Cleaning Methodology and Validation

IPA Best Practice Document on Cleaning Validation Lifecycle

Tuesday, 14 December 2021

Purpose

IPA Best Practices Document: Cleaning Validation Lifecycle provides a hands-on approach to support the pharmaceutical industry in the development and establishment of a compliant cleaning program and its validation that meets or exceeds regulatory expectations.

This Best Practices Document is **not intended** to interpret the GMP guidance provided by various regulatory agencies; however, it is intended to make an attempt and provide an approach towards setting up a cleaning and validation program that shall comply with requirements.

In Scope:

Active Pharmaceutical Ingredients (Drug Substance) and Finished dosage forms (Drug Products)

Out of Scope:

Biological, Vaccines and Medical devices

Evaluation of Cleaning Validation Practices across Industry

Cleaning Validation Approaches:
More than one approach was seen across Industry and all were found logical.

Following potential areas for improvement were identified:

- Multiple approaches for Worst case selections
- Traditional approach to Lifecycle approach
- Logical grouping of product and equipment matrix for identifying Worst case
- Risk based approach for developing Cleaning Procedures,
- Risk based approach for identifying hard to clean locations
- Bracketing of equipment (size group) for developing cleaning procedures
- Handling of Potent molecules in shared facility
- Handling of failures
- Qualification of Operators, Inspectors and Samplers
- Management of data using software-based applications
- Statistical evaluation of cleaning verification/validation

CV Approach across Pharma Companies

Approach	Company A	Company B	Company C	Company D	Company E	Company F
Worst case selection	1. API Solubility 2. Least Therapeutic dose (potency) 3. Toxicity (least PDE)	RPN based on below aspects: Solubility, Toxicity and Potency	Solubility	1. Difficult to clean products 2. Lowest Solubility 3. Lowest PDE 4. Hazardous category	Lowest Maximum Allowable residue and API solubility	Cleanability (Total insoluble components of formulation)
MACO (API)	Most Stringent of 10 ppm criteria, Dose criteria and PDE criteria	Most Stringent of Dose criteria and PDE criteria Calculates L0, L1, L2, L3 and L4	PDE	PDE	Most Stringent of Dose criteria and PDE criteria	Most Stringent of Dose criteria, 10 ppm & PDE criteria Calculates L1, L2, L3 and L4
MACO (Cleaning agent)	10 ppm criteria and PDE criteria	LD50	PDE	LD50	—	Most Stringent of LD50 & 100 PPM
Grouping	Option for both Equipment and Equipment Train	Product Matrix facility approach	Product along with Equipment grouping	Product group matrix on equipment train	Product group matrix on equipment train	Product along with Equipment grouping

CV Approach across Pharma Companies

Approach	Company A	Company B	Company C	Company D	Company E	Company F
Bracketing of equipment (size group)	—	—	—	—	—	Equipment grouping within 5:1 surface area
Statistical evaluation of cleaning verification/validation	—	—	—	Yes Defined in CVMP	—	Yes (Alert and Action limit to be derived)
Management of data using software-based applications	Yes	Yes	—	—	—	Yes

Traditional approach to Lifecycle approach

Technical clarity provided on how to approach towards Cleaning Validation from a *Traditional Approach* to a *Life Cycle Approach* (3 Stages)

Phase 1: Cleaning Process Design

Phase 2: Cleaning Process Qualification

Phase 3: Continued cleaning verifications (ongoing cleaning verifications)

Individual Phases of Life cycle approach are defined in details to understand the best practices available among industries which can be followed.

Feedback and feedforward mechanism from different phases of cleaning validation : A lifecycle approach

Multiple approaches for Worst case selections

Approach 1: Worst-case based on **Cleanability**

(Formulation assessment: Nature of API and excipients by selecting the worst case using the least soluble product).

Example of formulation assessment (to derive total insoluble material in Kg)

Product Name	Ingredients	Solubility	Comp Qty. (kg.)	Insoluble Qty. (kg.)	Total Insoluble material (kg) in batch
XXXXX Tablets USP YY mg	Active ingredient XXXXX	Insoluble	56.9	56.9	235
	Anhydrous lactose	Soluble	375	NA	
	Dibasic calcium phosphate anhydrous	Insoluble	131.85	131.85	
	Povidone (k-30)	Soluble	25	NA	
	Purified water	Soluble	26	NA	
	Sodium starch glycolate	Insoluble	30	30	
	Magnesium stearate	Insoluble	6.25	6.25	
	Opadry white	Insoluble	10	10	
	Purified water	Soluble	115	NA	

Examples included in Best Practice Document

Multiple approaches for Worst case selections

Approach 2: Based on risk prioritization (RPN)

a) *SRDD: Lowest therapeutic dose (or toxicity data LD50)*
b) *Lowest PDE*
c) *Solubility in water/cleaning solvent*
d) *Cleanability (Hardest to clean): experience from production*

Risk Factor	SRDD (mg)	PDE (mg/day)	Solubility in water/ cleaning solvent	Cleanability
5	Up to 1	Up to 0.01	Insoluble	Difficult
4	> 1 to 5	> 0.01 to 1.0	Very slightly soluble	------
3	> 5 to 50	> 1.0 to 10.0	Slightly/sparingly soluble	Moderate
2	> 50 to 250	> 10.0 to 100.0	Soluble	------
1	> 250	> 100.0	Freely/very soluble	Easy

Examples included in Best Practice Document

Quality Risk Management

Key Components of Risk Assessment :

- *Risk Assessment tool selection: Viz FMEA*
- *Identification of cross functional team (CFT)*
- *Equipment description*
- *Equipment **operation and cleaning** process: Manual or automatic*
- *Major components and sub-parts for **contact and non-contact parts***
- *Schematic diagram*
- *Identification of*
  - *Potential **failure modes for contamination/cross-contamination**.*
  - *Areas difficult to **visually inspect without dismantling**.*
  - *Identification of **powder adherence** probabilities on high risk indirect product contact surfaces, **including ducts,** drains, lower plenum, etc.*

Quality Risk Management contd...

- *Component-wise risk assessment to identify potential failure modes.*
- *Risk management preparedness for conducting FMEA*
  - ***Gemba Walk** to understand the assembling and dismantling of equipment in view of cleaning and probability of deposition of product residues.*
  - ***Interview** with shop floor persons to understand the existing cleaning process and identify action items for enhancement during FMEA assessment.*
- *OOS & deviation related to cleaning validation & line clearance failure respectively (**historical review**).*
- *Retrospective review of QMS events (OOS/Deviations) – <u>rating of probability</u> of occurrence.*

Quality Risk Management contd...

FMEA template:

Component	Sub-parts, if any	Photograph	Product Contact / Non-Contact	Failure Mode	Potential Effect(s) of Failure	Severity (S)	Rationale for Severity Rating	Potential Cause(s) of Failure	Probability of Occurrence (P)	Rationale for Probability Rating	Current Process Controls	How well you can detect the failure mode (D)	Rationale for Detection Rating	Risk Priority Number (RPN)	Risk Mitigation

- *Conclusion and Final Recommendations of assessment:*
  - *Precise instructions for dismantling and cleaning of subparts*
  - *Defining type of cleaning aids (scrubbers, brush, scraper etc)*
  - *Defining aids to examine visual cleanliness checks for components and parts of equipment (torch light, Go-Pro camera)*
  - *Exploring engineering solutions, for cleaning of large surfaces or ducts*

Cleaning checklist of FBD/FBP attached as an Exhibit

Adobe Acrobat Document

Key features:

- ✓ *Sequence of cleaning steps*
  - ➢ *Initial Dry cleaning/Dismantling*
  - ➢ *Pre-Wash/Initial wash,*
  - ➢ *Scrubbing of Equipment parts*
  - ➢ *Washing of Equipment parts and indirect contacts (Ducts)*
  - ➢ *Initial Inspection*
  - ➢ *Purified Water Rinse*
  - ➢ *Cleaning Verification & Inspection (dismantled form)*
- ✓ *Human Error Reduction format*
- ✓ *Pictorial display of key components*
- ✓ *Photographic display of Cleaning Aids*

Grouping and Bracketing Approach

Industry wide approach was brought on one place.

- **Product grouping:**
  - *Logical grouping (Facility, product mix & dosage forms)*
  - *Option provided for **Surrogate** Worst case product*
- **Equipment grouping**
  - *Clarity provided for grouping based on **complexity and sizes** of equipment*
  - *Equipment (**size group**) of not more than 5:1 can be grouped for developing cleaning procedures*
  - *Clarity provided for **confirmatory runs** on equipment group which are not covered under Worst case*
- **Combining Product and Equipment Grouping**

Examples included in Best Practice Document

Handling of Potent molecules in shared facility

Special consideration should be given in manufacturing:

- *Greater level of **personnel protective equipment** for operators*
- *May require **special additional cleaning** of equipment*

Two approaches:

- ***Placebo** batch between two cleaning process*
- *To perform a **second cleaning** before manufacture of the next product, exactly like the first cleaning.*
- ***Routine monitoring** for potent products*

Qualification of Operators, Inspectors and Samplers

Operator qualification :

- *Prerequisites defined (Eyesight check and Training)*
- *Template provided for formal execution*
- *Certification*

Inspectors qualification : (Factor & tools)

- *Distance of viewing,*
- *Angle of viewing*
- *Lighting type*
- *Tools for visual inspection (e.g., a torch or a GoPro camera),*
- *Need to examine key critical surfaces*

Sampler qualification :

- *Clarity provided on how to do sampler qualification*

Management of data using Software-based Applications

- Management of data using qualified and validated software-based applications, especially for facilities handling large number of products and/or equipment.

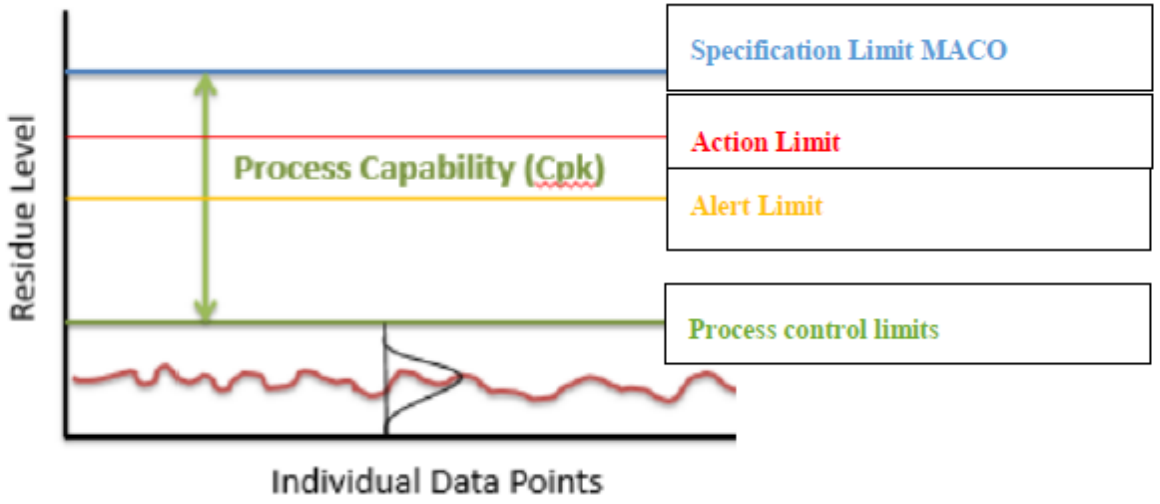
- **Key Benefits of Software:**

  - *Ease of management of the* ***product and equipment data matrix***
  - ***Paperless*** *Protocol & Report preparation*
  - ***Online*** *Study execution including* ***sampling and reporting***
  - ***Change assessment:***
    - *Addition/Deletion of* ***equipment****,*
    - *Addition/Deletion of* ***new product***
    - *Impact on existing Worst Case*
    - *Impact on existing MACO*
  - *Ease of* ***data retrieval***
  - *Online tracking of* ***periodic cleaning verification***
  - *Data* ***trending*** *(Capability analysis)*
  - *Assurance of Data reliability (21 CFR compliance)*

Statistical evaluation of cleaning verification/validation

- Alert and Action Levels may be derived
- Monitoring of drifts in residue results (data points)
- Periodic capability evaluation of cleaning process
- This may help understand:
  - *Effectiveness of manual cleaning*
  - *Effectiveness of cleaning procedure*
  - *Effectiveness of Test methods*
  - *Effectiveness of cleaning aids*
  - *Upkeep of Equipment*

- May trigger investigation or revalidation, case specific



Thank You