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
• 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
• 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

- Standardised cleaning method SOP
- Validated quantitative sampling method (i.e. swab)
- 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)
### CLEANSING VALIDATION EXAMPLE:  
#### 1. EQUIPMENT

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

**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:

\[
A \times BS \times SA \\
B \times ESA \times SF
\]

- 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)
• 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)
• 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