The Future of Sterile Compounding for Health-Systems

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Disclosures:

- Sterile Compounding Expert Panel (SCXP)
  - 2 Year Appointment
  - Pharmacy Stars

- Soigner Solutions
  - USP Compliance Consultation

Introduction to the Proposed Revisions

This presentation was designed to discuss the proposed version of USP <797> published December 2021 ….

- What to expect
- Preparation
- Changes that may be seen

Email – New USP <797> Standards to be Published

Fall 2022

Updates on Standards

Personalized Medicines

Upcoming Updates to USP General Chapters <795> and <797>: USP has received feedback from its stakeholders to ensure broad perspectives were included in the updated standards with a continuing focus on patient safety and access to quality medicines. The revisions will be published in the *USP-NF* and *USP Compounding Compendium* on November 1, 2022.

New **Compounding Compendium:** Significant changes are forthcoming, which will enhance the way users interact with USP Compounding Standards. The updated *USP Compounding Compendium* will migrate to an online platform. To learn more about the compendium, access the fact sheet here. For updates on the upcoming launch of the Compounding Compendium, sign up here.

Healthcare & Patient Safety Information

COMING SOON "Revised" USP COVID-19 Vaccine Handling Toolkit: A revised edition of the USP COVID-19 Vaccine Handling Toolkit provides frontline practitioners with the most updated

November 1st

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Today's Date – November 3rd

Objectives

- Identify the current changes in 2022 USP <797> that will become official in 12 months (Nov. 1, 2023)

- Describe the BUD that hospitals with full cleanrooms suites will assign to CSPs in the future.

The Future of Sterile Compounding for Health-Systems

USP <797> as of November 1, 2022 (and official in 12 months - November 1, 2023)

- ALBOP
- Regulatory agencies

Categories & Beyond Use Date

~~Proposed USP <797> (v.2021)~~

USP <797> (v. 2022) *with 12 month implementation (Nov. 1, 2023)*

Categories and Beyond Use Dating

- Compounding based on ”risk” associated (v. 2008)
  - High- Medium- Low- Risk
    - Number of manipulations / products

- Compounding based on Categories (v. 2022)
  - Category 1, 2, ~~3~~
    - Environment / Conditions CSP is compounded
      - Quality of garb
      - Cleaning (defined/documented)
      - Environmental monitoring
      - Sterilization / Sterility testing of CSP

Location: Cleanroom Suite

- Outside cleanroom suite
- Inside cleanroom suite

Outside of a Cleanroom Suite (2 options)

Immediate-Use Compounding		
USP <797>	**Risk**	**BUD***
v. 2008	Room air, aseptic technique	1 hour
v. 2022	Room air, aseptic technique	4 hours

Segregated Compounding Area (SCA)			
USP <797>	**Location**	**Condition**	**BUD***
v. 2008	SCA	PEC, 3 products/2 entries	12 hrs RT / 12 hrs refrig.
v. 2022	Category 1	PEC only - no limitations	12 hrs RT / 24 hrs refrig.

**"Glove Boxes" may no longer give BUD beyond 12 hours RT/24 hours refrigeration UNLESS inside a full cleanroom suite*

Inside a Cleanroom Suite (v. 2008)

USP <797> (v. 2008)		
Risk	**Associated Risk**	**BUD***
Low Risk	3 products, 2 entries	48 hours room temp 14 days refrigerated 45 days frozen
Medium Risk	> 3 products, > 2 entries, batching	30 hours room temp 9 day refrigerated 45 days frozen
High Risk	One or more non-sterile ingredient/component	24 hours room temp 3 days refrigerated 45 days frozen

Inside Cleanroom Suite (v. 2022) – Category 2

Category 2 CSP: USP <797> (v. 2022)*				
Preparation Characteristics		**Storage Conditions**		
Compounding Method	**Sterility Testing Preformed/Passed**	**Controlled Rm Temp (20°C-25°C)**	**Refrigeration (2°C-8°C)**	**Frozen (-25°C to -10°C)**
Aseptically Processed CSPs	No: Prepared from one or more nonsterile starting components.	1 day	4 days	45 days
	No: Prepared from only sterile starting components.	4 days	10 days	45 days
	Yes	30 days	45 days	60 Days
Terminally Sterilized CSPs	No	14 Days	28 Days	45 day
	Yes	45 days	60 days	90 days

"Glove Boxes" must be in a full cleanroom suite to assign Category 2 BUD

**USP <797> November 1, 2022: Table 13*

Inside Cleanroom Suite (v. 2022) – Category 2

Category 2 CSP: USP <797> (v. 2022)*				
Preparation Characteristics		**Storage Conditions**		
Compounding Method	**Sterility Testing Preformed/Passed**	**Controlled Rm Temp (20°C-25°C)**	**Refrigeration (2°C-8°C)**	**Frozen (-25°C to -10°C)**
Aseptically Processed CSPs	No: Prepared from one or more nonsterile starting components.	1 day	4 days	45 days
	No: Prepared from one or more sterile starting components.	4 days	10 days	45 days
	Yes	30 days	45 days	60 Days
Terminally Sterilized CSPs	No	14 Days	28 Days	45 day
	Yes	45 days	60 days	90 days

"Glove Boxes" must be in a full cleanroom suite to assign Category 2 BUD

**USP <797> November 1, 2022: Table 13*

Inside Cleanroom Suite (v. 2022) – Category 3

USP		
Preparation Characteri	ge Conditions	
Compounding Method	Refrigeration (2°C-8°C)	Frozen (-25°C to -10°C)
Aseptically processed, sterility tested passing all applicable tests for Categ	90 days	120 days
Terminally sterilized, sterility passing all applicable tests for C	120 days	180 days

Sterile garb, no skin in buffer area, monthly viable air, weekly viable surface, surface after each batch, weekly sporicidal in PEC, surfaces, passthroughs and floors.

**USP <797> November 1, 2022: Table 14*

NOTE on BUD

Literature to Support

- *Stability and compatibility of final preparation, physically and chemically compatible with:*
  - *fluid*
  - *container*
  - *final CSP concentration*
  - *under specific storage conditions*
- *Attention to leaching and sorption*

BUD (other) – In Use Times

Type of container	USP <797> 2008	USP <797> 2022 (current)
Ampule	NEVER	*NEVER*
SDV (or container)	6 hours in ISO 5 (rm air 1 hour)	*12 hours in ISO 5*
Bulk Compounded Solutions*		
MDV (or container)	28 days (or less per MFR)	*28 days (or per MFR)*
Pharmacy Bulk Container	Per MFR	*Per MFR*

** USP <797> November 1, 2022: Section 16.2 Use of Compounded Single-Dose CSPs and CSP Stock Solutions*

What is Compounding?

Compounding

- The process of:
  - Combining
  - Admixing
  - Diluting
  - Pooling
  - Reconstituting
  - Repackaging (absent in v. 2008)
  - Altering drug or bulk drug

NOT Compounding

- For only one patient and per manufacturer PI:
  - Mixing
  - Reconstituting
  - Other acts described
- Proprietary vial and bag systems
  - Docking, activating for immediate use*

*Docking for future use = compounding

Situation: Compounding Drug X to a concentration of 5 mg/mL in NS in a PVC container within an IV Room suite.

A) Category 1

B Category 2

C) Category 3

What would be the category as defined under USP <797> version 2022?

Situation: Compounding Drug X to a concentration of 5 mg/mL in NS in a PVC container within an IV Room suite.

A) Category 1 – No, we are compounding in a cleanroom suite

B Category 2 – Yes, we are compounding in a cleanroom suite

C) Category 3 – No, not in scope for hospital pharmacy

- *Requires increased regulation for garb, environmental sampling, cleaning, terminal sterilization and sterility testing of final CSP*

Situation: Compounding Drug X to a concentration of 5 mg/mL in NS in a PVC container within an IV Room suite.

Literature review:

- After reconstitution at 50 mg/mL stable for 14 days
- Stable diluted to 5 mg/mL in NS, D5W
  - Glass, PVC and polyolefin
  - 4 days at room temperature
  - 7 days under refrigeration

Abbreviated Category 2 CSP: USP <797> (v. 2022)		
Storage Conditions for Sterile-to-Sterile		
Controlled Rm Temp (20°C-25°C)	Refrigeration (2°C-8°C)	Frozen (-25°C to -10°C)
4 days	10 days	45 days

What is the refrigerated BUD for this CSP?

A) 10 days BUD

B) 14 days BUD

C) 7 days BUD

Situation: Compounding Drug X to a concentration of 5 mg/mL in NS in a PVC container within an IV Room suite.

Literature review:

- After reconstitution at 50 mg/mL stable for 14 days
- Stable diluted to **5 mg/mL in NS**, D5W
  - Glass, **PVC** and polyolefin
  - 4 days at room temperature
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Controlled Rm Temp (20°C-25°C)	**Refrigeration (2°C-8°C)**	**Frozen (-25°C to -10°C)**
4 days	10 days	45 days

A) 10 days BUD

B) 14 days BUD

C) 7 days BUD

Stability: Stable only for 7 days under refrigeration

Environmental Sampling

Viable Sampling (Surface and Air)

… to see if contamination is present at unacceptable levels

Environmental – Viable Surface Sample

- Viable Surface (agar with neutralizing agent)
  - Frequency
    - 2008: Periodically (best practice = monthly)
    - 2022: Monthly (Cat. 1 & 2)
      - Cat 3 = weekly and after each batch
  - Where: Inside PEC, equipment inside PEC, areas around PEC, passthroughs, other high touch areas (observation)
    - Need a map of locations
  - Time: Busiest time, after compounding, prior to cleaning

Environmental – Viable Air Samples

- Viable Air
  - Frequency
    - 2008: Every 6 months
    - 2022: Every 6 months (Cat. 1 & 2)
      - Cat. 3 = monthly
  - Where: Inside PEC, high traffic areas (takes observation)
    - Need a map of locations
  - Time: When most people present and working (dynamic conditions)

Incubation & Identification

Viable Sampling (Surface and Air)

Incubation & Identification (v. 2022)

(v. 2008: 48-72 hours / low- med- risk)

Incubation

- Incubate 30-35°C x 48 hours
  - Document cfu
- Incubate 20-25°C x 5 days
  - Document cfu

Alternative (2 samples per area) – Sec. 6, box 5 & 6

- *2 TSA Plates*
  - *One at 30-35 C x 48 hours – document cfu*
  - *One at 20-25 C x 5 days – document cfu*
- *TSA + MEA/SDA*
  - *TSA at 30-35 C x 48 hours – document cfu*
  - *MEA/SDA at 20-25 C x 5 days – document cfu*

Identification

- *No longer need to Identify to genus level unless limits exceeded*

- Highly pathogenic organisms
  - ~~Gram negative rods~~
  - ~~Coagulase-Positive Staphylococcus (S. aureus)~~
  - ~~Yeast~~
  - ~~Mold~~
  - ~~Fungus~~

Air/Surface Action Levels per ISO Area

Air/Surface Action Levels per ISO Area (v. 2022)		
ISO Classification	**AIR**	**Surfaces**
ISO 5	> 1	>3
ISO 7	>10	>5
ISO 8	>100	**>50**

Environmental Monitoring – Documented

Trends overtime (even with no excursion)

- Document

Excursion

- Identify CFU to the genus level
- Investigate
  - Identify source
- Remediate
- Proof remediation was effective

- Train employees

Excursions
Investigation
Remediate
Eliminate

Hand Hygiene & Garbing

Garbing

USP <797> v. 2008

- Dirtiest to cleanest
- Distinct order
  - Shoe covers
  - Head/facial hair cover
  - Mask/eye protection
  - Hand hygiene
  - Gown
- Alcohol hand scrub & gloving occurs in buffer room/SCA

USP <797> v. 2022

- Based on facility SOP surrounding placement of sink
- Gloving "must" occur in a classified room/SCA
  - **"Should" be in anteroom**
    - Minimizes exposed skin buffer room
- Gloves: **Breakthrough time for IPA**

Hand Hygiene

- No scrub brushes (v. 2008 stated not recommended)
- No electric hand dryers (v. 2008 was allowable)
- Disposable soap dispenser
- Alcohol-based hand scrub ~~*with persistent activity*~~

Best Practice

- Clock that reads seconds (hand washing – 30 seconds)
  - No singing the “Happy Birthday” song – keep conversation to minimum

Which of the following should we hold off on doing until we hear more from the ALBOP?

A) Ensure that agar for surface samples contain a neutralizing agent

B) Start donning gloves in the anteroom instead of buffer room

C) Stop identifying cfu to the genus level

Which of the following should we hold off on doing until we hear more from the ALBOP?

A) Ensure that agar for surface samples contain a neutralizing agent
   - This is required to neutralize cleaning agent residues

B) Start donning gloves in the anteroom instead of buffer room
   - This is best practice “should” don in anteroom to decrease exposed skin in buffer room

C) Stop identifying cfu to the genus level
   - **Correct: ALBOP may want to give direction**

Competency

Gloved Fingertip & Media Fill

- Compounding Personnel
- Those with direct oversight (not compounding)

Gloved Fingertip & Media Fill

Fingertips (Glove/Garb/Hand Hygiene)

- Initial: 3 consecutive = zero cfu
- 2022: Category 1 & 2
  - Compounder: **6 months**
  - Oversight: **12 months** (no compounding)
  - *Category 3 – every 3 months*
- **Documented observation: garbing and hand hygiene**

Media Fill

- 2022: Category 1 & 2
  - Compounder: **6 months**
  - Oversight: **12 months** (no compounding)
  - *Category 3 – every 3 months*
- FT post aseptic fill
- **Surface sample of DCA**

Certificate of Analysis (COA) for media

Incubation & Evaluation of FT and MF

Fingertips (min. 7 days total)

- Incubate 30-35°C x 48 hours
  - Document cfu
- Incubate 20-25°C x 5 days
  - Document cfu

Media Fill* (min. 14 days total)

- Incubate 20-25°C x 7 days
  - Document turbidity
- Incubate 30-35°C x 7 days
  - Document turbidity

**Order of incubation temperature must be described in SOPs*

Action Levels Associated with FT, MF, DCA Sampling				
USP <797>	Fingertip glove/garb	Media Fill	Fingertip post MF	DCA
v. 2008	> 0	no turbidity	> 3	n/a
v. 2022	> 0	no turbidity	> 3	> 3

Compounding Documentation

Master Formulation Records & Compounding Records

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Master Formulation and Compounding Records

Master Formulation Records (MFR)

- v. 2008: Mentions w/ no specific requirement
- 2022: Specific requirements (sec. 11.1/Box 9)
- **Required when compounding:**
  - **For more than one patient**
  - **Using non-sterile ingredients/components**

Compounding Records

- v. 2008: Mentions w/ no specific requirement
- 2022: Specific requirements (sec. 11.2/Box 10)
- **Required when compounding:**
  - **ALL Category 1, 2, & 3**
    - **Sterile or Non-Sterile components**
  - **Immediate-Use, if compounding for more than one patient**

Compounding Records: Box 10

Documents Compounding Process

- Prescription, med order or label may serve as compounding record
- IV workflow – if readily available

May need IT involvement to include all requirements for the compounding record.

Box 10. Compounding Records

CRs must include at least the following information:

- Name, strength or activity, and dosage form of the CSP
- Date and time of preparation of the CSP
- Assigned internal identification number (e.g., prescription, order, or lot number)
- A method to identify the individuals involved in the compounding process and individuals verifying the final CSP
- Name of each component
- Vendor, lot number, and expiration date for each component for CSPs prepared for more than one patient and for CSPs prepared from nonsterile ingredient(s)
- Weight or volume of each component
- Strength or activity of each component
- Total quantity compounded
- Final yield (e.g., quantity, containers, number of units)
- Assigned BUD and storage requirements
- Results of QC procedures (e.g., visual inspection, filter integrity testing, pH testing)

If applicable, the CR must also include:

- MFR reference for the CSP
- Calculations made to determine and verify quantities and/or concentrations of components

USP <797> Nov. 1, 2022: Section 11.2; Box 10

Training & Evaluation

- Trained
- Demonstrate knowledge of principles
- Show competency

Training and Evaluation - minimum (Section 2)

Initially and every 12 months

- Hand hygiene / garbing
- Cleaning and disinfecting
- Calculations, measuring and mixing
- Aseptic technique
- Achieving and/or maintaining sterility and apyrogenicity
- Use of equipment
- Documentation of compounding process (e.g., MFR and compounding records
- Principles of HEPA-filtered unidirectional airflow
- Use of Primary Engineering controls (PEC) – aka. Hoods
- Principles of movement of material and personnel withing the compounding area

Facility Build

Quick Checklist

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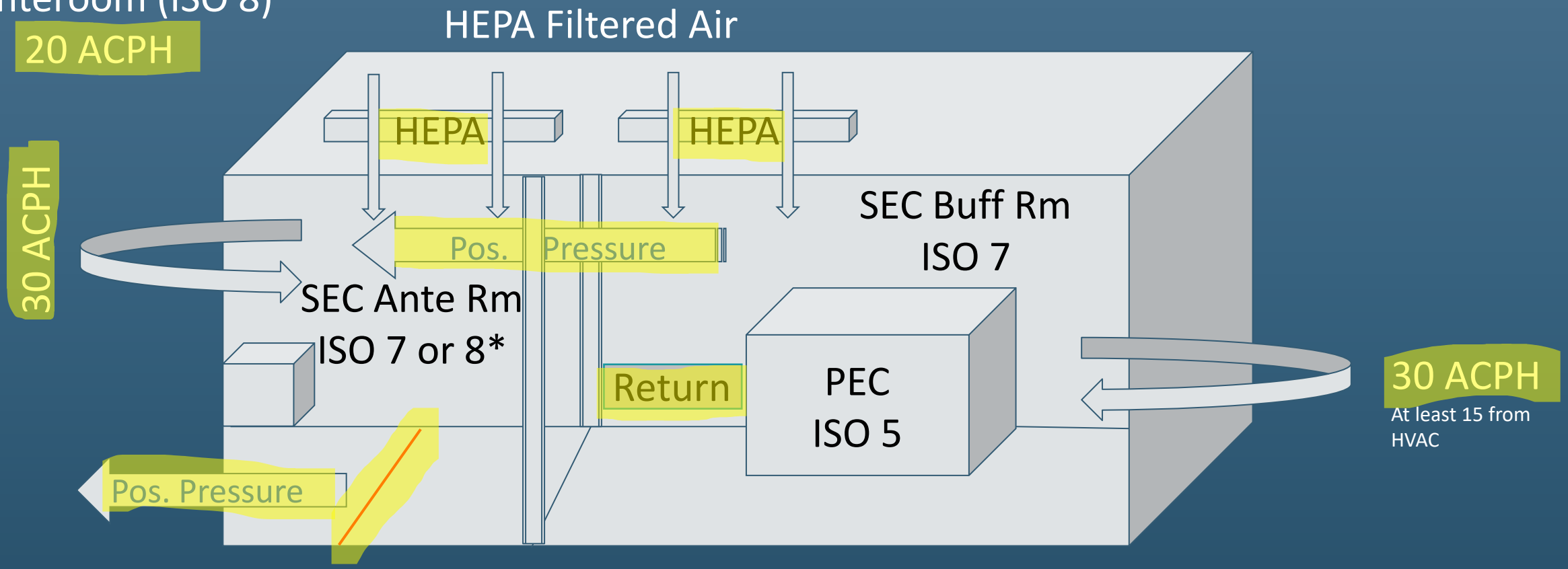
Cleanroom Suite (non-hazardous) – Cat. 2 & 3

Anteroom (ISO 8)*

- 20 ACPH



*Note: Anteroom must be ISO 7 w/ 30 ACPH if connected to negative pressure HD ISO 7 Buffer Room

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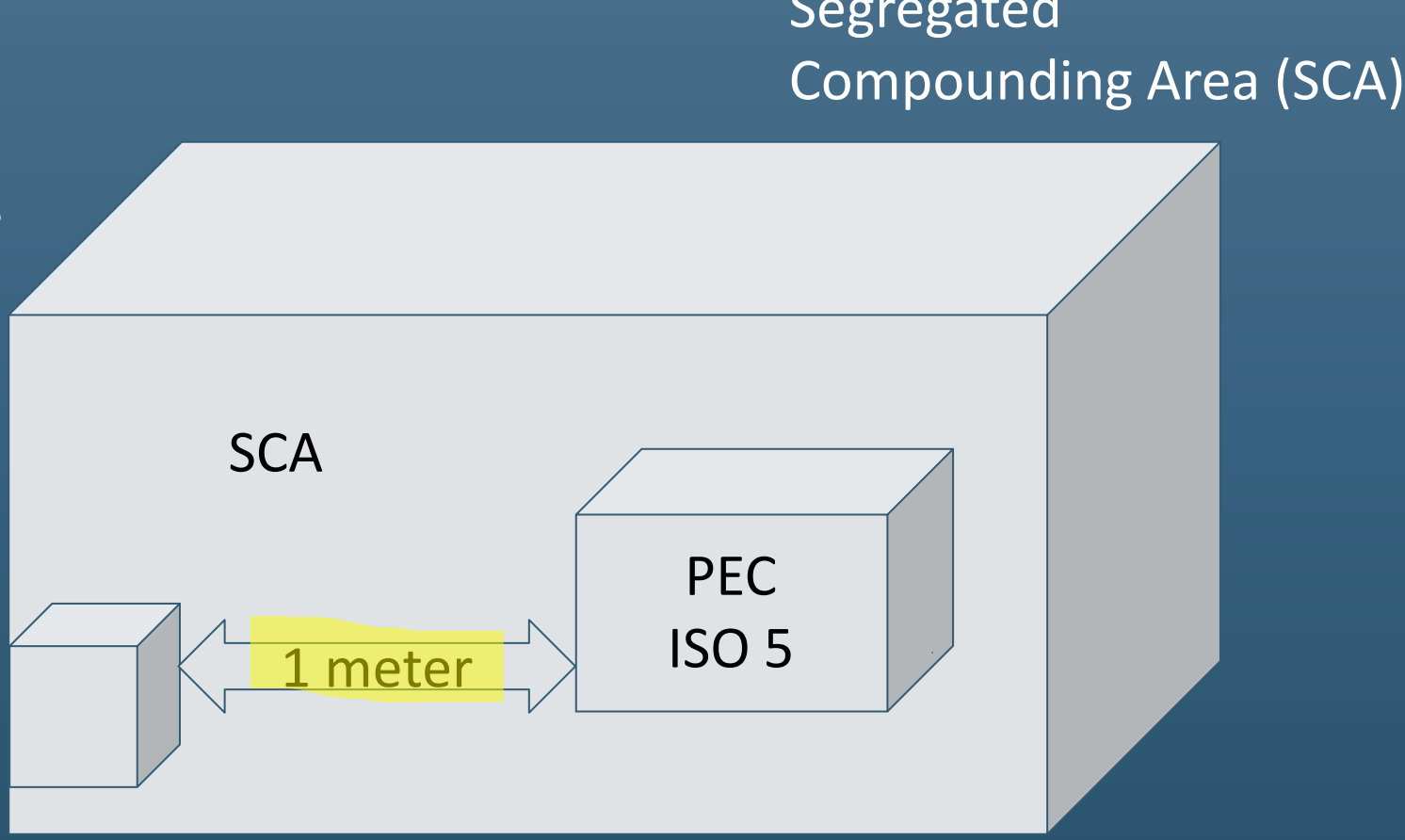
Unclassified Area for Sterile Compounding – Cat. 1

- **Unclassified** area w/ visible perimeter
- Away from other areas
- Limited: Category 1
  - 12 hr BUD RT
  - 24 hr BUD refrig.
- Sink:
  - Inside
  - 1 meter away



Cleanroom Suite: Quick Check Facility

- ✓ HEPA filter: In ceiling
- ✓ Low Wall Air Returns
  - Unless smoke study shows absence of stagnant air
- ✓ Pressure: +0.020”WC or greater
  - Pressure Differential Monitoring System
- ✓ Anteroom: Line of demarcation
- ✓ ACPH
  - ISO 7 ≥ 30 (buffer rm/anteroom)
  - ISO 8 ≥ 30 (anteroom)
    - Anteroom must be ISO 7 if adjacent to negative pressure buffer room
- ✓ Pass-throughs
  - Interlocking doors
  - Not able to open at same time

SCA: Quick Check Facility

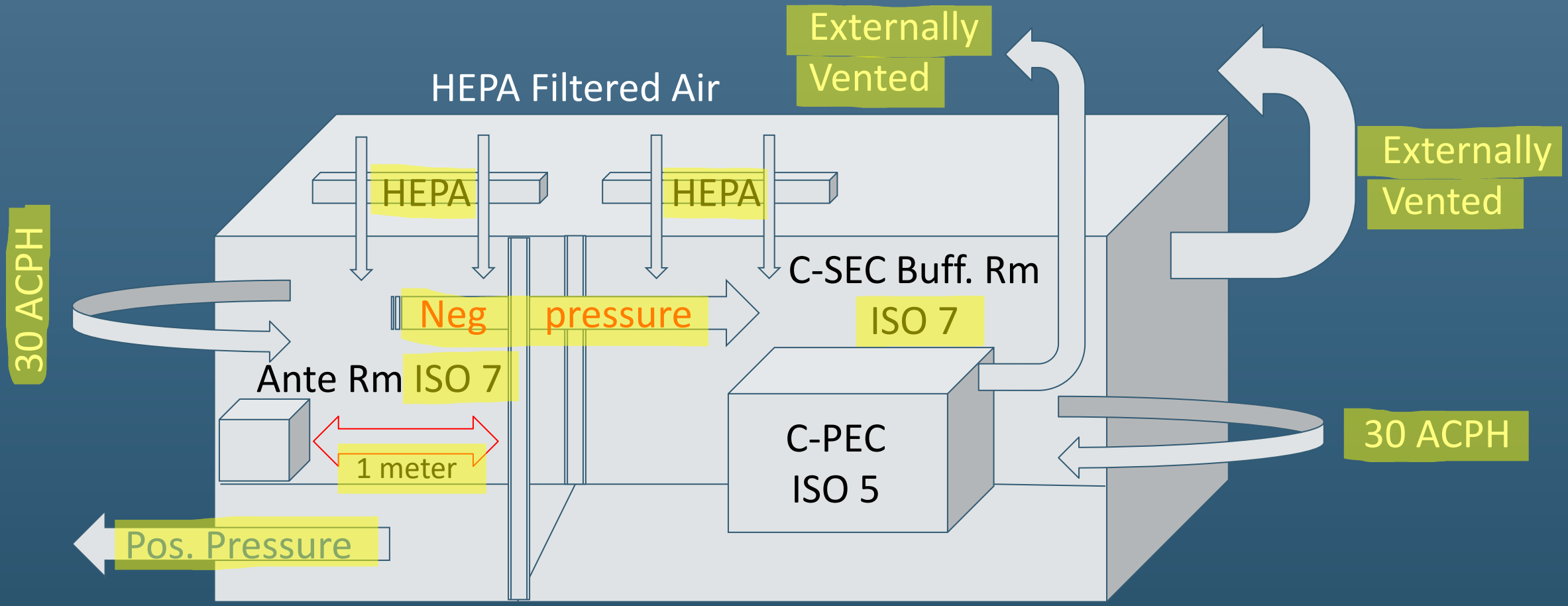
- ✓ Visible perimeter
- ✓ HEPA filter: none
- ✓ Low Air Return: none
- ✓ Pressure: None

- ✓ Sink
  - Inside SCA perimeter
  - 1 meter away from PEC
- ✓ Cat. 1 ONLY
  - 12 hour BUD RT
  - 12 hour BUD refrigerated

Facility Build: USP <800>

- Sterile and Non-Sterile Compounding Hazardous Drugs
- Receipt, storage, compounding, delivery/transport, administration, waste

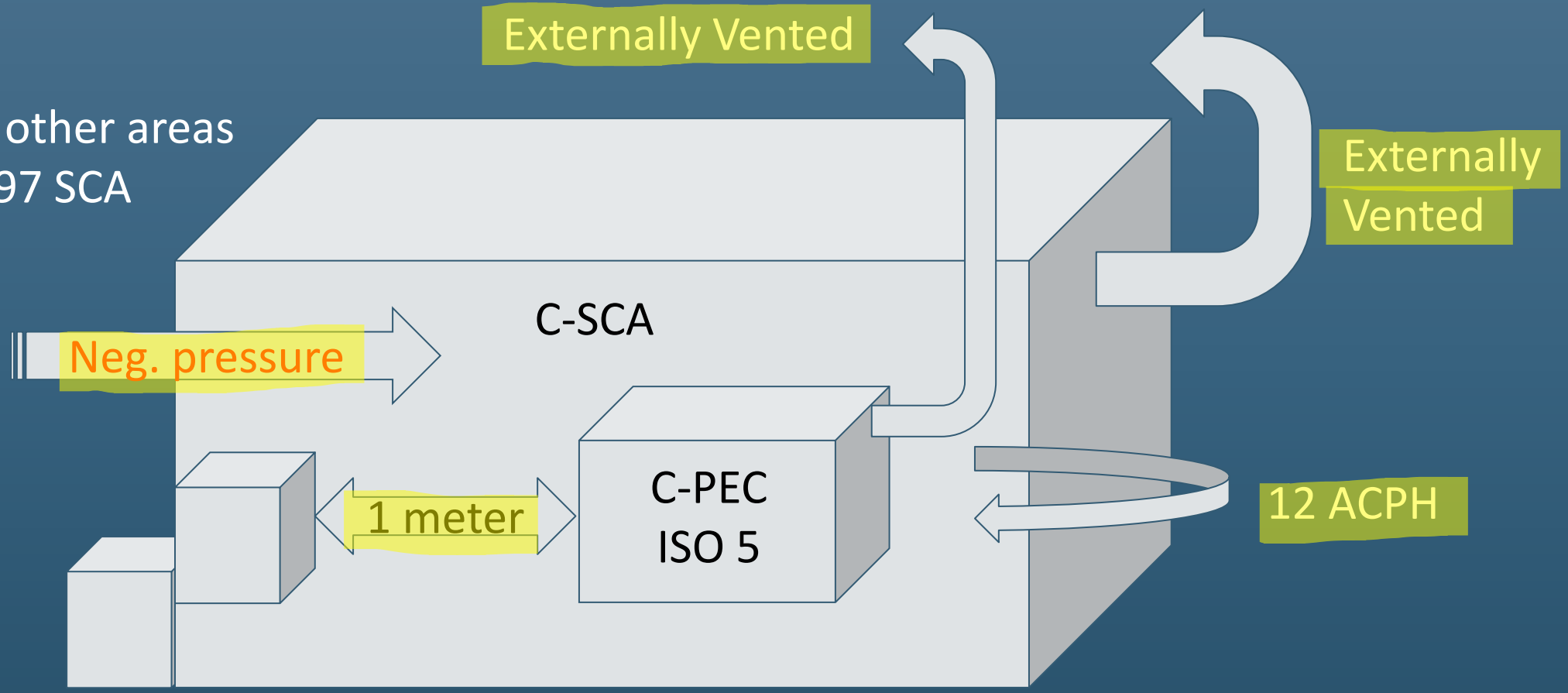
Sterile HD Cleanroom Suite: C-PEC/C-SEC



Sterile HD C-SCA: Unclassified Area

Containment Segregated Compounding Area (C-SCA)

- Fixed Walls
- Away from other areas
- BUD USP 797 SCA
- Sink



HD Cleanroom Suite: Quick Check Facility

✓ HEPA filter: In ceiling

✓ Pressure Differential Monitoring System
- Neg. Pressure Buffer: -0.01 to -0.03”WC
- Anteroom: +0.020”WC

✓ Room: Externally vented

✓ PEC: Externally vented

✓ Sink 1 meter from entrance to buffer room

✓ Anteroom: Line of demarcation

✓ ACPH
- ISO 7 buffer room ≥ 30
- ISO 7 anteroom ≥ 30

✓ Pass-throughs
- Interlocking doors
- Not able to open at same time

HD SCA: Quick Check Facility

- ✓ Fixed walls
- ✓ HEPA filter: none
- ✓ Low Air Exhaust: possible
- ✓ Pressure: -0.01 to -0.03”WC
  - Pressure Differential Monitoring System
- ✓ ACPH ≥ 12
- ✓ Room: Externally vented
- ✓ PEC: Externally vented
- ✓ Cat. 1 ONLY
  - 12 hour BUD RT
  - 12 hour BUD refrigerated
- ✓ Sink Inside or Outside SCA
  - 1 meter away from PEC

Reminders: USP 800 HD Compounding

- Double chemo glove
  - ASTM-rated chemo gloves
- Double shoe covers
- CSTD recommended for compounding HDs/Required for administration
- Deactivation/Decontamination
- Spill kit available
- Chemo Gown (coated, seamless, closes in back)
- Respiratory protection

Cleaning Controlled Environments

Section 7: Cleaning, Disinfecting and Applying Sporicidal Disinfects and Sterile 70% IPA

- Section 7, Table 10 (Cleaning & Disinfecting Table)

Definitions: Cleaning and Disinfecting

USP <797> 2022

- **Cleaning**: Removal of residues (dirt, debris, microbes, residual drugs/chemicals) using an agent w/ **surfactant** and **manual or mechanical processes.**
- **Disinfection**: Germicidal - Kills microorganisms (bacteria, virus, fungi)
  - Cleaning prior to disinfection (unless using an EPA-registered, or equivalent, one-step disinfectant cleaner
- **Sporicidal Activity**: Destruction of bacterial and fungal spores / spore-forming microbes.

USP <800> Hazardous Drugs

- ***Deactivation**: Rendering a compound inactive/inert*
- ***Decontamination**: Removal of HD residue*

Introduction of Component/Supplies

★ **Remember: "KNOW Your Products" & "KNOW Your Environment"**

Classified room, pass-through, SCA

- Wipe (mechanical) with sporicidal, EPA-registered disinfectant, sterile IPA 70%
  - Ensure dwell times (sporicidal/EPA-registered disinfectant)
  - Allow to dry (sterile IPA 70%)
- *Wipers and cleaning agents = "should" be sterile*

PEC (e.g. Hood, LFBW, BSC)

- Always wipe (mechanical) with Sterile IPA 70% - allow to dry
- Critical Sites: Sterile IPA 70% w/ mechanical motion
- *Wipers and cleaning agents = "must" be sterile*

**Intent of sterile items inside PEC is to reduce bio burden from manufacturer (not to keep sterile)*

Which of the following statements is FALSE?

A) Cleaning requires a chemical agent in addition to mechanical process to remove debris

B) Documented observation of glove/garbing is required

C) Compounding Records are required when compounding one product for one patient

D) Sterile IPA 70% is sufficient to use alone in cleanrooms

Which of the following statements is FALSE?

A) Cleaning requires a chemical agent in addition to mechanical wiping to remove debris

B) Documented observation of glove/garbing is required

C) Compounding Records are required when compounding one product for one patient

D) Sterile IPA 70% is sufficient to use alone in cleanrooms
   - IPA 70% is not a disinfectant, has long dwell times and does not deactivate spores

Acronyms / Synonyms

- CSP - Compounded Sterile Product
- PEC - Primary Engineering Control (LFWB) (aka. Hood)
- SCA - Segregated Compounding Area
- BUD - Beyond Use Date
- CFU - Colony Forming Units (viable, microbial)
- BSC - Biological Safety Cabinet (C-PEC)
- CSTD - Closed System Transfer Device
- DCA - Direct Compounding Area
- SEC - Secondary Engineering Control (Buffer, Ante)
- ACPH - Air Changes Per Hour

C-PEC, C-SEC: “C” indicates “containment” or otherwise for hazardous Drugs

References and Contact Information

References

- USP <797> 2008
- *USP <797> 2021 proposed revision*
- USP <800> 2020
- USP <797> November 1, 2022

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