

Systems-Based Inspections for Cleaning Validation

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Objectives

- Describe cleaning processes and approaches
- Identify various techniques utilized to measure the effectiveness of cleaning processes
- Identify documents associated with cleaning validation processes
- Identify significant issues and typical problems with cleaning validation

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Cleaning

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

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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**
 - Documented evidence of effectiveness
 - Also address cleaning agent and bioburden

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Non-critical cleaning?

- **Validation 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
 - For highly hazardous actives, may evaluate as part of a overall risk assessment
 - Some API intermediate steps (ICH Q7)

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Life Cycle Approach

- **Stage 1: Process Design (and Development)**
- **Stage 2: Process Qualification**
 - Utilities, equipment, facility
 - Process Performance qualification (PPQ)
- **Stage 3: Continued Process Verification (or maintenance of state of control, or validation maintenance)**
- Based on FDA Process Validation guidance

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Paradigm change

- Companies moving to "lifecycle" approach
- Legacy products 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 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

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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 protocol

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Systems-Based?

- Inspection starts with higher level documents to determine if appropriate practices are specified
- Moves to lower documents as appropriate to confirm compliance with higher level documents
 - SOPs (cleaning and cleaning validation)
 - Rationales
 - Protocols and protocol reports
 - Batch records
 - Validation maintenance documents

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Differences PV vs. CV

- Analytical values
 - PV has a goal for conc. of active (for example); want a *narrow range* (\pm)
 - CV has limits for active (for example) that firm wants to be *below* ($<$)

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Differences PV vs. CV (2)

- Sampling
 - PV based on statistics - uniformity throughout batch and from batch to batch
 - CV based on worst cases - swab sample locations most likely to have higher levels of residues (difficult to clean)

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Differences PV vs. CV (3)

- Processes
 - For production process, each manufacturing process is more or less unique
 - For cleaning process, firms prefer to use one cleaning process for all manufactured products

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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

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Cleaning agent options

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

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Cleaning parameters

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

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Cleaning parameters (cont.)

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

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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

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How apply

- **Static immersion**
 - Fill tank with water to slowly dissolve
- **Agitated immersion**
- **CIP (Clean In Place)**
- **Automated parts washer**
 - Like home dishwasher
- **Ultrasonic**
 - Use of sound waves to remove particles
- **Manual**
- **Solvent reflux**
 - Boil with organic solvent like methanol

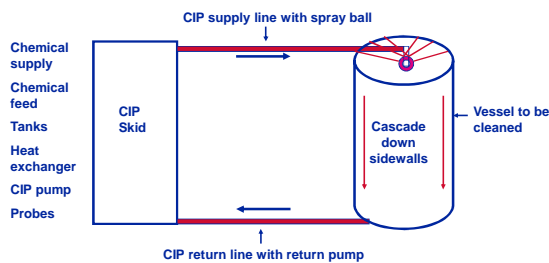
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Common steps

- **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**

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CIP parts



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Manual cleaning

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

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Manual issues

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

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Measuring effectiveness

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

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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

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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

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Residue limits

- For actives based on "safe daily amount"
 - Traditional approach is dose-based calculation
 - Newer approach is "health based exposure limit" (HBEL)
 - ADE: acceptable daily exposure
 - PDE: permitted daily exposure
- For compounds without dose (such as detergents), use ADI (acceptable daily intake) based on tox information (LD₅₀)

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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 reasonably avoidable
 - leave equipment visually clean
- Last four points in FDA's Q&A on CGMP (6/8/2015)

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Overall carryover equation

$$\frac{(S.D.A.) (B.S.) (S.A.)}{(\text{max. dose Prod.B})(S.S.A.)(S.E.A.)}$$

Where

S.D.A. = safe daily amount of active of A

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)²⁹

Other considerations

- For highly hazardous actives (allergens, cytotoxics, actives with reproductive concerns, etc.)
 - May set limit based on LOD (limit of detection) of analytical technique using best available procedure, **OR**
 - May dedicate equipment, **OR**
 - May set limit on ADE or PDE using the specific highly hazardous property (substitute for 0.001 minimum daily dose of active in equation in previous slide)

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Other considerations (2)

- For highly hazardous actives, may want to look at other modes of potential contamination (these are not strictly process equipment cleaning validation, but may be addressed by risk analysis)
- Non-product contact surfaces (from dusts that become airborne, settle on surfaces, become airborne again, and contaminate next product)
 - Containment practices (including HVAC)
 - Room cleaning practices
- Operator practices, garments

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Default limits

- Default limits are sometimes used if **more stringent** than values based on "safe daily amounts"
- Typical defaults
 - 10 ppm of active in next product (*not* 10 ppm in analytical sample)
 - 4 $\mu\text{g}/\text{cm}^2$ of active based on surface area (this is typical upper limit for visually clean)
- These address situations in which carryover could be excessively high, or address concerns about other product quality effects

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Limit for microbes

- Limits based on scientifically justified carryover calculations usually result in impractically high values
- Most will default to limit of ≤ 25 -50 CFU per 25 cm^2 (≤ 1 -2 CFU/ cm^2) for **non-sterile manufacture**
- For rinse water (non-sterile manufacturing), default to Purified Water specifications

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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

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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

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Specific method

- **Unequivocally** measure target residue in the presence of expected possible interferences
- Examples: HPLC, UPLC, UV, ELISA

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Specific method (2)

- Potential problems with specific methods
 - Interference from cleaning agent or cleaning process by-products
- Active degraded in cleaning process so that residues are degradants, not intact active
 - If degrades and use specific method for active, will always be non-detectable
- Addressed in method design and development

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Non-specific methods

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

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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

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Analytical method validation

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

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Sampling methods

- "Swab" sampling
 - Sometimes called "direct" sampling
- "Rinse" sampling
 - Sometimes called "indirect" sampling

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Swabs

- Advantages
 - Can focus on "worst-case" locations
 - Mechanical means of removing substances
- Issues
 - Interferences from swab
 - Swabbing is a manual procedure
 - Access to sampling sites

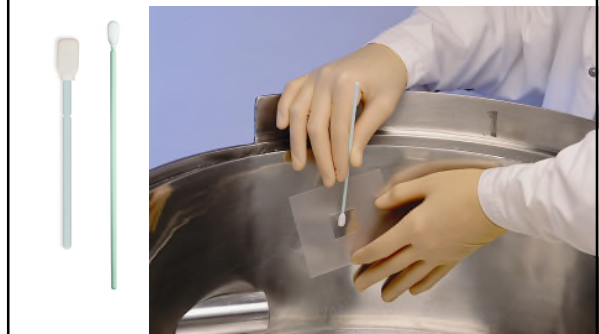
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Swabbing SOP

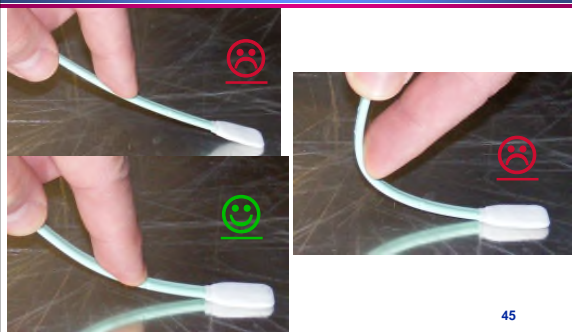
- Specify swab (supplier and part no.)
- Specify surface area to be swabbed (usually 25-100 cm²)
- Specify wet or dry (& solution, if wet)
- Specify template (if used)
- Specify number of swabs
- Specify swab pattern
- Specify vial
- Specify swab transport
- Specify blanks/controls

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Swabs



Pressure effects



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Template vs. "Eyeball"

- Template more consistent
- But template less useful on "non-flat"
- Non-flat surfaces are generally going to be the worst-case locations that require the eyeball method
- My preference: Rather than training on both methods, spend more time on training on eyeball method, since this will be on *most critical* surfaces

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Swab sampling locations

- Most difficult-to-clean locations
 - Good practical common sense
 - Prior experience
- Sites for non-uniform contamination
 - Different materials
 - Functional locations

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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

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"Rinse" sampling

- **Advantages**
 - Sample "inaccessible" locations
 - Provides overall picture
- **Issues**
 - Solubility of residue in rinse solution
 - Need to relate amount in rinse sample to potential contamination of next product

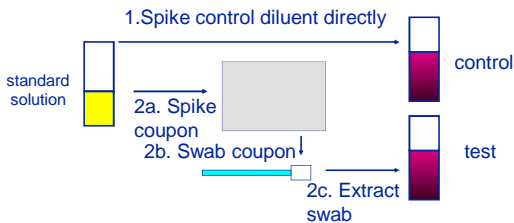
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Recovery studies

- 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

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Swab recovery schematic



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Acceptable recovery

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

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Challenges

- For PPQ 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

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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)

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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)

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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

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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
 - Criteria is change from baseline

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Grouping strategies

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

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Grouping conditions

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

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Representative product

- Representative: most difficult to clean
- Basis of selection
 - Historical
 - Solubility data
 - "Point system" based on several factors
 - Lab/pilot study

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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)

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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

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Grouping conditions

- Look for rationales for:
 - Forming groups
 - Selecting worst case
 - Selecting residue limits

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CV maintenance

- Monitoring
- Change control
- Deviations & CAPA
- Training and retraining
- Continuing control
- Note: "revalidation" is disappearing from FDA lexicon

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Monitoring objective

- Different companies may use the word "monitoring" differently
 - For me, *routine* monitoring is done every cleaning event initially, and then perhaps on a reduced schedule
- Collect data to determine process control
- Monitoring alert/action levels generally more stringent than limits in protocol

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Monitoring during routine 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

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Regular review

- Repeat of PPQ run on any *significant change*
- On a “regular” basis (such as yearly) evaluate consistency based on
 - Monitoring data
 - Change control data
 - Deviations
 - Quality records
 - Training

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