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Cleaning Validation

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Sections

- A Lifecycle Approach
- Quality Risk Management
- Types of Residues
- Setting Acceptable Limits
- Cleaning Methods
- Sampling & Testing
- Matrix Approach
- Regulatory Framework
- Deficiencies

Introduction

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**.


Cleaning Validation is not monolithic

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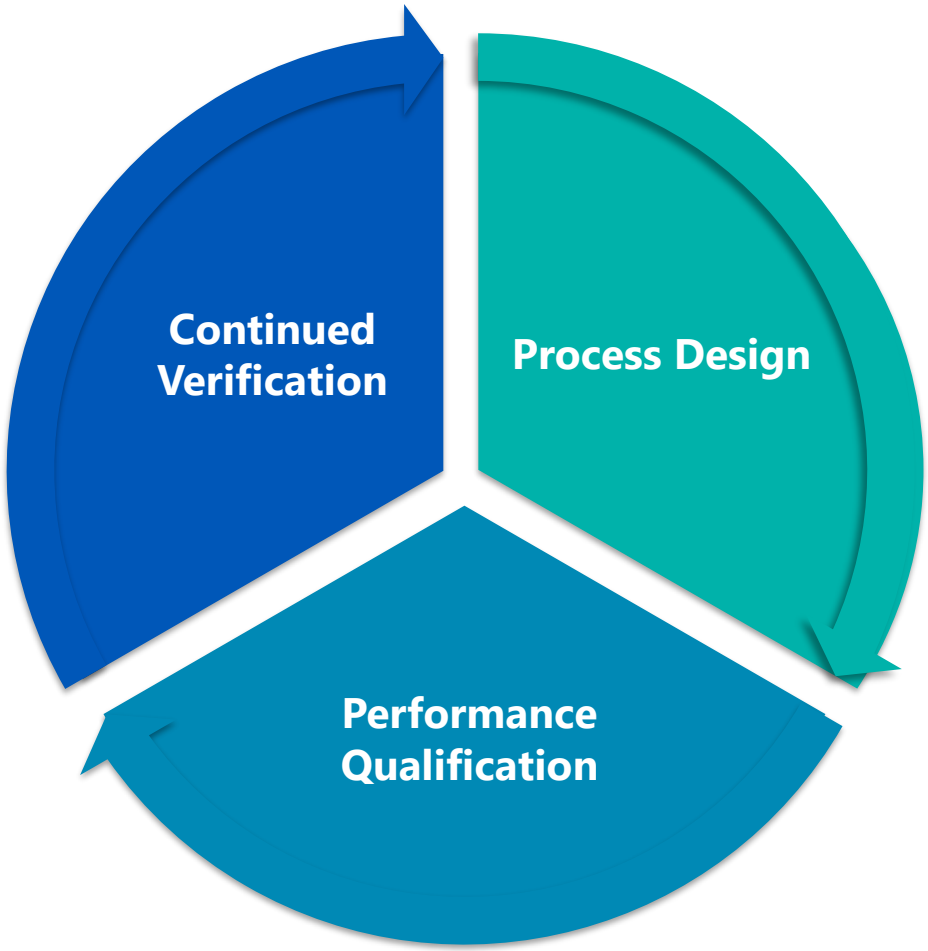
Cleaning Validation Lifecycle



Cleaning Validation Lifecycle*

** Annex 15: 'Qualification and Validation*

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Quality Risk Management approach

- Cleaning Validation is essential to all stages of manufacture
- Quality Risk Management approach followed
- To identify **high risk areas where** Cleaning Validation efforts should be **focused**
- This is more evident in **multiproduct facilities** (greater risk of cross-contamination)

Quality Risk Management approach

A **preliminary risk assessment** to determine the variables which may influence the effectiveness of cleaning procedure:

- Nature of the **residue**
- Equipment **design** (difficult to clean locations)
- **Grouping** of products and equipment & validating **worst-case combinations**
- **Solvent or detergent** (if needed) type needed to remove residue
- CIP vs COP
- **Level of Automation** as opposed to manual cleaning process
- **Processing times** & total number of cycles

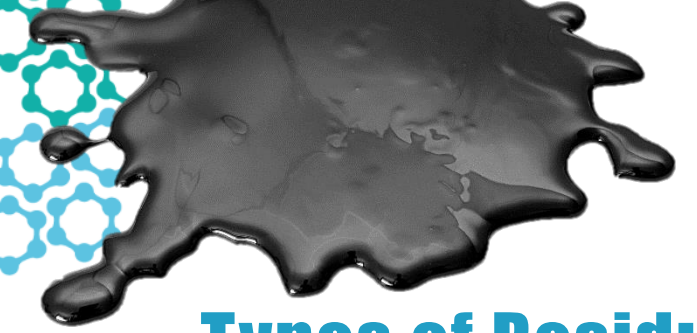
Quality Risk Management approach

Key factors to be taken into account (continued):

- Maximum **length of a campaign** and the impact it may have on cleaning effectiveness
- The influence of the time between manufacture & cleaning **(DHT)**
- The influence of the time between cleaning and use **(CHT)**

If cleaning procedures **not capable of cleaning down to an acceptable level** consider the prospect of using:

- Dedicated equipment or facilities
- Single-use technologies



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Types of Residues

Cleaning Validation should be based on:

- Identification & evaluation of potential residues
- Assigning appropriate acceptable residue limits.

Typical Residues:

- API (small molecule & macromolecule)
- Excipients
- Degradation Products
- Cleaning Agents
- Microbiological agents (Bioburden & Endotoxins)

Cleaning Methods considerations

Depending on available equipment:

- Automated vs Manual process (Automation level)
- Equipment design allows for cleaning-in-place (CIP)
- Disassembly required to clean out-of-place (COP)

The critical cleaning parameters typically include:

- Detergent type & concentration selection
- Temperature & Pressure of cleaning solution
- cleaning action
- Detergent contact & rinse times
- Number of cleaning cycles

Setting acceptable limits

Typically, limits are set to support:

- Visual cleanliness (No visible residues on surfaces)
- Microbiological cleanliness (Absence of Bioburden & Endotoxin)
- Chemical cleanliness (Effective removal of APIs, Excipients, Detergents)

Historically a number of methodologies have been used:

- 10 ppm criterion
- LD50
- 0.001 of dose method

Relying exclusively on these approaches may obscure true patient risk & presents a compliance gap

Health-Based Exposure Limits (HBELs)*

Cleaning Validation limits must be **scientifically justified & based on toxicological evaluation**

Health-Based Exposure Limits (HBELs) through Permitted Daily Exposure (PDE):

- Represents a substance-specific dose unlikely to cause an adverse effect to individuals
- If exposed to ≤ PDE dose (every day for a lifetime)

**Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities*

Health-Based Exposure Limits (HBELs)

PDE determination involves:

- NOAEL
- several adjustment factors to account for various uncertainties
- Weight adjustment for the individual

$$\mathrm{PDE} = \frac{\mathrm{NOAEL} \times \mathrm{Weight\ Adjusment}}{F_1 \times F_2 \times F_3 \times F_4 \times F_5}$$

Once HBEL confirmed, they should be used as part of QRM to:

- Determine what controls need to be in place
- Assess if existing control measures are adequate

Maximum Allowable Carryover (MACO)*

- PDE values are used in the determination of MACO levels
- The acceptable transferred amount of preceding product (α) that can be carried over to the next product (β)

$$MACO = \frac{(PDE_{\alpha} \times MBS_{\beta})}{MDD_{\beta}}$$

PDE_{α} : Permitted Daily Exposure Limit Product (α)
MBS_{β}: Minimum batch size of the next Product (β)
MDD_{β}: Maximum Daily Dose of the next Product (β)

**ISPE Guide: Cleaning Validation Lifecycle – Applications, Methods, and Controls*

Maximum Allowable Carryover (MACO)

$$\mathrm{SAL} = \frac{(\mathrm{PDE}_{\alpha} \times \mathrm{MBS}_{\beta})}{\mathrm{MDD}_{\beta}} \times \frac{sampled\ area}{cummulative\ surface\ area} \times RF\ ^{*}$$

Sample Acceptance Limit (SAL) : The individual swab or rinse sample acceptance limit

$sampled\ area$: The area sampled trough swab or rinse sampling

RF : Recovery factors that relate a single sample to total amount of residue

$cummulative\ surface\ area$: Product contact surface area of the equipment train

* Optional for this calculation

Would approaches other than PDE be possible?

Other approaches could be accepted **if adequately justified**

Example 1 (Therapeutic macromolecules)

- Degrade & denature when exposed to pH/heat extremes ➔ pharmacologically inactive
- HBELs-based PDE limits of (active & intact) product may not be required

Example 2 (Legacy Products)

- Other methods e.g. 10ppm may result in a lower MACO levels than PDE-based ones

ANALYTICAL METHODS

Selection of analytical method for the detection of residues:

- pharmacopeial or individually developed test method
- specific or non-specific methodology
- Capable of detecting (LOD) or quantifying (LOQ) residues

Specific methods include:

- HPLC, UPLC
- titration

Non-specific methods include:

- total organic carbon (TOC)
- pH levels
- conductivity

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CLEANING VALIDATION STUDIES

MACO levels defined for worst-case product

Cleaning cycle development

Analytical method defined

Cleaning Validation (under protocol)

Cleaning soiled equipment

Sampling & testing cleaned equipment

Report if residue reduced down to MACO? (Y/N)

Risk assess frequency of periodic revalidations

Sampling Methods

Through (post-cleaning) sampling ➔ Estimate of the **amount of residue** on equipment

Equipment can be sampled through:

- Rinse sampling
- Swabbing

Sampling locations & sampling method must be selected, based on:

- Equipment (type & design)
- Residue type
- Residue limit

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SWAB SAMPLING

- Used to collect residues directly from surfaces
- Preferred technique for easily accessible locations

RINSE SAMPLING

Flushing rinsing solution over surfaces

Residues measured in the rinse solvent

Preferred method for:

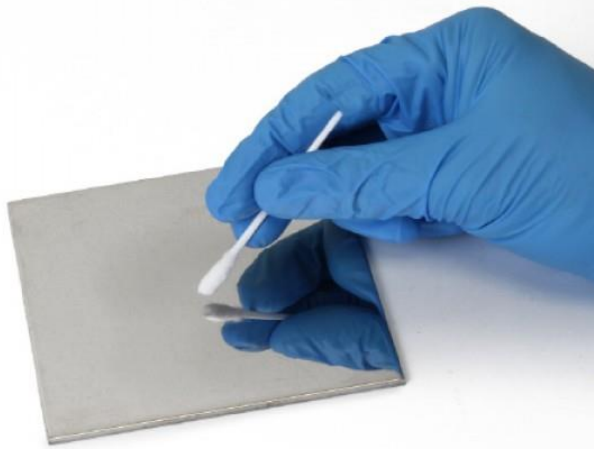
- ❑ Large surfaces
- ❑ Runs of piping
- ❑ Locations inaccessible to swabbing

VISUAL INSPECTION

- Combination of Swab, Rinse sampling & Visual Inspection selected
- Visual Inspection important part of the Cleaning Validation\Verification
- Supplementary to swab & rinse sampling
- Performed under the appropriate lighting conditions
- Borescopes & fiber-optic probes used for hard-to-reach locations

Recovery studies

- **Materials of construction** should be taken into account
- Spiking coupons with **known amounts of contaminants**
- Recovery factors established relating to the result of a **single sample** to **total residue of the sampled area**
- Similar to swab & rinse recovery studies, the level below which a residue is not visible should be determined



DHT, CHT, Campaign length

The following should be assessed & validated:

- Maximum length of a campaign
- Time between manufacture & cleaning **(DHT)**
- Time between cleaning & use **(CHT)** ➔ **Ingress of Microbiological load**

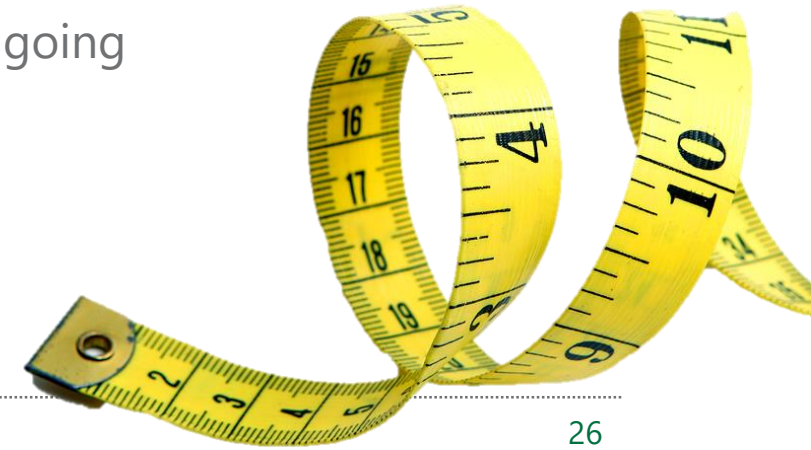
impact on cleaning effectiveness

Cleaning Verifications

Cleaning Verification refers to the practice of **gathering of evidence through measurement** with chemical analysis after each batch/campaign to show that the residues of the previous product or cleaning agents have been reduced below the scientifically set MACO level.

Meant to **provide assurance** that equipment is clean & available for further use in the following cases:

- Cleaning Validation campaign ongoing
- To support re-validations
- In the event of cleaning failures



The Matrix Approach

- Science & Risk-based approach used to streamline validation
- More prevalent in multiproduct facilities
- Grouping equipment and/or processes
- Validating “worst case” equipment/product combinations
- Assuming easier-to-clean equipment/product combination are adequately represented
- New product or equipment is introduced ➔New evaluation is performed to determine whether this constitutes a new worst-case

Deficiencies examples

Cleaning validation protocols & reports did not include swab locations

No periodic cleaning verification of manually cleaned equipment

The threshold at which product was readily visible, had not been established

Deficiencies examples

No PDE data for some of the active pharmaceutical ingredients (APIs)

Swab recovery studies were not performed for all types of surfaces swabbed

The volume of rinse solution used was not taken into account in the determination of the acceptance criteria for rinse samples

Deficiencies examples

The recovery factor identified in swab recovery studies was not applied in the determination and reporting of swab results

The validated LOD & LOQ were above the residue limit acceptance criteria

The MACO limit for the product was based on individual pieces of equipment within the equipment train, rather than on the total cumulative surface area, therefore resulting on significantly higher MACO levels

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Resources

- *EudraLex Volume 4, Part1, Annex 15: 'Qualification and Validation'*
- *EMA/CHMP/ CVMP/ SWP/169430/2012: 'Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities'*
- *ISPE Guide: Cleaning Validation Lifecycle – Applications, Methods, and Controls*

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Thank you