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# CLEANING VALIDATION: REVIEW

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**ABSTRACT**

Validation is the skill of designing and practicing the designed steps by the documentation. In pharmaceutical industries there is possibilities of contamination, microbial contamination, adulteration of drug with other active ingredients or contamination with other material like raw material, dust, lubricant, intermediates and air born particles. Cleaning validation validate the effectiveness of cleaning procedure for removal of excipient, product residue, degradation product and cleaning agent. Cleaning validation improves the potency and reliability of cleaning in given pharmaceutical production and equipment. The cleaning validation is essential part of the quality assurance. As a result, validating cleaning procedures is critical in the pharmaceutical sector to ensure the safety, efficacy, and quality of drug batches.

The purpose of this work is to provide information about importance of cleaning validation in pharmaceutical industry. It gives an insight on the various criteria to meet the regulatory requirement 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.

**Keywords:** Cleaning validation, cleaning method, contamination, sampling techniques, quality.

## INTRODUCTION

Validation is a systematic approach to identifying, measuring, evaluating, documenting and re-evaluating a series of critical step, in the manufacturing process that requires control to ensure a reproducible final product. It has become a necessary step to ensure better quality of medical product, throughout manufacturing, storage, handling and distribution.

The concept of validation was first proposed by two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, in the mid 1970's in order to improve the quality of pharmaceuticals. The goal of the validation is to ensure that quality is built into the system at every step, and not just tested for at the end, as such validation activities will commonly include training on production material and operating procedures, training of people involved and monitoring of the system in production.

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 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 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 and equipment size.[1]

### ❖ VALIDATION

Validation is defined as establishing documentary evidence demonstrating that a procedure, process, or activity carried out in production or testing maintains the desired level of compliance at all stages.

### ❖ Reasons for Validation

FDA, or any other food and drugs regulatory agency around the globe not only ask for a product that meets its specification but also require a process, procedures, intermediate stages of inspections, and testing adopted during manufacturing are designed such that when they are adopted, they produce consistently similar, reproducible, desired results which meet the quality standard of product being manufactured, such procedures are developed through the process of validation. This is to maintain and assure a higher degree of quality of food and drug products. A properly designed system will provide a high degree of assurance that every step, process, and change has been properly evaluated before its implementation.

## Cleaning Validation

Cleaning means to make any article, piece of equipment and area free from dirt, marks, or any unwanted matter. In pharmaceutical industry there is a great need of cleaning of equipment apparatus and processing area. The improper cleaning can lead to contamination and cross contamination. Pharmaceutical products can be contaminated by various materials such as residue of previously used active pharmaceutical ingredients, raw material, cleaning agents and dust particles.

The main objective of GMP consists of prevention of contamination and cross contamination of materials. Therefore, a perfect cleaning method is required for avoiding the possibilities of contamination and cross contamination, for this a validated program is required, this program is known as cleaning validation. “Cleaning validation is documented evidence which assures that cleaning of equipment, piece of equipment or system will obtain pre-determined and acceptable limits”. Cleaning validation helps in analytical investigation of a cleaning procedure. The purpose of cleaning validation is to verify the efficacy of the cleaning methods for removal of residues of previous product, preservatives, or cleaning agents and microbial contaminants. Cleaning validation fulfils the requirement of regulatory bodies and maintains product quality and safety of consumers.[2]

**When cleaning validation is to be performed?**

- ✓ 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.

**Why to clean?**

- ✓ It is performed to remove product and non-product contaminating materials which could affect 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.

### ❖ Advantages Of Cleaning Validation

1. Assurance of quality & safety
2. Government regulations
3. Batch integrity
4. Equipment reuse
5. Reduction of quality costs
6. Making good business sense
7. Fewer batch failures
8. Cross contamination integrity

## Importance and purpose of cleaning validation

Cleaning validation is

- Not only it is required to comply with regulations, but also it is necessary to satisfy customer's requirements.
- It ensures the safety, identity, purity, and strength of the product which are the basic prerequisites of cGMP (Current Good Manufacturing Practices).
- It provides manufacturers with enough confidence that internal control is well established.

## Objectives of Cleaning Validation

Equipment cleaning and cleaning validation is an Active Pharmaceutical Ingredient (API) area is needed to prevent contamination of a future batch with the previous batch material. Cleaning validation in an API service is really important as cross contamination in one of the pharmaceutical dosage forms will increase the problem therefore it is suitable to perform at least three repeated and successful applications of the cleaning procedure in order to prove that the method is validated.

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.

**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.

i. Historically, cleaning effectiveness was often monitored only visually.
ii. 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.[3]

## Cleaning Validation Program:

Equipment cleaning validation may be performed concurrently with actual production steps during process development and manufacturing. Validation program should be continued through full scale commercial production. The concept "Test-Until-Clean" should be applied. This concept involves cleaning, sampling and testing with repetition of this sequence until an acceptable residue limit is attained.

A validation program generally encompasses at least three consecutive successful replicate to establish that the procedure is reproducibly effective.

If the equipment of the similar size, design and construction is cleaned by the same procedure, studies need not be conducted on each unit as long as a total of three successful replicates are done on similar piece of equipment; this concept is known as equipment grouping.

Cleaning validation program created by a team of Indian industry experts, this Best Practices Document is intended as a reference for the cleaning lifecycle model and a practical guide for applying the theory and concepts to help create compliant cleaning program.

It is aligned with the principles described in the several regulatory guidance documents available on cleaning validation.

The validation of cleaning procedure consists of establishing the documented evidence that the procedure is effective and capable of removing the contaminants associated with previous products (active, byproducts), residue of cleaning agents, potential microbial contaminants associated with previous products (actives, byproducts), residue of cleaning agents, potential microbial contaminants as applicable.

**Lifecycle Approach:**

Cleaning validation traditionally emphasizes on demonstrating through a qualification program that the cleaning methods are effective, and work as intended. However, the current cleaning practices recognize that a better approach is to treat cleaning validation as a lifecycle, where the emphasis is shifted from performing cleaning qualifications to develop logical cleaning methods based on the product and type of equipment followed by qualification, together with ongoing cleaning verifications during use of a cleaning method.

There are three phases involved in lifecycle approach for cleaning validations:
Phase 1: - Cleaning process design
Phase 2: - Cleaning process performance qualification
Phase 3: - Continued cleaning process verification

## Sampling Techniques:

Sampling sites was selected based on the difficult clean geometries of the equipment and these locations are inaccessible i.e. their inaccessibility makes them difficult to clean therefore, before choosing for sampling sites one must be conscious in selecting the desired sampling locations. Equipment is characterized into hot spots and critical sites. Hot spot is the location that is likely to become dirty during the manufacturing process and it is difficult to clean. Critical sites are those locations if remain dirty will certainly show disproportionate level of contamination to the next exhibit batch.[4]

An example of hot spot is bottom of an agitator or instrument port inside a vessel that become soiled during the manufacturing process and proves to be difficult to clean during the cleaning process. Before selecting sample sites, one must evaluate a variety of locations i.e. hot spots and critical sites. The number of sample locations selected for individual equipment was based on the same consideration that was mentioned in sampling location selection i.e. difficult to clean geometries, representative location was disproportionately contaminate the portion of the next batch. Besides sampling sites and sample locations selected was influenced by:

1. Material of construction
2. Over all scale of the piece of equipment.

E.g. in a fluid bed granulator which is of nearly two stories tall may find difficulties to coverage side to side and top and bottom. To ensure adequate cleaning sample locations are preferred on the side wall of this equipment despite the fact that the side wall is made up of the same material of construction and may not find difficult to clean.

1. The common sampling method employed in cleaning validation is rinse sampling and swab sampling.

## A. Swab Sampling:

It usually requires materials which are absorptive and to physically wipe the surface and recover the analyte. Because the need to physically wipe the surface was the preferred method that is readily accessible to human hand or arm.

**Advantages of Swab Sampling:**

1. Dissolve and physically remove sample.
2. Adaptability to wide variety of surfaces.
3. Economically and widely available.
4. May allow sampling of a defined area.
5. Applicable to active, microbial, and cleaning agent residues.

**Limitation:**

1. An invasive technique that may introduce fibers.
2. Results may be technique dependent.
3. Swab material and design may inhibit recovery and specificity of the method.
4. Evaluation of large complex and hard to reach areas difficult.

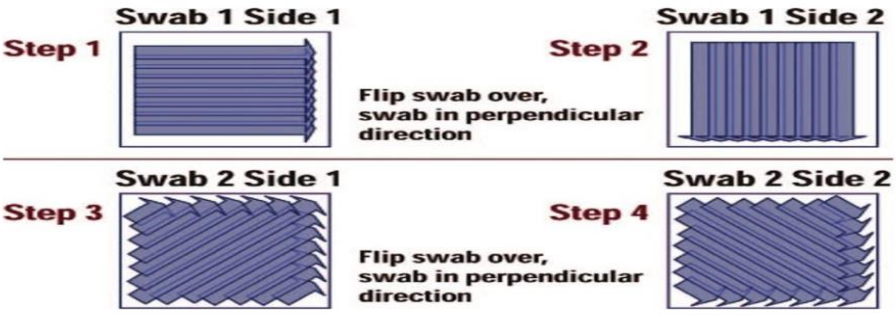


**Figure 1: Recommended directions and motions of swabbing**

## B. Rinse Sampling:

Rinse sampling does not employ mechanical action on the surface and the sample is collected as a final rinse or rinse applied specifically for collecting a validation sample.

**Advantages of rinse sampling:**

1. Easy to sampling
2. Allows sampling of a large surface area and porous area.

**Limitation:**

1. Limited information about actual surface cleanliness in some cases.
2. May lower test sensitivity.
3. Residues may not be homogenously distributed.
4. Inability to detect location of residues.
5. Insolubility of residues.
6. Residues physically occluded in the equipment.
7. Rinse volume is critical to ensure accurate interpretation of results.
8. May be difficult to accurately define and control the areas sampled, therefore usually used for rinsing an entire piece of equipment, such as vessel.

**Figure 2: Rinse sampling technique**

## C. Placebo Sampling:

Placebo is recognized as both potential cleaning techniques and potential sampling techniques. Placebo material comprises of all typical excipients but not the active ingredient. And the placebo batches were passed through a same line so that it will have possibility to scrub of the clean system. The principle involved in placebo is that it is passed through the same pathway as the product therefore; it will have the possibility to scrub off residual product along those pathways. And it usually employed for measuring system cleanliness. It majorly depends on:

1. Excipient solubility in placebo.

2. Appropriate contact time of the placebo for collecting representative sample.

3. Coverage of the placebo in-process pathways ensures removal of the placebo from all equipment location.

4. Quantity of the placebo and residue being matched should be detectable range and the distribution of residue uniformly in the placebo ensures the detection of sample at any portion of the placebo.

### D. Direct Sampling:

It is done by using FTIR or photoelectron emission techniques. By employing these techniques, specific spectra obtained from residue remaining on the surface will directly measure the quality of the surface. The advantage of using these techniques is that sampling and analysis will be taking place in one step and there will be no real loss of sampling system. Where as in swab sampling direct analysis of the surface is limited to the area that are accessible for inspection.[5]

## Detergents:

The efficiency of cleaning procedures for the removal of detergent residues should be evaluated. Acceptable limits should be defined for levels of detergent after cleaning. Ideally, there should be no residues detected. The possibility of detergent breakdown should be considered when validating cleaning procedures. 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 detergents should be known to the manufacturer. If such information is not available, alternative detergents should be selected whose composition can be defined. The manufacturer should ensure that he is notified by the detergent supplier of any critical changes in the formulation of the detergent.

## Analytical Methods:

The analytical methods should be validated before the cleaning validation is performed and the methods chosen should detect residuals or contaminants specific for the substances being assayed at an appropriate level of cleanliness (sensitivity).

The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminants.

Some of the analytical methods which can be used for the analysis of cleaning validation sample include:

- HPLC
- GC
- HPTLC
- TOC
- UV Spectroscopy
- pH
- Conductivity
- ELISA

These methods can be used alone or in combination depending upon the analysis required.

## Documentation:

A Cleaning Validation protocol should include the following:

1) The objective of the validation process.
2) Responsibilities for performing and approving the validation study.
3) Description of the equipment to be used.
4) The interval between the end of production and the beginning of the cleaning procedures.
5) Cleaning procedures to be used for each product, each manufacturing system or each piece of equipment.
6) The number of cleaning cycle to be performed consecutively.
7) Any routine monitoring equipment.
8) Sampling procedures, including the rationale for why a certain sampling method is used.
9) Clearly defined sampling locations.

10) Data on recovery studies where appropriate.
11) Analytical methods including the limit of detection and the limit of quantitation.
12) The acceptance criteria, including the rationale for setting the specific limits.

- The cleaning validation protocol should be formally approved by the plant management, to ensure that aspects relating to the work defined in the protocol, for example personnel resources, are known and accepted by the management. Quality assurance should involve in the approval of protocol and reports.

- A final validation report should be prepared. The conclusions of this report should state that the cleaning process has been validated successfully. Limitations that apply to the use of the validated method should be defined. The report should be approved by the plant management.

- The cleaning process should be documented in an SOP.

- Records of cleaning activity should include:

  a. The area or piece of equipment cleaned;
  b. The person who carried out the cleaning;
  c. When the cleaning was carried out;
  d. The SOP defining the cleaning process; and
  e. The product, which was previously processed on the equipment being cleaned.
  f. The cleaning record should be signed by the operator who performed the cleaning activity.

**Establishment of Limits:**

The rationale for selecting limits for product residues should be logically based on a consideration of the materials involved and their therapeutic dose. The limit should be practical, achievable and verifiable.

The approach for setting limits can be:

- Product specific cleaning validation for all products.

- Grouping into product families and choosing a "worst case" product.

- Grouping products according to risk, e.g. very soluble products, products with similar potency, highly toxic or difficult to detect products.

**ACCEPTANCE CRITERIA:**

| S.No. | Testing Parameter | Acceptance Criteria |
|---|---|---|
| **1** | Physical determination | The equipment should be visually clean i.e. no residue should be visible on equipment after cleaning. |
| **2** | Chemical determination | a) NMT 0.1% of the normal therapeutic dose of any product to appear in the maximum daily dose of the subsequent product.<br>b) NMT 10 ppm of any product to appear in the next product (basis for heavy metals in starting materials).<br>c) For certain allergic ingredients, penicillins, cephalosporins or potent steroids and cytotoxics, the |

| | | |
|---|---|---|
| | | limit should be below the limit of detection by best available analytical methods. |
| **3** | Microbial contamination | Total aerobic counts<br>a) NMT 10 cfu/100ml by rinse method.<br>b) NMT 5 cfu/25cm$^2$ by swab method. |

**CALCULATION OF THE MAXIMUM ALLOWABLE CARRY OVER (MACO):**

For the calculation by considering 0.1% safety factor

$$Limit\ (mg) = \frac{Daily\ therapeutic\ dose\ of\ product\ A\ (in\ mg)}{1000} \times \frac{Minimum\ batch\ size\ of\ product\ B\ (in\ mg)}{Max.qaily\ therapeutic\ does\ of\ product\ B\ (in\ mg)}$$

Where,

Product A = Product manufactured before cleaning

Product B = Next product after cleaning

**For considering 10 ppm as acceptance criteria**

The quantity equivalent to 10 mg/L of the batch size is considered as the acceptance criteria for the acceptance criteria as 10 ppm.

**Calculation of acceptance criteria for Swab samples**

$$Limit\ (PPM) = MACO \times \frac{1000}{C} \times \frac{D}{V}$$

Where,

C = Cumulative surface area of the equipments used (in $cm^2$)

V = Volume or solvent used to dispense swab

D = Swabbed surface area in $cm^2$

1000 is the multiplication factor to convert value in mcg from mg

**Calculation of acceptance for Rinse samples**

$$Limit\ (PPM) = MACO \times \frac{1000}{C} \times \frac{1}{V}$$

Where,

C = Cumulative surface area of the equipments used (in $cm^2$)

V = Volume of solvent used for rinse of the same in mL/$cm^2$ of equipment

1000 is the multiplication factor to convert value in mcg from mg

**Calculation of Recovery factor**

% recovery shall not be less than 75% unless otherwise specified and justified in individual protocol of analytical method validation.

Recovery factor shall be calculated as follows:

$$Recovery\ factor = \frac{100}{\%\ Recovery}$$

**Calculation of worst case**

$$Worst\ case = \frac{Smallest\ batch\ size}{Largest\ daily\ dose}$$

**Revalidation of cleaning procedure:**

Revalidation of cleaning procedure is required if any of the following occur:

- Cleaning procedure is changed
- Raw materials are changed
- Change in formulation
- New detergent
- Change in analytical method for determination of residue
- Major non-traceable contamination occurrence
- Failure during cleaning verification/validation

Revalidation of cleaning procedure shall be performed on a minimum of three cleaning cycles.

**Revalidation Criteria:**
A close view is placed to ensure that some changes can affect the whole cleaning process are identified and recorded. The changes are reviewed; if they have significant effect then the change proposal is made through the change control procedure, which is documented and authorized. If the change is minor or it has no direct effect on quality of the final product may be handled only by the documentation. Revalidation is necessary when;

1. The product has less solubility than the pre-considered worst-case product.
2. The new drug has low potency than the pre-considered worst-case product.
3. The equipment is change or there is any major modification, which can affect the contact surface area.
4. The cleaning agent or its concentration is changed.
5. The cleaning procedure is changed.
6. The procedure gets failed during routine monitoring.[6]

**Validation Reports:**

The validation report is then prepared which contains the result, conclusion and secured approval of the study.

The validation report includes the following:

1. The references/summary of the method used for cleaning, sample and test.
2. The analytical, physical and other observations of test result or reference.
3. The final conclusion with respect to acceptability of the results, and the status of the procedure(s) being validated.
4. If there is any a recommendation given on the basis of the result or information obtained during the study for example revalidation of process.
5. Approval of conclusion.
6. If there is any deviation occurred then protocol is reviewed.

**FDA Requirements:**

1. FDA requires, firm should have written SOPs with detailed cleaning procedure being used for different pieces of equipment.
2. If firm is using specific cleaning procedure for cleaning between two different batches of the same product and uses a different process for cleaning between product changes, FDA requires the written procedures to address these different scenarios.
3. The firms should have a clear written procedure to remove water soluble and water insoluble residue.
4. FDA requires the personnel responsible for performing and approving the study should comply with the acceptance criteria and the revalidation data.
5. FDA requires, firms should have a validation protocols in written before performing the cleaning validation for each manufacturing machine or piece of equipment also carry the sampling procedures, and analytical methods to be used including the sensitivity of those methods.
6. The firm has to conduct the validation according to the protocols and the results should be documented.
7. The regulatory board has to approve the final validation, this express that the cleaning procedure is validated or not.[7]

## CONCLUSION

The pharmaceutical industry should be free from any contamination or cross contamination, it would be safe for the consumer. With the help of cleaning validation any department of pharmaceutical industry can achieve high degree of assurance regarding the cleaning, with this we can minimize any kind of contamination or cross contamination which is may be any residue of previous product, substance of machine or any microbial contamination.

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