CLEANING VALIDATION: BASIC PRINCIPLES

WHY CLEANING VALIDATION?

- Any cross-contamination is considered unacceptable
- Some cross-contaminations are known to be critical, e.g. penicillins, cytotoxics
- Other cross-contaminations may have unpredictable effects, e.g. hypersensitivity, cross-reactivity
- Cross-contamination could affect the performance of the product, e.g. stability
- THEREFORE ….
- Cleaning validation is necessary to demonstrate that the methods used to clean manufacturing equipment are adequate to ensure that the risk of cross-contamination is acceptably low.

POSSIBLE CONTAMINANTS

- Product residues
- Cleaning agent residues and breakdown
- Airborne matter
- Lubricants, ancillary material
- Decomposition residues
- Bacteria, mould and pyrogens

SOME OR ALL MAY NEED TO BE CONSIDERED, BASED ON RISK ANALYSIS

REQUIREMENTS FOR A CLEANING VALIDATION STUDY

STANDARDISED CLEANING METHOD SOP

VALIDATED QUANTITATIVE SAMPLING METHOD (i.e. swab)

VALIDATED ANALYTICAL METHOD IN RANGE TO BE MEASURED

STANDARDISED CLEANING METHODS

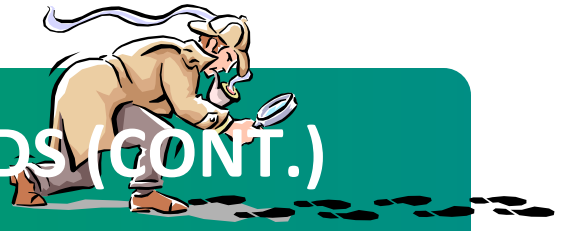
- MANUAL
  - Detailed procedure
  - Trained operators
  - Good documentation
  - Pre-validation data
- AUTOMATIC
  - Defined recipe
  - Equipment qualified
  - Process monitored
  - Pre-validation data

DEVELOPMENT OF CLEANING PROCESS NEEDED BEFORE VALIDATION STUDY

CLEANING INSTRUCTIONS AND RECORDS

- Equipment Cleaning Instruction and Records should include the following parameters:
  - Cleaning and sanitizing agents used (concentration and amounts)
  - Quality of water/solvent used
  - Equipment disassembly/re-assembly requirements
  - Temperature and pressure parameters
  - Flow rates for washes/rinses
  - Start/end times for each step
  - Volume/weight and number of rinses

CLEANING INSTRUCTIONS AND RECORDS (CONT.)



- Tools/utensils employed
- Agitation, recirculation and/or reflux
- Draining and drying
- Identification/inspection of dead-legs
- Method for indicating equipment cleaning status
- Verification of cleaning (incl. visual)
- Method for protecting clean equipment from contamination
- Maximum time intervals between use and cleaning (if any)

CLEANING DOCUMENTATION REQUIREMENTS: [A] MANUAL METHODS

- Sufficient detail to allow plausibility check that correct cleaning procedure has been applied
- Multistep cleaning requires a multistep record! i.e. a single signature for a complex multistep procedure is not adequate.
- Documentation should record key process parameters (times, materials, volumes etc. This is a mini BPR – max. hold times, operators).
- Documentation could be included in the BPR or as a separate form.
- Cleaning records/tickets should be included in the BPR for review.

CLEANING DOCUMENTATION REQUIREMENTS: [B] AUTOMATED SYSTEMS (CIP)

- CIP systems should print out a summary of the cleaning process
- Printout should contain sufficient data to be able to verify that correct programme has been delivered (volumes, temperatures, times)
- CIP printouts should be evaluated against the standard programme (documented procedure)
- Alarms should be investigated and included in deviation system, if appropriate
- CIP equipment should be subject to full calibration (including alarms), requalification and review, as appropriate.

VALIDATED SAMPLING METHODS

- SWAB
- RINSE
- VISUAL INSPECTION
- PLACEBO

SWAB SAMPLES

- Direct sampling method
- Reproducibility
- Extraction efficiency
- Document swab locations
- Disadvantages
  - Inability to access some areas
  - Assumes uniformity of contamination surface
  - Must extrapolate sample area to whole surface

RINSE SAMPLES

- Indirect method
- Recovery study from surface needed
- Useful for cleaning agents and other highly soluble residues
- Can reach inaccessible places (e.g. pipes)
- Sample very large surface areas
- Insufficient evidence of cleaning alone (e.g. need riboflavine test)

VISUAL INSPECTION

- Must always be included where possible
- Can be used after disassembling equipment (gaskets, valves, seals etc.)
- Can be validated (~ 50 ppm is lower limit)
- If equipment is visibly dirty after cleaning – no point in testing!

VALIDATED ANALYTICAL METHODS

- SPECIFIC:
  - HPLC
  - ELISA
  - GC
  - HPTLC
  - Preferred wherever possible as direct quantification
- NON-SPECIFIC:
  - TOC
  - pH
  - Conductivity
  - UV
  - Indirect methods require calibration prior to use

ANALYTICAL METHOD VALIDATION

- Precision, linearity, selectivity
- Limit of Detection (LOD)
- Limit of Quantitation (LOQ)
- Recovery, by spiking
- Consistency of recovery

Validation criteria depends on method and specific application

MICROBIOLOGICAL ASPECTS

- May be included in validation strategy
- Analyse risks of contamination
- Consider equipment storage time (clean and dirty)
- Equipment should be stored dry
- Pyrogen contamination may be included but usually considered separately

REQUIREMENTS FOR A CLEANING VALIDATION STUDY

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VALIDATED ANALYTICAL METHOD IN RANGE TO BE MEASURED

VALIDATION STUDY CAN BEGIN

CLEANING VALIDATION PROTOCOL (1)

- Should include:
  - Objective of the validation
  - Responsibility for performing and approving validation study
  - Description of equipment to be used
  - Risk assessment to determine hard to clean locations

CLEANING VALIDATION PROTOCOL (2)

- Should include:
  - Interval between end of production and cleaning, and commencement of cleaning procedure (HOLD TIMES)
  - Cleaning procedures to be used
  - Any routine monitoring equipment used
  - Number of cleaning cycles performed consecutively
  - Sampling procedures used and rationale
  - Sampling locations (clearly defined)

CLEANING VALIDATION STUDY

- Apply cleaning procedure according to SOP
- Perform visual inspection
- Take required swab and rinse samples according to protocol and SOP
- Analyse samples according to protocol and SOP to determine residues
- Calculate residues based on surface area (swabs) or rinse volume (rinse) to determine “theoretical” residue per equipment
- Calculate total residue per “process train”

SETTING LIMITS

- Regulatory Authorities do not set limits for specific products
- Limits must be justified based on risk assessment (nothing detected → 100 ppm)
- Limit must be achievable and verifiable
- High potency products versus low potency products
- Different limits for campaign changeover versus intra-campaign

EACH COMPANY MUST ESTABLISH ITS OWN LIMITS

SETTING LIMITS: TYPICAL VALUES

- Below level of detection using most sensitive available method (GOOD but DIFFICULT!)
- 10 ppm (generally accepted for “normal” products)
- 1/1000TH minimum dose (good for potent drugs if A. not achievable)
- Using toxicological data, e.g. LD50 (generally useless because levels are usually too high)
- 100 ppm (OK for intra-campaign cleaning)

CLEANING VALIDATION EXAMPLE: 1. EQUIPMENT

Equipment	Surface Area	Residue Measured Product A	Total Residue Product A
Mixer 1	150 m2	0.3 mg/m2	45 mg
Granulator	200 m2	0.43 mg/m2	86 mg
Blender	175 m2	0.66 mg/m2	115.5 mg
Tablet Press	75 m2	1.3 mg/m2	97.5 mg
Bulk Container	50 m2	0.03 mg/m2	1.5 mg

TOTAL THEORETICAL RESIDUE OF **PRODUCT A** IN THE EQUIPMENT: 345.5 mg

CLEANING VALIDATION EXAMPLE: 2. CROSS CONTAMINATION IMPACT

A. Using 10 ppm criterion

Scenario 1 (Product B): Batch size 100 Kg, 100 kg/345.5 mg = 3.45 ppm (OK)

Scenario 2 (Product C): Batch size 30 Kg, 30 kg/345.5 mg = 11.49 ppm (NOT OK)

B. Using 1/1000 therapeutic dose criterion

Product A has a 50 mg therapeutic dose

Scenario 1 (Product B): Patient takes 1 g of B. per day = 1 /14705 dose of A (OK).

Scenario 2 (Product C): Patient takes 0.5 g of C. per day = 1 /8771 dose of A (OK).

NB: Cross-contamination impact depends on size of the subsequent batch and the dosage of that batch taken by the patient

THE ‘MACO’ CONCEPT

- MACO: Maximum Allowable Carry Over
- Calculated using formula:

$$\frac{A \times BS \times SA}{B \times ESA \times SF}$$

- A = Lowest dose, Product A
- B = Maximum daily dose of Product B
- BS = Batch size of Product B
- SA = Swab surface area
- ESA = Surface area of shared equipment
- SF = Safety Factor

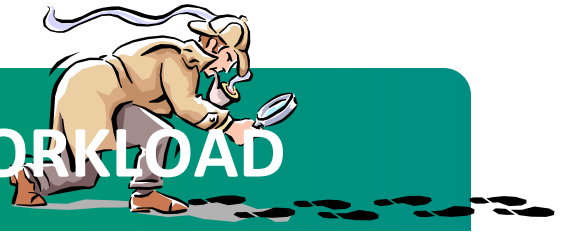
SAFETY FACTORS

- Topicals: 10 – 100
- Oral: 100 – 1,000
- Injectables 1,000 – 10,000
- Ophthalmics:
- Unknown compound: 10,000 – 100,000
- (Numbers expressed as reciprocal of dose)

CLEANING VALIDATION

- IDEAL SCENARIO:
  - Single cleaning procedure for all products
  - All values below LOQ/LOD
  - No restrictions on production sequence
  - No worst case
  - Detergents not needed
  - Automatic CIP
  - Revalidation or verification not needed unless changes are implemented
  -
  -
- REALITY:
  - Different products need specific cleaning
  - Repeated cleaning needed for “worst case”
  - Manual processes
  - Some equipment difficult to clean
  - Detergents required
  -
  - Revalidation or verification may be needed

CLEANING VALIDATION: REDUCING WORKLOAD



- Only test product “families” based on cleanability
- Use bracketing approach for highest/lowest dosages
- Only test a “worst case” product or construct
- Only test a single piece of equipment as a model for other identical items
- Using risk analysis (dedication, single use, product contact consideration)

PERIODIC REVIEW

- Validated cleaning procedures should be subject to a Periodic Review to verify that they continue to operate in a validated state
  - The results of the periodic review should be documented, reviewed, and approved.
  - The review may result in the need for additional studies (e.g. supplemental validation or revalidation)

- The documentation review should consider, but is not limited to the following:
  - Major changes
  - Impact of cumulative changes
  - Significant deviations, including investigations of failures, deviation frequencies and reasons
  - Performance Trends
  - SOPs, and training

- Could be incorporated into APQR (Annual Product Quality Review)

CHANGE CONTROL

- Planned and Unplanned Changes with potential to affect validated cleaning practices should be addressed by established change control and/or investigation procedures.

- Examples of planned changes include:
  - Configuration of equipment or equipment
  - assembly;
  - Change in minimum lot size;
  - Change in product mix produced in the equipment

- Risk assessment of equipment, facility and process changes to determine impact on cleaning procedure validity.

CONCLUSION

- The manufacturer needs a cleaning validation strategy
- Assess each situation on its merits
- Scientific rationale must be developed
  - Equipment selection
  - Contamination distribution
  - Significance of the contaminant
- “Visually clean” may be all that is required