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ENGINEERING CONSIDERATIONS FOR CERTIFYING CONTROLLED ENVIRONMENTS

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ENGINEERING CONSIDERATIONS FOR CERTIFYING CONTROLLED ENVIRONMENTS

- Basis of discussion
  - Lessons learned from applying certification principals applicable to GMP facilities to other regulated disciplines – Sterile Compounding Facilities
  - Guidance for Industry
    - FDA
      - Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice
    - USP (inspected by BOP, DPH, TJC)
      - Chapters <797> & <800> for Compounding sterile preparations
      - 503A facilities vs. 503B
  - What can we learn from certification of sterile compounding facilities to apply to Sterile Manufacturing facilities

CONCEPTS

- What is Certification?
  - Certification is an independent evaluation of critical environments using consensus-based industry standards to establish test procedures (SOPs) and acceptance criteria.
  - Certification is the process of determining if the performance criteria is met.
- Certification vs. Validation
- Certification as a component of Commissioning
- Commissioning's role in certification

CERTIFICATION

- What is Design Criteria?
  - Criteria that designers should meet in designing a system or device – general guidance
    - ISO Class X under dynamic operating conditions
    - HEPA filters located in the ceiling
- What is Performance Criteria?
  - A description of the characteristics to be assessed for a given task. Performance criteria must be specific to the device being tested – specific guidance
    - XX ACPH based on HEPA filtered air supplied to the room through the HVAC

WHAT QUALIFIES A CERTIFIER TO CERTIFY ENGINEERING CONTROLS

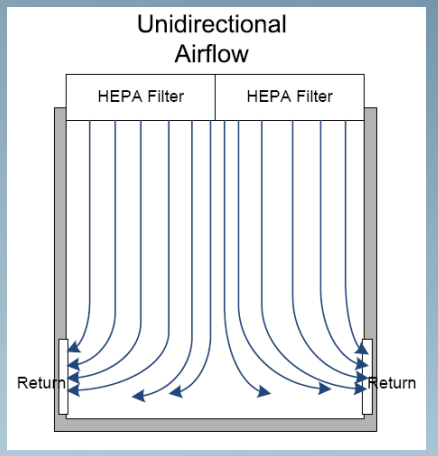
- There are two accreditation programs for Sterile compounding facility certification professionals
  - NSF International accreditation program for certification of Class II BSCs.
  - CETA International CNBT-SCF program for certification of sterile compounding facilities.
- There is no accreditation program for certifiers of GMP sterile manufacturing facilities.
  - Relies on in-house vetting of certifier capabilities

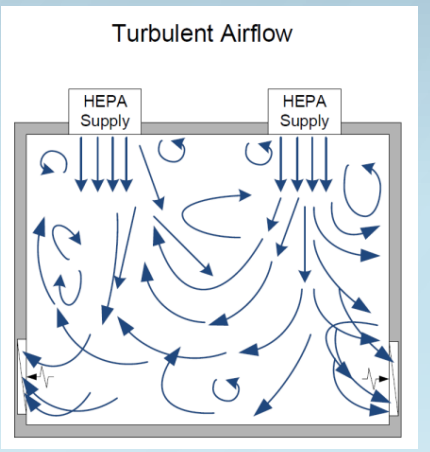
WHAT INDUSTRY GUIDELINES SHOULD BE USED FOR CERTIFICATION

- GMP Sterile Manufacturing facilities
  - Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice
  - CFR parts 210 and 211
- Sterile Compounding Facilities
  - CETA CAG-003-2006
    - The CETA document provides a list of recommended tests to be performed along with the appropriate industry standard for the each procedure. The industry standards referred to include:
      - CETA CAG-002-2006
      - ISO 14644-1
      - ANSI/NSF std 49
      - IEST-RP-CC006
      - IEST-RP-CC034

AIRFLOW TESTING IN PHARMACEUTICAL STERILE MANUFACTURING AREAS

- Critical Area (ISO Class 5)
  - Unidirectional airflow
    - Flow controlled areas are measured in terms of velocity.
    - IEST-RP-CC006
- Controlled Area (ISO Class 6,7,8)
  - Turbulent airflow
    - Dilution control areas are measured in terms of air change rates, volumetric airflow
    - IEST-RP-CC006





AIRFLOW TESTING

- Establish a "State of Control" for every Cleanzone
  - Repeatability vs. Accuracy
  - Use airflow visualization studies to verify or determine acceptance criteria in unidirectional airflow zones.
  - It is not unusual to have different acceptance criteria for similar devices depending on how the devices are used.
    - Loading (how much "clutter")
    - Powders vs. liquids
    - Flat surfaces vs. "stealth" surfaces

AIRFLOW TESTING

- Equipment for testing airflow velocity for unidirectional airflow
  - Thermal anemometer
    - +/- 3% of reading or +/-3 fpm
  - Multi-Point Array (Velgrid)
    - +/- 3% of reading +/-7 fpm
  - Where feasible, use a suitable stand to stabilize the readings.

AIRFLOW TESTING

- Acceptance Criteria for Unidirectional Airflow (Cleanrooms)
  - FDA Aseptic Processing Guide
    - "HEPA filtered air should be supplied in critical areas at a velocity sufficient to sweep particles away from the filling/closing area and maintain unidirectional airflow during operations. The velocity parameters established for each processing line should be justified…"
    - "A velocity of 90 FPM has generally been established, with a range of plus or minus 20% around the set point. Higher velocities may be appropriate in operations generating high levels of particulates"
  - USP <797>
    - "Unidirectional airflow must be maintained in the PEC. HEPA-filtered air must be supplied by the PEC at a velocity sufficient to sweep particles away from critical sites and maintain unidirectional airflow during operations."

AIRFLOW TESTING

- Acceptance Criteria for Unidirectional Airflow (LAFWs)
  - IEST-RP-CC002
    - References 80-100 fpm or as specified by the device manufacturer
  - Other
    - Defer to the device manufacturers recommendations
    - Default position is 80-100 fpm, but other ranges are acceptable if supported by airflow visualization studies

AIRFLOW TESTING

- Non-unidirectional airflow (Controlled Areas)
  - 2004 FDA Aseptic Processing Guide:
    - Minimum of 20 air changes per hour for Class 100,000 (ISO Class 8) support rooms
    - Significant more for cleaner classifications or areas prone to contamination
  - Required Test:
    - Airflow volume to determine air exchange rate

AIRFLOW TESTING

- Equipment for testing volumetric airflow
  - IEST RP CC006
    - "The measurement of supply airflow volume is preferable to the measurement of airflow velocity and is a more representative test of the final filter air supply"
  - Capture Hood
    - +/- 3% of reading +/-7 fpm

AIRFLOW TESTING

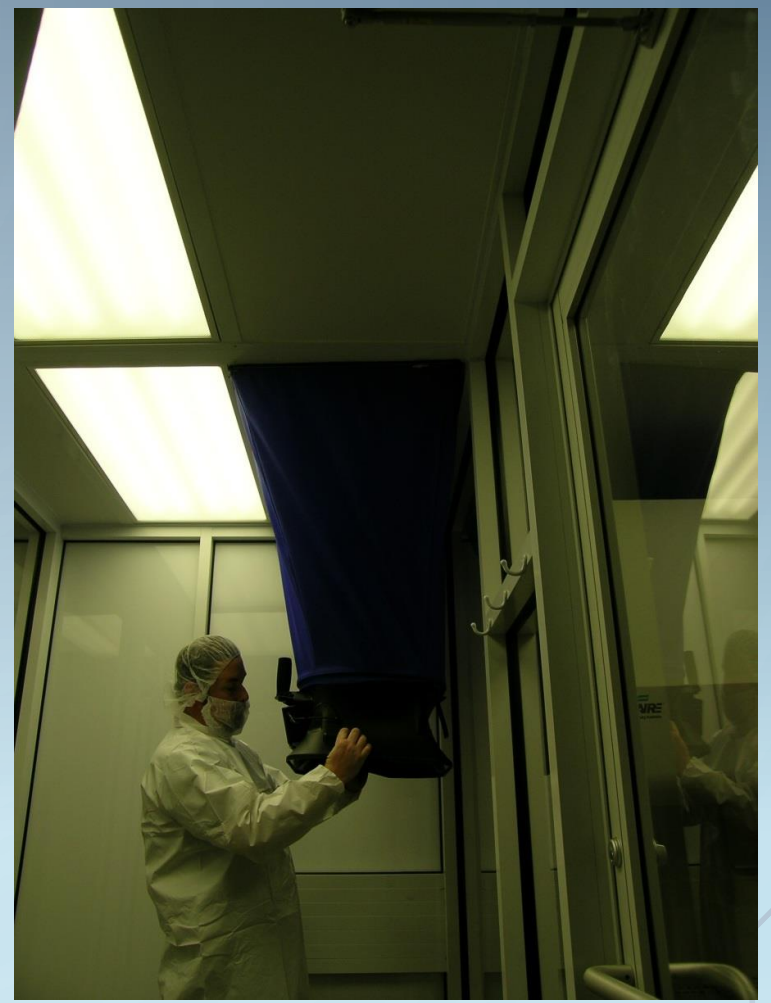
- Non-unidirectional airflow (Controlled Areas)
  - The rule of thumb for determining which air source contributes to the total room supply conditioned air is that the air must come from outside the room or exit the room & re-enter.
    - Laminar flow hoods recirculating within a room do not contribute to the total airflow. except…
      - Quench air supply that comes from outside the room.

AIRFLOW TESTING

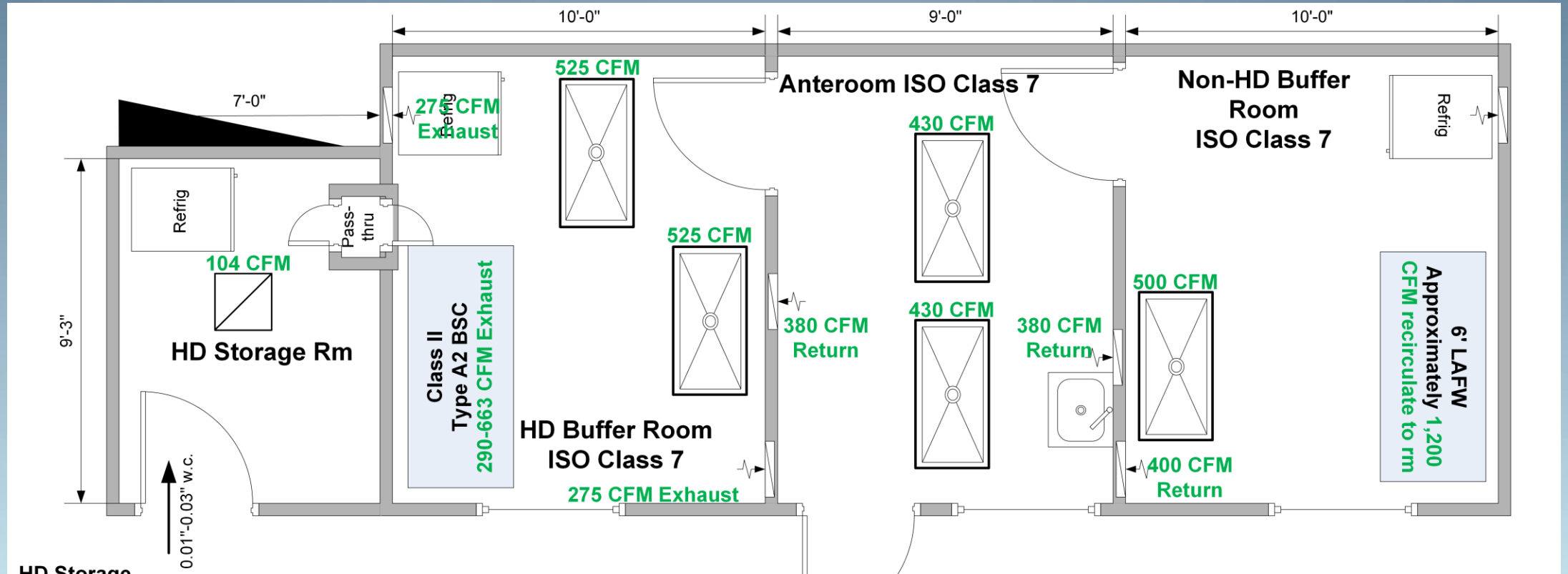
- Non-unidirectional airflow (USP Chapters)
  - Air change rates for purposes of maintaining ISO Classification are based on *Supply* air for positive **AND NEGATIVE** pressure rooms (priority to HEPA filtered air to dilute particulate burden).
    - In conflict with traditional balancing paradigms
      - Air exchange rates are typically based on whichever airflow volume is greatest

AIRFLOW TESTING

- Acceptance Criteria for turbulent airflow
  - GMP - FDA
    - Minimum 20 total ACPH for ISO Class 8
      - Significantly more for cleaner spaces
  - Compounding - USP
    - Minimum of 30 total Air Changes per Hour (ACPH) of HEPA filtered air for the ISO class 7 cleanroom.
    - Minimum of 20 total Air Changes per Hour (ACPH) of HEPA filtered air for the ISO class 8 cleanroom.
    - Use of recirculated HEPA filtered air from primary engineering control can contribute to the total as long as at least 15 ACPH comes from outside the room.
  - Establish "state of control" value
    - If initial test indicates significantly more than the minimum, the "state of control point" should be adjusted to design or actual.
    - The minimum is not adequate for every application



SAMPLE AIRFLOW PROJECTIONS- COMPOUNDING FACILITY



HD Storage

Rm Exhaust	104 CFM
HEPA Supply	**0 CFM**
RM. Volume	520 FT^3
Rm. Air Change	12 **ACPH**
Ceiling Height	8'

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	**58 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'

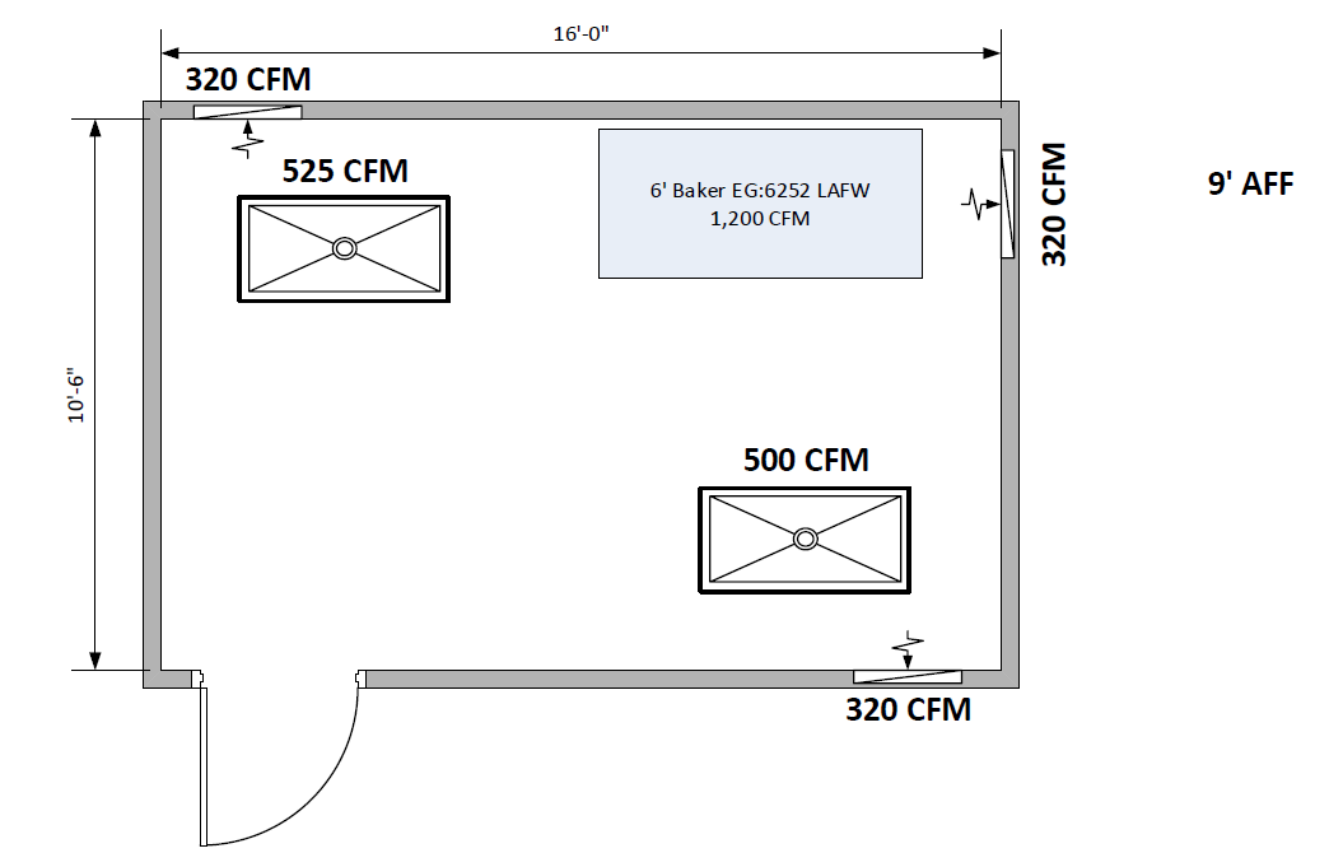
State of Control Points

REPORTABLE ACPH PER INDUSTRY

- What is the HEPA filtered air exchange rate for the following room?

Room Volume	1,512 FT^3	
HVAC	1025 CFM	41ACPH
Primary EC	1,200 CFM	48 ACPH
Functional (total)		89 ACPH

GMP?
Compounding?



CERTIFICATION OF SECONDARY ENGINEERING CONTROLS

- Smoke Pattern Test
  - An airflow smoke pattern test must be performed on all unidirectional airflow ISO class 5 clean-zones. A visible source of smoke such as a glycol based fog generator is generated directly downstream of the diffuser and then observed as it flows across the compounding area and to a return or out of the critical area.
    - Note that this test is not performed on a typical ISO class 7 room.

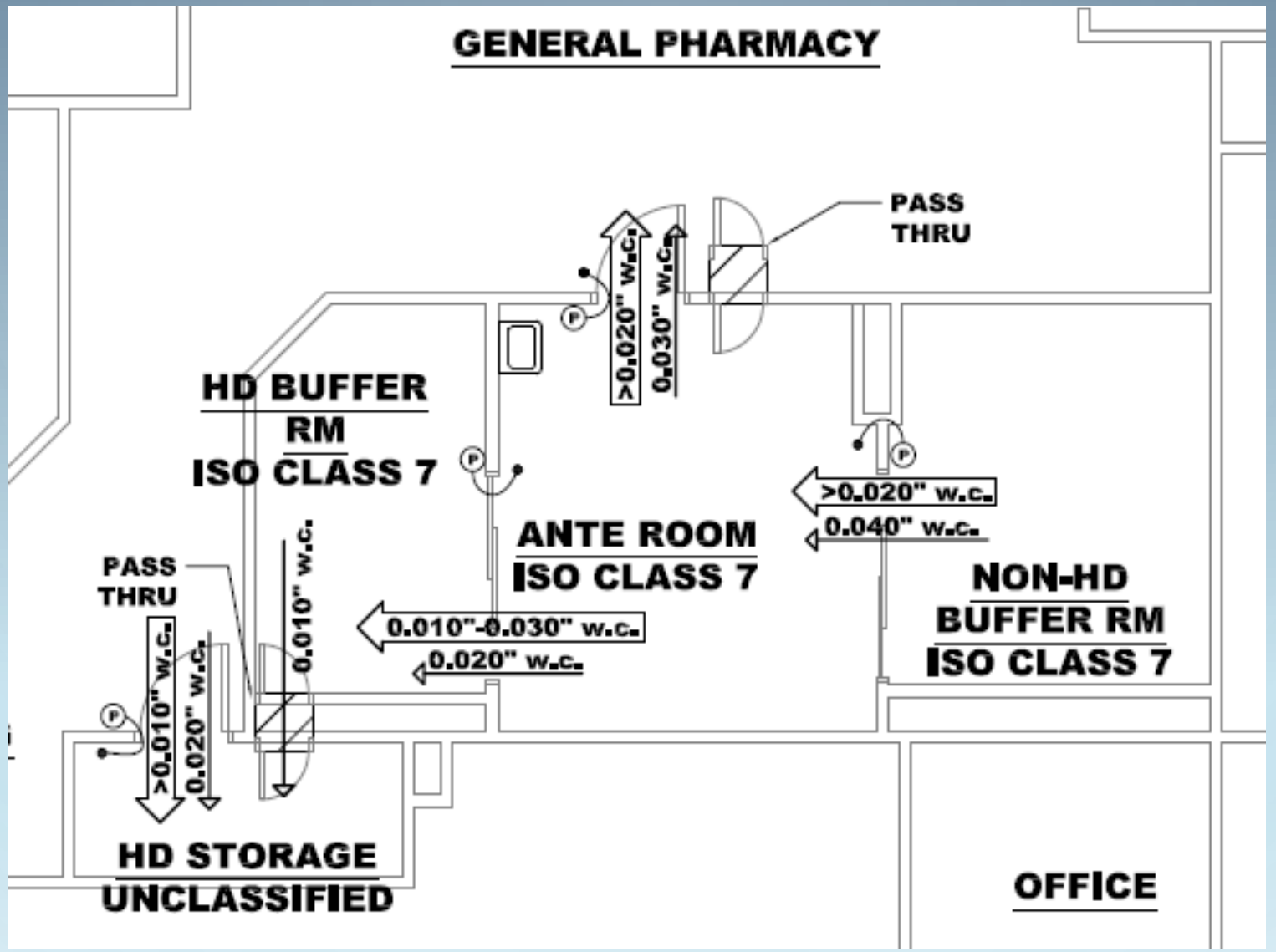
CLIP FROM COMPOUNDING TRAINING SMOKE STUDY

SMOKE STUDY FOR ISO CLASS 7 COMPOUNDING ANTEROOM WITH CEILING MOUNTED RETURNS

CERTIFICATION OF SECONDARY ENGINEERING CONTROLS

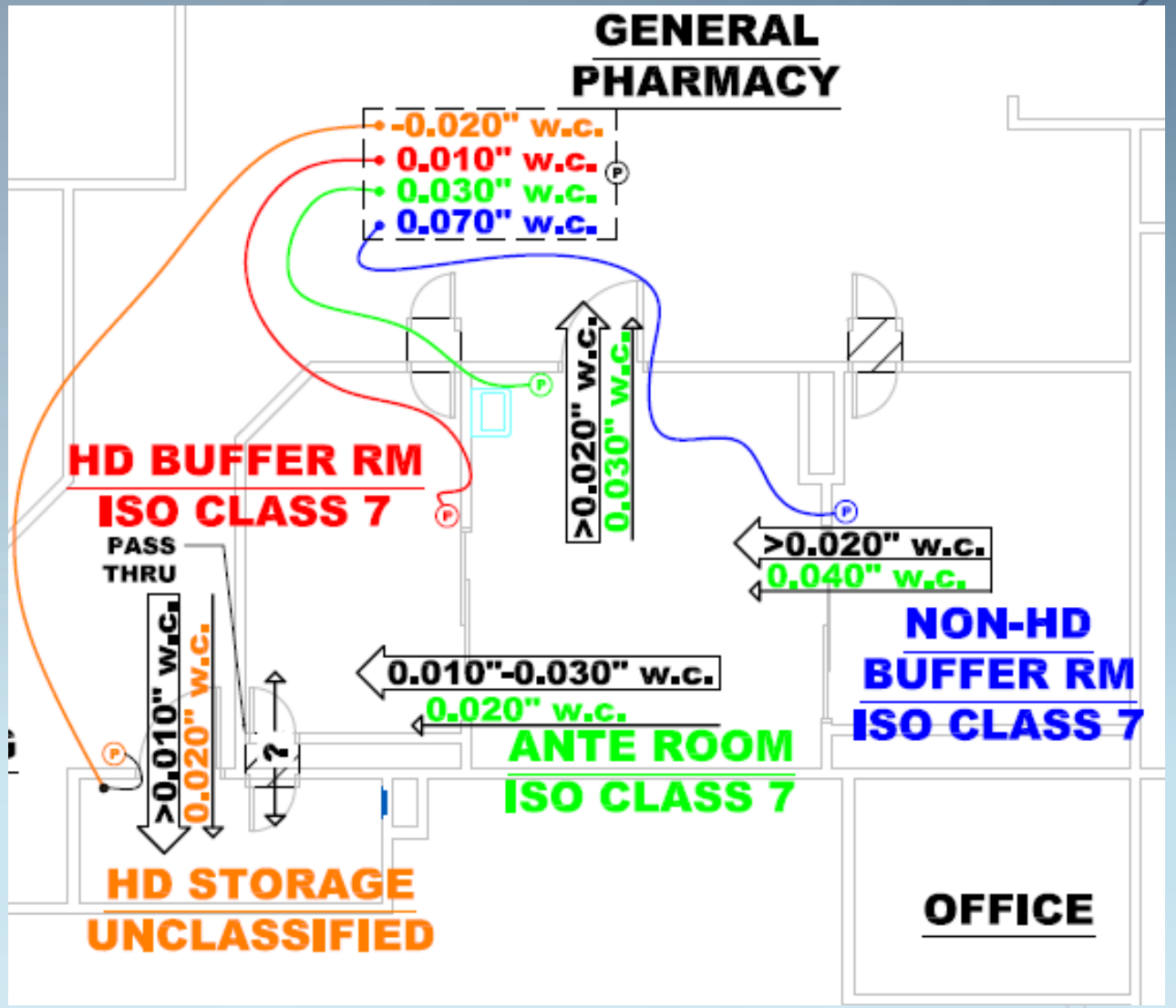
- Room Pressure – USP Chapters
  - Differential positive pressure is required to prevent airflow from an area with lower air-quality classification to another area of higher air-quality classification. The pressure differential between the ante-room and the unclassified area must not be less than 0.020-inch water column.
    - At least 0.020 inches water column (w.c.) positive pressure (<797>)
    - Between 0.010" to 0.030" w.c. negative pressure (<800>)
  - Must be continuously monitored
- Room Pressure – FDA Aseptic Processing Guide
  - At least 0.04" w.c. to 0.06" w.c. between rooms of differing classification
  - At least 0.05" w.c. between a classified and unclassified room

AIRFLOW STATE OF CONTROL-ROOM PRESSURE COMPOUNDING PHARMACY



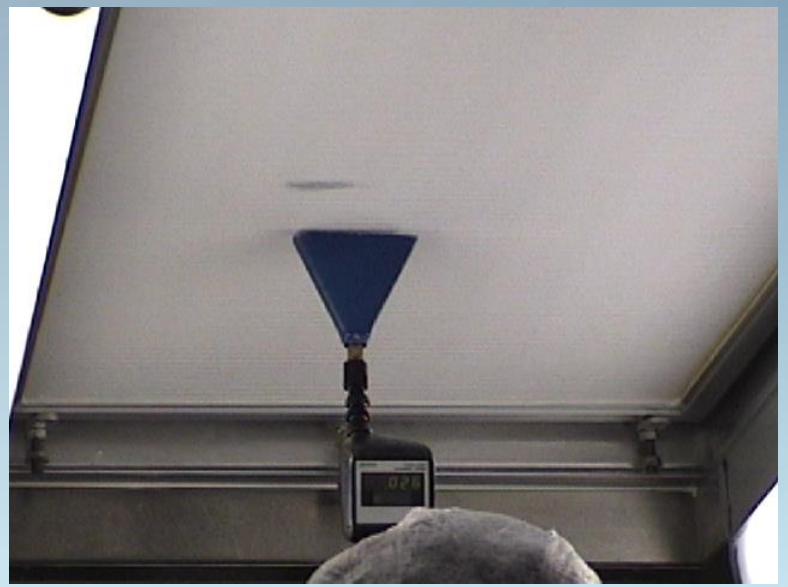
AIRFLOW STATE OF CONTROL-ROOM PRESSURE

- Room pressures to a reference point vs. at the door
- Affects of building pressure on room pressure
  - Seasonal differences
- State of Control Priority
  - Room air change rate or room pressure?
  - Control to priority



CERTIFICATION OF SECONDARY ENGINEERING CONTROLS

- HEPA Filter Installation Leak Test
  - GMP – FDA & Compounding USP <797>
    - All HEPA filters must be leak tested at every certification with an aerosol challenge and photometer.
    - IEST-RP-CC034
    - CETA CAG-003
  - Particle counters for HEPA filter leak testing not appropriate
    - NSF investigation
  - Aerosol Introduction
    - Room-Side-Introduction
    - Remote introduction systems



CERTIFICATION OF SECONDARY ENGINEERING CONTROLS

- Total Particle Count Survey – USP Chapters
  - Rooms shall be certified to the appropriate cleanliness levels at each certification – Every 6 months.
    - ISO 14644-1
      - Buffer room - ISO Class 7
      - Ante room - ISO Class 8 or 7
      - Count particles 0.5 micrometers and larger
      - Dynamic operating conditions
- Non-viable Particle Count Survey – FDA
  - During each production shift
    - Continuous monitoring

CERTIFICATION FREQUENCY

- USP chapter <797>
  - Every 6 months
- NIOSH alert @ hazardous drugs
  - Every 6 months
- CAG-003-2006
  - Not specified
- FDA
  - Every 6 months

SUMMARY

- Proper certification is required to be assured that the engineering control that is relied on for a particle free work environment is providing the required atmosphere. Most of the certification processes used in compounding facilities have been based on processes used in the GMP pharma world. Differences in processes have justified some differences in facility requirements and testing processes.