



# **Cleaning the Compounding Pharmacy – Understanding Contaminants and How to Remove Them**

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## **USP <797> and You**

### **<797> Pharmaceutical Compounding—Sterile Preparations**

This General Chapter provides procedures and requirements for compounding sterile preparations. General Chapter <797> describes conditions and practices to prevent harm to patients that could result from microbial contamination, excessive bacterial endotoxins, variability in intended strength, unintended chemical and physical contaminants, and ingredients of inappropriate quality in compounded sterile preparations.

[www.usp.org](http://www.usp.org)



## Maintaining Compounded Preparation Quality Through SOP's and Cleaning Process Control

The quality of any compounded sterile preparation (CSP) is the end result of every one of many individual processes functioning correctly at all times.

Failure and disaster occurs when processes do not consistently produce their intended outcomes.



## Cleaning the Compounding Pharmacy (CP)

1. The C P environment
2. Sources and types of contamination
3. Considerations for contaminant removal
4. Why clean?
5. Wipe considerations and selection
6. Using the right tools effectively
7. Disinfectants, sterilants, and proper use of solutions
8. Cleaning verification



## The Compounding Pharmacy (CP) Environment



## Compounding Pharmacy (CP) Environment





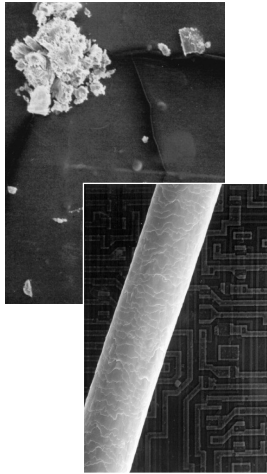
## Compounding Pharmacy (CP) Environment



## Sources and Types of Contaminants



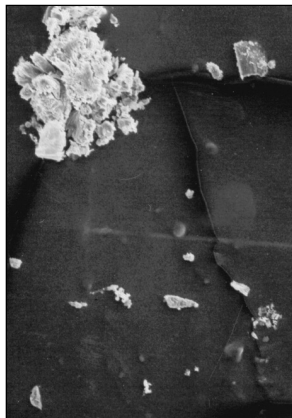
## C P Contaminants



- Particles
- Fibers
- Residues, films, and coatings
- Biological / molecular



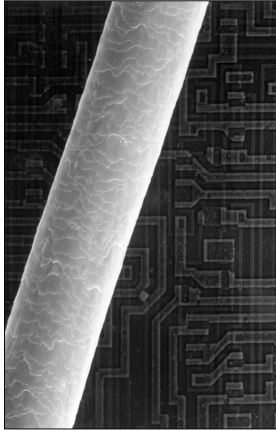
## C P Contaminants



- Particles
- A solid object that, as a general rule, measures from 0.0001 to 1000 micrometers (microns;  $\mu\text{m}$ ) in size



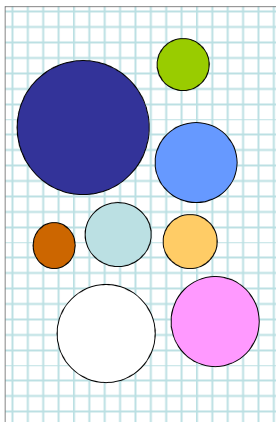
## C P Contaminants



- Fibers
- A solid object with an approximate length to width ratio of 10 : 1



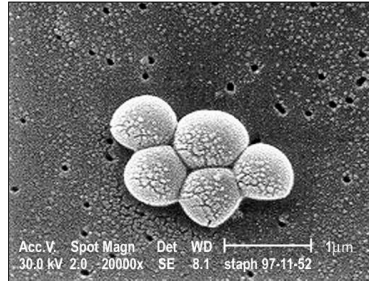
## C P Contaminants



- Residues, films, and coatings



## C P Contaminants

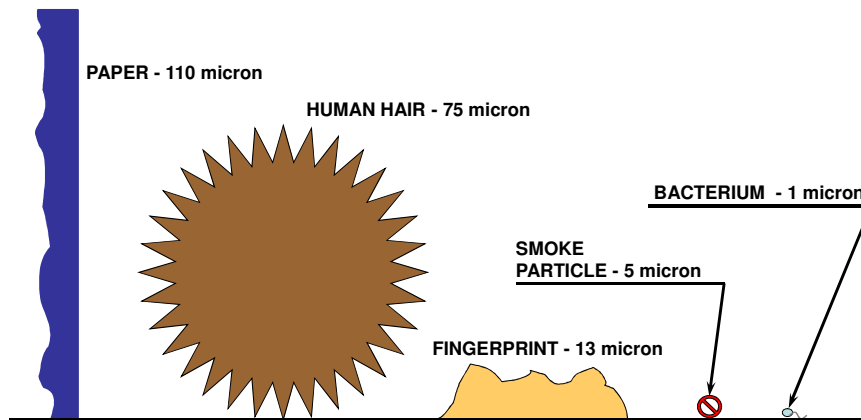


- Biological / molecular
- Contaminants that are, or once were, a living organism
- “Viable” organisms are still alive; “non-viable” are not



## C P Contaminants

- How small is *small* ?





## Sources of Contamination

- **People** are the greatest source of contamination
- Other sources include process contaminants and materials brought into the C P



## People Contaminants

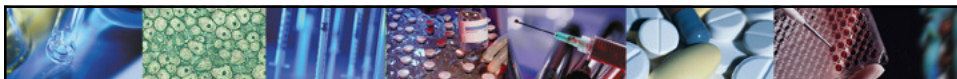
- Particle contaminants
  - Dust from clothes and body, hair, exhaled smoke particles
- Organic contaminants
  - Skin oils, skin flakes, saliva
- Microbial contaminants
  - Viruses, spores, bacteria, pyrogens





## Particles Travel

Activity	Distance	Velocity
Talking	0.6 – 1.0 meter	
Coughing	1.2 – 1.8 meters	
Sneezing	3.0 – 4.5 meters	300 km/hour



## Bacteria on Skin

- 1,000,000 bacteria live on 1 cm<sup>2</sup> skin
- We shed 1,000 bacteria carrying particles each minute



## Considerations for Contaminant Removal



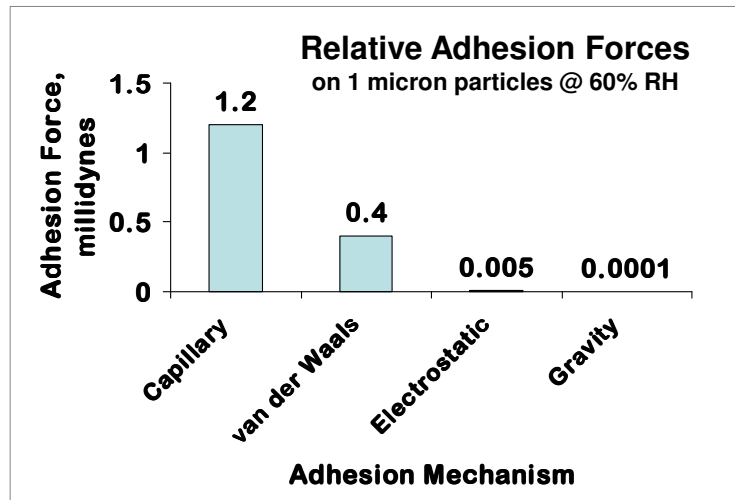
## Considerations for Contaminant Removal

### Particle Adhesion Mechanisms

- There are four mechanisms that hold particles to a surface:
  1. Gravity
  2. Electrostatic forces
  3. van der Waals (atomic) forces
  4. Hydroscopic, or capillary forces



## Particle Adhesion Mechanisms



## Particle Adhesion Mechanisms

- Particles are held to surfaces by a variety of forces
- These forces vary according to many factors including particle size and shape, surface texture, and humidity
- Small particles are more tightly held than large particles
- Removal of small particles requires force greater than that holding the particles



## Why Clean?



## Why Clean?

- Prevent product contamination
- Need to clean particles and residues we can see and those we cannot see
- Cleaning is the most important step to successful disinfection
- Residues and buildup can interfere with disinfecting agents
- Required by USP <797>



## USP <797> Cleaning Requirements

Minimum Cleaning Frequency of Cleaning and Disinfecting Compounding Areas	
Site	Minimum Frequency
ISO Class 5, Primary Engineering Control (e.g. LAFW, BSC, CAI, CACI)	-At the beginning of each shift before each batch, not longer than 30 minutes following the previous surface disinfection when ongoing compounding activities are occurring -After spills, and when surface contamination is known or suspected
Counters and easily cleanable work surfaces	Daily
Floors	Daily
Ceilings	Monthly
Storage Shelving	Monthly

\*USP <797> "Pharmaceutical Compounding: Sterile Preparations" 2008, US Pharmacopoeia, Rockville, MD

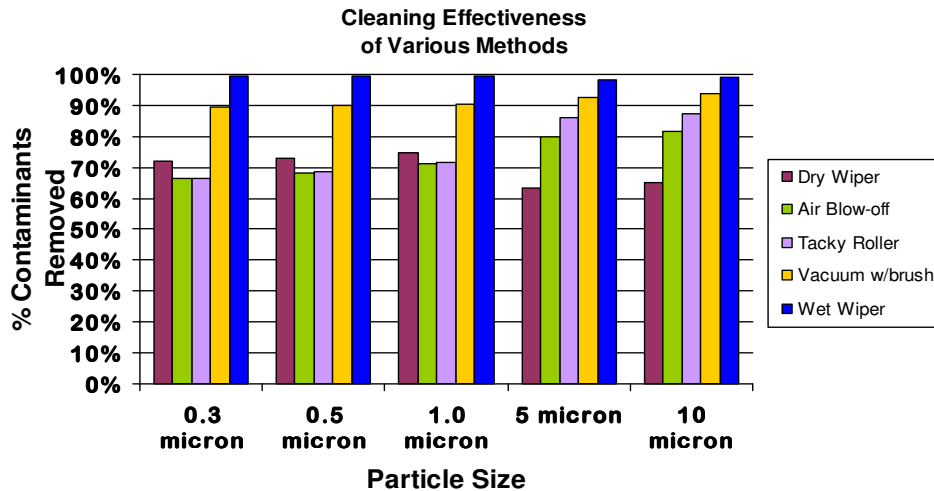


## Cleaning Methods and Consistency

- An effective cleaning method must remove as much of the unwanted contaminants as possible.
- An effective cleaning method must be as consistent and repeatable as possible.



## Contaminant Removal

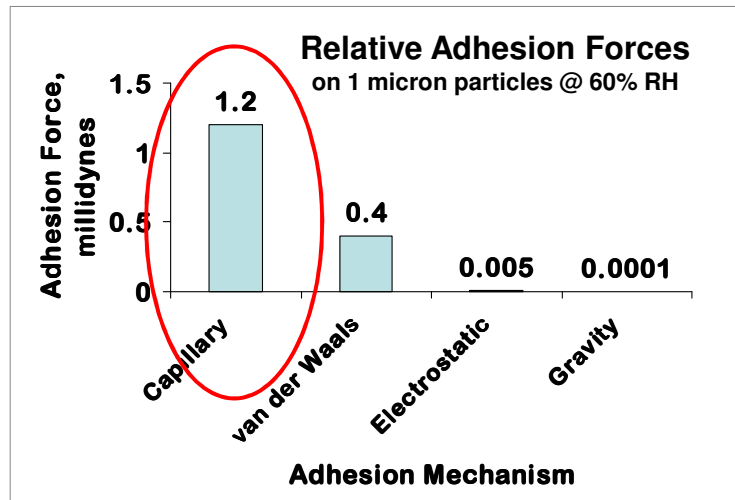


## Contaminant Removal

Comparison of cleaning methods shows wiping to be the most effective way to control contamination on surfaces.



## Particle Adhesion Mechanisms



## Dry vs. Presat wipes

Studies have shown that a specific level of wipe saturation provides the optimum surface cleaning performance and effectiveness

- Increases wiping consistency
- Reduces solvent usage
- Increases operator safety
- Very convenient





## Wipe Considerations and Selection



### What type of wipe

- USP <797> requires the following characteristics of wiping products:
  - “All cleaning materials, such as wipes, sponges, and mops, shall be nonshedding, preferably composed of synthetic micro fibers, and dedicated to use in the buffer or clean area, ante-area, and segregated compounding areas and shall not be removed from the areas except for disposal”
- USP <797> “Pharmaceutical Compounding: Sterile Preparations” 2008, US Pharmacopoeia, Rockville, MD Table 3, page 28





## What is Non-Shedding?

- Non-shedding typically means large visible gross contamination (i.e. paper towels)
- Fibers- small ( $\sim 100 \mu$  particles) that are visible with microscope
- Particles are very small and are measured at  $0.5\mu$



## Considerations for Wipe Selection

### Wipe cleanliness

- Wipe cleanliness is critical to minimizing deposition of new contaminants onto surfaces during wiping
- There is no such thing as a contaminant-free wipe
- Wipes made of synthetic fibers are generally much cleaner than wipes made of natural fibers



## Variables That Impact Wipe Characteristics

### **Material**

- Synthetic, natural, or blended fibers

### **Construction**

- Knitted, nonwoven, woven

### **Conversion**

- Cut or sealed edges

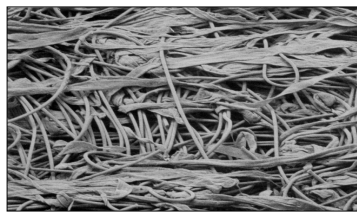
### **Treatments**

- Sorbency enhancers

### **Laundering**



## Wipe Materials and Construction



Nonwoven Polyester/cellulose



Nonwoven Polyester



Polyester/nylon Microfiber



Knitted Polyester Monofilament



## Determining Wipe Cleanliness

### Wipe cleanliness

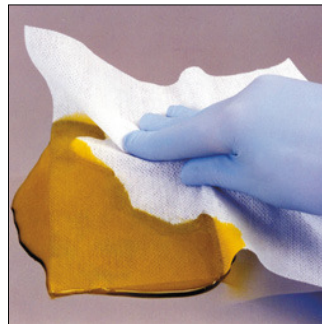
- Several test methods exist to determine the cleanliness of wipes
  - Institute of Environmental Sciences and Technology (IEST)
  - Manufacturers' test methods
  - End-user test methods
- Wipes are typically tested for:
  - particles and fibers
  - nonvolatile residues (NVR)
  - metallic and other ions
  - sorbency



## Comparison of Wipe Types

Particle evaluation of two leading gauze products vs. a Nonwoven Polyester/cellulose Wipe

- Medline Gauze, 0.5 $\mu$  particles:
  - 394 million/m<sup>2</sup>
- Caring Gauze, marketed as "lint-free", 0.5 $\mu$  particles:
  - 104 million/m<sup>2</sup>
- Nonwoven polyester/cellulose wipe, 0.5 $\mu$  particles:
  - 13.5 million/m<sup>2</sup>



- Test method: IEST-RP-CC004.2 Sec 5.1



## Considerations for wipe Selection

### Contaminant redeposition

- Redeposition of contaminants occurs when the wipe cannot retain the contaminant, whether particle or residue
- Oversaturation of the wipe is a primary cause of contaminant redeposition
  - Liquid left on a surface contains particulate and residual contamination
- Wipe substrate has great influence on redeposition
  - Particle entrapment ability
  - Sorbency



## Considerations for wipe Selection

### Sorbency

- Sorbency is the ability of a wipe to sorb liquids - either into the fibers themselves (absorb) or into the structure of the wipe (adsorb)
- Sorbency is critical for liquid removal
  - spill pickup
  - minimizing redeposition of contaminants by not leaving liquid on the wiped surface
- Wipes made with natural fibers have better sorbency than synthetic fiber wipes, but are not as clean

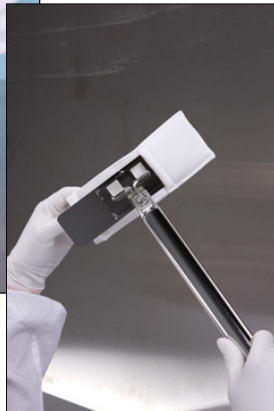
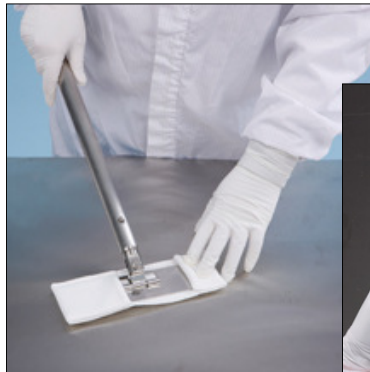


## ISO Class 5 - Laminar Air Flow Hoods, BSCs

Type of Wipe	<797> Requirement	Good	Better	Best
Wipes – dry (spill control, applying and removing solutions)		Nonwoven polyester/cellulose wipes	Knitted polyester wipes	Knitted polyester wipes, STERILE
Wipes – presaturated (general and routine cleaning)	Non-shedding wipes and sponges	Nonwoven polyester/cellulose wipes, presaturated with 70%IPA 30% DIW	Knitted polyester wipes, presaturated with 70%IPA 30% DIW	Knitted polyester wipes, STERILE, presaturated with 70%IPA 30% DIW
Mopping tools (Enclosure sides and top)	Non-shedding mops	Hand-held tools that enable reach, easy contact, and effective cleaning of all areas within an enclosure (LAFW, BSCs, fume hoods, etc.).		



## Tools for Cleaning Enclosures





## ISO Class 7 & 8 -Buffer Zone/Ante Area

Type of Wipe	<797> Requirement	Good	Better	Best
Wipes – dry	Non-shedding wipes and sponges	Nonwoven polyester/cellulose wipes	Knitted polyester wipes	Knitted polyester wipes, STERILE
Wipes – presaturated		Nonwoven polyester/cellulose wipes, presaturated with 70%IPA 30% DIW	Meltblown polypropylene wipes, presaturated with 70%IPA 30% DIW	Knitted polyester wipes, presaturated with 70%IPA 30% DIW
Mopping tools, for floors and walls	Non-shedding mops	Commercial flat or string style mops WITHOUT cotton or cellulose, PLUS a bucket/wringer system	Engineered flat or string style mops, PLUS a coordinated bucket/wringer system	Engineered flat or string style mops, PLUS a coordinated TWO bucket/wringer system



## Using the Right Tools Effectively



## Using the Right Tools Effectively

### Wiping and Mopping of CP Surfaces

- General rules
- Wiping methods
- Mopping methods
- Special considerations



## SOPs

- Standard Operating Procedures
  - Describe in detail the procedures, behaviors, practices, and tools to be followed and used in order to achieve a desired and expected outcome.
  - Describe activities necessary to respond to normal and abnormal situations in an operating system.
  - They describe normal operation, maintenance, and cleaning of the system, as well as normal operating parameters.



## Aseptic (sterile) Considerations

- Compounding pharmacies have unique challenges in creating and maintaining sterile environments
- Cleaning products used in aseptic areas must be sterilized, or provided sterile (or irradiated) by the supplier
- Products that are validated sterile provide greater assurance of sterility and simplify Standard Operating Procedures (SOP's)



## Using the Right Tools Effectively

### Pull and Lift Technique

Ensures most effective removal of contaminants

**LIFT  
while  
PULLING**

Start of  
Stroke

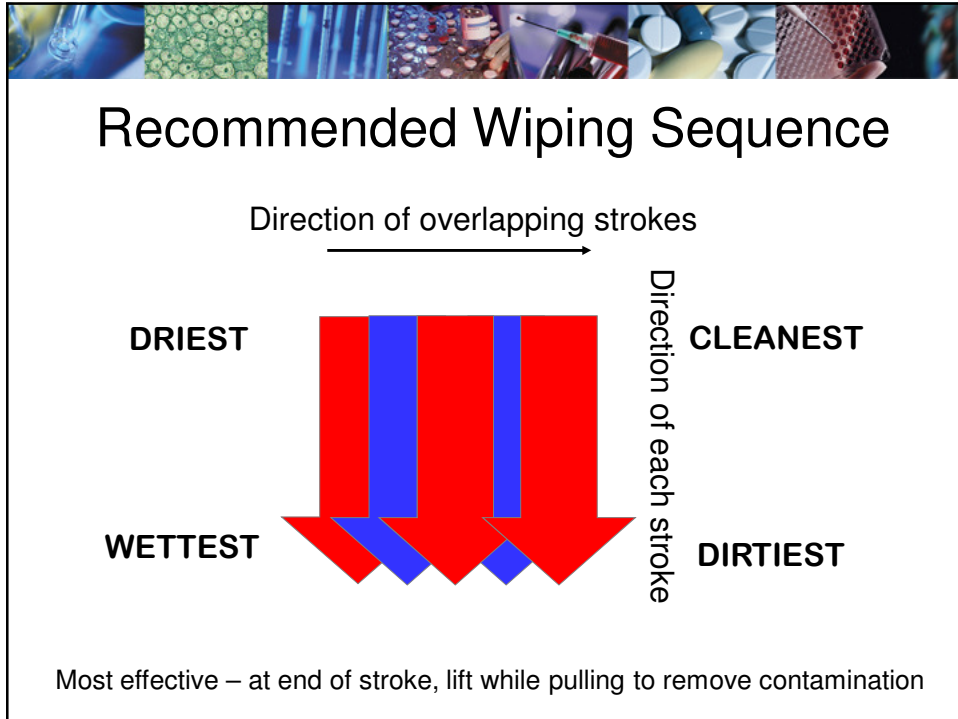
**PULL**

End of  
Stroke



Surface

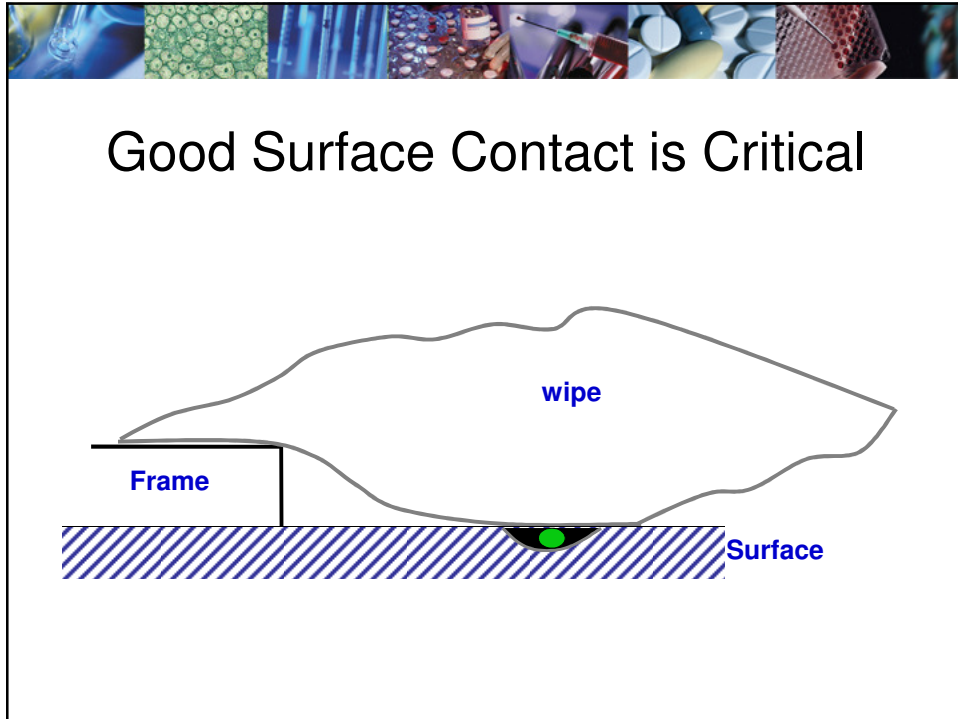




## Using the Right Tools Effectively


Special situations:

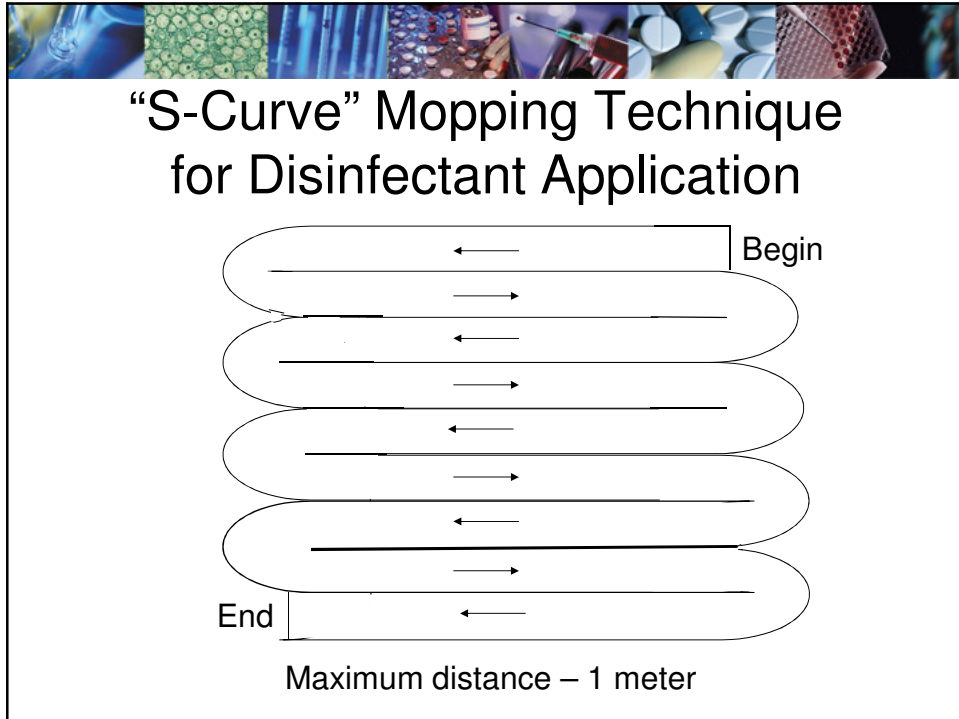
- Difficult features and areas
- Workstations with stationary equipment
- Mini-environments/ Isolators / hoods



## Floor Cleaning

- Place mop on the floor, and pull towards operator. This allows contaminants to be removed and prevents operator from walking on clean floor.
- Lift and move so next stroke is starts adjacent to and overlapping the first stroke
- Rinse if necessary





## Wall Cleaning & Disinfecting Method

- Begin at ceiling
- Work in vertical lines towards floor
- First clean with damp mop using overlapping strokes
- Follow with wet mopping to apply disinfectant





## Using the Right Tools Effectively

### Summary

- Choosing the right materials for cleaning involves many factors including cleanliness requirements of the environment, cleanliness of the materials to use, activities within the environment, contaminants to be removed, surfaces to clean, and cost.
- Following a few general rules provides a key to effective cleaning
- The cleaner the solution, the cleaner the surface



## Disinfectants, Sterilants, and Proper Use of Solutions



## Disinfectants, Sterilants, and Proper Use of Solutions

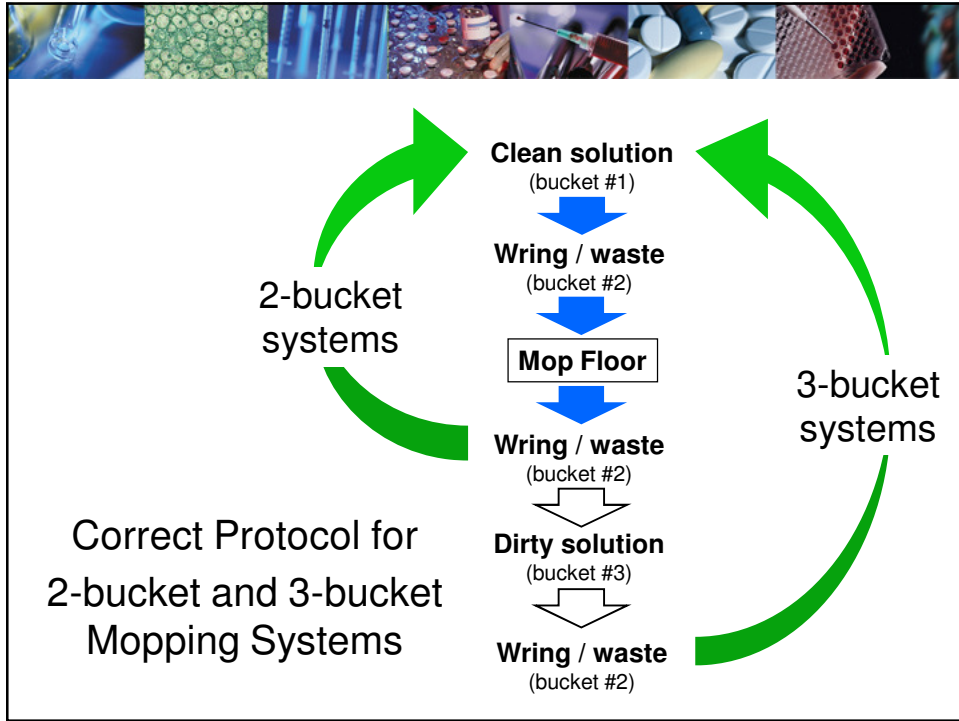
Disinfectants and other solutions  
used will be determined by the ICN  
or similar authority regarding  
biologic control



## Using Solutions Effectively

### Keeping Solutions Clean

- Disinfectants and other solutions used will be determined by the ICN or similar authority regarding biologic control
- Solutions can be water/detergent blends or disinfectants and are used in many different applications
- Frequency of solution changes is critical to creating and maintaining a clean and safe CP environment



# Cleaning Verification



## Cleaning Verification

- Visual
- Room particle counts
- Surface sampling
- Product contamination



## Cleaning Verification

- Visual
  - Visual inspection of cleaning effectiveness may be adequate for many clean areas or uncontrolled areas
  - Visual inspection can be used to determine if gross cleaning was completed



## Cleaning Verification

- Particle Counts
  - Particle counts of an area or a room are often used to determine the effectiveness of cleaning
  - Historical data also serve as a benchmark to determine if the room is as clean as required



## Cleaning Verification

- Particle Counts
  - Particle counting is a reliable method of checking for microscopic particles
  - In house staff may conduct periodic checks to catch unknown contamination





## Cleaning Verification

- Surface Sampling
  - This method can be used to check for unwanted biological contamination as well as other cross contamination from previously produced product
  - Samples can be taken with swabs or witness plates
  - These can be analyzed in house or by an outside lab



## Nonviable Particle Testing

Test Method	Particle Size
Visual wipe test	>50 $\mu\text{m}$
Ultraviolet light inspection	>20 $\mu\text{m}$
High-intensity white light inspection	>20 $\mu\text{m}$
Surface cleaning efficiency test	>20 $\mu\text{m}$
Counting and sizing particles with an optical microscope	>5 $\mu\text{m}$
Automated particle fallout (optical)	>5 $\mu\text{m}$
(laser)	>0.2 $\mu\text{m}$
Surface particle detector method	>0.3 $\mu\text{m}$



## Viabile Monitoring

- Air
- Surfaces
- Gloves
- Garments
- People



## Cleaning Verification

- Summary
  - Verification of cleaning is a must
  - This may be accomplished visually, with particle counters, through surface sampling, and by using process indicators
  - This process can prevent shutdowns from unforeseen events or allow you to track down contamination before it causes a problem



## **Summary**

**Compounding a safe and effective drug in a controlled (CP) environment involves much more than simply compounding the drug correctly.**

**In order to ensure both the quality of the compounded drugs and patient safety, every process and system must work correctly and consistently.**



## **Summary**

**These processes include the facility, the cleaning tools, solutions, and the pharmacists and assistants themselves.**

**Strict adherence to approved SOP's, combined with consistent quality tools, is critical to compounding success and maximizing patient health and safety.**



## Compounding Pharmacy (CP) Environment



**Thank You**