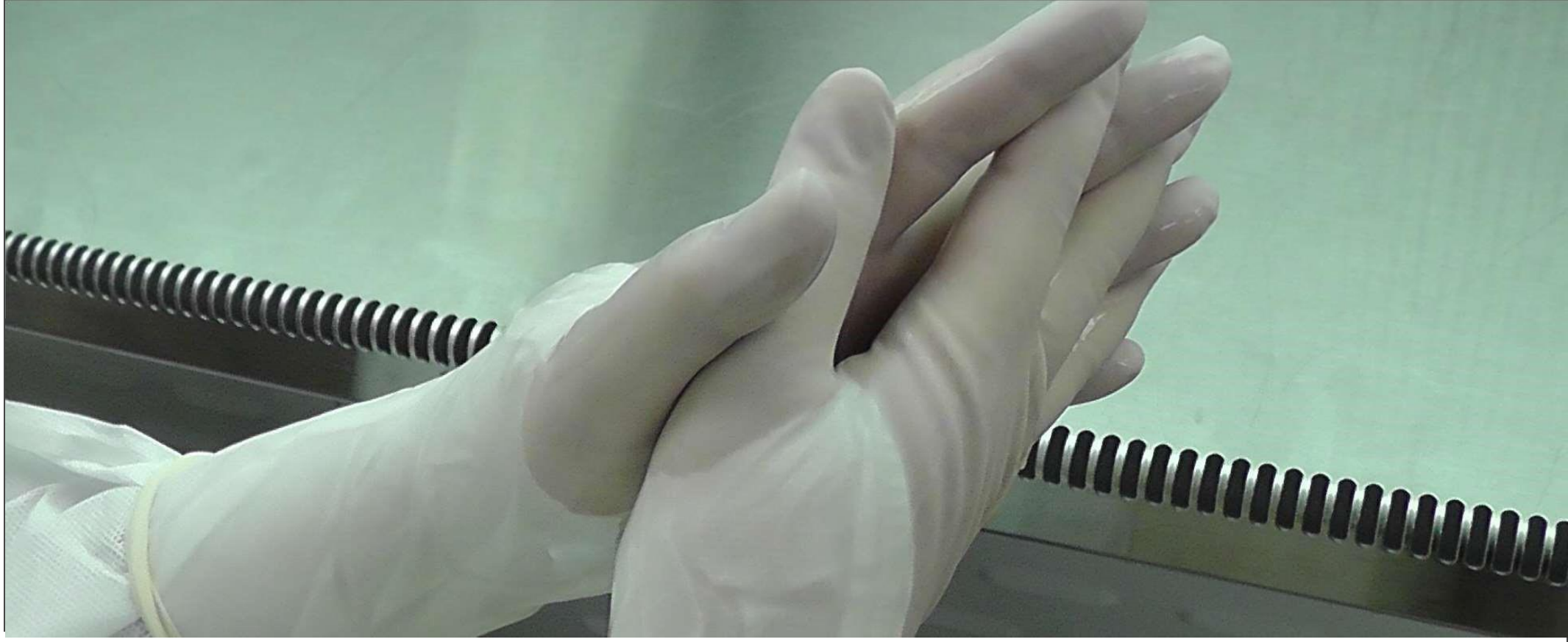


2018 Proposed Revisions to USP Chapter <797>

Eric Kastango, MBA, BS Pharm, FASHP

Abby Roth, BS Micro, ASQ-CQM/OE

criticalpoint

Disclaimer

The presenters are speaking in their individual capacity and not as representatives of any organization or committee regardless of their status, membership or affiliations with any entity.

The views and opinions presented are entirely their own.

They do not necessarily reflect the views of any other organization they may be associated with, nor should they be construed as an “official” explanation or interpretation of any USP chapter or any State Board of Pharmacy rule/law.

USP Compounding Chapters Timeline

Note: The current version of General Chapters <795> and <797> published in USP-NF are official.

Remember

- This is a discussion of many of the proposed revisions released on July 27, 2018.
- Anything discussed may change after public comments are received by USP and the chapter is finalized.
- The version of the chapter released in 2008 is the current version and will be until December 1, 2019.

Remember

- It is critical that you read the chapter in its entirety.
- The 2018 Proposed Revision of the chapter can be downloaded from the USP website
  - http://www.usp.org/compounding/general-chapter-797
- Submit comments by using link on the USP <797> landing web page

Discussion will include…

- Review of Category 1 and Category 2 CSPs
- Personnel Qualifications
- Primary and Secondary Engineering Controls (PEC and SEC) and Segregated Compounding Areas (SCA)
- Viable Environmental Monitoring (EM)
- Cleaning and Disinfection
- Beyond Use Dating (BUD)

Defining Category 1 and Category 2

- Category 1 CSP - based on facility configuration (SCA/C-SCA)
  - BUD of 12 hours or less at controlled room temperature
  - BUD of 24 hours or less when refrigerated
  - Only if made in accordance with applicable requirements for Category 1 CSPs
- Category 2 CSP – based on facility configuration (ISO classified ante and buffer rooms)
  - BUD of greater than 12 hours at controlled room temperature
  - BUD of greater than 24 hours when refrigerated
  - Only if made in accordance with applicable requirements for Category 2 CSPs
- Table 1 provides a summary of the minimum requirements for each category, but many requirements are not in the table because they apply to ALL CSPs.

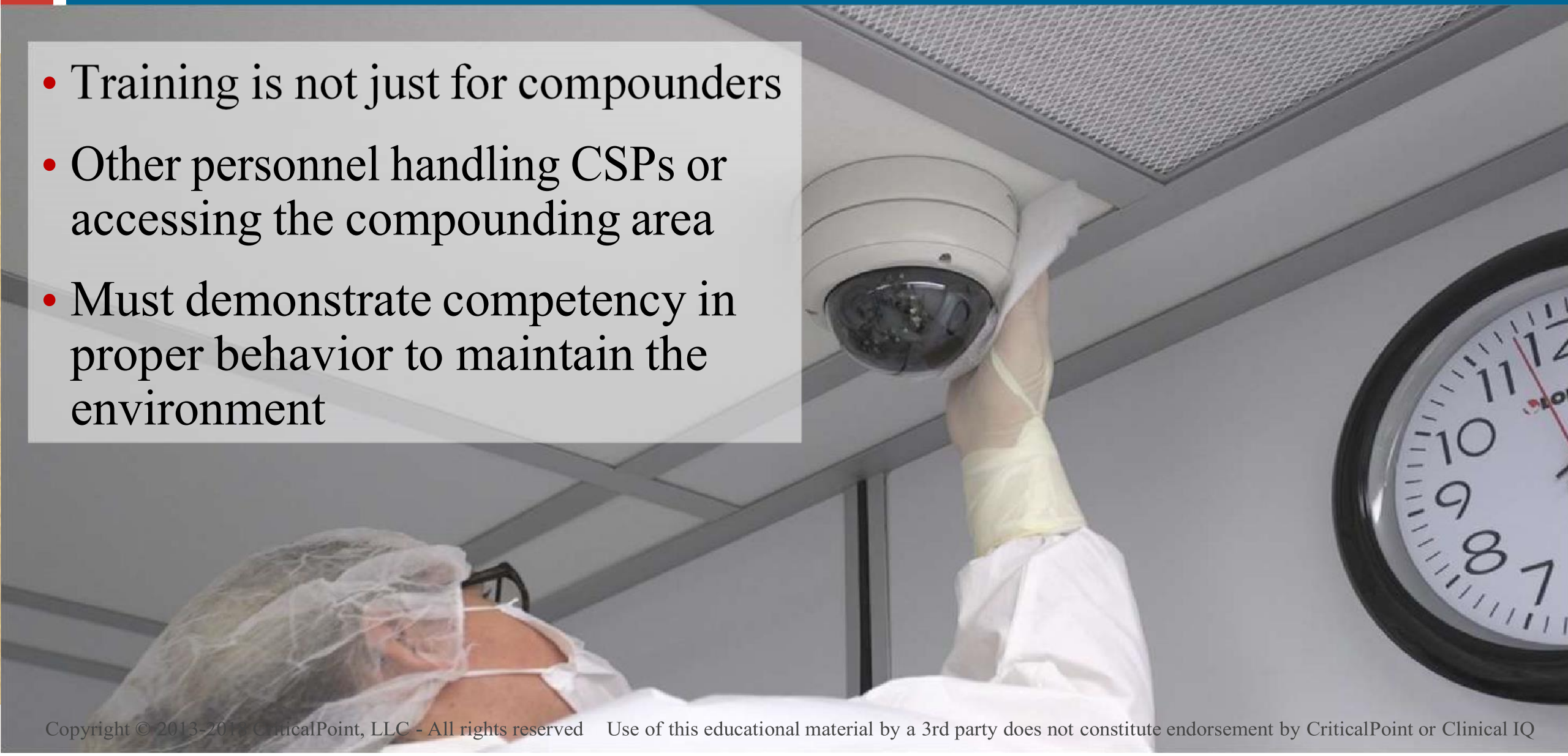
Personnel Qualifications

- Category 1 and Category 2 requirements are the same

Requirement	Frequency
Visual observation of hand hygiene and garbing	Every 6 months
Gloved fingertip and thumb sampling	Every 6 months
Media fill testing	Every 6 months
Requalification	Every 12 months

Requalification includes the demonstration of core competencies.

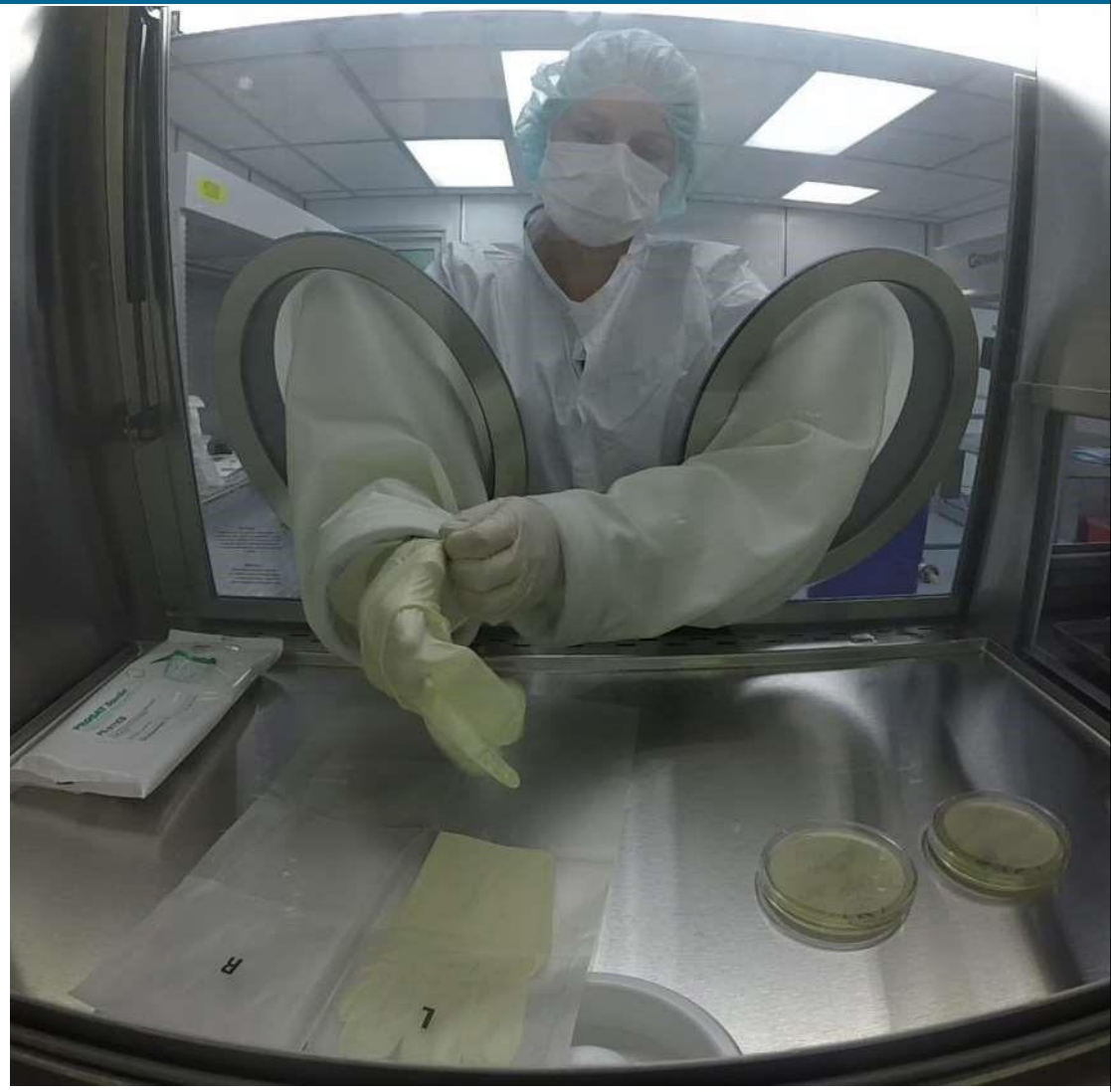
Other Personnel



- Training is not just for compounders
- Other personnel handling CSPs or accessing the compounding area
- Must demonstrate competency in proper behavior to maintain the environment

Garbing and Hand Hygiene

- Disposable nail cleaner must be used
- Garbing order is not specified
  - Up to the facility to decide
  - Define in SOP
- Gowns cannot be reused
- CAI and CACI
  - Disposable gloves under gauntlet gloves
  - Sterile gloves over gauntlet gloves



Gloved Fingertip and Thumb Sampling

- No changes to the number of times
- Clarifies that initial GFS is done after “separate and complete hand hygiene and full garbing”
- Box 2-1 indicates that fingers and thumb are rolled over the surface
- Gives multiple options for devices to use
- Provides incubation parameters that are longer and require two temperatures

Reevaluation, Retraining, Requalification

- Failure of any of the following will require successful reevaluation before personnel can resume compounding.
  - Hand Hygiene/Garbing
  - Aseptic Technique
  - GFS
  - Media Fill Testing
- How will this effect your ability to care for patients if you need to wait 14 days for media fill results?

Facility Requirements

Category 1 = Cleanroom Suite or SCA

Category 2 = Cleanroom Suite

You can no longer compound in a CAI or CACI in an SCA and get full dating!

Defining Cleanroom Suite

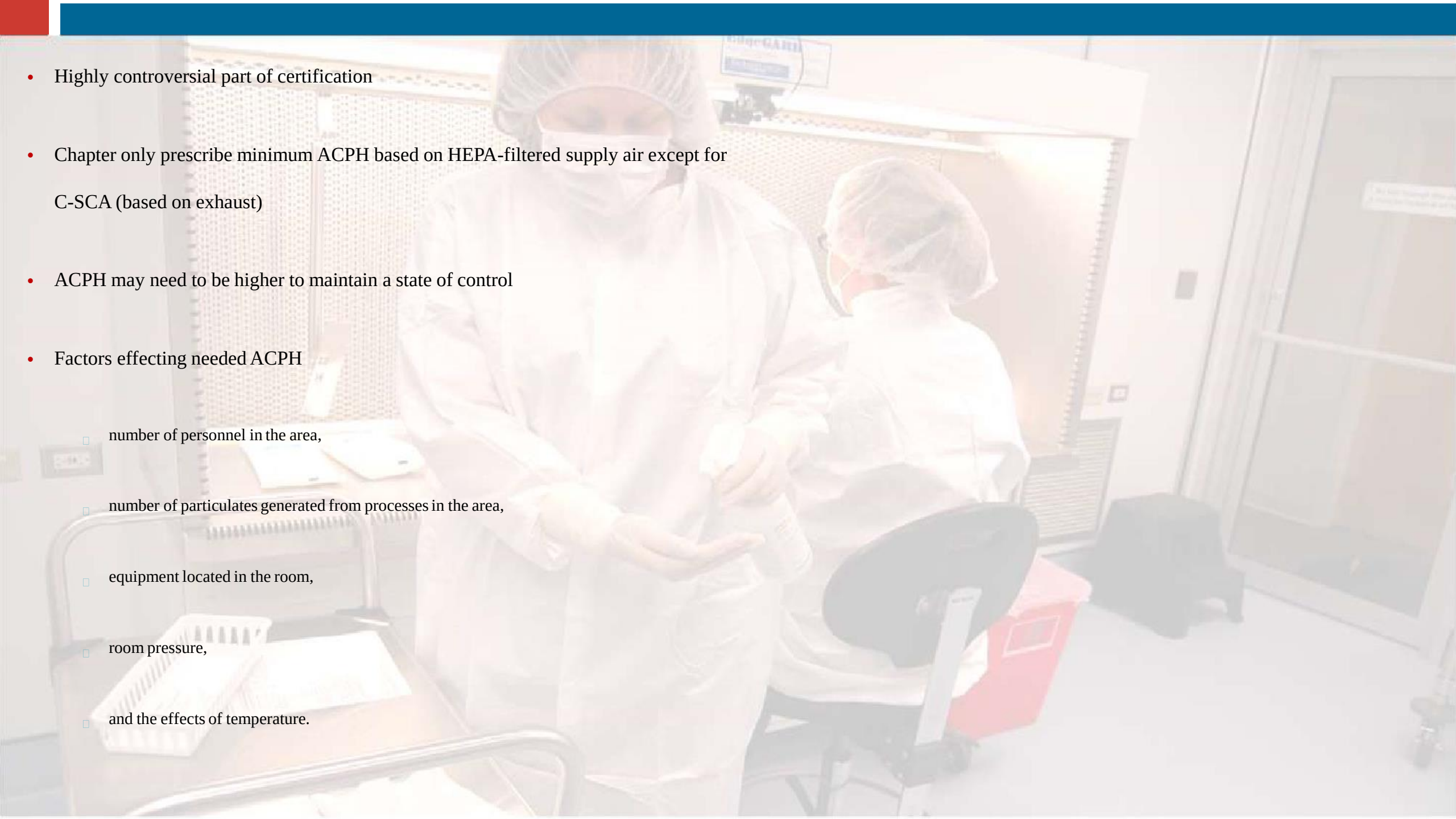
- ISO-classified ante-room with fixed walls and doors
- Controls to minimize the flow of lower-quality air into the more controlled areas
- Supply Air introduced through HEPA filters located in the ceiling
- Low wall returns unless a visual smoke study is performed
- Pressure-differential monitoring system
- Line of demarcation in the ante-room

Important “shoulds”

- Design of the facility should take into account
  - number of personnel and their movements
  - equipment, supplies, and components
- The cleanroom suite should
  - be at a temperature of 20° or cooler and at a relative humidity below 60%
  - provide comfortable conditions for personnel in required garb
- Pass-through doors
  - should be interlocking
  - that are not interlocking MUST never be opened at the same time

Air Exchanges

Compounding Area	ACPH Requirements (HEPA-filtered supply air)	Pressure Requirements
Unclassified SCA	None	None
Unclassified C-SCA	≥12 ACPH (exhaust) No HEPA air required	Negative 0.01 to 0.03” w.c.
ISO Class 7 Non-HD Buffer Room	≥30 ACPH (supply)	Minimum Positive 0.02” w.c.
ISO Class 7 HD Buffer Room	≥30 ACPH (supply)	Negative 0.01 to 0.03” w.c.
ISO Class 7 Anteroom	≥30 ACPH (supply)	Minimum Positive 0.02” w.c.
ISO Class 8 Anteroom	≥20 ACPH (supply)	Minimum Positive 0.02” w.c.



- Highly controversial part of certification
- Chapter only prescribe minimum ACPH based on HEPA-filtered supply air except for C-SCA (based on exhaust)
- ACPH may need to be higher to maintain a state of control
- Factors effecting needed ACPH
  - number of personnel in the area,
  - number of particulates generated from processes in the area,
  - equipment located in the room,
  - room pressure,
  - and the effects of temperature.

Air Change Specifics

ISO Class 7

- ≥30 ACPH
- ≥ 15 ACPH of
  must come f
  filters locate
- If the PEC is
  total ACPH re
  not be turne
- Certification
  from HVAC, A
  PEC, and the total ACPH

ISO Class 8

- ≥20 ACPH

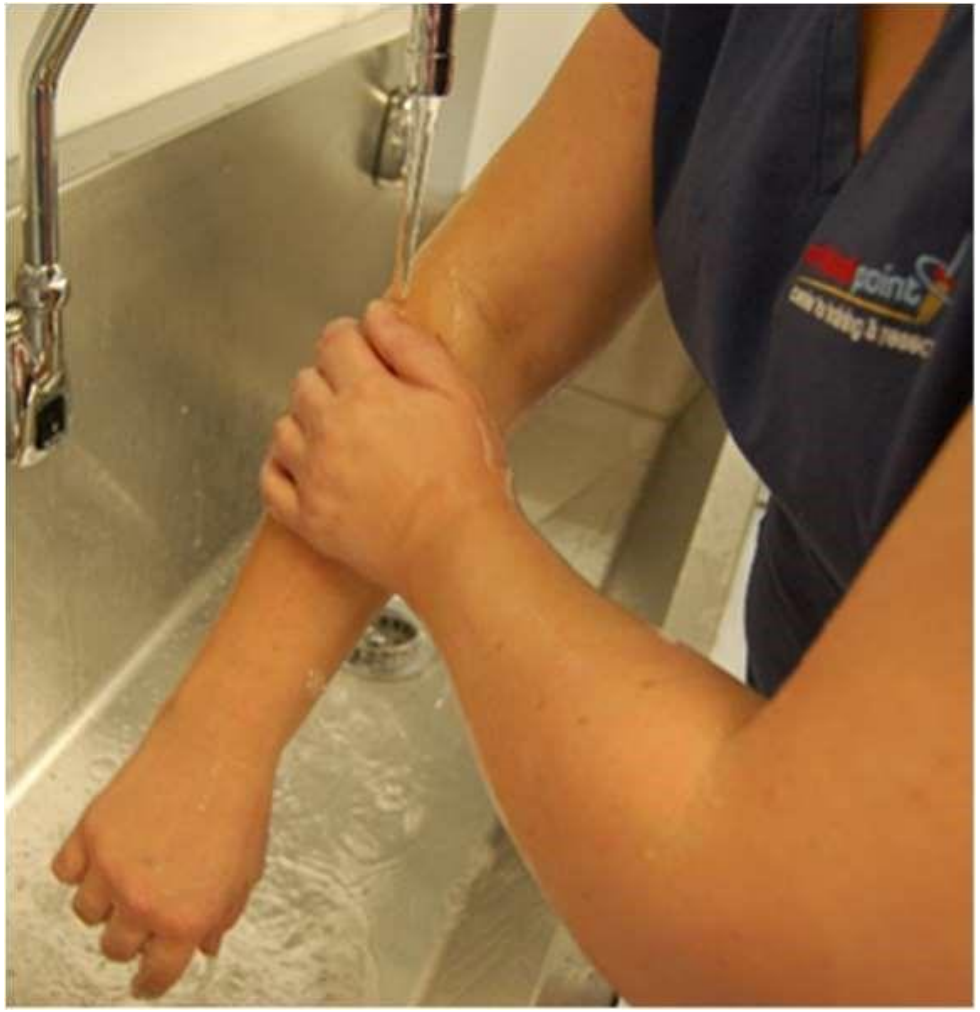
ous chapter did not
A Aseptic
d this minimum

l from the HVAC
ed in the ceiling

have total ACPH

Compounding area must be certified according to the CETA application guide for *Sterile Compounding Facilities* or an equivalent guideline.

Sink



- Should be hands free
- Cleanroom Suite
  - Inside the anteroom
  - Outside the anteroom
- SCA
  - Accessible
  - At least 1 meter from the PEC
  - Must not be in the SCA perimeter

Viable Environmental Monitoring

For Category 1 and Category 2

Viable Air Sampling

- Every 6 months

Surface Sampling

- Monthly

Section 5 Retitled

Environmental Monitoring (2015)

Microbiological Air and Surface Monitoring (2018)

Media and Incubation

- No longer required to sample in the SCA, only the classified areas
- TSA still the only type of media listed
  - Option given to use two pieces of media for each sample location
  - Open for SDA, MEA, etc.
- One plate of TSA
  - 30 °C to 35 °C for no less than 48 hours and
  - 20 °C to 25 °C for no less than 5 days
- Two plates
  - TSA - 30 °C to 35 °C for no less than 5 days
  - TSA, MEA, SDA - 20 °C to 25 °C for no less than 5 days

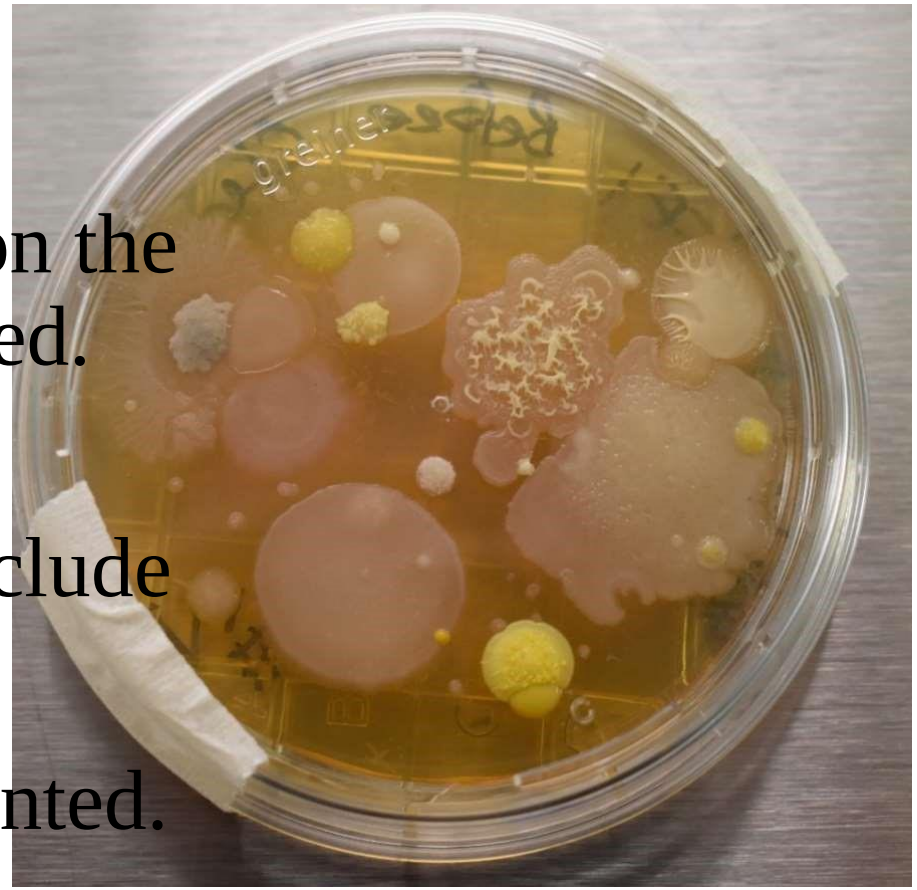
Action Levels

Classification	Air Sample (CFU/m^3)	Surface Sample (CFU/sample)
ISO Class 5	>1	>3
ISO Class 7	>10	>5
ISO Class 8	>100	>50

Only if the Action Level is exceeded, the genus of any microorganism recovere must be identified with the assistance of a microbiologist.

Exceeded Action Levels

- Cause must be investigated and corrective action must be taken.
- Corrective action plan must be dependent on the CFU count and the microorganism recovered.
- The extent of the investigation should be consistent with the deviation and should include an evaluation of trends.
- The corrective action plan must be documented.



What's missing?

Cleaning and Disinfecting

Cleaning frequency is not dependent on the CSP Category.

Cleaning Agent Classes: EPA Registered One-Step Disinfectant Cleaner

- No residues, no rinsing, not corrosive
- Effective against yeast, fungi, bacteria, virus and spores based on concentration
- Easy to store and stable

Peroxyacetic Acid & Hydrogen Peroxide Agents

- Broad-spectrum; sporicidal at low concentrations and ambient temperatures
- Inactivates gram+, gram-, fungi, yeasts, viruses and spores
- Not inactivated by organics and enhance their removal; Byproducts: oxygen, acetic acid and water

Phenolic Agents

- Many of these also EPA registered disinfectants on environmental surfaces
- Based on dilution are fungicidal, virucidal and bactericidal
- Unpleasant odor; leave gummy residue that requires rinsing; may damage surfaces

Quaternary Ammonium Compounds

- Never sporicidal; poor activity against mycobacterium; poor activity against hydrophilic viruses
- Must be rinsed; may be irritating to eyes
- Efficacy reduces by hard water and organic material

These are NOT Cleaning Agents!

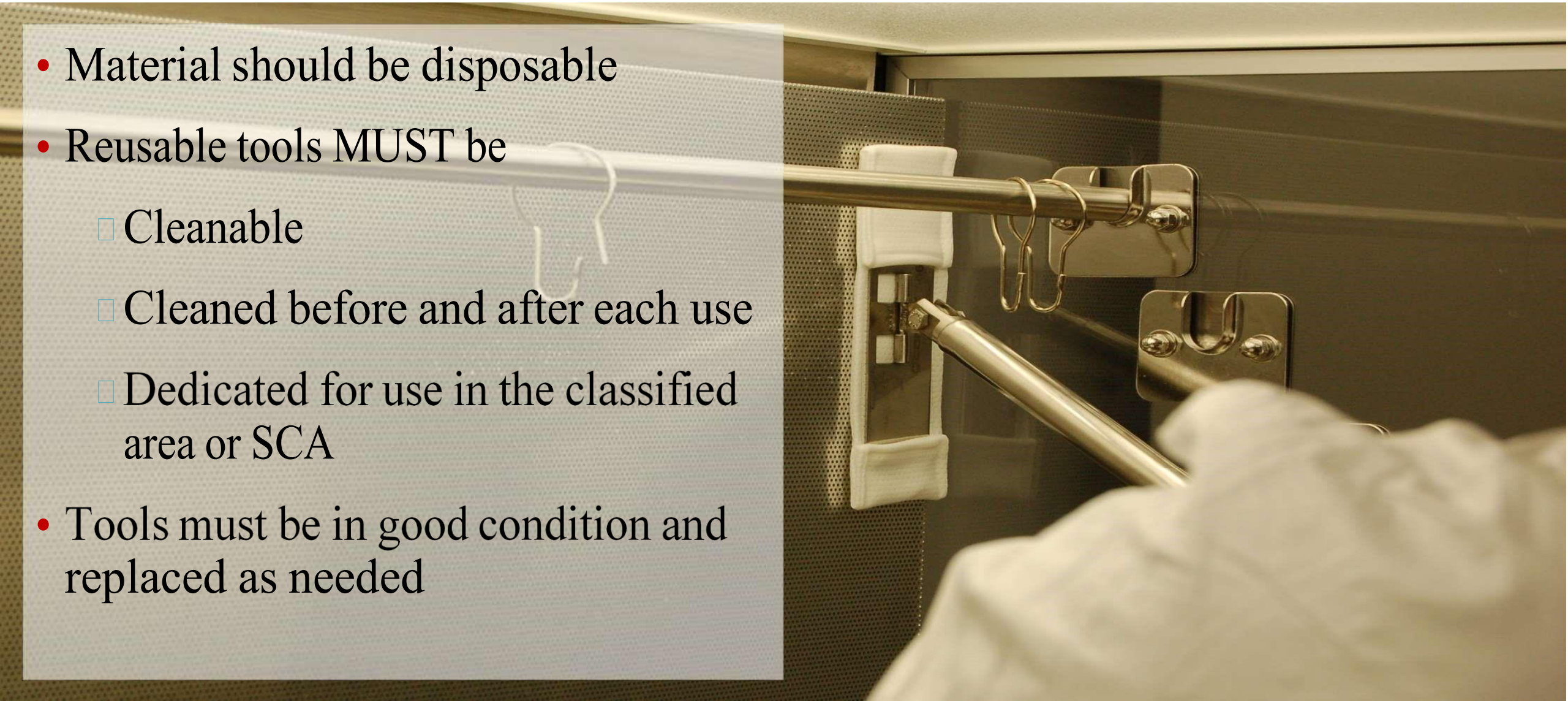
Sodium hypochlorite (Bleach)

- Bleach is not a cleaning agent
- Has sporicidal properties
- Does not have surfactant or detergent
- Has undesirable effects on most finishes over time

Isopropyl Alcohol (IPA)

- IPA is a disinfectant
- Does not have surfactant or detergent
- Is a disinfectant when applied immediately after cleaning
- Is a sanitizer when applied throughout the day but not immediately after cleaning

Cleaning Tools



- Material should be disposable
- Reusable tools MUST be
  - Cleanable
  - Cleaned before and after each use
  - Dedicated for use in the classified area or SCA
- Tools must be in good condition and replaced as needed

Cleaning the PEC (Table 8)

Cleaning

- Horizontal work surface at the beginning and end of each shift, after spills, and when surface contamination is known or suspected.
- Ceiling, walls, bars and any equipment inside the PEC on each day that compounding is performed and when contamination is known or suspected.

Disinfecting

- All interior surfaces of the PEC at the beginning and end of each shift, after spills, and when surface contamination is known or suspected.
- The horizontal work surface at least every 30 minutes while compounding if the compounding process takes 30 minutes or less.

Sporicidal Application

- Monthly

Cleaning the SEC and in the SCA Perimeter (Table 8)

Site	Cleaning	Disinfecting	Sporicide
Surface of sink	Daily	Daily	Monthly
Pass-through	Daily	Daily	Monthly
Work surface	Daily	Daily	Monthly
Floor	Daily	Daily	Monthly
Walls, doors	Monthly	Monthly	Monthly
Ceilings	Monthly	Monthly	Monthly
Storage	Monthly	Monthly	Monthly

Disinfecting the Critical Site

- Specifies sterile 70% IPA and wiping in one direction
- No mention of the type of wiper
  - Prep pads
  - Critical site wiper
- Revision reads as long as wiper is sufficiently wet, it can be used on multiple sites
- The critical site must be dry before puncturing the stopper/septum or breaking the necks of ampules.

Beyond Use Date

- Defined as…
  - Either the date or hour and date after which a CSP must not be used or administration must not begin.
  - The BUD is determined from the date/time that preparation of the CSP is initiated.
- Must be established based on Table 11 and Table 12 in the chapter
- Tables are based on microbial contamination risk, assuming the compound will be physically and chemical stable, and will maintain package integrity
- BUD must not exceed shortest remaining expiration date

Category 1 Requirements – no change from 2015

PEC placement	Not in ISO classified area
Sterility Testing	Not required
Endotoxin Testing	Not required
BUD	≤ 12 hours room temperature or ≤ 24 hours refrigerated

2015 Proposed Category 2

PEC placement	Placed in ISO classified air					
Sterility Testing	Based on BUD Assignment below					
Endotoxin Testing	Required if nonsterile components					
Storage	> 12 hour room temperature or > than 24 hours refrigerated					
BUD Assignment	***Method***	***Sterility Testing***	***Preservative Added***	***Controlled Room***	***Refrigerated***	***Frozen***
	Aseptically Prepared CSPs	***No***	***No***	Made from 1 or more non sterile components		
				4 days	7 days	45 days
				Made with sterile components		
				6 days	9 days	45 days
			Yes (USP 51)	28 days	42 days	45 days
		Yes	***No***	28 days	42 days	
			Yes (USP 51)	42 days	42 days	
	Terminally Sterilized CSPs	***No***	***No***	14 days	28 days	
			Yes (USP 51)	28 days	42 days	
		Yes	***No***	28 days	42 days	
			Yes (USP 51)	42 days	45 days	

2018 Proposed Category 2

*lowered from 2015 version

PEC placement	Placed in ISO classified air				
Sterility Testing	Based on BUD Assignment below				
Endotoxin Testing	Required if nonsterile components and if assigned a BUD that requires sterility testing				
Storage	> 12 hour room temperature or > than 24 hours refrigerated				
BUD Assignment	***Method***	***Sterility Testing***	***Controlled Room***	***Refrigerated***	***Frozen***
	Aseptically Prepared CSPs	***No***	Made from 1 or more non sterile components		
			1 days*	4 days*	45 days
			Made with sterile components		
			4 days*	9 days	45 days
		Yes	30 days	45 days	60 days
	Terminally Sterilized CSPs	***No***	14 days	28 days	45 days
		Yes	45 days	60 days	60 days

Achieving Sterility

Aseptic Preparation

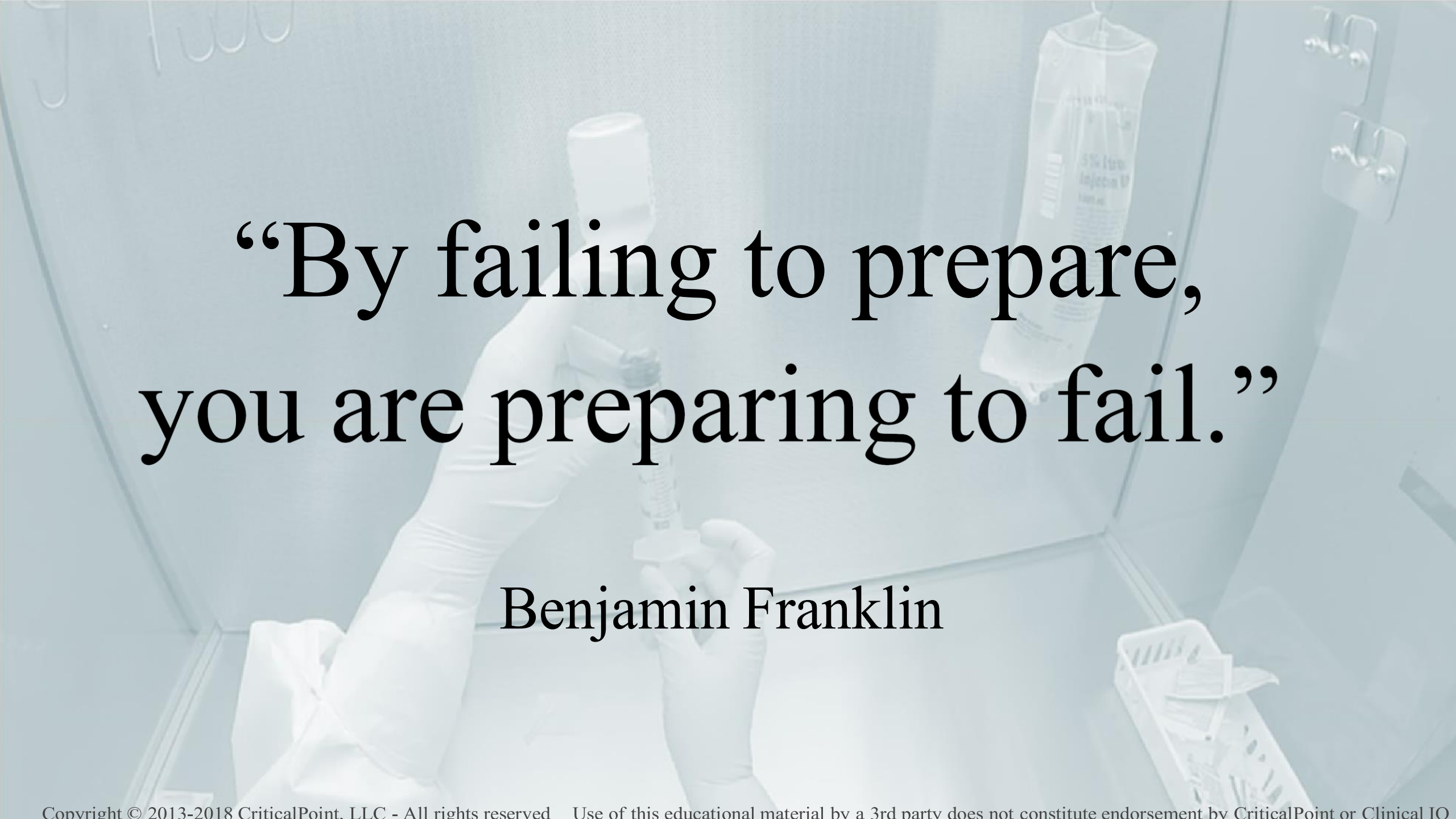
- Compounding with only sterile starting ingredient(s), or
- Compounding with nonsterile ingredient(s) followed by sterilization by filtration

Terminal Sterilization

- Compounding with sterile and/or nonsterile starting ingredient(s) and subsequent sterilization
- *CSP sterilized in its final container*
- The process is intended to achieve an Sterility Assurance Level (SAL) of 10^{-6}
- Dry heat, steam, or irradiation

Sterility Testing

- Table 12 indicates whether sterility testing is needed
- Testing done according to USP Chapter <71>
- Deviations from the batch size are now allowed
  - If between 1 and 39 CSPs are compounded in a single batch, the sterility testing must be performed on a number of units equal to 10% of the number of CSPs prepared, rounded up to the next whole number.
  - If 1 is compounded, 1 additional would be prepared.
- 40 or more in a single batch follows <71>



"By failing to prepare, you are preparing to fail."

Benjamin Franklin

Personnel Qualifications

- Category 1 and Category 2 requirements are the same

Requirement	Frequency
Visual observation of hand hygiene and garbing	Every 6 months
Gloved fingertip and thumb sampling	Every 6 months
Media fill testing	Every 6 months
Requalification	Every 12 months

Requalification includes the demonstration of core competencies.

Other Personnel

- Training is not just for compounders
- Other personnel handling CSPs or accessing the compounding area
- Must demonstrate competency in proper behavior to maintain the environment