Cleaning Validation
A regulatory perspective

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Overview

• Cleaning Validation and GMP requirements
• Risk-based approach to cleaning validation
• Establishing Health Based Exposure Limits
• Revalidation requirements
• Observed practices and common inspection deficiencies
• Summary
• Questions
Contamination control
Cleaning validation

“Cleaning validation is documented evidence that an approved cleaning procedure will reproducibly remove the previous product or cleaning agents used in the equipment below the scientifically set maximum allowable carryover level”

PIC/S Guide to GMP for Medicinal Products; Annex 15 Qualification & Validation
## Current GMP requirements

<table>
<thead>
<tr>
<th>PE009-8</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Part I</strong></td>
<td>Personnel, <strong>Premises &amp; Equipment</strong>, Documentation, <strong>Production</strong>, Quality Control, Contract Manufacture &amp; Analysis</td>
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<tr>
<td><strong>Part II</strong></td>
<td>Personnel, <strong>Buildings &amp; Facilities</strong>, <strong>Process equipment / cleaning</strong>, Materials management, <strong>Production &amp; Process controls</strong>, <strong>Packaging Cleaning validation</strong>, Contract manufacturers, Repackaging APIs by cell culture/fermentation</td>
</tr>
<tr>
<td><strong>Annexes</strong></td>
<td>1, 2, 3, 6, 7, 8, 9, 10, 13, 15</td>
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</tbody>
</table>

- GMPs not prescriptive - allowing flexibility and adoption of new technologies/science.
GMP developments

- PIC/S cGMP – PE009-13
  - Annex 15
  - Annexes 2 & 3
  - Part II - Implementation of QRM
  - Part I Chapter 3
  - Part I Chapter 5
  - Annex 1

- PIC/S adoption of setting health based exposure limit guidelines (EMA)
**Key concepts**

**Health Based Exposure Limits (HBELs)**

- A daily dose of a substance below which no adverse effects are anticipated, by any route, even if exposure occurs for a lifetime.

- Required for cleaning validation of hazardous products in shared facilities.

- Derived from a structured scientific evaluation of relevant data.

EMA/CHMP/CVMP/SWP/169430/2012
No Observable Adverse Effect Level (NOAEL)

- NOAEL must be established for all critical effects identified.
- The NOAEL is the highest tested dose at which no adverse effect is observed.
- If NOAEL is not calculable, the lowest-observed-effect level (LOEL) may be used.
- Determined by toxicological expert.
PDE or ADE?

- **Permitted Daily Exposure** (PDE) represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime.

- **Acceptable Daily Exposure** (ADE) represents a dose that is unlikely to cause an adverse effect if an individual is exposed, by any route, at or below this dose every day.

PDE and ADE are effectively synonymous.
MACO - Maximum Allowable Carryover

Mathematically calculated quantity of residue from a previous product when carried over into a different product that CAN represent potential harm to the patient.

- toxicity/pharmacology
- mode of administration
- batch size
- shared equipment surface area plus a safety factor
Risk-based approach

• Health Based Exposure Limits

• Good knowledge management (ICH Q10)

• Risk based approach (ICH Q9)
  ▪ Risk assessments for operations
  ▪ Cross contamination strategy links to protection of patient
  ▪ Shared facilities - scientific approach to ensure contamination risks are managed appropriately
Bracketing for cleaning validation

• Groups typically based on:
  – Equipment train
  – Cleaning procedure
  – Dosage Form

• Rationale explained in SOP or Cleaning Validation document

• Groupings from which ‘worst-case’ will be selected

• Any product that does not conform to ‘bracket’ must be validated individually
Worst-case determination

• Crucial step in defining contamination limits.

- Product potency
- Batch size
- Cleanability
- Release mechanism
- Product solubility
- Product contact area
- Product toxicity

Worst Case
Worst-case process conditions

- Campaign length (no. of batches or time elapsed)
- Dirty Hold Time
- Minimum limits for manual cleaning:
  - Time for Cleaning Steps
  - Temperature
- CIP programs
Establishing health based exposure limits

Step 1: Hazard Identification

Hazard

- LD$_{50}$
- Mechanism of Action
- Reproductive toxicity
- Genotoxicity
- Carcinogenicity
- Developmental toxicity

Repeat-dose toxicity
Establishing health based exposure limits

Step 2: “Critical Effects”
  • Clinical & non-clinical studies
  • Therapeutic effects
  • Adverse effects

Step 3: Determine NOAEL
  • Based on Step 1 and 2 evaluation
  • Requires toxicological expertise
  • Defined as mg/kg/day
Establishing health based exposure limits

Step 4: Calculate PDE

\[
PDE \text{ (mg/day)} = \text{NOAEL} \times \text{Weight Adjustment} \times F1 \times F2 \times F3 \times F4 \times F5
\]

**NOAEL**: Expressed as mg/kg/day

**Weight Adjustment**: 50 kg

**F1**: A factor (values between 2 and 12) to account for extrapolation between species

**F2**: A factor of 10 to account for variability between individuals

**F3**: A factor 10 to account for repeat-dose toxicity studies of short duration

**F4**: A factor (1-10) that may be applied in cases of severe toxicity

**F5**: A variable factor that may be applied if the no-effect level was not established.
ADE approach

\[
\text{ADE (mg/day)} = \frac{\text{NOAEL} \times \text{Weight Adjustment}}{\text{UFc} \times \text{MF} \times \text{PK}}
\]

**NOAEL:** Expressed as mg/kg/day

**Weight Adjustment:** 50 kg - 60 kg

**UFc:** Composite Uncertainty Factor similar to F1-F5 in PDE formula

**MF:** Modifying Factor

**PK:** Pharmacokinetic Adjustments
MACO determination

\[ \text{MACO (mg)} = \frac{\text{PDE} \times \text{MBS}_{\text{next}}}{\text{SF} \times \text{TDD}_{\text{next}}} \]

**PDE**: Obtained in Step 4  
**MBS\(_{\text{next}}\)**: Min. Batch Size  
**SF**: Safety Factor  
**TDD\(_{\text{next}}\)**: Standard Therapeutic Daily Dose (mg/day)

**Safety factors:**  
Topicals 10 - 100  
Oral products 100 - 1000  
Parenterals 1000 - 10000
## PDE Determination Strategy

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<tr>
<th>Hazard Type</th>
<th>YES</th>
<th>NO</th>
<th>UNKNOWN</th>
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<tbody>
<tr>
<td>Genotoxicant</td>
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<td>Reproductive developmental toxicant</td>
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<td>Carcinogen</td>
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<td>Highly sensitizing potential</td>
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### Basis for the PDE

Justification for selection of "lead" critical effect used for final PDE calculation NOAEL and applied adjustment factors upon which the PDE is based

### Reference(s)

Publication(s) used to identify the critical effect and dose

### Summary of the Expert CV
Revalidation requirements

- Introduction of new “worst-case” product
- Change in “product contact” equipment
- Change in bracketing approach
  - Validation should be assessed for impact
- Annex 15 (PE009-13)
  - Continuous process verification
  - Effectiveness of manual cleaning should be confirmed at a justified frequency
Microbiological risks

• Annex 15 (PE009-13)
  – More prescriptive clauses for cleaning validation
  – Microbial and endotoxin contamination risks

• Appropriate sampling method
  – Represents “worst-case” locations
  – Trained personnel
  – Sample handling before testing

• Validated Test Methods
  – Acceptable recovery
  – Objectionable organisms
Observed practices

Good Contamination Control Practices

• Documented Contamination Control Strategy
• Relies on good knowledge management (ICH Q10)
• Risk based approach (ICH Q9)
  – Risk assessments for operations
  – Cross contamination strategy links to protection of patient
  – Shared facilities - methods follow scientific approach to ensure contaminants and contamination risks are understood and managed appropriately.
• Guidance documents:
  – APIC “Guidance on Aspects of Cleaning Validation in API Plants” (2014)
  – ISPE Baseline® Guide - Risk MaPP
  – PDA TR 29 “Points to Consider for Cleaning Validation” (2009)
Common inspection deficiencies

Deficiency categorisation:

- Assessment of intrinsic hazards presented by the products/processes
- Design of facilities, utilities, equipment and processes
- Controls to address hazards
  - Technical and organisational controls
- Periodic review
Assessment of intrinsic hazards - issues

Poor assessment of molecules handled by the facility:
   • Limited or no data from product sponsor
   • No clear policies on what products are manufactured in which areas
   • Generic evaluation of risks presented by substances

Deficient assessment of processes:
   • No risk assessment for new processes
   • Campaign practices implemented without due validation
Assessment of intrinsic hazards - issues

There was no completed risk assessment in place to justify the current operation of the facility as a shared use, multi-product facility. It was noted that the lines and rooms used for the production of XXXXX were also used for the production of other cytotoxics, steroids, analgesics and non-β-lactam antibiotics in injectable forms. In addition, the site product range included hormonal products, e.g. methyl progesterone.
Assessment of intrinsic hazards - issues

The validation of all cleaning processes for all products and equipment trains used by the manufacturer was based on the cleaning validation of a single liquid product only, (“Product X”) Product X is a flammable liquid product, and the applicability of this specific cleaning validation exercise to the cleaning of powder, granule, tablet, cream, ointment and other liquid processes had not been scientifically established, justified and documented by the manufacturer.

- The written instructions for the cleaning of equipment used in the liquids manufacturing areas, differed to that in the solids manufacturing areas; the methods were not equivalent.
- The limits for allowable residues of Product X were based on a 10ppm carry over into the smallest flammable liquids batch size. It was not possible to extrapolate this calculated limit to other product types or equipment trains.
- Product X was a topical product, and the assessment of allowable carry over did not consider the route of administration for other dosage forms or product types.
Design of processes - issues

In relation to cleaning validation:

- There was no risk assessment or justification available to outline the manufacturer’s current approach to cleaning validation.

- The cleaning validation of the line 2 lyophiliser had been conducted based on the removal of sodium chloride only; multiple active cytotoxic materials were processed in the common lyophilisers.

- For the cleaning validation of XXXX, the locations for residue swabbing in the mixing vessel were not regarded as worst case or hard to clean surfaces. Other areas of the vessel, that were regarded by the inspector as being more difficult to clean, such as inlet ports, sample valves and under the impellor were not tested.

- Cleaning validation had not been performed on the glass “Schott” bottles used for API slurry formulation; these bottles were not labelled as dedicated to a specific active.
Design of Processes - issues

In relation to the existing cleaning validation studies XX & YY:

• The existing cleaning validation for the facility was limited to the AAA and BBB machines only; it was not apparent as to how the cleaning studies were applicable to other equipment trains.

• There was no cleaning validation study available for liquids/creams.

• There was no clearly defined cleaning method for the study; the cleaning SOP used at the time of the validation (Version 1) did not contain sufficient details regarding the specific cleaning methods used. (Also Clause 4.4)

• The cleaning agent used at the time of the validation was “XXXX” but the manufacturer now uses “YYYY” it was not clear as to whether these solutions were equivalent.
Design of processes - issues

In relation to the existing cleaning validation study:

- The surface area calculation was limited to the filling line equipment only, and did not include the upstream of filling process (i.e. formulation) equipment train.
- The study for the effective removal of detergent residues did not reflect the current practices used in manufacturing as the concentration of the detergent was not defined in the cleaning process.
In relation to the proposed cleaning validation study:

- The protocol **did not include consideration of product contact parts** used in the manufacture of dosage forms, e.g. plastic jugs, bowls and sieves used in the manufacturing area.
- The **cleaning method** described in the procedure **did not provide detail** regarding the soak times or method of mechanical removal of residues.
- Specific **swabbing locations** (worst case) within equipment trains **were not clearly defined and justified**; e.g. locations were identified as “hopper” or “perforated plate”
Lack of appropriate controls - issues

- The procedure for label issue (SOP 123) stated that **labels for the powders batches (penicillins)** were to be placed in a **grey box** and secured. The majority of the **boxes used for label issue to the non-penicillin area were grey**, and the mechanism to ensure that boxes that had accessed the penicillin building were not used in the general facility was not apparent.
Lack of Appropriate Controls - issues

The cleaning record for the paclitaxel compounding area indicated that the room was clean; however the inspector observed:

- A large pool of standing water was observed on the floor
- White powder residue was observed around the balances
- White residue was observed on the floor in the area
Lack of appropriate controls - issues

Re-usable equipment for CYTOTOXIC was stated to be dedicated, however the inspector observed that:

- Although the filling needles and carboy siphon tubes were marked, these filling needles and carboy siphon tubes were stored mixed up with needles and siphon tubes for other products.

- Although the Equipment Preparation List for CYTOTOXIC stated “use CYTOTOXIC dedicated equipment” the records available did not demonstrate that CYTOTOXIC dedicated equipment was used, and the system in place did not clearly demonstrate that CYTOTOXIC dedicated equipment was controlled in a manner to ensure that the dedicated equipment was not used for the manufacture of other products.

- The flasks used for the collection of CYTOTOXIC flush and priming solutions were not dedicated to CYTOTOXIC.
Ineffective periodic reviews - issues

The (cleaning) studies were last performed in 2007 and were based on the cleaning and carry-over from PROD A capsules. The cleaning validation had not been modified or reconsidered in light of new products or equipment introduced to the site since the completion of the study in 2007.

There was no available risk assessment of the current cleaning practices in light of the changes to the product range manufactured on site, i.e. the process ability to effectively clean residues from those additional products introduced into manufacturing since the 2007 study. (Also clauses 1.5 & 1.6)

A 2009 review of the cleaning validation study identified several issues with the 2007 study; issues were noted regarding the swabbing methods used, as well as the spiking of samples. However, those recommendations had not yet been actioned.
Summary

• International GMPs have incorporated HBELs approach to cleaning validation
• Knowledge management and transfer of information is key
• Will need expert advice in establishing PDE limits - sponsors play key role
• This change is important to maintaining patient safety
• Manufacturers and Sponsors need to remain vigilant regarding cleaning validation
Questions