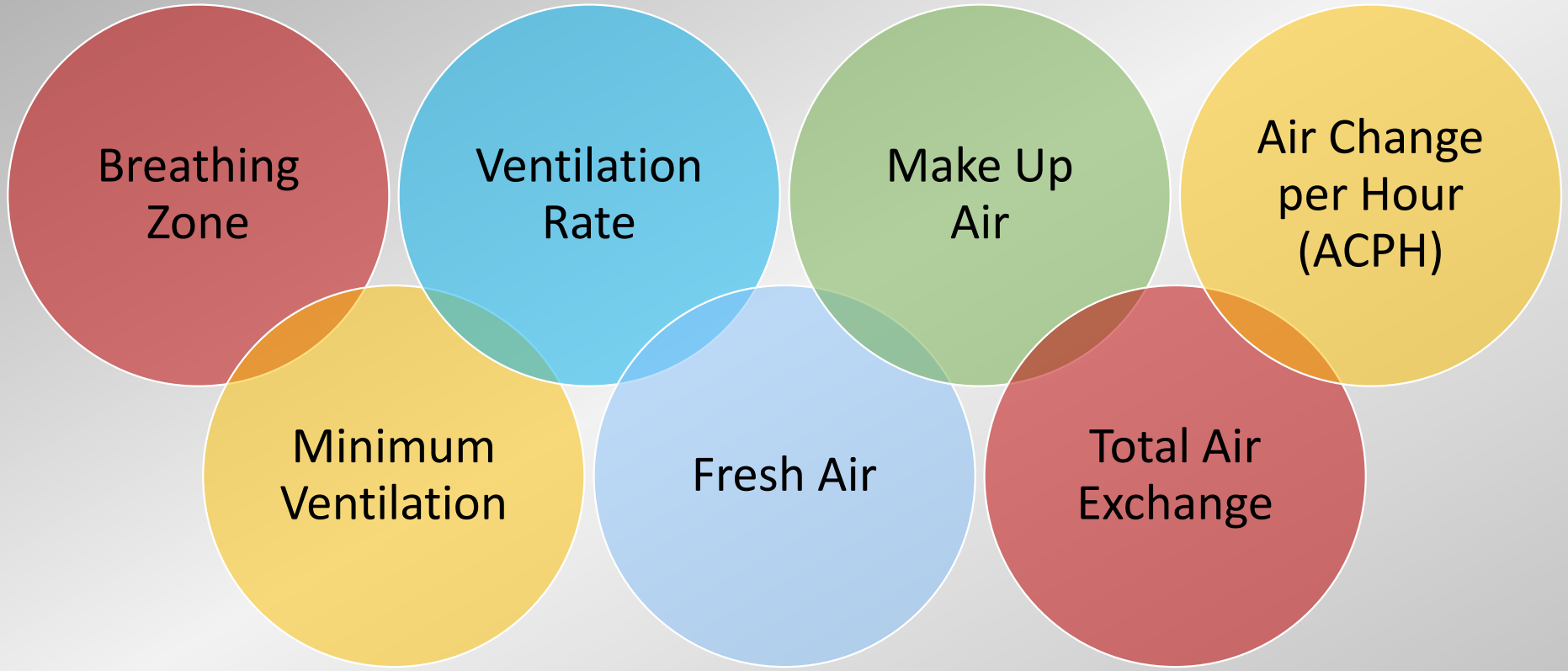

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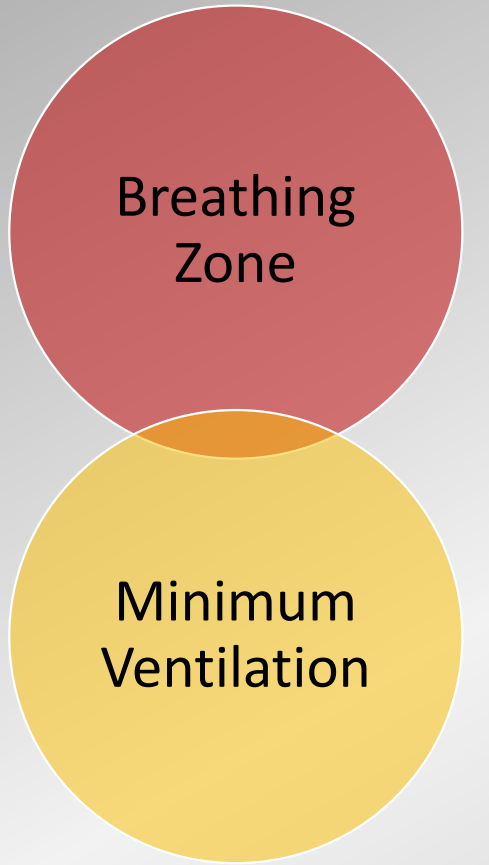

The region within an occupied space between 36” to 72” above the floor and more than 24” from walls or fixed AC equipment

The lowest indoor air quality (IAQ) that would be acceptable for human occupancy as intended for comfort and minimizing potential adverse health effects

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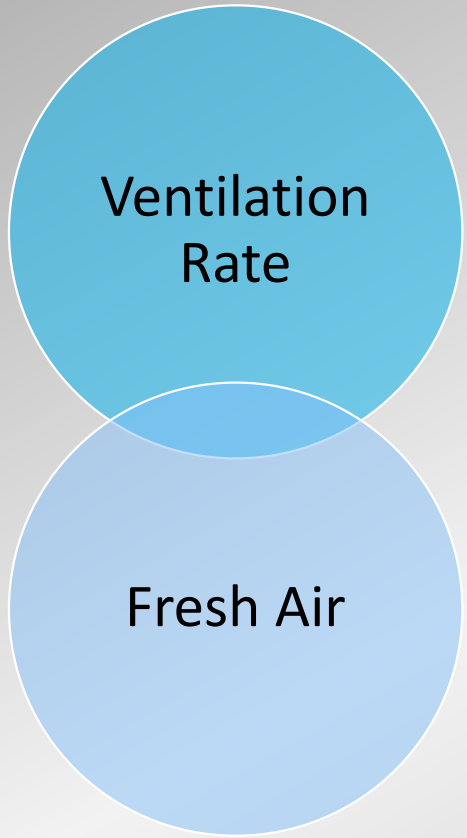

The flow of outdoor air into a building per unit of time; often expressed in cubic feet per minute (CFM)

Provides oxygen, pressurizes a building and increases IAQ by diluting polluted or stale air

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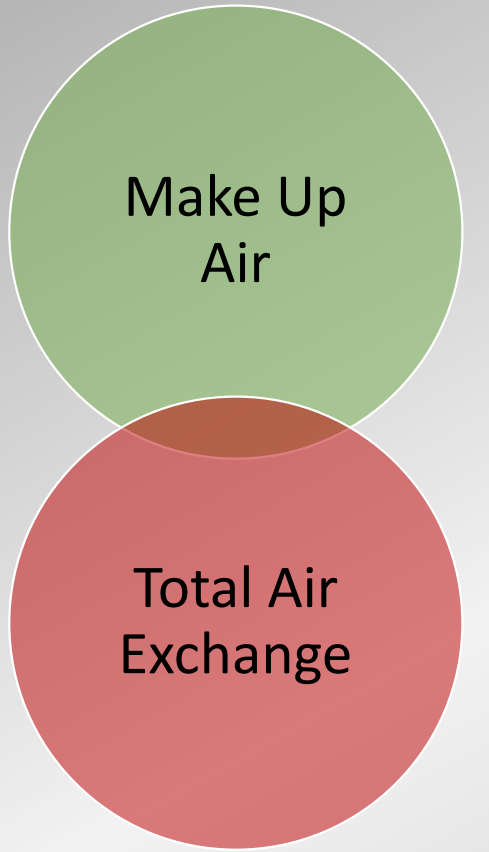

The compensated rate approximately equal to airflow lost through ventilation

The rate at which outdoor air replaces indoor air within a space; essential parameter in determining IAQ

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Air Change per Hour (ACPH)

The rate of measured air volume added or removed from any given space in the span of 60 minutes

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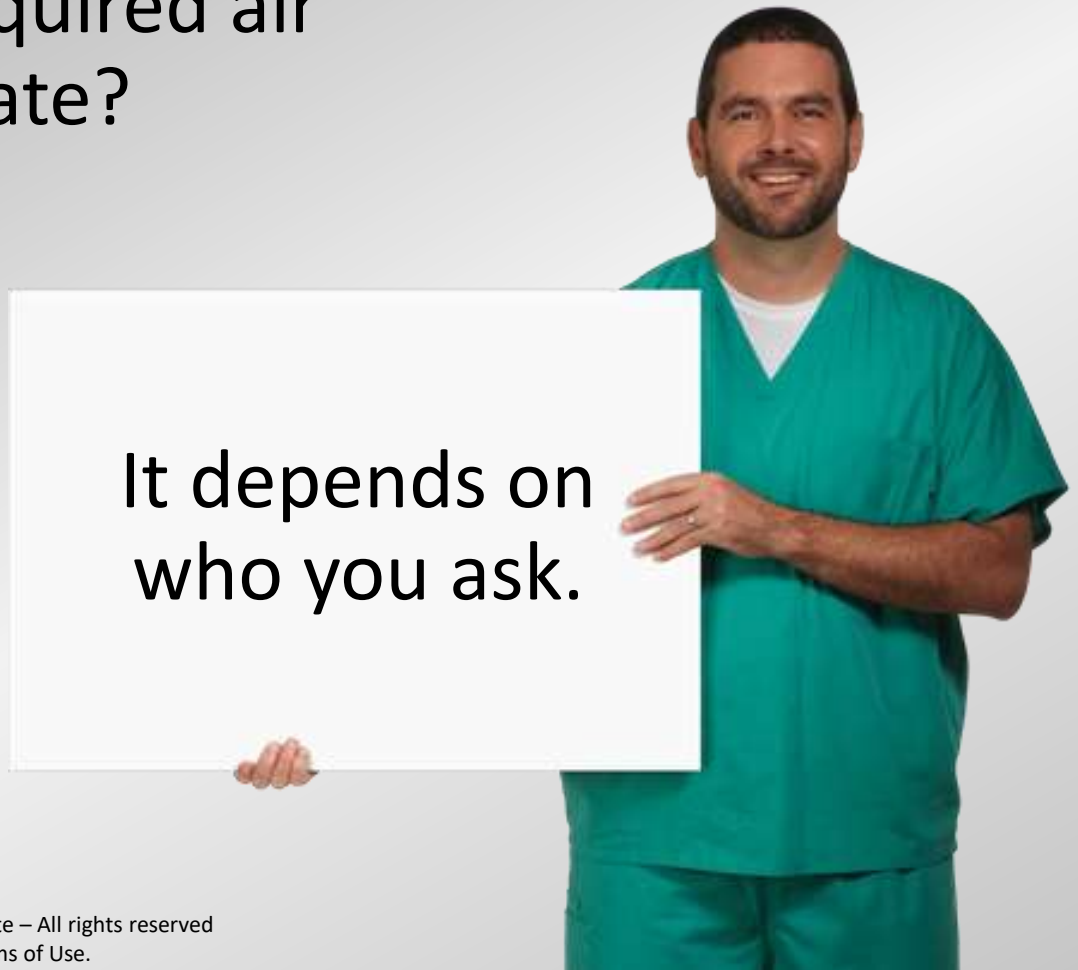
What is the required air change rate?



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Ventilation of a General Space

Ventilation

Referred to as supply (provide oxygen) and exhaust (dilute/remove pollutants) to a space that removes stale air

Recirculation

Regulates thermal conditioning but does not replenish oxygen and should not be used towards needed ventilation

Must be a balance between ventilation and recirculation for IAQ and energy conservation

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Air Change Rates According to ASHRAE

- Provides a balance of comfort and replenishing air, but still leaves behind some air that is not exchanged by the HVAC system
- Can mean that air volume is added or removed in a space for room exchange
- Often a mix of the two are designed within a space for general occupancy

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Air Change Rates According to ASHRAE (continued)

- ACH are designed at individual lower rates for each room.
  - 5 to 20 CFM/person which is 0.26 ACH to 1.04 ACH for a 12’x12’ room
- Total air exchange rates for building-to-occupant ratio is used to determine sufficient thermal conditioning and adequate IAQ.
- Multiple HVAC systems (HVAC zones) help facilitate total building air exchange and individual zone spaces for heating and cooling in large buildings.

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ACPH According to USP <797>

- HEPA filtration at 99.997% minimum efficiency is delivered through supply air
- Room is not uniform or perfectly mixed however
- Intent is that the room itself exchanges completely at the given ACPH rate from the HVAC system
- Microorganisms and specific particle sizes are reduced or removed from the environment

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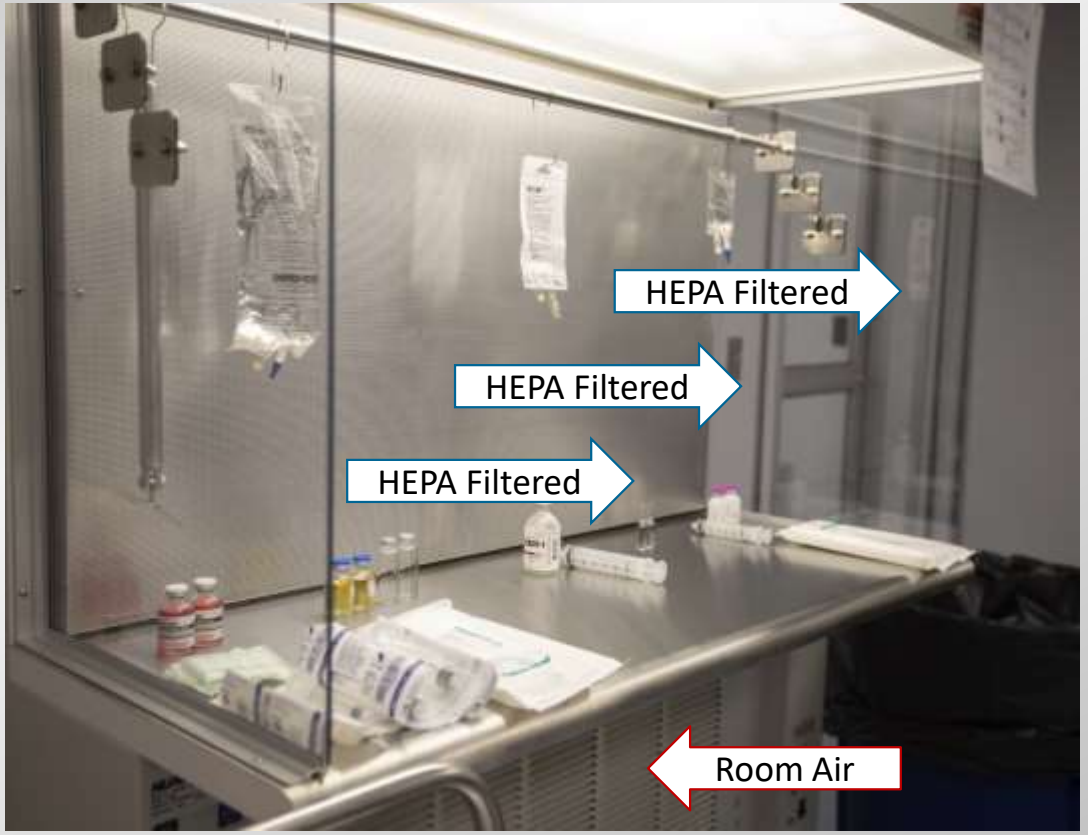
ACPH from the PEC

- Like HVAC recirculation, Primary Engineering Controls (PECs) can contribute to ACPH rates
- The intake of the PEC draws and capture contaminates while providing continuous HEPA filtered air



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ACPH From the Room

- Secondary Engineering Controls (SECs) rely on balance of HVAC systems for proper supply, exhaust and door-to-door pressure
- Must maintaining consistent and desirable temperature and humidity ranges

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HVAC for Cleanroom Suites

- ***Should*** have an individual HVAC zone considered operationally separate from the rest of the hospital HVAC systems
- ***Must*** run continuously for both supply and exhaust to maintain constant state of control

Energy efficiency is not priority!

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Operational Characteristics of a Cleanroom

How does a cleanroom work?

Removes pollutants, particles, and contaminants from outside air

What is a cleanroom concept?

The cleanroom design and it's operating parameters

Why is cleanroom certification performed?

To confirm that the parameters of the cleanroom concept is working

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Operational Considerations

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Design and Placement Considerations

- Improve effectiveness to sweep the contaminates out of the room
- Achieve top/down effect
- Grid placements of the terminal HEPA filters
- Exhaust/return grille placement

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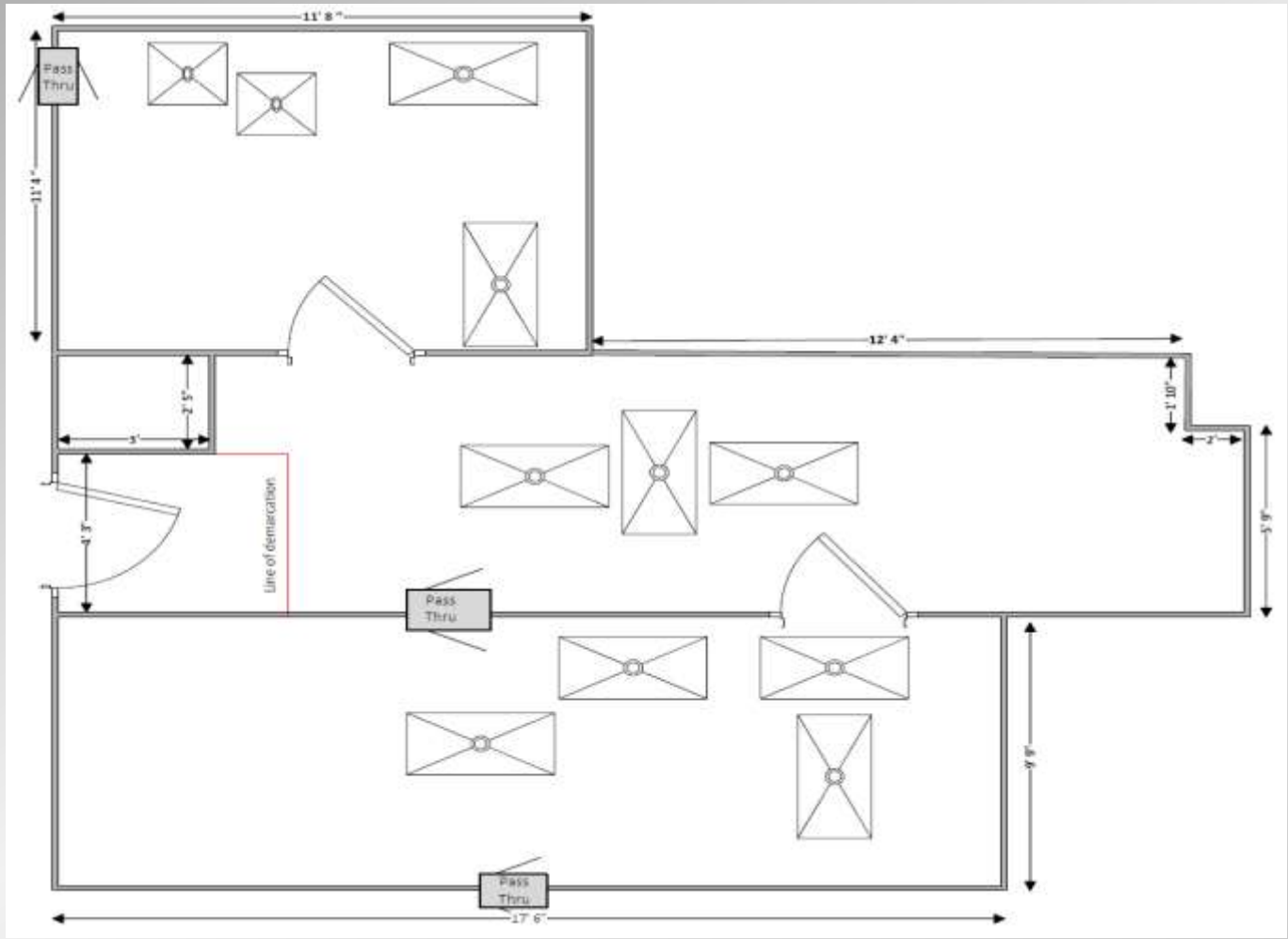

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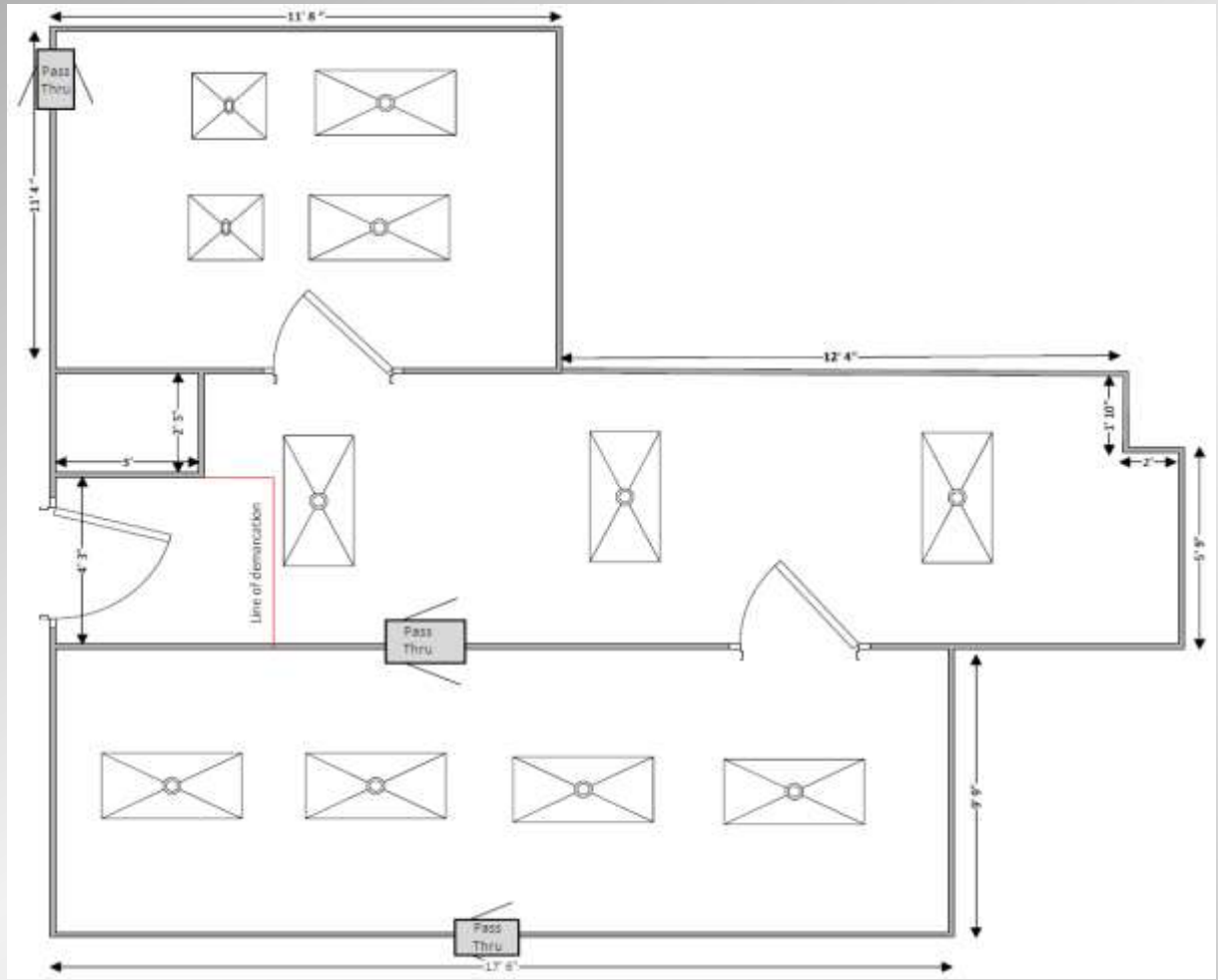

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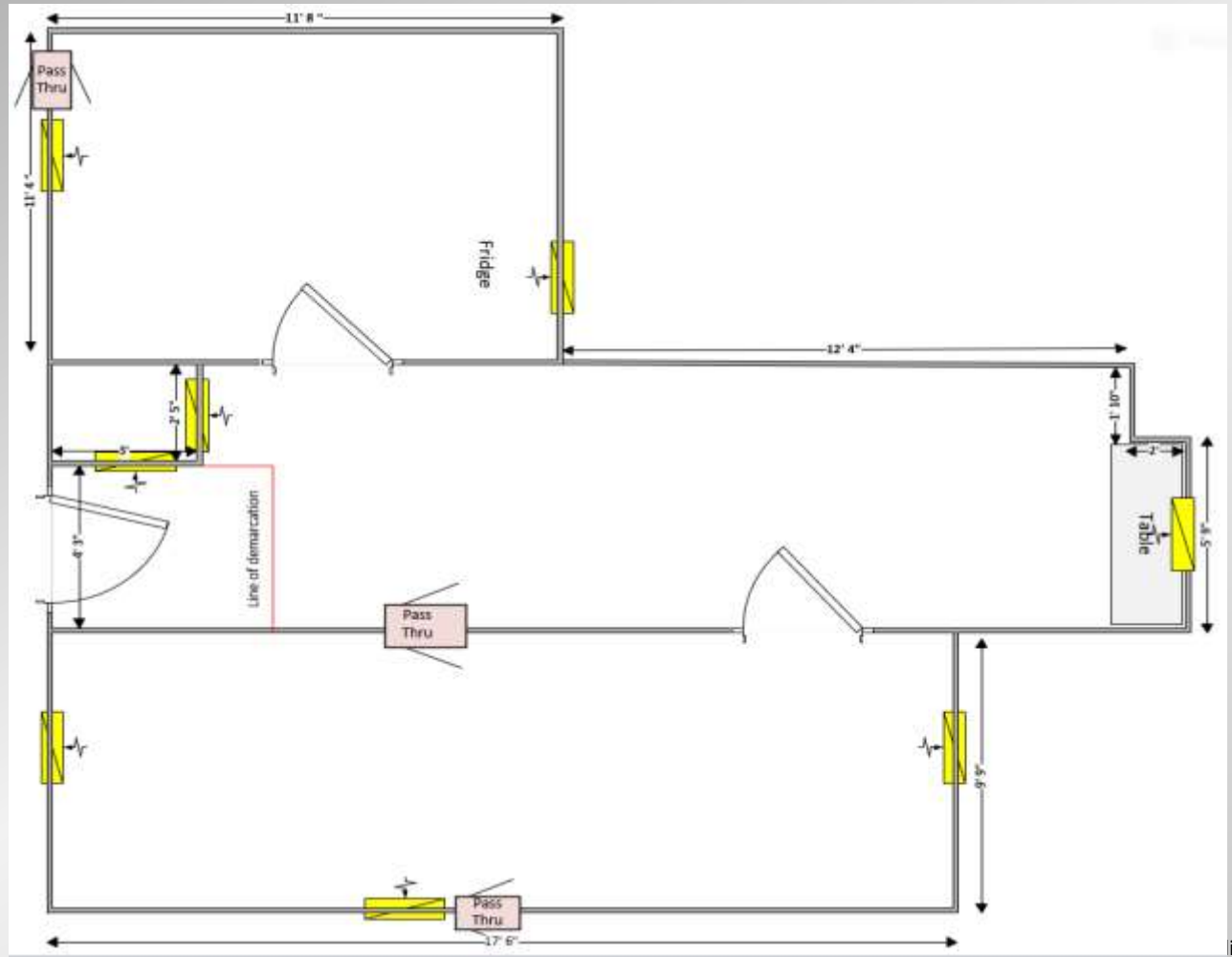

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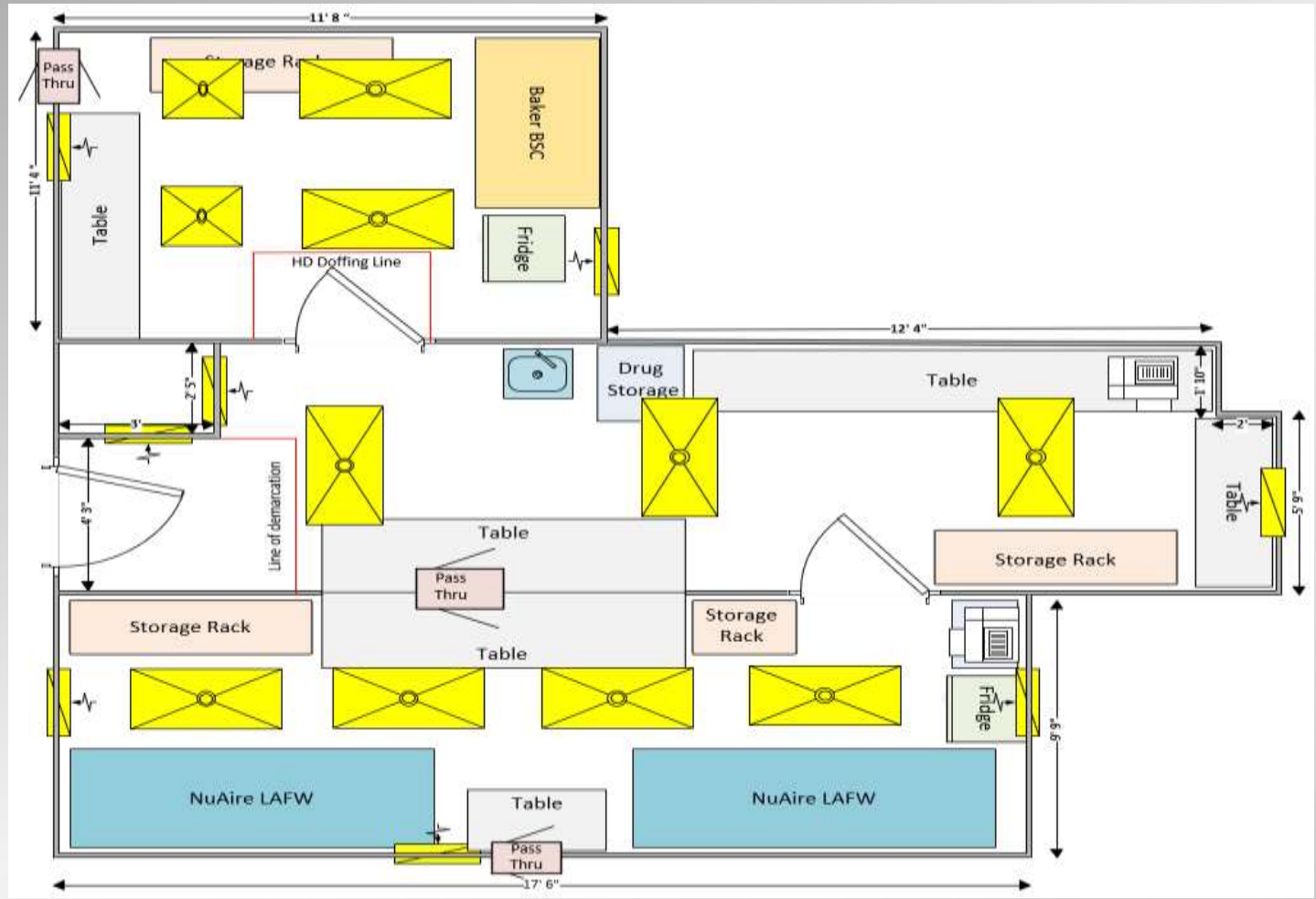

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We Need ***MORE*** than the Minimum

- Engineering controls (EC) that are designed to the minimum standard:
  - Operate at minimum functionality
  - Are unable to properly recover during normal dynamic conditions
  - Cannot overcome poor personnel behavior and garbing practices
- Setting up a sterile compounding facility with the minimum design requirements is setting the operation up for failure

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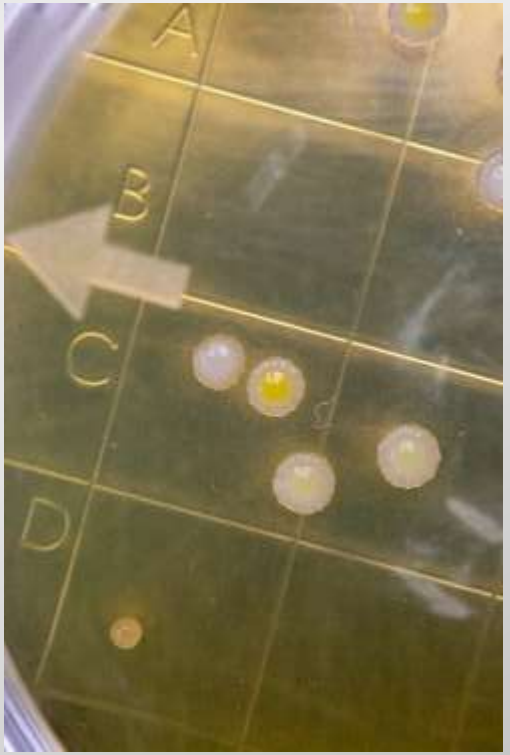
Designing to a Higher Standard

- ECs that are designed at higher values:
  - Exchange the room's condition faster through HEPA filtered air
  - Sweep out contaminates efficiently through proper room balance and supply-to-exhaust ratio
  - Work more effectively to remove microbial contaminates
- Maintaining a microbial state of control is one of the biggest concerns



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Establishing Design Criteria for Certification

- USP <797> ***Minimum*** Control Requirements
  - May not be enough for your rooms!
  - Chapter gives broad minimum requirements, ***not*** specific for individual facilities
  - Does not give the full compliance “story”

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Establishing Design Criteria for Certification

- Modified USP <797> Control Criteria
  - Use viable environmental monitoring trends to help determine air change rates
  - Consider exhaust/pressure values to determine air change rates
  - Activity level, equipment and staffing affect the state of control

Regulatory compliance versus operational compliance!

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Design Criteria

USP <797> ***Minimum***	USP <797> ***Modified***

• ISO 7 SECs
  • ≥ 30 ACPH
  • At least 15 ACPH from the room
• ISO 8 Ante-room: ≥ 20 ACPH
• Non-HD Pressures: ≥ 0.020” w.c.
• HD Pressures: Negative 0.010 to 0.030” w.c.
	• ISO 7 SECs
	  • ≥ 45 ACPH
	  • At least 30 ACPH from the room
	• ISO 8 Ante-room: ≥ 30 ACPH
	• Non-HD Pressures: ≥ 0.030” w.c.

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Regulatory Compliance vs Operational Compliance

- Achieving USP <797> and <800> compliance is important, but they are the ***minimum*** requirements
- Operational compliance is key!
  - Need to know that the design can handle the activity of the sterile compounding operation
- Planning for more than the minimum standards will ensure operational compliance

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How are engineering controls verified?

- Initial Certification or commissioning of the new suite
  - Airflow smoke pattern testing
  - Viable environmental monitoring
  - Non-viable environmental monitoring
  - State of control is only monitored and verified
  - Recommend testing at 3 occupancy states
  - As built, At rest and Dynamic

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Occupancy State Definitions

As Built	Complete and ready for operation, with all services connected and functional but without production equipment or operating personnel.
At Rest	Complete, with all services functioning and with equipment installed and operable and operating, as specified but without personnel in the cleanroom suite
Operational (Dynamic)	Normal operation, with all services functioning and with equipment and personnel performing simulated work functions

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Why is occupancy state verification important?

- Ensure ECs are performing to expected results during the final occupancy state; ***dynamic conditions***
- Testing systematic stages can determine if EC parameter settings will be adequate for desired operational function

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How soon can compounding begin after verification?

- Performing verification, commissioning and certification requires careful planning
- Viable testing results take the most time
- Expect testing to take 3 to 4 weeks for a fully compliant and commissioned cleanroom suite

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Energy Conservation

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Cleanroom suites require constant control

- Dedicated and total exhaust outlets waste temperature, Rh and energy efforts
- Seasonal changes affect cleanroom suite state of control and HVAC components
- HVAC design should anticipate control excursions

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Energy Conservation: HVAC System

- Lowered AHU pressure drop through efficient filtration
- Lessoned sharp angles in duct systems
- Tightly sealed ductwork
- Direct Current (DC) Fan powered HEPA Filter Units (FFUs)
- Lessened pressure load reduces HVAC volts per hertz (V/Hz)
- General energy efficient HVAC system components
- Preventative maintenance schedules

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Energy Conservation: Cleanroom Suite

- Minimal room design size (ante-rooms)
- Reduce room leakage and loss
- Energy efficient lighting and appliances
- Energy efficient PECs
- Pharmacy ownership of garbing policies and training
- Personnel presence limitations
- Area clearance of return/exhaust grilles
- Cleaning and general housekeeping

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Applying the Proper Cleanroom Technology

Do

- Design according to USP to facilitate sterile compounding
- Ensure effectiveness and efficiency
- Follow any USP or FDA requirements to ensure patient safety

Don't

- Model after IAQ air balance theory or reduced parameters for energy and cost savings
- Follow EPA/ASHRAE for cleanroom suite design

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Summary

- Commissioning is essential to ensure proper performance.
- Personnel activity, garbing and increased workload affects the state of control.
- Poor contamination control practices, environmental conditions and changes in season can result in HEPA filter loading over time.

It’s not over engineering, it’s operational compliance!

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Engineering Controls used for Sterile Compounding

Sterile Compounding Boot Camp

criticalpoint

Learning and Performance Objectives

At the end of this session, you will be able to:

- Distinguish between 1° and 2° engineering controls (EC) used for nonhazardous and hazardous sterile compounding and discuss the requirements of each according to USP 797.
- Use knowledge about airflow to compound with proper aseptic technique using first air regardless of the type of primary engineering control.
- Describe the function of HEPA filters and the application of airflow principles to create a sterile compounding environment.
- Differentiate ISO Class 5, 7 and 8 work environments related to cleanliness and particulate counts.
- Identify and differentiate between tests performed during certification of 1° and 2° ECs.
- Integrate an understanding of "**state of control**" into the certification report for primary and secondary engineering controls.

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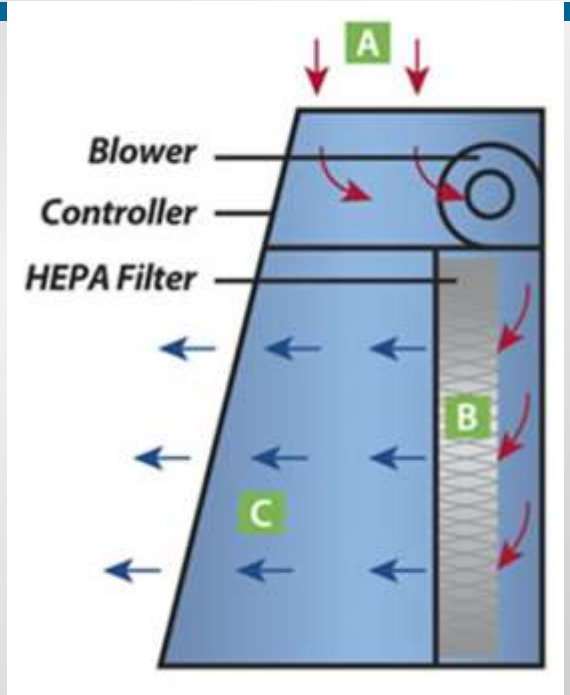
Engineering Controls for Sterile Compounding

Primary and Secondary Engineering controls employed in sterile compounding use ***Airflow*** through ***High Efficiency Particulate Air (HEPA) filters*** to create air of appropriate Cleanliness Classification

- Airflow
- Filtration
- Cleanliness Classification

Maintain a ***State of Control*** to obtain and confirm the ***Desired Outcome (Objective)***



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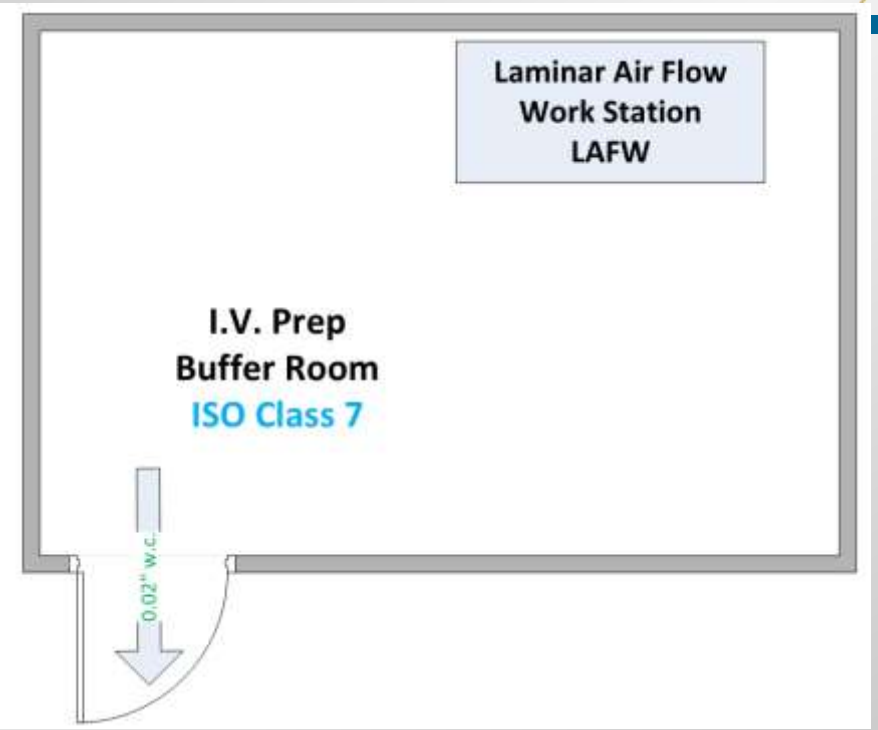
Definitions

- Primary Engineering Control relates to the point of use
- Secondary Engineering Control is facility design
- Positive Pressure
  - Net displacement of air *out* of the space
- Negative Pressure
  - Net displacement of air *into* the space



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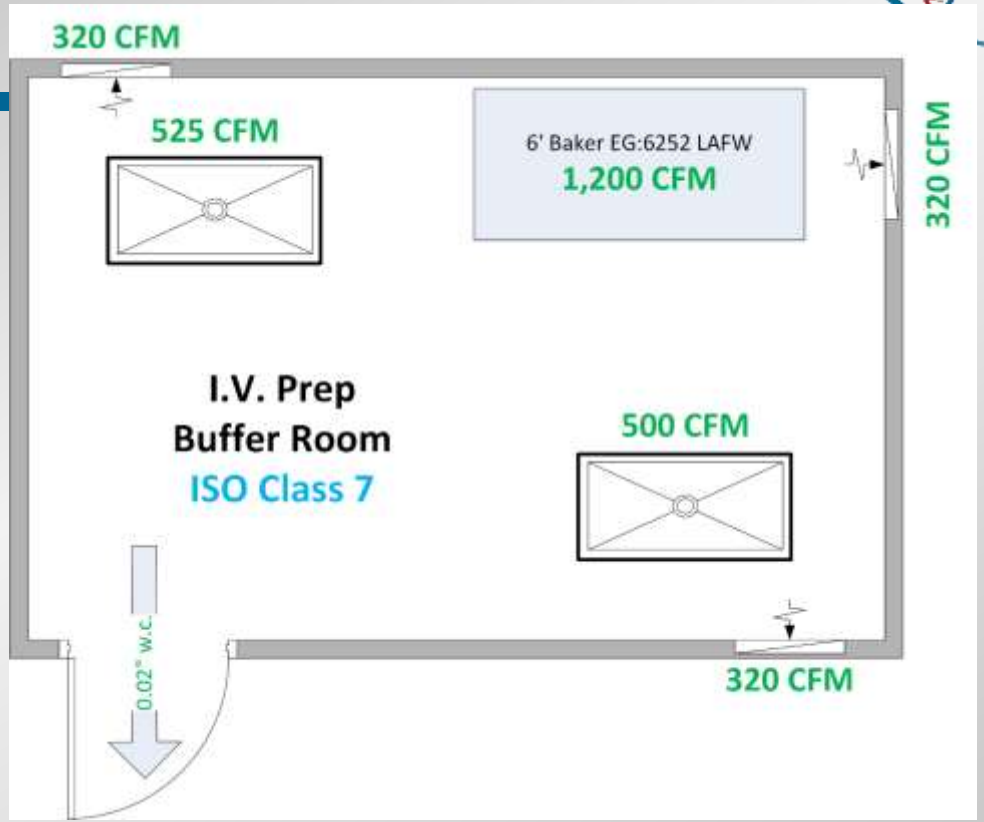
Definitions

- State of Control Points
  - Engineering issues that affect room performance (e.g., provide adequate HEPA filtered air to a cleanroom)
- Desired Outcomes
  - Objectives of state of control engineering criteria (e.g., maintain an ISO class 7 buffer room)



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Cleanliness Classification*

Class Name		Particle Count	
ISO Class	FS 209E	ISO m^3	FS 209E, ft^3
3	Class 1	35.2	1
4	Class 10	352	10
5	Class 100	3520	100
6	Class 1000	35,200	1000
7	Class 10,000	352,000	10,000
8	Class 100,000	3,520,000	100,000

*Classification of Particulate Matter in Room Air Limits are in particles 0.5 µm and larger per cubic meter (current ISO 14644-1) and cubic feet (former Federal Standard 209E) measured under dynamic operating conditions.

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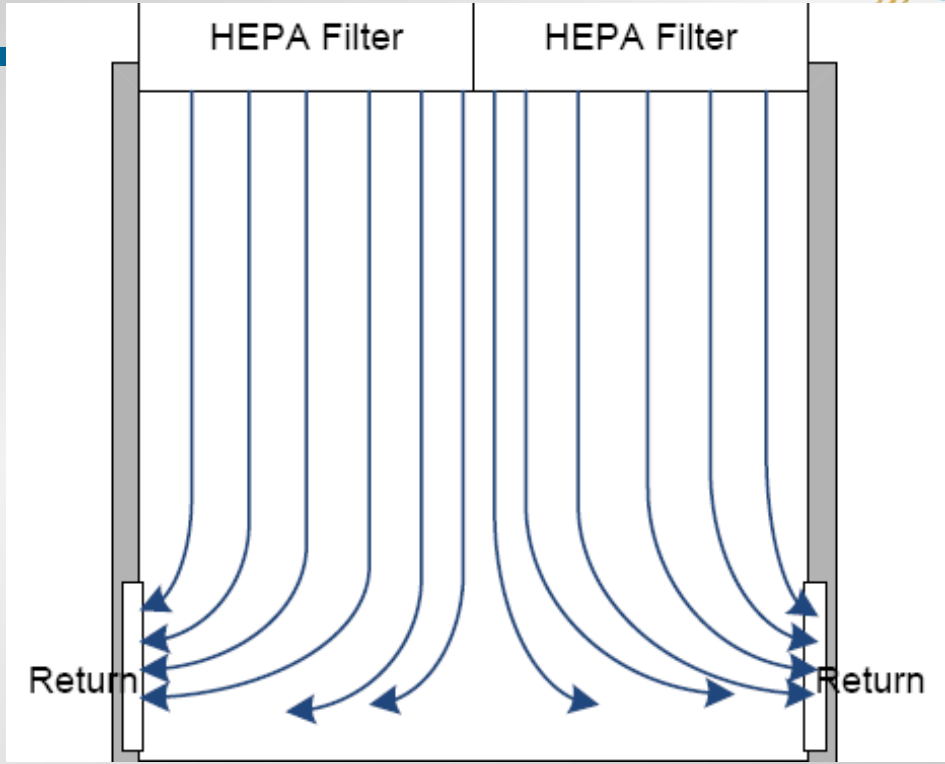
Airflow Definitions

- 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



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USP 797 Unidirectional Airflow Requirements

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

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Video of a smoke pattern test
being conducted as part of a new facility commissioning

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Primary Engineering Controls (PECs)

01

Laminar Air Flow Systems (LAFS)

- Laminar airflow workbenches or work stations
- Laminar air flow zones
- Biological Safety Cabinets (BSCs)

02

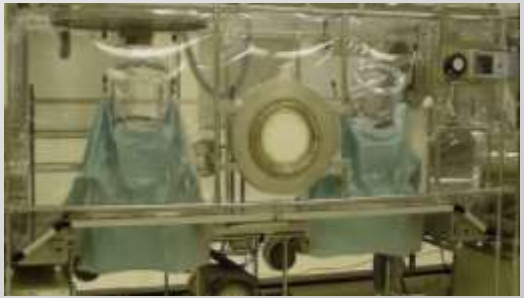
Restricted Access Barrier System (RABs)

- Compounding aseptic isolator (CAI)
- Compounding aseptic containment isolator (CACI)

03

Isolators

- Transfer ports
- Use sporicidal chemical decontamination
- Constant overpressure requirement



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LAFS: LAFWs

- Diffuser screens
- Cleaning
- Blower placement
- Horizontal vs. Vertical Flow

LAFS: BSCs

0
1

- A2 vs. B2
- Canopy connections
- Exhaust alarms
- Only source of exhaust

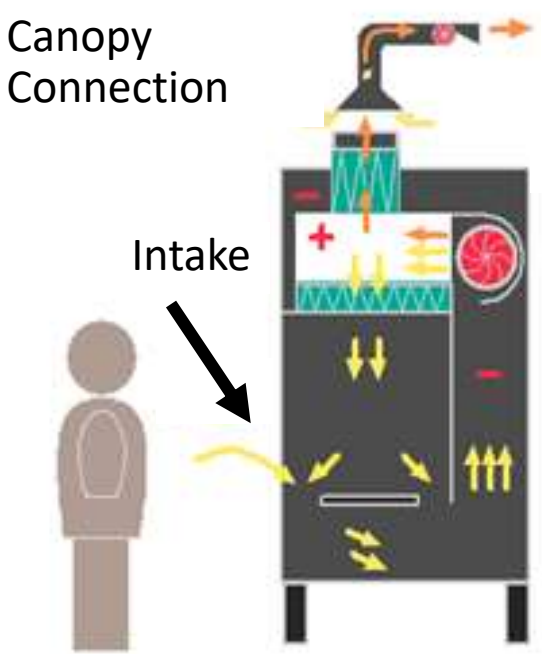
LAFS: BSCs (continued)

- Different types of Containment Primary Engineering Controls (C-PECs)
  - Class II, A2
  - Class II, B1
  - Class II, B2
  - Class III

C-PECs for Sterile HD Compounding:

Class II, A2

Class II Type A2 (A/B3) Airflow Schematic



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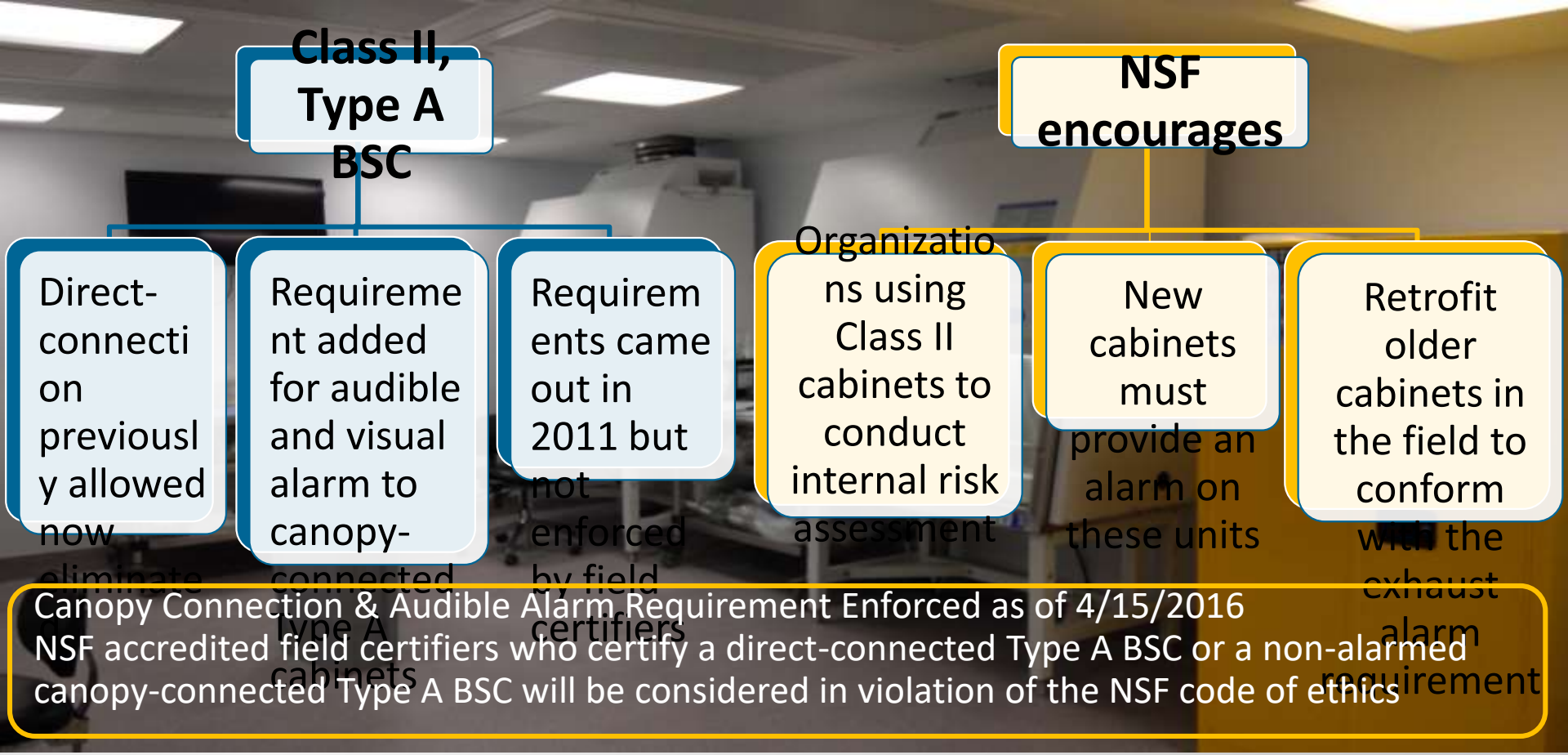

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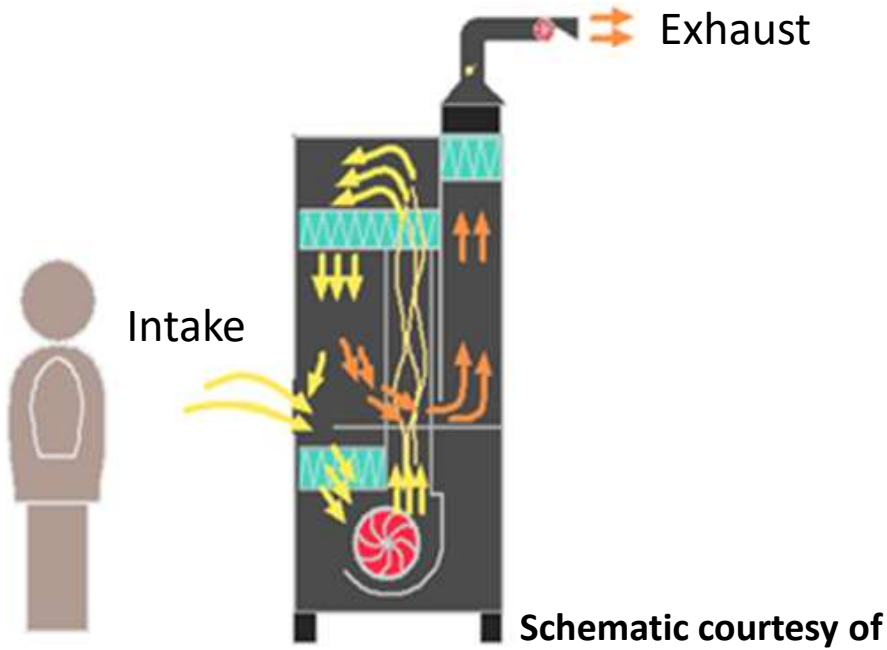
C-PECs for Sterile HD Compounding: *Class II, B1*

Class II Type B1 Airflow Schematic



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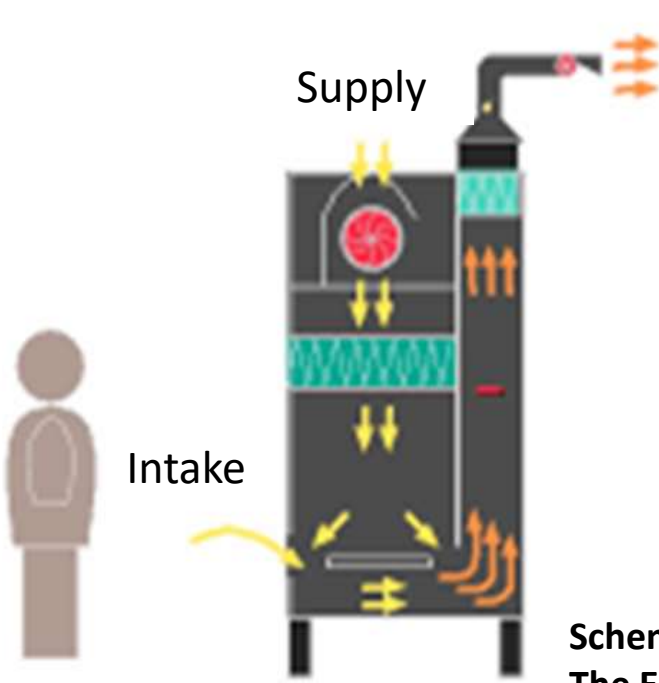
C-PECs for Sterile HD Compounding: *Class II, B2*

Class II Type B2 Airflow Schematic



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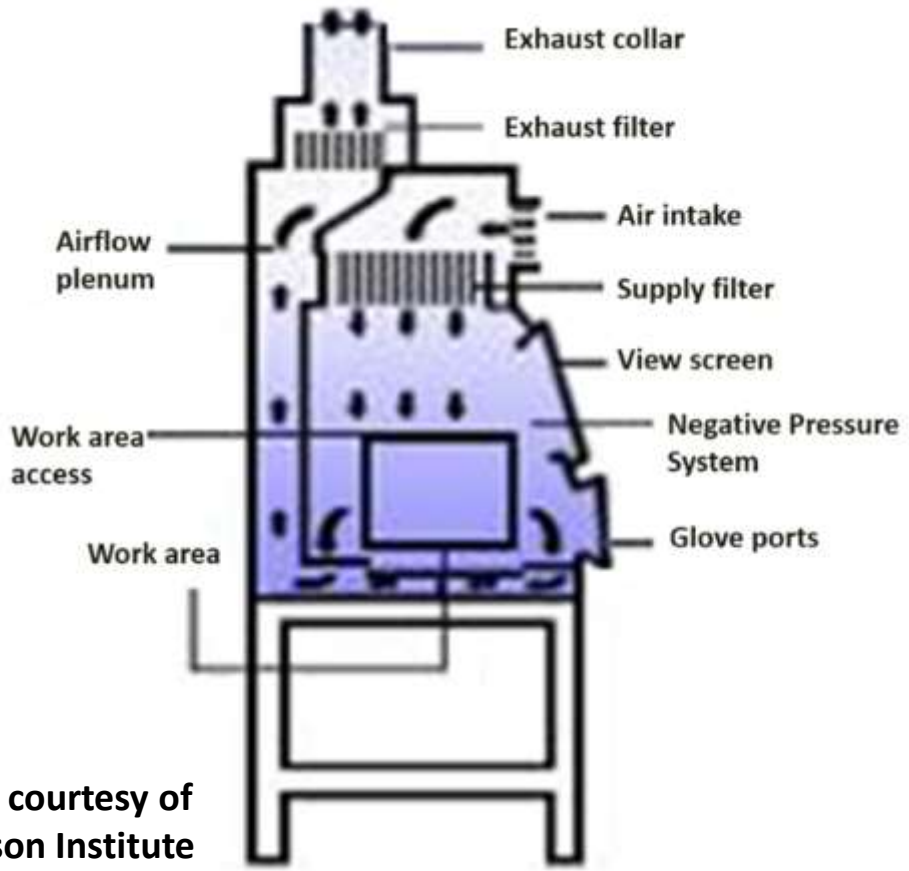
C-PECs for Sterile HD Compounding: *Class III*



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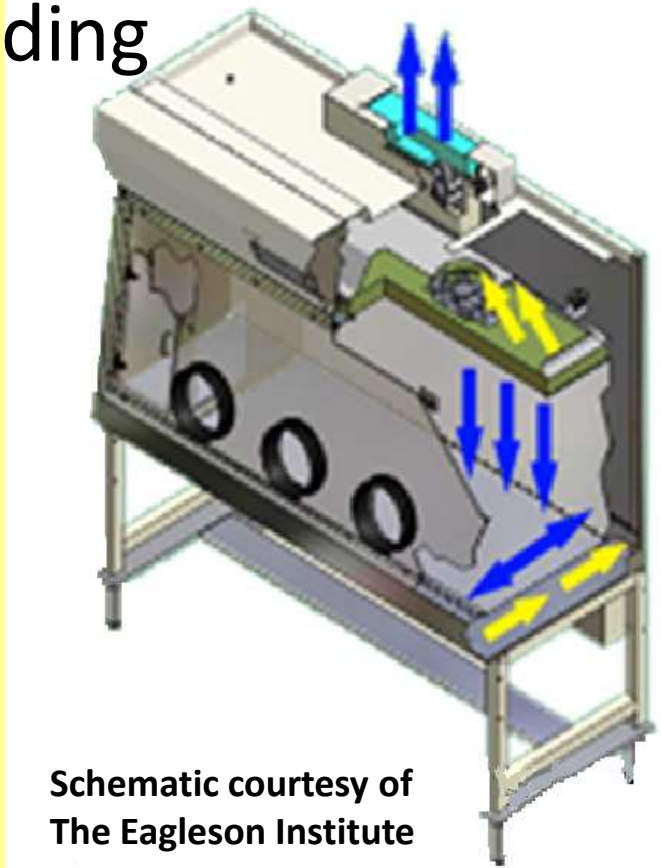
C-PECs for Sterile HD Compounding

- RABS type
- CACI
- Negative Pressure



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Chapter 800 Requirements for C-PEC Selection

- All C-PECs used for manipulation of sterile HDs must be externally vented.
- Class II, Type A2, B1, B2, Class III BSC, and CACI are all acceptable.
- For most known HDs, Type A2 BSCs offer a simple and reliable integration with the ventilation and pressurization requirements of the C-SEC.
  - A2 BSC less exhaust airflow than B2
  - B2 BSC adds complexity and do not integrate well in small rooms
  - CACI risk contamination if leak in glove, sleeve or cabinet

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LAFS: IVLFS

- Integrated Vertical Laminar Flow System (IVLFS)
  - Typically problematic
  - Immediate source of FDA and/or BOP scrutiny
  - What's wrong with this picture?

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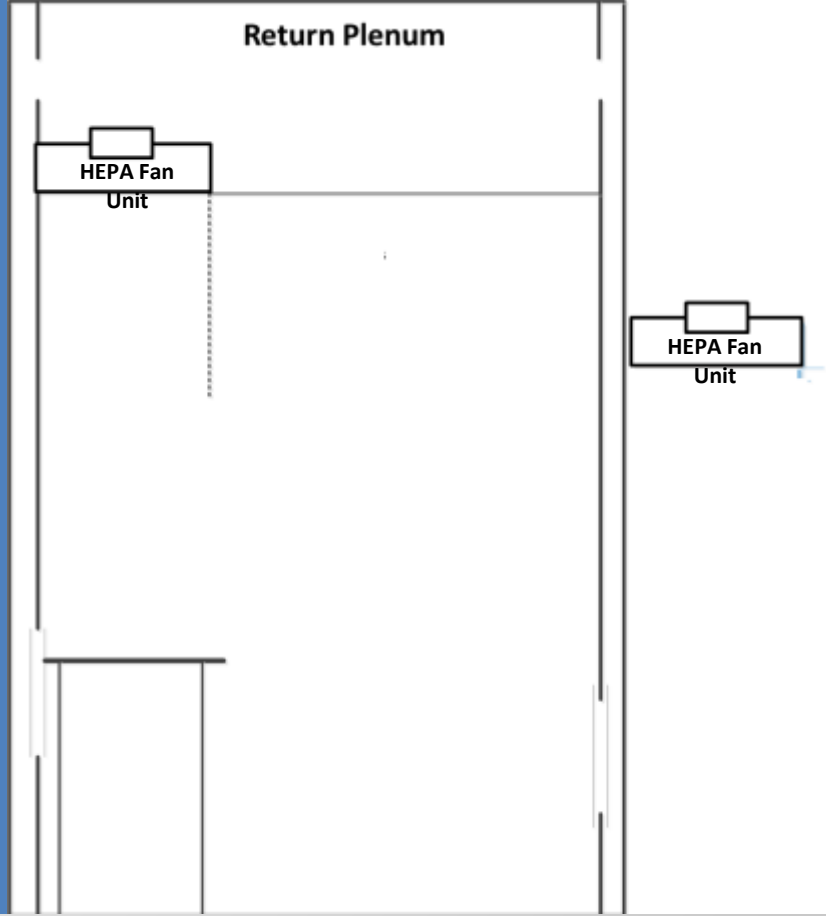
01 LAFS: IVLFS

- A mixed flow cleanroom combines the ISO class 5 unidirectional primary engineering control space directly into the ISO class 7 turbulent flow room. The ISO class 5 area should be separated from the ISO class 7 space with a physical barrier such as a plastic or Plexiglas curtain.
- This design option is usually more flexible for positioning larger equipment.



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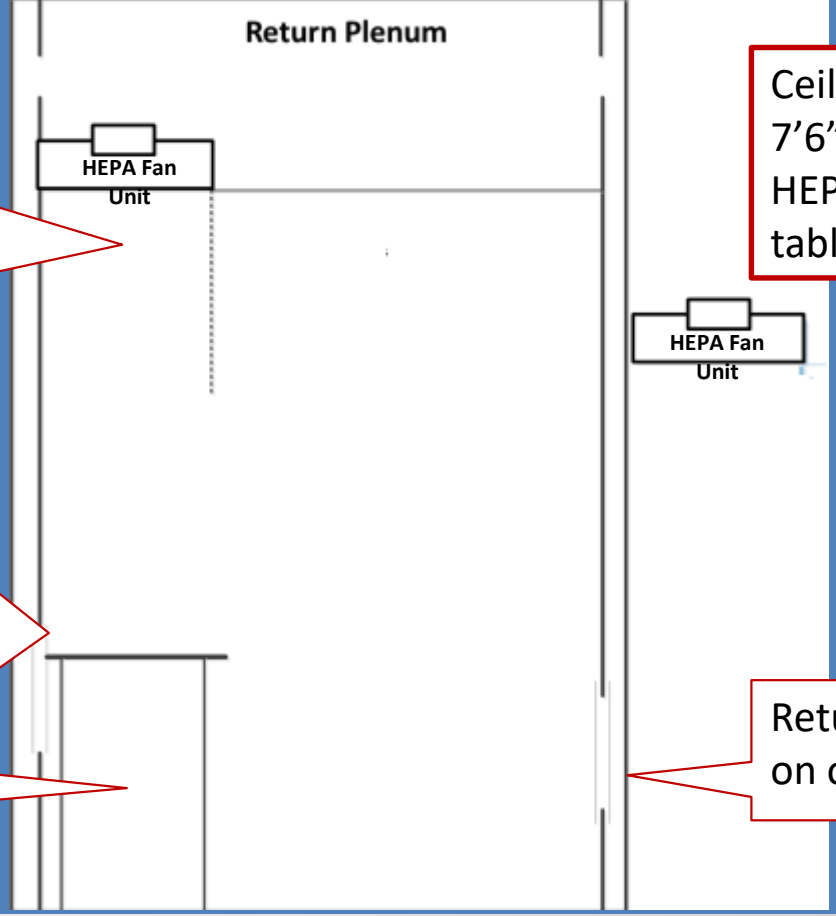

Lexan shield should be as close to HEPA filter media as possible. Height is best determined with field testing.

Ceiling height should be 7’6” to 8” to position VLF HEPA filters close to work table

Returns required on rear wall and position to straddle work surface. Returns should be a linear diffuser with minimal gaps and dead air spots.

Stainless steel table ≈ 24” deep

Return required low on opposite wall.

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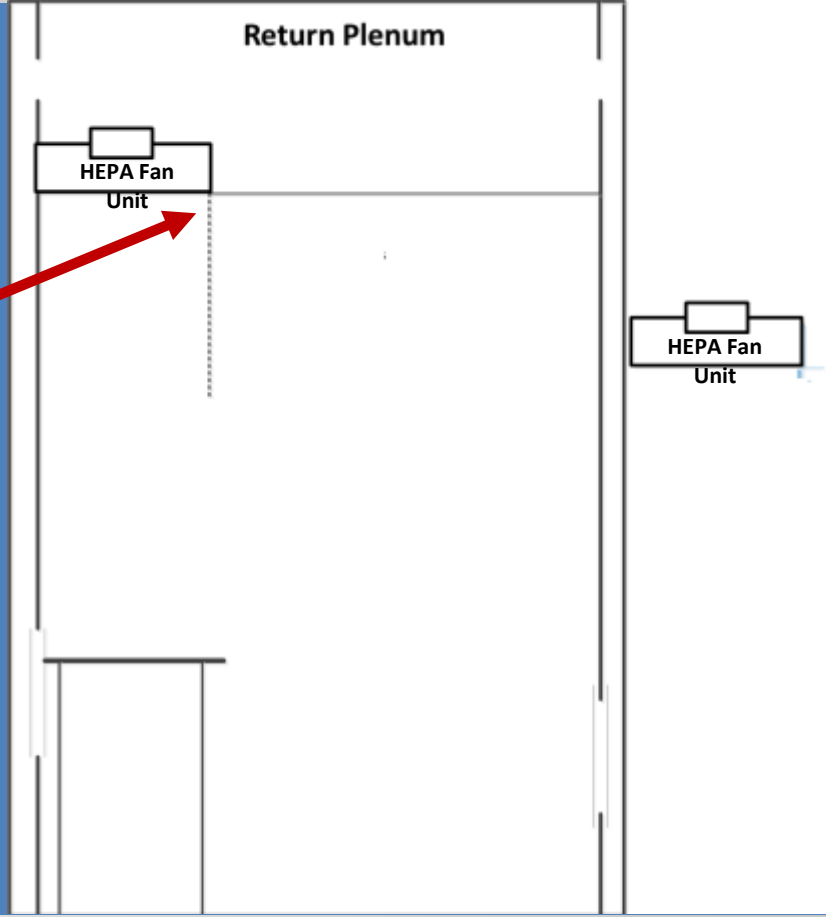
LAFS: IVLFS

- Sample detail for attaching Lexan shield to ceiling using simple “L” bracket.



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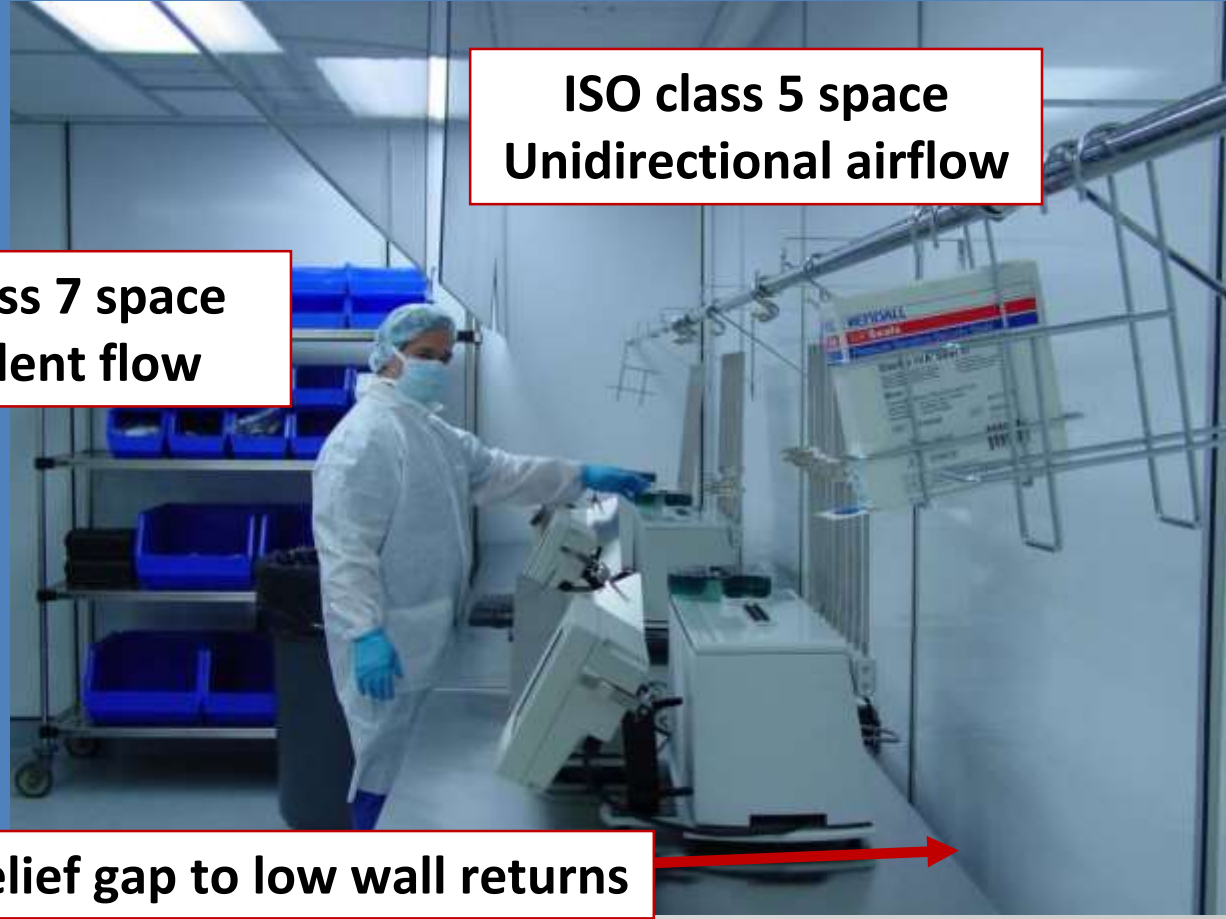
LAFS: IVLFS



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PEC User Suggestions

- PECs should not be turned off
- If shut down for valid reason:
  - Need recovery time and cleaning
  - Air balancing of room for externally vented devices

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PEC User Suggestions (continued)

- Prefilter Change Cycles
  - Position of prefilter on device matters
  - Cleanliness of room influences frequency of change

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PEC User Suggestions (continued)

- Understand monitoring gauges
  - Magnehelic gauge

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Facility Engineering Control Certification

- Certifier Qualification:
  - NSF Accreditation
  - CNBT Accreditation
- Certification reference material
  - Controlled Environment Testing Association (CETA)

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Certification

Current USP <797> (2008 version)	Proposed USP <797> (2019)	Regulatory Interpretations
"Certification procedures such as those outlined in …CAG-003…shall be performed by a qualified individual no less than every 6 month…"	"Before a compounding area is used to compound either Cat. 1 or Cat. 2 CSPs, it must be certified using procedures such as those outlined in the current CETA Certification Guide for Sterile Compounding Facilities."	FDA • 503A versus 503B • cGMPs BOPs • USP Chapters • CETA application guides

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PEC Certification

- CETA CAG-003-2006
- BSC: NSF\ANSI std. 49
- LAFW: ISO 14644-1
  - IEST RP CC 002
  - IEST RP CC 034
- Compounding Aseptic Isolators (CAI)
  - CETA CAG-002-006
  - ISO 14644-1

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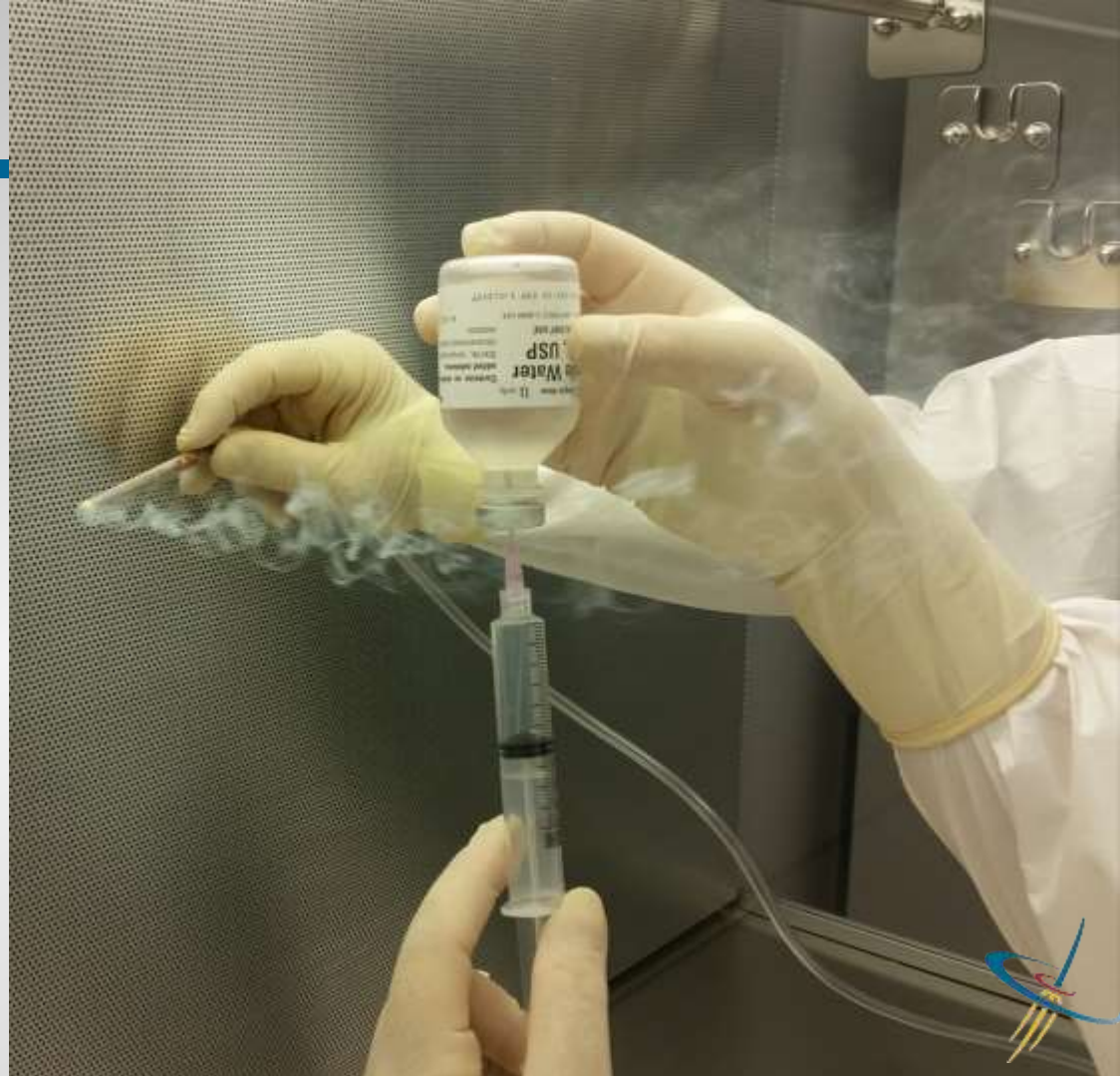
Dynamic Tests

- Dynamic Tests (Room Objectives) require interaction between the certifier and the compounding staff
  - Airflow smoke pattern test
  - Particle Count Survey



Traditional Primary Engineering Controls

TEST	LAFW	BSC (NSF International Criteria)
Placement of Primary Engineering Control	Placed in ISO Class 7 cleanroom; 0.02" w.c. *positive* or SCA	Placed in ISO Class 7 Cleanroom, 0.01 to 0.03"w.c. *negative* to anteroom (if placed in a C-SEC) or negative to the adjacent space (if placed in a C-SCA)
Airflow Velocity	Velocity 80 to 100 feet per minute (fpm) 6-12" from the filter	Downflow Velocity Profile and Face Velocity Tests
HEPA Filter Leak Test	HEPA filters must be certified to be free from leaks > 0.01% of upstream aerosol concentration	HEPA filters must be certified to be free from leaks > 0.01% of upstream aerosol concentration or aerosol penetration not > 0.005% of upstream concentration for filters that cannot be scanned
Airflow Pattern Smoke Test	An observation using smoke to visualize airflow under "dynamic operating" conditions (with pharmacy staff performing surrogate compounding) conducted to confirm that laminarity of the air is undisturbed by compounding processes. Specific smoke pattern tests to ensure the device is functioning properly is also performed under "at rest" conditions.	
Site Installation Assessment Tests	N/A	Verifies that the BSC is properly integrated into the facility by testing airflow and sash alarms; interlocks and exhaust system performance
Non-Viable Particle Counts	Particle counters capable of detecting 0.5 µm size particles are used to verify ISO Class 5 air conditions under dynamic operating conditions	

Adapted from CETA Certification Matrix for Sterile Compounding Facilities CAG-003-2006-13, USP <797>, Proposed USP <797> 2008 ASHP Guidelines on Compounding Sterile Preparations

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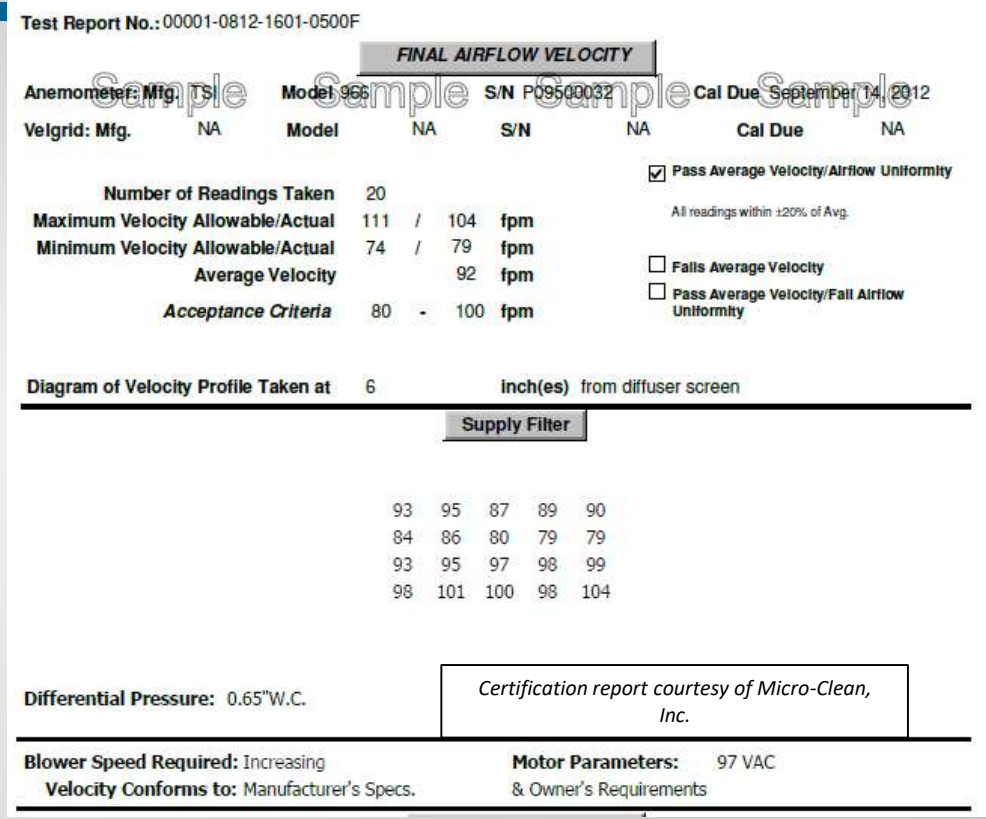
Certification Reports: LAFW

1. **Airflow Velocity:** 80 to 100 feet/minute 6 to 12” from the filter
2. **HEPA Filter Leak Test:** HEPA filters must be certified free from leaks > 0.01% of upstream aerosol concentration
3. **Airflow patterns smoke test:** An observation using smoke to visualize airflow under “dynamic operating” conditions (with pharmacy staff compounding) conducted to confirm that laminarity of the air is undisturbed by compounding processes. Specific smoke pattern tests to ensure the device is functioning properly is also performed under “at rest” conditions.
4. **Non-Viable Particle Counts:** Particle counters capable of detecting 0.5 µm size particles are used to verify ISO Class 5 air conditions under dynamic operating conditions



Test Report No.: 00001-0812-1601-0500F

FINAL AIRFLOW VELOCITY

Sample Sample Sample Sample

Anemometer: Mfg. TSI **Model** 966 **S/N** P09500032 **Cal Due** September 14, 2012

Velgrid: Mfg. NA **Model** NA **S/N** NA **Cal Due** NA

☑ **Pass Average Velocity/Airflow Uniformity**

All readings within ±20% of Avg.

Number of Readings Taken	20			
Maximum Velocity Allowable/Actual	111	/	104	fpm
Minimum Velocity Allowable/Actual	74	/	79	fpm
Average Velocity			92	fpm
Acceptance Criteria	80	-	100	fpm

☐ **Fails Average Velocity**

☐ **Pass Average Velocity/Fail Airflow Uniformity**

Diagram of Velocity Profile Taken at 6 **inch(es)** from diffuser screen

Supply Filter

93	95	87	89	90
84	86	80	79	79
93	95	97	98	99
98	101	100	98	104

Differential Pressure: 0.65"W.C.

Certification report courtesy of Micro-Clean, Inc.

Blower Speed Required: Increasing
Velocity Conforms to: Manufacturer's Specs.

Motor Parameters: 97 VAC & Owner's Requirements

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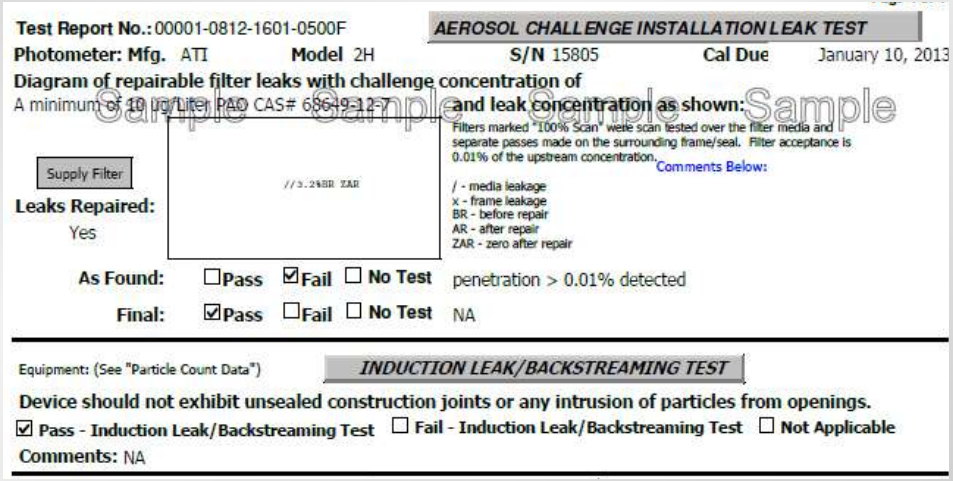
Certification Reports: LAFW (continued)

1. **Airflow Velocity:** 80 to 100 feet/minute 6 to 12” from the filter
2. **HEPA Filter Leak Test:** HEPA filters must be certified free from leaks > 0.01% of upstream aerosol concentration
3. **Airflow patterns smoke test:** An observation using smoke to visualize airflow under “dynamic operating” conditions (with pharmacy staff compounding) conducted to confirm that laminarity of the air is undisturbed by compounding processes. Specific smoke pattern tests to ensure the device is functioning properly is also performed under “at rest” conditions.
4. **Non-Viable Particle Counts:** Particle counters capable of detecting 0.5 µm size particles are used to verify ISO Class 5 air conditions under dynamic operating conditions



Test Report No.: 00001-0812-1601-0500F

AEROSOL CHALLENGE INSTALLATION LEAK TEST

Photometer: Mfg. ATI **Model** 2H **S/N** 15805 **Cal Due** January 10, 2013

Diagram of repairable filter leaks with challenge concentration of

A minimum of 10 ug/Liter PAO CAS# 68649-12-7 **and leak concentration as shown:**

Sample Sample Sample Sample Sample

Filters marked "100% Scan" were scan tested over the filter media and separate passes made on the surrounding frame/seal. Filter acceptance is 0.01% of the upstream concentration.

Comments Below:

/ - media leakage
x - frame leakage
BR - before repair
AR - after repair
ZAR - zero after repair

Supply Filter

//3.2%BR ZAR

Leaks Repaired: Yes

As Found: ☐ Pass ☑ Fail ☐ No Test penetration > 0.01% detected

Final: ☑ Pass ☐ Fail ☐ No Test NA

Equipment: (See "Particle Count Data")

INDUCTION LEAK/BACKSTREAMING TEST

Device should not exhibit unsealed construction joints or any intrusion of particles from openings.

☑ **Pass - Induction Leak/Backstreaming Test** ☐ **Fail - Induction Leak/Backstreaming Test** ☐ **Not Applicable**

Comments: NA

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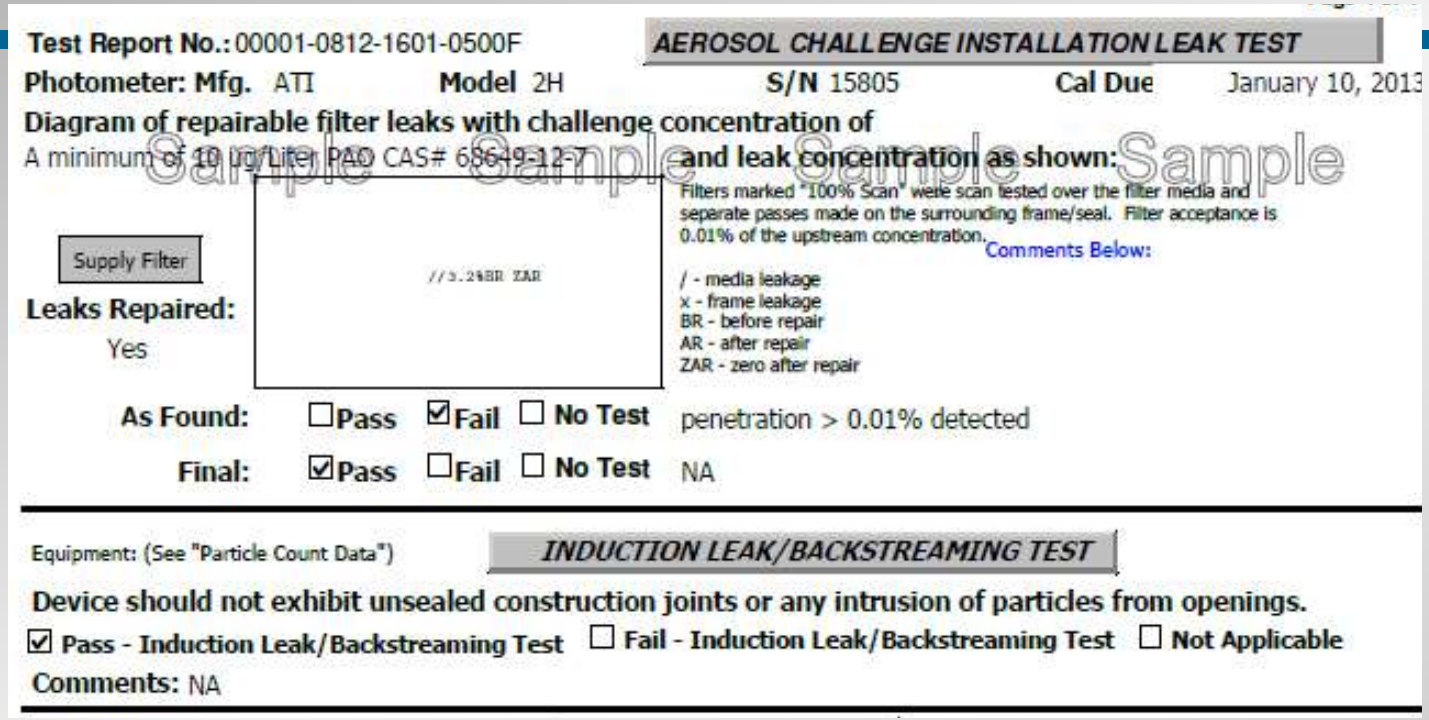
Certification Reports: LAFW (continued)



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Comments Below:

Supply Filter

//3.2%BR ZAR

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x - frame leakage
BR - before repair
AR - after repair
ZAR - zero after repair

Leaks Repaired:
Yes

As Found: ☐ Pass ☑ Fail ☐ No Test penetration > 0.01% detected

Final: ☑ Pass ☐ Fail ☐ No Test NA

Equipment: (See "Particle Count Data")

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Device should not exhibit unsealed construction joints or any intrusion of particles from openings.

☑ **Pass - Induction Leak/Backstreaming Test** ☐ **Fail - Induction Leak/Backstreaming Test** ☐ **Not Applicable**

Comments: NA

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Certification Reports: LAFW (continued)

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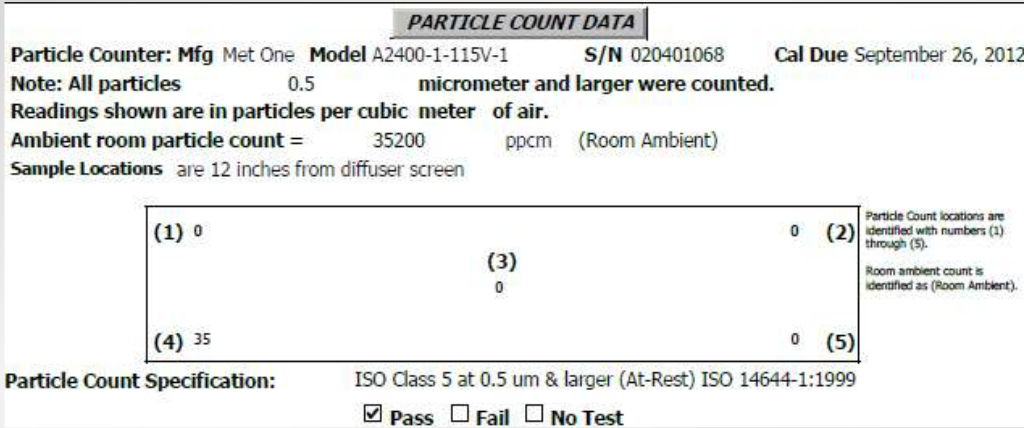

PARTICLE COUNT DATA

Particle Counter: Mfg Met One **Model** A2400-1-115V-1 **S/N** 020401068 **Cal Due** September 26, 2012

Note: All particles 0.5 **micrometer and larger were counted.**

Readings shown are in particles per cubic meter of air.

Ambient room particle count = 35200 ppcm (Room Ambient)

Sample Locations are 12 inches from diffuser screen

(1) 0 (2) 0

(3) 0

(4) 35 (5) 0

Particle Count locations are identified with numbers (1) through (5).

Room ambient count is identified as (Room Ambient).

Particle Count Specification: ISO Class 5 at 0.5 um & larger (At-Rest) ISO 14644-1:1999

☑ **Pass** ☐ **Fail** ☐ **No Test**

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Certification Reports: LAFW (continued)

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	(3) 0	
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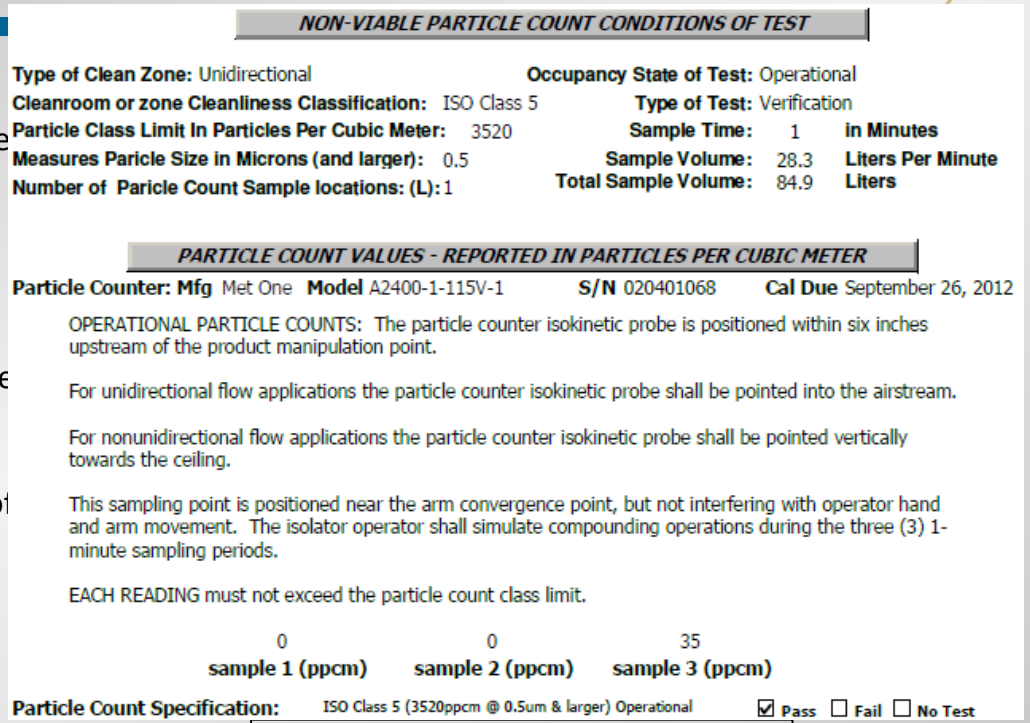

NON-VIABLE PARTICLE COUNT CONDITIONS OF TEST

Type of Clean Zone: Unidirectional
Cleanroom or zone Cleanliness Classification: ISO Class 5
Particle Class Limit In Particles Per Cubic Meter: 3520
Measures Paricle Size in Microns (and larger): 0.5
Number of Paricle Count Sample locations: (L): 1

Occupancy State of Test: Operational
Type of Test: Verification
Sample Time: 1 **in Minutes**
Sample Volume: 28.3 **Liters Per Minute**
Total Sample Volume: 84.9 **Liters**

PARTICLE COUNT VALUES - REPORTED IN PARTICLES PER CUBIC METER

Particle Counter: Mfg Met One **Model** A2400-1-115V-1 **S/N** 020401068 **Cal Due** September 26, 2012

OPERATIONAL PARTICLE COUNTS: The particle counter isokinetic probe is positioned within six inches upstream of the product manipulation point.

For unidirectional flow applications the particle counter isokinetic probe shall be pointed into the airstream.

For nonunidirectional flow applications the particle counter isokinetic probe shall be pointed vertically towards the ceiling.

This sampling point is positioned near the arm convergence point, but not interfering with operator hand and arm movement. The isolator operator shall simulate compounding operations during the three (3) 1-minute sampling periods.

EACH READING must not exceed the particle count class limit.

sample 1 (ppcm)	sample 2 (ppcm)	sample 3 (ppcm)
0	0	35

Particle Count Specification: ISO Class 5 (3520ppcm @ 0.5um & larger) Operational ☑ Pass ☐ Fail ☐ No Test

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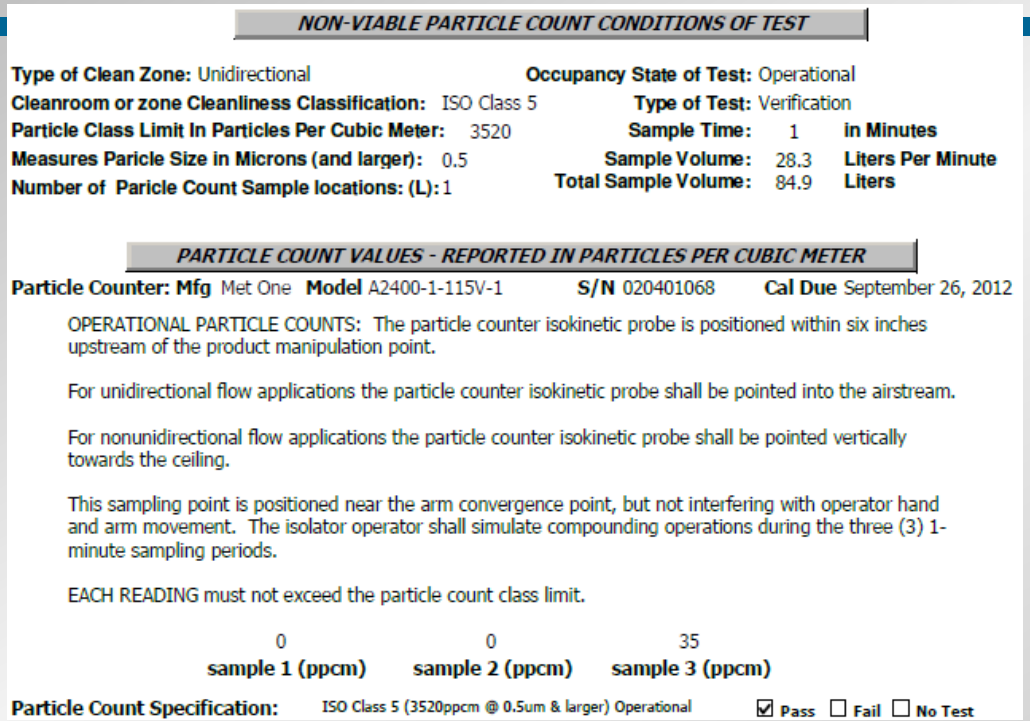
Certification Reports: LAFW (continued)



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EACH READING must not exceed the particle count class limit.

0	0	35
sample 1 (ppcm)	**sample 2 (ppcm)**	**sample 3 (ppcm)**

Particle Count Specification: ISO Class 5 (3520ppcm @ 0.5um & larger) Operational ☑ Pass ☐ Fail ☐ No Test

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RABS 02

- CAI/CACI:
  - Must be placed in ISO Class 7 for Category 2 (for full beyond-use dating)
  - If in unclassified area, restricted to 12 hour BUD per <800>
  - Separate rooms required!

RABS 02 (continued)

Compounding Aseptic Isolator

- Isolator specifically designed for compounding pharmaceutical preparations.
- Maintains an aseptic compounding environment inside the isolator throughout the compounding and material transfer processes.
- Air exchange from the surrounding environment should not occur unless the air has first passed through a microbial retentive filter (HEPA minimum).
- “The airflow in the PEC shall be unidirectional (laminar flow)…”

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RABS 02 (continued)

Compounding Aseptic Containment Isolator

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

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RABS 02 (continued)

2008 Version of USP <797> vs. 2019 Proposed Changes to <797>

- CAIs must be placed in ISO Class 7 cleanroom unless they meet all of the following conditions:
  - Must provide isolation from the room
    - Must maintain ISO class 5 during dynamic operating conditions
    - Transferring ingredients into and out of the isolator and during preparation of CSPs.
    - Tests to prove above conditions are detailed in CETA CAG-002-2006

- Category 1 is treated like a SCA, no more than 12 hour BUD
- Category 2
  - For more than 12 hour BUD, the facility must meet all ISO Class 7 buffer room requirements with an appropriate ante room appropriate for hazard level.
  - Non hazardous vs. hazardous

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RABS 02 Work Practice Conditions

- Need to establish SOPs to reduce the chance of bringing contamination into the isolator by compromising the barrier
- Procedures will vary by isolator design (unidirectional vs. turbulent, pass-through)
  - Ingress and egress of material
  - Recovery (purge) time
  - Cleaning and disinfection protocol

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Isolators (03) (cGMP specs)

- Isolators
  - Must be placed in ISO Class 8 for Category 2 (full dating)
  - High-Integrity transfer ports
  - Sporicidal decontamination process
  - Min. 0.05” w.c. positive
  - Continuously maintain ISO Class 5 (including material transfer)

Compounding Isolator Type Engineering Controls

Test	CAI	CACI	
Placement of PEC	Preferably room or area devoted to compounding but Proposed USP <797> requires placement in an ISO 7 area for full beyond-use dating	Placed in ISO Class 7 C-SEC that is 0.01 to 0.03"w.c. *negative* to anteroom	In C-SCA with at least 12 ACPH and 0.01 to 0.03" w.c. *negative* to adjacent space
Airflow Velocity	Measurement of actual airflow to manufacturer's design intent. The main chamber is expressed as a range of feet/min with a designated % uniformity.		
Chamber Pressure Test	Determines that ante-chamber and main chamber pressures adequate to provide isolator separation between main chamber and ambient spaces. Pressure range determined by manufacturer.		
Site Installation Assessment Tests	Tests to verify proper alarm function; pass-through door interlock function; and proper canopy or exhaust connection performance.		
HEPA Filter Integrity Leak Test	All HEPA filters in the secondary engineering controls are tested at each certification. Maximum allowable leakage is 0.01% of the upstream aerosol concentration.		
Airflow Smoke Pattern Test	An observation using smoke to visualize airflow under *dynamic operating conditions* (with pharmacy staff performing surrogate compounding) to confirm laminarity of the air is undisturbed		
Preparation Ingress and Egress Test	Determine if the pass-through system is capable of supporting material transfer while maintaining ISO Class 5 conditions during the transfer.		
Non-Viable Particle Counts	Particle counters capable of detecting 0.5 µm size particles are used to verify ISO Class 5 air conditions both at rest and during *dynamic operating conditions*.		

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Secondary Engineering Controls

Traditional ISO Class 7 Buffer room with LAFW

ISO Class 7 Buffer room with Integral ISO Class 5 VLF

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Facility Requirements

- The facility design must ensure:
  - the ability to get components into the primary engineering control without introduction of contamination into the Direct Compounding Area (DCA)
  - the ability to provide a safe working environment to the compounding staff and to protect the environment from products produced

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Material Handling

- No corrugated cardboard in controlled areas.
- Plastic-coated boxes limited to the anteroom and the hazardous drug buffer room.
- When unpacked from any shipping containers, components wiped down with the designated disinfectant (preferably a sporicidal) in general prep area or on dirty side of anteroom before moving into the pass-through or across line of demarcation into the buffer room.
- Components are wiped again with sterile IPA just prior to being placed inside the ISO class 5 device.
- Nothing but sterile components and disinfected materials are moved into the DCA within the ISO class 5 device.

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Activity of unwrapping to left or right of DCA

Ante room
Typically ISO 7 or 8

Buffer room

D C A

ISO Class 5 PEC

Wipe surfaces with sIPA just prior to placing in PEC

General Prep Area
Non classed

Wipe surfaces with agent that can disinfect (preferably with activity against mold spores)

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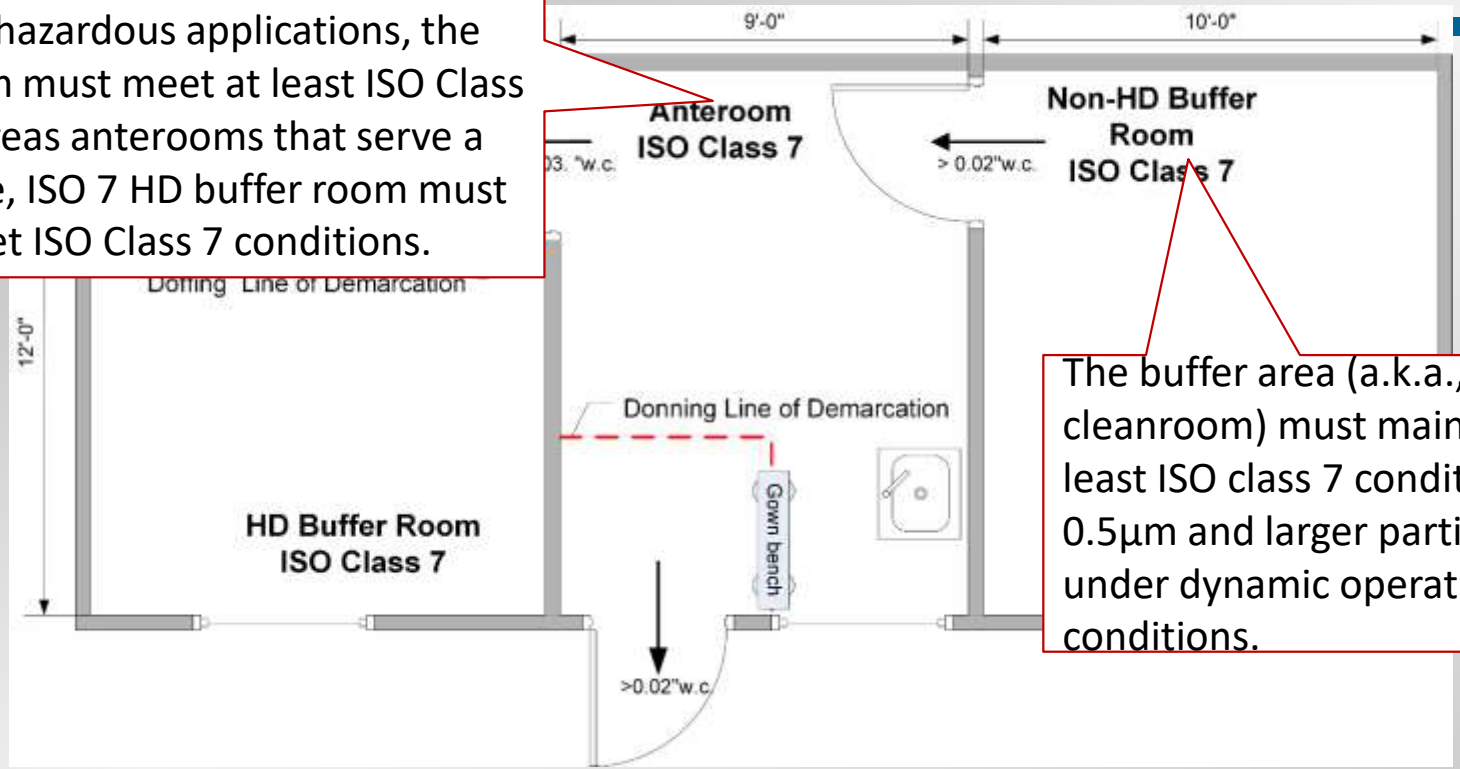
Building a Sterile Compounding Facility

In nonhazardous applications, the anteroom must meet at least ISO Class 8 whereas anterooms that serve a negative, ISO 7 HD buffer room must meet ISO Class 7 conditions.



The buffer area (a.k.a., cleanroom) must maintain at least ISO class 7 conditions for 0.5µm and larger particles under dynamic operating conditions.

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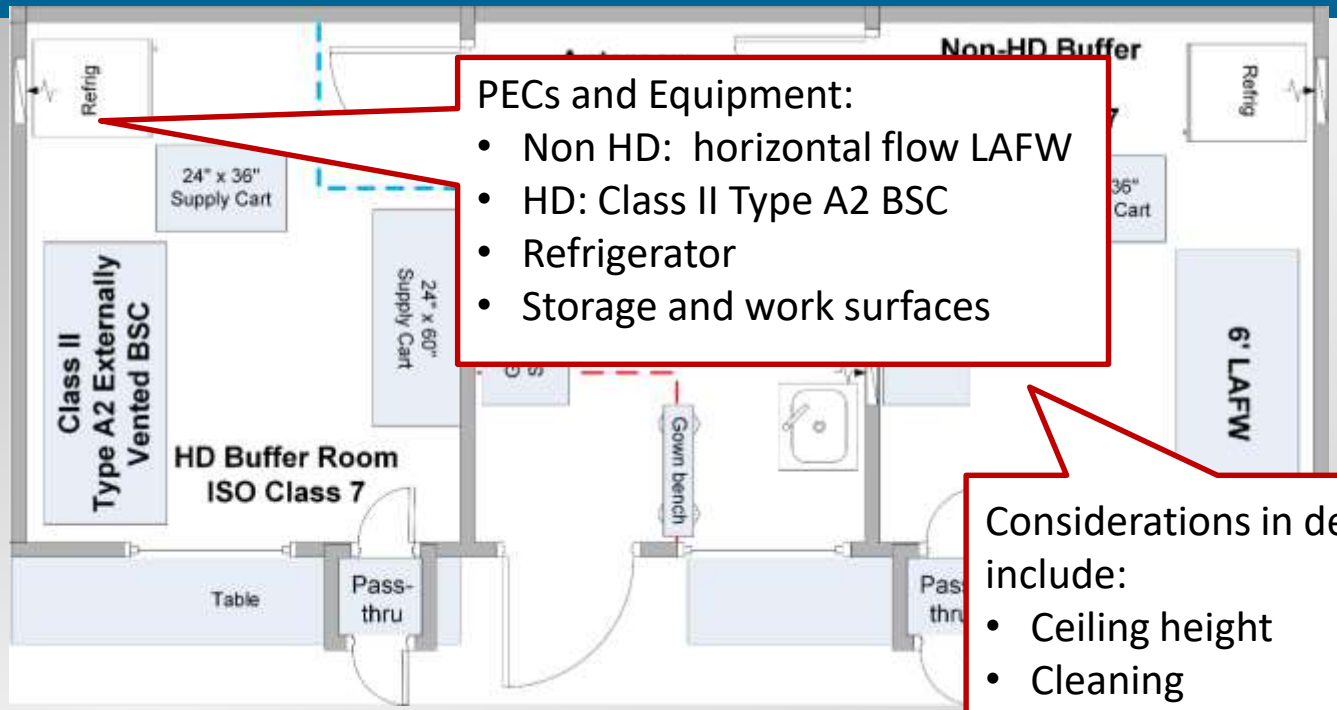
Building a Sterile Compounding Facility (PECs)



PECs and Equipment:

- Non HD: horizontal flow LAFW
- HD: Class II Type A2 BSC
- Refrigerator
- Storage and work surfaces

Considerations in design include:

- Ceiling height
- Cleaning
- Drug storage
- Equipment servicing

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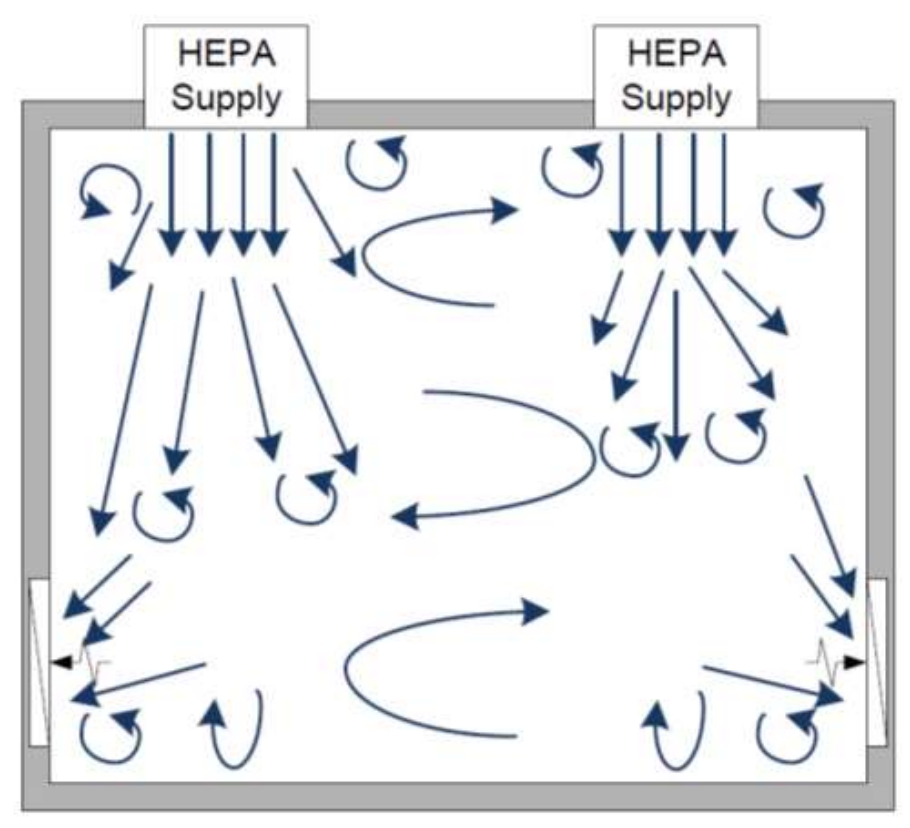
Airflow Definitions

- Turbulent flow
  - Dilution control to reduce particulate levels.
  - Adequate *HEPA-filtered airflow* supplied to the Cleanroom and Anteroom is required to maintain cleanliness classification during operational activity (ACPH).



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Secondary Engineering Control Certification

CAG-003-2006: CETA Certification Guide for Sterile Compounding Facilities:

- Airflow testing:
  - Room airflow
  - Room segregation
- Airflow smoke pattern test
- HEPA Filter Installation Leak Test
- Particle Count Survey
- Optional tests: Light, sound, temperature, humidity

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Secondary Engineering Controls

Test	Non Haz Buffer	Anteroom	C-SEC	C-SCA
Airflow	≥30 ACPH (at least 15 ACPH from outside the room) usually more	≥ 20 ACPH (from FDA guidance) but usually more is desirable	≥ 30 ACPH	≥ 12 ACPH for C-SCA or any place HDs are stored
Room Segregation	Minimum differential pressure of 0.020" w.c. *positive* from buffer to anteroom and then again from anteroom to adjacent spaces		Minimum differential pressure of *negative* 0.010 to 0.030" w.c. from C-SEC/C-SCA to adjacent space	
	If displacement airflow (will no longer be acceptable in next official version of Chapter <797>), then velocity of 40 feet/minute from cleanroom to the anteroom across the entire opening		Displacement airflow not allowed in HD compounding	
HEPA Filter Leak Test	All HEPA filters in the secondary engineering controls are tested at each certification. Maximum allowable leakage is 0.01% of the upstream aerosol concentration.			
Smoke Pattern Testing	Buffer rooms must be segregated from the ante-area and all other adjacent spaces. Use smoke around the opening of doors to ensure air is traveling in the correct direction.			
Non-Viable Particle Counts	ISO Class 7	ISO Class 8 unless it serves HD buffer then ISO Class 7	ISO Class 7 in buffer; No ISO classification required in C-SCA	
	Airborne particle counter used to sample particle levels in all ISO classified locations under *dynamic operating conditions*			
Temperature	Comfortable, typically a temperature of 64 to 66°F but Proposed USP 797 requires 20°C (68°F) or cooler			

CETA Certification Guide for Sterile Compounding Facilities CAG-003-2006 *-13* Revised May 20, 2015

Table of Contents

…The certifier should provide specific details of each test conducted either directly in the certification report or in a Standard Operating Procedure (SOP) referenced in the certification report. All calculations including intermediate values should be documented on the certification report. Calibration certificates should be provided for every test instrument used and the specific model number and serial number of each test instrument should be documented on the certification report. The certification report should include the name and address of the testing agency, the name and qualifications of the certification technician (including accreditations)…

The actual acceptance criteria for each test should be agreed to between the owner and certifier …

…The control points of interest are:

1. Assuring adequate HEPA filtered air supplied to the rooms and proper airflow velocities in unidirectional cleanroom spaces (airflow testing)
2. Assuring separation from rooms of different cleanliness classification and purpose (differential pressure and displacement airflow)
3. Assuring that the HEPA filters are leak-free (HEPA filter integrity test)
4. Providing visual verification that air flows from clean to less clean areas and that unidirectional airflow areas are free from turbulence and reverse flows (airflow smoke pattern test)
5. Assuring that the design when operating properly yields the intended cleanliness classification under dynamic operating conditions (particle count test)
6. Assuring the temperature within the compounding facility is appropriate for sterile compounding (temperature testing)
7. Assuring the humidity within the compounding facility is appropriate for sterile compounding (humidity testing)

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Secondary Engineering Controls

- Segregation
  - Differential positive pressure is required to prevent airflow from an area with lower air-quality classification to another area of higher air-quality classification. The pressure differential between the ante-room and the unclassified area must not be less than 0.020-inch water column.
    - At least 0.02 inches water column (w.c.) positive pressure (<797>)
    - Between 0.01” to 0.03” w.c. negative pressure (<800>)
  - Must be continuously monitored
  - Open concept (Displacement airflow)
    - ≥ 40 feet per minute (fpm) across the line of demarcation
    - May not be applied in high risk level compounding applications

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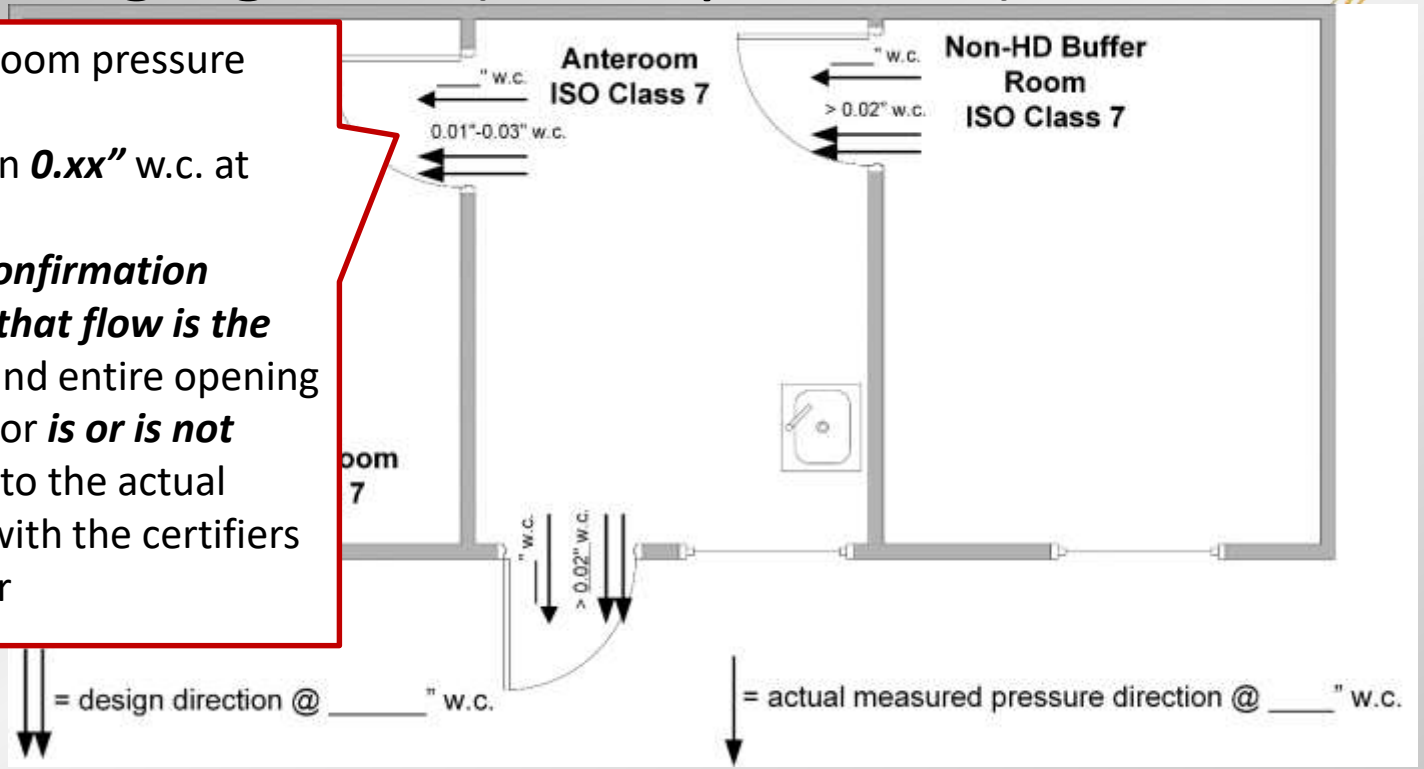
Certification: Segregation (room pressure)

Certification report of room pressure testing should include:

- Differential pressure in ***0.xx"*** w.c. at every door
- Statement of ***visual confirmation (smoke pattern test) that flow is the correct*** direction around entire opening
- Room pressure monitor ***is or is not*** performance verified to the actual pressures measured with the certifiers calibrated manometer



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Secondary Engineering Controls (continued)

- Adequate *HEPA filtered airflow* supplied to the cleanroom and anteroom is required to maintain cleanliness classification during operational activity through the number of air changes per hour.
  - Minimum of *30 HEPA filtered* Air Changes Per Hour (ACPH) in Buffer Area
    - No less than *15 ACPH* must be HEPA filtered air supplied through the room's HVAC system
    - This assumes additional HEPA filtered air is provided to the room through the primary engineering control.
  - Supply airflow typically not continuously monitored
    - Room pressure monitored
    - Read and record to the thousandths; do NOT round off to hundredths (0.019" w.c. not rounded to 0.02" w.c.)

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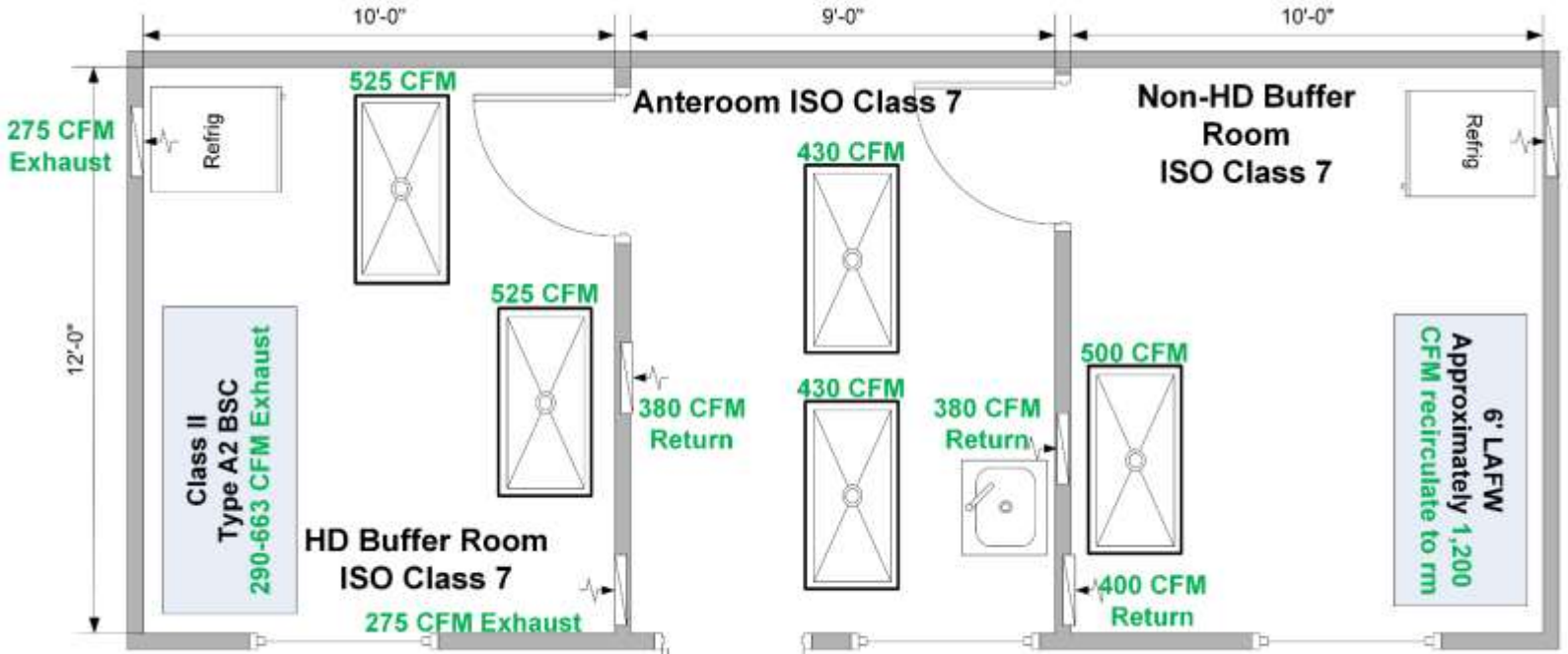
Sample Airflow Projections



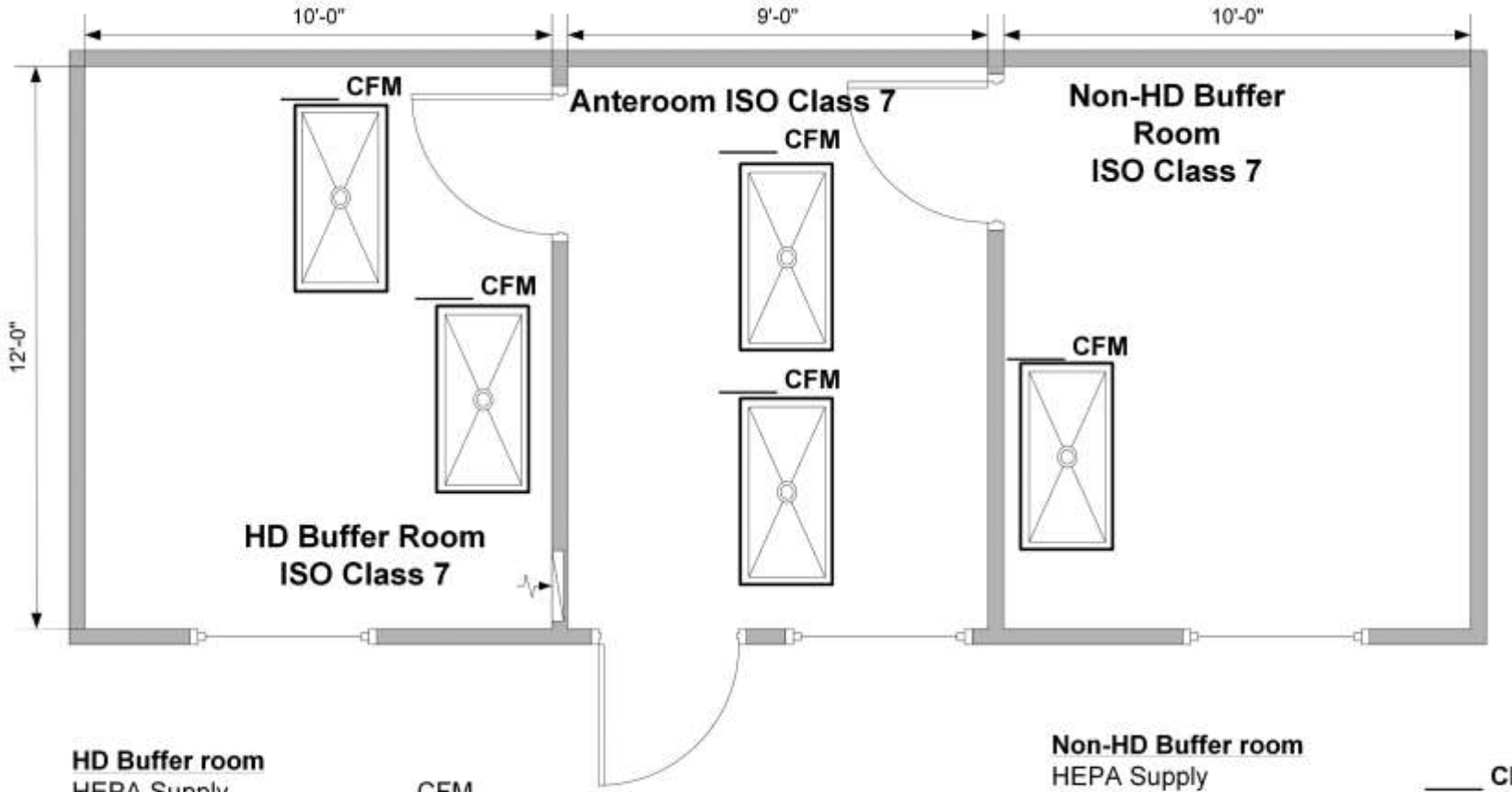
HD Buffer room	
BSC Ex.	600 CFM
Rm Exhaust	550 CFM
Transfer Air	100 CFM
HEPA Supply	1,050 CFM
RM. Volume	1,080 FT^3
Rm. Air Change	50 ACPH
Ceiling Height	9'

Anteroom	
HEPA Supply	860 CFM
Rm. Return Air	760 CFM
RM. Volume	860 FT^3
Rm. Air Change(HVAC)	60 ACPH
Ceiling Height	8'

Non-HD Buffer room	
HEPA Supply	500 CFM
Rm. Return Air	400 CFM
RM. Volume	1,080 FT^3
Rm. Air Change (HVAC)	28 ACPH
PEC recirculated ACPH	67 ACPH
Total Air Change	95 ACPH
Ceiling height	9'

State of Control Points

Certification: Airflow or Air Change Per Hour)ACPH)



HD Buffer room

HEPA Supply	____ CFM
RM. Volume	____ FT^3
Rm. Air Change	____ ACPH
Airflow from PEC	____ CFM
Total Air Change	____ ACPH
Ceiling Height	9'

Anteroom

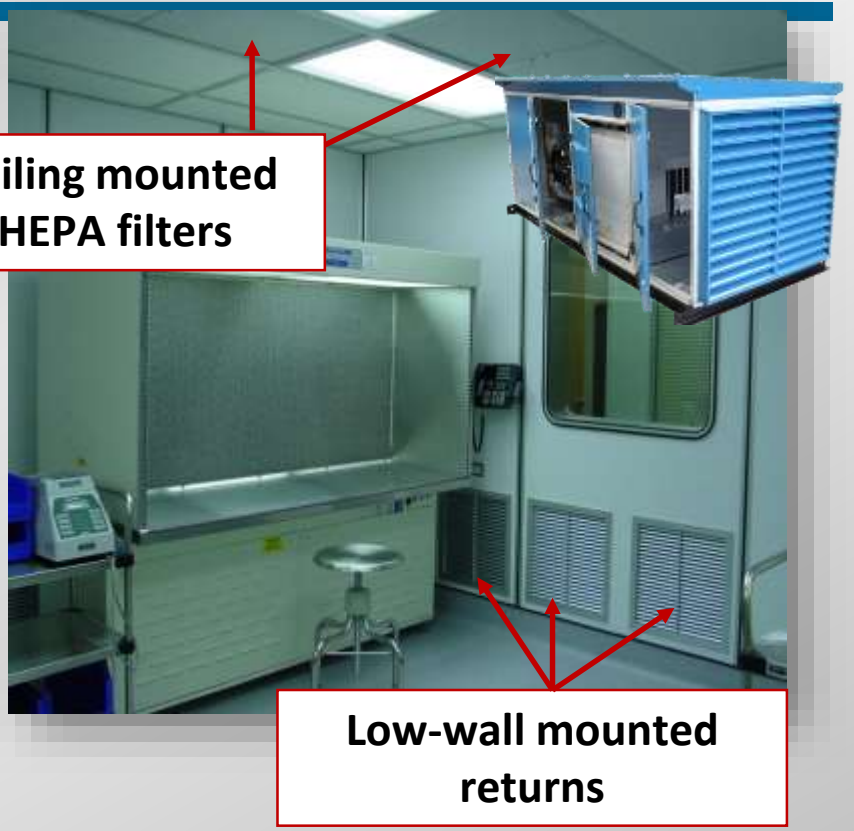
HEPA Supply	____ **CFM**
Rm. Return Air	____ CFM
RM. Volume	____ FT^3
Rm. Air Change(HVAC)	____ **ACPH**
Ceiling Height	8'

Non-HD Buffer room

HEPA Supply	____ **CFM**
Rm. Return Air	____ CFM
RM. Volume	____ FT^3
Rm. Air Change (HVAC)	____ **ACPH**
PEC recirculated ACPH	____ **ACPH**
Total Air Change	____ **ACPH**
Ceiling height	9'

HEPA-Filtered Supply for ISO Classified Rooms

- Air must be introduced through HEPA filters located in the ceiling of the buffer and anterooms
- Returns should be low on the wall, creating a general top-down dilution of area air.
- Current <797> says a remote HEPA filter bank permitted
- Proposed changes to <797> ***requires HEPA filters to be located in the ceiling***



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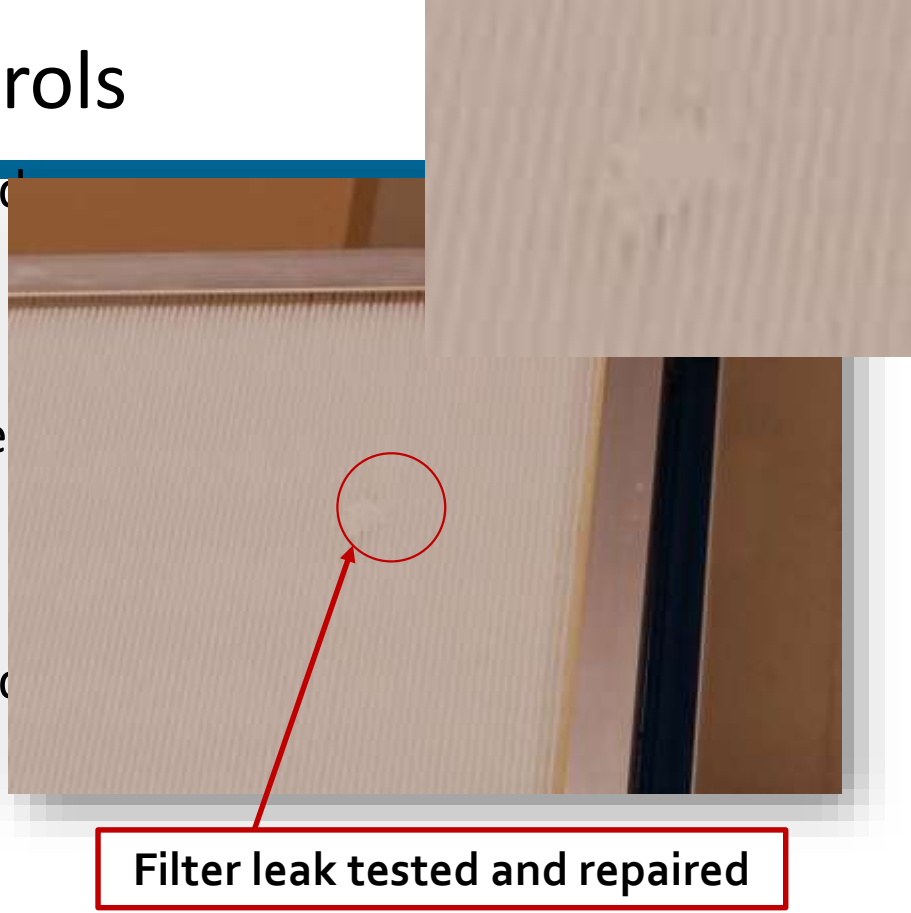
Secondary Engineering Controls

- All HEPA filters must be efficiency tested at the most penetrating particle size
  - leak tested at the factory and
  - leak tested again in situ after installation.
- IEST type C or K HEPA filter
- CETA guide CAG-003-2006 for field certification



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Certification (HEPA Integrity) Aerosol Introduction

- Penetrate ceiling to introduce challenge
- Run tubing from upstream of each filter to an outside location
- Aerosol introduction capable housings when aerosol is introduced in room
- Means to measure upstream challenge for every filter
- CEPA system

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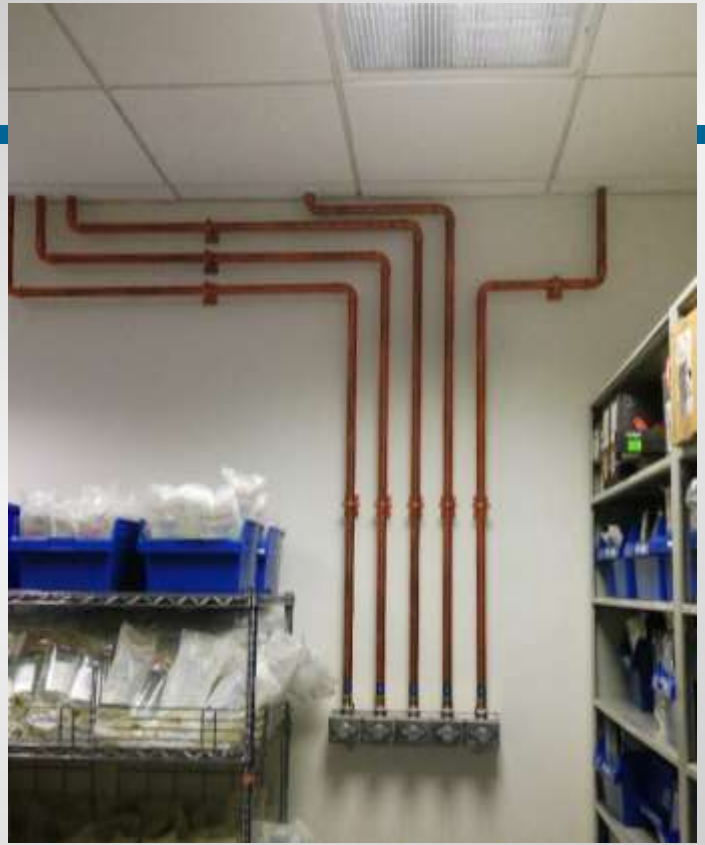

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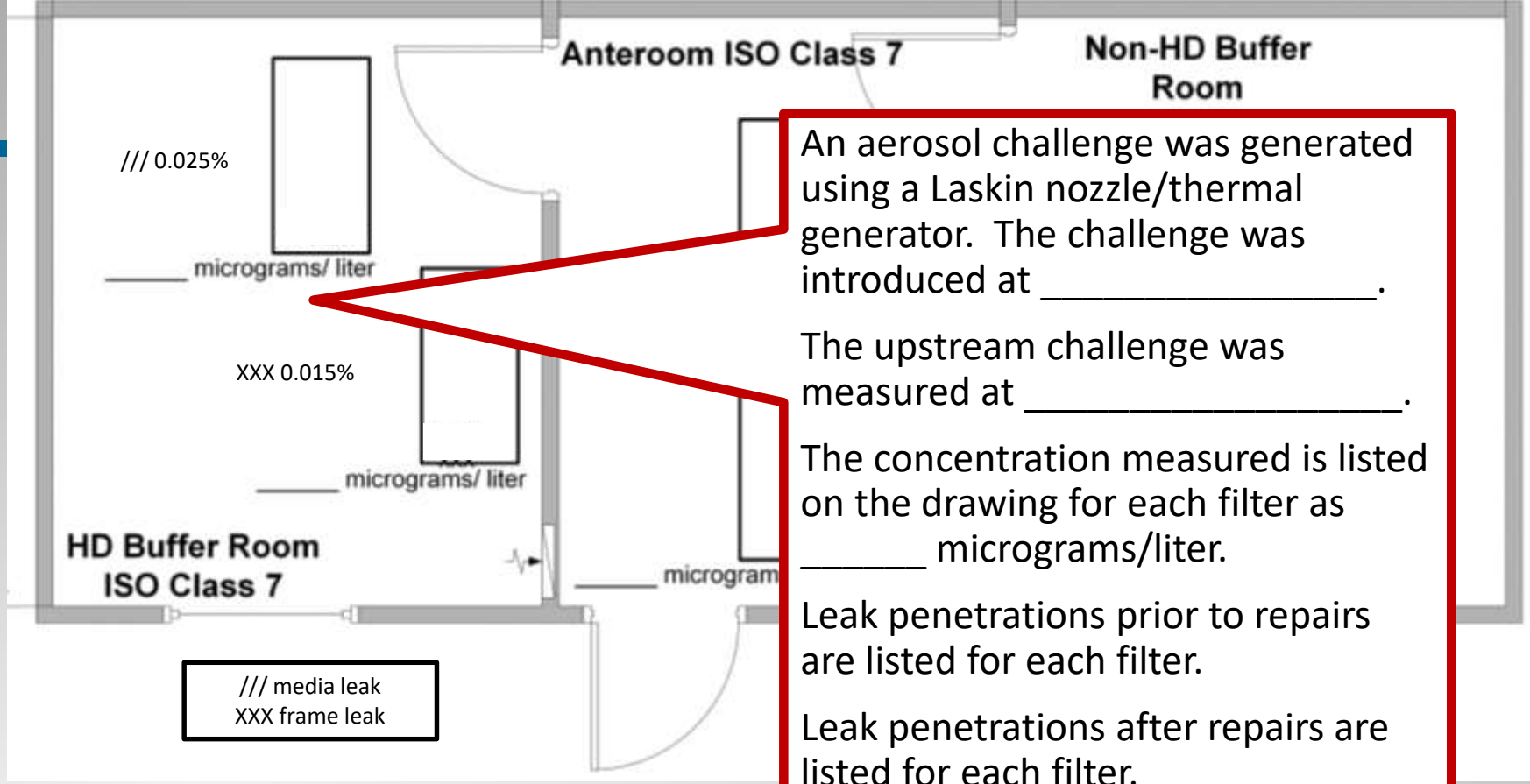
Certification: HEPA Filter Integrity Test



An aerosol challenge was generated using a Laskin nozzle/thermal generator. The challenge was introduced at _____.

The upstream challenge was measured at _____.

The concentration measured is listed on the drawing for each filter as _____ micrograms/liter.

Leak penetrations prior to repairs are listed for each filter.

Leak penetrations after repairs are listed for each filter.

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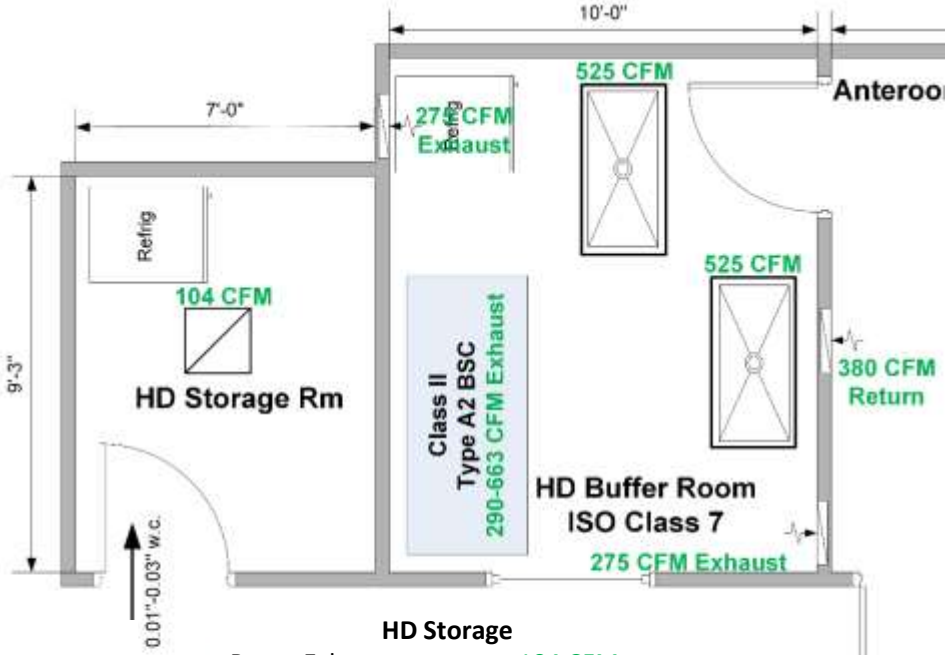
HD Applications: Storage

- Hazardous drugs shall be stored separately from other inventory in a manner to prevent contamination and personnel exposure.
  - Minimum of 12 ACP from exhaust
  - Negative pressure of 0.01 to 0.03” w.c.
- Storage in HD Buffer room OR separate HD Storage room



HD Storage

Room Exhaust	104 CFM
HEPA Supply	0 CFM
Room Volume	520 FT^3
Room Air Change	12 ACPH
Ceiling Height	8 feet

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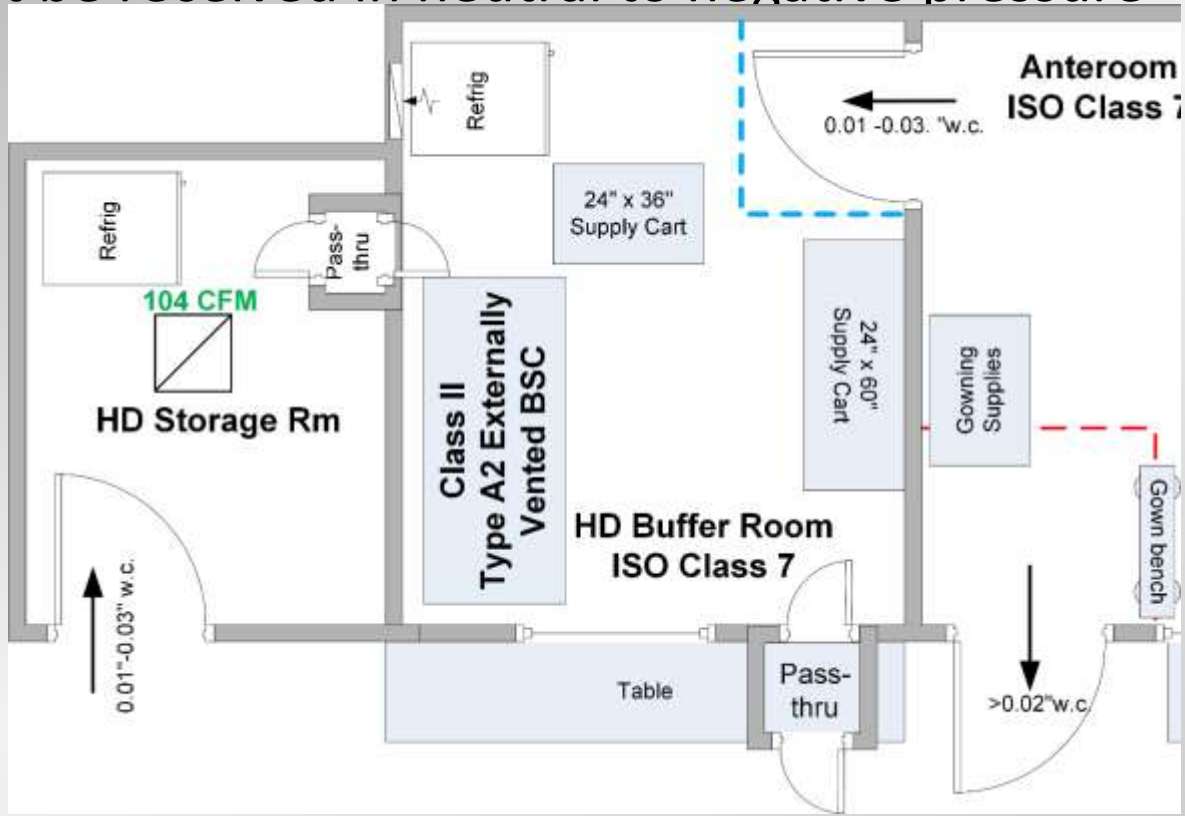
HD Applications: Receiving (<800>)

- HDs must be received in neutral to negative pressure



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Hazardous Drug (HD) Applications

- The ISO Class 5 BSC or CACI *shall be* placed in an ISO class 7 room that is physically separated, e.g., a different room from other preparation areas, and optimally has between 0.01 to 0.03” w.c. negative pressure to adjacent rooms.
- Must be vented ***outside*** of the facility
- The C-SEC used for sterile and non-sterile compounding must:
  - Be externally vented through high-efficiency particulate air (HEPA) filtration
  - Be physically separated
  - Have an appropriate air exchange

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External Venting/ Negative pressure




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Segregated Compounding Areas

- Low Risk with 12 Hour or Less BUD
- Appropriate for non-hazardous low risk compounding only
- Containment Segregated Compounding Areas for HD compounding
- Area does not need to meet environmental conditions of a cleanroom
  - Does need cleanable surfaces

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Segregated Compounding Areas

- Area MUST have:
  - Sink for hand washing
  - Sink can not be located adjacent to the ISO class 5 PEC (ideally at least 3 feet away from PEC)
- SCA may NOT have:
  - Have unsealed windows or doors that connect to high traffic or outside space
  - Be adjacent to construction sites
  - Be adjacent to warehouses
  - Be adjacent to food preparation

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HD Applications: C-SCA

- CACI or BSC in an unclassified room used to compound HDs
  - Must meet the minimum 0.01” w.c. negative pressure and 12 ACPH requirements.
- Defined perimeter to separate functions
- Room finishes same as cleanroom
- Dedicated to HD operations
- Reduced BUD (12 hours or 12 hours room and 24 hours refrigerated)

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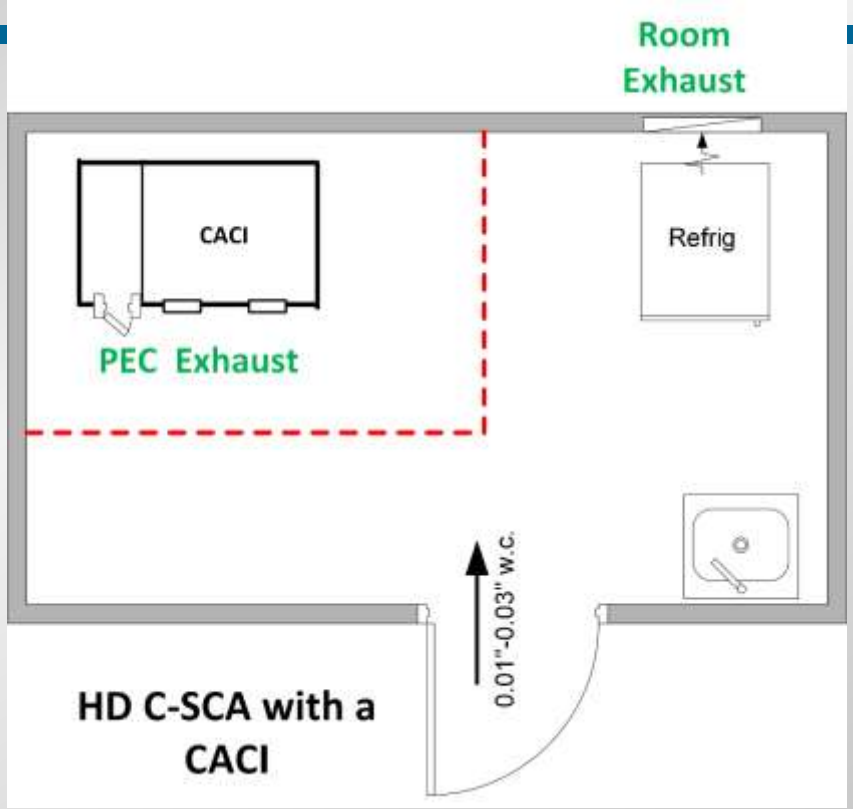
HD Applications: C-SCA (continued)

- Certification report must include
  - PEC certification
  - Room air change rate ____ACPH
  - Room pressure ____” w.c.



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C-PECs

- Must be dedicated to sterile HD compounding …
- … *unless* the non-HD preparation is placed into a protective outer wrapper after it is decontaminated inside the C-PEC and
- is labeled to require PPE handling precautions
- Accommodation for facilities that prepare a very low volume of HDs (e.g.,< 5 preparations/week) and use 2 tiers of containment (e.g., CSTD within a BSC or CAI)

Retrieved from Sen Sok International University Hospital on 2/7/2017

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General Facility Requirements

- Applies to Buffer Rooms, Anterooms and SCAs
  - Well-lit and comfortable working environment
  - The temperature and humidity must be monitored each day that compounding is performed, either manually or by a continuous recording device, and the results must be reviewed and documented. Temperature and humidity must be controlled through an efficient heating, ventilation, and air conditioning (HVAC) system. Free-standing humidifiers/dehumidifiers and air conditioners must not be used.
    - 20 °C (68 °F) or cooler
    - Relative humidity below 60%

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General Facility Requirements: Ceilings

- Epoxy-coated gypsum board (sheet rock)
- Anodized aluminum T grid with cleanroom ceiling tiles
  - Tiles must be caulked in place to ensure seal
  - Caulking of individual ceiling tiles allows caulking to be removed so servicing can occur then re-caulked
  - Smooth, non-porous tiles that stand up to disinfectants
- Wall junctions coved or caulked

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General Facility Requirements: Lighting

- Cleanroom lighting
  - Sealed
  - Flush Mounted
  - Easily cleaned

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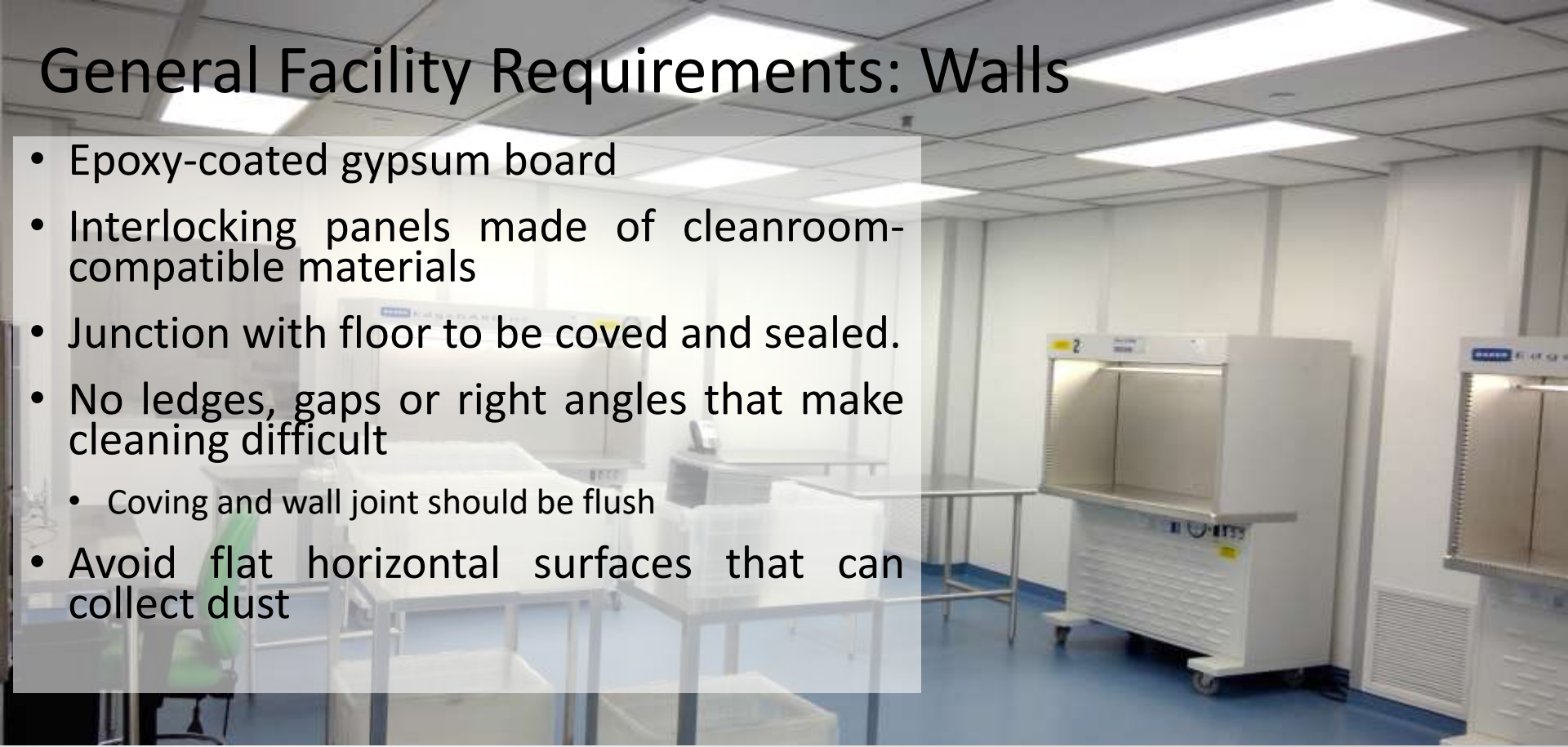
General Facility Requirements: Walls



- Epoxy-coated gypsum board
- Interlocking panels made of cleanroom-compatible materials
- Junction with floor to be coved and sealed.
- No ledges, gaps or right angles that make cleaning difficult
  - Coving and wall joint should be flush
- Avoid flat horizontal surfaces that can collect dust

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General Facility Requirements: Walls

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General Facility Requirements: Floors

- Monolithic
  - Wide-sheet vinyl flooring with heat-welded seams
  - Poured epoxy (smooth or rough?)
  - Must be coved to walls
  - Must withstand continuous cleaning with disinfectant agents
  - No gaps or crevices for microorganisms to accumulate and grow
  - No floor drains

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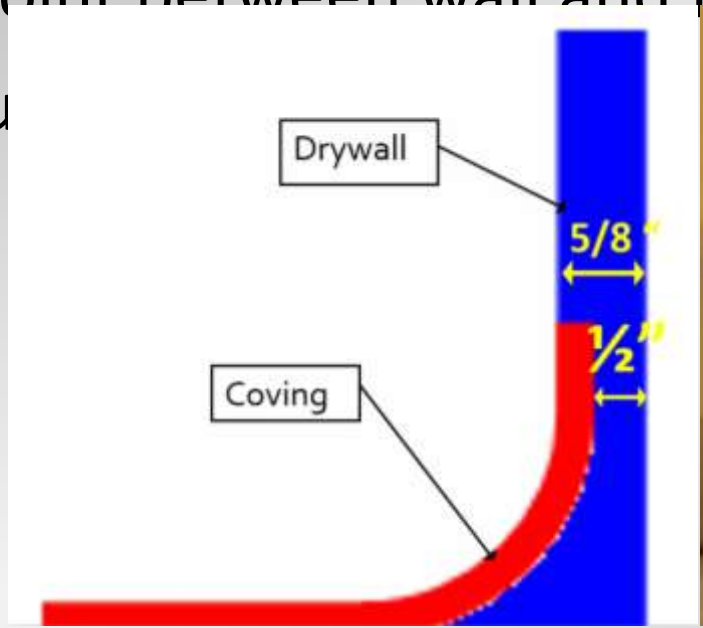
General Facility Requirements: Floors (continued)

- Ideal, flush joint between wall and floor coving
- All joints cau



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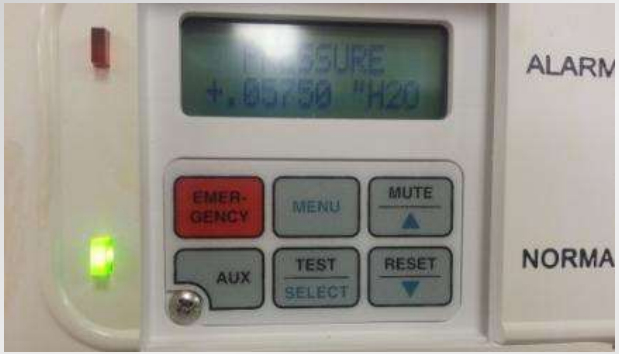
Monitoring: Differential Pressure Gauges

- Room pressures must be continuously monitored
- Results “reviewed and documented at least every work shift (at least daily) or by continuous recording device.”
- Alarm



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Pass Throughs

- Used to transfer materials from one room to another with limited particle transfer
- Materials of construction
- Interlocked so that bot doors are not able to b opened at the same time
- Sealed doors
- HEPA Purge?

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Pass Throughs (continued)

- Cart pass-through
  - Clean cart/dirty cart
  - Interlocked doors
  - Sealed doors
- Pass-Through Position
  - Classified to Classified
  - Classified to Unclassified
  - FDA Position
  - BOP Positions

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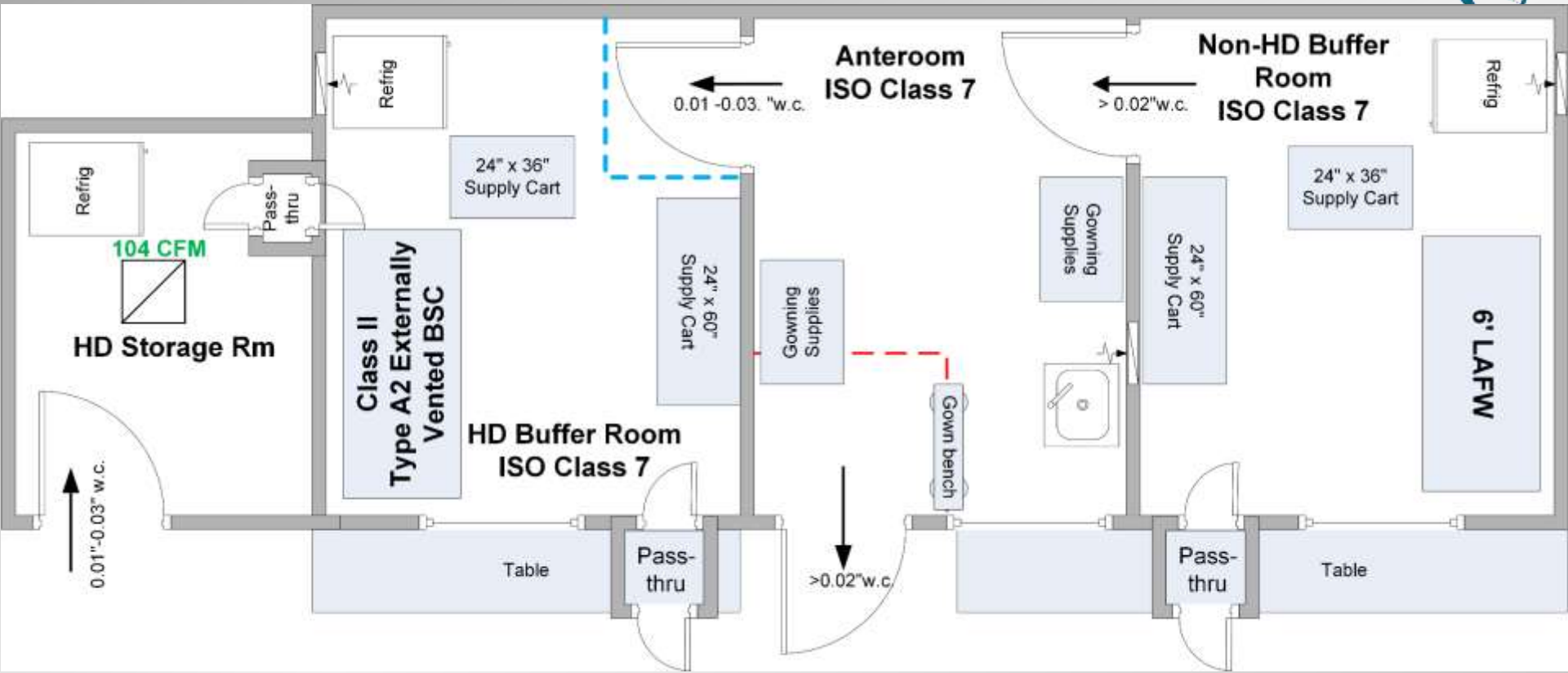

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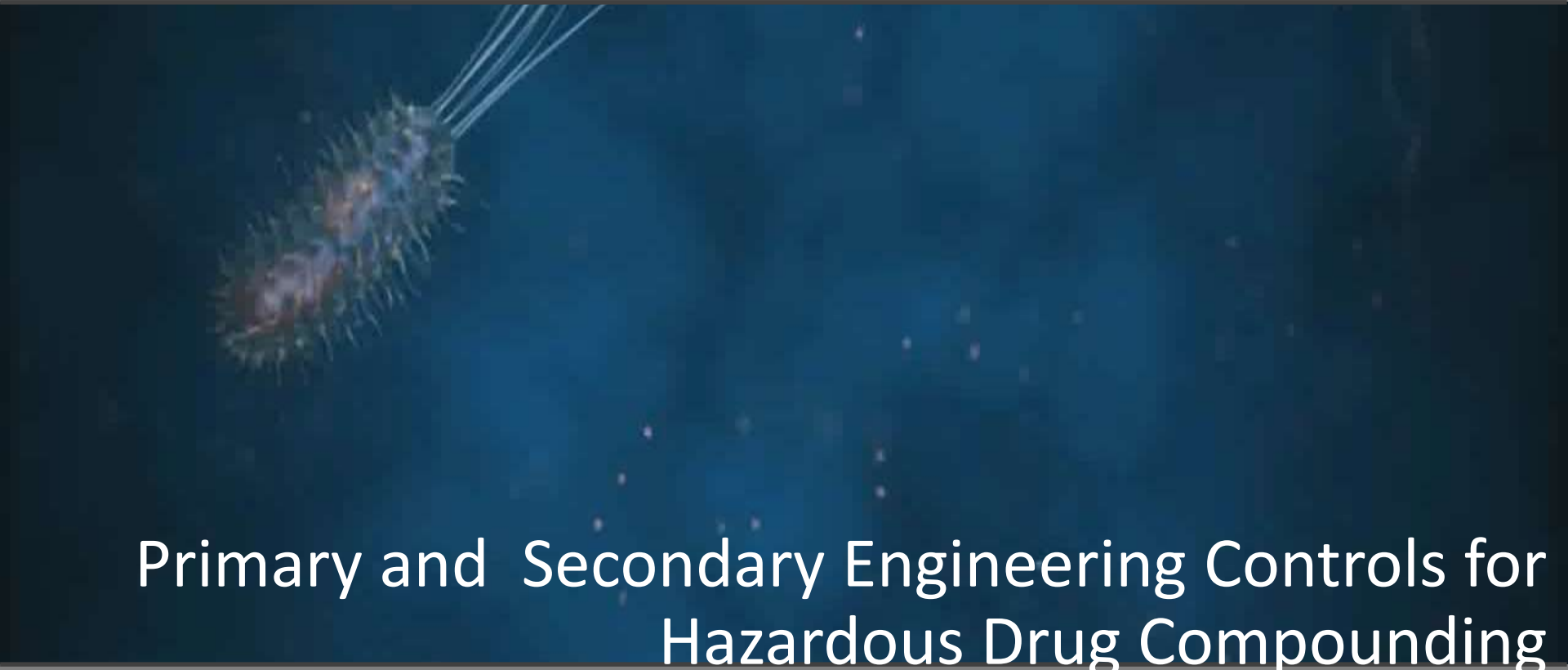

Primary and Secondary Engineering Controls for Hazardous Drug Compounding

criticalpoint

Learning and Performance Objectives

At the end of this session, you will be able to:

- Describe the types compliant of HD primary and secondary engineering controls for nonsterile and sterile HD compounding
- Discuss considerations relevant to the use of pass-throughs in HD applications
- Analyze the allowable but suboptimal designs of HD secondary engineering controls
- List strategies to compensate for suboptimal designs
- Describe the tests required for certification of primary and secondary engineering controls

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Storage of HDs

- USP <797>: shall be stored separately from other inventory
- <800> adds requirement for
  - Separate room
  - Negative pressure room
  - Exhaust ventilation
  - At least 12 air changes per hour

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C-PECs for Sterile HD Compounding

- Must provide personnel, product, and environmental protection
  - Class II Biological Safety Cabinet (BSC)
  - Compounding Aseptic Containment Isolators (CACI)
    - Proposed changes to <797> use term RABS
  - Isolators
- Must be unidirectional (laminar flow) a
- Must be externally vented
- Class II Type A2 BSC, B1, or B2 BSC acceptable
  - "For most known HDs, A2 cabinets offer a simple and reliable integration with the ventilation and pressurization requirements of the C-SEC. Class II Type B2 BSCs are typically reserved for use with volatile components."

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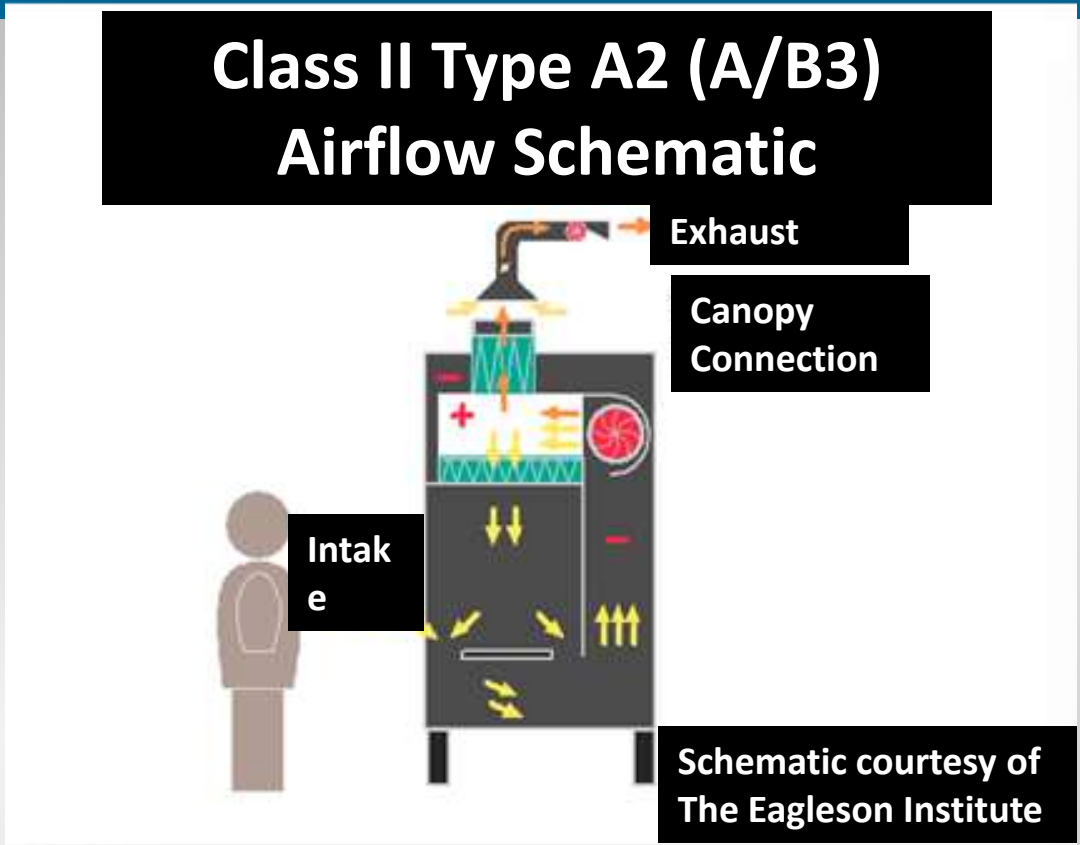
C-PECs for Sterile HD Compounding: Class II, A2



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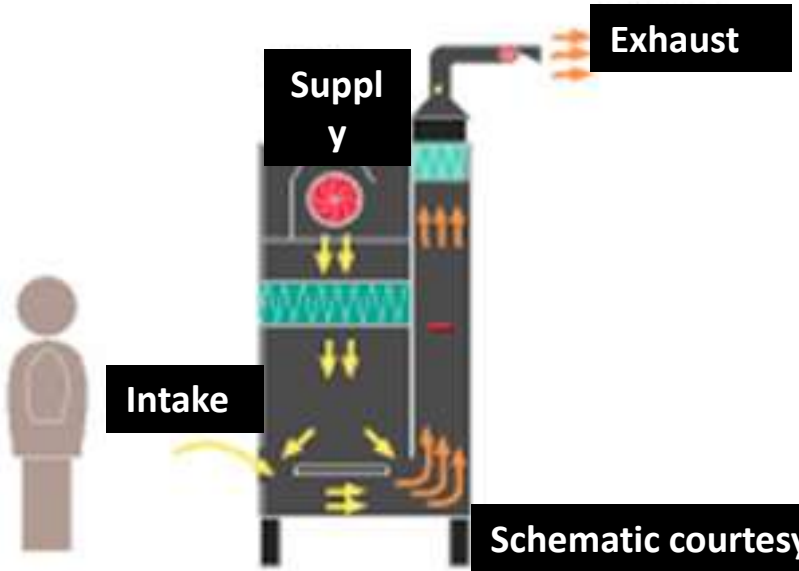
C-PECs for Sterile HD Compounding: Class II, B2

Class II Type B2 Airflow Schematic



Schematic courtesy of The Eagleson Institute

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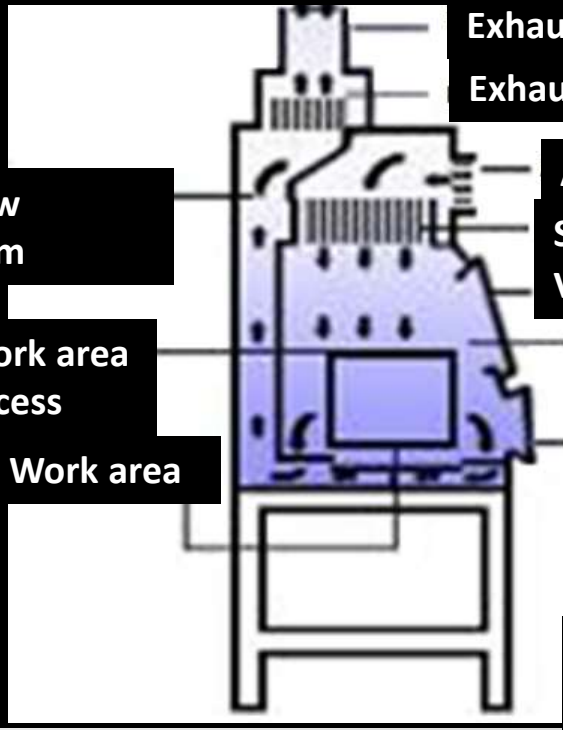
C-PECs for Sterile HD Compounding: Class III

Class III Airflow Schematic



Schematic courtesy of The Eagleson Institute

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C-SECs for Sterile HD Compounding

- Must maintain ISO Class 7 under dynamic operating conditions
  - *Minimum 30 ACPH required* (recommend minimum of 60)
  - Adequate exhaust air
    - C-PEC must be externally vented
    - Exhaust behind refrigerator or exhaust-free, solid-state refrigerator
    - Stack height must be 10 feet above roof
    - Exhaust distance from building intakes
- Room pressure *between* 0.01” to 0.03” w.c.
  - Can be higher negative pressure (greater than 0.03” negative) if no sterile compounding in the C-SEC

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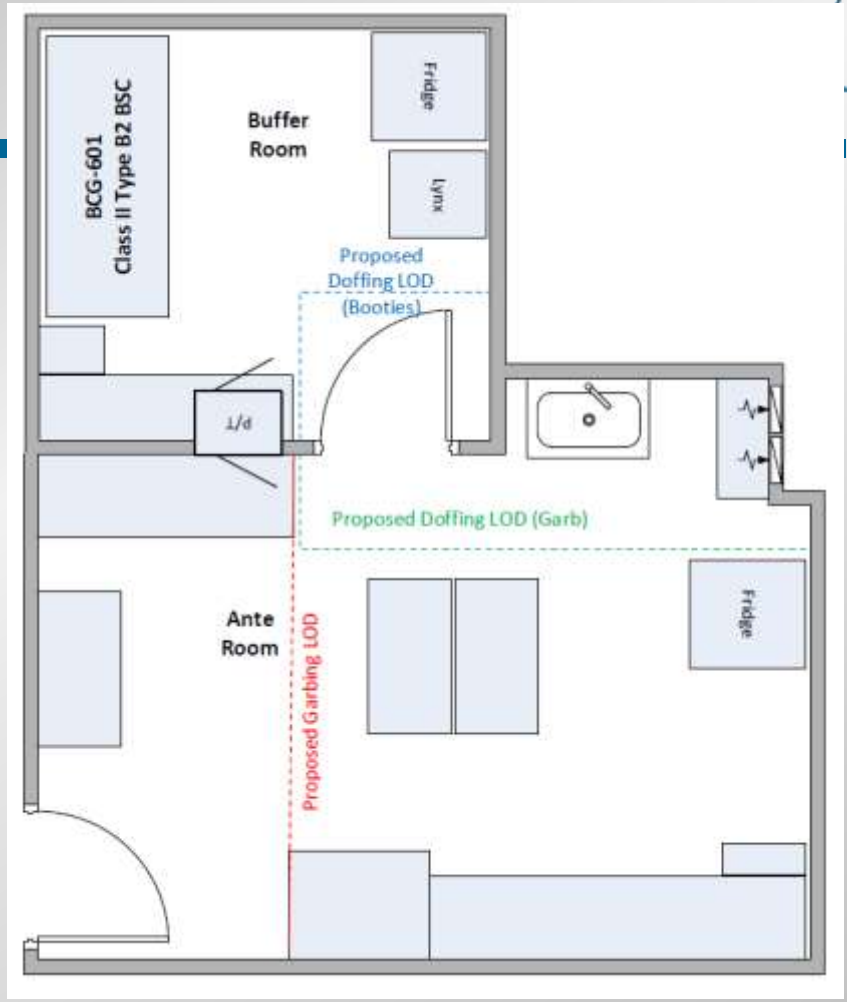
C-SECs for Sterile HD Compounding

- Ante room issues for HD compounding
  - ISO Class 7
    - Positive pressure
    - Minimum 30 ACPH
    - Sources of contamination
  - Sink placement
  - If entering an HD Buffer room from a Non-HD Buffer Room - “A line of demarcation must be defined within the negative-pressure HD buffer area for garbing and degarbing (donning and doffing).”



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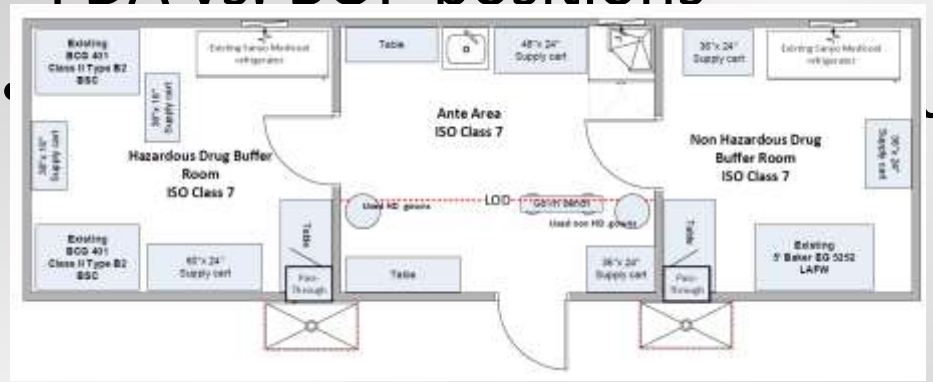
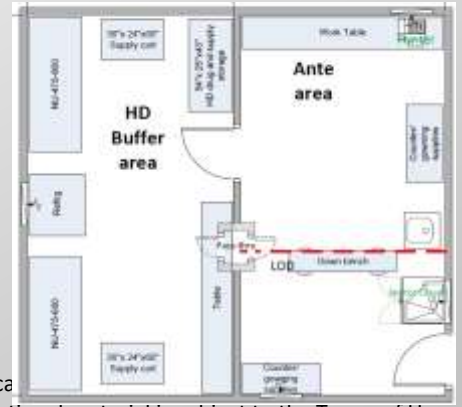
Pass-Throughs for HD Areas

- Transporting materials into and out of the HD buffer room
- Interlocks
- Verify that particles do not compromise the air quality in the buffer room during material transfer
- FDA vs. BOP positions





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Containment Segregated Compounding Area (C-SCA)

- A type of Secondary Engineering Control
  - Unclassified room with fixed walls dedicated to preparation of low to medium risk level HD CSPs
  - Defined perimeter to separate functions
  - Limited to 12 hour BUD (proposed 797 is 12 hour room/24 hour refrigerated)
  - PEC must be externally vented
  - Minimum 12 ACPH (probably have to request from certifier)
  - 0.01” w.c. to 0.03” w.c. negative pressure (request from certifier)
  - Hand washing sink at least 1 meter from C-PEC
    - Can be either inside or directly outside the C-SCA

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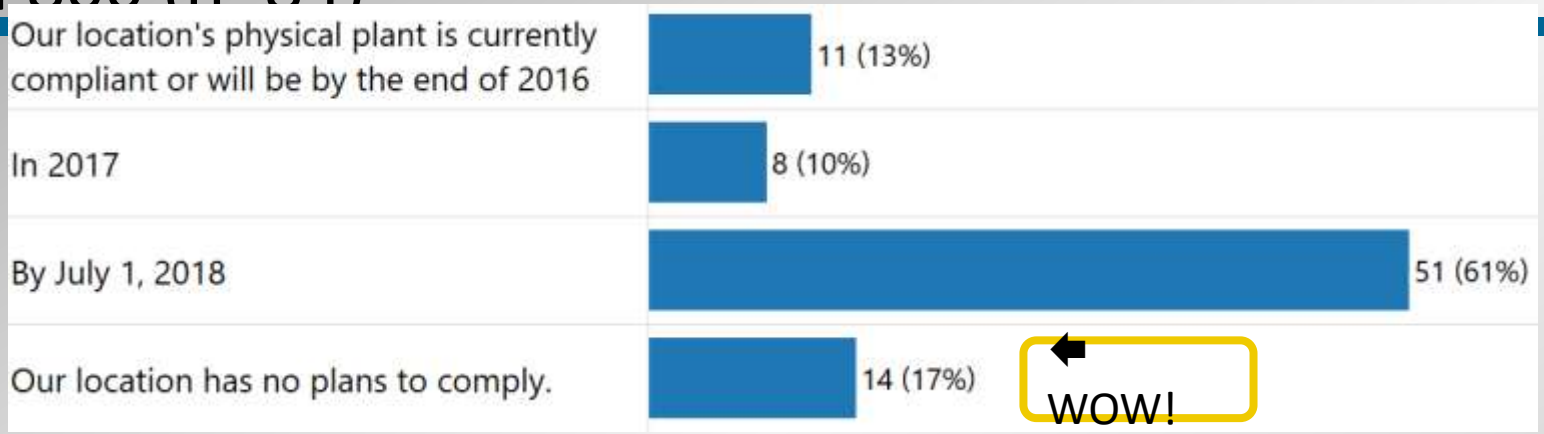
Hospital Expectation for Physical Plant Compliance with 800 (n=84)



By contrast 40% of non hospitals say they have no plans to comply but only 5 locations answered this question.

Demographics

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Secondary Engineering Controls

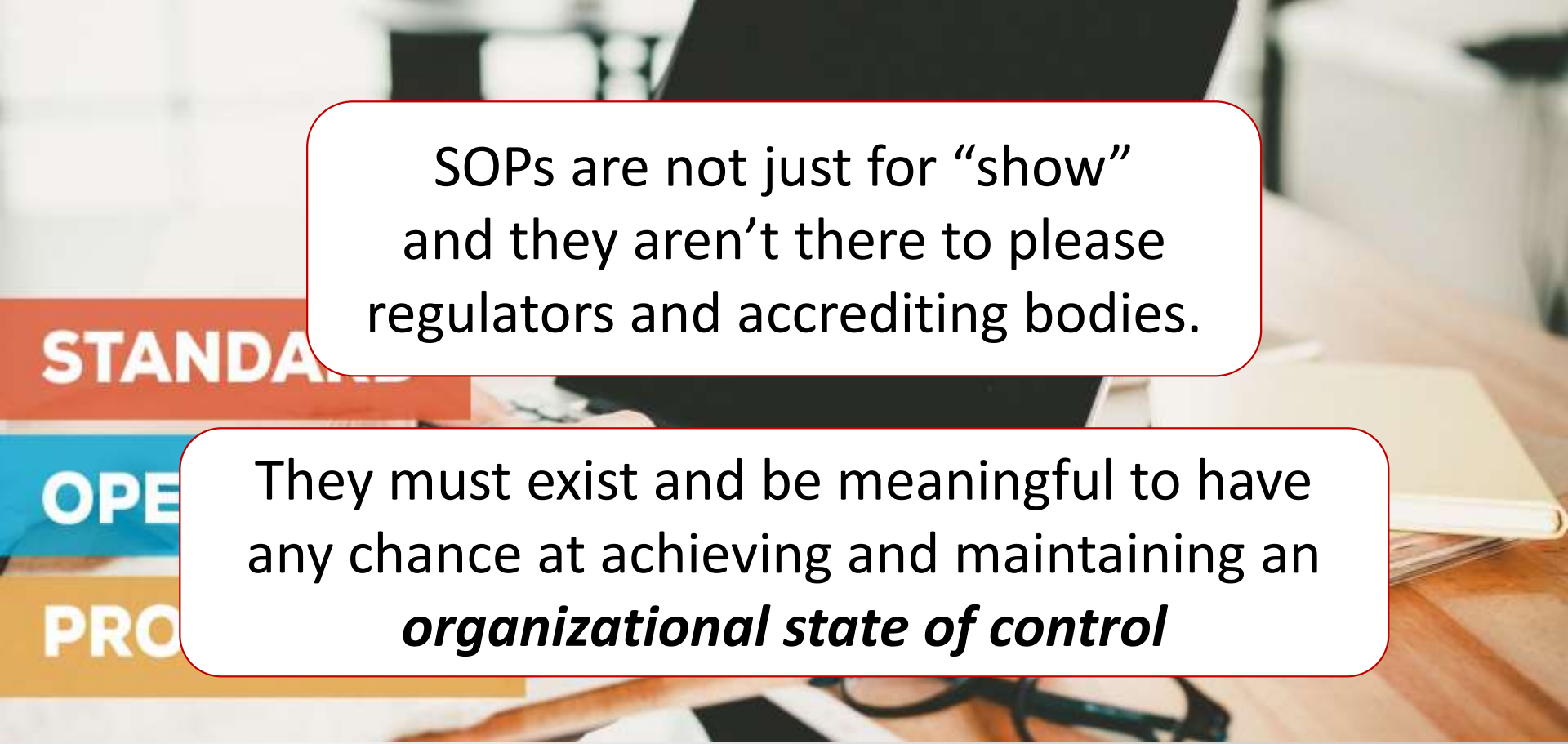
Test	Non Haz Buffer	Anteroom	C-SEC	C-SCA
Airflow	≥30 ACPH (at least 15 ACPH from outside the room)	≥ 20 ACPH (from FDA guidance) but usually more is desirable	≥ 30 ACPH	≥ 12 ACPH for C-SCA or any area where HDs are stored
Room Segregation	Minimum differential pressure of 0.02” w.c. positive from buffer to anteroom and then again from anteroom to adjacent spaces		Minimum differential pressure of negative 0.01 to 0.03” w.c. from C-SEC/C-SCA to adjacent space	
	If displacement airflow (will no longer be acceptable in next official version of Chapter <797>), then velocity of 40 feet/minute from cleanroom to the anteroom across the entire opening		Displacement airflow not allowed in HD compounding	
HEPA Filter Leak Test	All HEPA filters in the secondary engineering controls are tested at each certification. Maximum allowable leakage is 0.01% of the upstream aerosol concentration.			
Smoke Pattern Testing	Buffer rooms must be segregated from the ante-area and all other adjacent spaces. Use smoke around the opening of doors to ensure air is traveling in the correct direction.			
Non-Viable Particle Counts	ISO Class 7	ISO Class 8 unless it serves HD buffer then ISO Class 7	ISO Class 7 in buffer room No ISO required in C-SCA	
	Airborne particle counter used to sample particle levels in all ISO classified locations under dynamic operating conditions			
Temperature	Comfortable, typically a temperature of 64-66°F but Proposed USP 797 requires 20°C (68°F) or cooler			
	Not mandatory at this time but Proposed USP 797 requires relative humidity at or below 60% at all			

Traditional Primary Engineering Controls

TEST	LAFW	BSC (NSF International Criteria)
Placement of Primary Engineering Control	Placed in ISO Class 7 cleanroom; 0.02" w.c. *positive* or SCA	Placed in ISO Class 7 Cleanroom, 0.01 to 0.03"w.c. *negative* to anteroom (if placed in a C-SEC) or negative to the adjacent space (if placed in a C-SCA)
Airflow Velocity	Velocity 80 to 100 feet per minute (fpm) 6-12" from the filter	Downflow Velocity Profile and Face Velocity Tests
HEPA Filter Leak Test	HEPA filters must be certified to be free from leaks > 0.01% of upstream aerosol concentration	HEPA filters must be certified to be free from leaks > 0.01% of upstream aerosol concentration or aerosol penetration not > 0.005% of upstream concentration for filters that cannot be scanned
Airflow Pattern Smoke Test	An observation using smoke to visualize airflow under "dynamic operating" conditions (with pharmacy staff performing surrogate compounding) conducted to confirm that laminarity of the air is undisturbed by compounding processes. Specific smoke pattern tests to ensure the device is functioning properly is also performed under "at rest" conditions.	
Site Installation Assessment Tests	N/A	Verifies that the BSC is properly integrated into the facility by testing airflow and sash alarms; interlocks and exhaust system performance
Non-Viable Particle Counts	Particle counters capable of detecting 0.5 µm size particles are used to verify ISO Class 5 air conditions under dynamic operating conditions	

Compounding Isolator Type Engineering Controls

Test	CAI	CACI	
Placement of PEC	Preferably room or area devoted to compounding but Proposed USP <797> requires placement in an ISO 7 area for full beyond-use dating	Placed in ISO Class 7 C-SEC that is 0.01 to 0.03"w.c. *negative* to anteroom	In C-SCA with at least 12 ACPH and 0.01 to 0.03" w.c. *negative* to adjacent space
Airflow Velocity	Measurement of actual airflow to manufacturer's design intent. The main chamber is expressed as a range of feet/min with a designated % uniformity.		
Chamber Pressure Test	Determines that ante-chamber and main chamber pressures adequate to provide isolator separation between main chamber and ambient spaces. Pressure range determined by manufacturer.		
Site Installation Assessment Tests	Tests to verify proper alarm function; pass-through door interlock function; and proper canopy or exhaust connection performance.		
HEPA Filter Integrity Leak Test	All HEPA filters in the secondary engineering controls are tested at each certification. Maximum allowable leakage is 0.01% of the upstream aerosol concentration.		
Airflow Smoke Pattern Test	An observation using smoke to visualize airflow under *dynamic operating conditions* (with pharmacy staff performing surrogate compounding) to confirm laminarity of the air is undisturbed		
Preparation Ingress and Egress Test	Determine if the pass-through system is capable of supporting material transfer while maintaining ISO Class 5 conditions during the transfer.		
Non-Viable Particle Counts	Particle counters capable of detecting 0.5 µm size particles are used to verify ISO Class 5 air conditions both at rest and during *dynamic operating conditions*.		



SOPs are not just for “show”
and they aren’t there to please
regulators and accrediting bodies.

They must exist and be meaningful to have any chance at achieving and maintaining an ***organizational state of control***

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SOPs must reflect Actual Practice

- Must involve all employees who will have an effect, contribution or influence over the system
- Employees must be process owners and “buy into” the desired state
- The creation of a ***shared vision*** is critical to success
- Try to identify all the roadblocks to success

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Lean: Standard Work

The most efficient method of producing a product or performing a service. It is broken down into elements that are performed in a specified sequence, are organized and followed repeatedly.

Adapted from iSixSigma

1. The major cause of harm to all patients is variation in how procedures/processes are carried out[1]
2. So, if there is a lack of standardization, then by definition, practice is not based on best available evidence

[1]Irving AV. Policies and Procedures in Healthcare Organizations: A Risk Management Perspective. Patient Safety & Quality Healthcare. 2014.

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Maintenance Items

- HVAC Systems
- Exhaust Systems
- Emergency Power Systems
- Room Pressure and Humidity Monitors
- Door Interlock Systems and Operators
- Pass Throughs
- Walls, Floors and Ceilings

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