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Conducting a Gap Analysis for your Cleanroom and the steps towards USP Compliance

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Disclosure

I do not have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context or the subject of this presentation.

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Objectives

- *Understanding the process of conducting risk assessments in pharmacy cleanrooms*
- *Identify common cleanroom challenges*
- *Describe potential solutions and risk mitigation steps*

References…

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Overview

- Cleanroom engineering overview
- USP cleanroom requirements
- Commonly seen issues and solutions
- Performing your own Gap Analysis

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USP Enforcement

- The United States Pharmacopeia (USP) is a non-profit organization that creates reference standards that may be enforced by the federal government or the state
  - Florida Board of Pharmacy
  - The Agency for Health Care Administration
  - Joint Commission
  - FDA
- USP compliance is currently a key component of inspections by the Florida Board of Pharmacy and by TJC

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Cleanroom Engineering

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Engineering Controls

- Eliminate or reduce exposure to a chemical or physical hazard through the use or substitution of engineered machinery or equipment.
- Purpose: Exist to Reduce the risk of a
  - Contamination of a compounded sterile product (CSP)
  - Hazardous drug exposure to personnel
- Types:
  - Primary Engineering Controls (PEC)
  - Secondary Engineering Controls (SEC)

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SEC Requirements

Test	Buffer Room	Hazardous Buffer Room	Anteroom
Airflow	≥30 ACPH (min 15 ACPH from room supply)	≥30 ACPH	Iso 7 vs. 8
Pressure	Min differential Pressure of 0.02" w.c. positive from buffer room to ante room and from ante room to adjacent space	Min differential pressure of Negative 0.01-0.03" w.c. from Hazardous buffer room to adjacent space	Min differential Pressure of 0.02" w.c. positive from from ante room to adjacent space
HEPA filter leak test	All HEPA filters in Rooms are tested for leaks. Max allowable leakage is 0.01% of the upstream aerosol concentration		
Visual Smoke Study	A visible source of smoke, which is neutrally buoyant, is used to verify an absence of stagnant airflow where particulates can accumulate		
Non-Viable Particle Counts	ISO 7	ISO 7	ISO 7 (next to hazardous buffer room) ISO 8 (next to regular buffer room)
Temperature and Humidity	Final version of USP 797 has recommendations but nothing mandated. Temperatures at or below 20 degrees C or cooler and Humidity at or below 60%		

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Cleanroom Engineering

- Air coming into the room
  - Supply
- Air leaving the room
  - Return or Exhaust
- The difference in supply and exhaust/return creates differential pressure

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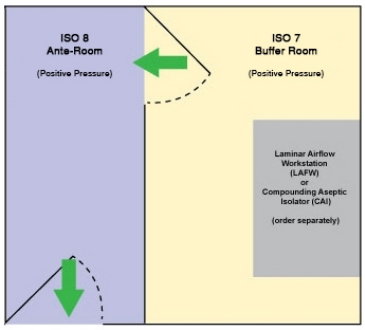

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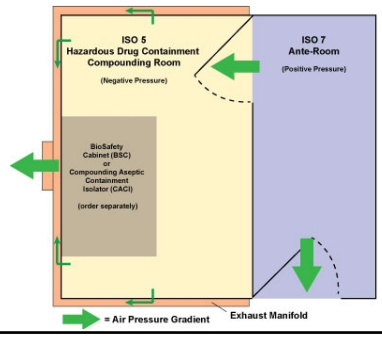

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Supply Air

- Air is supplied into a building through an air handling unit (AHU)

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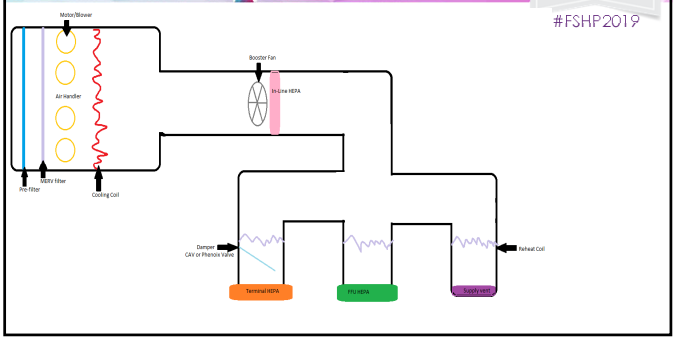

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Exhaust/Return Air

- Air can leave a room in a few different manners
  - Returns (non-hazardous rooms)
    - Will re-circulate
  - Exhaust (exhausted completely out or a room/building)
    - Exhaust from Biological Safety Cabinet
    - Exhaust from the hazardous compounding room or hazardous storage room

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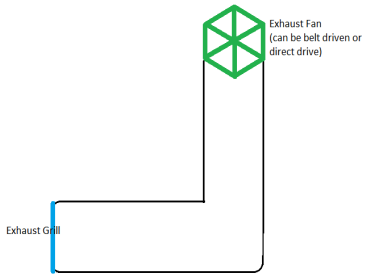

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USP Requirements

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PEC Requirements

Test	LAFW	BSC
Airflow Velocity	(Supply Air velocity) Velocity 80 -100 fpm 6-12" from the filter	Downflow Velocity Profile and Face(inflow)Velocity Tests
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Non-Viable Particles	ISO 5	ISO 5
Smoke Pattern Testing	Observation using smoke to visualize airflow under dynamic conditions to confirm the laminarity of the air is undisturbed by compounding processes.	
Site Assessment	NA	Window Sash alarm

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Common Cleanroom Challenges

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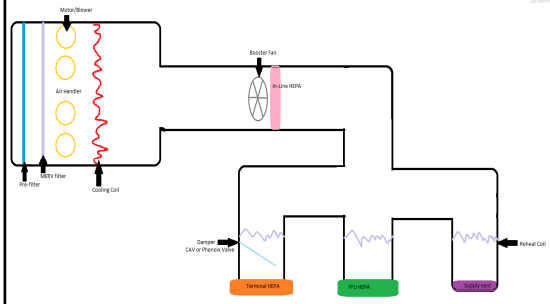

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Engineering and Design

Challenges:

- Poorly designed airflow
  - Insufficient Air Supply/Not enough or too much exhaust
  - Cause: Improper Engineering Design
    - Low capacity AHU
    - Non-dedicated AHU
    - Designing based on minimum standards
  - Effect:
    - Not enough ACPH or insufficient ACPH for the space
    - Room pressurization issues
    - Temperature/Humidity challenges
      - Need to consider location of cleanroom (Florida vs. Colorado)
      - Realistic expectations of temperature and humidity, considering size of space, equipment needed and number of personnel to be in the room as well as gowning requirements for the space
- Overloaded/damaged filters
- Broken fans
- Humidity
- Dampers

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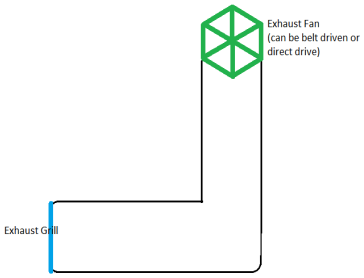

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Engineering and Design

Challenges:

- Belt driven exhaust vs. direct drive
- Preventative maintenance and challenge of repair/replacement
- Too much or too little exhaust
  - USP 800 requirements to consider

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Engineering and Design

Opportunity:

- Engineering challenges are complex and often need significant review to identify challenges
- Depending on the issue facilities, engineering and test and balance companies may need be used

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HEPA Filtration

Challenges:

- Damaged or inappropriately installed HEPA filters
  - Facilities departments have historically been installing filters
    - No expertise, considerable damage to the filters during install
      - Certifiers or another expert needs to be replacing/installing filters
      - NOTE: HEPA filters need to be tested and certified right after install
    - HEPA filters installed backwards
    - HEPA filters not tested for leaks
    - No HEPA filters
- In-Line vs. Terminal HEPA filters

Opportunity:

- Terminal 99.99% HEPA filters on all supply ducts/or FFU's
  - Port for leak testing
- Installed and certified by reputable CETA certifies upon install

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Primary Engineering Controls

Challenges:

- Non-Hazardous (LAWF, Flow Zones)
  - Rust
  - Non-stainless steel deck
  - Damaged HEPA filter
    - Often not tested
  - Broken plexiglass panels
- Failed smoke studies
  - Common with Laminar flow work zones
  - Fundamental design is flawed
- Biological Safety Cabinets
  - Lack of dampers
  - Lack of port in exhaust duct to check pressure/exhaust HEPA filter integrity
  - Belt Driven vs. Direct Drive Exhaust

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Primary Engineering Controls

Opportunity:

- Furnishing non-hazardous cleanroom with Laminar Flow Hoods which are the industry gold standard.
- Make sure you are using a reputable certifier and oversee certification
- Train staff on proper cleaning to not damage HEPA or diffuser screens
- Stainless steel deck

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State of Control

- Air and Surface testing (Viable Sampling) is required per USP <797>
  - Every 6 months for air sampling
  - Monthly for surface sampling
- The purpose is to identify living organisms outside of an acceptable range that increase the risk of contamination of compounded sterile products
- It is a necessary to identify sources of contamination and to remediate the underlying issues
  - Facilities design, improper gowning, HVAC, cleaning etc.

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State of Control

- Environmental sampling is one component of maintaining a clean environment
- It is very possible to pass environmental sampling even with dirty rooms or broken HEPA filters
- Passing EM's doesn't mean there are no issues with a cleanroom
- Out of Spec EM's are however indicative of underlying causes such as improper cleaning or personnel practices or facilities and engineering

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Cleanroom Layout

There are multiple layout options for cleanrooms, upcoming USP <800> specifies optimal and suboptimal cleanroom layouts to minimize contamination.

Challenges:

- No clear Line of Demarcation
- Improper location of sink in Ante room
- Hazardous room location

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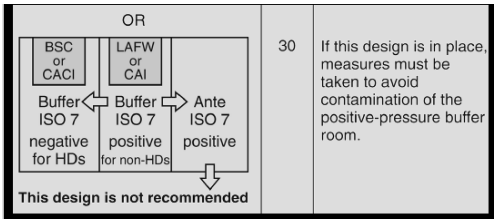
Cleanroom Layout



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Cleanroom Layout

Opportunity:

- Redesign cleanroom with recommended layout for hazardous sterile compounding per USP <800>
- Create LOD for hazardous and ante rooms
- Re-locate sink

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Room Airflow

"Air supplied to the cleanroom suite must be introduced through HEPA filters that are located in the ceiling of the buffer and ante-rooms. Air returns in the cleanroom suite must be low on the wall unless a visual smoke study demonstrates an absence of stagnant airflow where particulate will accumulate."

Challenges:

- Cleanroom has returns mounted into the ceiling
  - This type of return will circulate the air from the ceiling to the return adjacent to it
  - Will not allow for the air to properly circulate through the room to sweep away particulates to keep the air clean

Opportunity:

- Replace ceiling mounted return with low wall returns

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Pressure, Temperature and Humidity

- USP <800> requires pressure differential requirement of -0.01 to -0.03 in wc for hazardous rooms
- USP <797> requires positive pressure rooms to maintain pressure at 0.02 in wc or more
- Temperature and Humidity control and monitoring is required, guidelines recommend 68 degrees Fahrenheit or ideally less and <60% RH

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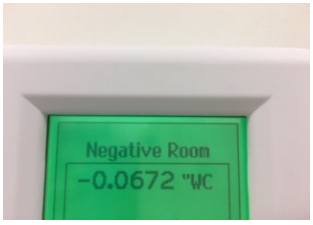
Pressure, Temperature and Humidity



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Pressure, Temperature and Humidity

Challenges:

- Challenge to maintain appropriate pressures
  - Issues with exhaust, generator testing, CAV programming, slow opening dampers
- Temperature control issues
- Humidity control issues

Opportunity:

- Engage appropriate SME's (engineers, air balancers) to evaluate needs of the space and develop appropriate action plan
- Find the right garb for staff to feel comfortable

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Pressure Relief Dampers

Challenge:

- The air in the cleanroom suite is balanced via pressure relief dampers on the doors/walls of the cleanroom
  - Increases risk of particulate and microbial contamination of hazardous compounding room and Ante room.
  - pressure Ante room are balanced via the use of pressure relief dampers

Recommendation:

- Rebalance space without use of pressure relief dampers
  - Will require Test and Balance/engineering

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Cleanability

- "The surfaces of ceilings, walls, floors, doors, door frames, fixtures, shelving, work surfaces, counters, and cabinets in the classified area must be smooth, impervious, free from cracks and crevices, and non-shedding so they can be cleaned and disinfected and to minimize spaces in which microorganisms and other contaminants can accumulate. Surfaces should be resistant to damage by cleaning agents, disinfectants, sporicidal agents, and tools used to clean. Junctures between the ceiling and the walls and between the walls and the floor must be sealed to eliminate cracks and crevices where dirt can accumulate. If ceilings consist of inlaid panels, the panels must be caulked around each panel to seal them to the support frame…. Classified areas should minimize dust-collecting overhangs such as utility pipes and ledges such as windowsills."

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Cleanability

Challenges:

- Cleanroom suite is designed with multiple ledges, window sills, cracks and crevices.

Opportunity:

- Remove windows/window sills and install flush mounted windows if window is necessary
- Ensure all flooring is sealed properly and caulked/welded
- Remove any unnecessary ledges on walls and caulk items that are not removable to create an angle to minimize dust from settling

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Cleanability

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Cleanability

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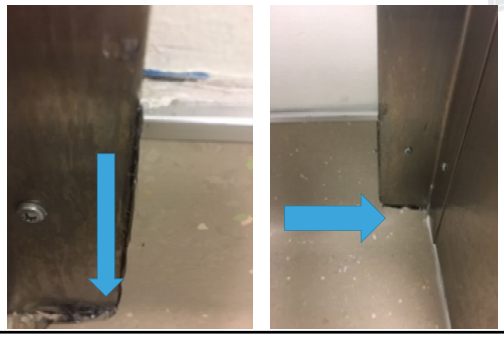

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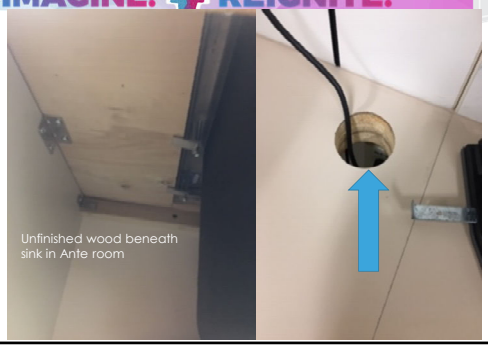

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Walls

"Walls must be constructed of, or may be covered with, durable material (e.g., epoxy painted walls or heavy-gauge polymer) and the integrity of the surface must be maintained. Panels must be joined together and sealed to each other and the support structure."

Challenges:
- Inappropriate paint on walls
  - The paint on the walls of the cleanroom easily rubs off with Isopropyl Alcohol.
- Basic wear and tear

Opportunity:
- Epoxy paint
- Wall covering (more durable)

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Pass-Throughs

Challenges:
- Non-Interlocking
- Rusty
- Gaps
- Refrigerated

Opportunity:
- Interlocking, non refrigerated fully sealed pass-through
- Consider HEPA filtration

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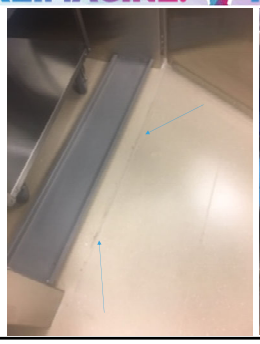

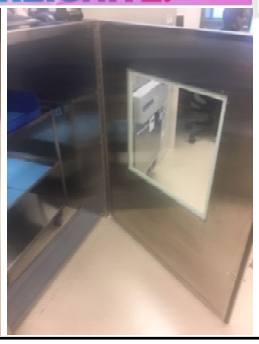

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Doors

Challenges:
- Regular doors (unfinished particle board on top
- Non-interlocking
- Not hands free

Opportunity:
- Replace doors with interlocking, hands free system

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Sinks

Sinks present a water source and therefore increase the risk of contamination

Challenges:
- Not hands free
- Small (causes splatter)
- Porcelain (microscopic cracks for bacteria to dwell)
- Particle board beneath
- Exposed pipes
- Rust

Opportunity:
- Stainless steel hands free surgical sink

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Flooring

"Junctures between the ceiling and the walls and between the walls and the floor must be sealed to eliminate cracks and crevices where dirt can accumulate…Floors must include coving to the sidewall, or the juncture between the floor and the wall must be caulked."

Challenges:

- Improperly sealed flooring creating gaps and crevices that cause particulate accumulation

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Ceilings and Lights

- "If ceilings consist of inlaid panels, the panels must be caulked around each panel to seal them to the support frame…..The exterior lens surface of ceiling light fixtures must be smooth, mounted flush, and sealed. Any other penetrations through the ceiling or walls must be sealed."

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Ceilings and Lights

Challenges:

- Uncaulked ceiling tiles
  - and are easily movable/removable which opens the room up to the unfiltered and uncontrolled environment above the ceiling.
- Non- cleanroom light fixtures were not intended for use in cleanrooms.
  - Open housing
  - Fixture is surrounded by a gap which is open to the plenum of ceiling.
  - Not flat – not cleanable

Opportunity:

- Cleanroom ceiling times or solid surface ceiling.
  - Consider gasketed grid for ceiling tiles
- Sealed cleanroom light fixtures

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Conducting your own Gap Analysis

- Review your certification reports
- Observe the next certification, ask questions and make sure you check off every single required test as being completed
- Engage your facilities department to understand your current AHU design
- Get in the cleanroom and look at everything

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References

- USP Chapter <797> *Pharmaceutical Compounding-Sterile Preparations*. United States Pharmacopeia 40-National Formulary 35.; 2019.
- USP Chapter <800> *Hazardous Drugs – Handling in Healthcare Settings*. United States Pharmacopeia 40-National Formulary 35.; 2019.

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