Before we begin...

We want to be clear!

1. Official USP wording in black versus best practices in blue
   • Unclear? Ask?
2. Wording matters in the USP

Words to understand before interpreting USP:

- SHOULD & SHALL
  - SHOULD: suggested best practice
  - SHALL: mandatory

- MUST
  - no "if's, and's, or but's"

Design of a Cleanroom
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Why learn about Cleanroom Design if you are not responsible for its design?

- Understanding the reasons for the design can help staff operate more effectively within it
- Maintaining the standards of a cleanroom is a team effort
- Everyone should be empowered to spot issues and report them (caulking defect, rust, water leak)

Control Strategies to Reduce Contamination

- Administrative Controls – what you do to reduce contamination
  - Standard Operating Procedures
  - Oversight of Procedures

- Engineering Controls – how your facilities are designed to reduce contamination
  - Primary engineering control (PEC) – a hood/cabinet that provides ISO 5 air quality for sterile compounding
  - Secondary engineering control (SEC) – area in which the PEC is placed

- Garbing – the last line of defense against contamination
  - To protect the compounded sterile preparation (CSP) from you
  - PPE (personal protective equipment) is for reduction of worker exposure to HDs

It is relatively easy to keep an unoccupied cleanroom clean.

Human activity is the primary source of contamination of a cleanroom.
**The Cleanroom Suite**

*Define areas from most to least clean*

*From outside toward the center*

*Each area is cleaner*

- LAPW or other PEC
- Buffer Room (SEC)
- Clean side of the Ante-room
- Dirty side of the Ante-room
- General pharmacy space

Goal is to reduce probability of contamination of CSPs

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**Segregated Compounding Area (SCA)**

A PEC may be located within an unclassified area, without an ante-room or buffer room. This type of design is called an SCA.

- Only Category 1 CSPs (12 hr BUD) can be compounded in an SCA.
- must be located away from unsealed windows, doors that connect to the outdoors, and traffic flow, all of which may adversely affect the air quality in the PEC.
- must not be located where environmental control challenges (e.g., restrooms, warehouses, or food preparation areas) could negatively affect the air quality of the PEC within the SCA.
- The impact of activities (e.g., patient care activities that will be conducted around or adjacent to the SCA must be considered carefully when designing such an area.
- A visible perimeter must establish the boundaries of the SCA.
- The SCA and all surfaces (e.g., walls, floors, counters, and equipment) in the SCA must be clean, uncluttered, and dedicated to compounding.
- Sink for handwashing must be accessible but located at least 1 meter from PEC.

Per proposed USP<797>

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**Levels of “Clean” in Classified Areas**

<table>
<thead>
<tr>
<th>Older Classification</th>
<th>Particle Count Lams/cu. Ft.</th>
<th>ISO Class</th>
<th>Particle Count Lams/m³</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>30</td>
<td>ISO 4</td>
<td>352</td>
</tr>
<tr>
<td>Class 100</td>
<td>100</td>
<td>ISO 5</td>
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<tr>
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<td>1,000</td>
<td>ISO 6</td>
<td>35,200</td>
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<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

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**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 (in PEC).

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

If Pharmacy air → through HEPA filter → critical compounding area,

- Could have too many particles to meet the specification
- Would have to replace the HEPA filter more often ($$$$)

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**HEPA Filters**

- US Dept of Energy standard
  - HEPA Filter removes at least 99.97% of particles > 0.3 microns in diameter
- European Union standard
  - H13 Filter removes at least 99.95% of a specific particle size
  - H14 Filter 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?

Proposed USP <797> is silent on pre-filters.

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 (USP)
• Only one entrance from the general pharmacy, no door sweep (USP), small gap
• Hands-free door (“should” per USP)
• Used for preparing to enter the “buffer room”
• Close line of demarcation divides “dirty” room or area from a “clean” room or area (USP)
• Enter the cleanroom suite through the “dirty” side (USP)
• Cover shoes or don “cleanroom shoes”
• Cross over to the “clean side”
• (Do not “dirty” the room)
• (Don’t open the door)—required for cleanroom
• (Thoroughly wash hands at the sink)
• Filtered air in the ante-room is turned over NLT 30 times per hour (USP)
• No paper or cardboard allowed in ante-room (produces particles) (per USP)
• Supplies are wiped down with sterile 70% isopropyl alcohol (IPA) or other
  • WHO?

Buffer Room (ISO 7 – 325,000 particles/m³)
• Often referred to as the “clean room”
• Only accessible from the ante-room clean side
• No sweep on door (USP), small gap
• Room pressure is higher than in the ante-room (USP)
• Except for hazardous compounding buffer room
• Filtered air in the buffer room is turned over NLT 30 times per hour (USP)
• “A necessary product and supplies

Segregated Compounding Area (SCA)
• Not considered a classified area — air quality
• No air flow requirements
• No environmental testing, except in the PEC.
• Handwashing is required.
• Garbing per the facility’s Standard Operating Procedures.
• Clean, uncluttered, space dedicated to compounding.
• Visible perimeter to establish boundaries of the SCA

Proposed <797>

Air Flow (PECs and Classified Areas)
• Linear Flow Rate (ft/min)
• Volumetric Flow Rate (cu ft/min)
  • Area of the filter (ft²)
  • 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 (ft³/min)
and others are expressed in volumetric flow rate (cu ft/min).
Air Changes per Hour (ACPH)

- ACHP 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
    - $\frac{500 \text{ cu. ft.}}{\text{min}} \times 60 \text{ min/hr} = 30,000 \text{ ft}^3/\text{hr}$
- Divide the volume flow rate of air into the room by the volume of the room → ACHP
  - $\frac{30,000 \text{ ft}^3/\text{hr}}{1000 \text{ ft}^3/\text{room}} = 30 \text{ ACHP}$

NOTE: ACHP is NOT the number of times all the air in the room is changed per hour. ACHP is the volume of air that is changed. There may still be dead zones.

HEPA-filtered air: in from ceiling, but out where?

- Identify potential dead zones (stagnant air)
  - Avoid compounding near dead zones
  - Avoid storing materials near dead zones
- Identify movements that disturb air flow creating turbulence or eddies
  - How does disturbance in the flow influence movement of contaminants?

Pressure difference between rooms

- 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.
- Measured using a differential pressure gauge. The pressure difference between rooms is at least 0.025 inches of water.
- HD buffer room pressure is lower by 0.01-0.03 inches of water.
- Air flows INTO the buffer room to contain any HD contamination.

**Important:** A buffer room pressure must be higher than any other room in the facility. When someone speaks of “negative pressure”, they are typically referring to the pressure in the buffer room being lower than the adjacent rooms.

HEPA-filtered air: in from ceiling, but out where?

- Placement and number of return vents
  - Impacts air flow pattern and dead zones
  - Low on the wall
  - Can be limited by existing infrastructure
  - Determined by HVAC professionals

If you are building or renovating:

- You must provide input and feedback to planners
  - Equipment type, size and placement
  - Stagnant air
  - Personnel and material movement
  - Pass-through placement per workflow
  - Ask about air source
  - Ask how humidity is controlled
  - Ask about capacity of heating and cooling units
  - Ask questions until you understand the answers

Pass-Through Chambers

- Acceptable locations not specified in proposed USP<797>
- Conveniently pass materials between rooms without garbing
- Doors must be interlocking, so both doors cannot be open simultaneously. (USP)
- Require additional cleaning and environmental monitoring. (USP)

Pass-through with interlocking doors

- Pass-through with HEPA-filtered air & interlocking doors

NEEDED IMPROVEMENT
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 = Cleanroom suite or SCA

Laminar (Unidirectional) Air Flow Workbench

Horizontal

Vertical

Biological Safety Cabinets

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

CAI and CACI

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

LAF = 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".
**Visualize flow pattern**

Laminar Airflow

Unidirectional Airflow

“First” Air

First air = the item of interest is the FIRST thing that the HEPA-filtered air makes contact with.

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**2 Types of Smoke Tests – Video**

- Dynamic airflow smoke pattern test
  - In PEC
  - Initially and every 6 months.
  - If equipment in PEC is moved, repeat study.
  - Under dynamic operating conditions

- Visual smoke study
  - In ISO 7 and 8 rooms
  - For certification and recertification (q 6 mo)
  - Verifies absence of stagnant air
  - Not under dynamic conditions

- Recommend thorough cleaning after smoke study to remove residue.

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**Additional design considerations**

- **Sink area**
  - USP specified
  - Location flexible
    - General pharmacy (in a clean space)
    - Ante-rooms (clean or dirty side)
  - No hand-driers
  - Hands-free water & soap
  - Non-refillable soap dispensers
  - Not in USP, but considered best practice
    - Deep sink to reduce splash
    - Or splashguards
  - No diffusers
  - Clock nearby
  - Fire sprinklers should be recessed and covered. (USP)
  - If plumbing in the ceiling or walls cannot be removed, add water sensors. (CT DPH)

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**Don’t believe arrows that vendors draw**

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**Additional design considerations**

- **Size of the rooms should be kept to a minimum**
  - Allowing for any future increase in compounding needs

- **Surfaces (floors, walls & ceilings) must be smooth, non-porous, and free from cracks, cavities, steps and ledges.**
  - Corners and junctions are covered (i.e., curved)
  - Ceiling tiles are sealed; No acoustic tiles
  - Flat ceiling, flat sprinkler heads and motion detectors
  - Walls – durable material (e.g., epoxy paint or heavy-gauge polymer)

- **No drains in floor**

- **Avoid dust-collecting overhangs such as ledges & sills**

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**Additional design considerations**

- **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
  - Nonporous, cleanable, with casters and wheels that are cleanable.
  - General pharmacy ⇒ dirty side of anteroom
  - Clean side of anteroom ⇒ buffer room
  - Within any area
- Shelving
  - Wire or sold?
  - Wheeled or stationary?
  - New Smoke Study?

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

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

- Cameras
  - Surveillance
  - Checking
- Trash bins
  - Wheeled – emptied from the anteroom

2017 Pennsylvania Pharmacy

OBSERVATION 1

The ISO 5 laminar air flow hood was not certified under dynamic conditions. Specifically, there is no evidence to demonstrate that dynamic studies of the ISO 5 laminar air flow hood were conducted to ensure that clean air is attained. Cold product products in the ISO 5 laminar air flow hood include Vancocycline 1 gram/5mL, 250 mg/5mL Neosporin Ointment, and Depneumynexi Normal Saline 15mg/5ml.

OBSERVATION 2

Disinfecting spots used in the ISO 5 laminar air flow hood are not sterile. Specifically, the same disinfecting solution (2017) was used on 2019 as a cleaning agent in the ISO 5 laminar air flow hood.

OBSERVATION 2

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically:
1. On 12/23/2017, 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 reinstalled and sealed prior to production. No certification of the room was conducted for aseptic cleanroom.
2. Pressure differentials between classified and unclassified areas are not monitored daily. Magnetic field gauges used were observed to be non-functional or incorrectly installed.
3. Environmental monitoring of ISO classified areas is conducted on 8(4) basis and 8(4) via an unqualified (3) 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:
1. Certification of your HVAC/EPA system has never been conducted. You did not provide data to support the integrity of your clean room was sufficient to perform sterile drug production prior to production.
2. 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 particulates into the clean room under positive pressure.
3. Multiple ceiling tiles were observed to be labeled with "do not seal" and confirmed to be unsealed.
### Key Points

<table>
<thead>
<tr>
<th>Learn</th>
<th>Check</th>
<th>Understand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learn your room and its weak points</td>
<td>Check certification reports</td>
<td>Understand your equipment</td>
</tr>
<tr>
<td>- Water source, air flow, personnel capacity</td>
<td>- Know how to read the report</td>
<td>- What does the PEC manufacturer manual indicate about maintenance and limitations?</td>
</tr>
<tr>
<td>- For an existing room, consider how to reduce contamination within limitations of the room.</td>
<td>- Recalculate ACHI to confirm</td>
<td>- Is all equipment (including advanced trash bins) nonporous and disposable?</td>
</tr>
<tr>
<td>- For room design, ask questions until you get answers you understand.</td>
<td>- Keep all study videos on file.</td>
<td></td>
</tr>
</tbody>
</table>

**Check questions:**