It is relatively easy to keep an unoccupied cleanroom clean.

Human activity is the primary source of contamination of a cleanroom.
Define areas from most to least clean

From outside toward the center
Each area is cleaner

Goal is to reduce probability of contamination of CSPs

Levels of “Clean”

<table>
<thead>
<tr>
<th>Older Classification</th>
<th>Particle(^1) Count Limit/cu. Ft.</th>
<th>ISO Class</th>
<th>Particle(^1) Count Limit/m(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1</td>
<td>1</td>
<td>ISO 3</td>
<td>35</td>
</tr>
<tr>
<td>Class 10</td>
<td>10</td>
<td>ISO 4</td>
<td>352</td>
</tr>
<tr>
<td>Class 100</td>
<td>100</td>
<td>ISO 5</td>
<td>3,520</td>
</tr>
<tr>
<td>Class 1,000</td>
<td>1,000</td>
<td>ISO 6</td>
<td>35,200</td>
</tr>
<tr>
<td>Class 10,000</td>
<td>10,000</td>
<td>ISO 7</td>
<td>352,000</td>
</tr>
<tr>
<td>Class 100,000</td>
<td>100,000</td>
<td>ISO 8</td>
<td>3,520,000</td>
</tr>
</tbody>
</table>

\(^1\) ≥ 0.5 microns in diameter
HEPA-filtered air
(even the “dirty side” of the garbing area should be cleaner than the general pharmacy)

HEPA-filters remove 99.9% of particles > 0.5 microns.

- Pharmacy air goes through a HEPA filter into the cleanroom
- Cleanroom air goes through a HEPA filter flows across the critical compounding area.

HEPA filter reduces the # of particles by 1000, a 3 log reduction.

If Pharmacy air through HEPA filter critical compounding area,
• Would have too many particles to meet the specification
• Would have to replace the HEPA filter often ($$$)
HEPA Filters

• US Dept of Energy standard
  • HEPA Filter \( \rightarrow \) Removes at least 99.97% of particles \( \geq 0.3 \) microns in diameter

• European Union standard
  • H13 Filter \( \rightarrow \) removes at least 99.95% of a specific particle size
  • H14 Filter \( \rightarrow \) removes at least 99.995% of a specific particle size

Be careful of terms such as “HEPA-like”

Pre-Filters for ISO 5 PECs

• Where to find the pre-filter on the unit?

• How often to replace?
To maintain the level of clean:

- Special filtration or treatment systems for incoming air
  - HEPA filtered air from the ceiling
- Air-lock entry portals
  - Currently uncommon
- Sticky mats to remove particulate matter from shoes
  - NOT inside the cleanroom complex. Perhaps near the entrance to the ante-room or a few feet from the entrance. Must be replaced often.
- Positive room air pressure to reduce contaminant entry from adjacent rooms
  - Pressure difference ≥ 0.020 inches of water (> 0.005% of an atmosphere [5 ten thousandths])
- Personnel movements should avoid creating turbulence
  - Do not move quickly.
  - When moving around in the cleanroom, think about airflow and how you are disturbing it.
  - Avoid restocking during compounding → no unnecessary movements during compounding.
- Personnel hygiene
  - Personal hygiene – dry shampoo
  - In house laundry? Dedicated cleanroom shoes?
  - Handwashing and garbing

Cleanroom Designs in Many Pharmacies in CT Are Being Updated
Ante-room (ISO 8 – 3,520,000 particles/m³)
• The first defense against airborne particulates from unclassified areas
• Pressure is higher than in the general pharmacy
• Only one entrance from the general pharmacy, no sweep, small gap
• Hands-free door
• Used for preparing to enter the “buffer room”
• Clearly divided into a “dirty” side or area and a “clean” side or area
• Enter on the “dirty” side
• Cover shoes or don “cleanroom shoes”
• Cross over to the “clean side”
• [Don garb (except gown) required for cleanroom]
• [Thoroughly wash hands at the sink]
• Filtered air in the ante-room is turned over NLT 30 times per hour
• No paper or cardboard allowed in ante-room (produces particles)
• Supplies are wiped down with sterile 70% isopropyl alcohol (IPA) or other [in the general pharmacy].
  • Now text is [clean side of ante-room or pass-through and must wear gloves]

Buffer Room (ISO 7 – 325,000 particles/m³)
• Often referred to as the “clean room”
• Only accessible from the ante-room, no sweep on door, small gap
• Room pressure is higher than in the ante-room
• Filtered air in the buffer room is turned over NLT 30 times per hour
• Avoid overstocking product and supplies
Air Flow

- Linear Flow Rate (ft/min)
- Volumetric Flow Rate (cu ft/min)
  - Area of the filter (ft²) x Linear flow rate (ft/min)

Area of the filter (2 ft²) x linear flow rate (5 ft/min) = 10 ft³/min = 10 cu ft/min

The flow rate of some filters is expressed in linear flow rate (ft/min) and others are expressed in volumetric flow rate (cu ft/min).

Air Changes per Hour (ACPH)

- ACPH is the number of times a volume of air equal to the volume of the room is changed each hour.
- Calculate the volume of the room
  - For a 10’ x 10’ x 10’ room
    - The volume is 1,000 cu. ft./room
- Calculate the volume flow rate of air into the room
  - A HEPA-filter in the ceiling with air flowing in at 500 cu. ft./min (CFM)
  - Convert to per hour
    - \( \frac{500 \text{ ft}^3}{\text{min}} \times \frac{60 \text{ min}}{\text{hr}} = 30,000 \text{ ft}^3/\text{hr} \)
  - Divide the volume flow rate of air into the room by the volume of the room \( \rightarrow \) ACPH
    - \( \frac{30,000 \text{ ft}^3}{1,000 \text{ ft}^3/\text{room}} = 30 \frac{\text{rooms}}{\text{hr}} \) = 30 room changes per hour = 30 ACPH

NOTE: ACPH is NOT the number of times all the air in the room is changed per hour. ACPH is the volume of air that is changed. There still may be dead spots.
HEPA-filtered air: in from ceiling, but out where?

- Placement and number of return vents
  - Low on the wall
  - Can be limited by existing infrastructure
  - Determined by HVAC professionals
  - You must provide input and feedback
- Identify potential dead zones
Pressure difference between rooms

- The pressure difference between rooms should be at least 0.020 inches of water.
- Measured using a differential pressure gauge.
- When buffer room pressure is higher, air flows from higher pressure to lower pressure through an open door.
- Pressure difference helps maintain the cleaner room cleaner.

Adjustment of pressure difference between rooms requires an HVAC professional.

There is no such thing as negative pressure. Think PV=nRT. When someone speaks of “negative pressure”, they typically mean a negative pressure difference.

Pass-Through Chambers

- Can be located between the buffer room and the ante-room.
- Conveniently pass materials between rooms without garbing.
- Doors must be interlocking, so both doors cannot be open simultaneously.
- [If HEPA-filtered pass through, can be located between the buffer room and the general pharmacy area. Remember to wipe down supplies going to buffer room.]
- Require additional environmental monitoring. Expensive and generate heat. Intermittent and continuously running.
Define areas from most to least clean
From outside toward the center
Each area is cleaner

Why primary “engineering control”? 
• Engineering controls are built into the facility to maintain “clean” 
• Administrative controls are the protocols and procedures to maintain “clean”
• Primary refers to the hood → PEC 
• Secondary refers to the room → SEC

Goal is to reduce probability of contamination of CSPs

Primary Engineering Control (PEC)
• LAFW – laminar air flow workbench 
  • Horizontal air flow – Air from the HEPA filter comes toward you 
  • Vertical air flow – HEPA filter is above and air flows down.
• BSC – biological safety cabinet 
  • More protection for staff than LAFW. Inward airflow through opening in front and downward HEPA-filtered airflow for protection of product. Certain BSCs can be used to prepare hazardous CSPs, such as chemotherapeutic agents.
• RABS – restricted access barrier system 
  • CAI – compounding aseptic isolator (for non-hazardous compounding only) 
  • CACI – compounding aseptic containment isolator (for compounding hazardous drugs)

Secondary Engineering Control = Buffer room
Laminar (Unidirectional) Air Flow Workbench

Horizontal

Vertical

Biological Safety Cabinets

Class 1 provides protection to the compounder, but no protection to the CSP. It is unsuitable for sterile compounding.
CAI and CACI

- CACI – CAI with exhaust to outside of the building.
- CAI – Isolator designed for sterile compounding.

<table>
<thead>
<tr>
<th></th>
<th>Non-Hazardous</th>
<th>Hazardous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>Compounding Isolator</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
</tbody>
</table>
LAFH = Laminar Air Flow Hood
LAFW = Laminar Air Flow Workbench
LAFS = Laminar Air Flow System

- Laminar air flow
  - Streamlines of air that do not mix

- Turbulent air flow
  - Multidirectional flow that mixes air

Considers no other flows or obstacles. Obstacles disturb laminar flow. Laminar flow is the ideal situation, for air flow.

The terminology is moving away from “laminar” to “unidirectional” flow. I prefer “first air”.

Slow flow
- Flow around a cylinder

Rapid forced flow

Visualize flow pattern with smoke test

Laminar Airflow
Unidirectional Airflow
“First” Air

First air ≡ the item of interest is the FIRST thing that the HEPA-filtered air makes contact with.
Don’t believe arrows that vendors draw

Additional design considerations

• Size of the rooms should be kept to a minimum
  • Allowing for any future increase in compounding needs
  • With larger spaces divided into separate rooms

• Surfaces (floors, walls & ceilings) must be smooth, non-porous, and free from cracks, cavities, steps and ledges.
  • Corners and junctions are coved (i.e., curved)
  • Ceiling tiles are sealed; No acoustic tiles
  • Flat ceiling, flat sprinkler heads and motion detectors
  • No drains in floor

• Avoid dust-collecting overhangs such as ledges & sills
Additional design considerations

- Sink area
  - No hand-driers
  - Hands-free water & soap
  - Non-refillable soap dispensers
  - Deep sink to reduce splash
    - Or splashguards
  - No diffusers
  - Clock nearby
- If plumbing above the cleanroom cannot be removed, add water sensors.

Specifications in USP “should” – Temperature ≤ 68°F  Humidity ≤ 60%

- Ask how the heating/cooling/humidification system works.
- Most industrial systems bring in “outside air”, cool it to remove water, then reheat it and add water for humidification.
  - What is your air source and how well controlled is that source (temp and humidity)?
- Humidification systems can be a source for microbial growth.
  - Ask how easy it is to gain access to humidification system to test/inspect, if needed.
- Remember that HEPA filtration generates a lot of heat.
  - Be sure the HVAC folks take the equipment (with its heat or thermal load) into account when planning the capacity of the HVAC system.
- Ask what the limits of the system are.
  - How warm and humid a day can be handled?
  - How cold and dry a day can be handled?
Equipment Selection – How clean & cleanable?

• Garbing Bench

• Buffer Room Chairs
  • Wheeled or stationary?

• Carts
  • General pharmacy → dirty side of anteroom
  • Clean side of anteroom → buffer room
  • Within area from pass-through → compounding

• Shelving
  • Wire or solid?
  • Wheeled or stationary?

Specify the grade of stainless steel:
“316 stainless”, not 304 or 430.
• Resists corrosion
• Pharmaceutical grade
• Recommended for cleanrooms

Equipment Selection – How clean & cleanable?

• Communication
  • Intercom
  • Handset
  • Sign language at window (amateur charades)

• Cameras
  • Surveillance
  • Checking

• Trash bins
  • Wheeled – emptied from the anteroom
2017 Pennsylvania Pharmacy

DURING AN INSPECTION OF YOUR FIRM (I) WE OBSERVED:

OBSERVATION 1

The ISO 5 laminar air flow hood was not certified under dynamic conditions.

Specifically, there is no evidence to demonstrate that dynamic smoke studies of the ISO 5 laminar air flow hood have been conducted in order to assess uni-directional air flow under actual conditions. Sterile products produced in the ISO 5 laminar air flow hood include Vancomycin 1.4gm/D5W, Penicillin G Potassium 20000000 Unit Solution, and Daptomycin in Normal Saline 170mg/10ml.

OBSERVATION 2

Disinfecting agents used in the ISO 5 laminar air flow hood are not sterile.

Specifically, the non-sterile disinfecting solution (b) (4) was used on (b) (4) as a cleaning agent in the ISO 5 laminar air flow hood.

On 10/31/17, we observed the HEPA filter patch in hood (b) (4) to be greater than (b) (4) in size. The HEPA filter patch was measured by your firm to be 4.5” X 1.5”; however, your vendor’s procedure states that (b) (4) should exceed or be greater than (b) (4) in size. Since this HEPA filter repair dated 11/18/16, your firm has continued to aseptically process drug products such as Enoxaparin, Neupogen, and Procrit for patients in hood (b) (4)
OBSERVATION 2
Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically,
A. On 12/10/2018, sterile drug production was conducted after observing water dripping from the ceiling tile of the clean-room. The ceiling tile was subsequently removed but not re-installed and sealed prior to production. Recertification of room was not conducted for approximately 90 days.
B. Pressure differentials between classified and unclassified areas are not monitored daily. Manhelic gauges used were observed to be either non-functional or incorrectly installed.
C. Environmental monitoring of ISO classified zones is conducted on (b) (4) basis and (b) (4) via an unqualified (b) (4) sampling method at unknown locations.

OBSERVATION 4
Aseptic processing areas are deficient regarding air supply that is filtered through high-efficiency particulate air filters under positive pressure.

Specifically, your ISO classified zones lack sufficient data to substantiate the current classifications. For example:
A. Certification of your HVAC/HEPA system has never been conducted. You did not provide data to support the design of your clean-room was sufficient to perform sterile drug production prior to production.
B. Lighting equipment used in your aseptic processing area was observed to be insufficient. Light fixtures used are not designed to maintain ceiling integrity and prevent infiltration of particulate into the clean room under positive pressure.
C. Multiple ceiling tiles were observed to be labeled with “do not seal” and confirmed to be unsealed.
Later, it’s your turn to design a cleanroom suite

Group 1 at 2:15 -3:15 & Group 2 at 3:30-4:30

• With a partner
• Given
  • Floor plan (1 inch = 2 feet)
  • Ceiling plan
  • 3 sheets of Components
  • Scissors
  • Glue stick
  • Ruler
Questions?