CLEANING VALIDATION PROCESS INVOLVED IN PHARMA INDUSTRY: A REVIEW

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Abstract:

Cleaning validation of manufacturing site plays a vital role.[1] Cleaning validation is carried out to prevent the cross contamination and adulteration of drug products with other API or microbial contamination.[2] As per USFDA cleaning validation is defined as, Utensils & equipment should be cleaned, sanitized, and maintained to prevent malfunctions or contamination that would alter the identity, safety, strength, quality or purity of the drug product. The purpose of cleaning validation is to define the documented evidence with a rising degree of confidence that the regular cleaning process is followed according to the SOP and the results should not exceed the predetermined acceptance limit.[3] The primary goal of this study is to know the importance of cleaning validation and the various problems encountered in the pharmaceutical industry.[4] The case studies on cleaning validation were discussed in this paper.[5]

Keywords: *Cleaning validation, Contamination, Purity*

1. Introduction:

As per USFDA, 21 CFR part 211, subpart D, Cleaning validation is defined as Equipment & utensils shall be cleaned, maintained & sanitized at appropriate intervals to prevent contamination, cross contamination or malfunctions that would alter the safety, identity, strength, quality, or purity of the drug product. Cleaning validation is carried out to prevent the cross contamination and adulteration of drug products with other API or microbial contamination. It provides the evidence that cleaning process for manufacturing equipment prevents the product contamination.[6] As per ICH Q7 guidelines, cleaning validation could be directed to the steps where contamination or carryover of materials creates the greatest risk to API quality. The goal of washing validation is to ensure that cleaning procedures are effective in removing residues from prior products, preservatives, or cleaning chemicals, as well as microbiological contamination. Cleaning validation should meet all the regulatory requirements and to maintain the product quality & customer safety.[7] In recent updates found that, handling multiple cleaning validation process plays a major role in the pharmaceutical industry due to company mergers & contracting activities among the industry.[8] Traditional cleaning validation process could be very challenging due to the defects, compliance risk, lack of data integrity, failure to access & review data in a single depot. In modern method they used ValGenesis system, where ValGenesis is a validation life cycle management, that controls the entire validation life cycle process electronically.[9] This system provides the solution for inefficiencies that plagued paper-based cleaning validation processes.[10]

2. Problems encountered in cleaning validation:

1. Cleaning challenges during R&D
2. Detergent selection
3. Problems faced during cleaning process
4. Effects of excipients
5. Problems encountered during scale-up
6. Characteristic of API
7. Potency of product
8. Maximum allowable carryover
9. Appearance of product
10. Microbial growth
11. Manufacturing process

2.1 Cleaning challenges during R&D:

It is easy to clean small scale R&D equipment by hand using the solvents. But sometimes, you may use potentially problematic solvents for rinsing and cleaning which may lead to further contamination. Hence follow the appropriate cleaning methods and solutions for cleaning process as per the guidelines.[11]

2.2 Detergents selection: Manual cleaning method is carried out at R&D process but it is time-consuming process. Due to safety and environmental- concerns there are some solvents that are not used for cleaning purpose. Hence selection of detergents plays a vital role in the pharmaceutical industry.

2.3 Problem faced during cleaning process:

The process of cleaning is carried out in companies in which they use a single cleaning product for all the process which may lead to the contamination. The physical & chemical properties of the cleaning agents should be known and it should be within the predetermined acceptance limits as per the guidelines. Pharma expertise needs to recognize that every process, product & phase of production may involve wildly in different cleaning challenges.[12]

2.4 Effects of excipients:

Some pharma companies ignore the effects of excipients which may lead to cross contamination and contamination that affects the product quality, purity, safety & efficacy. Physical properties, chemical properties and nature of excipients should be known very well before selecting the cleaning detergents.

2.5 Problems encountered during scale-up:

Potential detergents should be properly evaluated during small scale investigation, so that it may not cause any problem during large scale process. Preventive measures could be carried out to prevent the contamination and the problems associated with those process.[13]

2.6 Characteristic of API

2.6.1. Solubility: The solubility of API plays an important factor in cleaning validation process because the API which is insoluble may cause contamination.

2.6.2. Toxicity: Toxicity of API is calculated by the LD50 value, where the API that contains higher LD50 value have less toxic effect.

2.6.3. Concentration: The residues containing higher concentration of API affects the other product as compared to the product having lower concentration.

2.7 Potency of product:

Products containing a lower amount of API are highly potent and vice versa, hence highly potent products are more active.

2.8 Maximum allowable carryover (MACO):

The product which contains lower MACO value will be less toxic when compared to the higher MACO value.

2.9 Appearance of Product:

The product which containing colors are difficult to clean as they are insoluble in water.

2.10 Microbial growth:

Microbial growth may occur on the equipment surface that may cause the contamination and affects the product quality and purity.

2.11 Manufacturing process:

Products which are manufactured by the wet granulation method(aqueous) might have high possibilities to develop microbial growth on the equipment contact surface & may affect the nature and quality of the product.

3. Case studies:

Table:1 Case studies carried out in pharma industry

S.NO	Name of the instrument:	Error	Reason for the error	Guidelines to be followed	Failed to follow the guidelines
1	HPLC	Shown additional peak in HPLC chromatogram during the swab test	Due to the presence of oligomers in polyester(swab), an additional peak was identified.	Before selecting the swab, they should carry out some important test such as: 1.Minimum extractable interferences 2.High recovery rate 3.Solvent compatibility 4.Low particle generation	Failed to carry out the test for the selection of swab as per the guidelines.[14]
2	HPLC	The Unknown peak was determined on the HPLC chromatogram.	Due to the presence of the hydrophobic flavoring ingredients in the formulation.	As per the guidelines, they should determine the physical & chemical properties and whether they are within the predetermined acceptance limits.	Failed to carry out the physical and chemical test.[15]
3	HPLC	Presence of residual soil was determined during the sampling process.	The analytical lab confirmed that insufficient solvent on the swab causes failure in the	As per the guidelines, during the sampling method, the wetting of the swab with organic	Failed to follow the guidelines, as a result they got residual content beyond the limits.[16]

			residue recovery process.	solvent is required to dissolve the residues from the equipment sample. Hence the vaporization of sampling solvent will be decreased.	
4	All analytical instruments	Presence of contamination.	Inadequate cleaning and sanitizing the instruments.	As per the guidelines, equipment and utensils should be cleaned and sterilized to prevent the contamination.	Failed to follow the guidelines in cleaning validation.[17]
5	All analytical instruments	The Presence of dust particles on the instruments and failed to maintain the records.	Improper maintenance of cleaning validation documents.	As per the guidelines, cleaning validation documents should be maintained.	Failed to maintain the documents.[18]
6	All analytical instruments	Failed to maintain the SOP for cleaning the equipment.	The SOP is not updated as per the guidelines.	As per the guidelines, the SOP should be in an updated version.	Failed to maintain the SOP.[19]

4. Conclusion:

Cleaning validation plays prominent role in the pharmaceutical industry in order to get the drug product in quality, purity, safety and efficacy.[20] Troubleshoot in the process should be evaluated and monitored regularly but it is impossible to achieve 100% of cleaning level.[21] One of the key methods to get success in pharmaceutical industry is to adopt a proper cleaning validation as per the guidelines.[22] The various case studies was discussed in this paper, which implies the importance of cleaning validation in the pharmaceutical industry. Documents should be maintained in the pharmaceutical industry which provides the documentation evidence for the process. Hence to achieve the high quality, purity & safety of any product it is necessary to do the cleaning validation of any product.[23].

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