Objectives

- Define terminology
- Describe cleaning processes and approaches
- Techniques to measure effectiveness
- Significant issues and/or problems

Cleaning

- Definition: The process of removing potential contaminants from process equipment such that the equipment can be safely used for subsequent product manufacture
- Focus is process equipment, not cleanroom cleaning

Critical cleaning?

- Critical cleaning must be validated
- Cleaning between products
- Focus on product contact surfaces
  - Significant indirect product contact surfaces
- Applies to drug products and APIs
- Dedicated equipment (7356.002)
- Documented evidence of effectiveness
- Also address cleaning agent and bioburden

Non-critical cleaning?

- Not required for non-critical cleaning
- Floors, walls, outside of vessels
  - Still have cleaning SOP
  - Residues on such surfaces are addressed by containment procedures and personnel practices
  - Only loosely adherent residues can become airborne for cross-contamination
- Some API intermediate steps (ICH Q7)

Life Cycle Approach

- Stage 1: Process Design (and Development)
- Stage 2: Process Qualification
  - Utilities, equipment, facility
  - Performance qualification (PQ)
- Stage 3: Continued Process Verification (or maintenance of state of control, or validation maintenance)
- Based on FDA January 2011 Process Validation guidance
Cleaning validation
- Documented evidence (reports)
- High degree of assurance (data)
- Consistency (traditionally multiple PQ runs)
- Predetermined quality attributes (of equipment)
  ➔ For repeated cleaning processes
  ➔ Throughout life cycle

Cleaning verification
- Documented evidence
- High degree of assurance
- For unique or non-repeatable events
- Quality attributes may be evaluated later depending on next product
  ➔ For clinical products cleaning, infrequent production, cleaning after maintenance or deviations
  ➔ One time

Qualification parts (1)
- IQ (Installation Qualification)
- Is equipment the correct equipment, and is it installed (e.g., wired) correctly
- Focus on equipment installed for automated cleaning (CIP equipment, spray devices, monitoring devices)

Qualification parts (2)
- OQ (Operational Qualification)
- Does installed cleaning equipment operate correctly
  • Pumps
  • CIP valve sequencing
  • Cleaning agent dilution
  • Spray device coverage testing (riboflavin testing)

Qualification parts (3)
- PPQ (Process Performance Qualification)
  • Traditionally 3 consecutive cleaning runs
    • PAT and new process validation guidance effect
    • Challenge cleaning procedure within normal parameters
    • Measure residues & compare to acceptance limits

Paradigm change
- Move to "lifecycle" approach is slow
- Will see some companies adopting it
- Most will be in traditional paradigm
- But --
  • Design and development has always been done
  • Monitoring and control after validation runs has always been done
- So, don't be afraid to ask for it
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Cleaning process

- Cleaning agent
- Cleaning parameters
- Cleaning method

ALL three are critical for defining and controlling the cleaning process
- Addressed initially in design phase, but may be modified based on info from qualification and validation maintenance phase

Cleaning agent options

- Organic solvents
  - e.g., methanol
- Water
- Commodity chemicals (aqueous)
  - e.g., caustic, phosphoric acid
- Detergents
  - Surfactants
  - Formulated aqueous cleaners

Detergents

- Formulation disclosure
- Consistent components
- Notification of changes
- Very low levels remain, readily rinsable

Cleaning parameters

- Time (3 aspects)
  - Time before cleaning
  - Time of cleaning steps
  - Time after cleaning
- Action (agitation or impingement)
- Chemistry (includes concentration)
- Temperature

Cleaning parameters (cont.)

- Water quality
- Rinsing
- Soil condition
  - Dried during manufacture
  - Dried during dirty hold time
- Soil levels (amount on surfaces)
Application methods

- Objective of application method is to contact the cleaning solution with **ALL** the surfaces to be cleaned to meet the requisite cleaning parameters
  - Time
  - Action
  - Temperature

How apply

- Static immersion
- Agitated immersion
- **CIP** (Clean In Place)
- Automated parts washer
- Ultrasonic
- Manual
- Solvent reflux

Common steps

- Pre-rinse
  - Water or solvent to remove bulk of residue
- Wash step
  - Utilizes cleaning agent or detergent
- Rinse
  - May include a final rinse with purer grade of solvent or water
- Drying and storage

CIP parts

- Chemical supply
- Chemical feed
- Tanks
- Heat exchanger
- CIP pump
- Probes
- CIP Skid

CIP skids

- Fixed (CSI)
- Portable (CSI)
Manual cleaning

- Types
  - Wipe
  - Soak
  - Brush
  - Spray
  - Combinations of above

Manual issues

- Control through...
  - More detail in SOP
    - Disassembly
    - Cleaning agent preparation
    - Specific cleaning actions
    - Rinsing
    - Drying
    - Reassembly
    - Storage
  - Training/qualifying of operators

Design phase

- Identify and understand cleaning situation
- Determine sources of variation
- Control variation consistent with risk
- Lab studies and scale-up studies may be utilized in this phase

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Measuring effectiveness

- Key aspects
  - Setting residue limits
  - Analytical techniques
  - Sampling techniques

Residues measured

- How selected?
- Should be based on what cleaned, how cleaned, and effects on next product
- Minimum is usually active, cleaning agent, and bioburden
- Others that may be important
  - Endotoxin
  - Degradants or byproducts
Key aspect of CV
- “Intersection” of two products
  - Product just manufactured- good cleaning to remove residues to acceptable level
  - Product subsequently manufactured- “acceptable level” is based on possible contamination of this product
- Must always evaluate effects on subsequently produced product

Residue limits
- For actives, dose-based calculation
  - Also called Maximum Allowable Carryover (MAC or MACO) calculation
- For compounds without dose (such as detergents), use ADI (acceptable daily intake) based on toxicity information (LD$_{50}$)

Care in terminology
- Manufacturers avoid
  - “No” residue
  - “None detected”
- Confusion in use of term “limit”
  - “10 ppm” of what measured in what?
- How low is low enough?

How low?
- May contain measurable residues, but no contaminants
- A “contaminant” is an “unacceptable” residue
- Any residue must…
  - be medically safe
  - not affect product quality
  - be unavoidable by practical means
- Last three points in Human Drug CGMP Note, 2nd Quarter 2001

In subsequent drug product
- Concentration which results in no more than 0.001 minimum dose of active in maximum dose of subsequent product,
  - OR (if used a default)
- 10 ppm in subsequent product

“Default” limits
- Typically 10 ppm for finished drug manufacture
- Typically 50-100 ppm for API manufacture (limit in next API)
- NOT “either/or” with dose calculation; only use default if lower than dose calculation
Maximum allowable carryover

- MAC (or MACO)
- In units such as µg or mg
- Determined as concentration limit in next product times batch size of next product

Limit per surface area

- In units such as µg/cm²
- Determined as MAC divided by shared surface area

In analytical test sample

- In units such as µg per swab or µg/mL
- For swabs, determined by multiplying limit per surface area by surface area swabbed
- For solution, determined by limit per swab divided by amount solvent used for extraction
  - \( \text{NOT necessarily same as limit in next product} \)

Overall equation

\[
(0.001)(\text{min. dose Act.A})(\text{B.S.})(\text{S.A.})
\]
\[
(\text{max. dose Prod.B})(\text{S.S.A.})(\text{S.E.A.})
\]

Where
- B.S. = minimum batch size Prod.B
- S.A. = sampled area
- S.S.A. = shared surface area
- S.E.A. = solvent extraction amount

(For finished drug product manufacture)

Assessing protocol compliance

- Most common approach is to make sure each sample taken meets the analytical sample (or surface area) limit
- Result is significant overkill, because compliance controlled by worst case sampling location
- Alternative is “stratified sampling”
  - Compliance determined by total carryover
  - Integrates surface area and residue level for that surface

Other considerations

- For allergens, cytotoxics, actives with reproductive concerns
- Will set limit based on LOD (limit of detection) of analytical technique using best available procedure, OR
- May dedicate equipment, OR
- May set limit based on ADE (Acceptable Daily Exposure) from ISPE RiskMaPP document
- May also see demonstration of deactivation of such actives
  - Through cleaning process
  - Through additional deactivation step (e.g., peracetic acid)
Indirect Contact Surfaces

- Indirect product contact surfaces are surfaces in near proximity to product where residues have significant probability of transferring to product
- Examples
  - Lyophilizer shelves
  - Isolator interiors
- May include in cleaning validation program
- Typically set limits by requiring such surfaces to be visually clean, or to be as clean as adjacent product contact surfaces, or to be within limit of 10 ppm
- Don’t include surface area in limits calculations

Still other considerations

- Are products dosed the same (oral vs. topical vs. injectable)?
- Are patient populations equivalent (adult vs. child, pregnant vs. non-pregnant female)
- Doses based on body weight or body surface area

Limit for microbes

- Calculations based on scientifically justified limits usually result in impractically high values
- Most likely default to limit of \( \leq 25-50 \) CFU per 25 \( \text{cm}^2 \) (\( \leq 1-2 \text{ CFU/cm}^2 \)) for non-sterile manufacture
- For rinse water (non-sterile manufacturing), default to Purified Water specifications

Visual cleanliness

- Include visual inspection
- Complements rinse and/or swab sampling
- Key is to not have cleaning residues left behind
- Issues
  - Background variations
  - Rouge - may be indicative of a maintenance problem, but generally not a cleaning problem

Visual cleanliness alone

- Based on European PIC/S guidance, some may utilize visually clean alone as the most stringent criteria
- May apply for non-potent drugs, API manufacture
- Generally not applicable for potent drug products
- Key items to consider
  - Angle, distance, lighting, viewer
  - Typical level is 1-4 \( \mu \text{g/cm}^2 \)
  - Must relate visually clean to actual levels in spiking studies

Analytical method

- Is it a direct measure of residue?
- Is LOD/LOQ appropriate for limit in analytical sample?
- Both specific and non-specific methods may be used
Specific method
- Unequivocally measure target residue in the presence of expected possible interferences
- Other thing equal, preferred by manufacturer because it tells exactly how much is present, making it easier to meet acceptance criteria
- Examples: HPLC, UPLC, UV, ELISA

Specific methods (cont.)
- Possible issues with specific method
- Degradation of API in cleaning process such that it is no longer analyzed by HPLC method
- Interferences from cleaning agent

Non-specific methods
- Measure any species with a certain response
- Most common is TOC (Total Organic Carbon)
- See Q&A on cGMP for Drugs, May 2005 for issues in proper use

Why TOC acceptable?
- Residue limit is NOT goal
- Goal is to be below limit
- If treat all measured Carbon as if it were from the target residue (worst case), AND it is below the acceptance limit, can have assurance that residue is below limit

Analytical method validation
- Generally done for cleaning validation
  - LOD/LOQ
  - Accuracy - closeness to true value
  - Precision - closeness among measurements
  - Range
  - Linearity
- For cleaning verification in clinical manufacture, may have less analytical method validation (pass/fail test, for example)

Sampling methods
- “Swab” sampling
- “Rinse” sampling
- Placebo
- Direct surface (FTIR w/fiberoptics)
Swabs

- Advantages
  - Can focus on “worst-case” locations
  - Mechanical means of removing substances
- Issues
  - Swab must release analyte
  - Care in swab handling procedures
  - Interferences from swab
  - Swabbing is a manual procedure
  - Access to sampling sites

Swabbing SOP

- Swab (supplier and part no.)
- Surface area to be swabbed (usually 25-100 cm²)
- Template (if used)
- Number of swabs
- Wet or dry (& solution, if wet)
- Swab pattern
- Vial for extraction
- Extraction conditions
- Blanks/controls

Swab pattern example

- Start
- Flip swab
- End

Swab sampling locations

- Most difficult-to-clean locations
  - Good practical common sense
  - Prior experience
  - Sub-optimal cleaning process (time, concentration, temperature, rinse)
- Sites for non-uniform contamination
- Different materials
  - Glass, steel, gaskets
- Functional locations
  - Blades, tank walls, fittings

Number of swab sites

- Not based on a certain percentage of surface area
- Not based on 1 site per XXX cm²
- Swab sites not identical, so don’t base on statistics
- Want worst-case locations, not average
Rinse sampling

- Definition: Using a solvent to contact all surfaces of sampled item to quantitatively remove target residue
- Solvent can be water, water with pH adjusted, or organic solvent
- Must contact all surfaces
- Residue measured in collected sample

Two types

- Separate sampling rinse
  - Done after process rinse is complete
  - Rinse solution may be different from process rinse
- Sample of the final process rinse
  - Most common for CIP
  - Key is to correlate with next product limit

“Rinse” sampling

- Advantages
  - Sample “inaccessible” locations
  - Provides overall picture
  - Use of different solution from process rinse
- Issues
  - Solubility of residue in rinse solution
  - Need to relate amount in rinse sample to potential contamination of next product

Reputation of rinse sampling

- “Bad name” because of misuse – assumption that if rinse water met USP specs, that equipment was clean
- Failure to tie analytical results to specific residues of concern
- Failure to demonstrate removal of residue by rinse solution (recovery study)

Recovery studies

- Recovery study - swabs & rinse
- Procedure
  - Spike coupon with known amount
  - Remove in swab or simulated rinse procedure
  - For swab, desorb
  - Analyze sample
  - Done at or below surface acceptance limit
  - In method validation or separate study

Recovery study

1. Spike control diluent directly
2a. Spike coupon
2b. Swab coupon
2c. Extract swab
Acceptable recovery

- >80% is good
- >50% may be okay
- <50% is questionable
- Caution: May use recovery factor to correct measured analytical value or acceptance limit (but not both)

How utilize

- Most common: Utilize recovery percentage for correction
- Option: Require minimum percent recovery to qualify sampling, but do NOT correct analytical values
  - Minimum for this option is generally 70-80%

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Emphasis: scientific adequacy

- Documentation, decisions have to demonstrate cleaning is adequate
- Must meet expectations of “current” in cGMPs
- But, NOT a requirement that each step be the best choice
- Examples (cleaning time, swabs)

Bulk biotech manufacture

- Because of degradation of protein in hot, alkaline cleaning agent, almost always use TOC to measure residue of active
- Clearance of degraded fragments usually occurs with chromatographic purification processes
- For bulk manufacture (through final purification), limits based on process capability (1-10 ppm TOC), not dose-based (MACO) calculations

Challenges

- For PQ runs
  - Process conditions (within normal process conditions)
  - Different operators for manual cleaning
  - Bioburden
  - Dirty hold time
  - Clean hold time
- Under life cycle approach, may be addressed in design/development
## Dirty Hold Time

- **What?**
  - Time between end of manufacture and beginning of cleaning
- **Why?**
  - Manufactured product may be harder to clean (dries, bioburden growth)
- **Issues**
  - Sometimes cleanability does NOT change with time (e.g., dry products)

## Dirty Hold Time (2)

- **What do?**
  - Specify a maximum hold time in cleaning SOP
  - Challenge worst-case condition in validation (at least one run at maximum if not addressed in design/development)

## Clean Hold Time

- **What?**
  - Time from end of cleaning to beginning of manufacture
  - Sometimes called expiry period
- **Why?**
  - Equipment may become recontaminated during storage (bioburden, dust)
- **Issues**
  - If dry and sealed, should not be recontaminated

## Clean Hold Time (2)

- **What done?**
  - Specify maximum hold time in SOPs
  - For extended storage, dry equipment (as part of cleaning SOP)
  - For extended storage, seal/wrap equipment appropriately
  - Measure residues before and after storage (may be in separate protocol)
  - Usually are measuring bioburden and visual cleanliness; may also use TOC
  - Criteria is change from baseline

## Grouping Strategies

- **Grouping**
  - By product (soil)
  - By equipment
  - Also called matrixing, family approach, bracketing
- **Rationale**
  - Simplify amount of validation work

## Grouping Conditions

- **Conditions to meet for product grouping**
  - Similar product type
  - In same equipment train
  - Identical cleaning process
    - Cleaning agent
    - Cleaning method
    - Process parameters
### Representative product

- **Representative**: most difficult to clean
- **Basis of selection**
  - Historical
  - Solubility data
  - Lab/pilot study

### Representative limit

- **Residue limit selection**
  - Lowest limit among group
  - OR
  - Validate most difficult to clean (at its limit) and most “toxic” (product with lowest limit)

### Equipment grouping

- Must be similar type
- Identical equipment (identical for cleaning purposes)
- May involve simple equipment of different sizes
  - Example: 300L, 500L and 1000L tanks
- Alternatives --
  - Validate separately largest & smallest sizes
  - Validate together testing extremes

### CV maintenance

- Monitoring
- Change control
- Deviations
- Training and retraining
- Continuing control
- Note: “revalidation” is disappearing from FDA lexicon

### Routine monitoring during cleaning

- May monitor key control parameters
  - Time(s)
  - Temperature(s)
  - Cleaning agent concentration
  - Pressure
- May monitor key indicators of control
  - Rinse water TOC or conductivity
  - Visual examination

### Change control

- Change control SOP
- Planned vs. unplanned changes
  - In cleaning process
  - In manufacturing process
- Keys
  - Evaluate impact of change
  - May require lab studies, IQ, OQ, or PPQ
- Document
**Process deviations**

- Deviation of process once cleaning process is validated
- Look for
  - Their investigation into causes & effects
  - Corrective or preventive action

**Regular review**

- Repeat of PPQ run on any significant change
- On a "regular" basis, evaluate consistency based on
  - Monitoring data
  - Change control data
  - Deviations
  - Quality records
- See CGMP NOTE, Q2 2001

**Other considerations**

- Training records
- Operators
- Samplers
- Analysts
- Validation specialists
- Computer validation

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