International Journal of PharmTech Research
CODEN (USA): IJPRIF, ISSN: 0974-4304
Vol.9, No.3, pp 415-421, 2016

Review on Cleaning Validation in Pharmaceutical Industry

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Abstract: The purpose of this review is to provide information about importance of cleaning validation in pharmaceutical industry. It gives an insight on the various criteria to meet the regulatory requirements and the various cleaning agents used in pharmaceutical industries. It explains briefly about sampling methods and the methods of calculating acceptance criteria. Finally it provides the requirement for the documentation of the cleaning validation protocol.

Introduction

Cleaning validation is an essential part of good manufacturing practices (GMP). Cleaning procedures should normally be validated. Cleaning validation should be directed to process steps where contamination of materials produces the greatest risk to active pharmaceutical ingredient quality.

The U.S. Food and Drug administration (FDA) issued its guide to inspections by title "validation of cleaning process" in 1993. An increased attention has been done from that time in cleaning processes in pharmaceutical manufacturing environments[1].

The prime regulatory concern is to carry the need for cleaning validation is cross-contamination of the desired drug substance either by active pharmaceutical ingredient from previous batch or by residues from the cleaning agents used.

Cleaning validation is a documented evidence to establish that cleaning procedures are removing residues to predetermined levels of acceptability, taking into consideration factors such as batch size, dosing, toxicology & equipment size (WHO TRS 937)[2].

Objective of cleaning validation[3]

It is to prove that the equipment is consistently cleaned of product, detergent and microbial residues to an acceptable level, to prevent possible contamination & cross-contamination.

When cleaning validation is to be performed?[3]

- ✓ It is not necessarily required for non-critical cleaning such as that which takes place between batches of the same product (or different lots of the same intermediate in a bulk process) or of floors, walls, the outside vessels.
- ✓ It should be considered important in multi-product facilities and should be performed among others for equipment, sanitization procedures & garment washing.

Cleaning: Removal of residues and contaminants to a controlled level.

Why to clean?[4]

- ✓ It is performed to remove product and non-product contaminating materials which could effect patient health & or the quality of medicines.
- ✓ Effective cleaning is an essential component of quality assurance and GMP patient safety.
- ✓ Ineffective cleaning can lead to adulterated product, which can be contaminated by the previous product, by cleaning agents and by other extraneous materials introduced into, or generated by the process.

Why to validate cleaning procedures?

- ✓ Customer requirement – it gives the assurance of safety and purity of the product.
- ✓ Regulatory requirement – in manufacturing of API product.
- ✓ It ensures the quantity of the process from an internal control and compliance point of view.

Potential Contaminants

- Airborne particulate matter
- Dust
- Lubricants
- Product residues
- Decomposition residues
- Cleaning agents
- Micro- organisms & endotoxins
- Operator interface
- Previous product
- Solvents & other materials used in the process of manufacturing

Level / degree of cleaning

The cleaning validation mainly depends on

- ✓ The equipment usage (daily or not)
- ✓ The stage of manufacture (early, middle, later)
- ✓ The nature of the potential contamination (toxicity, solubility etc.)

Why regulatory agencies are focusing so much on Cleaning?

- ✓ In the process of manufacture of medicinal products of manufacture of medicinal products and API's, the cleaning of facilities and equipment is an important measure to avoid cross contamination and contamination.
- ✓ With the regulations of GMP cleaning is performed and documented according to the described procedures.
- ✓ Expectations from regulatory –

a. Historically, cleaning effectiveness was often monitored only visually.
b. However, residues of API's excipients, degradation are increasingly an issue in inspections and audits.

Cleaning and regulatory requirements

Cleaning procedures had to be validated to satisfy the following agency requirements

- ✓ FDA published guide to inspections of validation of cleaning processes – 1993.
- ✓ PIC/S guideline to validation – PI-006-3 (2007).
- ✓ Annex 15 address cleaning validation in a separate chapter moreover, the ICH guideline Q7 "GMP for API's" also requires cleaning validation.

Cleaning agents:[2]

Selection criteria-

a. Suitability to remove product residues.
b. Compatibility with the equipment.
c. Ease and sensitivity of assay method.
d. Ease of removal & verification of removal.
e. Toxicity should be low.

Typical cleaning agents

- Alkaline Chemical – NaOH
- Acidic Chemical – Phosphoric acid
- Oxidizer chemical - NaOCl > pH 7
- Detergent formulation
- Water

Cleaning cycle is defined by TACT:

a. Contact time
b. Action (cleaning action, process action, flow rate , pressure)
c. Cleaning reagent concentration
d. Temperature

Sampling method selection[5]

It includes choosing sampling type between rinse water sampling, swabbing surfaces, coupon sampling or placebo sampling.

1. **Rinse water sampling:** In this collecting a sample of an equilibrated after final rinse that has been recirculate overall surfaces. It should be correlated to a direct measuring technique.

2. **Swabbing surface:** Collection of sample in this is by using wipe or swab that is moistened with high purity water (WFI) that is typically wiped over a defined area in a systematic multi-pass way always going from clean to dirty areas to avoid recontamination i.e,10 side by side strokes vertically, 10 horizontally and 10 each with the flip side of the swab in each diagonal direction as shown in figure 1.

3. **Coupon sampling:** It involves the use of a coupon sampling or an actually removable piece of pipe that is dipped into high purity water to extract residues for analysis.

4. **Placebo sampling:** It involves using placebo product and analyzing for residues from the previous batch.

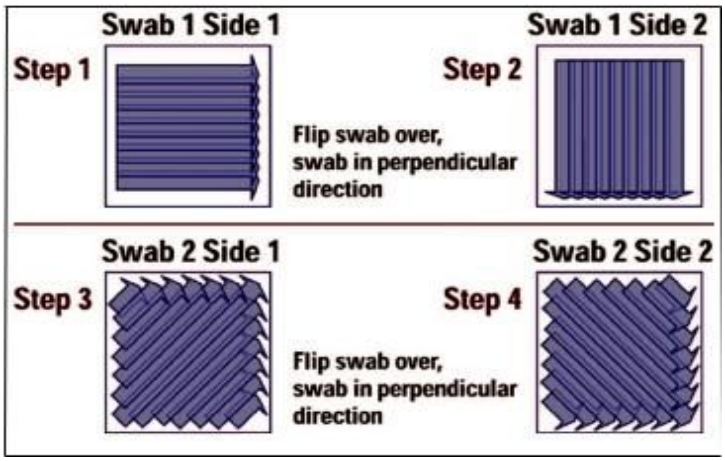

Figure.1: Recommended directions and motions of swabbing

Acceptance Criteria[6]

Companies must demonstrate during validation that the cleaning procedure routinely employed for a piece of equipment limits potential carryover to an acceptable level. That limit established must be calculated based on sound scientific rational.

Methods of Calculating Acceptance Criteria

1. Based on Therapeutic Daily Dose

The principle for the requirement is that the standard Therapeutic Daily Dose (TDD) of the following substance ('contaminated' substance, in this case called "next") may be contaminated by no more than a certain proportion (usually 1/1000 part) of the TDD of the substance investigated in the cleaning validation (contaminating substance, in this case called "previous"). This method only applies when the therapeutic daily dose is known. It is generally used for final product changeover API Process "A" to API Process "B.

Procedure

Establish the limit for Maximum Allowable Carryover (MACO) according to the following equation.

$$MACO = \frac{TDDprevious \times MBS}{SF \times TDDnext}$$

MACO Maximum Allowable Carryover: acceptable transferred amount from the investigated product ("previous")
$TDD_{previous}$ Standard therapeutic dose of the investigated product (in the same dosage form as **TDD_{next}**)
TDD_{next} Standard therapeutic dose of the daily dose for the next product
MBS Minimum batch size for the next product(s) (where MACO can end up)
SF Safety factor (normally 1000 is used in calculations based on TDD)

Example 1:

Product A will be cleaned out. The product has a standard daily dose of 10 mg and the batch size is 200 kg. The next product B has standard a daily dose of 250 mg and the batch size is 50 kg. Both A and B are administrated orally and SF is set to 1000. Calculate the MACO for A in B.

$$MACO = \frac{10\ (mg) \times 50000000\ (mg)}{1000 \times 250\ (mg)} = 2000\ (mg)$$

Result: **MACO is 2 g (2000 mg)**

Example 2:

Now product B in example 1 will be cleaned out. The following product is product A in example 1. Calculate the MACO for B in A.

$$MACO = \frac{250\ (mg) \times 200000000\ (mg)}{1000 \times 10\ (mg)} = 5000000\ (mg)$$

Result: **MACO is 5 kg (5 000 000 mg)**

In API manufacture it is possible to obtain a very high MACO figure. In example 2, the figure obtained is clearly unacceptable. Although there would be no effects expected, the equipment would be obviously dirty and a general GMP limit should be chosen.

Instead of calculating each potential product change situation, the worst case scenario can be chosen. Then a case with most active API (lowest TDD) is chosen to end up in the following API with the smallest ratio

of batch size divided with TDD (MBS/TDD ratio). This could be done if the safety factor is the same for all products (otherwise the lowest MBS/(TDDxSF) ratio should be chosen).

2. Based on Toxicological Data

In cases in which a therapeutic dose is not known (e.g. for intermediates and detergents), toxicity data may be used for calculating MACO.

Procedure

Calculate the so called NOEL number (No Observable Effect Level) according to the following equation and use the result for the establishment of MACO.

$$NOEL = \frac{LD\,50\frac{g}{Kg} \times 70\,(Kg\ a\ person)}{2000}$$

From the NOEL number a MACO can then be calculated according to:

$$MACO = \frac{NOEL \times MBS}{SF \times TDDnext}$$

MACO	Maximum Allowable Carryover: acceptable transferred amount from the investigated product ("previous")
NOEL	No Observed Effect Level
LD_{50}	Lethal Dose 50 in g/kg animal. The identification of the animal (mouse, rat etc.) and the way of entry (IV, oral etc.) is important.
70 kg	70 kg is the weight of an average adult
2000	2000 is an empirical constant
TDD_{next}	Largest normal daily dose for the next product
MBS	Minimum batch size for the next product(s) (where MACO can end up)
SF	Safety factor

The safety factor (SF) varies depending on the route of administration. Generally a factor of 200 is employed when manufacturing APIs to be administered in oral dosage forms. SF can vary depending on substance/dosage form according to (suppose tox values from oral administration) as for example as presented on the next page.

Safety factors:	Topicals	10 – 100
	Oral products	100 – 1000
	Parenterals	1000 – 10 000

Remarks: API`s in development may require higher safety factors due to lack of knowledge.

Calculation of MACO values from toxicological data is frequently done when therapeutic dosage data is not available or not relevant. It is generally employed if the previous product is an intermediate and the following product an API

3. General Limit

If the calculation methods based on therapeutic doses or toxicological data result in unacceptably high or irrelevant carryover figures, or toxicological data for intermediates are not known, the approach of a general limit may be suitable. Companies may chose to have such an upper limit as a policy. The general limit is often set as an upper limit for the maximum concentration (MAXCONC) of a contaminating substance in a subsequent batch.

The concentration (CONC) of the investigated substance which can be accepted in the next batch, according to dose related calculations, is:

	CONC = MACO / MBS
MACO	Maximum Allowable Carryover: acceptable transferred amount from the investigated product ("previous"). Calculated from therapeutic doses and/or tox data.
$MACO_{ppm}$	Maximum Allowable Carryover: acceptable transferred amount from the investigated product ("previous"). Calculated from general ppm limit.
CONC	Concentration (kg/kg or ppm) of "previous" substance in the next batch. Based on MACO calculated from therapeutic doses and/or tox data.
MAXCONC	General limit for maximum allowed concentration (kg/kg or ppm) of "previous" substance in the next batch.
MBS	Minimum batch size for the next product(s) (where MACO can end up)

A general upper limit for the maximum concentration of a contaminating substance in a subsequent batch (MAXCONC) is often set to 5-100 ppm depending on the nature of products produced from the individual company (e.g. toxicity, pharmacological activity, 10 ppm in APIs is very frequent).

If the calculated concentration (CONC) of the previous product (based on MACO calculated from therapeutic doses/tox data) exceeds the general upper limit (MAXCONC), then MAXCONC level will be the limit.

Procedure

Establish $MACO_{ppm}$, based on a general limit, using the following equations.

$MACO_{ppm}$ =MAXCONC x MBS

E.g. for a general limit of 100 ppm: MACO = 0.01% of the minimum batch size (MBS), and for a general limit of 10 ppm: MACO = 0.001% of the minimum batch size (MBS).

Remarks: The ICH impurity document (Q 3) indicates that up to 0.1% of an individual unknown or 0.5% total unknowns may be present in the product being tested.

Example 3:

A product B will be cleaned out. The product has a standard daily dose of 250 mg and the batch size is 50 kg. The next product A has a standard daily dose of 10 mg and the batch size is 200 kg. The general limit of the company is 10 ppm. Calculate the $MACO_{ppm}$ for B in A!

$MACO_{ppm}$ = 0.00001 (mg/mg) x 200 000 000 (mg)= 2000 (mg)

***Result*:** **$MACO_{ppm}$ is 2 g (2000 mg)**

In the worst case a maximum of 2 g of B may appear in API A. This is more reasonable than the limit 5 kg calculated in example 2

4. Swab Limits

If homogeneous distribution is assumed on all surfaces, a recommended value can be set for the content in a swab. This can be used as basic information for preparation of a method of analysis and detection limit.

Procedure

Establish the target value for swab limit for the whole equipment train, using the following equation:

$$\textbf{Target value } [\mu\ g/dm^2] = \frac{\textbf{MACO } [\mu\ g]}{\textbf{Total surface } [dm^2]}$$

Also other methods with different swab limits for different surfaces in a piece of equipment and/or equipment train can be used. Using this approach, the total amount found on the equipment train has to be below the MACO.

5. Rinse Limits

The residue amount in the equipment can be assumed to be equal to the amount of residue in the last wash /boil) or rinse solvent portion. The assumption is based on the worst case consideration, that a further washing or rinsing run (or any reaction) would not wash more than the same amount of residue out of the equipment as the analysed solvent portion did.

The MACO is usually calculated on each individual product change over scenario and individual acceptance criteria are established using the following equation:

$$\textbf{Target value } \left[\frac{mg}{l}\right] = \frac{\textbf{MACO } [mg]}{\textbf{Volume of rinse or boil } [l]}$$

For quantitation a solvent sample is taken, the residue in the sample is determined by a suitable analytical method and the residue in the whole equipment is calculated according to the following equation:

$M = V \times (C - C_B)$

Where,

M Amount of residue in the cleaned equipment in mg.
V Volume of the last rinse or wash solvent portion in l.
C Concentration of impurities in the sample in mg/l.

C_B Blank of the cleaning or rinsing solvent in mg/l. If several samples are taken during one run, one and the same blank can be used for all samples provided the same solvent lot was used for the whole run.

Requirement: M < Target value.

Documentation[7]

A Cleaning Validation Protocol is required laying down the procedure on how the cleaning process will be validated. It should include the following: -

- ✓ The objective of the validation process

- ✓ Responsibilities for performing and approving the validation study
- ✓ Description of the equipment to be used
- ✓ The interval between the end of production and the beginning of the cleaning procedures
- ✓ Cleaning procedures to be used for each product, each manufacturing system or each piece of equipment
- ✓ The number of cleaning cycles to be performed consecutively
- ✓ Any routine monitoring equipment
- ✓ Sampling procedures, including the rationale for why a certain sampling method is used
- ✓ Clearly defined sampling locations
- ✓ Data on recovery studies where appropriate
- ✓ Analytical methods including the limit of detection and the limit of quantitation of those methods
- ✓ The acceptance criteria, including the rationale for setting the specific limits
- ✓ Other products, processes, and equipment for which the planned validation is valid according to the "bracketing" concept; and - When Re-validation will be required.

Conclusion

Cleaning validation provides a means of proving that the contamination levels of proving that the contamination levels have been reduced below contamination acceptable limits.

Cleaning validation programme should be based on detailed cleaning procedures, a validation protocol, validated methods, a change control programme, and a validation report

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