

DESIGN CONSIDERATIONS FOR USP <800> FACILITY COMPLIANCE



USING BIOSAFETY EXPERIENCE TO SUPPORT
PHARMACY

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1



Presenter: Jim Wagner
Controlled Environment Consulting (CEC)

OBJECTIVES

- This presentation will:
 - Analyze the options for building out a HD Sterile Compounding Facility
 - Define the impact the PEC selection has on the HVAC system
 - Relate facility requirements to the certification and environmental monitoring processes

USP CHAPTER <797>

(797) PHARMACEUTICAL COMPOUNDING – STERILE PREPARATIONS

Change to read:

1. INTRODUCTION AND SCOPE

This chapter describes the minimum standards to be followed for the preparation of compounded sterile preparations (CSPs) for human and animal drugs. Sterile compounding is defined as combining, admixing, diluting, pooling, reconstituting, repackaging, or otherwise altering a drug product or bulk drug substance to create a sterile preparation.

The requirements in this chapter must be followed to minimize harm, including death, to human and animal patients that could result from 1) microbial contamination [nonsterility], 2) excessive bacterial endotoxins, 3) variability from the intended strength of correct ingredients, 4) physical and chemical incompatibilities, 5) chemical and physical contaminants, and/or 6) use of ingredients of inappropriate quality.

Aseptic techniques, processes, and procedures must be followed for preparing any sterile medication. Processes and procedures must be in place to minimize the potential for contact with nonsterile surfaces, introduction of particulate matter or biological fluids, and mix-ups with other products or CSPs.

The use of technologies, techniques, materials, and procedures other than those described in this chapter is not prohibited as long as they are noninferior to those described herein and validated for the intended purpose (e.g., *Validation of Alternative Microbiological Methods* (1223) and *Validation of Compensial Procedures* (1225)).

Unless otherwise specified in each section, the requirements of this chapter apply to compounding all categories of CSPs.

1.1 Scope

1.1.1 CSPs affected: The requirements in this chapter must be met to ensure the sterility of any CSP. Although the list below is not exhaustive, the following must be sterile:

- Injections, including infusions
- Irrigations for internal body cavities (i.e., any space that does not normally communicate with the environment outside of the body, such as the bladder cavity or peritoneal cavity). [NOTE—Irrigations for the mouth, rectal cavity, and sinus cavity are not required to be sterile.]
- Ophthalmic dosage forms
- Aqueous preparations for pulmonary inhalation. [NOTE—Nasal dosage forms intended for local application are not required to be sterile.]
- Baths and soaks for live organs and tissues
- Implants

1.1.2 Specific practices

Allergenic extracts: Licensed allergenic extracts are mixed and diluted to prepare prescription sets for administration to patients. A prescription set is a vial or set of vials of premixed licensed allergenic extracts for subcutaneous immunotherapy that have been diluted with an appropriate diluent for an individual patient. Because of certain characteristics of allergenic extracts and allergy practice, preparation of allergenic extract prescription sets is not subject to all of the requirements in this chapter that are applicable to other sterile CSPs. The standards for compounding allergenic extracts, which are described in *21. Compounding Allergenic Extracts*, are applicable only when

1. The compounding process involves transfer via sterile needles and syringes of conventionally manufactured sterile allergen products and appropriate conventionally manufactured sterile added substances; and
2. Manipulations are limited to penetrating stoppers on vials with sterile needles and syringes and transferring sterile liquids in sterile syringes to sterile vials.

Blood-derived and other biological materials: When compounding activities require the manipulation of a patient's blood-derived or other biological material (e.g., autologous serum), the manipulations must be clearly separated from other compounding activities and equipment used in CSP preparation activities, and they must be controlled by specific standard operating procedures (SOPs) to avoid any cross-contamination. Handling of blood components and other biological materials must additionally comply with laws and regulations of the applicable regulatory jurisdiction.

Hazardous drugs: Handling of sterile hazardous drugs (HDs) must additionally comply with *Hazardous Drugs – Handling in Healthcare Settings* (800).

Repackaging: Repackaging of a sterile product or preparation from its original container into another container must be performed in accordance with the requirements in this chapter.

Sterile radiopharmaceuticals: Compounding of radiopharmaceuticals is not required to meet the standards of this chapter as they are subject to the requirements in *Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging* (825).

1.1.3 Personnel and settings affected: This chapter describes the minimum requirements that apply to all persons who prepare CSPs and all places where CSPs are prepared. This includes but is not limited to pharmacists, technicians, nurses, physicians, veterinarians, dentists, naturopaths, and chiropractors in all places including but not limited to hospitals and other healthcare institutions, medical and surgical patient treatment sites, infusion facilities, pharmacies, and physician or veterinarian practice sites. Any person entering a sterile compounding area, whether preparing a CSP or not, must meet the requirements in *3. Personal Hygiene and Garbing*.

The compounding facility must designate one or more individuals (i.e., the designated person(s)) to be responsible and accountable for the performance and operation of the facility and personnel in the preparation of CSPs and for performing other functions as described in this chapter.

- Pharmaceutical Compounding-Sterile Preparations
- Current official version -2008
 - Changes approved November 2022
 - Changes effective November 2023
- Recognized as the national standard of practice for compounding sterile preparations since 2004
- Used as inspection guidance by most regulatory agencies
- Minimum practice and quality standards for compounding sterile preparations

OTHER USP CHAPTERS RELATED TO COMPOUNDING

• USP <795>

- Compounding Nonsterile preparations
- Official November 1, 2023

• USP <800>

- Hazardous Drugs
- Official date December 1, 2019.
- Informational status until 795 and 797 official
- November 1, 2023

• USP <825>

- Radiopharmaceuticals
- Official November 2020
- Informational status until 795 and 797 become official
- November 1, 2023

STERILE COMPOUNDING FACILITY LAYOUT



Non-Hazardous Buffer Rm.

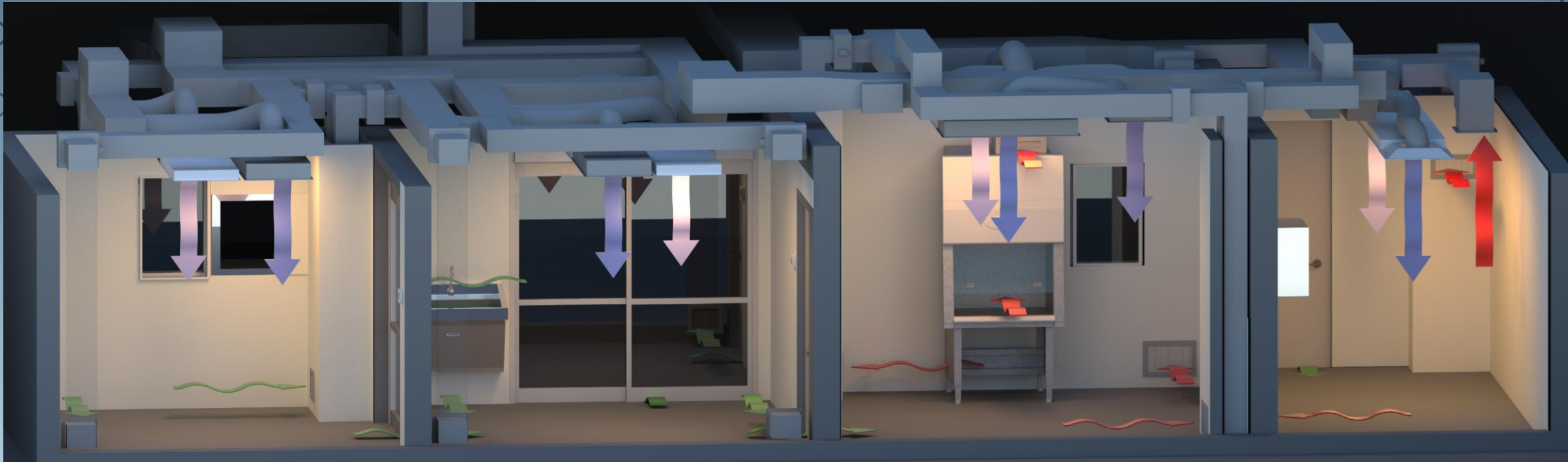
Ante Rm.

HD Buffer Rm.

HD Storage Rm.

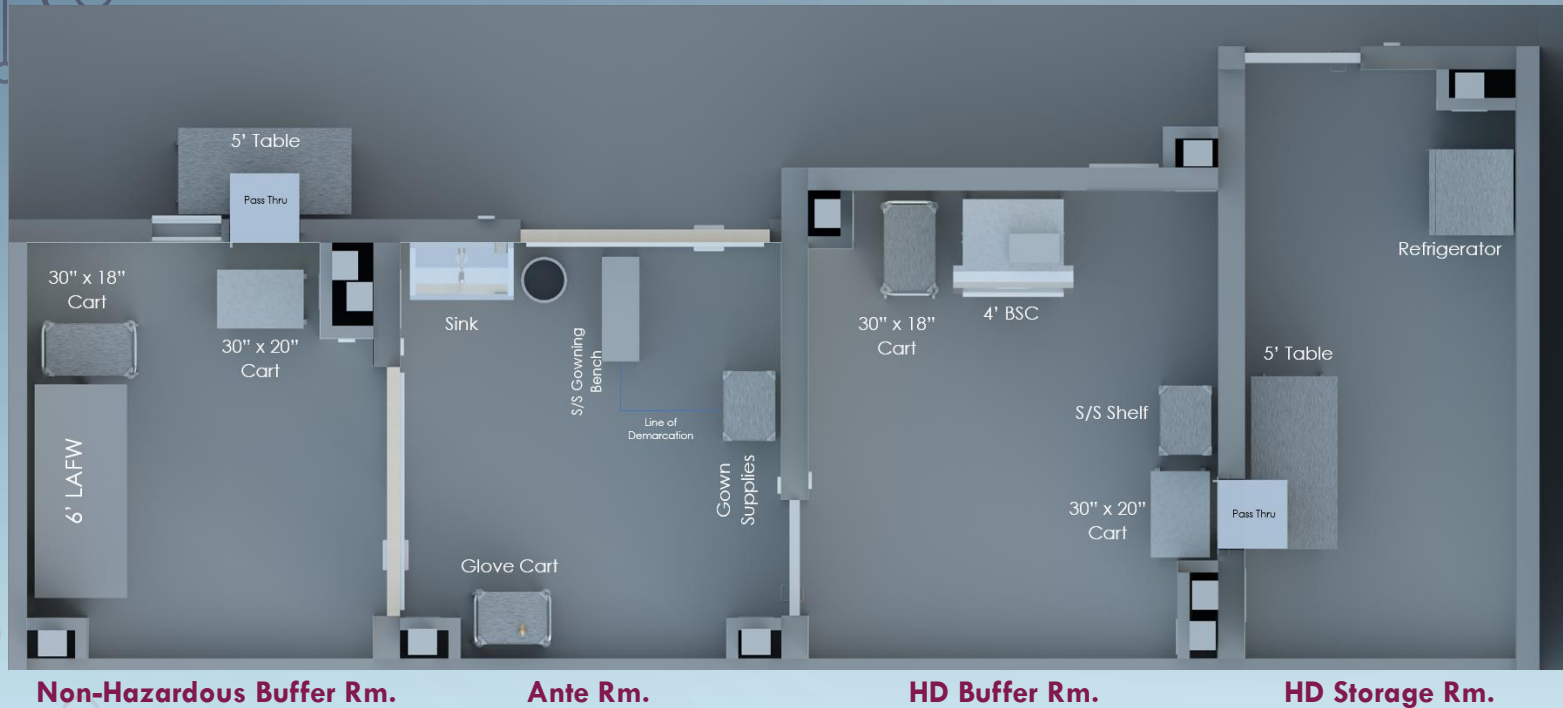
Apply USP Chapters <797> and <800> and other relevant standards to create a sterile compounding facility

STERILE COMPOUNDING SUITE STANDARDS



- A cleanroom is a complex interactive ventilation device
 - Mechanical requirements
 - The core of a compounding cleanroom is the HVAC system that serves it
 - USP <800>, <797>, CETA CAG-003 & 009, ASHRAE 170, Building Codes
 - Architectural requirements
 - The skeleton of a cleanroom are the walls, floors, ceilings, doors, pass-throughs that support it
 - USP <797>, <800>, lots of mistakes, a few successes

HAZARDOUS DRUG RECEIVING/STORAGE

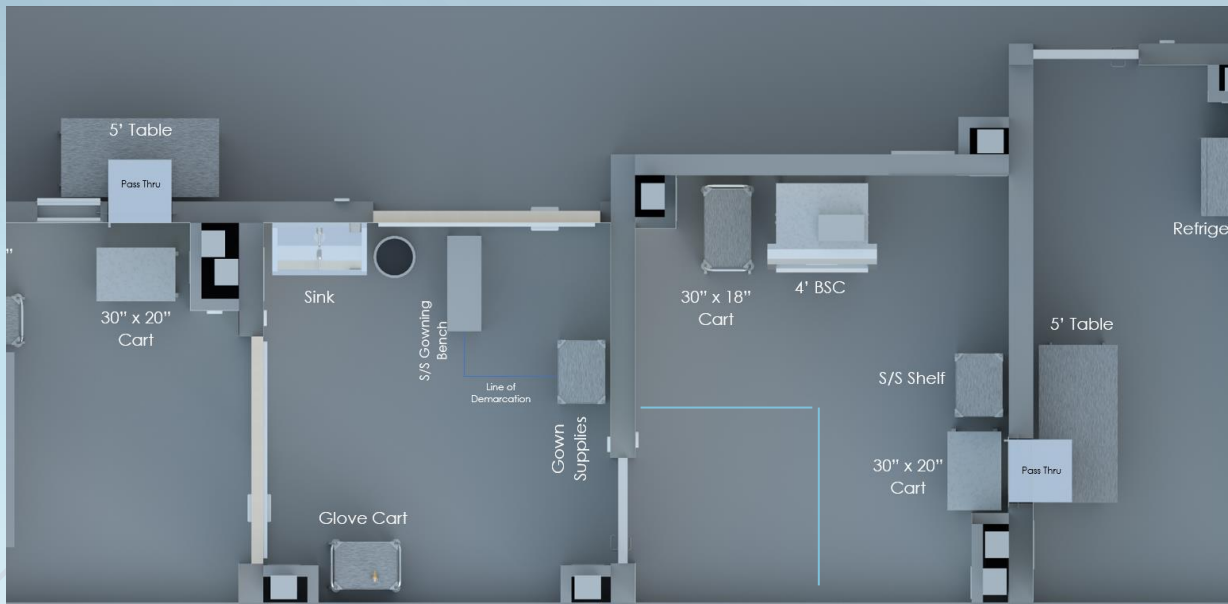


- Receiving
- Storage
- Adjacencies
- Movement of HDs



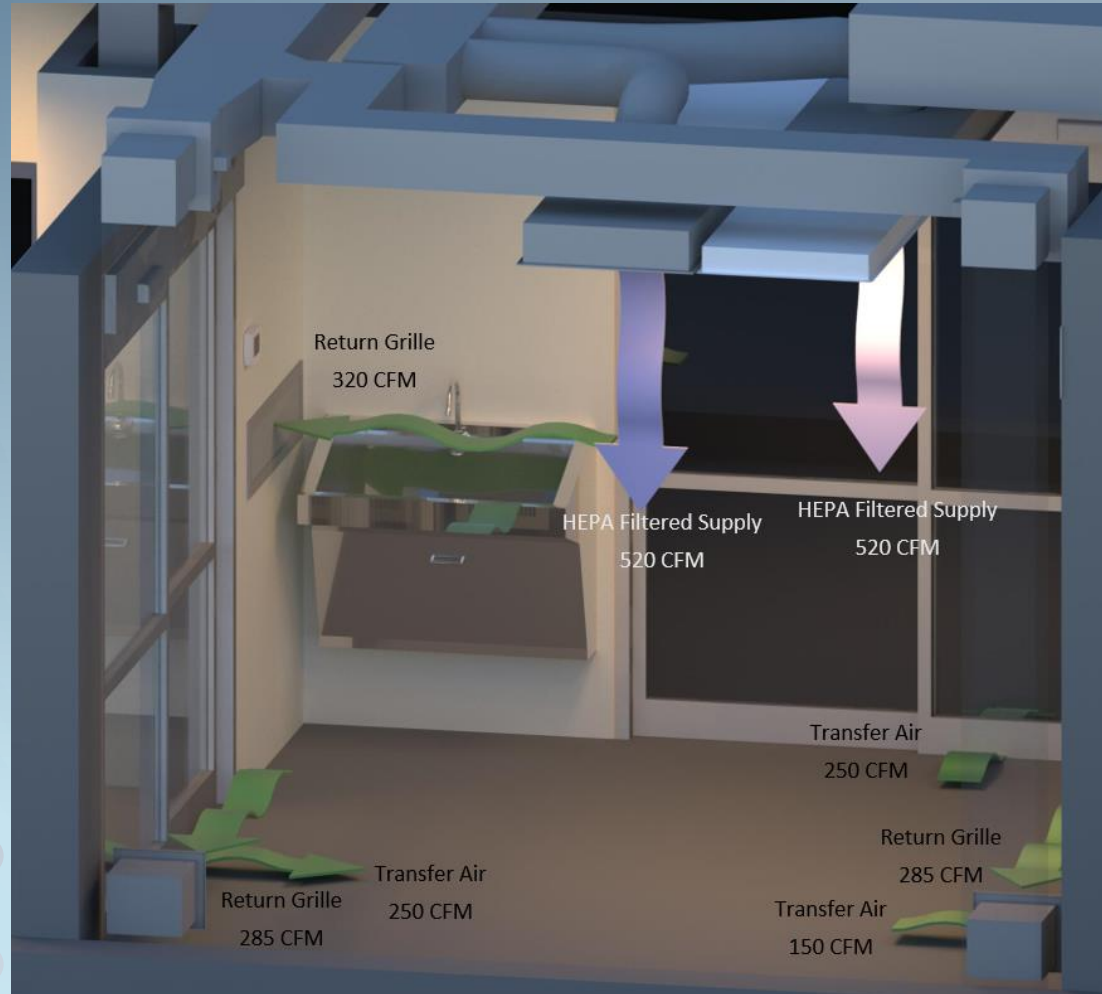
- USP <800>
- HDs must be delivered to the HD storage area immediately after unpacking.
- HDs must be unpacked in neutral to negative pressure
- Antineoplastic HDs must be stored separately from non-HDs and in negative pressure

ANTE ROOM



- Gowning process dictates layout
- Sink
 - location
 - Impact on environmental monitoring
 - Hands free
 - splashing
- LOD
- PPE cart
- Gowning Bench
- Mirror
- Hand drying accommodations
- Gloving Cart
 - Alcohol-based hand rub
- Waste containers

ANTE ROOM HVAC RECOMMENDATIONS



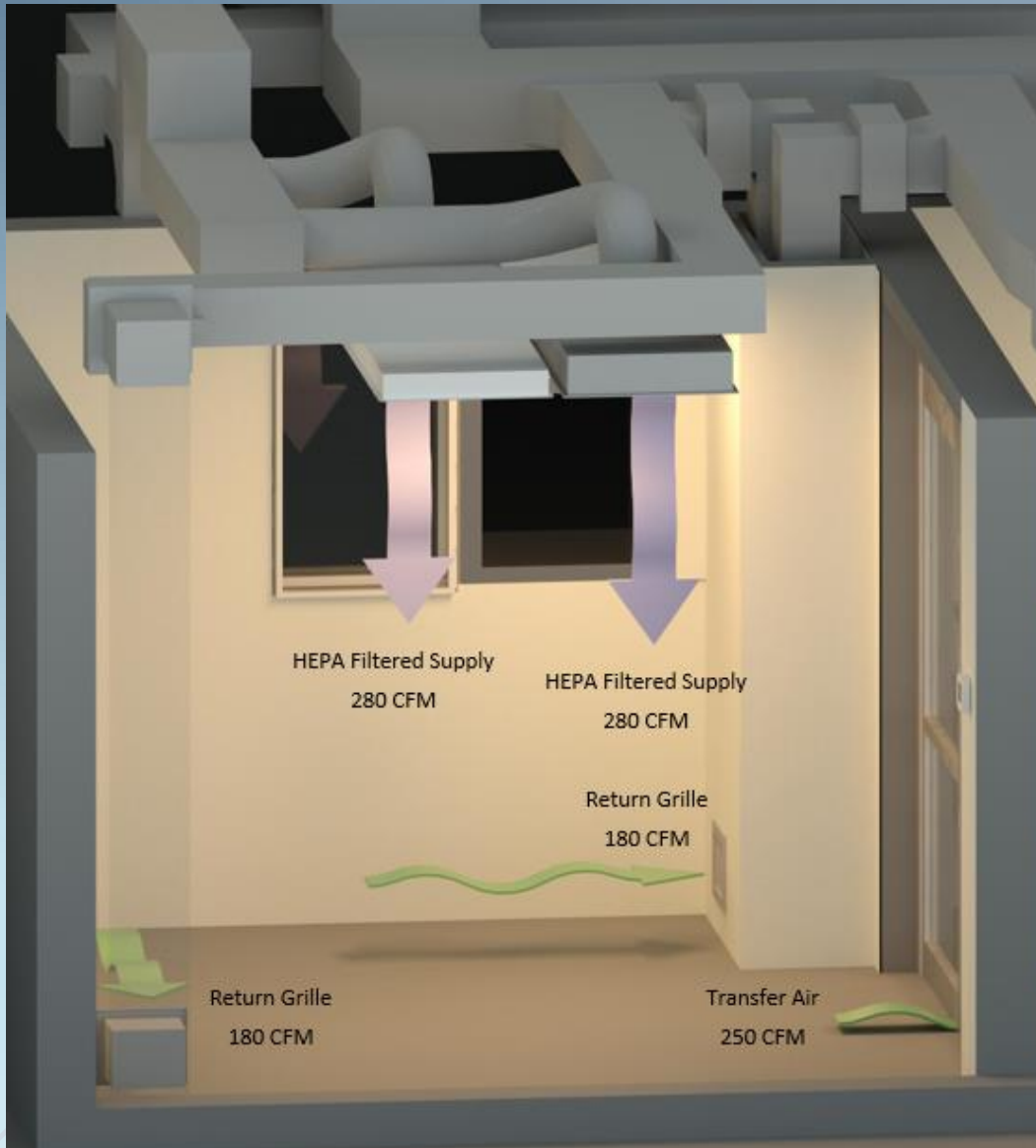
- ISO Class 7
 - Min. 0.020" w.c. Positive pressure to General Pharmacy
 - Positive to the HD buffer room
 - Return to HVAC
 - HEPA filters Must be located in the ceiling
 - Return locations
 - Low on the wall except where contamination removal is needed
 - Minimum 30 ACPH required
 - 50-60 ACPH recommended
 - Air change rates based on HEPA filtered air supplied to the room

NON-HD BUFFER ROOM



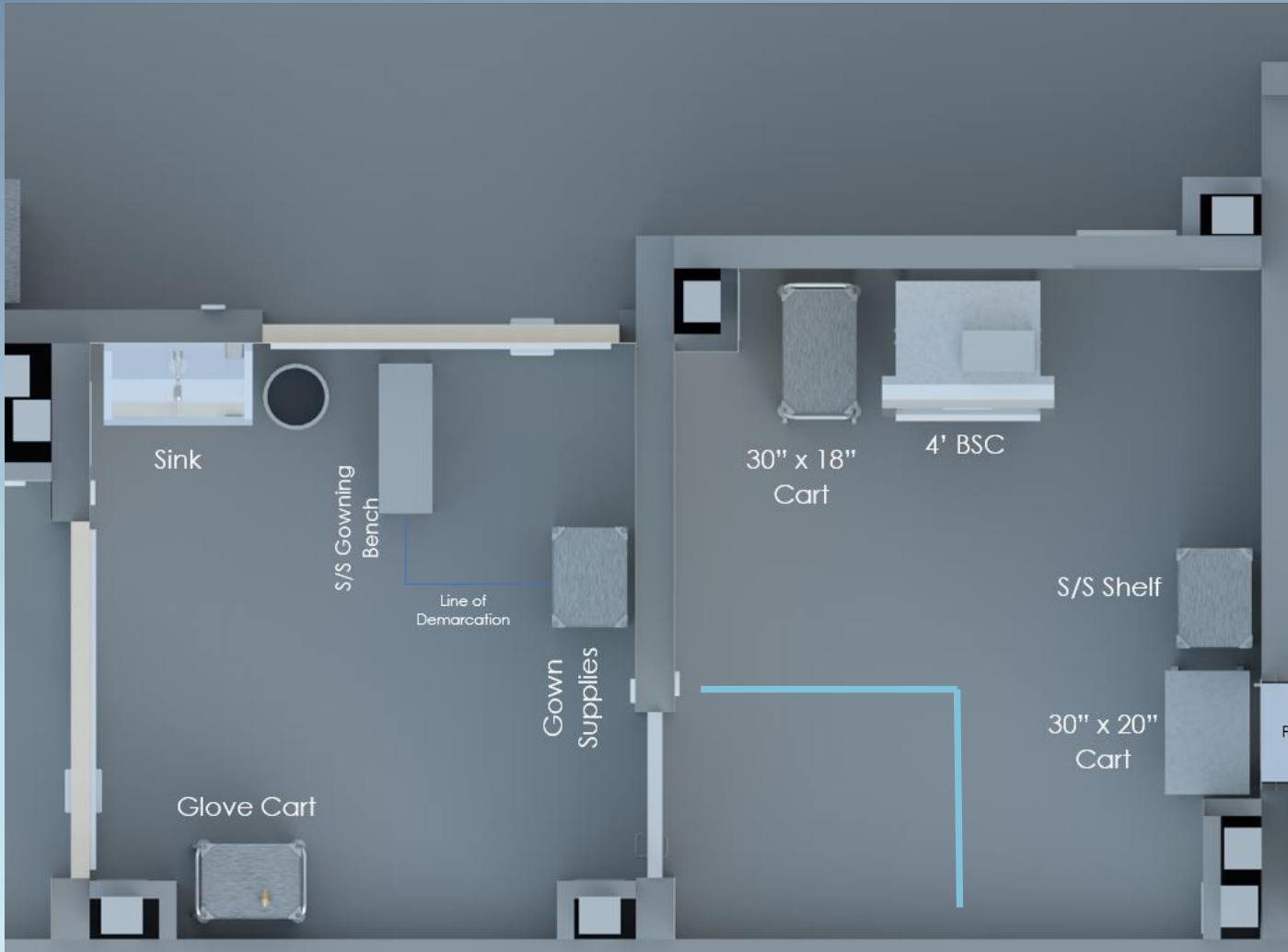
- Waste disposal
- Windows, line of site
- Cleanability
 - Solid shelves
 - casters
- PEC
 - LAFW
 - Blower position
 - Casters
 - Diffuser Screen

NON-HD BUFFER ROOM HVAC RECOMMENDATIONS



- ISO Class 7
 - Min. 0.020" w.c. Positive pressure to Ante Rm.
 - Return to HVAC
 - HEPA filters Must be located in the ceiling
 - Return locations
 - Low on the wall except where contamination removal is needed
- Minimum 30 ACPH required
 - LAFW augments total ACPH
- Rm. air change rates based on HEPA filtered air supplied to the room

HD BUFFER ROOM



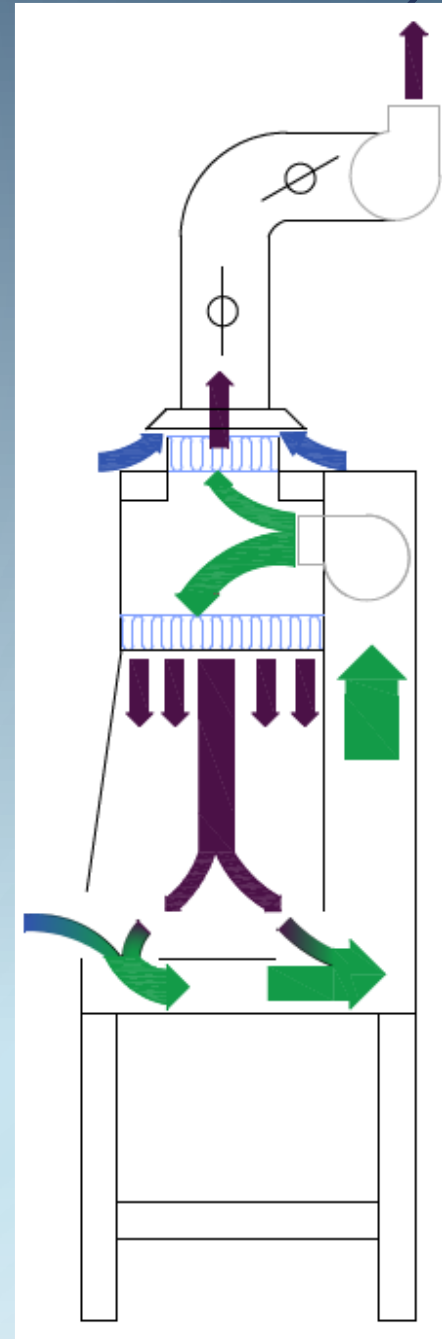
- HD storage
 - Shelf unit
 - Refrigerator
- Cleanability
 - Solid shelves
 - Casters
- LOD
- Waste disposal
- Windows, line of site
- Waste Disposal
- Material Transfer

HD PEC

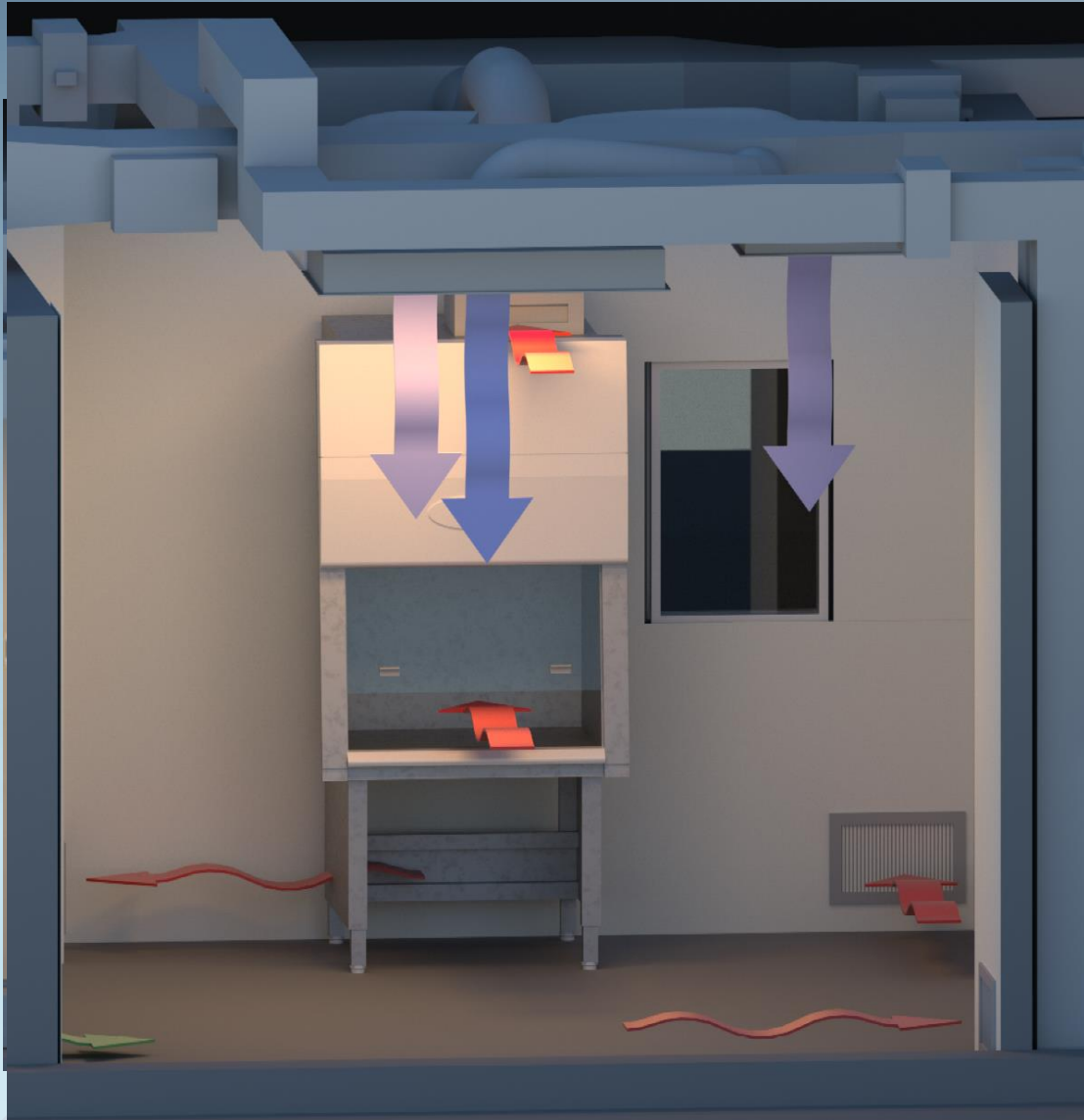


- Class II Type A2 BSC
 - NSF/ANSI std. 49-2019 N-5
- Externally vented
 - Canopy connection
 - Minimize exhaust from canopy
- Ceiling height
- Exhaust adjustment
 - Manual vs. BMS
 - Site installation assessment

All C-PECs used for manipulation of sterile HDs must be externally vented. Sterile HD compounding must be performed in a C-PEC that provides an ISO Class 5 or better air quality, such as a Class II or III BSC or CACI. Class II BSC types A2, B1, or B2 are acceptable. **For most known HDs, type A2 cabinets offer a simple and reliable integration with the ventilation and pressurization requirements of the C-SEC.** Class II type B2 BSCs are typically reserved for use with volatile components.



HD BUFFER ROOM HVAC RECOMMENDATIONS

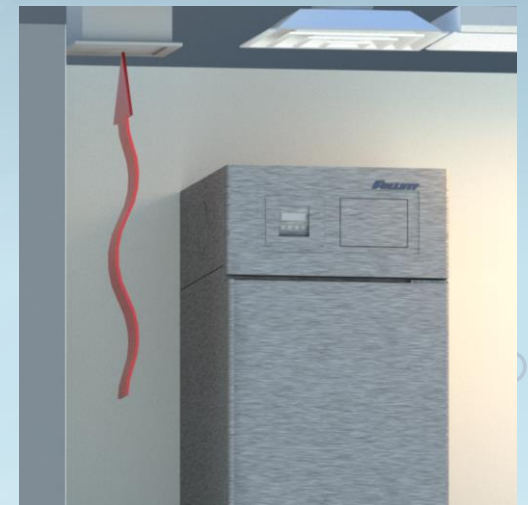


- ISO Class 7
 - 0.010 – 0.030” w.c. Negative pressure to Ante Rm.
 - All PEC and room air exhausted to outside
 - HEPA filters Must be in the ceiling
 - Exhaust grille locations
 - Low on the wall except where contamination removal is needed
 - Minimum 30 ACPH required
 - 50-60 ACPH recommended
 - Air change rates based on HEPA filtered air **supplied** to the room

EXHAUST GRILLES TO REMOVE CONTAMINATION

USP <797>

“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. This smoke study along with environmental monitoring must be repeated whenever a change to the placement of equipment within the room is made or any other alteration is performed within the cleanroom suite that affects the quality of the air (e.g., HVAC alterations, change of HEPA filter units).”



EXHAUST

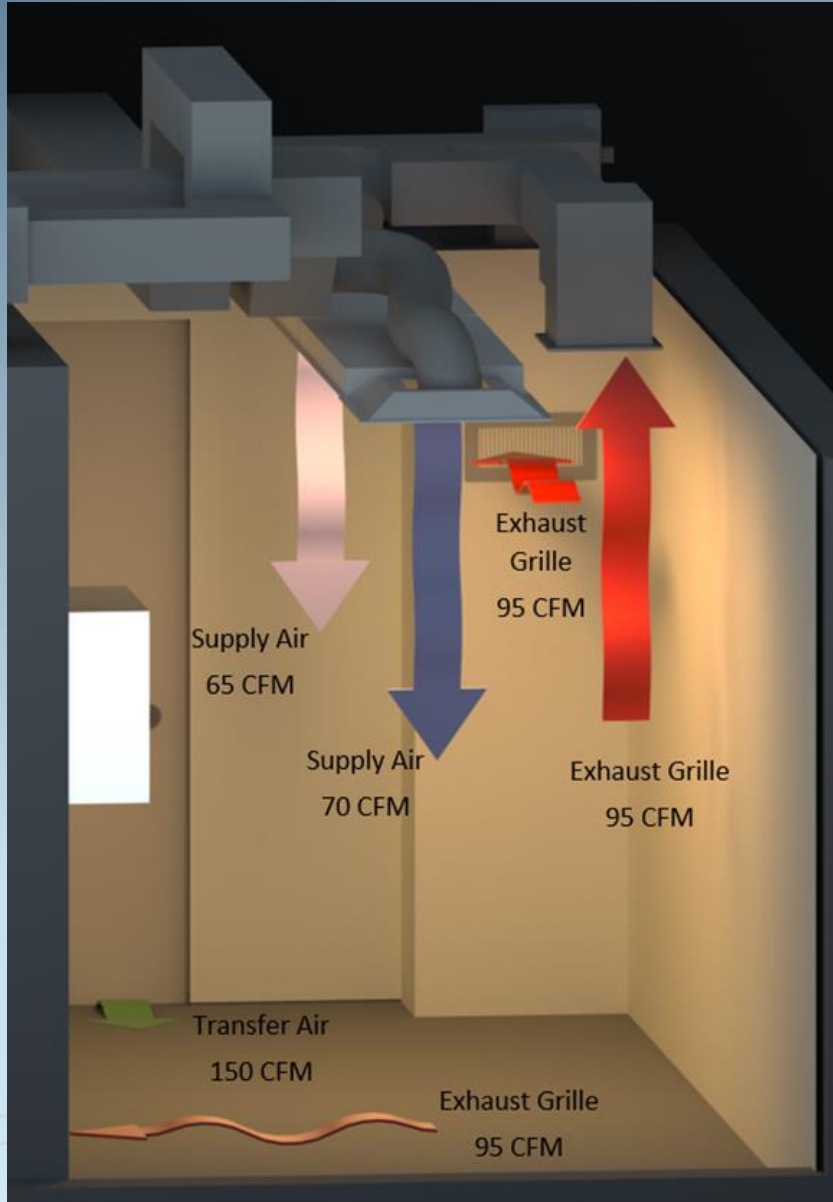
- USP <800>
 - Antineoplastic HDs requiring manipulation other than counting or repackaging of final dosage forms and any HD API must be stored separately from non-HDs in a manner that prevents contamination and personnel exposure. These **HDs must be stored in an externally ventilated, negative-pressure room with at least 12 air changes per hour (ACPH).**
 - Sterile and nonsterile HDs must be compounded within a C-PEC located in a C-SEC. The **C-SEC** used for **sterile and nonsterile** compounding must:
 - **Be externally vented**
 - Be physically separated (i.e., a different room from other preparation areas)
 - Have an appropriate air exchange (e.g., ACPH)
 - Have a negative pressure between 0.01 and 0.03 inches of water column relative to all adjacent areas
 - All **C-PECs** used for manipulation of sterile HDs **must be externally vented.**
 - The C-PECs used for manipulation of nonsterile HDs must be either externally vented (preferred) or have redundant-HEPA filters in series. Nonsterile HD compounding must be performed in a C-PEC that provides personnel and environmental protection, such as a Class I Biological Safety Cabinet (BSC) or Containment Ventilated Enclosure (CVE).
- ASHRAE 170
- NSF/ANSI 49
- National and Local Building Codes



ASHRAE 170



HD STORAGE RM. HVAC RECOMMENDATIONS



- NO ISO Classification
 - Min. 0.010" w.c. negative pressure to adjacent room
 - Exhausted to outside
 - HEPA filtration not required
 - Return locations
 - Low on the wall except where contamination removal is needed
- Minimum 12 ACPH required
- Air change rates based on **Exhaust**

HVAC SUPPLIED AIR CHANGE RATES

Room	ISO Classification	USP Minimum Air Change	Best Practice Minimum Air Change Rate	Source
Ante-Area	ISO Class 8	20 ACPH	30-40 ACPH	HVAC supply through HEPA filters located in the ceiling
Ante-Area	ISO Class 7	30 ACPH	50-60 ACPH Assumes no PEC in room to augment total ACPH	HVAC supply through HEPA filters located in the ceiling
Non-HD Buffer Room	ISO Class 7	30 ACPH	30 ACPH Assumes a minimum of one 4' LAFW in room to augment total ACPH	HVAC supply through HEPA filters located in the ceiling
HD Buffer Room	ISO Class 7	30 ACPH	50-60 ACPH Assumes PEC vented outside	HVAC supply through HEPA filters located in the ceiling
HD Storage Room	Unclassified	12 ACPH exhaust	12 ACPH exhaust	Exhaust

SECONDARY ENGINEERING CONTROLS ROOM SEGREGATION

- Room Pressure
 - 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

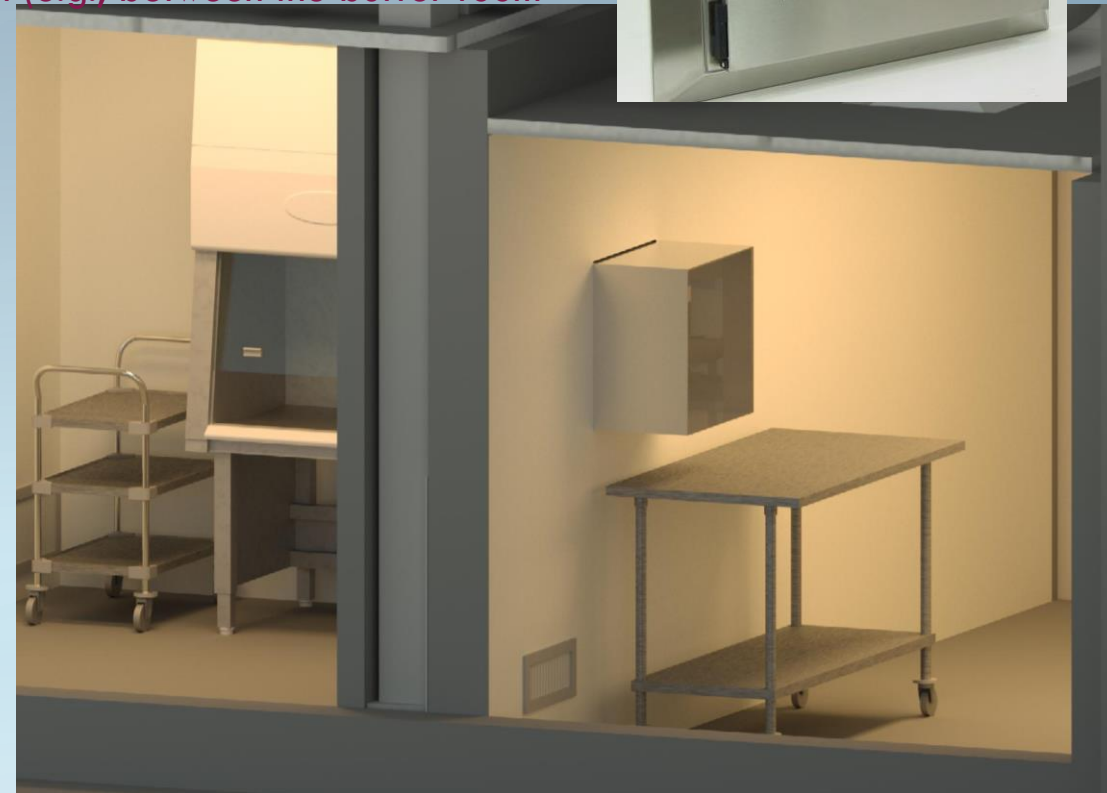


MATERIAL TRANSFER

4.2:

It is also critical to control materials (e.g., supplies and equipment) as they move from classified areas of lower quality to those of higher quality (e.g., ISO Class 8 ante-room to ISO Class 7 buffer room to ISO Class 5 PEC) to minimize the influx of contaminants. Airlocks and interlocking doors may be used to facilitate better control of air balance between areas of differing ISO classification (e.g., between the buffer room and ante-room), or between a classified area and an unclassified area (e.g., between the ante-room and an unclassified area such as a hallway). If a pass-through is used, both doors must never be opened at the same time, and doors should be interlocking.

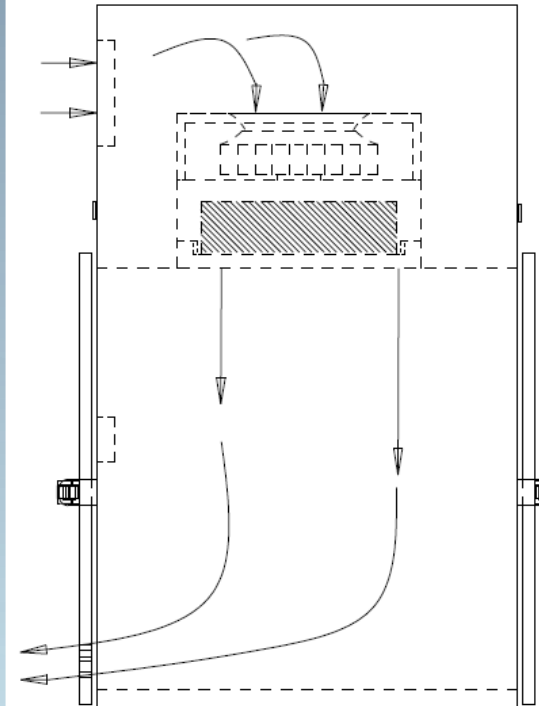
- **Airlock:** A space with interlocked doors, constructed to maintain air pressure control when items move between two adjoining areas (generally with different air cleanliness standards). The intent of an airlock is to prevent ingress of particulate matter and microbial contamination from a lesser-controlled area.
- **Pass-through:** An enclosure with sealed doors on both sides that should be interlocked. The pass-through is positioned between two spaces for the purpose of minimizing particulate transfer while moving materials from one space to another.



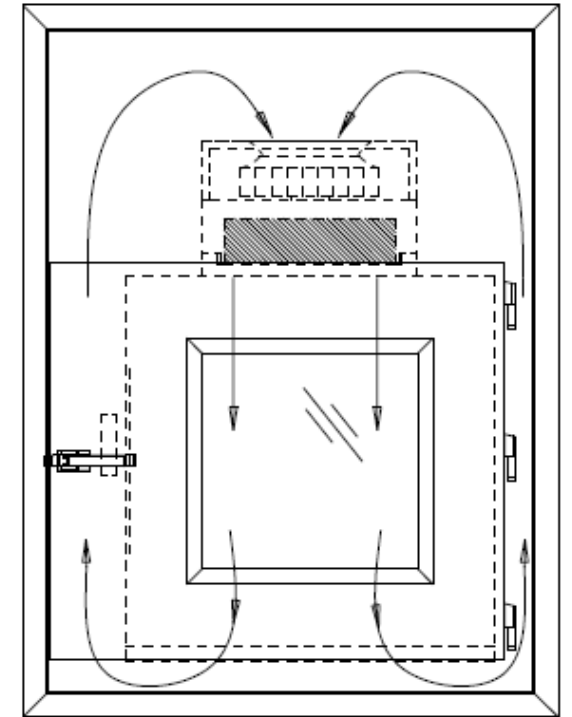
MATERIAL TRANSFER

Pass-through discussion

- To HEPA or not to HEPA
 - ISO Classified to non-classified
 - Certification
 - Electrical needs
 - Noise
 - Cost
- Materials of construction
- Sealed doors
- Interlocked



SINGLE PASS HEPA FILTRATION
(FAN RUNS CONTINUOUSLY)



RECIRCULATING HEPA FILTRATION
(FAN ON AN ADJUSTABLE TIMER)

CONTAINMENT SEGREGATED COMPOUNDING AREA (C-SCA)

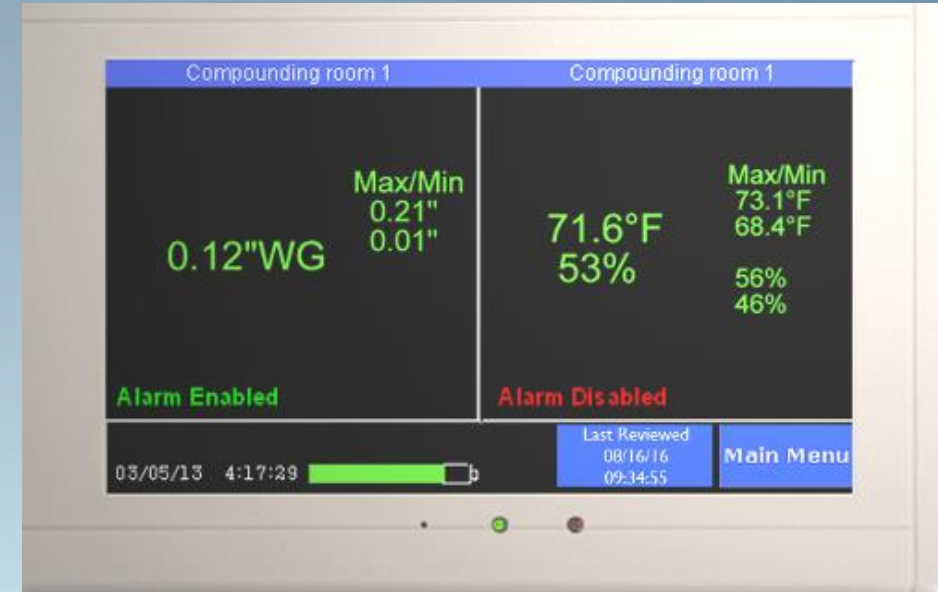
- Dedicated space for compounding hazardous sterile preparations
- Separate room with a defined perimeter to separate functions
- Limited to 12-hour BUD (proposed 797 is 12-hour room/24 hour refrigerated)
- PEC/room must be externally vented
- Certification criteria
 - Minimum 12 ACPH (probably have to request from certifier)
 - 0.010" w.c. to 0.030" w.c. negative pressure (request from certifier)



GENERAL FACILITY REQUIREMENTS

Applies to buffer rooms, ante-rooms and SCAs

- Well-lit and comfortable working environment
- Temperature/humidity controlled through an efficient heating, ventilation, and air conditioning (HVAC) system.
 - Free-standing humidifiers/dehumidifiers and air conditioners may NOT be used.
 - 20 °C (68 °F) or cooler
 - Relative humidity below 60%
- Monitor temperature and humidity every day (manually or by a continuous recording device)
 - Document and review results



ROOM FINISHES <797>

4.3:

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 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.**

Questions & Answers



GENERAL FACILITY REQUIREMENTS: CEILINGS

Ceilings

- Gypsum (epoxy paint)
 - Access doors, locations, amount needed
 - Cleanable
- Cleanroom tiles
 - Tiles must be caulked in place to ensure seal
 - Caulking of individual ceiling tiles allows caulking to be removed so servicing can occur then re-caulked
 - Smooth, non-porous tiles that stand up to cleaning agents
- Concealed Sprinkler Heads
- Wall junctions coved or caulked

Lights

- 4.3:
The exterior lens surface of ceiling light fixtures must be smooth, mounted flush, and sealed.



ROOM FINISHES

Walls

- 4.3
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.
 - Paint
 - Stand up to disinfectants
 - Epoxy issues
 - Some don't hold up
 - Odors
 - Touch up
 - Cleanroom wall panels
 - Wall coverings
 - must be joined together and sealed to each other and the support structure.



ROOM FINISHES

Floors

- 4.3
Floors must include coving to the sidewall, or the juncture between the floor and the wall must be caulked.
- Monolithic
 - Wide-sheet vinyl flooring with heat-welded seams
 - Poured epoxy (smooth or rough?)
- Must be coved to walls
- Must withstand continuous cleaning with cleaning agents
- No gaps or crevices for microorganisms to accumulate and grow
- No floor drains



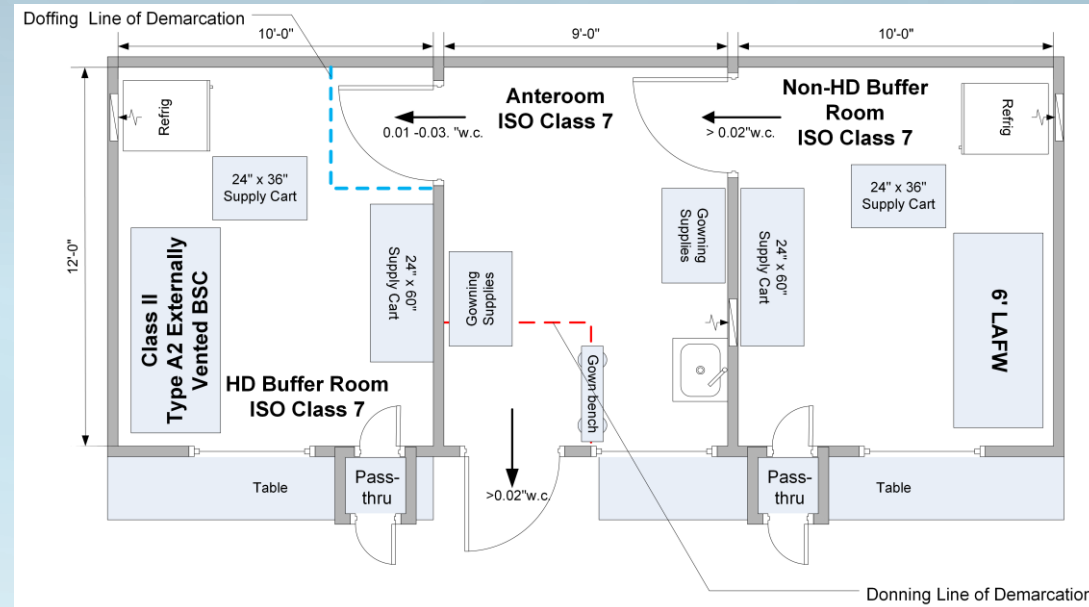
ROOM FINISHES

Doors

- Due to the interdependence of the various rooms or areas that make up a sterile compounding facility, it is essential to carefully define and control the dynamic interactions permitted between areas and rooms. Consider the placement of door closures, door surfaces, and the movement of the doors, all of which can affect airflow. Seals and sweeps should not be installed at doors between buffer and ante-rooms. Access doors should be hands-free. Tacky mats must not be placed within ISO-classified areas.



- Materials
- Interlocks
- Sliding vs. hinged
- Hinged Door Swing



Room Pressure and Conditions that Affect Room Pressure

- The room pressure differential in doorways between adjacent rooms
- Positive pressure
 - Minimum of 0.020" w.c. (not a range of 0.02 - 0.05" w.c.)
- Negative Pressure range of 0.010 - 0.030" w.c. (range is critically important)
- Seals and sweeps should not be installed at doors between buffer rooms and anterooms



MORE ABOUT SPRINKLER HEADS THAN A CERTIFIER NEEDS TO KNOW



Solder on cover melts faster than glass bulb. Air must flow past bulb to get hot enough to melt. If room is negative to ceiling, air might not get hot enough to melt.

