WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 7, 563-575. Review Article ISSN 2277– 7105

CLEANING VALIDATION

Poonam Ingalwad*, Vikram Veer and Ashok Bhosale

PDEA's Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Kharadi, Pune-14, Maharashtra, India.

Article Received on
07 May 2020,

Revised on 27 May 2020,
Accepted on 17 June 2020

DOI: 10.20959/wjpr20207-17822

***Corresponding Author**
Dr. Poonam Ingalwad
PDEA's Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Kharadi, Pune-14, Maharashtra, India.

ABSTRACT

Validation is art of designing. The purpose of this review is to give information about importance cleaning validation. Cleaning validation that play an important role in preventing risk to patient by assuring that cross-contamination between products is curtailed to acceptable levels. Pharmaceutical substance, excipient, API i.e. active pharmaceutical ingredient may contaminated by other products or APIs, by cleaning agents, microorganisms or by other materials e.g. dust, lubricant, raw material, intermediates. The main purpose of cleaning validation is to improve the effectiveness, prevent cross contamination. The benefits of cleaning validation are compliance with federal regulations, and identification, correction of potential problems.

KEYWORDS: Importance of Cleaning Validation**,** Cross Contamination & Contamination, Cleaning Validation Guideline, Methodology, Sampling Techniques.

1. INTRODUCTION

Validation is documented confirmation which provides or gives a high degree of assurance, It is a process of establishing documentary evidence demonstrating that a procedure of process carried out in testing, after that production department maintains the desired level of compliance at all stages. Method validation is required because it minimize analytical and instrumental error.

It is used to ensure the quality of the test result. To be assured of the correctness of result. Cleaning validation is assure that a cleaning process remove residues of the active, inactive or detergent ingredients of the product. Cleaning validation is majorly applicable to the cleaning of process manufacturing equipment in pharmaceutical industry. It is needed to have effective cleaning programs in place because of regulatory requirements.[1]

1.1. Objective of cleaning validation

- It reduces the risk of regulatory non-compliance.
- To minimize contamination and cross contamination.
- Reduce defect cost.
- Reduce the chances of product re-call.[2]

1.2. Importance of cleaning validation

- Customer requirement – it ensure the purity and safety of the product.
- Cleaning validation is regulatory requirement in pharmaceutical, Bio-chemical industries.
- Essential to establish adequate cleaning method.
- Help to identify root cause of problem.
- It maintains company's public image and health care community.
- It is heart of pharmaceutical company.[3]

1.3. When cleaning validation is require

- Initial qualification of process/ equipment.
- Critical change in a cleaning procedure.
- Critical change in formulation.
- Significant change in formulation.
- Change in a cleaning process.
- Change in a cleaning agent.

➢ **Advantages**

- Validation can increased operator safety. Appropriately calibrated, validated instruments and gauge used to reduce accident and results in safety.
- Working easier and safer
- To enhances efficiency[4,5]

1.4. Why cleaning validation is require

- To make sure the efficacy of cleaning procedures.
- To make sure no risks are associated with cross contamination of active ingredient or detergents/sanitizer.[6]

1.5. Cleaning validation team and their responsibility

1. **Validation officer:** Coordinating all team, monitoring process and compiling data, preparing final result.
2. **Production department officer:** Prepare SOP's for process and equipment, collection of validation data.
3. **Packaging department:** Prepare SOP's for packaging, collection of validation data.
4. **Maintenance department:** defining requirement, training.
5. **Quality control department:** provide data for cleaning agent and active ingredient.
6. **Quality assurance department:** reviewing and approving the validation.[7,8]

1.6. Cross Contamination and Contamination

- Mostly cross contamination and contamination by a foreign material are 2 types of contamination. Cross contamination is generally through an active ingredient from one product carrying over into subsequent manufactured product.

- Cleaning validation play important role in contamination and cross contamination. It's prevent contamination. Throughout the process foreign substances, microorganisms or bacteria are unintentionally transferred from one substance or object to another, with harmful effect. Mostly cross contamination and contamination by a foreign material are two types of contamination. Cross-contamination is generally through an active ingredient from one product carrying above into subsequent manufactured product. However, carryover of other product component similarly excipients can also be problematic and may degrade and final quality of product.

- The product of contaminated batch with particular level of residual active ingredient from a previous batch may pose obvious problem to consumer or patients from unintended contaminants.

- Cleaning of equipment and maintenance provide the potential for contamination with items such as lubricant and equipment parts. Sanitizing agent/cleaning agent which is based upon chemical and bit of cleaning tools can occur problems ranging from poor pharmaceutical elegance to exceeding acceptable levels of particulate matter in parenteral products to inadvertent inclusion of toxic compounds in the product.[9,10,11]

1.7. Cleaning agent selection

There are several broad categories

- Formulated cleaning agent
- Water
- Commodity chemicals
- Solvent

- **Formulated cleaning agent**

It is the biggest class of cleaners. This category involved solvent and aqueous formulations. It may be include 1 or more than 1 alkalinity or acidity sources, Chelants, surfactants builders & either a solvent or water & for industrial applications, unlike consumer-use products, these substance are formulated to be less foaming and therefore are more readily rinsable and are appropriate for high impingement or high turbulence cleaning.

- **Water (H_20)**

We all know water is the universal solvent. Water is cheap, nontoxic. If just H_2O will helpfully clean the product without excessive time or physical effort to remove the residues, by all means employ H_2O alone. For many, however the H_20 alone requires an unacceptable increase in time to get the cleaning accomplished. For these one of the other approaches must be sought.

- **Commodity chemicals**

In this, chemicals such as sodium hydroxide can be used for cleaning as well. Like their solvent counterparts, there may be effluent issues, hazard issues, associated with these materials. Their mostly low acidity or high alkalinity, however, often makes them helpful in inactivation processes. Although these chemicals lack the detergency of a formulated cleaning agent and they may be difficult to rinse, taking larger volumes of water to rinse free from systems than would a formulated cleaning agent.

- **Solvent**

These are mostly applied in processes where solvent usage is already called for by the manufacturing process. e.g., mother liquors are typically used as the solvents for cleaning of APIs.[12,13]

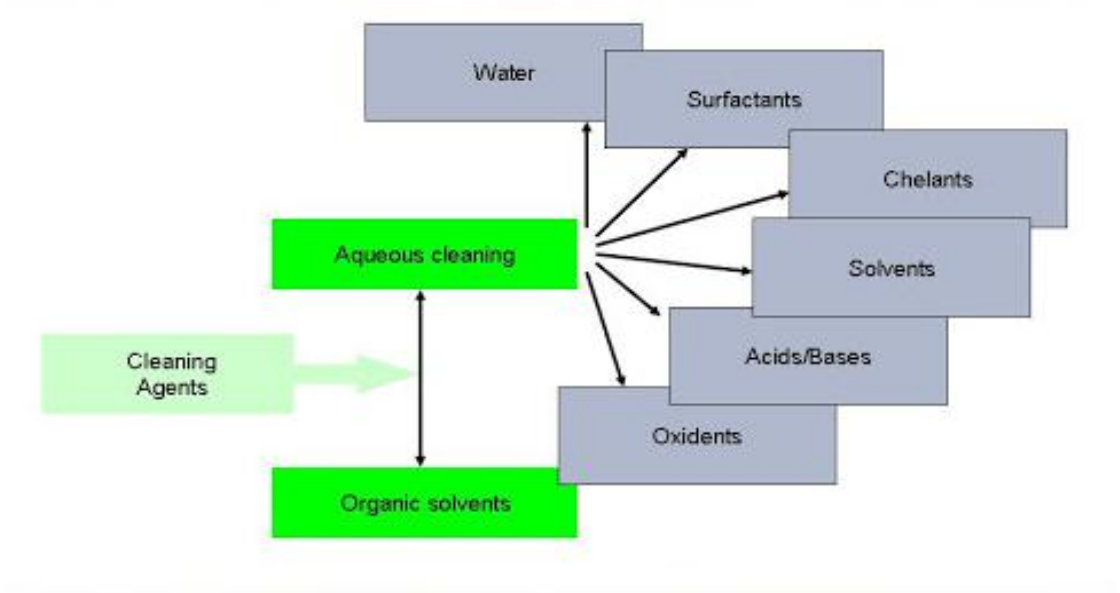

Fig. 1: Cleaning method.

1.8. Critical process parameters and critical quality attributes

- Time (dirty and clean hold times; process run rime).
- Chemical (concentration).
- Temperature (cleaning temperature).
- Activity (chemical exposure).

Critical process parameters are key variables affecting the production process. That are observe to detect deviations in standardized production operations and product output quality or changes in critical quality attributes.[14,15,16]

1.9. Process of cleaning validation

Stage 1:

Determination the most appropriate cleaning procedure for the equipment.

↓

Develop and validate the sampling and choosen analytical method

for the compound being cleaned.

↓

Evaluate equipment surface.

Stage 2: Develop a cleaning validation protocol for the product and equipment being cleaned.

Stage 3: Develop interim and cleaning validation reporton clean by clean basis detailing the acceptability of the cleaning procedure for the euipment and the product.

Stage 4: Creat a cleaning validation report detailing the acceptability of the cleaning procedure for the equipment and the product.[17,18,19]

1.10. Cleaning validation guideline

1.10.1. U. S. Food and Drug Administration (USFDA)

1. Acceptable residue: FDA has mentioned neatly in the Questions & Answers on Current Good Manufacturing Practices Equipment that the Contamination that is reasonably avoidable and removable is never considered acceptable. Therefore, Cleaning Procedures must not be designed sub-optimally to remove a calculated "acceptable" level of residue but rather based on scientific understanding of the substance and its interaction with other resources within the manufacturing facility. Similarly, analytical methods should not be designed solely on the basis of the acceptable residue that needs to be achieved.

2. Total organic carbon: FDA has come to terms with using TOC as an acceptable method for monitoring residues routinely and for cleaning validation given that the contaminating material(s) is organic and contains C_2 that may be oxidized under TOC test conditions.

3. Rinse Sampling: For cleaning validation, rinse samples alone would not be acceptable; firms should also measure the contaminant on the equipment surface using a direct method such as swab (if feasible).

4. Continuous Process Verification (CPV): Many firms have not implemented this yet. Food and Drug Administration **(**FDA) is very clear that a Continuous Verification Program needs to be in place for routing residue monitoring after Cleaning Validation. The frequency of this program will need to be determined based on risk.[20,21,22]

1.11. METHODOLOGY

There are a different of methods available to test cleaning validation samples. The method of choice is often the one with which we have familiarity, method like conductivity and pH may give cleaning data and require only instrument calibration. Many methods that require validation.

1.11.1 HPLC

The benefit of High Performance Liquid Chromatography for the testing of samples use for cleaning validation is well established and may address all validation parameters. It is a chromatographic method that involves a sample in a liquid stream that passes through a packed column and separates from the other components of the sample. HPLC method can separate the residue of interest from the components of the formulation as well as the detergent. A good designed HPLC recovery study can demonstrate range, accuracy, precision, linearity, LOD and LOQ in a single run.

Particularly, High Performance Liquid Chromatography (HPLC) methods for assay are designed to quantitate levels down to 0.1% of the API, making sensitivity well below most calculated ARLs. Although, the sensitivity of HPLC which is dependent on the detector and the chemical structure of the residue of interest, which can quantitate the residue and residue with no UV chromophore requires specific a specialized detector (fluorescence, electrochemical) or derivatisation to achieve the desired sensitivity.

HPLC assay methods can be tedious, 30-40 minutes per injection, could be an issue for quick turnaround of samples.[23]

1.11.2. Gas chromatography

Gas chromatography (GC) has also been used to test cleaning validation samples. This methodology is analogous to HPLC i.e. High Performance Liquid Chromatoghraphy with sensitivity and comparable selectivity. The sample carrier is in a stream of gas which passes through a column for the separation and a detector. Detectors are not limited to compounds with UV chromophores. The validation parameters and their demonstration are identical to (HPLC) High Performance Liquid Chromatoghraphy. GC is limited to residues that are volatile at the temperatures generated in the instrument.

1.11.3. Mass spectrometry

A MS is an instrument that measures the atomic mass of a sample. There are various types of Mass spectrometry instruments but the atmospheric ionization models are mostly used for cleaning validation.

A Mass Spectrometer detector can be coupled with a High Performance Liquid Chromatography 9 (HPLC9), or cleaning samples can be inserted directly. It separates the

residue of interest through mass selectivity from the components of the formulation and the detergent. This method of analysis is very sensitive down to the ppb or ppm level and a recovery study may demonstrate range, accuracy, precision, linearity, LOD and LOQ in a single run.[24,25]

1.12. Sampling method selection

1.12.1. Placebo sampling

Placebo is identify as both potential cleaning techniques and potential sampling techniques. The placebo material comprises of all particular excipients but not the active ingredient. The placebo batches of were passed through a same line so that it will have possibility to scrub of the clean system. The principle which is 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 mostly depends on

- Excipients solubility in placebo.
- Contact time which is suitable of the placebo for collecting representative sample.
- It ensures to removal of the placebo from all equipment location
- The placebo quantity or volume and residue being matched must be in detectable range and the distribution of residue uniformly in the placebo ensures the detection of sample at any portion of the placebo.[26]

1.12.2. Swab sampling (Direct surface sampling)

The visible residue on surface can be easily clean but main challenge is for invisible residue present in extremely small amounts, are collected and delivered to the instrument for measurement. The correct type of swab for sampling is one with a head made of laundered polyester knit fabric, since that material gives the lowest levels of releasable particles. The lowest background & highest recovery when TOC i.e. total organic carbon measurements are employed as the analytical technique. To the surface on sample, the swab is moistened then drawn across the surface in a thorough and reproducible manner to collect residue into the interstices of the polyester knit fabric.

The swab is then deposited into a desirable collection vial, then the residues extracted from the swab head for subsequent analysis. Sampling was selected based on the clean geometries

of the equipment and these locations are inaccessible i.e. their unavailability makes them difficult to clean so, before choosing for sampling sites one must be conscious in selecting the desired sampling locations. The commonly sampling method employed in cleaning validation is rinse sampling and swab sampling. It mainly requires materials which are absorptive & to physically wipe the Surface and recover the analyte. Because the necessary to physically wipe the surface was the preferred method that is readily accessible to human hand or arm.

➢ **Limitation**

- An Invasive technique that may introduce fibers.
- Results may be technique dependent.
- Swab material, design may inhibit recovery and specificity of the method.
- Evaluation of complex, hard and large to reach areas difficult.

➢ **Advantages**

- Physically remove sample or dissolve it.
- Adaptability to wide variety of surfaces.
- Economically available.
- It may allow sampling of a defined area.
- Applicable to microbial, active and cleaning agent residues.

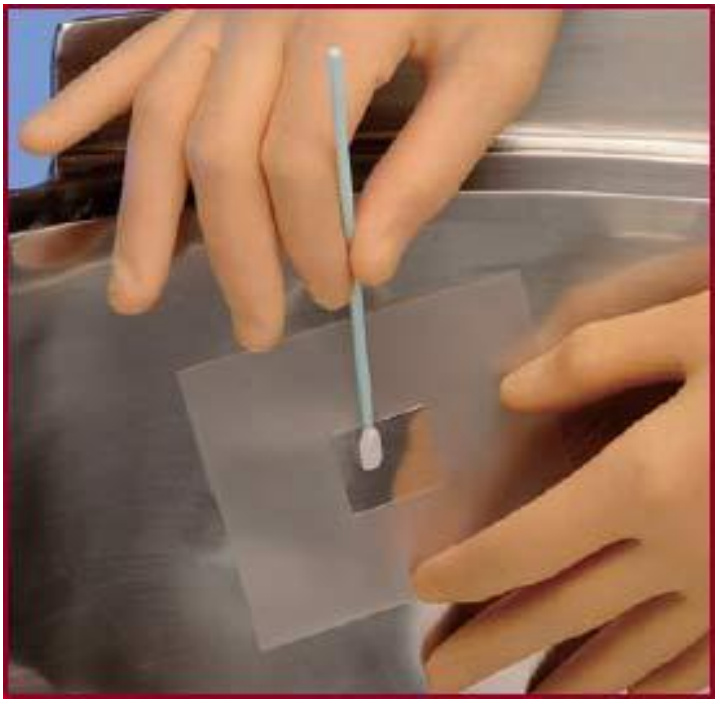

Fig. 2: Swab technique.

1.12.3. Rinse Sampling (Indirect method)

RS does not employ mechanical action on the surface and the sample is collected as a final rinse applied specifically for collecting a validation sample. In this indirect method a measured area of clean surface is rinsed or washed with solvent and the solvent is collected and tested for traces of contaminants. Rinse sampling methods allow sampling of a large surface. This method should be used in combination with other sampling methods such as surface sampling.

Fig. 3: Rinse sampling.

- **Limitation**

- Finite information about actual surface cleanliness in some cases.
- It may lower test sensitivity.
- residue cannot be homogenously distributed of
- Inability to detect location of residues.
- critical to ensure accurate interpretation of results by rinse volume
- It can be difficult to accurately define and control the areas sampled, therefore usually used for rinsing an entire piece of equipment, such as vessel.[28,29]

2. CONCLUSION

It is concluded that cleaning validation is a documented process that gives the effectiveness and consistency in cleaning of pharmaceutical equipment. It is essential to have effective cleaning program in place because of the regulatory requirement. Although, more fundamental reason that to produce products that as pure and free from contamination. The main valid reason of cleaning validation is to establish 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. And this article primarily covers all aspects related to cleaning validation like mechanism of sampling procedure, cross contamination, different levels of cleaning, cleaning procedure, product grouping and equipment characterization, cleaning agent selection, elements of cleaning validation.

3. REFERENCES

1. ICH Q7: ICH Harmonised Tripartite Guideline: Good manufacturing practice guide for active pharmaceutical ingredients, 2000; 4: 10.
2. Adcock, P. and Motise, P .FDA statement: Human Drug cGMP Notes.
3. APIC: Cleaning Validation in Active pharmaceutical Ingredient manufacturing plants, 1999; 3-7.
4. APIC: Guidance on aspects of cleaning validation in active pharmaceutical ingredient plants, 2000; 16-19.
5. US FDA: Guide to inspections validation of cleaning processes.
6. Gil Bismuth and Shosh Neumann, "Cleaning Validation: A Practical Approach," Interpharm Press, 2000.
7. Code of Federal Regulations, 2011; 67(4): 21.
8. Amit Kailaschand M. Process validation of cephalosporin antibiotics cefuroxime axetil 500 mg tablets. Karnataka: Rajiv Gandhi University of Health Sciences, 2011.
9. Robert Fredrick: The Basic Facts of Cleaning Validation. Canada: Pharmainfo.net, 2004. Available from http://www.pharmainfo.net/reviews/basic-facts-cleaning-validation
10. Patel Hiren Popatbhai et al: Process validation of Benzepril HCL 5 mg tablet. International Research Journal of Pharmaceutical and applied sciences, 2012; 2(4): 1-16.
11. Kathiresan K: Cleaning validation of acetaminophen tablets. Rasayan Journal, 2010; 3(3): 503-506.
12. Robert A Nash. Alfred H W: A Text Book of Pharmaceutical Process Validation. Marcel Dekker, 2003; 3: 500-541.

13. Agallaco J. Frederick Carelton J: A Text Book of Validation of Pharmaceutical Process. Spring Publisher, 2008; 3: 525-565.
14. Bodavula Samba Siva Rao: Cleaning validation of albendazole tablet 400 mg. Pharma Innovations, 2012; 1(4): 76-94.
15. Kumar S: A review on concept of cleaning validation in pharmaceutical Industry. International Research Journal of Pharmaceutical Sciences, 2012; 3(7): 17-19.
16. Active Pharmaceutical Ingredient Committee (APIC) group of EEFIC: Guide to cleaning validation in API plants. APIC Publications, 1999; 2-2.
17. FDA, "Guide to Inspection of Validation of Cleaning Processes," (Division of Field Investigations, Office of Regional Operations, Office of Regulatory Affairs, July, 1993.
18. Annex to the EU Guide to GMP, Brussels, 2001; 15.
19. United States Pharmacopeia Vol 30, National Formulary, 2007; 25: 680-683.
20. A. H. Schmidt, "Validated HPLC Method for the Determination of Residues of Acetaminophen, Caffeine, and Codeine Phosphate on Swabs Collected from Pharmaceutical Manufacturing Equipment in Support of Cleaning Validation," J. Liq. Chrom & Rel. Technol, 2006; 29: 1663-1673.
21. M. A. Boca, Z. Apostolides and E. Pretorius, "A Validated HPLC Method for Determining Residues of a Dual Active Ingredient Anti-Malarial Drug on Manufacturing Equipment Surfaces," J. Pharm. & Biomed. Anal., 2005; 37: 461-468.
22. R. J. Forsyth and D.Haynes, "Cleaning Validation in a Pharmaceutical Research Facility," Pharm. Technol., 1998; 22(9): 104- 112.
23. P. Yang, K. Burson, et. al., "Method Development of Swab Sampling for Cleaning Validation of a Residual Active Pharmaceutical Ingredient," Pharm. Technol, 2005; 29(1): 84- 94.
24. T. Mirza, R. George, et. al., "Capillary Gas Chromatography Assay of Residual Methenamine Hippurate in Equipment Cleaning Validation Swabs," J. Pharm. & Biomed. Anal, 1998; 16: 939-950.
25. K. J. Kolodsick, H. Phillips, et. al., "Enhancing Drug development by Applying LC-MS-MS for Cleaning Validation in Manufacturing Equipment," Pharm. Technol, 2006; 30(2): 56-72.
26. K. Payne, W. Fawber, et. al., "IMS for Cleaning Validation," Role of Spectros, 2005.
27. A.H.Mollah, "Risk-Based Cleaning Validation in Biopharmaceutical API Manufacturing," Bio Pharm Inter, 2005; 30(11): 54- 68.

28. K. M Jenkins, A. J. Vanderwielen, et. al., "Application of Total Organic Carbon Analysis to Cleaning Validation," PDA J.Pharm. Sci. & Technol, 1996; 50(1): 6-15.
29. R. J. Forsyth and V. Van Nostrand, "Visible Residue Limit for Cleaning Validation and its Potential Application in a Pharmaceutical Research Facility," Pharm. Technol, 2004; 28(10): 58-72.