

Cleaning Validation in Pharmaceutical Industry- An Overview

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ABSTRACT

Manufacturing of Pharmaceutical products shall demonstrate a control to reproduce consistently the desired quality of product, wherein the control of cross-contamination plays an important role. An effective cleaning shall be in place to provide documented evidence that the cleaning methods employed within a facility consistently controls potential carryover of product (including intermediates and impurities), cleaning agents and extraneous material into subsequent product to a level which is below predetermined levels. Pharmaceutical manufacturers must validate their cleaning process to ensure compliance with cGMP regulations. So it is necessary to validate the cleaning procedures to ensure safety, efficacy, quality of the subsequent batches of drug product and regulatory requirements in Pharmaceutical product manufacture. In this article cleaning validation and cleaning validation program discussed in brief.

Key words: Contamination, cleaning validation, cleaning validation program.

INTRODUCTION ^[1,2]

Cleaning validation is documented evidence with a high degree of assurance that one can consistently clean a system or a piece of equipment to predetermined and acceptable limits. The objectives of good manufacturing practices (GMP) include the prevention of possible contamination and cross-contamination of pharmaceutical starting materials and products. Pharmaceutical products can be contaminated by a variety of substances such as contaminants associated with microbes, previous products (both active pharmaceutical ingredients (API) and excipient residues), residues of cleaning agents, airborne materials, such as dust and particulate matter, lubricants. Adequate cleaning procedures play an important role in preventing contamination and cross-contamination. Validation of cleaning methods provides documented evidence that an approved cleaning procedure will provide clean equipment, suitable for its intended use.

DEFENITION ^[3,4]

• To attain documented evidence, which provides a high degree of assurance that the Cleaning procedure can effectively remove residues of a product and a cleaning agent from the manufacturing equipment, to a level that does not raise patient safety concerns.

- Cleaning validation is a documented process that proves the effectiveness and consistency in cleaning a pharmaceutical production equipment
- Validations of equipment cleaning procedures are mainly used in pharmaceutical industries to prevent cross contamination and adulteration of drug products hence is critically important

ADVANTAGE OF CLEANING VALIDATION ^[5]

- Assurance of quality & safety.
- Government regulations.
- Product integrity,
- Microbial integrity,
- Cross contamination integrity,
- Batch integrity,
- Equipment reuse,
- Reduction of quality costs.
- Making good business sense.
- Less down time, fewer batch failures and may operate / clean more efficiently.

CLEANING MECHANISM

Several basic mechanisms exist to remove residues from equipment, including **Mechanical action** refers to physical actions such as

- brushing
- scrubbing
- pressurized water to remove particulates.

Dissolution involves dissolving residues with a suitable solvent. The most common and practical solvent is water because of its advantages: water is non-toxic, cheap, does not leave residues, and is environment friendly.

However, in some cases it may be preferable to use a non-aqueous solvent or a combination of both aqueous and non-aqueous solvents due to the solubility characteristics of the materials.

Alkaline or acidic solvents, for example, can enhance dissolution of the materials and could be advantageous.

Detergency requires the use of surfactant, usually in an aqueous system. Detergents act in four different ways:

- wetting agents
- solubilizers
- emulsifiers, and
- dispersants.

Usually detergents possess all these properties which broaden their action.

Chemical reactions such as oxidation and hydrolysis in which the residues are chemically changed. Example: Sodium Hypochloride

CLEANING AGENT

- Detergents should facilitate the cleaning process and be easily removable. Detergents that have persistent residues such as cationic detergents which adhere very strongly to glass and are difficult to remove, should be avoided where possible.
- The composition of the detergent should be known to the manufacturer and its removal during rinsing, demonstrated.
- Acceptable limits for detergent residues after cleaning should be defined. The possibility of detergent breakdown should also be considered when validating cleaning procedures.
- Detergents should be released by quality control and, where possible, should meet local food standards or regulations.

Example of few solvent listed below-

- aqueous cleaning- water
- organic solvent- acetone, methanol, ethyl acetate
- water surfactant- SLS, SDS

- chelants solvent (acid EDTA, NTA, SHMP /base NaOH, KOH)
- Acid- Glycolic acid, citric acid
- oxidant- NaOCl, H₂O₂

CLEANING VALIDATION PROGRAM ^[6,7,8,9,10,11,12,13,14]

- A. Selection of cleaning Level (Type)
- B. Selection of cleaning method
- C. Selection of sampling method
- D. Selection of Scientific basis for the contamination limit (acceptance criteria)
- E. Selection of Worst case related to the equipment
- F. Selection of Worst case related to the product
- G. Establishing the storage period after cleaning (hold time study)
- H. Selection of analytical method
- I. Documentation

A. SELECTION OF CLEANING LEVEL (TYPE)

TYPE A: MINOR → This type of cleaning takes place between two batches of same product or between different strengths of the same product. For minor cleaning, cleaning validation is not required, since cross contamination is not an issue.

TYPE B: MAJOR → This type of cleaning takes place between two products.

In this case, validation of the effectiveness of the cleaning procedure in removing residues to the required level is mandatory.

B. SELECTION OF CLEANING METHOD

- Manual cleaning
- Semi automatic procedures
- Automatic procedures
- CIP (Clean-in-place)
- COP (Clean-out-of-place)

Clean-In-Place (CIP) Method

- Cleaning of the equipment is performed in place without disassembling
- Cleaning process may be controlled manually or by an automated program.
- Very consistent and reproducible cleaning method.
- Can be validated readily.
- Being a closed system visual inspection of all components is difficult.

Clean-Out-Of-Place (COP) Method

- Cleaning of disassembled equipment is performed in a central washing machine.

- The washing machine also requires validation such as the temperature, ultrasonic activity, cycle time, cleaning operation sequence, detergent quantity dispensed etc.

Manual Cleaning Method

- Difficult to validate
- Most extensive and elaborate cleaning procedures are required.
- A high quality and extensive training program is required.

The risk involved in manual cleaning processes is taken care of with following:

- Proper washroom design with drying, protection and storage requirement.
- Detailed cleaning SOP
- Training / Qualification of cleaning operators

C. SELECTION OF SAMPLING METHOD

Generally there are two types of sampling that are accepted. The most desirable is the direct method of sampling the surface of the equipment, another method being the use of rinse sampling.

1. Rinse samples (indirect method)

This method is based on the analytical determination of a sample of the last rinsing solvent (generally water) used in the cleaning procedure. The volume of solvent used for the last rinse must be known to allow for the quantitative determination of the contamination.

Advantages

- Ease of sampling.
- Evaluation of entire product contact surface.
- Accessibility of all equipment parts to the rinsing solvent.
- Best fitted to sealed or large scale equipment and equipment which is not easily or routinely disassembled.

Disadvantages

- No physical removal of the contaminant.
- The rinsing solvent may not reach inaccessible or occluded part of equipment.
- Use of organic solvents for water insoluble materials.

2. Swab sampling

It is also known as direct surface sampling method. This method is based on the physical removal of

residue left over on a piece of equipment after it has been cleaned and dried. A swab wetted with a solvent is rubbed over a previously determined sample surface area to remove any potential residue, and thereafter extracted into a known volume of solvent in which the contaminant active ingredient residue is soluble. The amount of contaminant per swab is then determined by an analytical method of adequate sensitivity.

Advantages

- Direct evaluation of surface contamination.
- Insoluble or poorly soluble substances may be physically removed from the equipment surfaces.
- Hard-to-clean but accessible areas are easily incorporated into the final evaluation.

Disadvantages

- Difficult to implement in large-scale manufacturing equipment.
- Extrapolation of results obtained for a small sample surface area to the whole product contact surface area.

Sampling Method Selected

Looking at the advantages and disadvantages of both the sampling methods swab sampling method was selected. The cleaning procedure uses water as a solvent and we have dosage forms having active ingredient which is insoluble in water.

Sampling Location and Number of Samples

The sample locations are dictated by worst-case conditions. The equipment's hard to clean locations are identified based on cleaning experience and the design of equipment. The number of samples should take into consideration the equipment surface area, design, shape, operating principle and construction material.

Sample Surface Area

Sample surface areas usually vary from 25 sq.cm to 100 sq.cm.

Swab Recovery Study

A swab recovery study is performed to determine the ability of the swab to quantitatively remove the contaminant from the surface sampled.

Once the acceptance limit of cleaning validation is determined swab recovery study should be carried out. Product solutions of 50%, 100% and 150% of the acceptable limit of area are prepared and spiked on the model surface equivalent to the swab surface area. Surface is dried under gentle airflow. Surface is sampled as per the standard swabbing technique, which will be used for sampling. The swab is tested as per the Validated Analytical procedure.

$$\% \text{ Recovered by the swab} = \frac{\text{Test result reported}}{\text{Known amount of product spiked}} \times 100$$

There should be evidence that samples are accurately recovered.

For example, a recovery of > 80% is considered good, > 50% reasonable and < 50% questionable.

Recovery factor shall be taken into consideration while calculating the Acceptable limit for residue.

D. SELECTION OF SCIENTIFIC BASIS FOR THE CONTAMINATION LIMIT (ACCEPTANCE CRITERIA)

1. Approach 1 (Dose criterion)

No more than 0.1% of the normal therapeutic dose of one product will appear in the maximum daily dose of a subsequent product.

2. Approach 2 (10 ppm criterion)

No more than 10 ppm of one product will appear in another product

3. Approach 3 (Visually clean criterion)

(No residue should be visible on equipment after cleaning.)

Spiking studies should determine the concentration at which most active ingredients are visible. This criterion may not be suitable for high potency, low-dosage drugs.

The acceptance limit calculation for chemical residue shall be based on Dose Criteria and 10 ppm Criteria. Minimum value obtained among these two criterions shall be selected as L1. The calculation for Dose and 10 ppm criteria is given as below.

As per dose criteria

There have been a number of examples of industry guidance documents implementing some form of the toxicology based approach proposed by Dr. Hall.

NOEL (No observed effect level) is amount of drug in mg that does not have any effect on human health.

$$\text{NOEL} = \text{LD}_{50} \times 70 \text{ KG} / 2000$$

where

LD_{50} = Lethal Dose for 50% of animal population in study

NOEL = No observed effect level

70Kg = Average adult dose

2000 = Constant

Now NOEL used to calculate Maximum Allowable Carry Over (MACO).

$$\text{MACO (L1)} = \text{NOEL(A)} \times \text{MBS/SF} \times \text{TDD(B)}$$

Where

NOEL = No observed effect level

MBS = Maximum batch size

TDD = Total daily dose

SF = Safety factor

(A) = Previous product

(B) = Incoming Product

As per 10 ppm criteria

1. MACO (L1) = (Minimum therapeutic dose of product A X safety Factor) / Maximum daily dose of product B

2. L1 = 10 mg of product A per Kg of product B

3. MACO limit of product A into total batch size of the Product B (L2) shall be calculated as per below formulae;

$$\text{L2} = \text{L1} \times \text{minimum batch size of product B}$$

4. MACO limit of product A per sq cm surface area (L3) shall be calculated by using following formulae;

$\text{L3} = \text{L2} / \text{Cumulative product contact surface area of the equipments}$

5. MACO limit of product A per swab area (L4) shall be calculated as per following formulae;

$$\text{L4} = \text{L3} \times \text{swab area (cm}^2\text{)}$$

6. MACO limit of product A per rinse (L4) shall be calculated as per following formulae;

$$\text{L4(Rinse)} = (\text{L3}) \times (\text{area rinsed}) / (\text{Amount of rinsing solvent})$$

E. SELECTION OF WORST CASE RELATED TO THE EQUIPMENT.

Bracketing by equipment should be done only when it is similar equipment, or the same equipment in different sizes (e.g. 300-L, 500-L and 1000-L tanks). An alternative approach may be to validate the smallest and the largest sizes separately.

The worst case for a group of equipment is represented by the equipment with the larger product contact surface and the hardest-to-clean locations.

F. SELECTION OF WORST CASE RELATED TO THE PRODUCT

Only one product out of a group of product processed in a piece of equipment is selected for the cleaning validation study, based on the lowest solubility of the active ingredient and its therapeutic dose.

G. ESTABLISHING THE STORAGE PERIOD AFTER CLEANING (HOLD TIME STUDY)

The objective for establishing time limit between equipment cleaning and reuse is to ensure that the equipment remains clean till the next use. This needs demonstration that there is no microbial proliferation in cleaned equipments during storage. For establishing the time limit, the equipment should be dried. Initial swab samples for surface should be taken. Thereafter, the equipment should be protected as prescribed in the SOP and stored in its designated area. Periodic samples of product contact surface for microbiological contamination should be taken. (1st day, 2nd day, 3rd day etc.)

Based on the data generated establish the acceptable time limit.

H. SELECTION OF ANALYTICAL METHOD

There are many analytical techniques available that can be used in cleaning validation

The Basic Requirements for the Analytical Method.

1. The sensitivity of the method shall be appropriate to the calculated contamination limit.
2. The method shall be practical and rapid, and, as much as possible use instrumentation existing in the company.
3. The method shall be validated in accordance with ICH, USP and EP requirements.

4. The analytical development shall include a recovery study to challenge the sampling and testing methods.

1. SPECIFIC METHODS

- Chromatographic methods such as GC, HPLC etc.
- Thin layer chromatography
- Specific ion meter

Of the above methods, chromatography methods are the methods of choice, as they separate analytes, are highly specific, highly sensitive, and quantitative. But the methods are costly and time consuming.

2. NON-SPECIFIC METHODS.

- Spectrophotometric methods in the visible, infrared, or UV ranges
- Total organic carbon (TOC)
- Other Methods

For monitoring cleaning procedure TOC method is used. It offers at a moderate cost and in addition to its rapidity, a detection capability down to the *ppb* range.

I. DOCUMENTATION

1. Detailed cleaning procedure(s) are to be documented in SOPs.
2. A Cleaning Validation Protocol is required to define 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 procedure.
- The number of lots of the same product, which could be manufactured during a campaign before a full cleaning is done.
- Detailed 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 requirement.
- Sampling procedures, including the rationale for why a certain sampling method is used.

- Clearly defined sampling locations.
 - Data on recovery studies where appropriate.
 - Validated 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 a “bracketing” concept.
 - Change Control/ Re-validation.
3. Depending upon the complexity of the system and cleaning processes, the amount of documentation necessary for executing various cleaning steps or procedures may vary.
 4. When more complex cleaning procedures are required, it is important to document the critical cleaning steps. In this regard, specific documentation on the equipment itself which includes information about who cleaned it, when the cleaning was carried out, the product which was previously processed on the equipment being cleaned should be available. However, for relatively simple cleaning operations, the mere documentation that the overall cleaning process was performed might be sufficient.
 5. Other factors such as history of cleaning, residue levels found after cleaning, and variability of test results may also dictate the amount of documentation required. For example, when variable residue levels are detected following cleaning, particularly for a process that is believed to be acceptable, one must establish the effectiveness of the process and of the operator performance. Appropriate evaluations must be made, and when operator performance is deemed a problem, more extensive documentation (guidance) and training may be required.
 6. A Final Validation Report should be prepared. The conclusions of this report should state if the cleaning process has been validated successfully. Limitations that apply to the use of the validated method should be defined (for example, the analytical limit at which
 7. Cleanliness can be determined). The report should be approved by management.

REVALIDATION CRITERIA

A change control system is in place to ensure that all changes that might impact the cleaning process are assessed and documented. Significant changes should follow satisfactory review and authorization of the documented change proposal through the change control procedure. Minor changes or changes having no direct impact on final or in-process product quality should be handled through the documentation system.

Revalidation shall be carried out in case of following;

1. If the solubility of the new product being added is less than the previously considered worst-case product.
2. If the potency of the new drug is lower than the previous worst case product.
3. Change or any major modification to the equipment, which has significant effect on the contact surface area.
4. Change in cleaning agent or its concentration wherever applicable.
5. Change in cleaning procedure (SOP).
6. Failure during routine monitoring.

VALIDATION REPORTS

A validation report is necessary to present the results and conclusions and secure approval of the study.

The report should include the following:

1. Summary of or reference to the procedures used to clean, sample and test.
2. Physical and analytical test results or references for same, as well as any pertinent observations.
3. Conclusions regarding the acceptability of the results, and the status of the procedure(s) being validated.
4. Any recommendations based on the results or relevant information obtained during the study including revalidation practices if applicable.
5. Approval of conclusions.
6. Review any deviations for the protocol that occurred.
7. In cases where it is unlikely that further batches of the product will be manufactured for a period of time it is advisable to generate interim reports on a batch by batch basis until such time as the cleaning validation study has been completed.

FDA REQUIREMENTS ^[8]

1. FDA expects firms to have written standard operating procedures (SOP) detailing the cleaning process used for various pieces of equipment.
2. If firms have a specific cleaning process for cleaning between different batches of the same product and use a different process for cleaning between product changes, FDA expects the written procedures to address these different scenarios.
3. If firms have one process for removing water-soluble residues and another process for non-water soluble residues, the written procedure should address both scenarios and make it clear when a given procedure is followed.
4. It is required by the FDA, in the general validation procedure, that the personnel responsible for performing and approving the study should comply with the acceptance criteria and the revalidation data.
5. FDA expects firms to prepare specific written validation protocols in advance for the studies to be performed on each manufacturing system or piece of equipment which should address such issues as

sampling procedures, and analytical methods to be used including the sensitivity of those methods.

6. It is expected that firms conduct the validation studies in accordance with the protocols and document the result of studies.

7. Final validation report is to be approved by the regulatory board which states whether or not the cleaning process is valid.

CONCLUSION

There is practically impossible to prove that production equipment is "clean" at the level of 100%. However, it is possible to prove that the traces of active product remaining spread through the equipment parts are within an acceptable limit and that we are capable of detecting and quantifying these trace levels. A cleaning validation program should contain the assessment of equipment and products, assessment of the impact of a process on routine process, determination of an appropriate cleaning agent and method, determination of acceptance criteria for the residues, determination of a degree of evaluation required to validate the procedure, This article contain a defined cleaning validation program.

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