Journal Of Harmonized Research (JOHR)

Journal Of Harmonized Research in Pharmacy
7(1), 2018, 19-27

ISSN 2321 – 0958

Original Research Article

IMPLEMENTATION OF CLEANING VALIDATION PROGRAM IN FORMULATION MANUFACTURING PLANT

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Abstract: Equipment cleaning and equipment cleaning validation are two activities that play a critical role in preventing risk to patients by assuring that cross-contamination between products is curtailed to acceptable levels. Incomplete or incorrect cleaning can lead to contaminated product, with residues from previous product batches, cleaning agent and / or other extraneous material being introduced into the product manufacturing process. Cleaning validation is important as current trends show an increase in potent and complex drug substances and biotechnology products. This article will cover all elements of cleaning validation in pharma industry.

Index Terms: Validation, Cleaning Validation, Pharmaceuticals

Introduction: Cleaning validation: Cleaning validation provides documented evidence of the highest assurance that a piece of equipment can be consistently cleaned to levels which are predetermined and acceptable.[2] An important reason for performing equipment cleaning validation is to ensure compliance with regulations of the health agencies. Validation of any process is it cleaning or manufacturing serves an important benefit in identifying and correcting potential complications in the process which may have an impact on the safety, efficacy, purity or quality of the product. This is especially true when succeeding batches of drug product produced using the same equipment [3]. The first FDA guidelines on the subject of cleaning validation were published in the year 1991, following the Barr Laboratories Court Case. Since then, there has been a sea change in cleaning validation procedures. From barely filling a single page of the Bulk Pharmaceutical Chemical and Biopharmaceutical guidance, the documents were extended to provide the Guide to Inspection of Cleaning Validations by FDA (first published in 1992 as a Mid-Atlantic Inspection Guidance, then reissued as an FDA guidance document in 1993). Several GMP

For Correspondence:
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Received on: February 2018
Accepted after revision: March 2018
DOI: https://doi.org/10.30876/johr.7.1.2018.19-27

regulations have been derived from cleaning validation. The origins can be traced to Upton Sinclair's novel "The Jungle," in 1906 which exposed the poor conditions of the meat industry, leading to promulgation of new federal food safety laws. These formed the basis for the cGMPs for both food and drugs as we know them today. Although cleaning was always a part of GMP regulations, there was no unambiguous position regarding cleaning as a process that must be validated. All the grounds were overturned when GMPs were challenged during the Barr Laboratories court case. In that decision, Judge Wolin ruled that cleaning must be treated as a process and must therefore be validated. In 1996, draft revisions to the GMPs were proposed by the FDA to redefine the manufacturing process as that which begins with cleaning operations. The FDA then published "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach" in August 2002. This and the report on the progress of the approach in September 2004, reinforced validation as a requirement in pharmaceutical manufacturing. Even though use of risk-assessment in arriving at decisions for establishing scientific rationales for long formed the basis of cleaning validation requirements, there have been renewed efforts to ensure incorporation of risk analysis documentation in cleaning programs.[1]

Objective: The objective of a cleaning validation program is to validate the effectiveness of equipment cleaning procedure in removing traces of product residues, including degradation products, excipients and /or cleaning agents and also control microbial contamination of equipment. It is essential to validate the cleaning procedures for following reasons: Medicinal products and API can be contaminated by other products manufactured on the same equipment, cleaning agents and certain micro-organisms. In addition, it is a regulatory requirement for pharmaceutical product manufacture. The end objective for both, medicinal products and API is the same - assurance that equipment is clean and that product quality and safety are not adversely impacted. It also provides assurance from an internal control and compliance point of view of manufacture to protect product integrity; to reuse the equipment; to verify the effectiveness of cleaning procedures and to ensure no risks are associated due to cross contamination from other active ingredients or detergents. Why Cleaning Validation [4]: Cleaning validation is also required in following situations, for initial qualification of process/ equipment; critical changes in cleaning procedure; critical changes in formulation; changes in cleaning cycle and change in cleaning agent.

Essential Programs that ensure continued validated status of equipment and required elements: Routinely conducted compliance initiatives on site that maintain quality and affect the company's ability to ensure continued validated status are as follows. Cleaning and testing for product residues must be performed whenever a new product is introduced of equipment is repaired after major breakdown. Monitoring of cleaning after completing validation is vital to ensure validated status. Other important programs include Failure investigation; Change control; Preventive maintenance; Calibration; Revalidation (of equipment & processes); Routine review of procedures for Equipment Cleaning and Cleaning Validation (including equipment sampling procedures for cleaning assessments, e.g., swab, rinse); Development of cleaning procedures (especially for manual cleaning operations); Equipment cleaning and use logs; Visual inspection requirements for cleaned equipment; Equipment quarantine and release procedures.

I. Cleaning Validation Master Plan

Master Plan should [1]: Provide an overview of the site/facility/area that is governed by the Master Plan, provide an overview of the typical manufacturing processes that are to be performed in the area and the dosage forms that are produced, provide an overview of the types

of cleaning that are to be used (e.g., automated Clean-In-Place or Clean-Out-of-Place, semi-automated cleaning or manual cleaning), provide the responsibilities of the various departments having a role in cleaning validation activities and provide the minimum requirements for the cleaning validation program. The process flow is described in Figure 1 below.

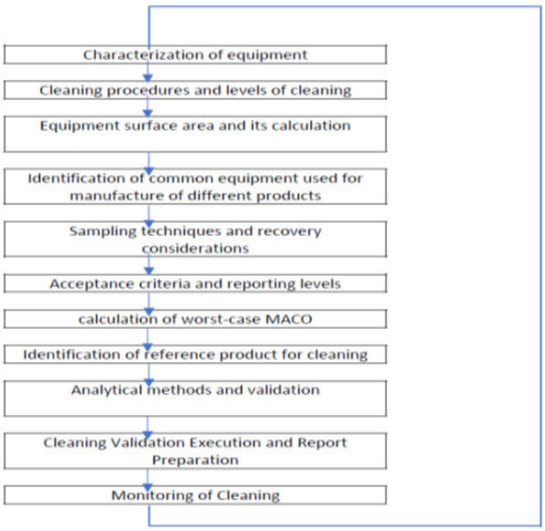

Figure 1: Cleaning validation process flow

II. **Equipment Characterization by Matrix Approach (17):** When multiple products are manufactured in a facility with non-dedicated equipment, the matrix approach may be applied to determine products that must be referenced for cleaning validation. This requires grouping of products or grouping of equipment to arrive at a shared equipment-product matrix from which the worst-case product can be selected.

Product Grouping and Equipment Grouping

Grouping of equipment [1, 8]: All equipment must be used to produce products from the same product group, additionally must be cleaned with the same cleaning agent, and cleaned with the same cleaning method, equivalent in terms of position or role in the manufacturing process. Similar functionality, Similar design e.g., It is a method by which similar or equivalent equipment are grouped for the purpose of cleaning validation. When considering similar equipment, a worst-case area of the equipment or site is selected for demonstrating cleaning validation. When considering equivalent equipment, any area of the equipment or site may be selected as representative of any other area of the equipment or site. Bracketing, a term that appears in EU GMP Annex on cleaning validation, has an equivalent meaning to grouping, although it may include an added burden for testing the extremes of population. Grouping may be used to simply prioritize cleaning validation studies or may be used to eliminate some of the numerous possible combinations of product and equipment studies that might otherwise need to be performed.

Grouping for products [1, 8]: All products must be: Manufactured on the same equipment group, cleaned with the same cleaning agent, cleaned with the same cleaning procedure. Grouping considerations for products include: Similar patient risk levels (e.g., therapeutic indication, potency, toxicity for drugs/ devices/ nutraceuticals/ cosmetics)

III. **Cleaning Procedures:** Standard cleaning procedure for each part of equipment and process should be prepared. It is important that the equipment design is evaluated in detail before preparation of the cleaning procedure to ensure removal of product residues.

The ability to clean equipment is dependent on several variables that must be considered in a given cleaning situation. The critical variable is water and solubility of the residue in water. Other factors include time, action and temperature. Water is important as it is the solvent of choice in cleaning a majority of equipment. Along with the selected type of cleaning agent, it determines the effectiveness of the cleaning process.

Following are the major considerations when water and solvents are used:

- Use of chemicals like alkalis (NaOH)
- Use of formulated cleaning agents (such as Teepol, Laboline, manufactured by leading companies)

The duration of time that a residue is in contact with equipment surface must also be considered when cleaning procedures are developed. The action of cleaning, mainly soaking & brushing using the cleaning agent (for manual cleaning) and agitation (for automated cleaning) also plays a role in the cleaning procedure.

Parameters to be considered during cleaning procedure preparation:

A. Equipment Parameters to be evaluated

1. Identification of the equipment to be cleaned
2. 'Difficult to clean' locations
3. Material of construction
4. Whether equipment can be dismantled
5. Portability of the equipment

B. Residues to be cleaned

1. Acceptable cleaning levels
2. Solubility of the residues
3. Intervals between cleaning

C. Cleaning agent parameters to be evaluated

1. Preferably materials that do not affect the process
2. Detergents available (as a general guide, minimize use of detergents unless absolutely necessary)
3. Solubility in water
4. Effect on environment
5. Effect on human health and safety

D. Cleaning techniques to be evaluated

1. Manual cleaning
2. CIP (Clean-in-place)
3. COP (Clean-out-of-place)
4. Semi-automatic procedures
5. Automatic procedures
6. Cleaning duration
7. Cleaning cycles required

IV. Levels of Cleaning

Levels of Cleaning: The level or degree of cleaning and validation required for the manufacturing process of drug substances mainly depends on:

- Usage of equipment (dedicated equipment or not)
- Manufacturing stages (early, intermediate or final step)
- The nature of the potential contaminants (solubility, toxicity)

In case of Drug Products: Different cleaning situations may arise during the manufacturing of drug products, such as;

a. Batch to batch changeover cleaning.

b. Product to product changeover cleaning

In case of non-dedicated drug product manufacturing facility, different cleaning procedures may exist depending on the manufacturing step and nature of the next manufacturing step to be followed in the same equipment. This results in two different levels of cleaning as explained below.

Level 1 Cleaning: This is used between manufacturing of different batches of the same product.

Example – In a manufacturing Campaign for product A, there are 3 batches to be manufactured as shown below.

Batch 1 – level 1 cleaning - Batch 2 – level 1 cleaning - Batch 3

For a given equipment &/or equipment train, if batch 1 in the campaign is to be followed by batch 2 in the campaign, then level 1 cleaning is required.

Level 2 Cleaning: This is used between manufacturing of different batches of different product and / or at the end of manufacturing campaign even if same product is planned for the next campaign.

The above two degrees or levels of cleaning differ from each other in terms of the degree of risk associated with it, acceptance limit, degree of cleaning & method of verifying the cleaning process.

Table 1: Comparison between cleaning levels

Factors	Level 1	Level 2
Risk	Low	High
Acceptance limit	High	Low
Degree of cleaning	Minimal	Extensive
Verification of cleaning	Visual inspection	Analytical testing

V. **Sampling Techniques:** Sampling sites are selected based on the difficult to clean geometries of the equipment and these locations are inaccessible i.e., their inaccessibility makes them difficult to clean. Therefore, before choosing sampling sites one must be conscious in selecting the required 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 which if remain dirty will certainly result in disproportionate level of contamination to the next exhibit batch. The common sampling methods employed in cleaning validation are indirect or rinse sampling and direct surface sampling or swab sampling [5, 6].

Direct surface sampling: Direct sampling depends on the type of sampling material used and its impact on the test data to check interference of the sampling material with the test. Therefore, early in the validation program or during development studies, it is crucial to assure that the sampling material and solvent are satisfactory and be readily used.

Advantages

- Areas hardest to clean and which are reasonably accessible can be evaluated,
- Physical removal of residues that are "dried out" or are insoluble.
- Sampling and analysis will be taking place in one step and there will be no real loss of sampling system.

Swab Sampling: It usually requires materials which are absorptive & to physically wipe the surface and recover the analyte. Swabs used should be compatible with the active ingredients and should not interfere with the assay. They should not cause any degradation of the compound. The solvent used for swabbing should provide good solubility for the compound and should not encourage degradation.

Advantages

- Dissolve and physically remove sample.
- Adaptable to different types of surfaces.
- Swabs are economical and commonly available
- Permits sampling of a specific defined area.
- Applicable to active, microbial, and cleaning agent residues.

Normally used in conjunction with specific analytical techniques like HPLC

Limitation

- An invasive technique that may introduce fibers.
- Results may be dependent on individual technique.
- Swab material and design may affect recovery and specificity of the method.
- Sampling of large, complex and hard to reach areas difficult [12,13].

Rinse Sampling: This does not involve sampling the equipment and does not employ mechanical action on the surface. The sample is collected indirectly as a final rinse or rinse applied specifically for cleaning validation. Sampling and testing of rinse samples for residual active ingredient is a commonly adopted method to evaluate cleanliness. This is a fairly convenient method in many cases and requires control over the solvent used for rinsing, the contact time and the mixing involved. The solvent used should be selected based on the solubility of the active ingredient and should either simulate a subsequent batch of product or provide adequate solubility. Absence of absence of residual product or contaminants in the rinse solvent would infer the absence on equipment surface.

Advantages

- Adaptable to on-line monitoring
- Permits easy sampling
- Non-invasive technique
- Permits sampling of a large surface area.

It is normally used in conjunction with non-specific methods like TOC, conductivity or pH measurement.

Limitation:

- Limited information about actual surface cleanliness in some cases.

- May lower test sensitivity.
- Solvent may not cover all areas or residues may not be homogenously distributed.
- Difficult to detect location of residues in large equipment
- Volume of rinse is critical to ensure accurate interpretation of results.
- May be difficult to accurately define and control the areas sampled, hence normally used for rinsing single piece of equipment, such as vessel. [10,11]

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 are passed through the same line so as to scrub the equipment clean. The principle involved in placebo is that it is passed through the same pathway as the product. Therefore, it has the likelihood to scrub off residual product along those pathways. It is usually employed for measuring system cleanliness and mainly depends on;

1. Solubility of active in placebo.
2. Appropriate contact time of the placebo for collecting representative sample.
3. Coverage of the placebo in process pathways to ensure removal of the placebo from all equipment location.
4. Quantity of the placebo and residue should be in detectable range and the distribution of residue uniformly in the placebo ensures the detection of sample in any portion of the placebo

Coupon Sampling

This is used very rarely.

A comparative evaluation of commonly used sampling techniques is provided in Table 2 below.

Table 2: Comparative Evaluation of commonly used Sampling Techniques

Attributes	Swab	Rinse	Direct	Placebo
Physical sampling of equipment surface	✓	✗	✗	✓
Technique dependent	✓	✗	✓	✗
Invasive technique	✓	✗	✗	✓
Sampling of difficult to clean areas	✓	✓	✗	✓
Sampling of defined areas	✓	✗	✓	✗
Homogeneity of samples	✓	✗	✗	✗
Prolonged contact with equipment surface	✗	✓	✗	✗
Suitability for online monitoring	✗	✓	✗	✗
Usage	High	High	Moderate	Low

Key: ✓: indicates suitability for use; ✗: not suitable

VI. **Acceptance Limits: Current approaches in determining the acceptance limits for cleaning validation [9, 10 and 11]:**

Approach 1 (Dose criterion): Not more than 0.001 of minimum daily dose of any product will appear in the maximum daily dose of another product.

Maximum allowable carry-over of product A per 10 sq.cm swab area = A x B x C x RF / D x E

A = 0.001 ($1/1000^{th}$) of the lowest strength of product A manufactured (in milligrams of active)

B = Number of dosage units per batch of product B

D = Maximum number of dosage units of product B per day

E = Equipment surface in common between product A & B in square centimeters

C= Swab area (10 sq.cm)

RF= Recovery Factor (75% i.e., 75/100 =0.75)

2. Approach 2 (10 ppm criterion): No more than 10 ppm of a product will appear in another product.

Maximum allowable carry-over of product A per 10 sq.cm swab area = A x B x C / E

A = 10mg active ingredient of product A in one kg of product B

B = Number of kilograms per batch of final mixture of product B

E = Equipment surface in common between product A & B in square centimeters

C = Swab area (10 sq.cm)

3. Approach 3 (Visually clean criterion): No quantity of residue should be visible on the equipment after cleaning procedures are performed.

VII. **Worst Case Rating:** In facilities with a very large number of products manufactured using common equipment, quantum of cleaning validation studies can be reduced and need for frequent re-validation may be avoided by identifying the worst-case soil (residue for cleaning). During the validation, limits are set at low levels such that potential for re-validation can be reduced. A worst-case product may be chosen for cleaning based on solubility in subjected solvent. Other considerations include:

- Maximum Toxicity
- Minimum Therapeutic Dose
- Difficult to Clean
- Lowest Limit based on therapeutic dose / toxic data, batch sizes, surface areas, etc

VIII. **Reference Product for Cleaning:** Typically, groups of worst case situations are established with one piece of equipment representing a group of similar or easier-to-clean equipment. Similarly, product residues are grouped and one residue is chosen to represent a group of similar or easier-to clean residues. The chosen product is termed "Reference Product" which is most difficult to clean based on the ingredient's water solubility as well as practical experience in cleaning that product.

Here, the assumption is made that the reference product will simulate the most potent product of the group that will consumed as a potential residue, in the highest formulated daily dosage of the next product having the smallest batch size. Cleaning validation is then performed on selected reference product.

IX. **Analytical Techniques:** Choosing the appropriate analytical technique depends on a variety of factors. The most important factor is to determine the specifications or parameters to be measured. The limit should always be established prior to the selection of the analytical tool [14, 15].

Analytical methods are of two types: Specific method, non-specific method.

A specific method detects unique compounds in the presence of potential contaminants eg., HPLC. Non-specific methods are those methods that detect any compound that produces a certain response eg. Total Organic Carbon (TOC), pH and conductivity. Additional techniques used: Apart from the above-mentioned techniques, the biopharmaceutical industry utilizes a wide variety of techniques such as TLC for the qualitative determination of surfactants, Atomic absorption spectroscopy for the determination of inorganic contaminants, bio-luminescence for biologicals. It also includes Enzyme-Linked Immuno-Sorbent Assay (ELISA) and LAL [16].

Analytical methods for the selected reference product must be validated before being used for estimation of residues.

Table 3: Comparative Evaluation of commonly used analytical methods in cleaning validation

Attributes	TOC	Conductivity	Direct surface FTIR	HPLC /UV
Specific	✗	✗	✓	✓
Detection in presence of other contaminants	✗	✗	✓	✓
Requires soluble residue	✓	✓	✗	✗
Real time monitoring	✓	✓	✓	✗
Use of reagents / mobile phase	✗	✗	✗	✓
Special sample preparation	✗	✗	✗	✓
Economical and time consuming	✗	✗	✗	✓
Usage	High	Moderate	Moderate	High

Validation Protocol: A Validation Protocol is necessary to define the specific items and activities that will constitute a cleaning validation study. It is advisable for companies to have available a Master Validation Plan indicating the overall Cleaning Validation strategy for the product range / equipment type / entire site. The protocol must be prepared and approved prior to the initiation of the study and must either include or reference the documentation required to provide the following information:

Specific Background, Purpose of the validation study, Scope of the validation study

Responsibilities for performing the validation study

Sampling procedure to be used and testing method to be used

Acceptance criteria, Change control requirements, Deviations during the study

Validation Report: A validation report is necessary to present the results and conclusions and provide approval of the study. The report should include the following:

Physical and analytical test results or references for same, as well as any pertinent observations; Conclusions regarding the acceptability of the results, and the status of the procedure(s) being validated; any recommendations based on the results or relevant information obtained during the study including revalidation requirements, if applicable; approval of conclusions; Review of any deviations that occurred. 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.

Subsequent to validation, an appropriate level of verification is required for routine operations.

Conclusion: From this review article it can be concluded that cleaning validation is a process of attaining and documenting sufficient evidence to prove the effectiveness of cleaning process. Cleaning is directly related to safety and purity of the pharmaceutical product therefore it is an important and primary activity. Hence, it is necessary to have effective cleaning program in place because of the regulatory requirement. This article covers all aspects related to cleaning validation like Residue selection, acceptance criteria for the validation, different levels of cleaning, cleaning procedure, sampling procedure, product grouping and equipment characterization, cleaning agent selection.

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