Section 1
Introduction and Scope

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Learning Objectives

After this lecture, the learner will be able to:

- Identify the CSPs and practices to which the chapter applies.
- List the activities that are beyond the scope of USP <797>.
- Differentiate Category 1, Category 2, and Category 3 CSPs.

Sterile compounding is defined as…

- combining
- admixing
- diluting
- pooling
- reconstituting
- repackaging
- otherwise altering

a drug product or bulk drug substance to create a sterile preparation.

Alternatives to the Chapter

- Can use technologies, techniques, materials, and procedures other than those described in the chapter if they are:
  - noninferior to those described in the chapter
  - validated for the intended purpose
- Check out
  - Validation of Alternative Microbiological Methods <1223>
  - Validation of Compendial Procedures <1225>

What to Follow for Specific Practices

Allergenic extracts	Section 21 if certain criteria are met
Blood-derived, biological materials	Applicable regulatory requirements
Hazardous drugs	USP <800>
Repackaging	USP <797>
Sterile radiopharmaceuticals	USP <825>

Designated Person

- Person or persons responsible and accountable for…
  - performance and operation of compounding facility
  - personnel preparing CSPs
  - performing other functions as described in this chapter
- Have more than one person!
  - technicians
  - pharmacists

Administration

- Is the direct application of a sterile product or preparation to a single patient by injecting, infusing, or otherwise providing a sterile product or preparation in its final form
- Beyond the scope of this chapter
- Need to start administration by beyond-use date
- Stability needs to be considered for “hang time”

Immediate-Use CSPs

- Couple of changes from 2008
  - no longer strictly for emergent use
  - 4-hour BUD
  - 3 products
- Goal is to improve patient access
- When all conditions are met, compounding of CSPs for direct and immediate administration is not subject to the requirements for Categories 1, 2, and 3 CSPs

Immediate-Use CSPs

1. Written and followed aseptic techniques, processes, and procedures
2. Personnel are trained and demonstrate competency in aseptic processes
3. Performed according to approved labeling or evidence-based information
4. Not more than 3 different sterile products
5. SDC are discarded after use and not used for more than one patient
6. Administration begins within 4 hours
7. CSP is labeled unless administered by preparer or administration witnessed by preparer

Preparation per Approved Labeling

- NOT COMPOUNDING
- Out of the scope of the chapter if
  1. performed in accordance with directions contained in approved labeling or supplemental materials provided by the product's manufacturer
  2. the product is prepared as a single dose for an individual patient
  3. approved labeling includes information for the diluent, the resultant strength, the container closure system, and storage time

Proprietary Bag and Vial Systems

Immediate Activation

- Docking and activation per manufacturer's labeling for immediate administration is not compounding
- May be performed outside of ISO Class 5

Future Activation

- Docking for future activation and administration is considered compounding
- Must be performed in ISO Class 5
- Follow the chapter except for BUDs

Knowledge Check!

Which is a chapter requirement when preparing a CSP according to the package labeling?

A. It must be prepared for a single patient.

B. The labeling information must include hold time.

C. It must be prepared as a multiple-dose container.

D. The starting components must include bulk drug substances.

Wrap-Up

- Going from risk levels to compounding categories is a huge paradigm shift but allows more flexibility in caring for patients.
- The chapter better defines what is and what is not compounding. Review and update SOPs as needed to comply with the revisions.
- Review the immediate-use provisions with those who will be performing this type of compounding.

Section 14 Establishing Beyond-Use Dates

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Learning Objectives

After this lecture, the learner will be able to:

- List the parameters that must be considered when assigning beyond-use dates to CSPs.
- Define the beyond-use dates for Category 1, Category 2, and Category 3 CSPs.

Terms

BUD

- Either the date, or hour and date, after which a CSP must not be used
- The BUD is determined from the date and time that preparation of the CSP is initiated.

Applies to all CSPs

Expiration Date

- The time during which a product can be expected to meet the requirements of the USP–NF monograph, if one exists, or maintain expected quality provided it is kept under the specified storage conditions

Applies to all conventionally manufactured products, APIs, and added substances

Establishing BUDs for CSPs

Should

- be established conservatively to ensure that the drug maintains its required characteristics until its BUD

Must

- consider chemical and physical stability properties of the drug and/or its formulation
- evaluate materials of composition of the container closure system and compatibility of the container closure system with the final preparation

BUDs are based on…

- Environment in which the CSP is prepared
- Aseptic processing and sterilization method
- Starting components
- Whether or not sterility testing is performed
- Storage conditions

Image courtesy of Contec, Inc.

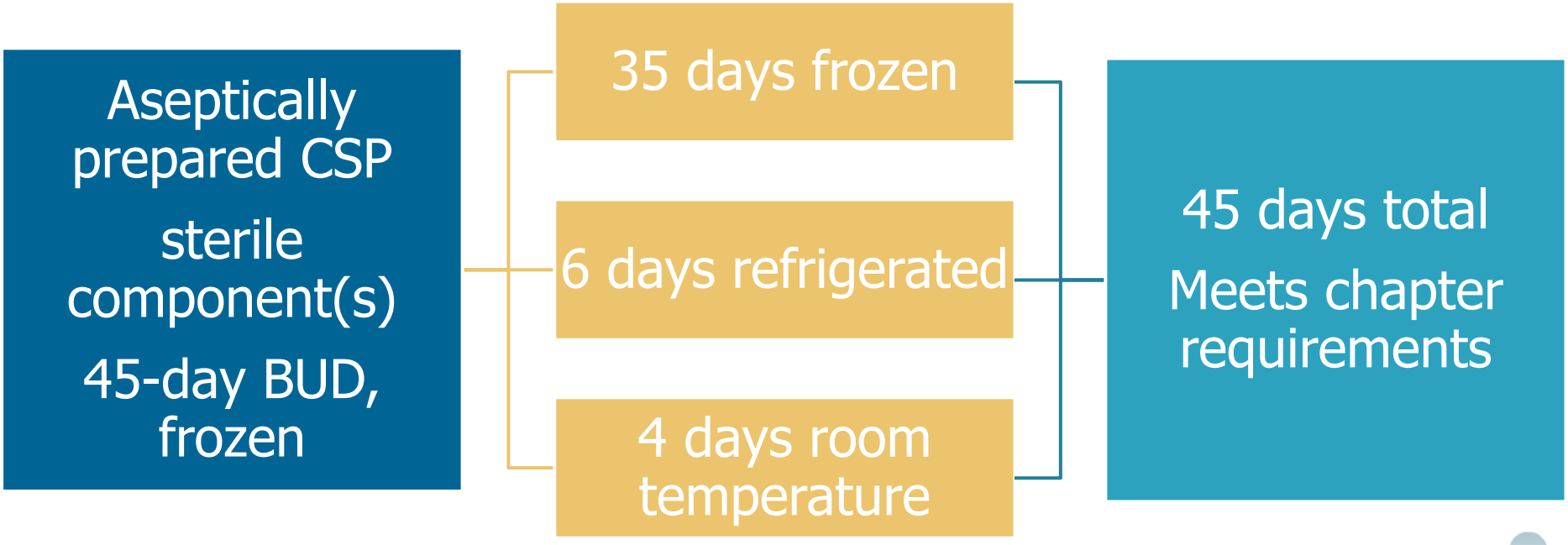
Frozen CSPs

- CCS must be able to withstand the physical stress.
- CSP must be thawed in appropriate conditions to avoid compromising the physical and chemical stability of the preparation and its components.
- Once thawed, CSP must not be refrozen.

Storage Conditions

- A CSP may be stored under different conditions before use.
- Storage time must not exceed the original BUD placed on the CSP for its labeled storage condition.
- BUDs must not be additive.
- Once a CSP has been stored under a condition that would require a shorter BUD it must be used within the time frame for that storage condition.

Acceptable Storage Example



Establishing a BUD

- BUDs for CSPs must be established in accordance with Tables 12, 13, and 14.
- One day is equivalent to 24 h.
- The CSP formulation must remain chemically and physically stable, and its packaging must maintain its integrity for the duration of the BUD.

Establishing a BUD (continued)

- A shorter BUD must be assigned when the stability of the CSP or its components is less than the hours or days stated in the applicable table.
- The BUD must not exceed the shortest remaining expiration date of any of the commercially available starting components.
- For CSPs prepared from one or more compounded components, the BUD **should generally** not exceed the shortest BUD of any of the individual compounded components.

Category 1

PEC Placement	Not in an ISO-classified room
Sterility Testing	None
Endotoxin Testing	None
Storage	Up to 12 hours RT or up to 24 hours refrigerated

Category 1

Preparation		Storage Conditions		
Compounding Method	Sterility Testing?	Controlled Room	Refrigerated	Frozen
Category 1				
Aseptically prepared	No	≤12 hours	≤24 hours	N/A

Category 2

PEC Placement	Must be placed in ISO 7 buffer room served by ISO 7/8 anteroom
Sterility Testing	Based on assigned BUDs
Endotoxin Testing	Required if nonsterile ingredients used and BUD requires sterility; injectables only
Storage	Greater than 12 hours room or 24 hours refrigerated

Category 2

Preparation		Storage Conditions		
Compounding Method	Sterility Testing?	Controlled Room	Refrigerated	Frozen
Category 2				
Aseptically prepared	No	Made from nonsterile components		
		1 day	4 days	45 days
		Made from sterile components		
		4 days	10 days	45 days
	Yes	30 days	45 days	60 days
Terminally sterilized	No	14 days	28 days	45 days
	Yes	45 days	60 days	90 days

Category 3

PEC Placement	Must be placed in ISO 7 buffer room served by ISO 7/8 anteroom
Sterility Testing	Must be done to assign longer BUDs
Endotoxin Testing	Required if nonsterile ingredients used; injectables only
Storage	Greater than 12 hours room or 24 hours refrigerated

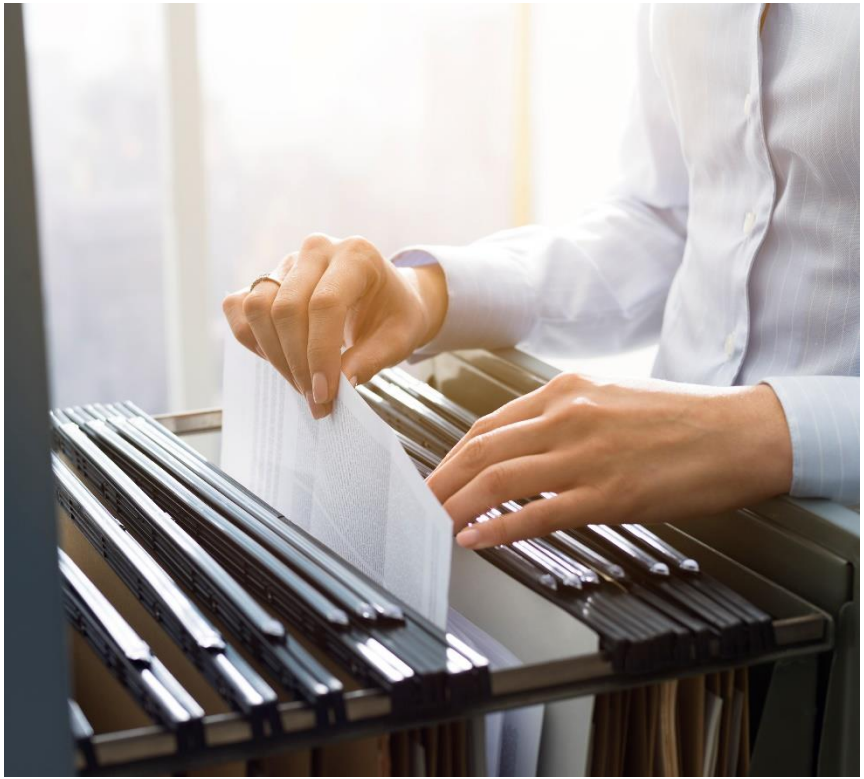
Category 3

Preparation		Storage Conditions		
Compounding Method	Sterility Testing?	Controlled Room	Refrigerated	Frozen
Category 3 – CSPs must pass all category 3 tests				
Aseptically prepared	Yes	60 days	90 days	120 days
Terminally sterilized	Yes	90 days	120 days	180 days

Category 3 Stability Method

- BUD assigned must be supported by stability data obtained using a stability-indicating analytical method.
- Method must
  - distinguish the active ingredient from its degradants and impurities.
  - quantify the amount of the active ingredient.
  - be validated based on characteristics such as those described in ⟨1225⟩.

Stability Study Documentation



"The compounding facility must have documentation of the stability study, including a description of the methodology (e.g., number of samples taken, storage conditions), validation of the method, the stability-indicating analytical method, and all of the results of the study."

Category 3 CSPs must be…

- prepared according to the exact formulation from which the stability data are derived.
- packaged and stored in a container closure of the same materials of composition as that used in the study.

Knowledge Check!

Which passing test result is a requirement to assign a Category 3 BUD?

A. Total Organic Carbon

B. Conductivity

C. Exotoxin

D. Sterility

Wrap-Up

- Labeling is a critical part of the compounding process. Review your labels and labeling for the chapter requirements.
- Remember, the Categories have nothing to do with the starting components. A Category 1 CSP could be prepared from nonsterile components.
- For those compounding multiple-dose CSPs, it is critical to have a relationship with a contract lab.

Section 2
Personnel Training and Evaluation

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Image courtesy of Contec, Inc.

Learning Objectives

After this lecture, the learner will be able to:

- Describe the requirements of the two chapter-defined competencies.
- Recall the steps to perform gloved fingertip and thumb sampling.
- Identify the appropriate corrective actions in the event of a competency test failure.

Designated Person's Role In Training

- Responsible for
  - creating and implementing a training program for personnel
  - ensuring staff are initially trained and qualified in maintaining the quality of the sterile compounding environment before being allowed to perform their job functions independently
    - compounders
    - personnel who have direct oversight of compounders
    - personnel who perform restocking
    - personnel who perform cleaning and disinfection

Trainers

"Training and observation may be performed by the designated person(s) or an assigned trainer."

Training Documentation

- Must develop a written training program that describes the
  - required training
  - frequency of training
  - process for evaluating performance
- Program must
  - equip personnel with the knowledge needed
  - train staff in the skills necessary to perform their assigned tasks
- SOPs should specify the training required for such tasks
- Training and evaluation must be documented

Compounders and Those Who Oversee Compounding Training and Competency Frequency			
	Initial	Ongoing	
	Both	Compounder	Oversee
Maintaining the Quality of the Sterile Compounding Environment	Yes	Not required	Not required
Sterile Compounding Principles and Practices	Yes	At least every 12 months	At least every 12 months
Garbing Competency (Including GFT)	Yes	Category 1 and Category 2 at least every 6 months Category 3 at least every 3 months	At least every 12 months
Media Fill with Post-GFT and Surface Sampling	Yes	Category 1 and Category 2 at least every 6 months Category 3 at least every 3 months	At least every 12 months

Chapter-Defined Competencies

Defined in the Text

- Garbing and Hand Hygiene
  - visual observation
  - gloved fingertip and thumb testing (GFT)
- Aseptic Manipulation (AM)
  - visual observation
  - media-fill testing
  - GFT
  - surface sampling of the DCA

Listed in Tables 2 & 3

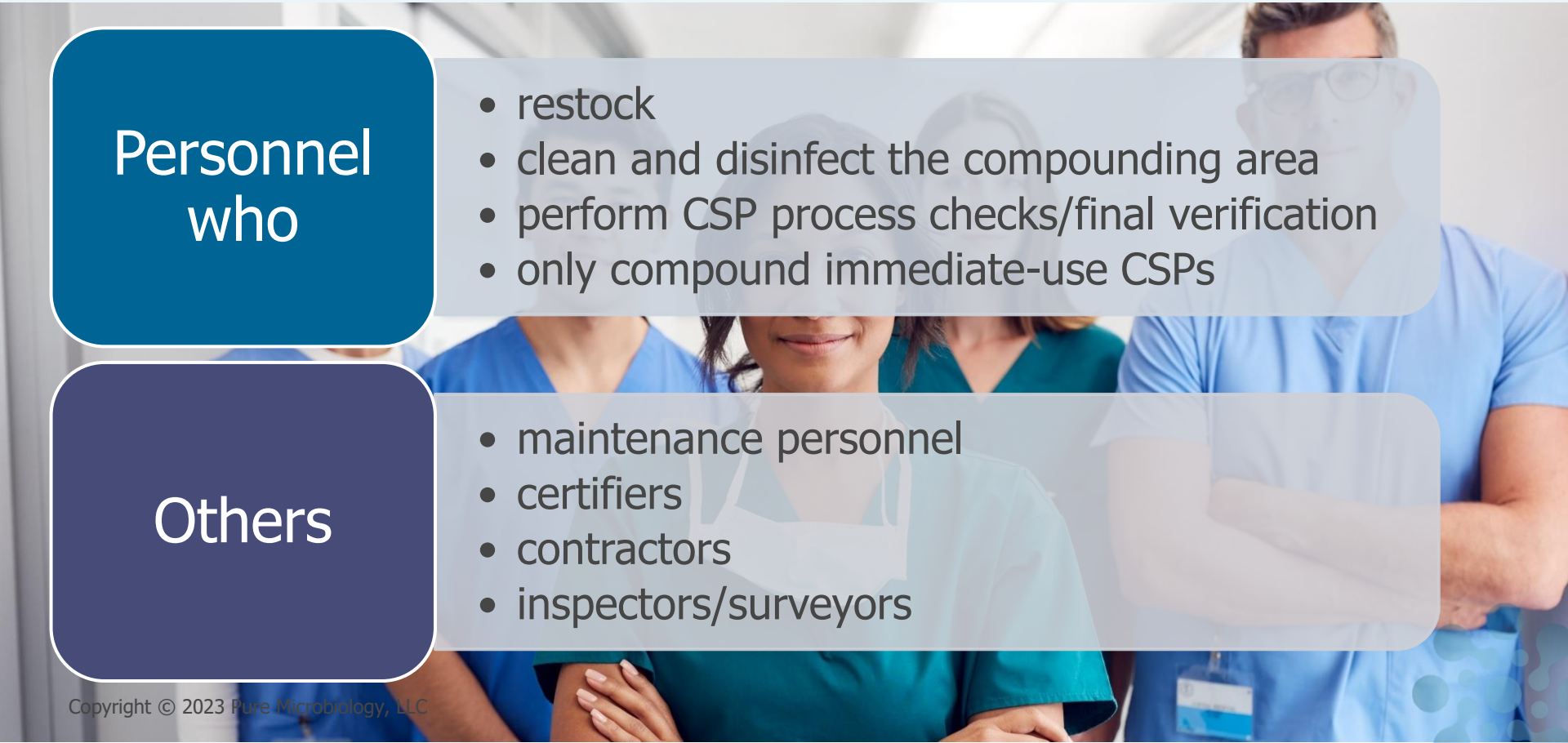
- Maintaining the Quality of the Sterile Compounding Environment
  - Table 2 only
- Sterile Compounding Principles and Practices
  - Tables 2 & 3

Chapter-Defined Competency Frequencies

Categories 1 and 2 compounders	Category 3 compounders	Those who oversee compounding
Initially and at least every 6 months	Initially and at least every 3 months	Initially and at least annually

- Evaluation should correspond to activities they oversee but does not require the same quantities.
- If they oversee compounding and compound, they must complete competency based on the CSPs prepared.

Training for Everyone Else



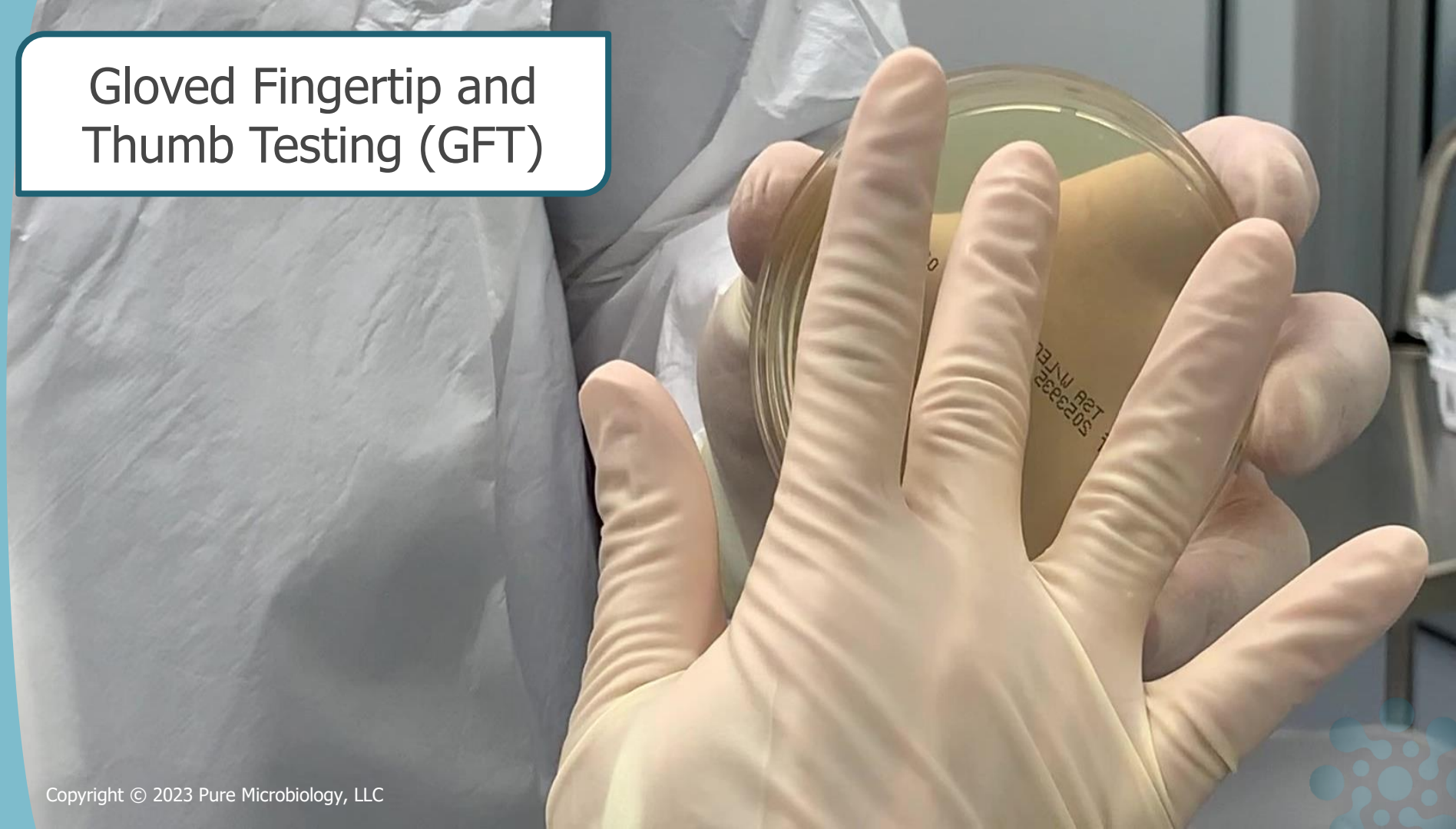
Personnel who

- restock
- clean and disinfect the compounding area
- perform CSP process checks/final verification
- only compound immediate-use CSPs

Others

- maintenance personnel
- certifiers
- contractors
- inspectors/surveyors

Gloved Fingertip and Thumb Testing (GFT)



GFT after garbing verifies that new staff can don sterile gloves without contaminating them.

Images courtesy of Contec, Inc.

GFT Media

- Devices containing general microbial growth media supplemented with neutralizing additives
  - contact plates
  - settle plates
  - contact slides
  - paddles
- TSA with lecithin and polysorbate 80

GFT After Garbing Frequency

Initially

- 3 occurrences in association with the hand hygiene and garbing competency
- Must pass consecutively

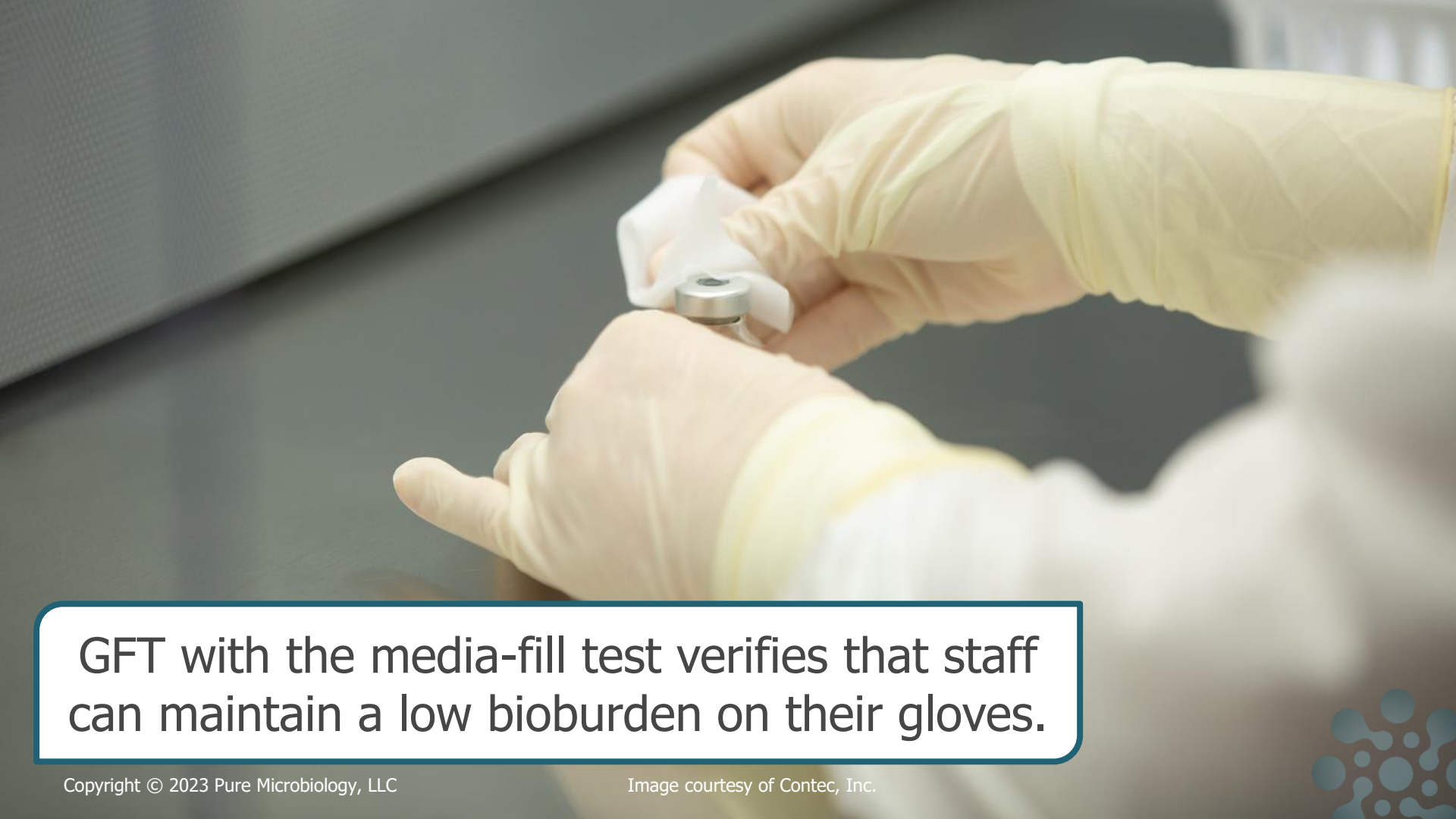
Ongoing

- 1 occurrence every 3 or 6 months depending on category compounded

Image courtesy of Contec, Inc.

GFT After Garbing Summary

Purpose	Verify staff can don sterile gloves without contaminating them
Who	All staff
When	With hand hygiene and garbing competency. Initially, 3 times. Ongoing, 1 time.
Where	Location where gloves are donned
Action Level	>0 CFU per both hands and must pass consecutively



GFT with the media-fill test verifies that staff can maintain a low bioburden on their gloves.

Image courtesy of Contec, Inc.

GFT with Media-Fill Testing

- Samples collected in the PEC
- Initially before allowed to compound independently
- Category 1 and Category 2
  - at least every 6 months
- Category 3
  - at least every 3 months

Image courtesy of Contec, Inc.

Action level is >3 CFU per both hands.

Image courtesy of Contec, Inc.

GFT after Media-Fill Testing Summary

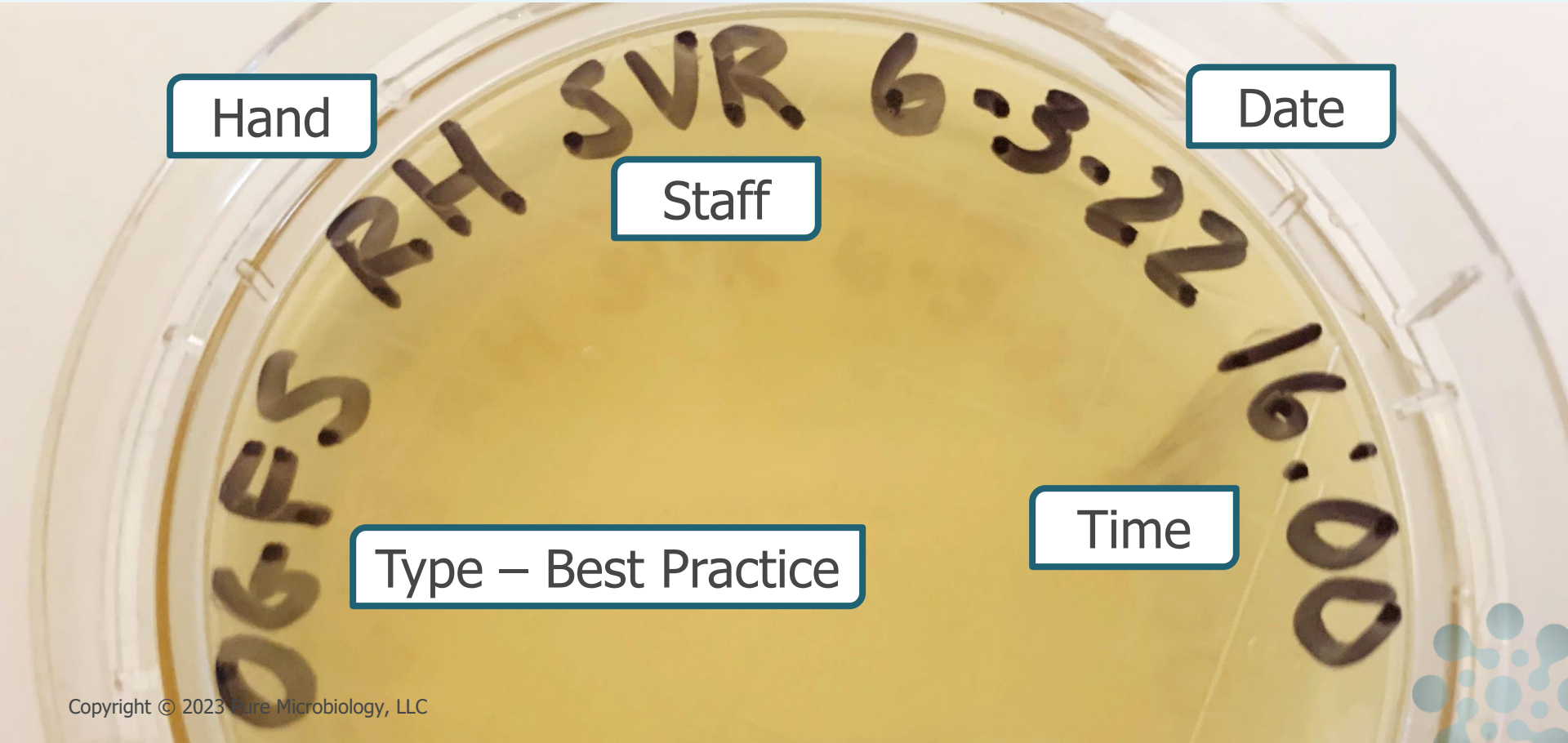
Purpose	Verify staff can keep the microbial bioburden on their gloves low
Who	New and tenured staff
When	Categories 1 and 2: at least every 6 months Category 3: at least every 3 months
Where	In the PEC
Action Level	>3 CFU per both hands

Sample Collection

No spraying gloves with IPA before sample collection!

- One plate per hand
- Rolling motion over the surface
- Sample the pad of the finger
- Adequate pressure

Labeling the Sample



Gloved Fingertip & Thumb Test Incubation

1. Inverted at 30 to 35 °C for at least 48 hours
2. Inverted at 20 to 25 °C for at least 5 days
3. Count and record number of CFU per both hands

Image courtesy of Contec, Inc.

Media-Fill Testing

Image courtesy of Contec, Inc.

Test Media

- Replace all components with tryptic soy broth (TSB), aka soybean-casein digest medium (SCDM)
- Sterile-to-sterile use sterile broth
- Nonsterile-to-sterile use nonsterile powder and sterile water
- Must have certificate of analysis (COA)
- Must do growth promotion if preparing own sterile media

Image courtesy of Contec, Inc.

Test Design

- Must closely simulate frequently used, complex manipulations
- Must capture elements that could potentially affect the sterility of the CSP, including but not limited to:
  - factors associated with the length of the process that can pose contamination risk (e.g., fatigue, quality of equipment)
  - number of aseptic additions or transfers
  - number, type, and complexity of manipulations
  - number of personnel in the buffer room or SCA

Who is tested?

- New and tenured staff who compound CSPs
- Anyone who oversees compounding must be tested, even if they don’t regularly compound!

Image courtesy of Contec, Inc.

Media-Fill Testing Frequency and Location

- Initially
- Category 1 and Category 2 at least every 6 months
- Category 3 at least every 3 months
- Testing occurs in the PEC

Image courtesy of Contec, Inc.

Media-Fill Testing Summary

Purpose	To evaluate aseptic technique
Who	New and tenured staff
When	Once initially Categories 1 and 2: at least every 6 months Category 3: at least every 3 months
Where	In the PEC
Action Level	Any visual manifestations of growth

Media-Fill Test Incubation

Incubation must be in an incubator!

Option 1

- Stage 1: 20 to 25 °C for at least 7 days
- Read at end of 1st incubation
- Stage 2: 30 to 35 °C for at least 7 days
- Read at end of 2nd incubation

Option 2

- Stage 1: 30 to 35 °C for at least 7 days
- Read at end of 1st incubation
- Stage 2: 20 to 25 °C for at least 7 days
- Read at end of 2nd incubation

Image courtesy of Contec, Inc.

Media-Fill Test Analysis

- Look for “turbidity or other visual manifestations of growth”
- Growth on or before 14 days is a failure

GFT and Media-Fill Testing Documentation

- ✓ Name of the person evaluated
- ✓ Evaluation date/time
- ✓ Media/Components used (manufacturer)
- ✓ Expiration date and lot number
- ✓ Starting temperature for each incubation
- ✓ Dates of incubation
- ✓ Results
- ✓ Name of the observer and who reads/documents the results

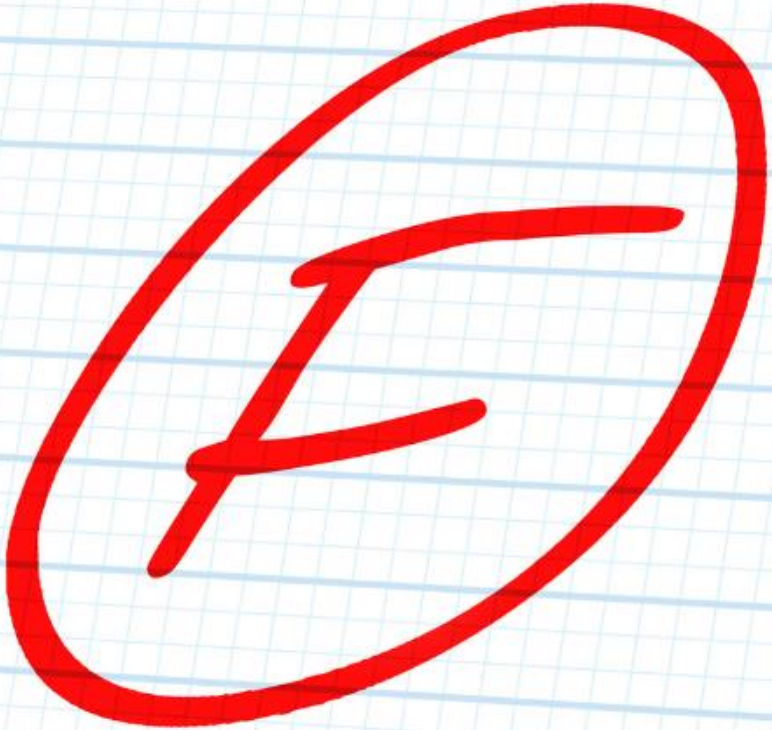
Aseptic Manipulation Failure

Media-fill test	• Visible turbidity of other visual manifestation of growth in one of more of the units during the incubation period • Identification not required
GFT	• >3 CFU per both hands • Identification not required
Surface sample	• >3 CFU per sample • Identification required

A failure in the

- media fill,
- GFT, or
- surface sample

constitutes an overall failure.



Knowledge Check!

According to USP <797>, by whom may training be performed?

A. Assigned trainer or designated person

B. Assigned trainer or consultant

C. Designated person or Pharmacist In Charge

D. Designated person or consultant

Wrap-Up

- The chapter clearly defines two competencies but requires additional competency testing that must be developed and defined by the facility.
- Media-fill tests must be designed to reflect the most challenging compounding conditions. More than one media-fill test procedure will be needed.
- Be sure anyone reading GFT or media-fill tests is trained.

Section 3

Personal Hygiene and Garbing

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Image courtesy of Contec, Inc.

Learning Objectives

After this lecture, the learner will be able to:

- List the conditions that prevent an individual from compounding.
- Describe the requirements for personnel preparation and hand hygiene.
- Explain the garbing requirements for Category 1, Category 2, and Category 3 compounding.

Personal Hygiene

- 2008 version does not mention personal hygiene, but the 2022 version does.
- "Individuals entering a compounding area must be properly garbed and must maintain proper personal hygiene to minimize the risk of contamination to the environment and/or CSPs."

"Individuals who may have a higher risk of contaminating the CSP and the environment must report these conditions to the designated person(s)."

Have an SOP that addresses:

- an evaluation of the individual by the designated person
- alternate work options
- documentation of the condition and how work was managed

Image courtesy of Contec, Inc.

Garbing Noes

- Items that are not easily cleanable
- Items that are not necessary for compounding
- Personal outer garments
- Cosmetics
- Hand, wrist, and other exposed jewelry
- Earbuds or headphones
- Electronic devices that are not necessary for compounding or other required tasks
- Nail products

Garbing Accommodations

"The designated person(s) may permit accommodations as long as the quality of the CSP and environment will not be affected. Accommodations must be documented."

"Cover any jewelry that cannot be removed."

Image courtesy of Contec, Inc.

Garbing Order

- Up to the facility to decide based on the sink location
- Order must be documented in the facility's SOPs
- Glasses must be wiped, if worn

Hand Hygiene Dos and Don’ts

Do	Don’t
• Use a disposable nail cleaner under warm running water • Wash hands and forearms with soap and water for at least 30 seconds • Dry hands and forearms completely with low-lint disposable towels or wipers.	• Use brushes • Use hand dryers • Refill or top off soap containers

Hand Sanitizing and Donning Gloves Musts

- Sanitize hands with alcohol-based hand rub before donning sterile gloves
  - requirement for persistent activity removed
- Don sterile gloves in a classified room or SCA
- Use alcohol-based handrub prior to donning garb if hand hygiene is completed outside the classified area

Hand Sanitizing Steps

Apply an alcohol-based hand rub to dry skin.

Rub hands together covering all surfaces of hands and fingers until hands are dry.

Allow hands to dry thoroughly before donning sterile gloves.

Images courtesy of Contec, Inc.

Glove Musts

- Sterile
- Powder free
- Inspected for holes, punctures, or tears
- Replaced immediately if defects are detected

"Application of sterile 70% IPA to gloves must occur immediately before compounding and regularly throughout the compounding process."

RABS and Isolator Considerations

"…sleeves and gloves should be changed per the manufacturer's recommendations and as defined in the facility's SOPs."

Garbing Musts

- Any person entering a compounding area where Category 1, Category 2, or Category 3 CSPs are prepared must be properly garbed.
- This mean full garb in the SCA!
- The required garb, manner of storage, and order of garbing must be determined by the facility and documented in the facility's SOPs.

Garbing Musts

- Garb must be donned and doffed in an order that reduces the risk of contamination.
- Skin must not be exposed inside the ISO Class 5 PEC.

Image courtesy of Contec, Inc.

Garbing Shoulds

- Donning and doffing garb should not occur in the same area at the same time.
- When preparing Category 2 or Category 3 CSPs, all garb should be donned in a classified area before entering the buffer room.

Image courtesy of Contec, Inc.

Minimum Category 1 and 2 Requirements

Low lint

- Garment with sleeves that are snug around the wrists and closed at the neck
- Covers for shoes
- Head cover that covers hair and ear, and, if needed, cover for facial hair
- Face mask

- Sterile powder-free gloves

Minimum Category 1 and 2 Requirements

- RABS
  - Disposable gloves SHOULD be worn inside the gloves attached to the RABS sleeves
  - Sterile gloves must be worn over the gloves attached to the RABS sleeves

This means the compounder would be wearing 3 pairs of gloves!

Garb Integrity and Storage

- Garb must be replaced immediately if it becomes visibly soiled or if its integrity is compromised.
- Gowns and other garb must be stored in a manner that minimizes contamination.

Image courtesy of Contec, Inc.

Garb Reuse

- If compounding Category 1 and Category 2 CSPs, gowns may be reused within the same shift by the same person if the gown is maintained in a classified area or adjacent to, or within, the SCA in a manner that prevents contamination.
- When personnel exit the compounding area, garb, except for gowns, cannot be reused and must be discarded or laundered before reuse.
- The facility's SOPs must describe disinfection procedures for reusing goggles, respirators, and other reusable equipment.

Category 3 Garbing

"...additional garbing requirements must be continuously met in the **buffer room** in which Category 3 CSPs are prepared regardless of whether Category 3 CSPs are compounded on a given day..."

The Additional Category 3 Requirements

1. No exposed skin in the buffer room.
2. All low-lint outer garb must be sterile, including the use of sterile sleeves over gauntlet sleeves when a RABS is used.
3. Disposable garbing items must not be reused.
4. Laundered garb must not be reused without being laundered and resterilized with a validated cycle.
5. SOPs must describe disinfection procedures for reusing goggles, respirators, and other reusable equipment.

Image courtesy of Contec, Inc.

Knowledge Check!

A facility has their sink on the clean side of the line of demarcation. Which garbing sequence is correct?

A. Don gown, don shoe covers, perform hand hygiene

B. Don shoe covers, wipe glasses, perform hand hygiene

C. Wipe glasses, don head and face covers, don shoe covers

D. Perform hand hygiene, don head and face covers, don gown

Wrap-Up

- USP <797> provides requirements for hand hygiene and garbing, but it is silent on a number of common garbing challenges.
- It is the responsibility of the sterile compounding organization to clearly define garbing expectations.
- Be careful with accommodations. One can lead to many. You must be able to defend the rationale for allowing the accommodation to inspectors and surveyors.

Sections 4 and 5

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Image courtesy of Contec, Inc.

Learning Objectives

After this lecture, the learner will be able to:

- Describe the facility design requirements for a cleanroom suite and segregated compounding area.
- Differentiate between the primary engineering controls used in sterile compounding.
- List the certification requirements for primary and secondary engineering controls.

Section 4 Facilities and Engineering Controls

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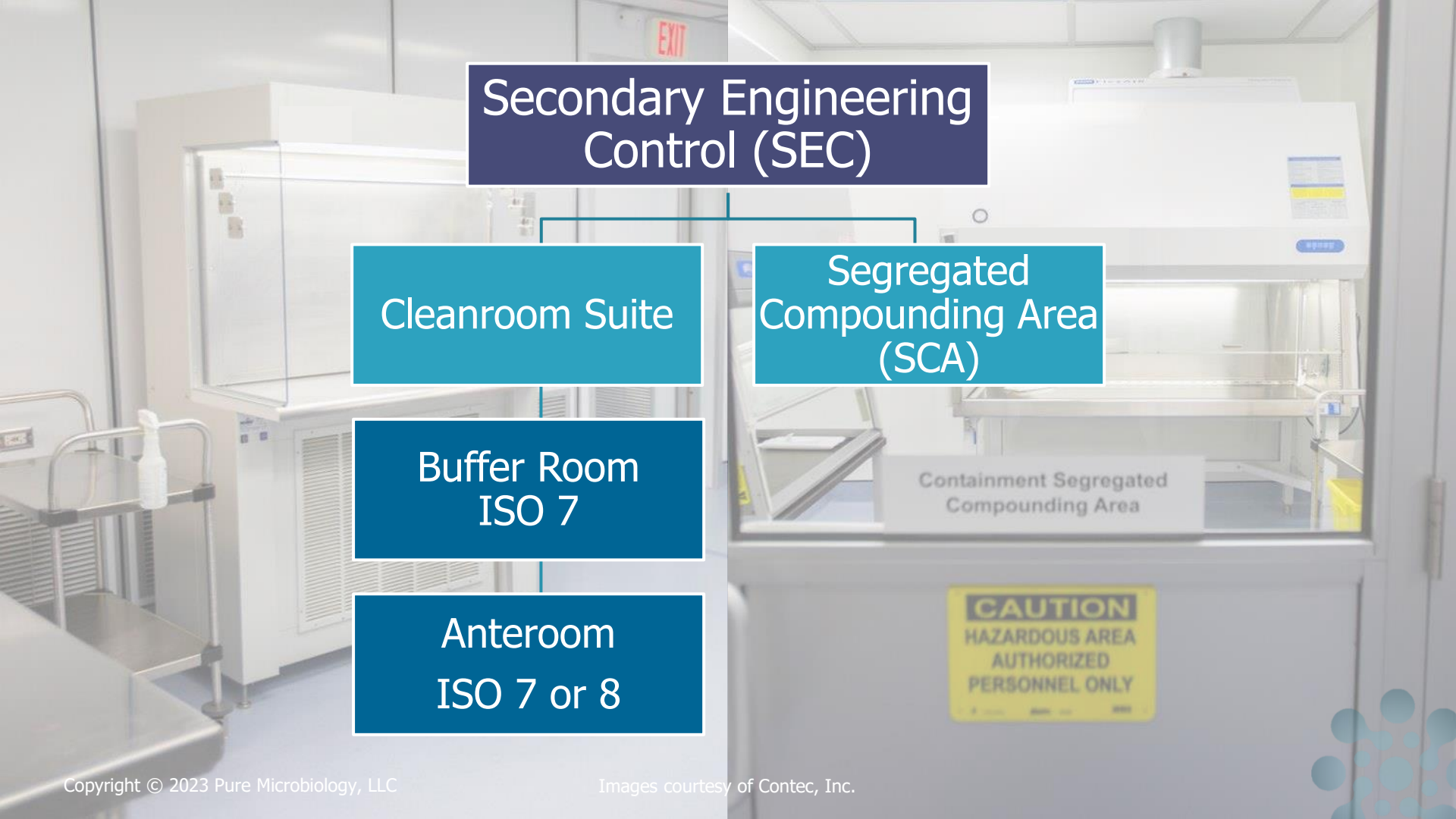
Image courtesy of Contec, Inc.

Secondary Engineering Control (SEC)

- Cleanroom Suite
  - Buffer Room ISO 7
    - Anteroom ISO 7 or 8
- Segregated Compounding Area (SCA)



Images courtesy of Contec, Inc.

Designated Person must ensure…

- each area related to CSP preparation meets the classified air quality standard appropriate for the activities conducted in that area.
- the ISO Class 5 areas are:

located	operated	maintained	monitored	certified

to have appropriate air quality.

General Considerations

- Air quality must be achieved and maintained through PECs and SECs.
- Anteroom, buffer room, and SCA must be separated from areas not directly related to compounding.
- Anteroom and buffer room must be appropriately controlled to achieve and maintain the required air quality classifications.

Facility design should consider the…

- number of personnel and their movements.
- placement of equipment, supplies, and components.
- number of operations being performed.
- type of equipment.
- complexity of the compounding procedures.

The facility “must be designed and controlled to provide a well-lighted and comfortable working environment.”

Image courtesy of Contec, Inc.

ISO Air Cleanliness Classifications

ISO Class	Particle Count Per m^3	Engineering Control
5	3520	PEC
7	352,000	Buffer room or anteroom
8	3,520,000	Anteroom

- Count particles 0.5 µm and larger
- Reported per cubic meter (current ISO 14644-1)
- Minimum 1 min. sample time
- Minimum 2 liters of air volume

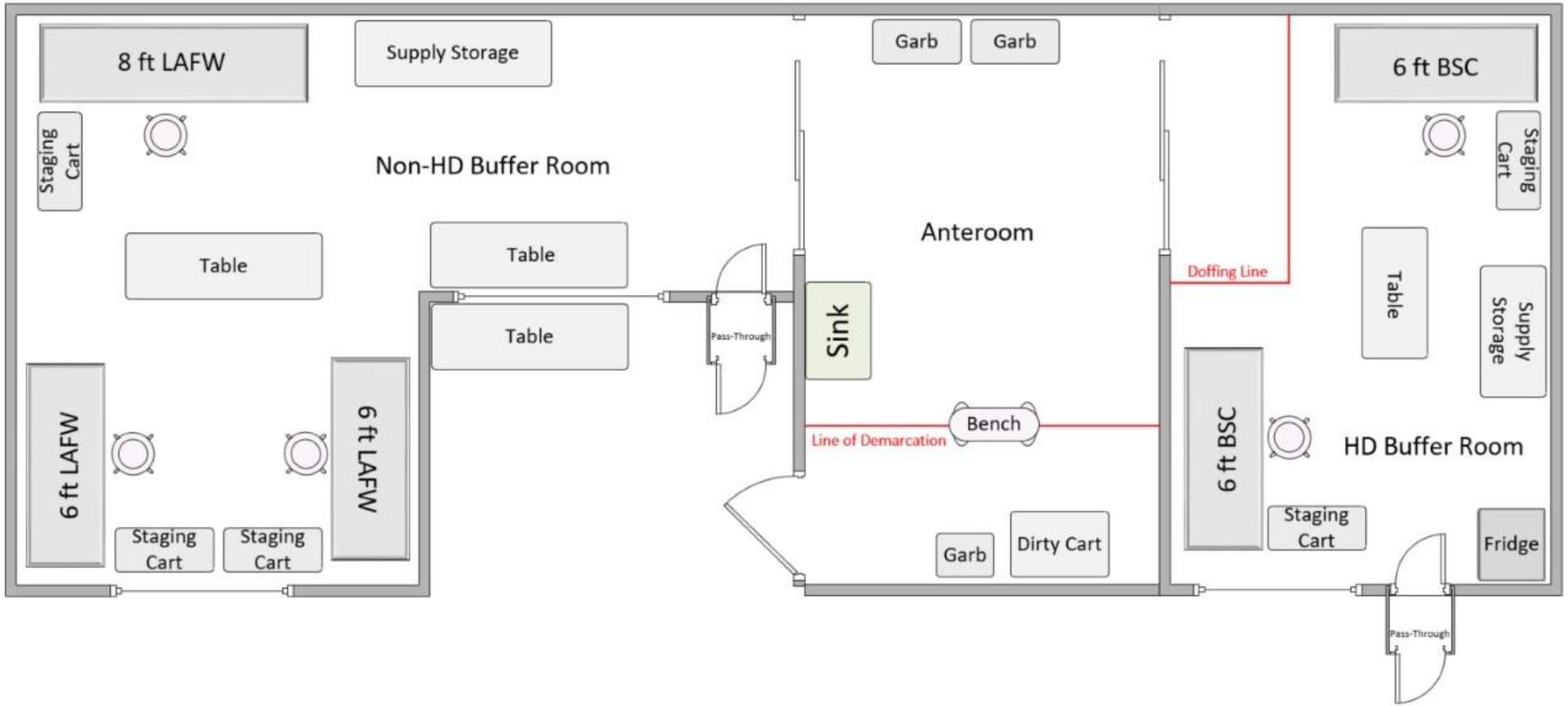
PECs must be…

- certified to meet ISO Class 5 or better conditions during dynamic operating conditions.
- designed to minimize the risk of contamination during compounding of CSPs.
- able to maintain unidirectional airflow HEPA-filtered air.
- able to supply a velocity sufficient to sweep particles away from critical sites and maintain unidirectional airflow during operations.

PEC	Airflow	Type of CSP	Location
Laminar Airflow System (LAFS)			
Laminar Airflow Workbench (LAFW)	Horizontal or vertical	Nonhazardous	ISO 7 buffer room or SCA
Biological Safety Cabinet (BSC)	Vertical	Nonhazardous and hazardous	ISO 7 buffer room or SCA
Integrated Vertical Laminar Flow Zone (IVLFZ)	Vertical	Nonhazardous	ISO 7 buffer room
Restricted Access Barrier System (RABS)			
Compounding Aseptic Isolator (CAI)	Vertical	Nonhazardous	ISO 7 buffer room or SCA
Compounding Aseptic Containment Isolator (CACI)	Vertical	Hazardous	ISO 7 buffer room or SCA
Pharmaceutical-Grade Isolator			
Isolator	Vertical	Nonhazardous	ISO 8 buffer room or SCA

The Cleanroom Suite

Image courtesy of Contec, Inc.



Temperature and Humidity

- Cleanroom suite SHOULD be maintained at 20 °C or cooler and a relative humidity of 60% or below.
- Must be controlled through a heating, ventilation, and air conditioning (HVAC) system.
- Freestanding air conditioners, humidifiers, and dehumidifiers must not be used within the classified area (or the SCA).

Temperature and Humidity Monitoring

- Monitoring devices must be verified for accuracy at least every 12 months or as required by the manufacturer.
- Must monitor in each room of the cleanroom suite each day that compounding is performed, either manually or by a continuous recording device.
- Results must be documented at least once daily or stored in the continuous recording device and must be retrievable.
- Readings must be reviewed as described in the facility's SOPs.

Airflow musts

1. Supplied through HEPAs in the ceiling
2. Low wall returns unless a visual smoke study is performed

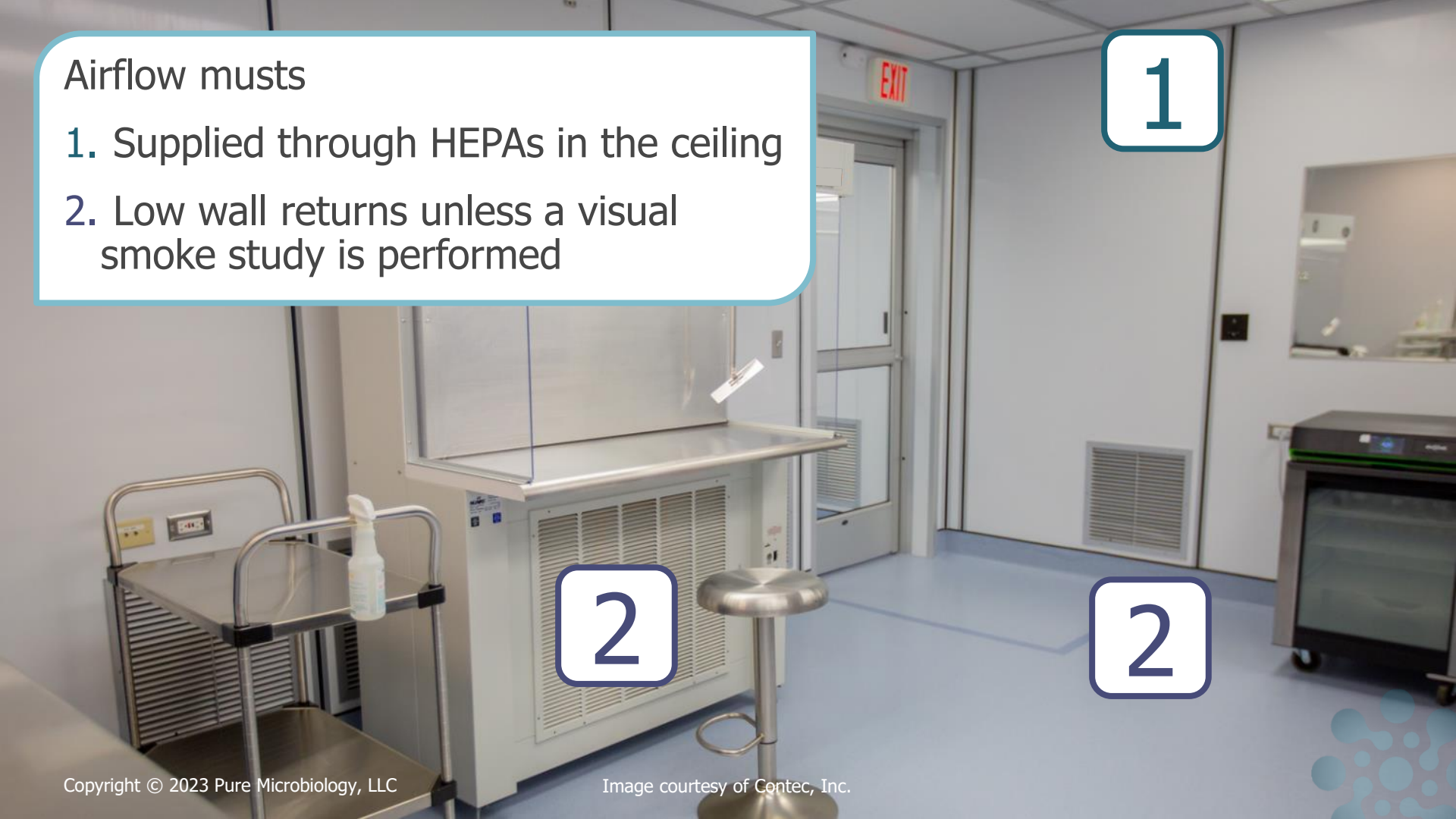


Image courtesy of Contec, Inc.

Visual Smoke Study

"A test, used in ISO Class 7 and ISO Class 8 rooms that do not have unidirectional airflow, in which a visible source of smoke, which is neutrally buoyant, is used to verify an absence of stagnant airflow."

- Sterile compounders don't have unidirectional airflow cleanrooms!
- Study needs to be done if returns are not low on the wall.
- Study and environmental monitoring must be repeated whenever a change is made to the placement of equipment within the room or any other alteration that affects the quality of the air.

Factors in Determining ACPH Needed

- May need to be higher than chapter minimums to maintain the required ISO classification and microbial state of control
- Consider
  - Number of personnel permitted to work in the area
  - Number of particles that may be generated from activities
  - Processes in the area
  - Equipment located in the room
  - Room pressure

Minimum Cleanroom ACPH

ISO Class 7 Room	ISO Class 8 Room
Minimum of 30 HEPA-filtered ACPH	Minimum of 20 HEPA-filtered ACPH
At least 15 ACPH must come from the HVAC through HEPA filters located in the ceiling	
Remaining HEPA-filtered ACPH can come from a PEC, which must not be turned off	

Pressure Musts

- Classified rooms must be equipped with a pressure differential monitoring system.
- Continuous differential positive pressure at a minimum of 0.020-inch water column is required between adjacent ISO-classified areas and between an ISO-classified area and the unclassified space.
- A monitoring device must be used to continuously monitor.
- Quantitative results must be reviewed and documented at least daily on the days when compounding is occurring.

Surfaces of

ceilings

walls

floors

doors

door frames

fixtures

shelving

work surfaces

counters

cabinets

Must be

smooth

impervious

free from cracks

free from crevices

non-shedding

Should be

resistant to damage from cleaning agents and tools

Image courtesy of Contec, Inc.

Pass-throughs

"If a pass-through chamber is used, both doors must never be opened at the same time, and doors should be interlocking."

Image courtesy of Contec, Inc.

Sinks

- Sinks SHOULD enable hands-free use.
- Sink must be cleaned and disinfected each day of use, and a sporicidal disinfectant applied monthly.
- The sink used for hand hygiene may be placed
  - on the clean side of the line of demarcation.
  - on the dirty side of the line of demarcation.
  - outside of the anteroom.

Must be in a clean space

Image courtesy of Contec, Inc.

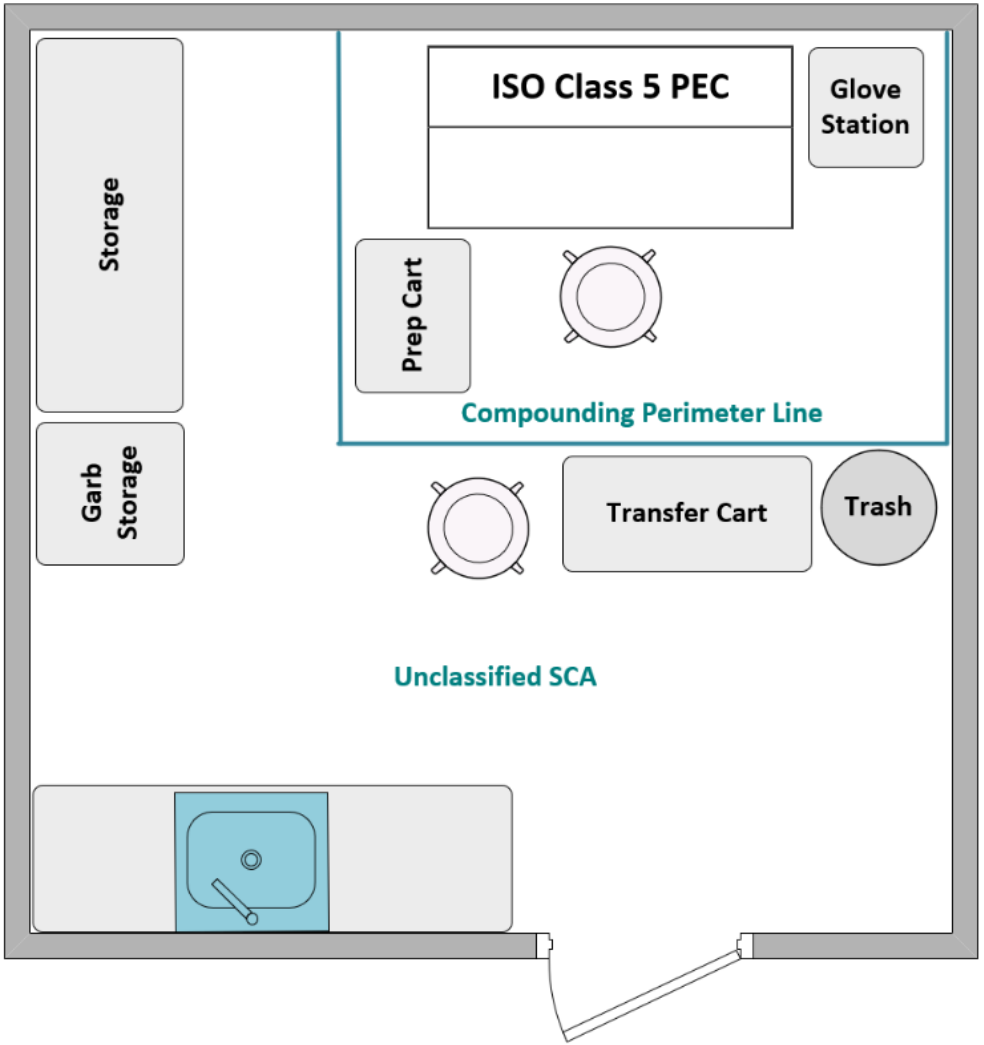
Other Water Sources

- The buffer room must not contain plumbed water sources.
  - sink
  - eyewash
  - shower
  - floor drain
- The anteroom must not contain floor drain(s).
- If installed, sprinkler systems SHOULD be recessed and covered, and the covers should be easily cleanable.

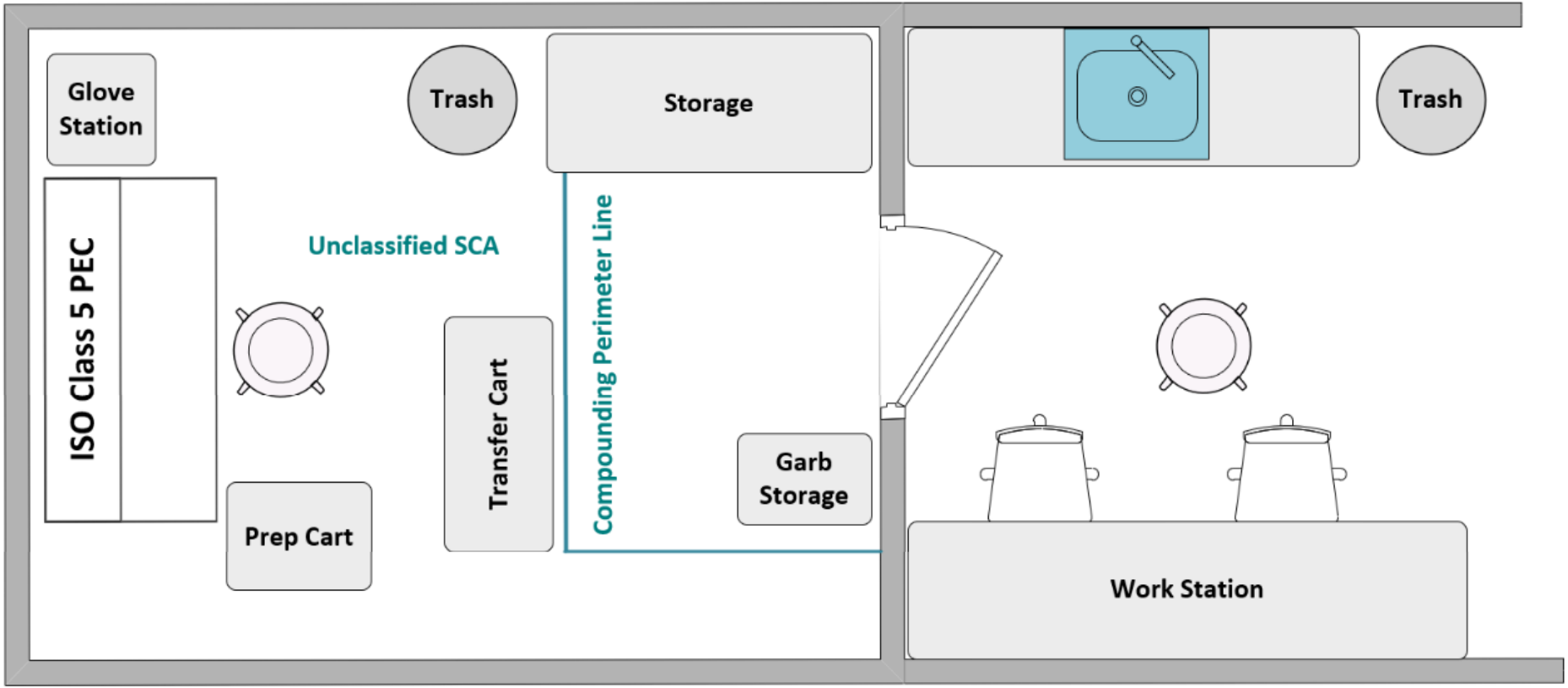
The Segregated Compounding Area

Image courtesy of Contec, Inc.

Sink inside the SCA



Sink outside the SCA



SCA

- A PEC within an unclassified area used to compound Category 1 CSPs
  - no HEPA filtration, pressure differentials, or required ACPH
- Located away from

unsealed windows	doors that connect to the outdoors	traffic flow
restrooms	food preparation areas	warehouses

SCA Use

- Area within 1 m of the PEC SHOULD be dedicated only for sterile compounding and not used for:
  - storage
  - hand hygiene
  - donning and doffing garb
  - patient care
  - other highly particle-generating activities

Surfaces must be

clean

uncluttered

dedicated to compounding

Minimize dust-collecting overhangs and ledges. If present, they must be easily cleanable.

Surfaces should be

smooth

impervious

free from cracks

free from crevices

non-shedding

resistant to damage from cleaning agents and tools

Image courtesy of Contec, Inc.

SCA Water Sources

The sink must be placed not closer than 1 m to the PEC and may be either inside the SCA or in close proximity to the SCA.

Knowledge Check!

The use of which item ensures a state of control can be achieved in a sterile compounding facility?

A. Sterile garb

B. Engineering controls

C. Portable HEPA filter units

D. Sporicidal disinfectant cleaners

Section 5
Certification and Recertification

pure microbiology

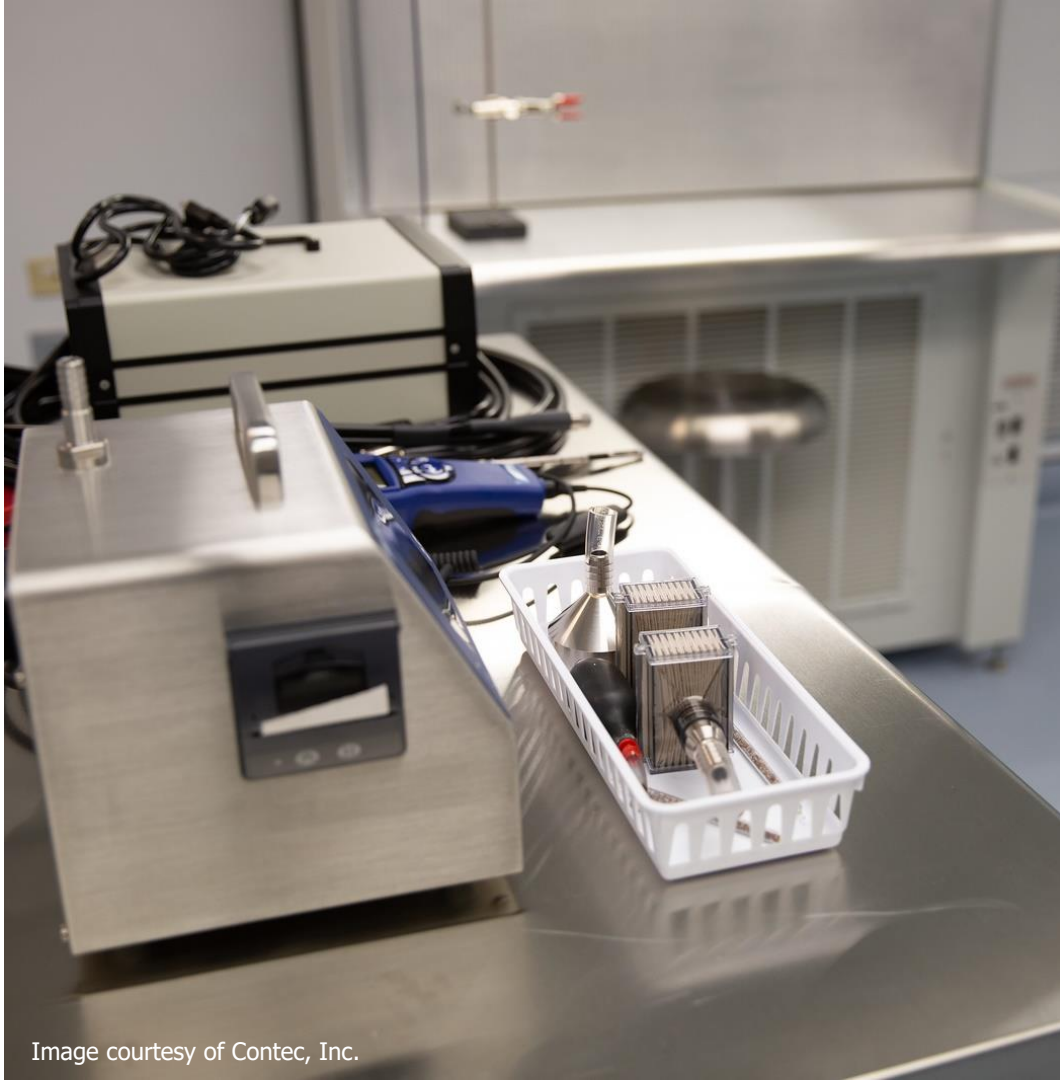


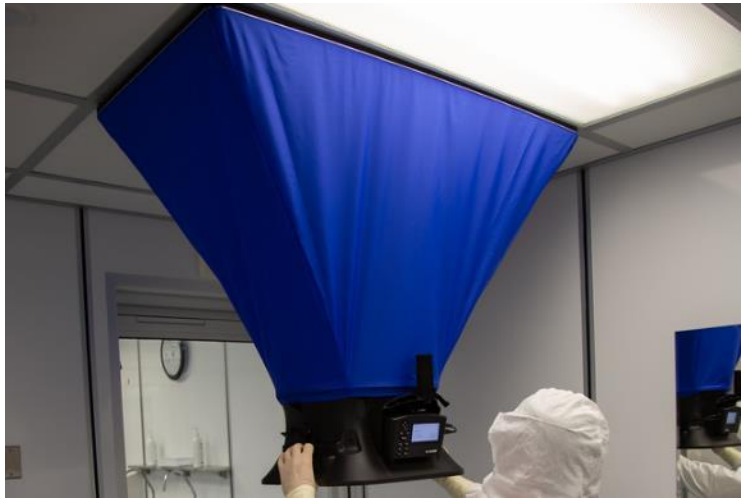
Image courtesy of Contec, Inc.

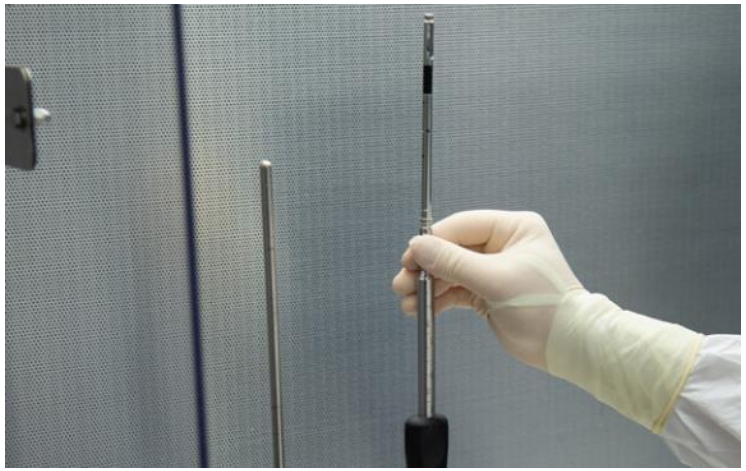
Certification

Why	To show the compounding area is meeting its design and air quality specs
Who	Independent body
When	Initially before compounding CSPs and at least every 6 months
What	Per the chapter requirements and when applicable, manufacturer specifications

Chapter Required Certification Tests

- Airflow Testing
- HEPA Filter Integrity Testing
- Total Particle Count Testing
- Dynamic Airflow Smoke Pattern Testing





Airflow Testing

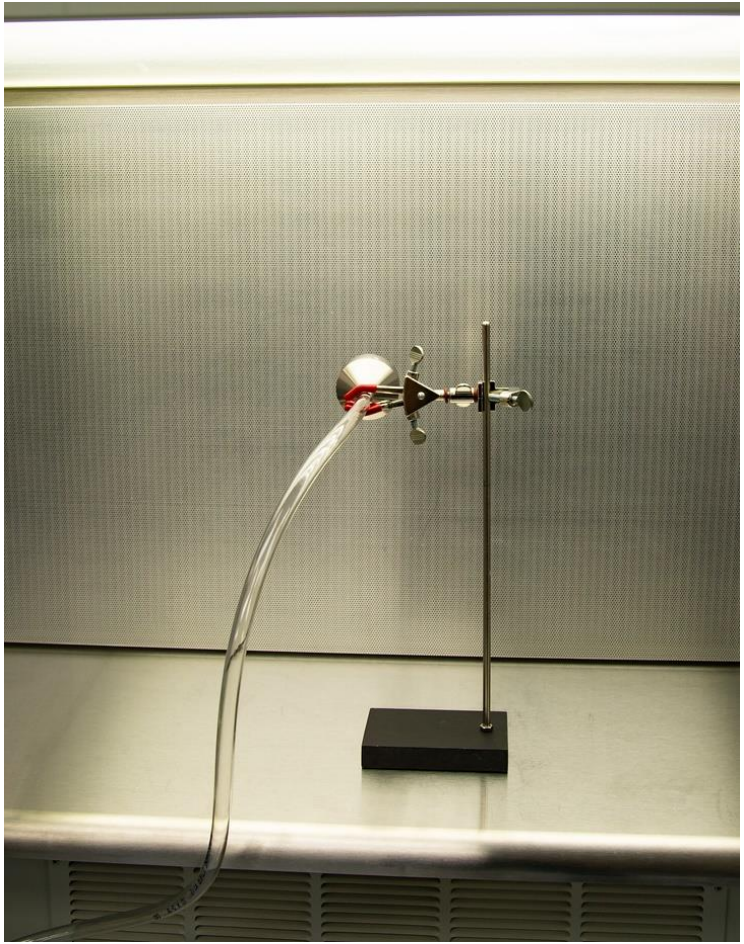
- Performed to determine acceptability of the
  - air velocity
  - room air exchange rate
  - room pressure differential
- Different testing for PECs and cleanroom

Images courtesy of Contec, Inc.

HEPA Filter Integrity Testing

- HEPA filters must be leak tested
  - at the factory
  - after installation
  - as part of recertification
- PEC and cleanroom filters must be tested

Images courtesy of Contec, Inc.



Total Particle Count Testing

- Determines ISO classification
- Must be performed under dynamic operating conditions
- Must use calibrated electronic equipment
- PECs and cleanroom tested

Image courtesy of Contec, Inc.

Dynamic Airflow Smoke Pattern Test

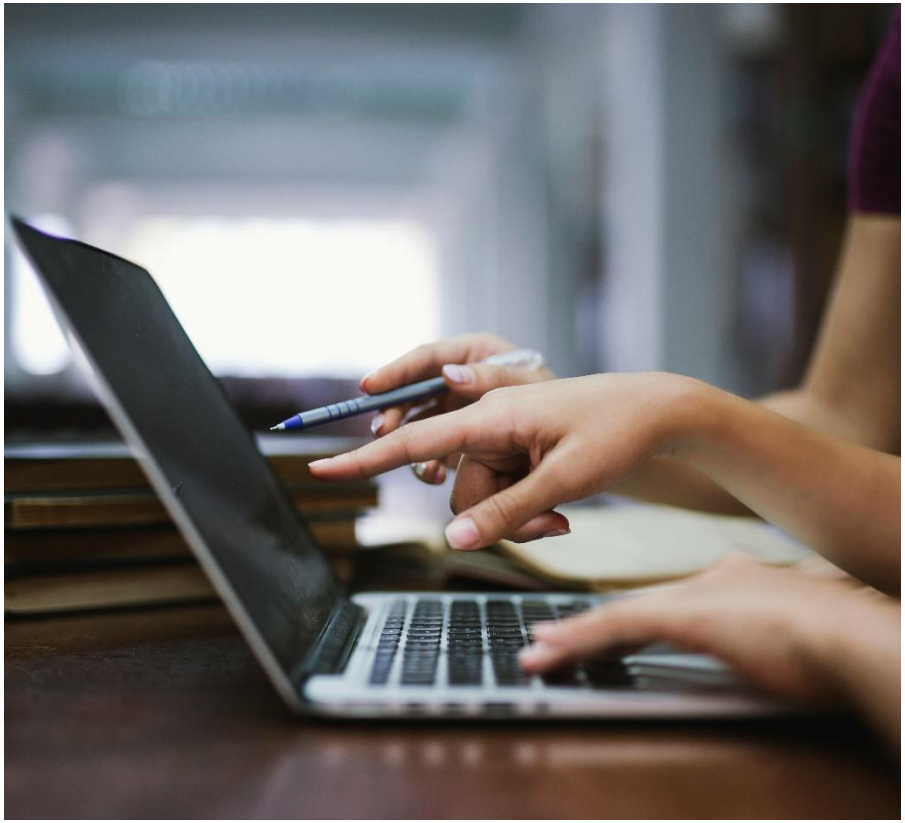
- Performed for each PEC to demonstrate
  - unidirectional airflow
  - sweeping action over and away from the preparation(s)
- Must be under dynamic operating conditions

Image courtesy of Contec, Inc.

Recertification

- Classified areas must be recertified if there are changes to the area such as:
  - redesign
  - construction
  - replacement or relocation of any PEC
  - alteration in the configuration of the room that could affect airflow or air quality

Designated Person Responsibilities



"All certification records must be reviewed by the designated person(s) to ensure that the classified environments meet the minimum requirements in this chapter."

Certification Documentation

- Records must be maintained according to Section 20
- Certification report must include
  - number of personnel present in each PEC and SEC during total particle count tests and dynamic airflow smoke pattern tests
  - the air changes per hour (ACPH) from HVAC, ACPH contributed from the PEC, and the total ACPH

Certification Failures

- A corrective action plan must be implemented and documented in response to any out-of-range results.
- Data collected in response to corrective actions must be reviewed to confirm that the actions taken have been effective.

Knowledge Check!

What is the purpose of cleanroom airflow testing?

A. Room classification

B. ACPH calculation

C. Leak detection

D. Stagnant air identification

Wrap-Up

- Maintaining a compounding area is a never-ending task. Train staff to identify facility-related insanitary conditions.
- The chapter minimums for ACPH are likely not enough for a cleanroom suite. Evaluate your contamination control risks to determine if more ACPH are warranted.
- Be prepared to research and learn more about the certification testing necessary to ensure the proper functionality of the SECs and PECs.
- Form a relationship with your certifier. This will make the discussion about failures so much easier.

Section 6 Microbiological Air and Surface Monitoring

pure microbiology

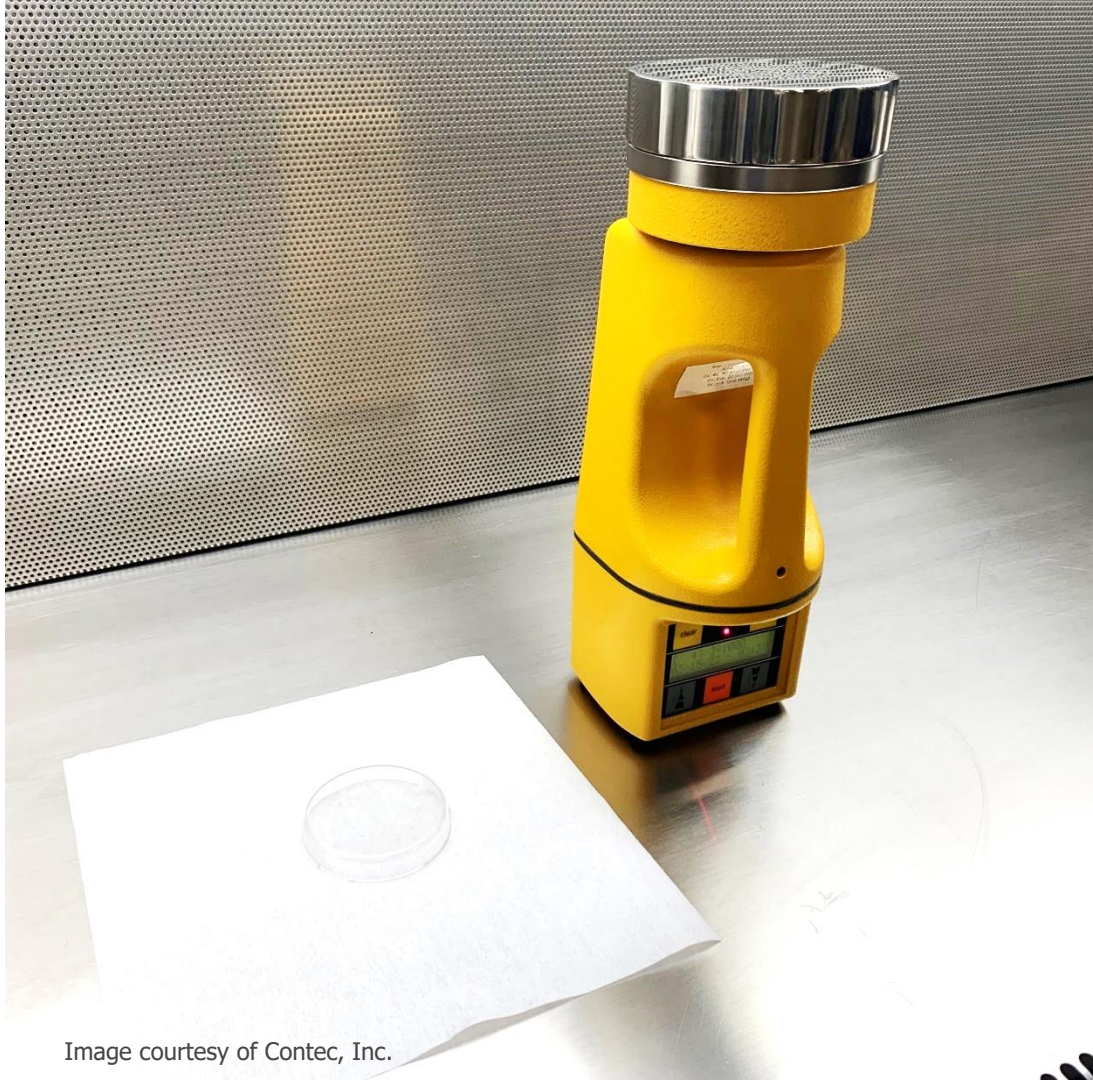


Image courtesy of Contec, Inc.

Learning Objectives

After this lecture, the learner will be able to:

- List when viable air and surface sampling are required.
- Describe the sampling and incubation process for viable air and surface sampling.
- Explain the appropriate steps to take when investigating an exceeded action level.

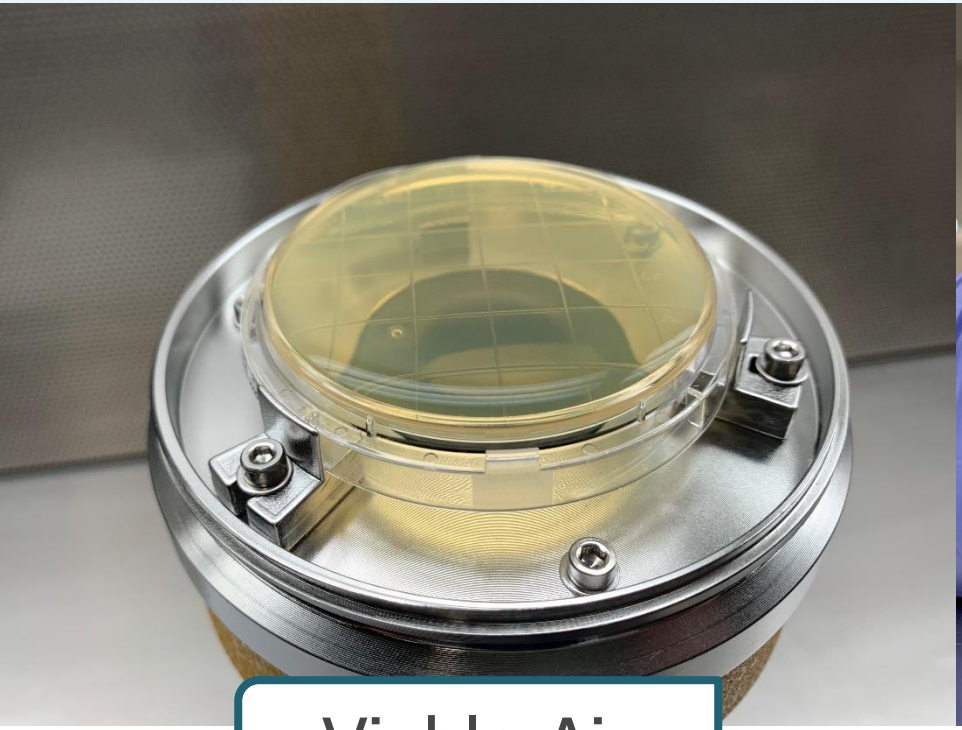
Sampling Program and Documentation

- Must develop and implement written procedures for microbiological air and surface monitoring
- Must document and retain records for all microbiological air and surface monitoring procedures, the test results, and the corrective actions
- Must review data collected in response to corrective actions to confirm the actions taken are effective

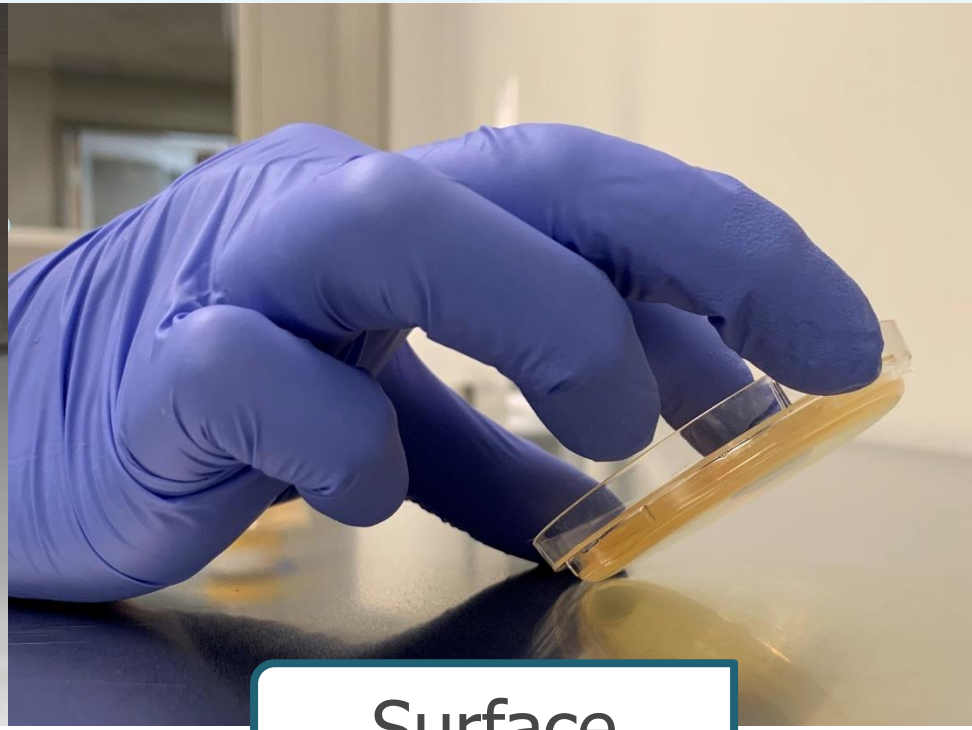
Data Review

- Regular review of the sampling data must be performed to detect trends and the results of the review must be documented.
- Results from microbiological air and surface sampling must be reviewed in conjunction with personnel data to assess the state of control and to identify potential risks of contamination.
- Corrective action in response to any adverse findings is required to maintain the necessary environmental quality for preparation of CSPs.

Types of Sampling



Viable Air



Surface

General Sampling Frequency

- Initially to establish a baseline
- In conjunction with the certification of new facilities and equipment
- After any servicing of facilities and equipment
- In response to:
  - identified problems
  - identified trends
  - changes that could impact the sterile compounding area

Sampling Frequency Requirements

Chapter Version	Viable Air	Viable Surface
2022 Categories 1 & 2	At least every 6 months	At least monthly
2022 Category 3	• Completed within 30 days prior to the start of any Category 3 compounding • At least monthly regardless of the frequency of compounding Category 3 CSPs	• Completed prior to assigning a BUD longer than the chapter limits • At least weekly regardless of the frequency of compounding Category 3 CSPs • Conducted within the PEC used to prepare Category 3 CSPs at the end of each batch before cleaning and disinfection occurs

And don't forget about the surface sample collected during the aseptic manipulation competency!

Air and Surface Monitoring Program

- Must be described in the facility's SOPs and include:
  - a diagram of the sampling locations (sampling plan)
  - procedures for collecting samples
  - frequency of sampling
  - size of samples
  - time of day of sampling in relation to activities
  - action levels that will trigger corrective action

Times and Locations

- The times and locations of sampling should be carefully selected based on their relationship to the activities performed in the area.

Time	Locations
Air and surface sampling must be conducted during dynamic operating conditions	Choose locations that pose the highest possible risk of contamination to the CSP
Surface sampling should be performed at the end of a compounding activity or shift but before the area has been cleaned	Choose locations that are likely to be representative of the conditions throughout the area.

Program Design

- Program must be designed and conducted to minimize the chance that the sampling will cause contamination of the CSP or the environment.

Image courtesy of Contec, Inc.

USP <797> Sample Locations

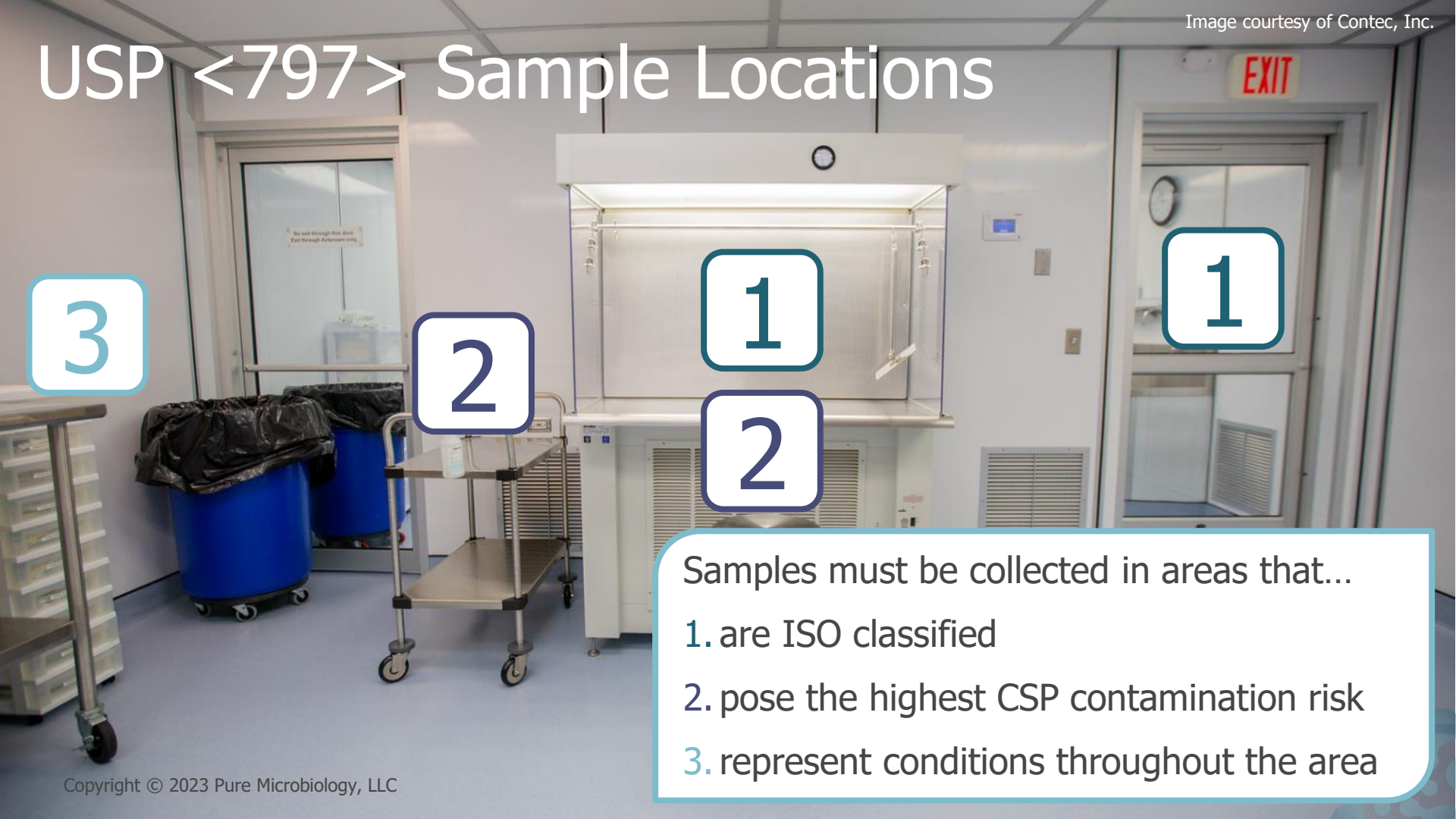


Image courtesy of Contec, Inc.

Samples must be collected in areas that…

1. are ISO classified
2. pose the highest CSP contamination risk
3. represent conditions throughout the area

Additional Surface Sample Locations

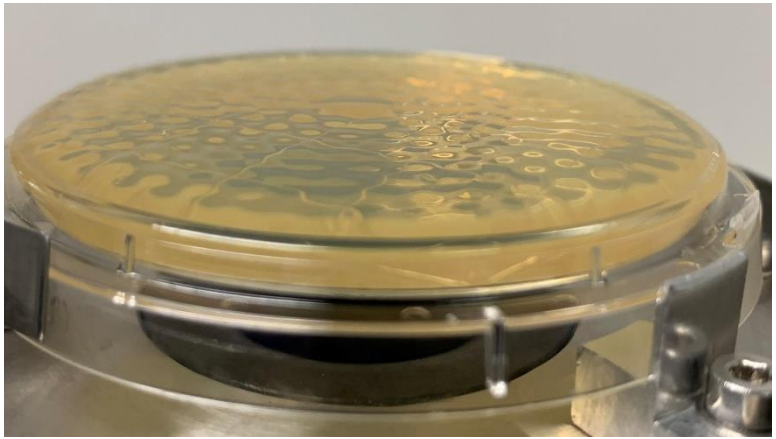
- MUST be collected on the interior of the:
  - PEC
  - pass-through
- SHOULD be collected on:
  - equipment contained in the PEC
  - staging or work area(s) near the PEC
  - frequently touched surfaces

Training and Equipment

- "It is important that personnel are trained and competent in air and surface sampling procedures to ensure accurate and reproducible sampling."
  - Does not say "must be," but that is the expectation
- All impaction air samplers must be serviced and calibrated as recommended by the manufacturer.

Viable Air Sampling Equipment

- Volumetric — defined volume of air
- Active — physically draws in air
- Impaction — air impacts the media surface



Notice the dimpling where the air impacted the agar.

Viable Air Sampling Media

- A general microbiological growth media that supports bacteria and fungi must be used.
  - trypticase soy agar (TSA)
- Fungal media may be used.
- COAs from the manufacturer must verify expected
  - growth promotion
  - pH
  - sterilization requirements

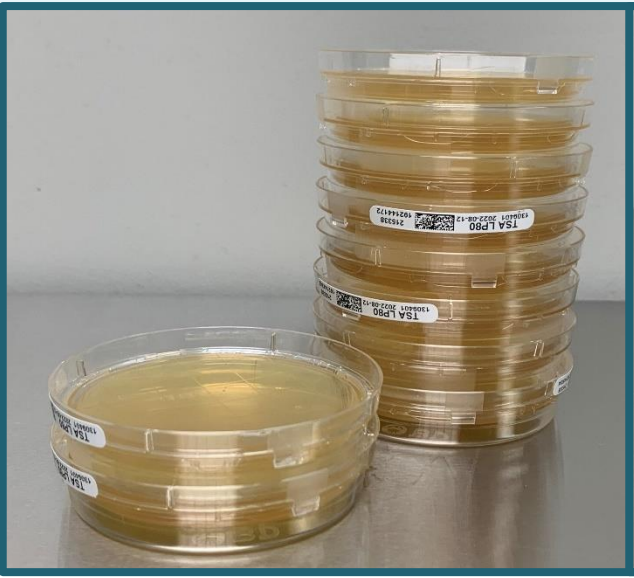
Viable Air Sampling

- Sample according to the manufacturer's instructions
- Collect at least 1000 L of air from each location
- Handle/Store media devices to avoid contamination
- Incubate inverted

Surface Sampling Media

- Devices containing general microbial growth media supplemented with neutralizing additives
  - TSA with lecithin and polysorbate 80
  - Must have a raised convex surface
- COAs from the manufacturer must verify expected
  - growth promotion
  - pH
  - sterilization requirements

Surface Sampling Device Options



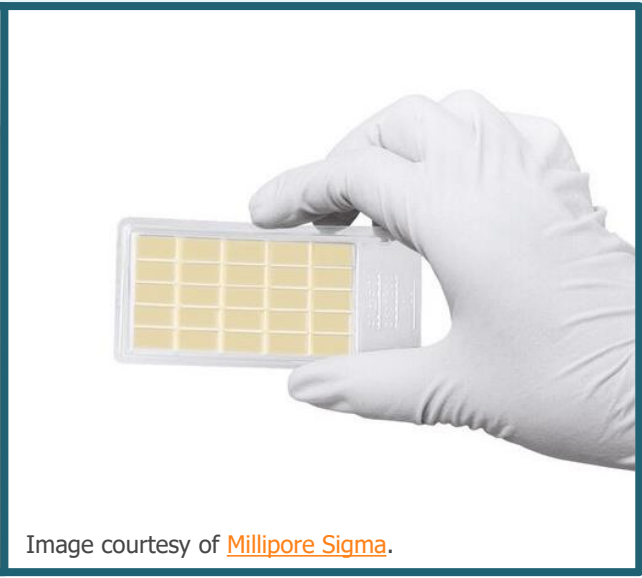


Image courtesy of Millipore Sigma.

Contact plates

- flat surfaces
- easy to use

Swabs

- irregular surfaces
- requires extraction

Slides/Paddles

- difficult to reach areas
- careful handling

Surface Sampling

- Remove cover, firmly roll over surface
- Return cover, clean and disinfect surface
- Handle/Store media devices to avoid contamination
- Incubate inverted

Incubator Musts

- Placed in a location outside of the sterile compounding area
- Monitored during incubation, either manually or by a continuous recording device
- Results reviewed and documented as described in the facility's SOPs

Air and Surface Incubation Parameters

Single-Plate Method			
Stage 1 30 to 35 °C for at least 48 hours	Read at end of 1st incubation	Stage 2 20 to 25 °C for at least 5 days	Read at end of 2nd incubation

Air and Surface Incubation Parameters

Dual-Plate Method			
TSA 30 to 35 °C for at least 48 hours	Read at end of incubation	TSA/Fungal 20 to 25 °C for at least 5 days	Read at end of incubation

Action Levels

ISO Class	Air Action Level CFU/m^3	Surface Action Level CFU/device
5	>1	>3
7	>10	>5
8	>100	>50

Knowledge Check!

When is viable sampling performed?

A. In response to identified problems

B. Immediately before a media-fill test

C. In conjunction with the hiring of new staff

D. Immediately after wiping a surface with sterile IPA

Wrap-Up

- Viable air and surface sampling is a critical component of environmental monitoring.
- USP <797> provides requirement guidance, but it is critical that those performing and responsible for viable air and surface sampling are familiar with other industry documents.
- Make sure staff have received appropriate training if they will be collecting air and surface samples.

Sections 7 and 8

pure microbiology

Images courtesy of Contec, Inc.

Learning Objectives

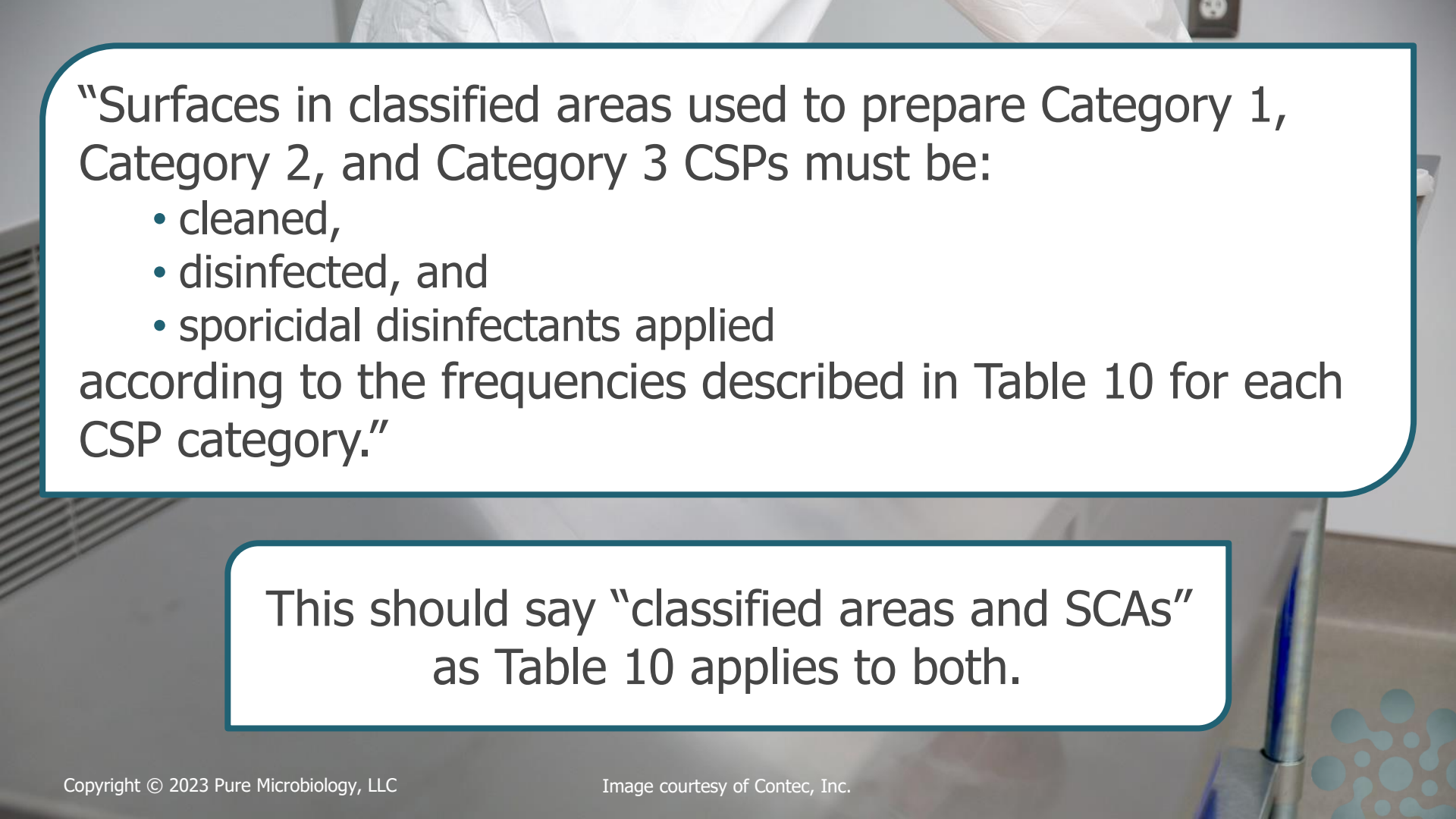
After this lecture, the learner will be able to:

- Recall the cleaning frequencies of the different surfaces found in a cleanroom suite and segregated compounding area.
- Choose the appropriate agents and materials to clean primary and secondary engineering controls.
- List the agents and materials needed to transfer items into the primary and secondary engineering controls.

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

pure microbiology

Image courtesy of Contec, Inc.



"Surfaces in classified areas used to prepare Category 1, Category 2, and Category 3 CSPs must be:

- cleaned,
- disinfected, and
- sporicidal disinfectants applied

according to the frequencies described in Table 10 for each CSP category."

This should say "classified areas and SCAs" as Table 10 applies to both.

Image courtesy of Contec, Inc.

sIPA must be applied in the PEC…

- after cleaning and disinfecting, or after the application of a one-step disinfectant cleaner or sporicidal disinfectant to remove any residue.
- immediately before initiating compounding.
- during compounding to the horizontal work surface, including any removable work trays, at least every 30 min if the compounding process takes 30 min or less.
  - If the compounding process takes more than 30 min, compounding must not be disrupted, and the work surface of the PEC must be disinfected immediately after compounding.

Term	Process	Agent
Cleaning	• involves removing organic and inorganic materials from surfaces • usually manual or mechanical • with a cleaning agent	• usually containing a surfactant • used for the removal of substances from surfaces
Disinfecting	• involves destruction of microorganisms • usually with a chemical agent	• chemical or physical • used on inanimate surfaces and objects to destroy fungi, viruses, and bacteria
Sporicidal	• involves the destruction of bacterial and fungal spores	• chemical or physical • destroys bacterial and fungal spores • expected to kill all vegetative microorganisms

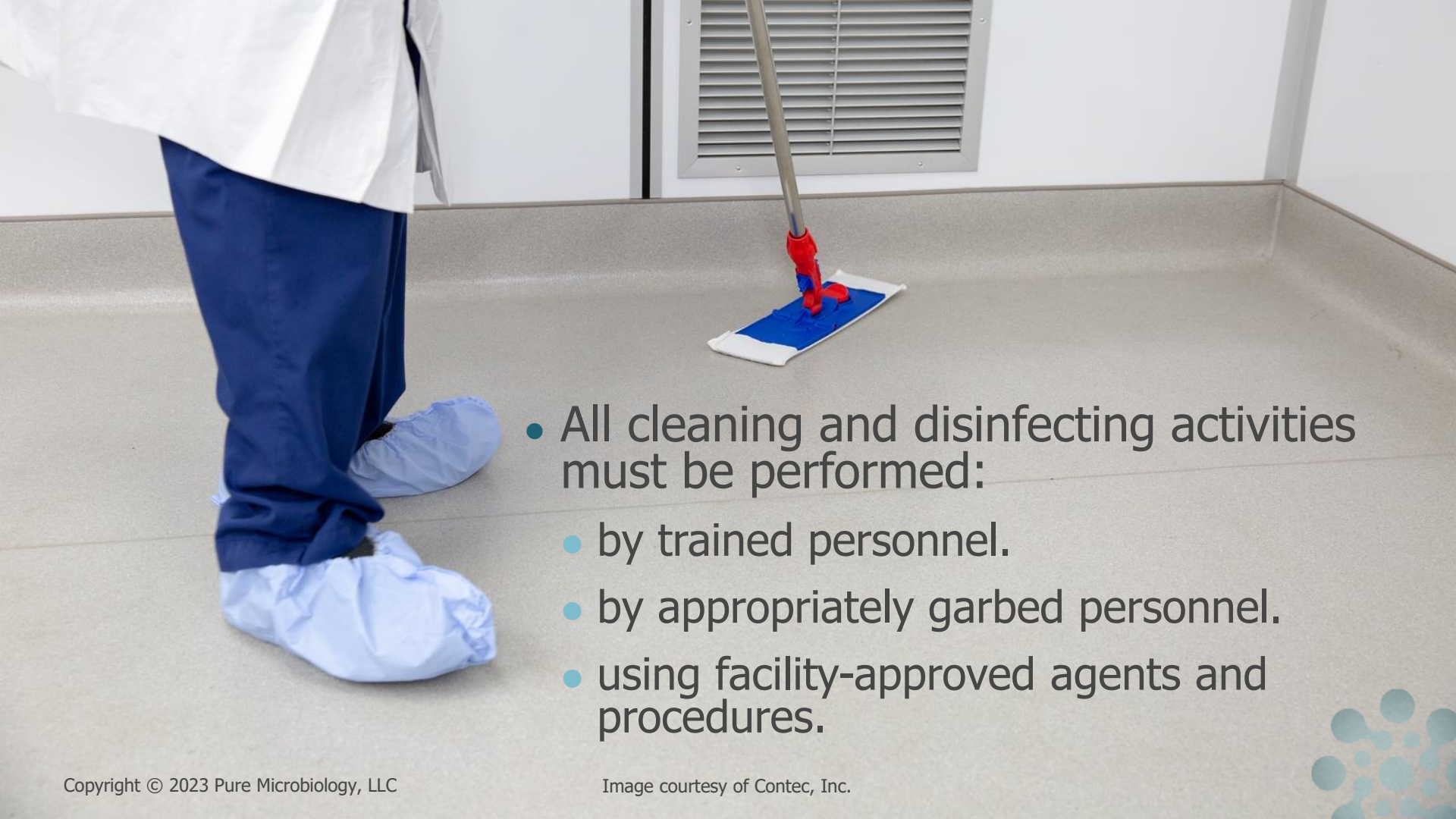
Basic Cleaning Steps

Separate Agents

- Clean with a cleaning agent.
- Disinfect with an EPA-registered disinfectant.
  - bactericidal
  - sporicidal

One-Step Agents

- Clean and disinfect with an EPA registered one-step disinfectant cleaner.
  - bactericidal
  - sporicidal



- All cleaning and disinfecting activities must be performed:
  - by trained personnel.
  - by appropriately garbed personnel.
  - using facility-approved agents and procedures.

Image courtesy of Contec, Inc.

Cleaning-Related SOPs

- Agents and procedures must be described in written SOPs.
  - frequency
  - method(s)
  - location(s) of application
  - use of agents in accordance with the manufacturer’s instructions
- Document all cleaning activities according to facility SOPs.
- SOPs must be followed by all cleaning personnel.

Contact Time

- Agents
  - Follow the manufacturer's directions or published data for the minimum contact time.

Image courtesy of Contec, Inc.

- sIPA
  - Allow to dry.

Cleaning Specifics

- Must be performed in the direction of clean to dirty.
  - Carefully describe this in your SOPs.
- Same floor mop may be used in both the buffer and anteroom but only in that order.
- Mops used in areas where HDs are compounded must be dedicated to those areas.
  - This should include all tools!

Category 1 and 2 Cleaning Frequency

	Daily on days when compounding occurs	Monthly
Agent	• One-step bactericidal disinfectant cleaner • In the PEC; follow with sIPA	• One-step sporicidal disinfectant cleaner • In the PEC; follow with sIPA
PEC	• Interior • Work surface of removable work tray • Equipment	• Interior • Removable work tray • Under removable work tray • Equipment
SEC	• Work surfaces outside PEC • Pass-throughs • Floor(s)	• Work surfaces outside PEC • Pass-throughs • Floor(s) • Wall(s) • Door(s) and doorframe(s) • Ceiling(s) • Storage shelving and bin(s) • Equipment outside the PEC(s)

Everything!

Category 3 Cleaning Frequency

	Daily on days when compounding occurs	Weekly	Monthly
Agent	• One-step bactericidal disinfectant cleaner • In the PEC; follow with sIPA	• One-step sporicidal disinfectant cleaner • In the PEC; follow with sIPA	• One-step sporicidal disinfectant cleaner • In the PEC; follow with sIPA
PEC	• Interior • Work surface of removable work tray • Equipment	• Interior • Equipment	• Interior • Removable work tray • Under removable work tray • Equipment
SEC	• Work surfaces outside PEC • Pass-throughs • Floor(s)	• Work surfaces outside PEC • Pass-throughs • Floor(s)	• Wall(s) • Door(s) • Doorframe(s) • Ceiling(s) • Storage shelving and bin(s) • Equipment outside the PEC(s)

Everything!

Agents

PEC

- Agents must be sterile.
- Sterile water must be used to dilute concentrated agents.

Classified Area

- Agents should be sterile.
- Sterile water should be used to dilute concentrated agents.

SCA

- Not addressed.

Image courtesy of Contec, Inc.

Supplies

"All cleaning and disinfecting supplies (e.g., wipers, sponges, pads, and mop heads) with the exception of tool handles and holders must be low lint."

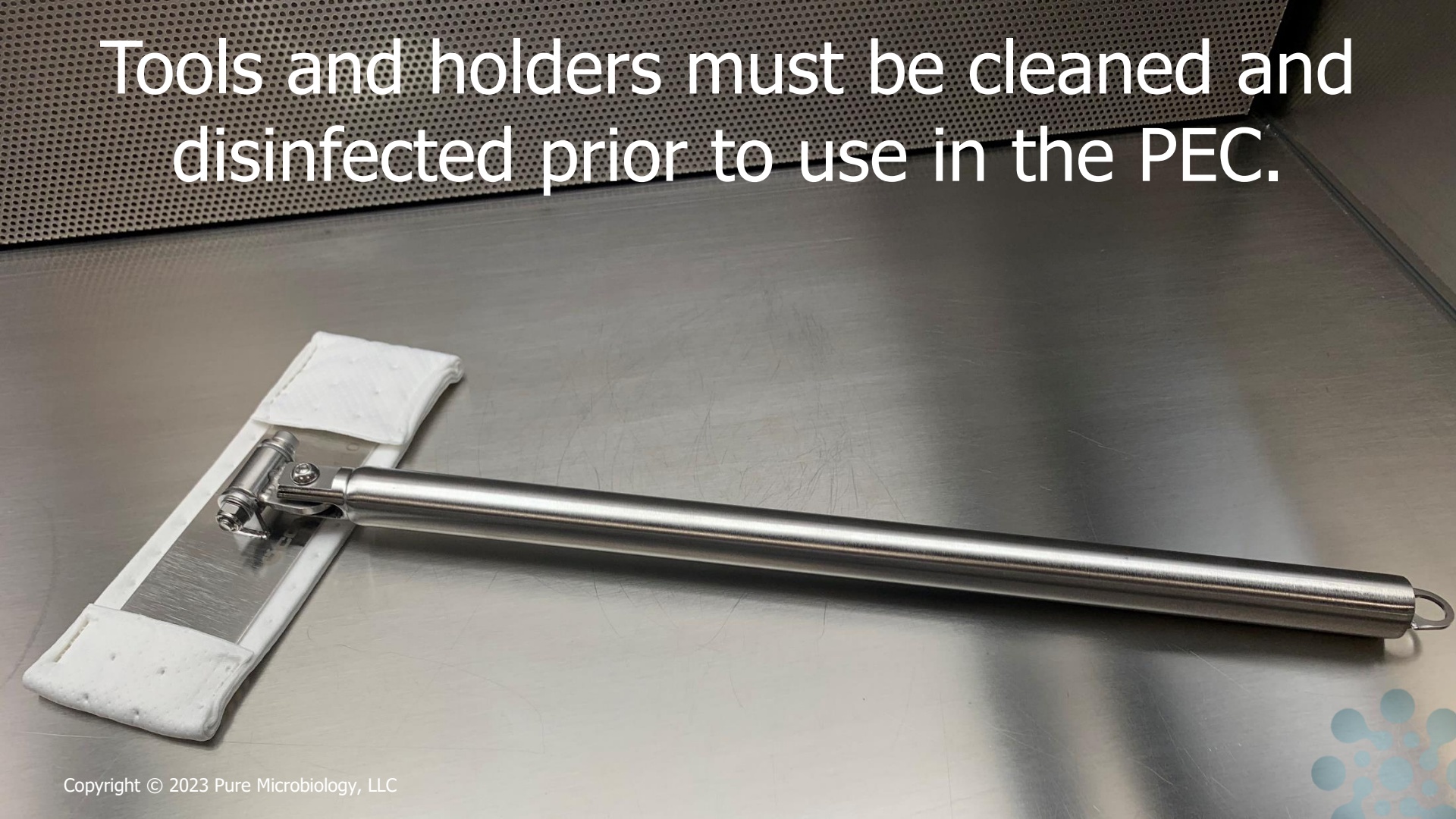
- This doesn't make sense.
- Make sure all tools are appropriate for use in compounding areas.

Image courtesy of Contec, Inc.

Wipers, sponges, pads, and mop heads…

- must be low lint.
- should be disposable.
  - If disposable cleaning supplies are used, they must be discarded after each cleaning activity.
- must be sterile if used in the PEC.

Tools and holders must be cleaned and disinfected prior to use in the PEC.



Reusable cleaning tools must be…

- made of cleanable materials.
- cleaned and disinfected before and after each use.
- dedicated for use in the classified areas or SCA and must not be removed from these areas except for disposal.
- discarded as determined based on the condition of the tools.

Cleaning Supply Disposal

"Cleaning supplies used in the classified areas and SCAs must be disposed of in a manner that minimizes the potential for dispersing contaminants into the air (e.g., with minimal agitation, away from work surfaces)."

Image courtesy of Contec, Inc.

Agent and Supply Usage

"Once opened, sterile cleaning and disinfecting agents and supplies (e.g., closed containers of sterile wipers) and sterile 70% IPA may be reused for a time period specified as by the manufacturer and/or described in the facility written SOPs."

Image courtesy of Contec, Inc.

Cleaning the PEC and Equipment Within

Remember all agents and supplies used in the PEC must be sterile!

If necessary, remove visible debris with a solution and low-lint wipers.

Using a low-lint wiper, apply an EPA-registered one-step disinfectant cleaner.

- bactericidal
- sporicidal — must be applied under the work surface

Ensure the contact time specified by the manufacturer is achieved.

Using a low-lint wiper, apply sIPA.

Allow the surface to dry completely before beginning compounding.

Knowledge Check!

Which is a USP <797> requirement of reusable cleaning tools?

A. Cleaned and disinfected weekly

B. Discarded after one year of use

C. Stored in the janitorial closet

D. Made of cleanable materials

Section 8 Introducing Items into the SEC and PEC

pure microbiology

Image courtesy of Contec, Inc.

Before any item is introduced

into the clean side of the anteroom	placed into a pass-through chamber	brought into the SCA

it must be wiped with a(n)

sporicidal disinfectant	EPA-registered disinfectant	sIPA

using low-lint wipers by staff wearing gloves.

Introducing Items into the SEC

EPA-registered disinfectant or sporicidal disinfectant	must be allowed to dwell for the minimum contact time specified by the manufacturer
sIPA	must be allowed to dry

The wiping procedure **should** not compromise the packaging integrity or render the product label unreadable.

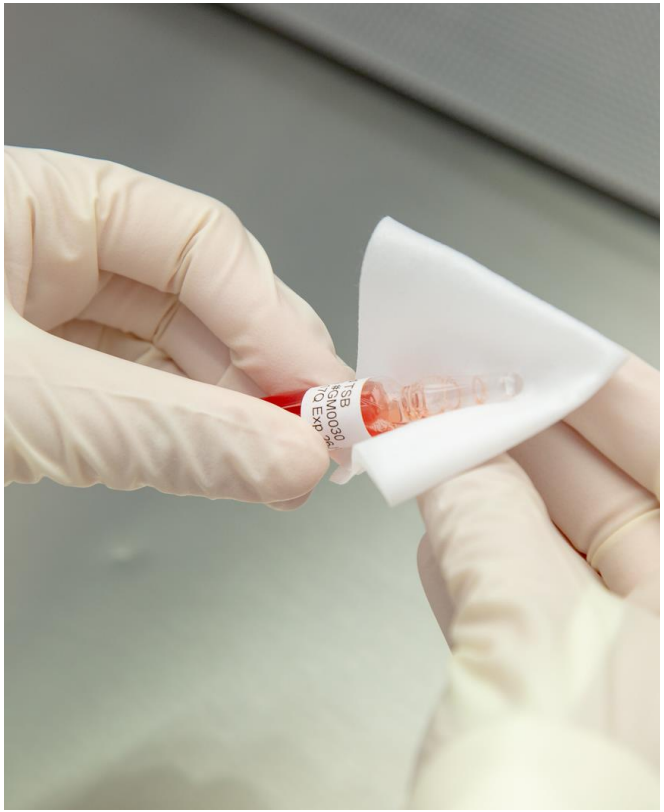
Image courtesy of Contec, Inc.

Introducing Items into the PEC

- Items must be…
  - wiped with sIPA using sterile low-lint wipers.
  - allowed to dry before use.
- The wiping procedure **must** not affect product label.
- Sterile items received in sealed coverings designed to maintain sterility may be removed from the covering as the supplies are introduced into the PEC without the need to wipe the individual items.

Image courtesy of Contec, Inc.

Critical Sites



- Must be wiped with sIPA in the PEC
  - vial stoppers
  - ampule necks
  - intravenous bag septums
- This provides both chemical and mechanical actions to remove contaminants.
- sIPA must be allowed to dry.

Image courtesy of Contec, Inc.

Knowledge Check!

When transferring items into the PEC, which is a chapter requirement?

A. Applying a sporicidal agent

B. Holding the item until it dries

C. Using sterile wipers

D. Wearing a respirator

Wrap-Up

- Daily, weekly, and monthly cleaning are essential to the maintenance of the sterile compounding environment.
- Use an EPA-registered one-step disinfectant cleaner. Anything else will result in more work.
- Before materials are transferred into the PEC, they are wiped down at least twice.