Systems-Based Inspections for Cleaning Validation

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1

Objectives

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

2

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

3

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

4

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)

5

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

6

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

7

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

8

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

9

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

10

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* (<)

11

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 location most likely to have higher levels of residues (difficult to clean)

12

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

13

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?

14

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

15

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

16

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

17

Other documents to review

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

18

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

19

Cleaning agent options

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

20

Cleaning parameters

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

21

Cleaning parameters (cont.)

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

22

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

23

How apply

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

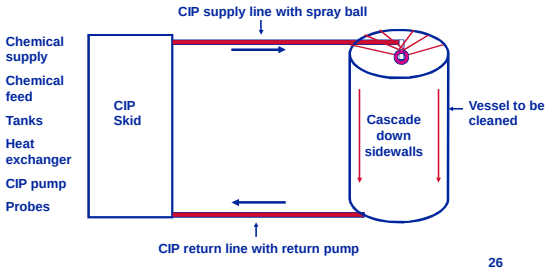
24

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

25

CIP parts



26

Manual cleaning

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

27

Manual issues

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

28

Measuring effectiveness

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

29

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

30

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

31

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})

32

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 FDA's *Human Drug CGMP Note*, 2nd Quarter 2001

33

Overall 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)

34

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)

35

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

36

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

37

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

38

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

39

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

40

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

41

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

42

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)

43

Sampling methods

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

44

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

45

Swab sampling locations

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

46

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

47

"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

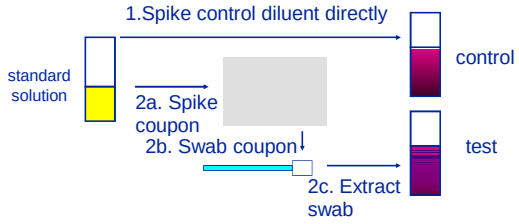
48

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

49

Swab recovery schematic



50

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)

51

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

52

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)

53

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)

54

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

55

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

56

Grouping strategies

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

57

Grouping conditions

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

58

Representative product

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

59

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)

60

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

61

Grouping conditions

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

62

CV maintenance

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

63

Monitoring objective

- Collect data to determine process control
- Monitoring alert/action levels generally more stringent than limits in protocol

64

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

65

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

66