Maintaining Product Quality Through SOP's and Cleaning Process Control

Presented by

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Contec, Inc.

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Maintaining Product Quality Through SOP's and Cleaning Process Control

Product quality 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.

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Maintaining Product Quality Through SOP's and Cleaning Process Control

1. Why cleanliness is critical
2. The cleanroom environment
3. Sources and types of contamination
4. Considerations for contaminant removal
5. Using the right tools effectively
6. SOP's and verification

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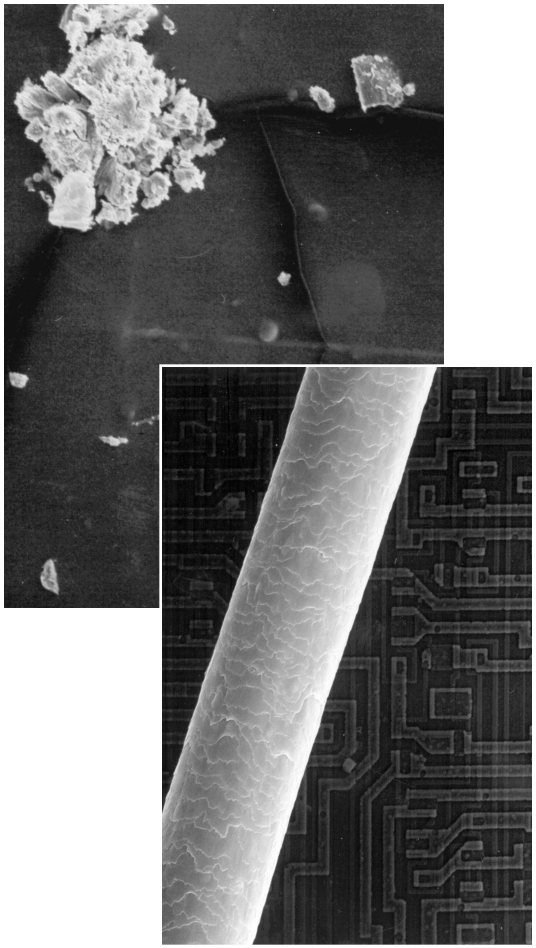
Why Cleanliness is Critical

- Prevent product contamination
  - Product quality
  - Manufacturing yield
  - Product performance
  - Health and safety
- Cleaning is the most important step to successful sanitation
- Residues and buildup can interfere with disinfecting agents

The Cleanroom Environment

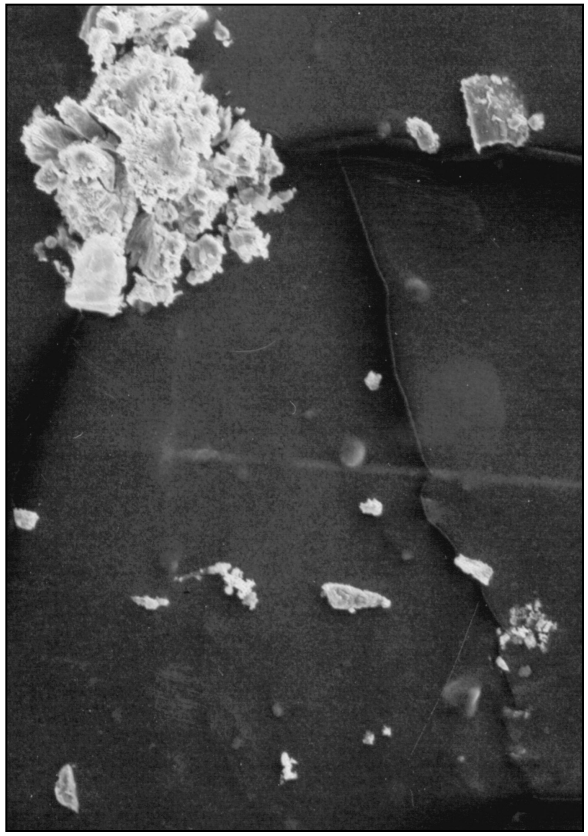
ISO Designation		FDA Clean Area Classification	FDA Microbiological	FDA Microbiological	EU Classification	
Class	> 0.5 µm particles/m^3	> 0.5 µm particles/ft^3	Active Air Action Levels (cfu/m^3)	Settling Plates Action Levels (diam. 90mm; cfu/4 hours)	At Rest Grade/ 5 µm particles/m^3	Operational Grade/ 5 µm particles/m^3
5	3,520	100	1	1	A / 1 B / 1	A / 1
6	35,200	1,000	7	3		
7	352,000	10,000	10	5	C / 2,000	B / 2,000
8	3,520,000	100,000	100	50	D / 20,000	C / 20,000

Cleanroom Contaminants



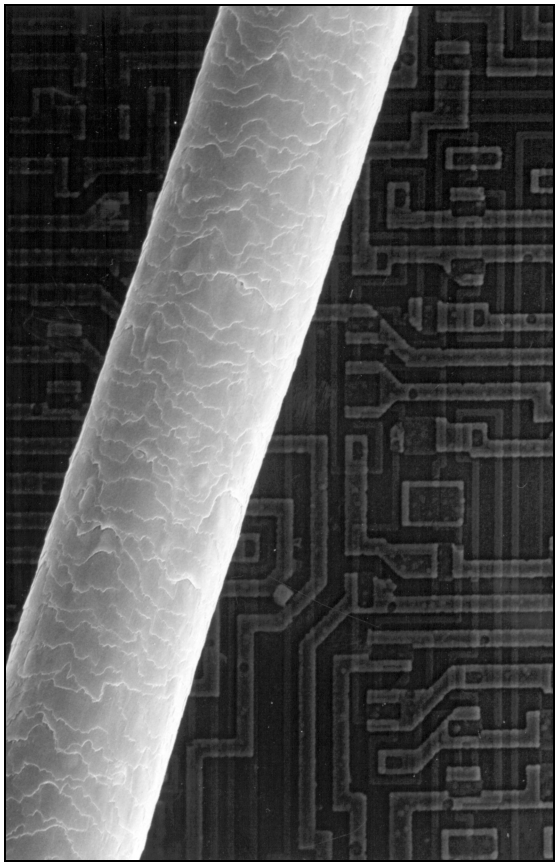
- Particles
- Fibers
- Residues, films, and coatings
- Biological / molecular

Cleanroom Contaminants



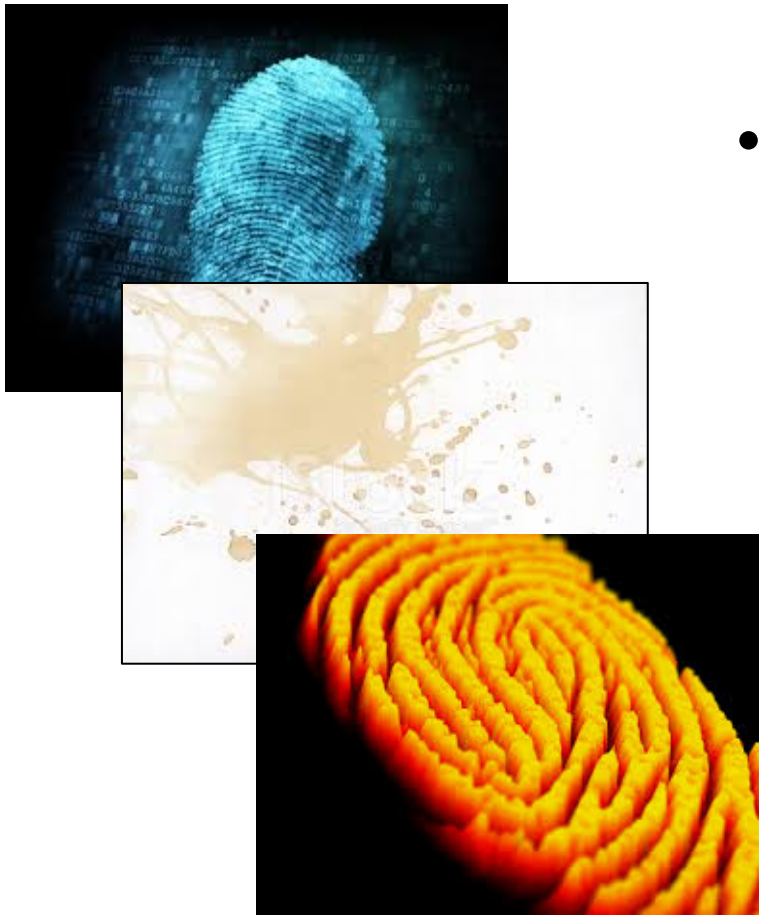
- Particles
- A solid object that, as a general rule, measures from 0.0001 to 1000 micrometers (microns; μm) in size

Cleanroom Contaminants



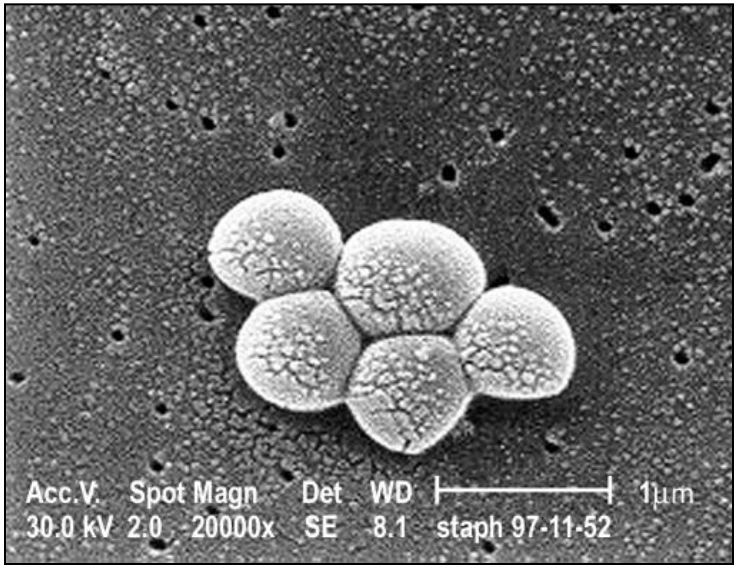
- Fibers
- A solid object with an approximate length to width ratio of 10 : 1

Cleanroom Contaminants



- Residues, films, and coatings

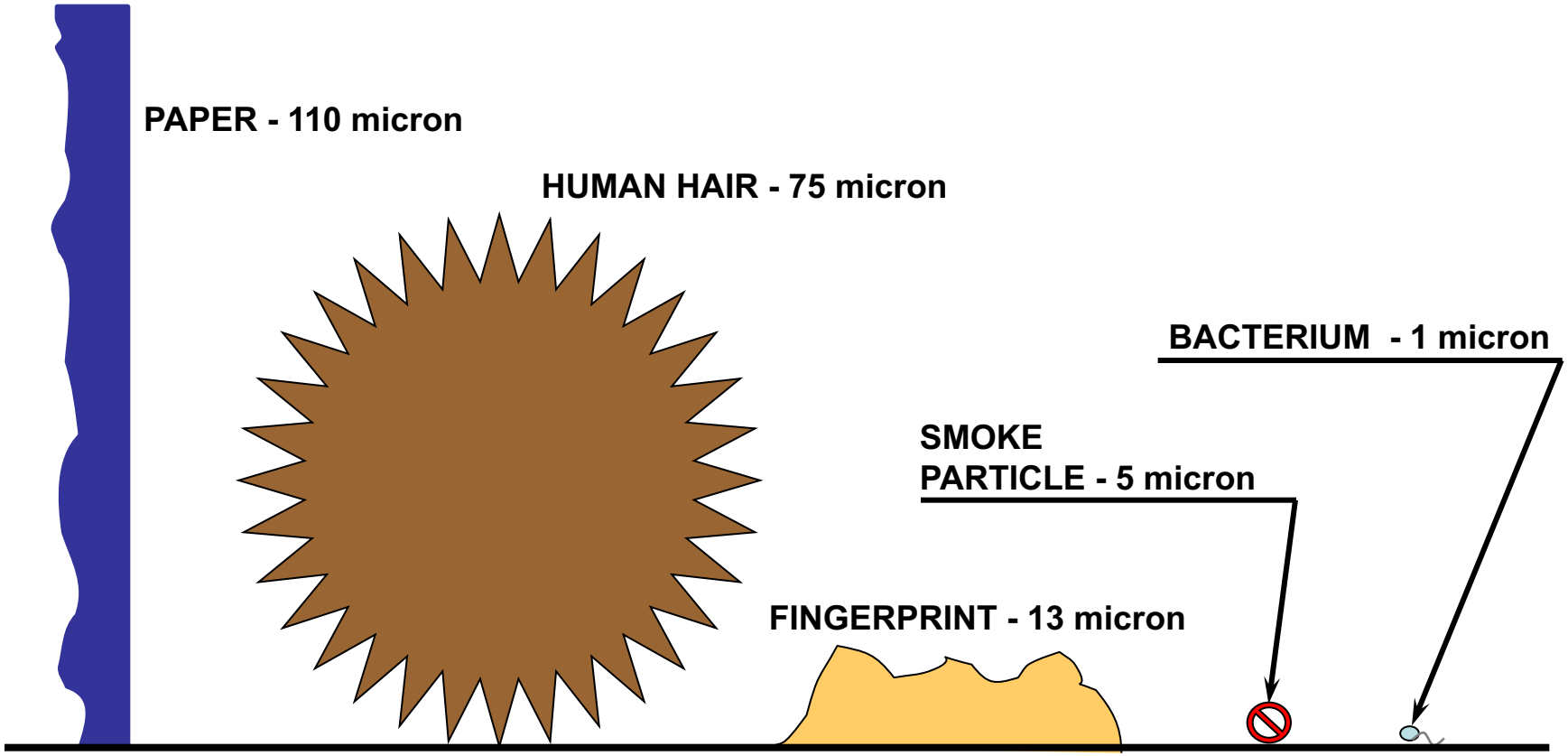
Cleanroom Contaminants



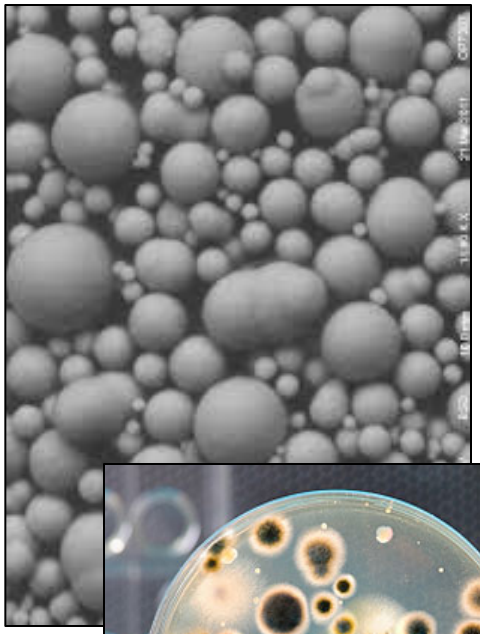
- Biological / molecular
- Contaminants that are, or once were, a living organism
- “Viable” organisms are still alive; “non-viable” are not

Cleanroom Contaminants

- How small is *small* ?



The Challenge of Clean Manufacturing



- We need to clean particles and residues we *can* see and those we *cannot* see

Sources of Contamination

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

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^2 skin
- We shed 1,000 bacteria carrying particles each minute

Particle Adhesion Mechanisms

- The more we understand particle behavior, the better we understand how to control contamination

"Know Thy Enemy"

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

Gravity

- adhesion force from gravity depends only on the mass of the object or particle
- for particles less than 100 microns in size, gravity is not the strongest force holding the particles to a surface

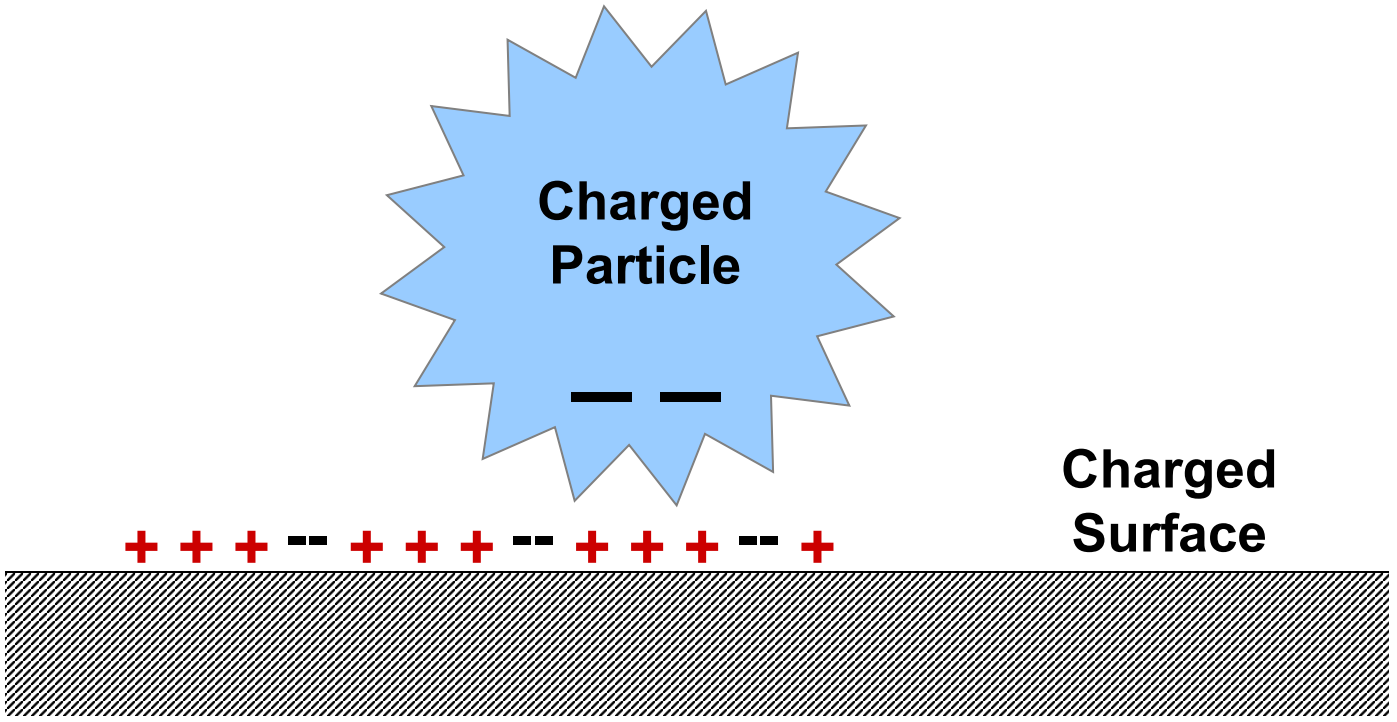
Particle Adhesion Mechanisms

Electrostatic forces

- electrostatic forces can both attract and hold a particle to a surface
- electrostatic forces decrease with increased humidity
- electrostatic forces may be minimized through use of static elimination devices
- electrostatic forces are not the most dominant forces holding a particle to a surface

Particle Adhesion Mechanisms

Adhesion by Electrostatic Forces



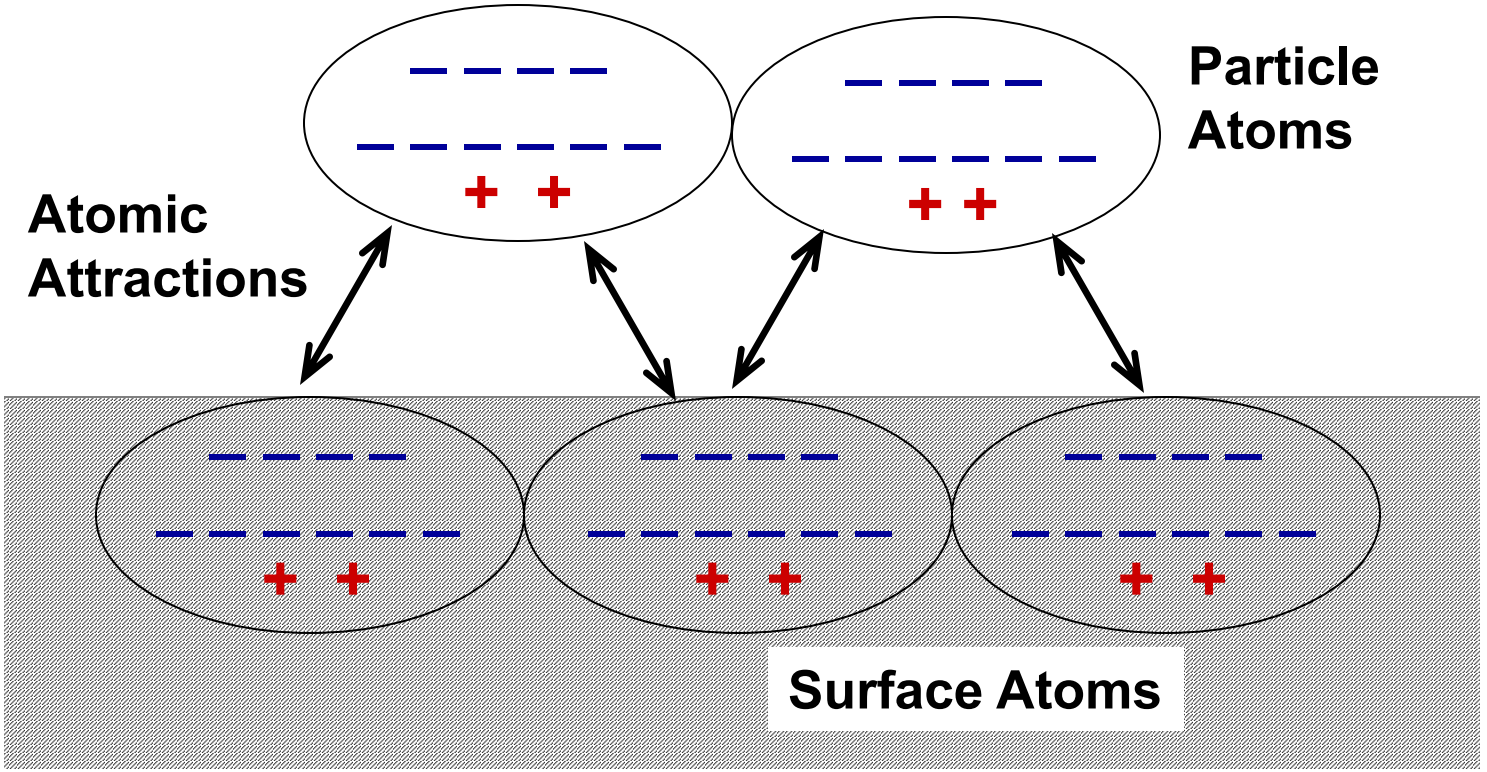
Particle Adhesion Mechanisms

Van der Waals forces

- caused by attraction of unevenly grouped electrons in the atoms of the particle and the surface
- also called “intermolecular” forces
- these forces come into play when the particle is very near the surface
- van der Waals forces are independent of humidity and static
- one of the two most dominant forces holding small particles to a surface

Particle Adhesion Mechanisms

Adhesion by van der Waals Forces



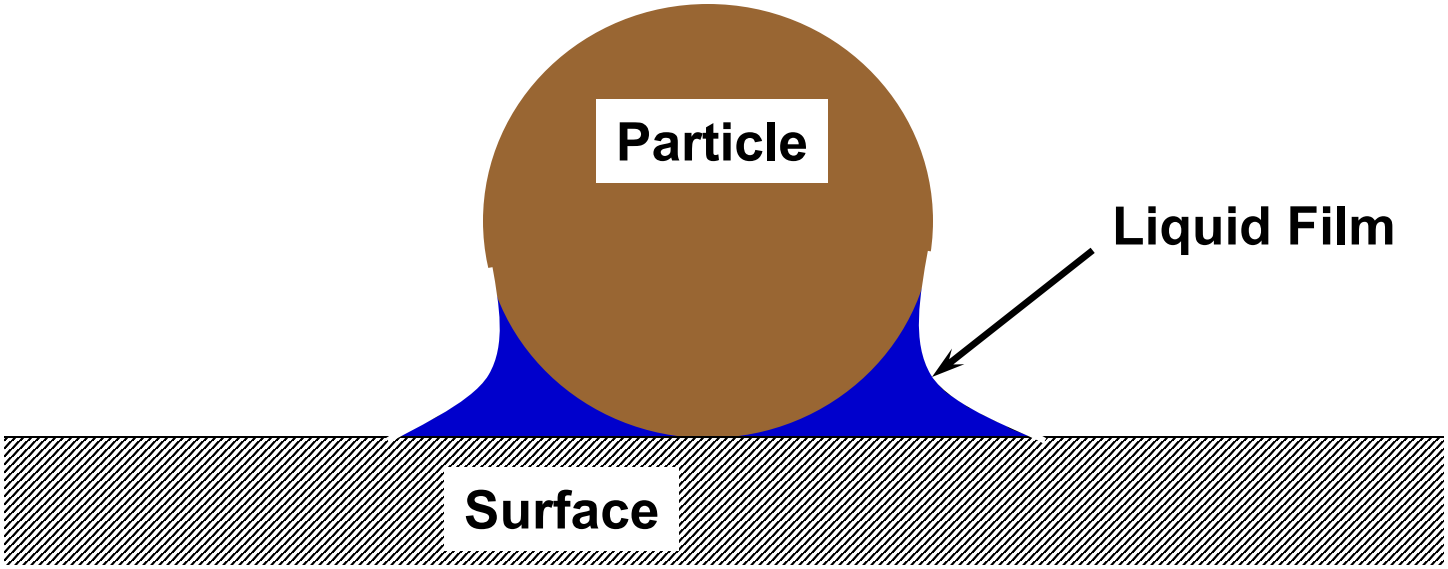
Particle Adhesion Mechanisms

Hydroscopic forces

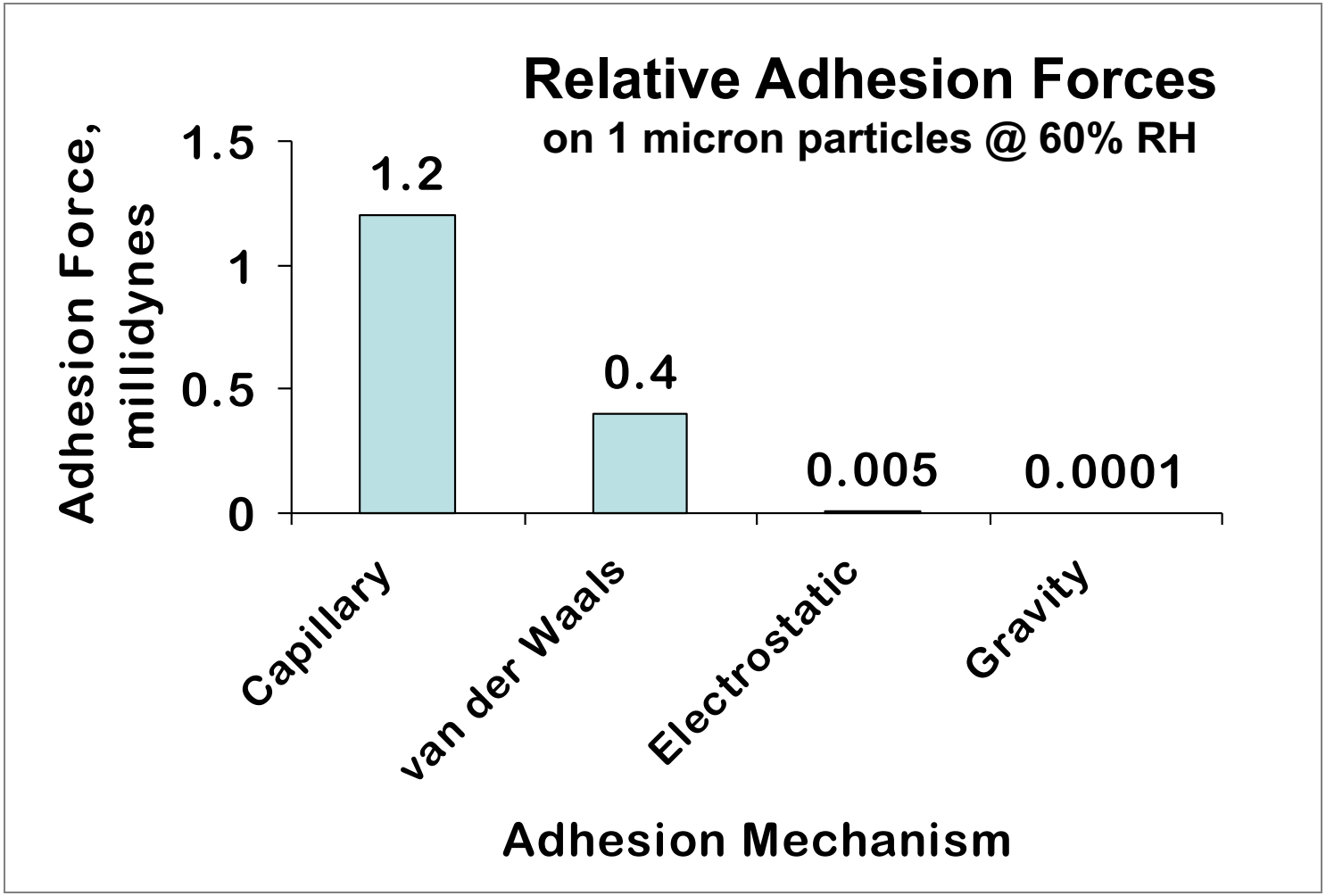
- also called capillary forces
- caused by thin liquid layer between a particle and a surface
- adhesion increases with contact area of particle with surface - large, flat particles, and long thin fibers adhere more strongly
- capillary force increases with humidity or the presence of other liquid vapor on the surface

Particle Adhesion Mechanisms

Adhesion by Hydroscopic Force



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

Process Fact #1

The cleanroom is part of the process.

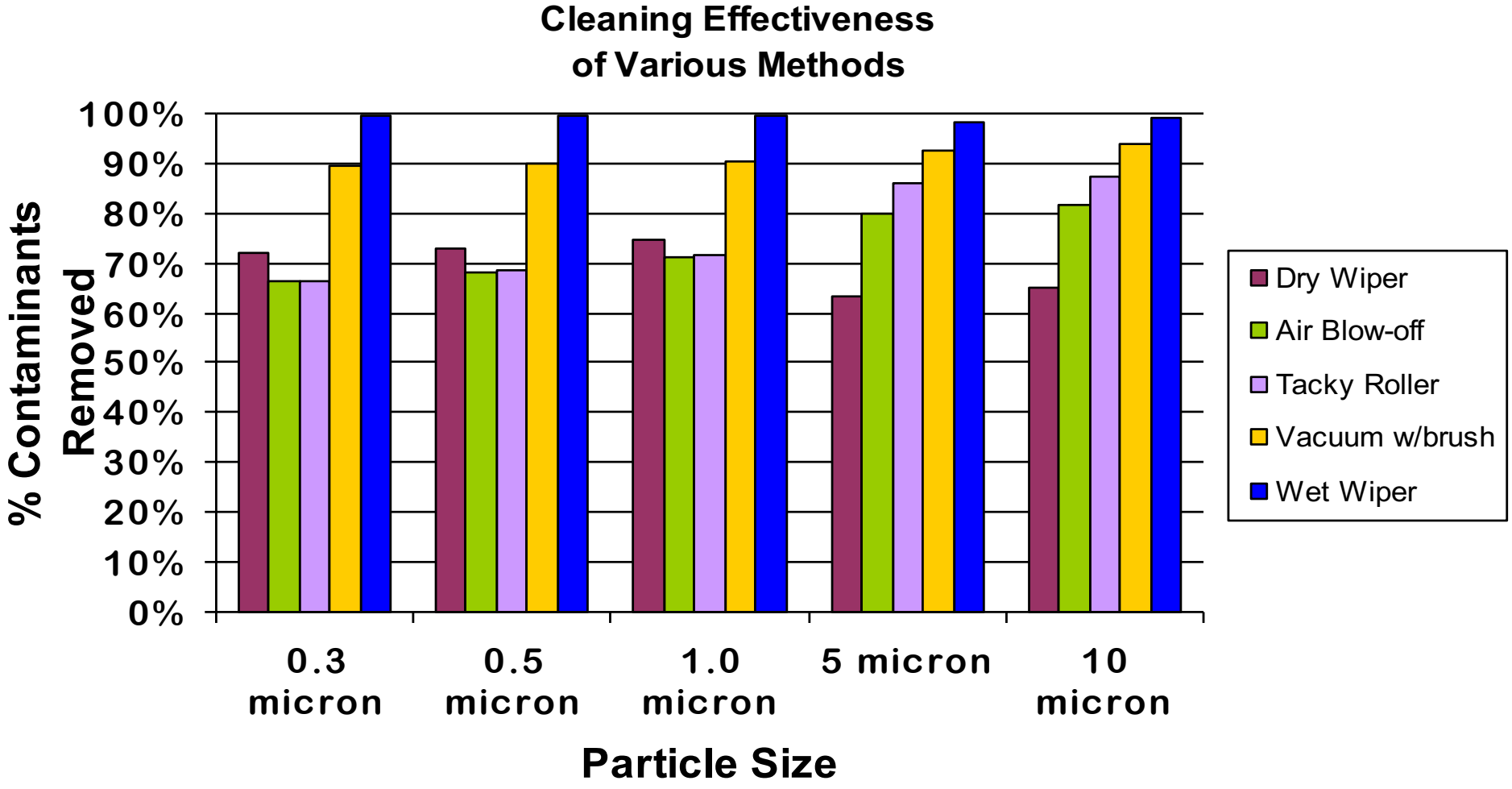
Variation or deficiency in environmental conditions will result in failure and disaster.

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.

Hand wipe cleaning

Wall and ceiling mopping

Floor mopping

Using the Right Tools Effectively

Effective Wiping and Mopping

- General rules
- Wiping methods (demonstration)
- Mopping methods (demonstration)
- Keeping solutions clean

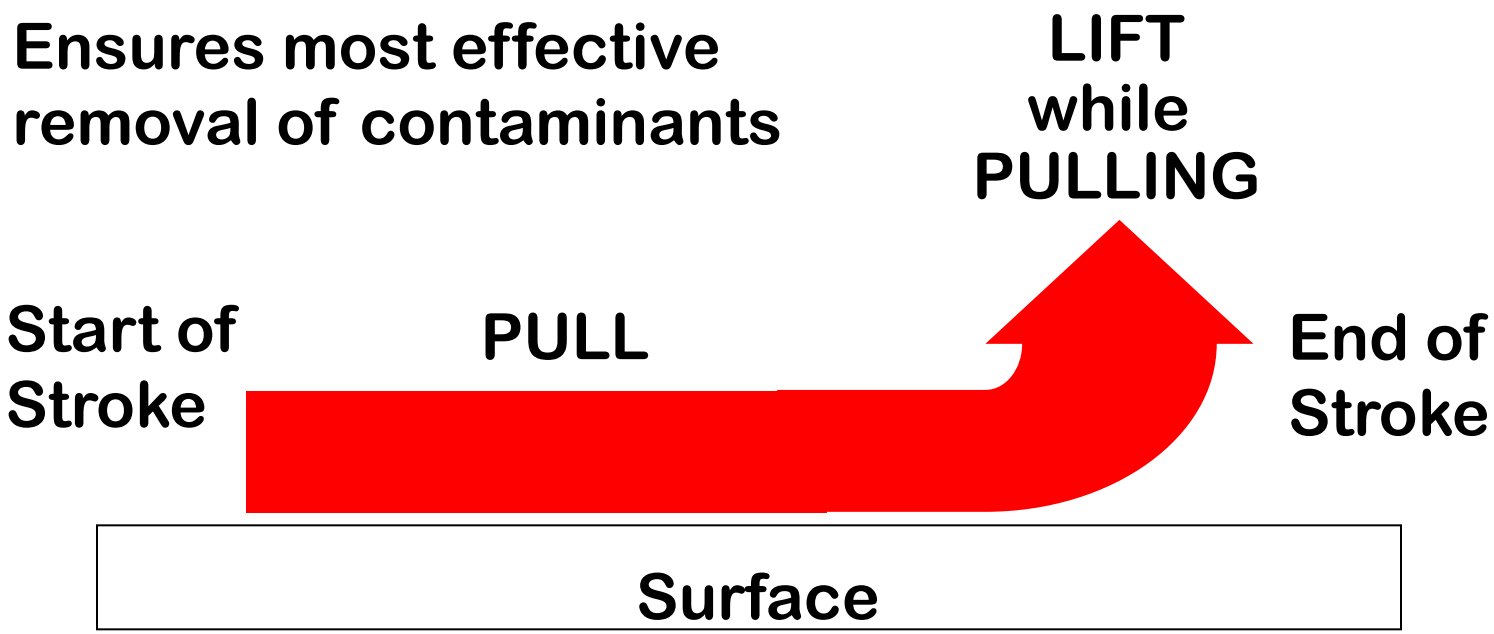
Important

Always follow your company's SOPs

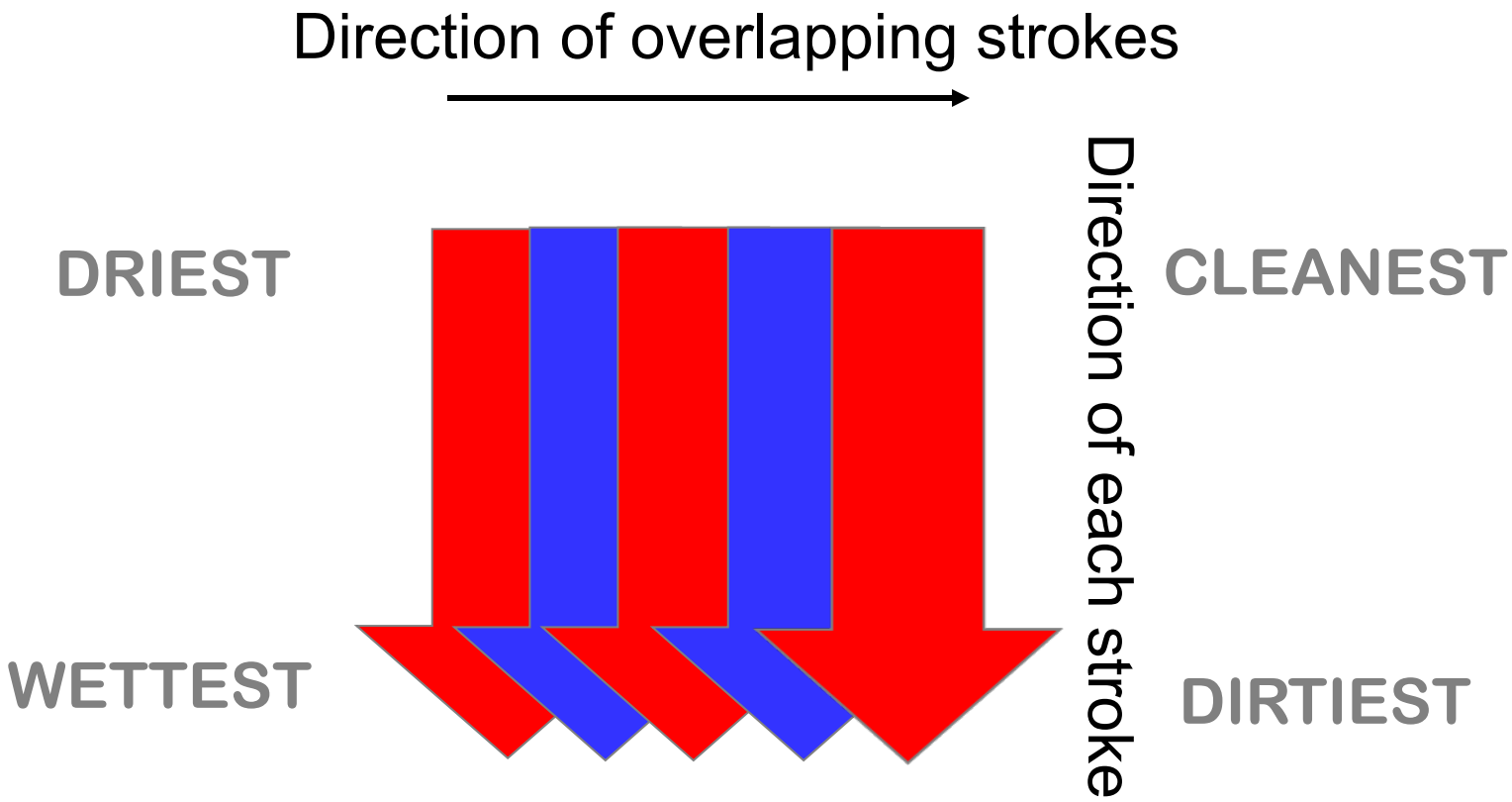
Using the Right Tools Effectively

Pull and Lift Technique

Ensures most effective removal of contaminants



Recommended Wiping Sequence



Most effective – at end of stroke, lift while pulling to remove contamination

Using the Right Tools Effectively

Special situations:

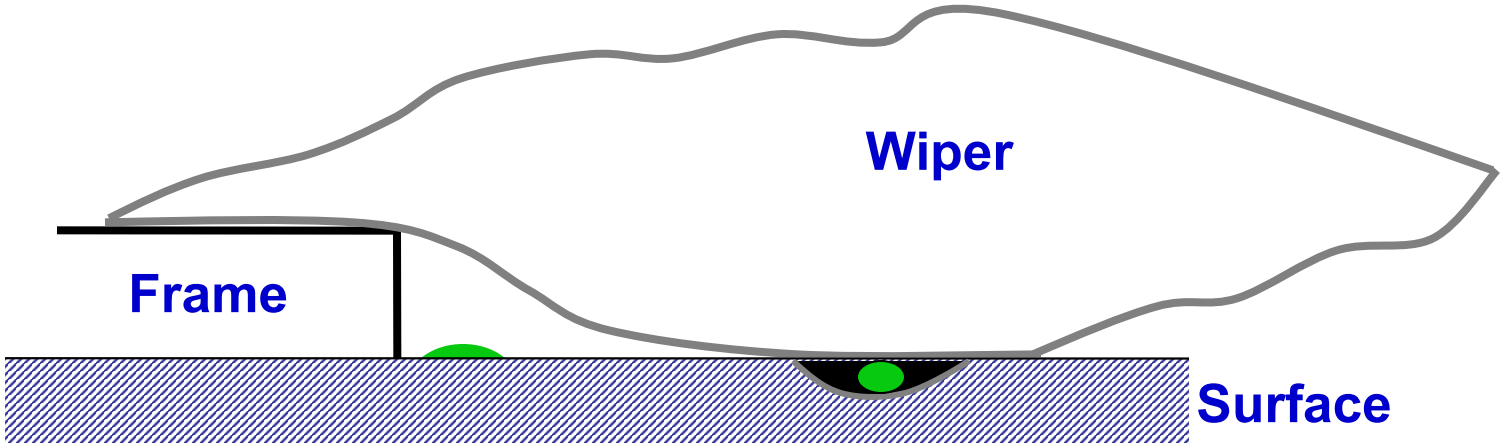
Difficult features and areas

Workstations with stationary equipment

Mini-environments/ Isolators / hoods

Swabs as micro-wipers

Good Surface Contact is Critical



Using the Right Tools Effectively

Using more cleaning solution than the wiper or mop can hold will result in less effective cleaning.

- Oversaturation of a wiper or mop will always leave behind contaminants that would otherwise be removed. This can often leave the surface less clean than before the procedure began.

- An exception is the application of disinfectant solutions in aseptic or sterile processing areas.

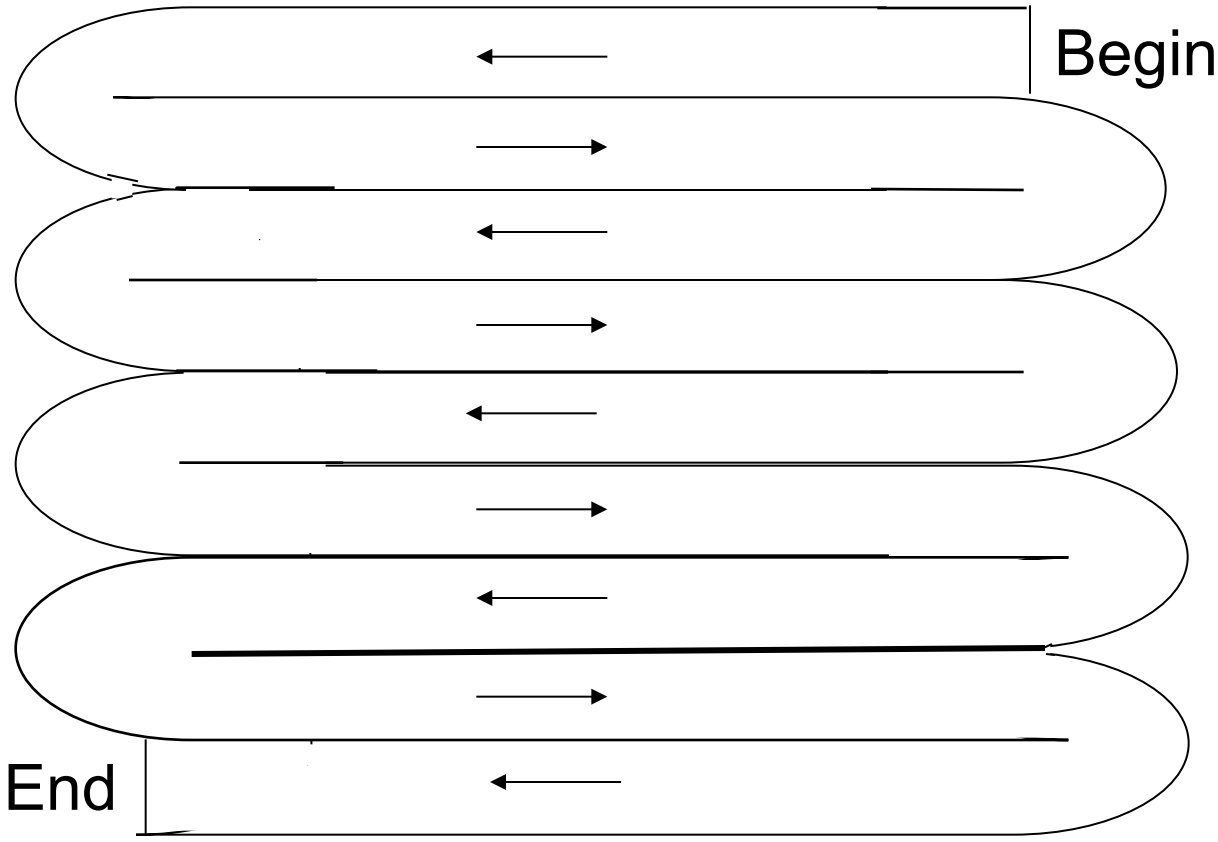
Cleaning Floors, Walls, and Ceilings in Pharmaceutical Plants

- Often a two step process
  - Cleaning
  - Disinfecting
- Cleaning first is required to eliminate contaminants which could interfere with the disinfecting process

Floor Cleaning

- Place vacuum or 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
- Damp mop using the same technique
- Rinse if necessary

“S-Curve” Mopping Technique for Disinfectant Application



Maximum distance – 1 meter

Wall Cleaning & Disinfecting Method

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

The Environment to Clean

Cleaning Frequency

Cleanroom ISO Class	Tables & Surfaces	Walls	Floors	Equipment
Class 3	Shift	Shift	Shift	Day
Class 4	Day	Week	Day	Week
Class 5	Day	Month	2/Week	Week
Class 6	Week	Quarter	Month	Month
Class 7	Week	Month	Month	Month
Class > 7	2/Month	Quarter	Quarter	Week

Process Fact #2

The tools (wipers, mops, etc.) are part of the process.

Variation in quality, materials, and use will result in failure and disaster.

Using Solutions Effectively

Keeping Solutions Clean

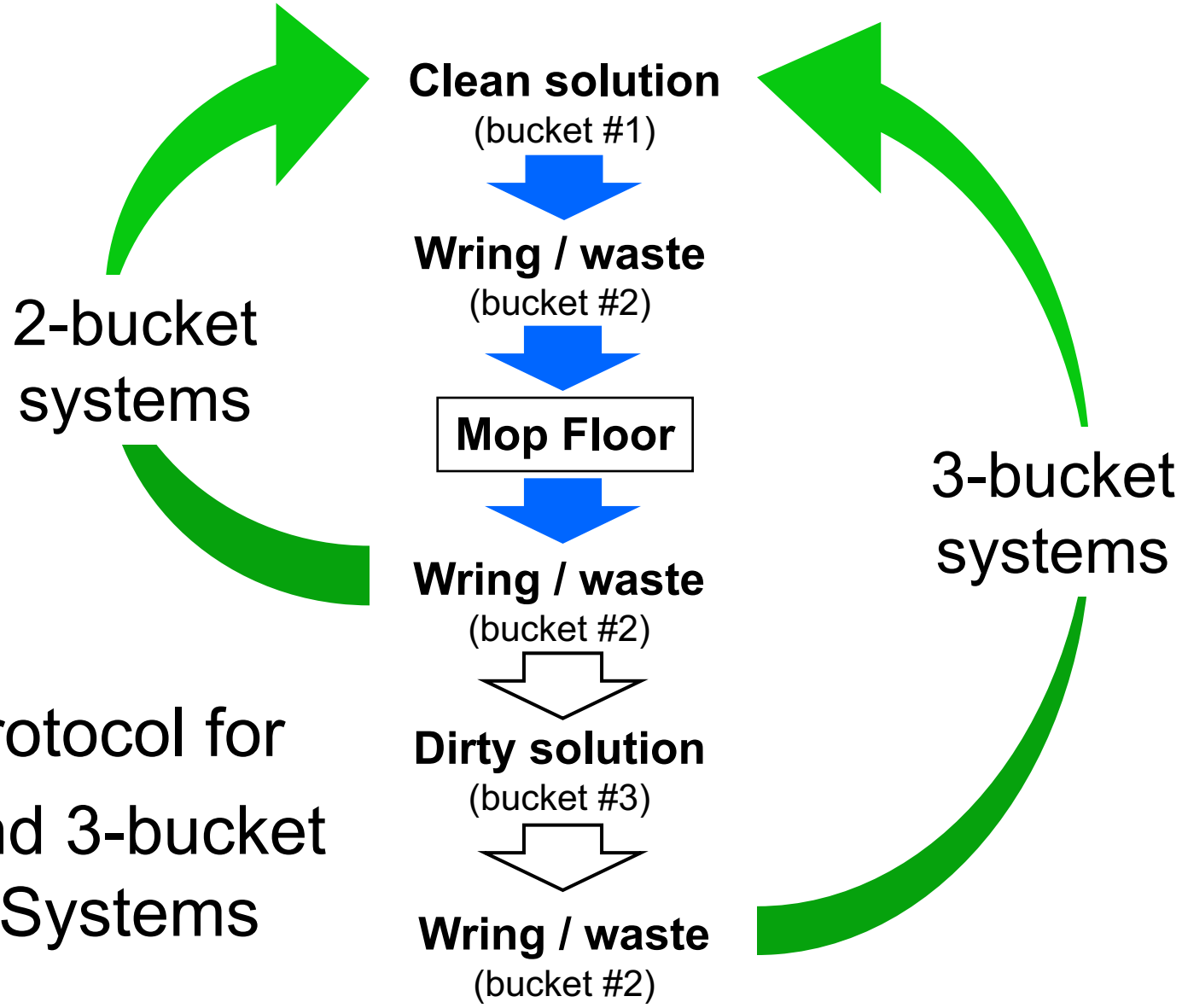
- Frequent solution changes minimize the risk of contaminant redeposition
- Solutions can be solvent blends or disinfectants and are used in many different applications.
- Frequency of solution changes is based on the type of environment, the contaminants to be removed, and the type of cleaning being performed.

Using Solutions Effectively

Keeping Solutions Clean

- Because organisms become tolerant to disinfectants over time, aseptic processing requires a regular rotation of disinfectants to maintain sterility in the aseptic environment.
- Multiple bucket mopping systems are often used to support solvent rotation

Correct Protocol for 2-bucket and 3-bucket Mopping Systems



Using Solutions Effectively

Biotech, pharmaceutical, and medical device manufacturers are required to perform validation studies to determine the effective cleaning protocols, including solution changes.

Process Fact #4

The cleaning and disinfecting solutions and the proper use of them are part of the process.

Variation in solution, application, and dwell time will result in failure and disaster.

SOP’s and Verification

SOPs

- Standard operating procedures
  - Describe activities necessary to respond to normal and abnormal situations in an operating system.
  - SOPs may include a troubleshooting checklist, list of personnel to contact, etc.
  - They describe normal operation, maintenance, and cleaning of the system, as well as normal operating parameters.

Cleaning Verification

- Visual
- Room particle counts
- Surface sampling
- Process indicators

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 should 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

Cleaning Verification

- Process Indicators
  - Items that could help you to determine cleaning effectiveness
    - Yield loss
    - High particle counts
    - Subassembly failures
    - Machinery shutdowns
  - This type of information should be used to track down the source of the contamination

Environmental Monitoring

- Monitoring to meet the ISO standards
  - Nonviable and viable particle monitoring

Nonviable Particle Testing

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

Viable 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
  - Will also provide historical data so that certification can go smoothly

Process Fact Summary

Production in controlled environments is not simply the output of a line of machines, but the combined result of every process and system working correctly and consistently. These processes include the facility, the cleaning tools, solutions, and the operators themselves.

Strict adherence to validated SOP's, combined with consistent quality tools, is critical to manufacturing success and minimizing failures.

Thank You

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