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Cleaning Validation: An Important Aspect in Accessing Pharmaceutical Residues.

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ABSTRACT

The quality should be built in to the pharmaceutical product and the margin of errors should be none because it deals with the health. Pharmaceutical product can be contaminated either by previous drug manufacturing process in the industry, other exicipents, API, air borne contamination, dust, raw materials, etc. The cross contamination of the product can occur by the same or by other previous products. So proper cleaning should be ensured in order to avoid contamination. The interaction of pharmaceutical product with other substances may cause severe degree of damage to the quality, efficacy and safety of the product. Due to these reasons the cleaning of the equipment and various accessories should be done in order to prevent the contamination of the processing product and so the quality of the product can be retained. But cleaning alone cannot make things sure that there is no more interaction, so after cleaning the effectiveness of the cleaning can be measured by the validation. A cleaning validation provides documented evidence that the cleaning has been effectively performed and the chance of cross contamination and carryover of the previous products is negligible. By cleaning validation ensure the safety and purity of the product; it's a regulatory requirement, and assures that quality is built into the product.

Keywords: Cleaning validation, Quality, Residue, Validation guidelines.

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INTRODUCTION

Validation is the documented evidence that a procedure or activity will consistently give expected results. Cleaning validation is the documented evidence that ensures the equipment and the part of equipment is effectively cleaned and provides consistent results. It gives reliability that the equipment used for production are free from older API, Cleaning materials, and other micro-organisms. The cleaning procedures are followed to prevent cross-contamination and the adulteration. If cleaning not performed adequately then the potential damage might cause to the product quality and safety of the patients health. Though cleaning validation is the requirement of the federal and regulatory bodies, it is also very important from an industry perspective to increase the quality and have no contamination of the products produced. Cleaning validation for the surfaces which get contact with drug is normal but the validation is also to be considered for parts where product can migrate to non-contact parts. Thus there would be no compromise in the quality and safety of the product [1,2].

Objective

The objective of cleaning validation is to prevent the contamination and adulteration of the present batch with various residues, excipients, microbes, detergent agents, which are used in previous batch. The cleaning validation of the areas where it is difficult to reach and areas where there is no direct contact of the drug like fans, flanges, shafts, heating elements are to be considered.

Why is cleaning validation required?

Need by regulatory authorities so control and quality can be maintained.
Conformity of safety and purity of the product.
Assurance to consumers that product is safe and quality is built into it.
Cleaning validation ensures process quality and builds internal control [2].

Types of contamination

- *Cross contamination:* Contamination which can be caused by residues of the previous batch interacting with present batch. This interaction cannot be tolerated because this can cause high adverse effects to the consumers. It may also cause synergetic effects when interacted with other drugs causing various pharmacological actions.
- *Contaminated by unintended materials:* The various unintended materials like equipment parts, lubricants, chemical agents, cloth fibers, brushes etc…used for cleaning may interact with drug causing unwanted interaction.
- *Microbial contamination:* Microbes may get evolve due to presence of residues either by storage or during the process [3,4].

Requirements of FDA

- A SOP should be present for each cleaning process for different equipment.

- If the companies prefer a specific cleaning procedure for each batch of same product produced, a separate SOP should be written cleaning procedure.
- A SOP should be written for different cleaning procedure for product changes by the firms.
- If firms follow separate procedures for cleaning the water soluble residues and non-water soluble residues FDA expects a written procedure for each process.
- A written document is required for each validation procedure performed in specific equipment.
- Personnel performing validation should check with procedures, limits and acceptance criteria before reporting and approving.
- The firms should follow the protocols and document the results of the studies.
- The regulatory authorities are the end bodies to approve the final reports which confirms cleaning is effective and product safety [4].

Acceptance limits for cleaning validation

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

Milligrams of active ingredient: I×K×M, in product A permitted per J×L, 4 inch^2/swab area.
Where,

I = 0.001 of the smallest strength of product A manufactured per day expressed as mg/day and based onthe number of milligrams of activeingredient.
K = Maximum number of dosage units of product B per day.
L = Equipment surface in common between product A & B expressed as squareinches.
M = 4 inch^2/swab.

Approach 2: Any active ingredient can be present in a subsequently manufactured product at a maximum level of 10 ppm.
Milligrams of active ingredient = R × S × U, in product A permitted per T, 4 inch^2/swab area.
Where,
R = 10mg active ingredient of product A in one kg of product B.
S = Number of kilogramsper batch of final mixture of product B.
T = Equipment surface in common between product A & B expressed as square inches.
U = 4 inch^2/swab.

Approach 3: Residues of any quantity should not be visible after the cleaning has performed. [5,6].

Cleaning procedures [1,16]

Standard cleaning procedures for all equipment and parts of equipment should be prepared. Complete evaluation should be done from the equipment, residues, use of

washing solvents, and cleaning techniques. Cleaning procedures should remove all the potential threats.

Also, there are several equipment related parameters which are to be considered during cleaning validation process as mentioned in Fig. No. 1.

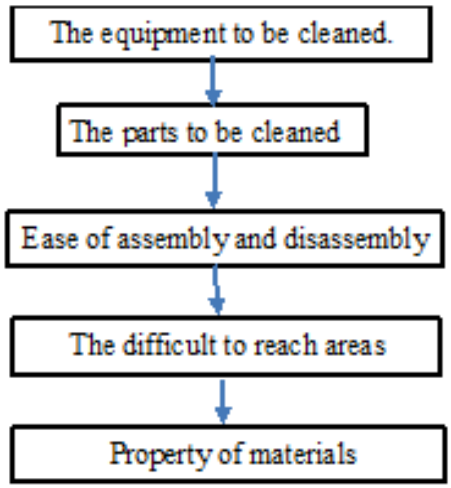

Fig No.1: Parameters of equipment to be considered

Cleaning agent

Cleaning agent used, scientifically justified and based on different aspects. The solubility of the materials to be removed should be considered. The design and construction of the equipment and surface materials to be cleaned should be studied. The degree of safety of the cleaning agent should be known. The detection feasibility and ease of removal should be possible. (See Fig. No. 2) [7].

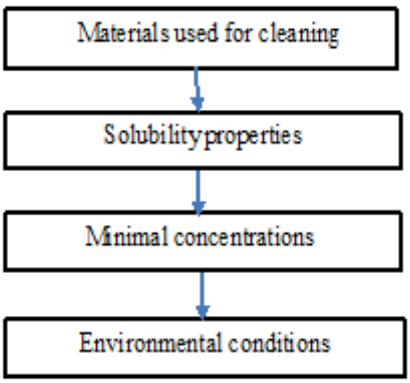

Fig No.2: Criteria for cleaning agents to be used

Sampling types

There are mainly two types of sampling, A) Direct sampling B) Rinse sampling

Direct sampling: The materials used for sampling are very important, the sampling materials and the sampling medium affects the samples to be recovered so they should be suitable for use. It is important that the sampling materials and the medium used are satisfactory and does not affect the sample recover.

The advantages of direct sampling are hard areas can be cleaned. Residues which are dried, insoluble got attached can be analyzed by physical removal [9,10].

Swab sampling: It is the direct sampling method. Cleaning may be performed by alcohol, various chemicals and various materials are used to remove the residues of previous materials. Now the cleaned surfaces should be sampled so that cleaned surfaces can be validated the followed cleaning procedure. Thus the swabs are the one of the choice. By using swab sampling technique it would reach more restricted areas like non reachable parts.Swabs used should be compatible with the active substances and should not interfere with the assay. The swabbing material and solvent used should not degrade the active compounds [11].

Rinse sampling: the active ingredients and the residues have been checked in the rinse samples which are used for cleaning. These rinse samples should be selected in a way that can make the residue or active ingredients soluble. Though rinse sampling might not solubilize the residues and may be physically occluded in the equipment. Though this method is not direct because it occurs after cleaning, it covers entire area and difficult to reach areas [10].

The important parameters to be considered during cleaning of residues are mentioned in Fig. No. 3.

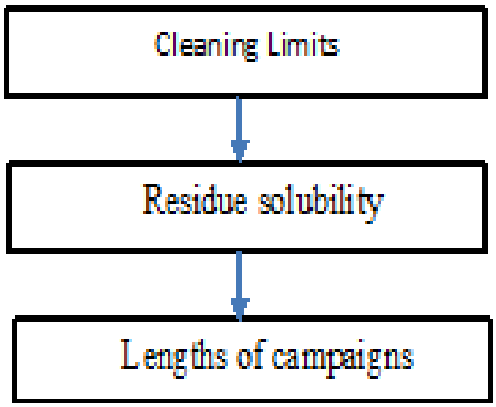

Fig No.3: Parameters to be considered during cleaning of residues

Testing methods

There are few requirements and criteria for selecting an analytical method:

- The analytical method selected should have ability to detect the residues with a consistency.

- Target should be identified in the presence of other materials.
- There should be calculation for the amount of residue that has been detected.

Sample analysis

There are many analytical methods choosing for cleaning validation. But the important method is selected on the parameters to be measured.

Specific and non-specific methods

The specific methods are finding the compounds uniquely in presence of whole residue. In which a HPLC method can able to detect uniquely compounds based isolation or separation. Non-specific methods are those methods which detect based on the response produced by the compounds. Example: total organic carbon, pH, and conductivity [12,13].

Method validation: The limit of the residue should be established before choosing the method those are limits of residue in analytical sample and in next product. This will help the method to detect and quantitate the limits. The method chosen will have to be validated to show the method is rugged and robust under various conditions [14].

Validation Report

- A summary of procedures followed used to clean, collect, test.
- All the test observations should be given.
- Conclusions of the results or the methods followed.
- Changes or modifications from standard protocol should be reviewed.
- A review should be made on deviations or un-satisfied results and problems encountered
- A batch by batch report would be suggested if manufacturing of further batches takes more time.
- The report should conclude with an appropriate verification after the validation. [4,15,17].

Effective cleaning validation maintenance

Performing couple of cleaning validation runs and achieving results under acceptance criteria is fine for few times but as the time progress the consistency and efficiency breaks down slowly.

This is because:

- Operator variability.
- Aging and repair of the equipment.
- Potential non representative results and monitoring programs.
- Product, equipment and process changes [1,2].

Operator variability: There arises few questions form operator perspective.

- Is the equipment scrubbed by hand or better with solvent and which has more efficiency?
- What is degree of variability of manual cleaning from batch to batch and after the change of products?

The operator variability can be made more productive by conducting training programs in manufacturing companies. These training programs may include equipment disassembly, preparation of detergents, step-by-step cleaning procedures, drying process, etc….it is difficult for the same operator to perform same function in the same degree every time and this variation is increased if different operator works. So to minimize the variability the successive path is proper training of the personnel [1].

Equipment aging and repair

The equipment after using a certain period gets older and some parts get more wear out than others. The more equipment gets older the cleaning becomes harder. The residue can get stuck in the critical parts of the equipment causing difficult to clean or remove those residues. An alternative for this is buying new parts as the equipment gets older and proper periodical maintenance helps in cleaning. Also, periodical checking the functionality of the equipment more important [8].

Monitoring Cleaning validation

A monitoring program helps to ensure consistency in followed cleaning program. Monitoring program is required mostly for the difficult to reach areas and difficult to clean products. The parts of equipment which are easy to clean require moderate monitoring.

The degree of monitoring is applied based on three categories as follows:

- Most *'difficult to clean'* equipment and product requires the most intensive monitoring schedule.
- *'Easier to clean'* equipment and product that requires a moderate monitoring schedule.
- *'Easiest to clean'* equipment and product that requires only periodic monitoring.

By monitoring the critical problems can be resolved and the efficiency of the cleaning validation as well as effectiveness of equipment can be improved [8,18].

Changes to the products, equipment and process

When new products, equipment are added to the production line there is a need for rechecking the acceptance limits of original study. The acceptance limits criteria is based on parameters like product, equipment matrix, potency, daily dose and batch size [1]. A recheck and expansion in the validation program helps reliability on procedures when there is change in the lineup by either a product change or equipment change [3,4].

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CONCLUSION

The cleaning should be performed on the equipments and necessary areas, the assessment of the equipment and products should be performed by cleaning validation process. The critical parameters, method of cleaning, solubilities of residues, detergents used, equipment or tools used for cleaning should be determined. The cleaning validation testing methods and there procedures should be mentioned as analytical methods. An out of path results or critical paths should be reviewed. Cleaning agents should pass the acceptance criteria as extended by regulatory authority. All the procedures, types, testing methods, in charge personnel signatures, study documents, threats, results, reports and revalidation policy should be documented and stored for future use.

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