INTERPHEX 2019 APRIL 2-4 JAVITS CENTER | NYC

Cleaning Cycle Development for Parts Washer

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Agenda

- Introduction
- Cleaning Cycle Development
- Common Challenges

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Introduction

- Parts Washer
  - Automated washer
  - Cleaning disassembled parts
  - Examples, cabinet washer
- Why Cleaning Cycle Development ?
  - To determine optimal cleaning parameters
  - To have a successful Cleaning Validation

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Guidance on Cleaning Validation

"**Documented** evidence that an approved cleaning procedure will consistently reduce active pharmaceutical ingredients (API), process residues, cleaning agents and microbial residues from product contact equipment surfaces to acceptable levels for the processing of drug products"

Reference: FDA; Guide to Inspections Validation of Cleaning Processes, 1993

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Typical Questions to be Addressed

- Where do I start ?
- When to perform cycle development ?
- How to determine cleaning parameters ?
- Is it required to use cleaning agents ?
- What type of soil to be used for cycle development ?
- What is the grouping strategy ?

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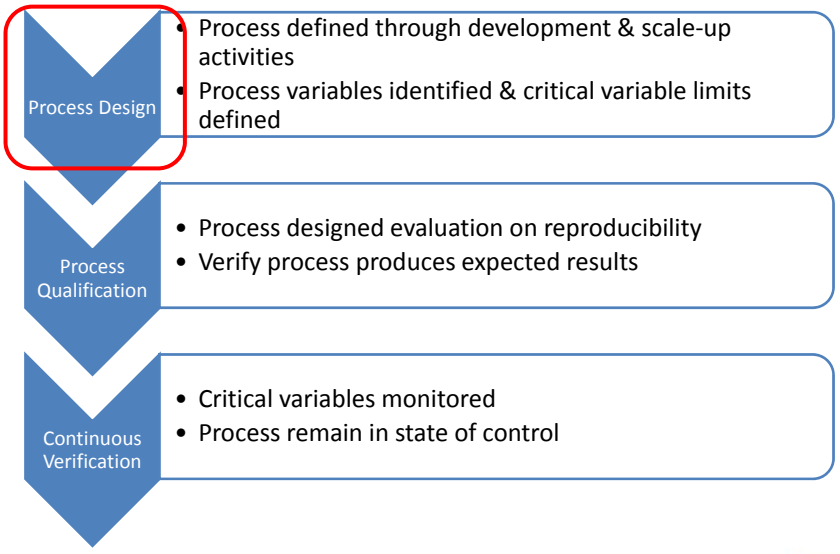
Cleaning Validation Lifecycle



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Considerations for Parts Washer Cleaning Cycle Development

Load Configuration	• Production efficiency driven • Assign parts to each load
Rack Design	• Custom made • Designed to ensure good coverage for parts
Cleaning Parameters	• Cleaning agent • Concentration • Temperature • Time

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Considerations for Parts Washer Cleaning Cycle Development

Grouping Strategies	• Bracketing • Worst case load risk assessment
Critical Quality Attributes	• Visually clean • Product/cleaning agent residues detection • Bioburden
Analytical / Sampling Methods	• Rinse & swab sampling • Specific & non-specific analytical method

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Load Configurations - Considerations

Identify All Parts	Assign Parts to Different Load	Number of Loads
• All parts that need to be clean out of place	• Production efficiency driven • Assign all parts in same load that is required in next process step	• Minimize number of loads • Reduce production cycle time • Ensure coverage is achieved

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Rack Design

- Custom-designed rack
  - To clean specific item.
    - > Stopper bowl
    - > Hoses & tubings
    - > Valves
    - > Filling needles

  - Spindle for cleaning various sizes of:
    - > Beakers
    - > Carboys

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Rack Design

- Basket
  - To clean small parts. Example, gaskets, triclamps, etc.
  - Quantity and orientation of parts defined in basket
  - Location of basket defined on rack
- Rack design need to take into consideration coverage

No coverage = No cleaning

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Cleaning Cycle Development

Soil

Cleaning Agent

Surface

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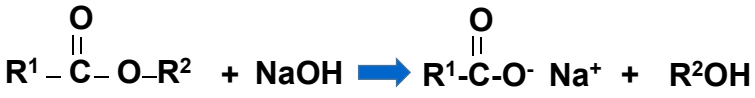
Cleaning Chemistry: Hydrolysis



Larger MW	Smaller MW
Less polar	More polar
Less water soluble	More water soluble

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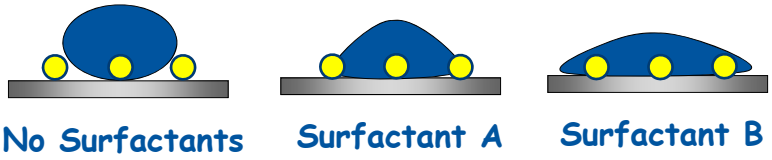
Cleaning Chemistry: Wetting

- Influence of Surfactants on Wetting
  - Reduce surface tension
  - Increase surface contact



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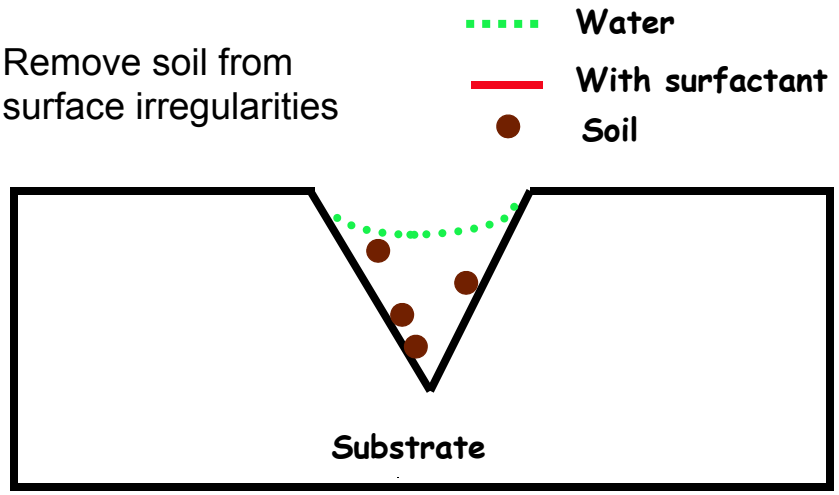
Cleaning Chemistry: Wetting

Remove soil from surface irregularities



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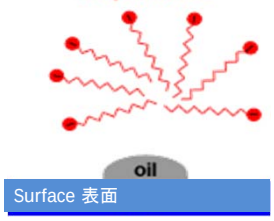
Emulsification Behavior of Surfactants

CH_3- CH_2- CH_2- CH_2-CH_2-$(CH_2)_n$- CH_2- C- O^- Na^+

Lipophilic

Hydrophilic



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Cleaning Agent Options

Water	• Solubility
Commodity Chemicals	• Solubility • Hydrolysis
Formulated Chemistry	• Solubility • Hydrolysis • Wetting Emulsification Dispersion Chelation

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Formulated Chemistry

- Alkaline(Base) Detergents– pH>9
  - Majority of cleaning applications
    - Organic acids, Proteins
    - Oil, waxes, fats
    - Tableting excipients, Polysaccharides
- Acid Detergents– pH < 6
  - Small percentage of cleaning applications
    - Inorganic compound (Bicarbonates, carbonates)
    - Metal oxides
    - Hard water scale
- Detergent Additives
  - Used to boost cleaning efficacy of other products

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Cleaning Parameters

- Determine Cleaning Parameters
  - Identify and characterize the soils
  - Perform lab scale study to determine critical cleaning parameters

T - Temperature
A - Action
C - Coverage
C - Chemistry
C - Concentration
T - Time

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Lab Evaluation



- Coat coupon with soil
- Simulate process conditions and dirty hold time

T - Temperature
A - Action
C - Chemistry
C - Concentration
T - Time

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Critical Cleaning Parameters

- Temperature
  - Higher generally better
  - Critical for wax excipients
    - > Must approach melting point for emulsification
  - Strong influence on mechanisms
- Cleaning Action
  - Related to force on the surface
  - Helps to dislodge residues
  - Uniformity to assure effectiveness
  - Impingement, Cascading flow for parts washer

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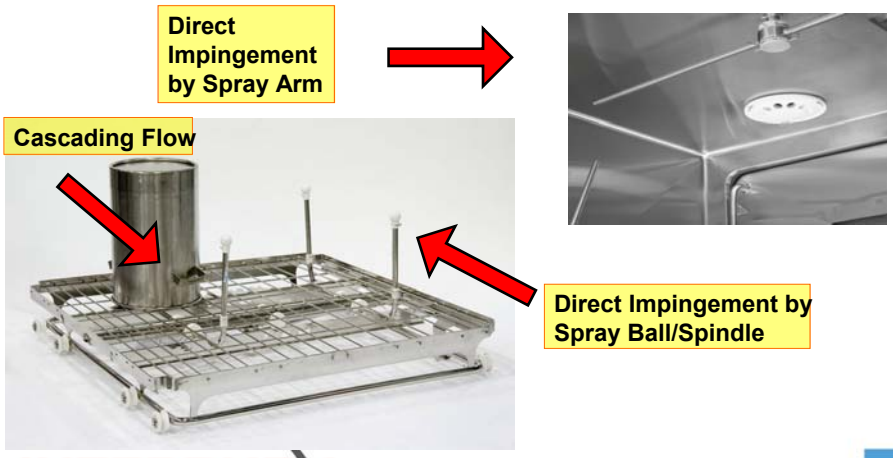
Cleaning Action



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Cleaning Parameters

- Concentration
  - Higher generally better
  - Inverse relationship with time and temperature
  - Materials compatibility issues
  - Neutralization issue
- Time
  - Related to contact time of cleaning agent on the surface
  - Shorter the better
  - Inverse relationship with temperature and concentration

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Other Time Considerations

- Clean Hold Time
  - How long equipment remains “clean” before reuse.
  - Not concerned with process residue
  - Focus is on controlled storage (bioburden proliferation)
- Dirty Hold Time
  - How long “dirty” equipment can remain dirty prior to cleaning
  - Generally, longer DHT → increasingly difficult to clean
  - Be aware of potential changes in active/excipient physical or chemical properties

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Coverage

- Orientation of parts may pose challenges to coverage
- Critical to ensure good coverage
  - All surfaces are in contact with cleaning solution
- Example, use riboflavin for coverage studies

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Coverage – Riboflavin Test

- Spray riboflavin on inside surfaces of load items
- Position load items on rack
- Spray riboflavin on
  - Chamber surfaces
  - Rack
  - Load items on rack
- Dry for a few hours at ambient temperature
- Short rinse cycle is run
- Check the presence of riboflavin using UV light

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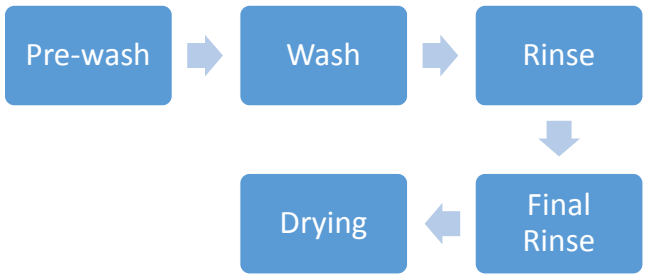
General Cleaning Cycle Steps



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General Cleaning Cycle Steps

Step	Type of Solution	Function
Pre-rinse	Ambient temperature purified water	Remove bulk of soluble and other non-adhering residues
Cleaning solution	Cleaning solution.	Depending on type of soil, alkaline cleaning solution can be used in this cleaning step
Water rinse	Purified water	Rinse away cleaning solution
Cleaning solution (Optional)	Cleaning solution	Depending on type of soil, acidic cleaning solution can be used if required
Water rinse (Optional)	Purified water	Rinse away cleaning solution
Final rinse	Water For Injection or Purified Water	Highest grade of water and elevated temperature is used
Drying	Filtered Compressed air	Dry the parts after washing

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Parameters and attributes of cleaning processes

- Critical Quality Attributes
  - Visual Inspection
  - Analytical residue limits (Example, HPLC or TOC)
  - Microbial (Bioburden/Endotoxin)
  - Conductivity

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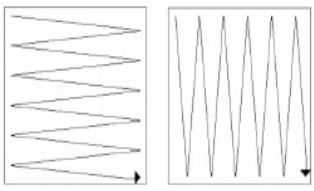
Analytical & Sampling Method

- Analytical method
  - Specific method (Example, HPLC, Ion Chromatography)
  - Non-specific method (Example, TOC, Conductivity)
- Sampling method
  - Swab sampling
    - > Direct method
    - > Single swab or 2 swabs



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Analytical & Sampling Method

- Sampling method (Cont)
  - Rinse sampling
    - > For area that are inaccessible
    - > Sterile stomacher bag
- Recovery values need to be established for both swab and rinse recovery

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Grouping Strategies

- Bracketing
  - Based on largest & smallest sizes
- Worst case load
  - Risk assessment on parts. Example,
    - > Complexity of parts
    - > Drainability
    - > Surface area

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What can go wrong ?

- Accumulation of pool water at the end of cleaning cycle
  - Drainability
  - Orientation of parts
- Failed visual inspection / Swab samples
  - Residue left
  - Inappropriate cleaning agents
  - Cleaning parameters

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What can go wrong ?

- Failed final rinse sampling
  - Review rinse sampling procedure
  - Inappropriate cleaning agents
  - Insufficient rinse steps
- Addition of new parts to load
  - Need to repeat cycle development studies ?
  - Based on risk assessment

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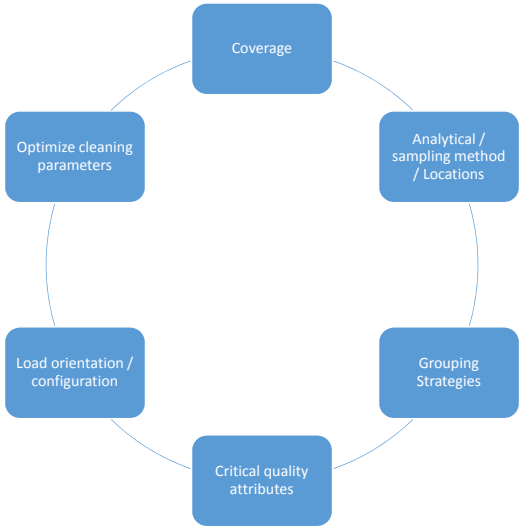
Conclusions



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References

1) Cleaning Validation Considerations for Automated Washing Systems Pharmaceutical Engineering March – April 2017 Vol 37, No 2. Paul Lopolito, Olivier Van Houtte, Marcel Dion.

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