Cleaning Validation

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Husband:
I don't know, how to clean..

Wife :
Your mom did not teach you well…!

Your whole family is lazy…..

Cleaning in Kitchen : to be used for next…dish..

Helpful:

- ✓ To avoid traces of previous food.
- ✓ Hygiene.
- ✓ No Microbial proliferation

Objective:

To avoid cross contamination, cleaning is important.

Pharmaceuticals Manufacturing
Shared equipment/ Facilities.

SHARED FACILITIES ARE BEING USED IN PHARMACEUTICALS

CLEANING IS ESSENTIAL TO CONTROL CARRY OVER OF PREVIOUS PRODUCT INTO NEXT PRODUCTS.

VISUAL INSPECTION OF EQUIPMENT FOR ITS CLEANLINESS IS A PRIMARY EVIDENCE

RINSE/SWAB ANALYSIS AND CONTROL

Discussion points

Cleaning validation

Cleaning procedures.

Analytical method to determine traces after cleaning

Sampling methods(Rinse and Swab)

Setting limits

- MACO
- MACO Under Rinse/Swab

Questions and answers

Cleaning validation

Objective: To avoid cross contamination in shared facilities

- Definition

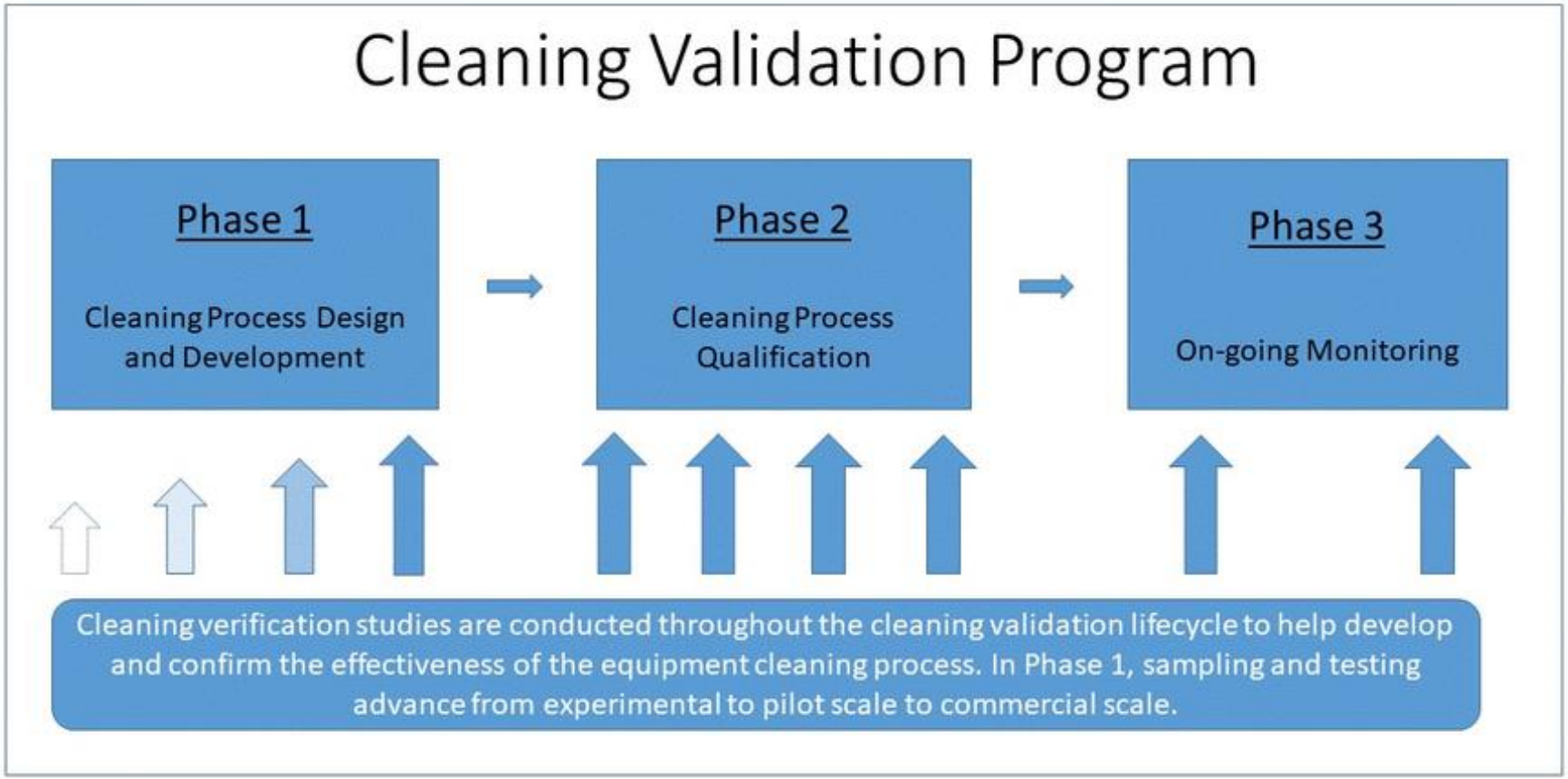
  A defined Cleaning procedure shall be used to clean an equipment.

  After cleaning the equipment, the cleanliness shall be verified using sampling methods(Rinse/Swab)

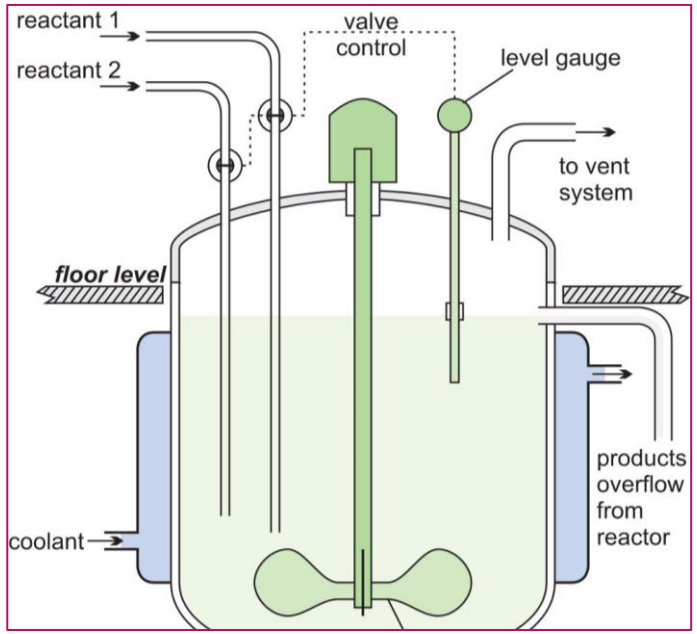
  The results should meet the the predetermined limits consistently, when tested on rinse and swab samples.

Note :

Repeated cleaning and retesting until acceptable residue results are obtained is not considered an acceptable approach.


Cleaning Validation Program
Phase 1
Cleaning Process Design and Development
Phase 2
Cleaning Process Qualification
Phase 3
On-going Monitoring
Cleaning verification studies are conducted throughout the cleaning validation lifecycle to help develop and confirm the effectiveness of the equipment cleaning process. In Phase 1, sampling and testing advance from experimental to pilot scale to commercial scale.

Typical Pharmaceutical Equipment



1. Reactor

2. Centrifuge

3. Tray drier

Cleaning procedure

- Typical cleaning procedure
  - Initially , Remove all the residues from all the parts of the equipment and clean the dirty equipment using cleaning agents/ water / suitable solvent
  - Scrubbing helps to remove residues
  - Reflux / Flush using suitable solvent
  - Finally, dry the equipment
  - Inspect visually.

Selection of cleaning solvent and its good solubility plays a key role in cleaning.

Sampling methods

Two sampling methods are preferred to estimate the residue only one method can not independently give reliability

The two methods are complemented each other.

1. **Rinsing**

   Rinsing solvent, splashing

   Cylindrical shape equipment is normally selected for rinse.

   Where we can not have access to sample directly, rinse is appropriate

   Eg: Reactor

2. **Swabbing (Direct sampling)**

   Where rinsing is not possible, Swab is appropriate

   Difficult to clean areas (corners of equipment) can be helpful by Swabbing.

   Eg: Reactor, drier trays,

Rinsing

- **Advantages of using rinse samples are that**
  - A larger surface area is sampled,

Disadvantage :

A disadvantage of rinse samples is that the residue or contaminant may not be soluble or may be physically occluded in the equipment. In the evaluation of cleaning of a dirty pot, particularly with dried out residue, one does not look at the rinse water to see that it is clean; one looks at the pot.

Procedure

- Rinsing of equipment with a suitable solvent(Solubility) with an appropriate quantity, collect the quantities for analysis.

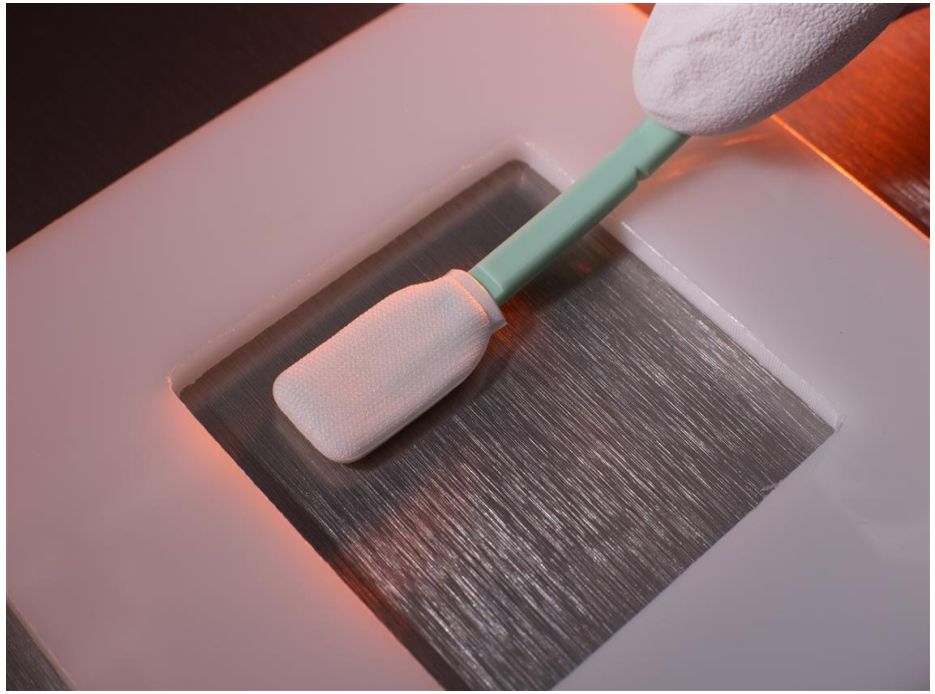
Swabbing

Swabbing

- Using a swab stick, swab a definite area(eg: 100 square cm.) of an equipment.
- Difficult to clean areas shall be assessed by direct swab sampling
- Advantages of direct sampling are that areas hardest to clean and which are reasonably accessible can be evaluated, leading to establishing a level of contamination or residue per given surface area. Additionally, residues that are "dried out" or are insoluble can be sampled by physical removal.
- Disadvantage : Limited access to cover entire area

How swabbing is done

- **Select a template with an area of 10 cm x 10 cm from an equipment**
- **Critical area(Difficult to clean areas) shall be selected,**
- **Wet the swab using diluent,**
- **Swab the area both horizontally and vertically(flip the swab),**
- **Insert the swab into diluent,**
- **Sonicate or squeeze to get the residue into diluent,**
- **Analyze the solution using analytical technique.**



Cleaning agents:

example: Detergents

- **Cleaning agents :**

1. When selecting cleaning agents, ensure that their composition is known.
2. Ensure that cleaning agents are easily removable.

Dirty/Clean hold time

- Dirty hold time :

  time period between “after operation and before cleaning”

- Clean hold time :

  time period between “After cleaning and before batch charging”

This is to provide confidence that routine cleaning and storage of equipment does not allow microbial proliferation.

Setting limits
MACO: max allowable carry over

- *Determine MACO*
- *Determine MACO Under Rinse*
- *Determine MACO Under Swab*

Setting acceptance criteria

- Determination of MACO
- Setting limits on HBEL(Health based exposure limits)

Determination of MACO

- **3** ways of determination is normally used.
  - Using dose based (Previous product Minimum dose and Max dose of next product)
  - Using PDE (Permitted daily exposure)
  - General criteria(Maximum concentration calculation applies) where PDE and Dose criteria is not available

10 ppm criteria is also acceptable where there is no data available(eg : preclinical moities).

For intermediates, the acceptance level is 100 ppm, in general.

Dose based calculation

Requires following inputs

- Previous product minimum dose / PDE / Maximum concentration(eg:0.01%)
- Next product Max daily dose/ standard dose
- Minimum batch size of next product
- Safety factor

PDE and TTC

The 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.

The TTC represents the genotoxic impurity exposure level associated with a theoretical cancer risk of 1 additional cancer in 100,000 patients when exposed over a lifetime.

It should be noted that the PIC/S Guideline also states that the PDE and ADE (Allowable Daily Exposure) are effectively synonymous.

MACO Calculation

Formula : Dose based

Previous product minimum dose in mg x Minimum batch size mg

Maximum dose of next product in mg x Safety factor

Formula : Based on PDE/ADE /NOEL

PDE/ADE /NOEL in mg x Minimum batch size mg

Maximum dose of next product in mg x Safety factor

Formula : Based on Maximum concentration

Maximum concentration x Minimum batch size mg

Safety factor

Table I: Safety factors for the determination of cleaning validation acceptance limits.

Safety factor	Formulation type
10–100	Topical products
100–1000	Oral products
1000–10,000	Injections; eye and ear preparations
10,000–100,00	Research, investigational products

Table I: Safety factors for the determination of cleaning validation acceptance limits

MACO using PDE

Product A will be cleaned out. The product has an ADE of 2 µg and the batch size is 200 kg. The next product B has a standard daily dose of 250 mg and the batch size is 50 kg. Calculate the MACO for A in B.

$$\textbf{MACO} = \frac{\textbf{0.002}\ (\text{mg}) \times \textbf{50 000 000}\ (\text{mg})}{\textbf{250}\ (\text{mg})} = \textbf{400}\ (\text{mg})$$

Result: **MACO is 0.4 g (400 mg)**

Dose based calculation MACO

- Example :

  Product to be cleaned : A, Minimum dose 10 mg

  Next product : B, Maximum dose 200 mg

  Next product batch size: C,50 kg (50000000 mg)

  safety factor for orals : D, 1000

$$\text{MACO (mg)} = \frac{A \times C}{B \times D}$$

$$= \frac{10 \times 50000000}{200 \times 1000}$$

$$= 2500 \text{ mg}$$

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MACO Results per rinse

The MACO resulted in Mg.

Rinse limit(ppm) : $\frac{\text{MACO in mg X RF}}{\text{Rinse volume in liters}}$

Note :

Recovery factor(RF) shall be applied only when the recovery is less than 80%

MACO per swab

Swab limit(ppm) : $\frac{\text{MACO in µg x (swab area in cm}^2\text{/volume in ml) X RF}}{\text{Equipment surface area cm}^2}$

Note :

Recovery factor(RF) shall be applied only when the recovery is less than 80%

Consideration of Equipment train..
(series of equipment used in a process)

When series of equipment are utilized in a single process, all the equipment shall be considered in- terms of

- **Total rinse volume**
- **Total swab points(area and volume used to soak the swab stick)**
- **Total equipment area**

Units shall be noted cautiously during calculations.

Mapping of equipment

Moving One product to many other products

- Calculate MACO using one product to all other product separately
- Out of all the MACO values, Take minimum value
- Consider this minimum value is the final MACO value.
- Then calculate Rinse and swab limits.

Analytical methods and Validation

- Precision
- Accuracy
- Linearity
- Specificity
- LOQ/ LOD

Ensure the LOQ should be 30% of the specification limit.

Run the %Recovery during validation and establish recovery factor.

Analytical method validation and Recovery studies

- Methods should be validated prior to cleaning process samples analysis
- Accuracy, LOQ, LOD is the key parameters.
- For Accuracy, the Recovery shall be ensured by spiking the residue on a suitable plate(SS plate , 10 x 10 cm2) and recover the residue with rinse and swab techniques.
- If the total amount(100%) is recovered, the recovery factor is 1.
- The recovery below 50% is not acceptable. If the recovery is not attaining, alternative procedures shall be developed(eg: suitable solvent with good solubility improves the recovery)

Analytical techniques

- HPLC method are used for lowest limits like 1 ppm , 2 ppm etc..
- UV Spectroscopy methods are most widely used for the limits “10 ppm”.
- UV methods are sensitive to even 1 ppm some products.
- Standard absorbance from validation study can be considered. This helps to avoid standard preparation and analysis during evaluation and calculation of residue.

- Example :

$$\frac{\text{Sample absorbance x 10}}{0.2055}$$

0.2255 AU is the standard absorbance for 10 ppm concentration. Its constant here.

Determining the Recovery factor

- **Recovery factor :**
  Amount determined
  Amount added(spiked)

Example :
5 ppm
10 ppm

= 0.5

= the result should be multiplied by 2 times(1/ 0.5)
Recovery between 0.8 to 1.2 is valid and does not need any correction.

Questions and answers:

Which MACO procedure is accepted across all the regulations.

Answer :

PDE based MACO evaluation is more appropriate method and regulators are expecting this PDE based calculations

If Rinse and swab limits are not comparable, will it be acceptable ?

- Yes. It is acceptable.
- Consider the lowest value and keep a common limit for both rinse and swab

When Higher MACOS OBTAINED !!

If the MACO values are very high like more than 1000 ppm ? Can we follow the same

- Answer:

  In this case, keep 10 ppm acceptance criteria as a worst case.

If cleaning validation is un-successful, what is the way forward

- Answer:

Use dedicated equipment only. Other approaches with a risk assessment is acceptable.

Is the CHT and DHT is part of cleaning validation

- Yes

Question: What about sampling of wire-mesh filters of fabrics filters?

- Answer:

Wire mesh filters of fabrics filters is only possible via rinse sampling.

Is testing rinse solution only enough to support residue determinations for cleaning validation?

- No, Both rinse and swab is required.
- Both are complementary to each other

Difference between verification and validation

- Verification is process of testing each sample to confirm the cleanliness
- Validation is a process to get confidence on the cleaning process is effective and testing can be omitted, or it can be verified periodically based on risk assessment and available data.
- Routine testing can be avoided, after successful validation with a risk-based approach.


Thank You!