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

suggested best practice

MUST

mandatory

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].
It is relatively easy to keep an unoccupied cleanroom clean.

Human activity is the primary source of contamination of a cleanroom.

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
The Cleanroom Suite
Define areas from most to least clean
From outside toward the center
Each area is cleaner

LAFW 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

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>
Levels of “Clean” in Classified Areas

<table>
<thead>
<tr>
<th>Older Classification</th>
<th>Particle Count Limit/cu. Ft.</th>
<th>ISO Class</th>
<th>Particle Count Limit/m³</th>
</tr>
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<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>
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<tr>
<td>Class 100</td>
<td>100</td>
<td>ISO 5</td>
<td>3,520</td>
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<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>

‡ ≥ 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 (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 ($$$)
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.

To maintain the level of clean:

• Special filtration or treatment systems for incoming air (required by USP<797>)
  • HEPA filtered air from the ceiling

• Air-lock entry portals
  • Mostly in 503B outsourcing facilities

• Tacky mats to remove particulate matter from shoes
  • NOT inside the cleanroom complex (USP). 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 (USP)
  • Pressure difference ≥ 0.020 inches of water (> 0.005% of an atmosphere [5 ten thousandths])

• Personnel and materials movement should avoid disrupting air flow (USP)
  • 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 (USP)
  • Personal hygiene – dry shampoo
  • In house laundry? Dedicated cleanroom shoes?
  • Handwashing and garbing
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”
- Clear 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”
- [Don garb (except gown) required for cleanroom]
- [Thoroughly wash hands at the sink]
- Filtered air in the ante-room is turned over NLT 30 20 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
  - WHERE?

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)
- Avoid overstocking 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)
    - 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
    - \( \frac{30,000 \text{ ft}^3}{\text{hr}} \div \frac{1,000 \text{ ft}^3}{\text{room}} = 30 \text{ room changes per hour} = 30 \text{ ACPH} \)

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 zones.

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
  - Including shelving
  - 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
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 0.020 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.

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

- 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

NEEDS 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
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.
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”.

Not really laminar
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.

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.

Dynamic operating conditions: Conditions in the compounding area in which operating personnel are present and simulating or performing compounding. The conditions should reflect the largest number of personnel and highest complexity of compounding expected during routine operations as determined by the designated person(s).
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
  • Walls – durable material (e.g., epoxy paint or heavy-gauge polymer)
  • No drains in floor

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

• Sink area
  • USP specified
    • Location flexible
      • General pharmacy (in a clean space)
      • Ante-room (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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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 solid?
  - 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

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 (b) (4) 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 30 days.
B. Pressure differentials between classified and unclassified areas are not monitored daily. Magnehelic 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.
### Key Points

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

### Questions?