REVIEW ARTICLE

Cleaning Validation: A Crucial Step in Assuring Quality During Pharmaceutical Manufacturing

Saurabh Dahiya*[1], Diwan Chand[2], Yachika Goyal[2], Chanchal Sharma[2]

[1]*Department of Pharm Chemistry and Quality Assurance, Delhi Institute of Pharmaceutical Sciences and Research (DIPSAR), Delhi Pharmaceutical Sciences and Research University, Tughlakabad, New Delhi, India*
[2]*Delhi Institute of Pharmaceutical Sciences and Research (DIPSAR), Delhi Pharmaceutical Sciences and Research University, Tughlakabad, New Delhi, India*

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ABSTRACT

Cleaning procedures for manufacturing equipment have been shown to prevent product contamination through the cleaning validation process. This review aims to understand how the cleaning validation plays a critical role in managing contamination or cross-contamination issues during good manufacturing practices (GMP). Emphasis on the quantity of cleaning required for the machinery, the elimination of contamination during manufacturing procedures are discussed here. The article describes various cleaning agents as well as sampling methods for cleaning equipment. Focus is laid on the elements of cleaning validation, objectives of the cleaning validation, regulatory significance of requirements for cleaning validation, etc. Also, it provides information on the different cleaning standards to meet regulatory requirements by the pharmaceutical industry.

Keywords: Cleaning agents, Cleaning validation, Contamination and cross-contamination, Sampling techniques.

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INTRODUCTION

Cleaning validation is an important part of good manufacturing practices (GMP). Cross-contamination of the targeted drug substance by an active pharmaceutical component from a prior batch or by cleaning agent residues is the main regulatory issue concerning cleaning validation.[1] Any pharmaceutical plant's primary goal is to reliably produce goods with the desired attributes and quality at the lowest feasible cost.[2] When it comes to any product, the most important factor to consider is its quality. As a result, medicines must be developed in order to provide a predictable therapeutic response to a medication contained in a formulation capable of mass production while retaining the highest standards of quality in the finished product. Validation is a crucial component of having a product approved for commercialization.[3] In the mid-1970s, two food and drug administration (FDA) employees, Ted Byers and Bud Loftus, suggested validation to enhance medication quality. It was designed in response to a number of issues with sterility in the large-volume parenteral industry.[4] As per U.S. food and drug administration (USFDA) "validation is documented evidence that provides a high degree of assurance that a specific process will consistently produce a product that meets its predetermined specifications and quality attributes".[5]

Cleaning protocols should be in place for every action involved in the manufacture, storage, handling, and distribution of active pharmaceutical components, according to current good manufacturing practice (cGMP) recommendations. Cleaning processes should be verified to establish that no contamination, cross-contamination, or carryover poses a significant risk to API quality.[6] Cleaning validation is documented proof with a high level of certainty that a system or piece of equipment can be cleaned on a regular basis to defined and accepted limits. A cleaning process must be validated to ensure it complies with all applicable laws and regulations. The main advantage of performing such validation work is identifying and correcting previously noted potential weaknesses that can affect the quality, safety, or efficacy of ensuing batches of pharmaceutical products produced inside the machinery.[7]

Cleaning operations must precisely adhere to techniques of execution that have been rigorously designed and confirmed.[8] Cleaning validation verifies the "efficacy" of the cleaning technique in eliminating product residues, degradation products, preservatives, excipients, and pollutants as well as the control of microbiological pollutants that might be present. However, it is necessary to guarantee that there is no possibility

*Author for Correspondence: saurabhdahiya@dpsru.edu.in

of cross-contamination of active substances. Cleaning procedures must adhere to precise guidelines that have been meticulously defined and procedures that have been tested.[9]

Objectives of Cleaning Validation

In order to avoid potential contamination and cross-contamination, it is important to show that the equipment is properly cleaned on a regular basis to remove product, detergent, and microbiological residues.[1] Thus, the objectives include making working more convenient and secure, establishing a recognized standard of quality and ensuring ntegrability.[8] The primary objective of equipment, utensils, and component cleaning validation is to provide sufficient documented evidence that the cleaning procedure can reliably remove product residue below the stipulated acceptance criteria.[10] The goals of equipment cleaning and cleanliness validation in an API area are the same as in a pharmaceutical manufacturing area. In each of these cases, more effort is required to avoid contamination of a subsequent batch with material from the preceding batch. One of the essential considerations in equipment cleaning validation is cleaning difficult-to-reach surfaces.[3] Cleaning validation is done to get rid of contaminants, both product and non-product related, that might compromise the patient's health or the medication's effectiveness. Effective cleaning is a crucial element of GMP, patient safety and quality assurance. A product that has not been properly cleaned may be contaminated by the product that came before it, cleaning agents, and other foreign objects introduced into the process or produced by it.[1] It is not only important to comply with legislation but also vital to meet the needs of customers. It gives the maker enough assurance that internal control has been appropriately created.[11,12] It aids in the preservation of product quality. It allows the equipment to be reused[7] and reduce the likelihood of a product recall.[13]

Contamination and Cross Contamination

Two common forms of contamination are cross-contamination and contamination by a foreign substance. Cross-contamination often occurs when an active component from one product leaks into a later-produced good. However, carrying over other product components like excipients might also be an issue and harm the end product's quality. Consumers or patients may experience problems from unintentional contamination if one batch of a product is contaminated with a high quantity of residual active component from a prior batch. Any possible synergistic interactions between pharmacologically active substances that may be relevant to clinical practice need to be taken seriously. It is widely acknowledged that inert compounds used in pharmaceutical goods are secure for human consumption and daily usage. Cleaning and maintaining equipment bears the potential to contaminate items, such as equipment parts and lubricant. Chemical cleaning agents and washing equipment can result in issues ranging in parenteral goods having particle matter levels beyond permitted limits to accidentally introducing dangerous substances into the product. Additionally, when exposed to trace pollutants, several activities are negatively impacted and may vary in stability or bioavailability.

The second sort of contamination is caused by alien objects, which might be bacterial or actual equipment. Unwanted microbes may have the chance to multiply inside processing equipment due to poor maintenance, cleaning, and storage practices. This might lead to increased pyrogen production, decreased guarantee of sterility from equipment sterilizing processes, etc. Additionally, it poses a severe difficulty for the production of non-sterile dosage forms, especially for unpreserved pharmaceuticals that encourage microbial development.[14]

Types of Ccontaminations

- Cross-contamination with active ingredient
- Microbiological contamination
- Contamination by cleaning or sanitizing agents
- Contamination by miscellaneous other materials.[15]

Active Ingredient Cross-contamination

One of the significant concerns of active ingredient cross-contamination is that it results in a multi-component product rather than a single active ingredient. The contamination may augment or cancel the activity, or the contaminant may have totally other medical consequences, depending on the clinical effects.

Microbiological Contamination

This kind of contamination can happen at any time, even after cleaning. Equipment placement in a moist state is a key contributing element. This creates a natural environment for germs to thrive.[14,16]

Contamination by Cleaning or Sanitizing Agents

Certain pharmaceutical companies may find it inevitable to employ fairly poisonous and dangerous products for tenacious residues. This is particularly true when it comes to the production of active pharmaceutical ingredients (APIs). These materials have the potential to be a product contaminants.

Other Types of Contamination

A variety of additional less likely materials can potentially contaminate goods in a pharmaceutical operation. Filling tools, packaging brush bristles, excipients, paper filters, micron filters, fibers from gloves, rubber bits from gloves, brush bristles from cleaning tools, fabric from rags, and cotton fibers from wiping products, lubricants, and other items are included as contaminants.[15]

Elimination of Cross-contamination in Pharmaceutical Manufacturing may be dealt by

- Production through a "closed system" or in distinct zones
- Installing a sufficient air-lock and air-treatment system to stop the recirculation or re-entry of air that has not been properly or treated enough.
- Providing detailed guidance on how to properly dispose of garments used in places where items with a high risk of cross-contamination are processed.
- Cleaning and disinfection treatments that have been proven to be effective

Table 1: Level of cleaning as per APIC[7,17,19]

Level	*Thoroughness of cleaning*	*Cleaning Validation*
2	The preceding product must be carried over. Cleaning is essential until strict carryover limits have been fulfilled.	Essential
1	The prior product's carryover is less important. Cleaning should minimize the risk of carryover to a lower level than that necessary for level 2.	(Lower acceptable Carryover limits) Increase from not needed to required
0	Only do a thorough cleaning if the preceding product's carryover isn't a concern.	Not required

- Testing for contaminants and labeling equipment with cleaning status labels.[11]

Cleaning Method

- CIP (Clean-in-place)
- COP (Clean-out-of-place)
- Manual cleaning
- Semi-automatic procedures
- Automatic procedures.[17,18]

Level of Cleaning

Cleaning levels are primarily determined by the following factors: Equipment use, Manufacturing stage, And kind of potential contamination.[8,14] Levels of cleaning are explained in Table 1.

In case of Drug Products

When it comes to drug products, many cleaning situations, such as

- Batch–to–batch changeover cleaning, may occur throughout production.
- Cleaning during product switching.
- Depending on the production step and the nature of the manufacturing step to be followed in the same equipment, multiple cleaning methods may exist in non-dedicated drug product manufacturing facilities, this leads to two distinct levels of cleaning.

Level 1 Cleaning: This is employed when producing various batches of the same product.

Level 2 Cleaning: This is employed in between the creation of various batches of various products and/or at the conclusion of the manufacturing task.

The above two levels of cleaning are different from one another in terms of the level of danger involved, the acceptable limit, the level of cleaning, and the technique used to confirm the cleaning process.

In case of drug compound

During the manufacture of pharmaceutical items, many cleaning situations might occur, including:

- Cleaning during batch-to-batch transitions
- Change from the first stages to the intermediate of the same product.

Table 2: Comparison between different levels of cleaning based on APIC guidance on cleaning validation[7,17,19]

Factors	*Level 0*	*Level 1*	*Level 2*
Risk	Lowest	Low	Highest
Acceptance limit	Visual inspection	General limit 500 ppm	10 ppm
Degree of cleaning	Less extensive	Less extensive	More extensive
Verification of cleaning	Visual inspection	Visual inspection	Analytical testing

- Change from one product's intermediate to another product's intermediate.
- The transition from an earlier stage of one product to a later stage of another product.
- Switching from one end product to another
- When manufacturing non-dedicated drug substances.[18]

Cleaning Agents

Cleaning agents should be chosen based on their capacity to remove product residues, equipment compatibility, and cost analytical technique sensitivity and ease of use. The ease of removal and verification of removal, as well as the most significant factor, toxicity should be minimal since it might damage cleaning personnel or affect another batch that is being prepared. There are a few different types, such as water, commodity chemicals, formulated cleaning agent, solvent.[13,14] Water is the universal solvent, inexpensive and non-toxic and may be used to clean the product when it is easy to remove the residues. Solvents are used for cleaning when the manufacturing process also requires the use of solvents. Mother liquors, for example, are commonly employed as API cleaning solvents. The difference between the different types of level of cleaning are shown in Table 2. Other common chemicals/cleaning agents such as NaOH can also be utilized. These materials could be connected with hazards or effluent problems, much as their solvent equivalents. However, they frequently prove beneficial in inactivation procedures because of their normally high alkalinity or low acidity. But these chemicals lack the detergency of a designed cleaning agent, and they could be challenging to rinse, requiring more water to rinse them out of systems than a formulated cleaning agent would. A specially prepared cleaning product is the most popular kind of cleaner. This group includes both aqueous formulations and formulations based on solvents. Cleaning solutions frequently contain one or more alkalinity or acidity sources, surfactant builders, sequestrants, chelants, and either a solvent or water. These materials, designed for industrial us rather than consumer use, have minimal foaming, making them simpler to rinse and suited for cleaning under high impingement or high turbulence.[18]

Sampling

In general, there are two sorts of sampling methods that are used. The direct way of sampling the outside of the equipment and another selective approach is the use of rinse sampling.

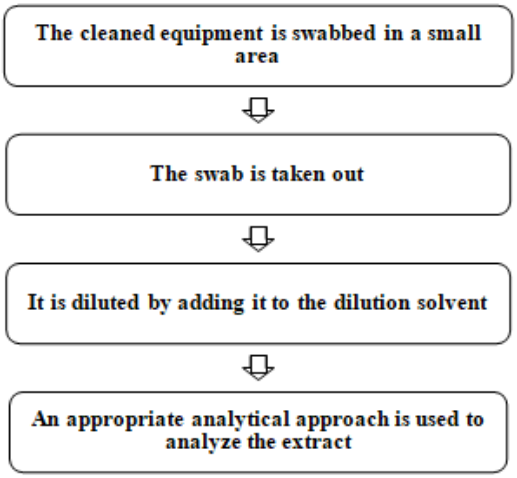

Figure 1 : Swab sampling technique.[21]

Swabbing or rinsing are the most common sample methods, although there are a variety of other approaches of interest, such as direct extraction paths for determining soluble and insoluble residues.[20,21]

Swab sampling technique: The process of physically removing any residue that a piece of equipment may have after being cleaned and dried is the basis for this procedure. To eliminate any possible residue, a swab dipped in solvent is rubbed over a surface area designated for the sample that is extracted into a solvent volume with a known solubility for the contaminated active component residue. Next, the amount of contamination per swab is determined quantified using a sensitive analytical approach.[21,22,23] Advantages of this procedure include removing the sample physically and dissolving it, the capacity to adapt to a broad range of surfaces, being financially feasible and broadly accessible, it is possible to sample a specific location, applicable to active, microbiological, and cleaning agent residue (Figure 1).[17,19]

Rinse sampling technique: Rinse sampling takes place as a final rinse or rinse delivered specifically for collecting a validation sample and does not include mechanical activity on the surface. Maximum allowable carry over (MACO) is normally determined on each individual product change using the equation: MACO (mg)/Volume of rinse or boil (L) = Target value (mg/L).[9,19,21] This method is advantageous in terms of easy sampling, adaptability to online monitoring, non-intrusive, appropriate for active ingredients and excipients, makes it possible to sample a lot of surface area.[17,19]

Placebo and product sampling: Placebo sampling can be used to identify residues on equipment as part of the post-cleaning processing of a batch. Product sampling is similar to placebo sampling, except it involves the usage of real product.[22] This method is suitable for hard-to-reach surfaces; placebo contacts the same surfaces as the product, no further sample procedures are required.

Solvent sampling: To optimize residue recovery, this procedure employs a solvent not generally used in the cleaning process.[19] Bulk chemical plants often use this procedure, it is applied to active ingredients, cleaning agents, and excipients, typically provide greater analytical specificity and lower recovery loss than swabs, makes it possible to sample a broader surface area, enables surface sampling from porous and fragile surfaces and increases recovery for rinsing.

Methods used to Establish the Acceptability Limits for cleaning validation-

Approach 1 (Dose criterion) (MACO)[3]

Maximum Allowable Carryover

$$\mathrm{MACO(mg)} = \mathrm{SF} \times \mathrm{LHDp(mg)} \times \frac{\mathrm{BSs\ (g)}}{\mathrm{IFs} \times \mathrm{MDs(g)}}$$

SF: Safety Factor
LHD_p: Lowest Human Therapeutic Dose of Past Product
BS_s: Batch Size of the Next Product
IF_s: Intake Frequency of Subsequent Product
MDs = Mass of the Dosage form of the Subsequentproduct.[14,21]

Approach 2 (10 ppm criterion)[3]

The batch size's equivalent of 10 mg/L is thought to be the threshold for the 10 ppm acceptability requirement. For chemicals for which there are no toxicological data available, it is a pharmacopeial limit test. It is also employed to determine the requirements for accepting heavy metals in raw materials.

$$\mathrm{MACO(mg)} = 10\ \mathrm{ppm}\ \left(\frac{\mathrm{mg}}{\mathrm{kg}}\right) \times \mathrm{BSs\ (kg)}$$

Batch Size of the Next Product (BSs)

Recognizing Residue and Selecting a Detection Approach

A list of all potential residues the cleaning operation can leave behind on important production surfaces, including cleansers, basic components, excipients, decomposition products, and preservatives should be compiled. High-performance liquid chromatography (HPLC), ion selective electrodes, flame photometry, derivative UV spectroscopy, enzymatic detection, and titration are examples of specific techniques used to test for a single constituent. Conversely, general techniques such as total organic carbon (TOC), pH levels, and conductivity test for the presence of contaminants.[7] Drug substance manufacturing, in general, entails chemical and/or physical alteration as a result of several processing procedures. Equipment trains, equipment, and/or auxiliary systems can be used for both dedicated specialized items and multi-product production. Insufficient cleaning procedures or techniques may result in the following leftovers migrated as contaminants in the subsequent batch produced using the same machinery such as precursors to drug substances, byproducts and/or breakdown products of the pharmacological substance, an item from an earlier batch, excipients used in the production process, such as solvents, microorganisms, lubricants and cleaning products.

Regulatory Aspects, Cleaning Processes Inspections and Validation

It is not new for the food and drug administration (FDA) to demand that equipment should be clean before use; the 1963 GMP regulations and later the 1978 cGMP standards have a clause on cleaning equipment. The major justification for ensuring clean equipment is to stop drug items from being contaminated or adulterated. FDA anticipates organizations to have documented SOPs that outline the cleaning process step-by-step and are supported by rational, scientific principles. The company must have a cleaning validation policy that details how the cleaning technique is validated for its intended purpose. Regulatory agencies emphasize on using direct sampling whenever possible; if the sampling site is inaccessible, rinse sampling should be used. The individuals in charge of carrying out and approving the studies must adhere to the acceptance criteria and the revalidation data, following the FDA's general validation method. For tests to be conducted on each production system or piece of equipment, the FDA wants organizations to submit detailed written validation protocols in advance. Such protocols should cover topics like sampling procedures and the analytical methods that will be used, including their sensitivity. The results should permit the assertion that residual levels have been brought down to acceptable level.[6,19] Cleaning techniques should typically be verified and targeted at situations or phases when material contamination or carryover is the greatest danger to quality. Validation of cleaning methods should take into account real patterns of equipment usage. The computation of residual limits based on potency, toxicity, and stability should be used to validate cleaning based on the solubility and difficulty of cleaning. The equipment to be cleaned, the processes to follow, the products to use, the permissible cleaning levels, the parameters to be tracked and controlled, and the analytical techniques should all be included in the cleaning validation methodology. The protocol must specify the kind of samples to be obtained as well as their collection and labeling procedures. As appropriate, swabbing, rinsing, or alternative techniques (like direct extraction) should be used during sampling to find soluble and insoluble residues. The sampling techniques used should be capable of measuring the amounts of residues left on equipment surfaces after cleaning in a quantitative manner. Only validated analytical techniques that are sensitive to impurities or residues should be used. The most harmful residue should be used as the basis for realistic, achievable, verifiable residual limitations. After validation, it is important to evaluate cleaning techniques at regular intervals to make sure they are still effective when utilized in regular production. Analytical testing and visual inspection can be used to check the cleanliness of the equipment wherever possible.[6]

Microbiological issues of equipment cleaning and the cleaning of processing equipment should be taken into account. This mostly comprises on preventive actions instead of the elimination of contamination that has already taken place. There should be proof that regular maintenance cleaning and equipment storage prevents microbial growth. For instance, equipment should be dried before storage, and water should never be allowed to stand still in equipment after cleaning operations. Utensils and equipment must be regularly cleaned, sanitized, and maintained to avoid contamination that can change the medication product's identification, identity, strength, quality, or purity. The FDA requires businesses to have documented standard operating procedures that outline the cleaning process step by step and are rational and scientifically sound. FDA expects the guidelines to cover various eventualities such as employing one cleaning agent/ method for cleaning among batches of the same product and another process for cleaning between product changes. The stated method should cover all cases and make it obvious when a certain approach is performed if the industry has separate processes for eliminating water-soluble residues and non-water-soluble contaminants. The individuals in charge of carrying out and approving the investigation must adhere to the established standards and the revalidation data, following the FDA's general validation method. The FDA anticipates that businesses will create detailed, written validation protocols in advance for the studies that will be conducted on each manufacturing system or piece of equipment. These protocols should cover topics like sampling procedures and the analytical methods that will be used, including their sensitivity. Companies are obliged to carry out validation studies in line with protocols and record study findings. The cleaning validation should prove that the cleaning process does not introduce unacceptable amounts of residual materials into the equipment and that it consistently reduces residues of the substance previously created to acceptable levels. The boundaries established must be reasonable, doable, and justifiable. There could be undesirable byproducts and partial reactants during the production of active pharmaceutical ingredients that haven't been chemically characterized. As a result, it could be required to concentrate on both the principal reactant and its byproducts. Businesses should base on their selection of the residue to measure on strong scientific reasoning. The cleaning validation should show that both the cleaning process and the consistency with which remnants of the product that was previously created are consistently removed down to acceptable levels. Limits for product residues ought to make sense and be based on the components used and their therapeutic dosage. The limits must be reasonable, practical, and verifiable.[19,25]

Challenges in Cleaning Validation

Cleaning validation is one of the most crucial processes in the pharmaceutical production process. To maintain the quality and safety of the items, the cleaning process must be effective and efficient. Cleaning validation is difficult, but it is worthwhile if the final result is a safe and high-quality product. Some of the difficulties that may arise during cleaning validation are- to be assured that all impurities are gone, the cleaning process may need to be done several times, the cleaning environment may require certain temperature and humidity levels to be

maintained, the cleaning equipment used may need to be kept in good working order, if the first results are not satisfactory, the testing protocols used to validate the cleaning process may need to be altered, if the cleaning technique is not effective in removing all impurities, it may need to be adjusted, if the cleaning method is causing damage to the equipment utilized in the process, it may need to be adjusted. All of these obstacles are worthwhile to overcome if the final result is a safe and high-quality product. Cleaning validation is a critical step in ensuring that this occurs.[2]

CONCLUSIONS

Cleaning validation offers a way to demonstrate that contamination levels have been brought down to acceptable limits. However, it is nearly hard to ensure the complete cleaning of the production equipment yet it is possible to ensure that the trace quantities of active product that are dispersed throughout the components of the equipment are in acceptable ranges and that we are able to identify and measure these trace levels. To ensure cGMP compliance, pharmaceutical manufacturers must validate their cleaning procedures so as to comply the regulatory requirements, safety, effectiveness, and quality of the succeeding batches of medication products.

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CONFLICT OF INTEREST

None

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