Systems-Based Inspections for Cleaning Validation

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Objectives

- Describe and/or identify:
  - Cleaning processes and approaches
  - Techniques to measure effectiveness
  - Inspectional approach
  - Cleaning Validation documents
  - Significant issues and problems

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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 (7356.002)
  - Documented evidence of effectiveness
  - Also address cleaning agent and bioburden

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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
    - 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

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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* (±)
  - 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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Where to start?

- Assumes you have knowledge of firm's products and production methods
- Start with high level CV document called various things
  - CV Master Plan (term I will use)
  - CV Policy
  - CV Quality Standard
  - Other?

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What's in Master Plan?

- Describes company's approach to CV
- Key items include:
  - What processes covered
  - Limits approach
  - Sampling approach
  - Analytical method approach
  - Grouping/matrixing approach (if used)
  - Number of PPQ (Process Performance Qualification) runs
  - Validation maintenance approach

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What's in Master Plan? (2)

- Other items may include:
  - When verification used in place of validation
  - Deviations / non-conformances
  - Worst case challenges, including dirty hold time and clean hold time
  - Documentation practices
  - Manual cleaning issues
  - Design issues

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What you really want

- Some companies will have high level documents which are *not specific*
- Example: "Limits shall be practical, achievable and verifiable"
  - That's good, but any firm could say this
  - Dig for the document that *clearly states how limits* are set
  - Examples: Dose-based calculations, toxicity/health-based values, industry standard practices

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Other documents to review

- Cleaning procedure (including design)
- Cleaning validation SOP
- Protocols and reports
- What residues and how limits set
- Analytical method selection/validation
- Sampling methods and approach
- Clean and dirty hold times approach
- Validation maintenance/monitoring
- Training records

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

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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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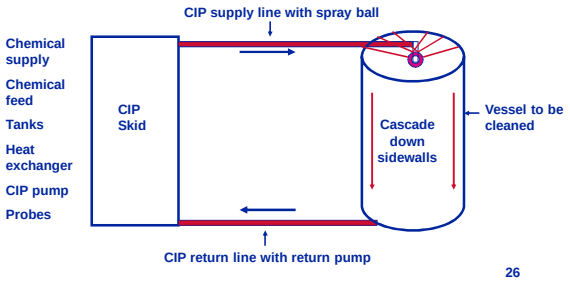
CIP parts



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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
  - Traditional approach is dose-based calculation
  - Newer approach is "health based limit"
    - ADE: acceptable daily exposure
    - PDE: permitted daily exposure
- For compounds without dose (such as detergents), use ADI (acceptable daily intake) based on toxicity information (LD_{50})

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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 dose-based equation

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

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)

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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

- 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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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 cleanness

- 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
- Possible issues: interference from cleaning agent, degradation of active during cleaning process

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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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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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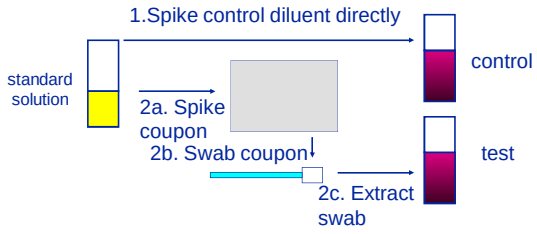
Swab recovery schematic



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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 cleanness
  - 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
- 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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