Cleaning Processes and Microbial Controls

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Fitting that Cleaning is First…

- Cleaning effectively is our first and one of our best defenses for microbial control
  - Remove contamination that arose during the manufacturing event by cleaning
  - Prevent the introduction of contamination during the cleaning process by controlling supplies / conditions
  - Eliminate sources of food and shelter for flora
  - Eliminate water by drying equipment
  - Prevent micro propagation through proper storage

Cleaning is the "first" step in getting ready for the next process.

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What do the Regulators say?

- Microbial control measures in cleaning and cleaning validation are more “preventive” in nature rather than focusing on the removal or destruction
- Designing a process / process equipment for cleanability is a critical first step

Don’t forget your ASME Bio-Processing Equipment standards for designing for cleanability!

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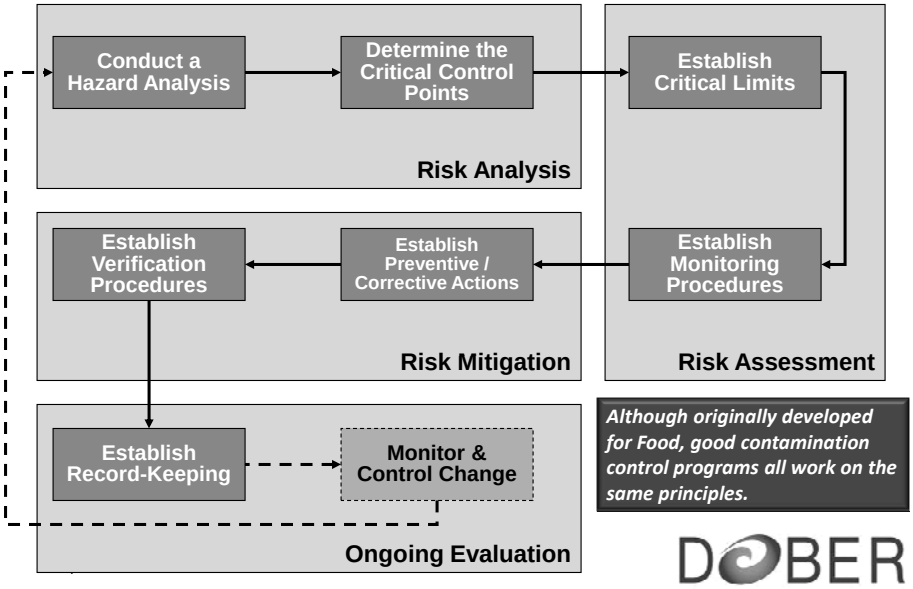
Principles of HACCP



Although originally developed for Food, good contamination control programs all work on the same principles.

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Elements of an Effective Cleaning Program that Help to Control Micro

- Dirty Hold Time
- Control over Cleaning Agents
- Control over Utilities (Water, HVAC, Comp. Air)
- Validated Cleaning Processes
- Ongoing Monitoring
- Defined Storage Requirements
- Clean Hold Time

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Dirty Hold Time

- Limit the time after use before cleaning
  - Limits microbial propagation on surfaces
  - Limits ongoing environmental exposure
  - Prevents residues from becoming harder to clean and falling outside of validated process performance
- Some firms rinse after use then have a longer hold time before cleaning

BEWARE! Micro propagation in residual water on surfaces can be intense!

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Control Over Cleaning Agents

- Pharmaceutical cleaning agent suppliers control their formulations
  - Consistent manufacture = validated cleaning
- Cleaning agents can contain ingredients that help to remove or destroy microorganisms:
  - Caustic or Acid
  - Chelants such as EDTA
  - Surfactants
  - Solvents

Get a commitment to consistency and change control from your cleaning agent supplier.

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Cleaning is NOT Disinfection

- While some ingredients may have bactericidal effects, cleaning is NOT disinfection
- You need to remove soils from surface before effective disinfection can begin
- Disinfection requires specific adherence to application methods and times to generate “kill”
- Although not disinfection, cleaning can help to flush or inactivate a large portion of our bioload

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Cleaning & Disinfection Do NOT Depyrogenate

- Primary source of endotoxin are gram negative bacteria
- Primary source of gram negative bacteria is water
- Destroying the bacteria releases the lipopolysaccharides from the cell membrane which have a pyrogenic effect
- Primary methods to depyrogenate hot caustic for LONG periods of time or dry heat

Result? Water quality is key. Dry water from surfaces ASAP.

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Control Over Utilities

- Critical utilities used in cleaning include water and compressed air
- Critical utilities in hold times and storage include HVAC and humidification
- Ensure that these utilities are qualified before you embark on cleaning validation for the most consistent cleaning and bioburden results

Utility qualification should include aspects of both chemical and microbial quality as well as sufficiency.

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Control Over Utilities During Cleaning Validation

- Consider including control samples for critical utilities that might influence cleaning validation outcomes:
  - Sample supply source for rinse water
  - Collect compressed air samples from source for drops that might be used for blowing down equipment
- Clean and store equipment only in areas with validated HVAC that has an ongoing monitoring program

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Validated Cleaning Processes

- Having a validated cleaning process is your best defense – ensuring cleaning is sufficient for:
  - Worst-case dirty hold times
  - Worst-case soil loads
  - Worst-case process excursions in action, time, temperature (as challenged during the validation)
  - Variations between personnel
  - Worst-case clean hold times

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What Makes a Validated Cleaning Procedure?

- T.A.C.T. ← Critical Process Parameters
  - Time
  - Action
  - Concentration/Chemistry
  - Temperature
- W.I.N.S. ← Critical Quality Elements
  - Water
  - Individual
  - Nature of the Soil
  - Surface

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Regulatory Expectations

- Equipment bioburden "validation" will be included in your cleaning validation program
  - "Validation" of bioburden is more like a first step on a long journey than it is a study to complete and put in the drawer
  - So-called "Rule of 3" has little relevance here
- Many firms keep their equipment bioburden sampling under a separate protocol
- Failures in chemical cleaning have few potential causes; failures in microbial validation have many possible explanations because micro is literally all around us

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Ongoing Monitoring

- Monitoring:
  - Occurs after validation is complete
  - Ensures that cleaning remains consistent over time (changes in personnel, training, wear-in, etc.)
  - Proves the efficacy of scientific approaches such as grouping or bracketing
  - Performed (most commonly) for manual cleaning processes due to inherent variability

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Challenges with Monitoring

- Study design:
  - How many products to study?
  - How frequently?
  - What non-invasive sampling / test methods can be used?
  - All equipment or a subset?

Monitoring is a risk-based study design.

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Let the Data Direct You

- What products are most likely to have high bioloads after processing or after clean hold times?
  (e.g., high water activity or non-preserved formulae)
- What equipment is difficult to clean or difficult to dry?
- What materials of construction or surface finishes might harbor contamination?
- What equipment is stored in a susceptible environment? Or in at at-risk fashion?
- What did original validation results show?
- What does previously collected monitoring data show?

Remember HACCP or similar tools.

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Defined Storage Conditions

- Guidances agree that equipment should be stored:
  - Dried
  - Covered or closed
- HVAC should be positive to surroundings
- Equipment should be clearly tagged with expiration
- Guidance can't control (these should be managed by your SOPs):
  - Organization within the space
  - Personnel interventions to find equipment

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Clean Hold Time

- Risk based decision driven by:
  - Defined storage conditions
  - Criticality of possible particulate and micro residues to next product
  - Post-storage treatment (e.g., sterilization, pre-use flush)
  - Clean Hold Time historical data
    - Product bioburden results
    - Equipment bioburden results

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Equipment Expiration and the Pre-Use Flush

- Justification for no clean hold time or for prolonged clean hold times are frequently based on the use of a pre-use flush
- Beware that you ensure that the pre-use flush will be aggressive enough to remove the potential residues left behind after storage (including environmental “dust”, micro and endotoxin)
- Prove it! What does your microbial monitoring show you?

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Keys to Success

- Sound risk-based decision-making
  - Documented
  - Periodically Re-evaluated
- Monitoring to prove ongoing consistency
  - Remember flora change and adapt
  - Trending and interpretation

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Questions?

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