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A Review Article on Cleaning Validation

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Abstract
Pharmaceutical product can be contaminated by other pharmaceutical products or Active pharmaceutical ingredients (APIs) or by cleaning agents, by microorganisms or by other materials e.g. air borne particle, dust, lubricants, raw materials, intermediates. Mainly cleaning is performed to remove product and non-product contaminating material. Ineffective cleaning can lead to contaminated product, which may be contaminated from previous product batches, cleaning agent or other extraneous material introduced into generated by the process. In pharmaceutical industry the same equipment may be used for processing different products. To avoid cross contamination source or facility configuration there is a need to ensure that cleaning procedure must strictly follow carefully established and validated method of execution.

Keywords: Cleaning Validation, MACO (Maximum Allowable Carryover) limit

Introduction

Validation is documented evidence which provide a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes.

Cleaning validation is a documented evidence with high degree of assurance that one can consistently clean a system or piece of equipment to predetermined and acceptable limits. Cleaning validation is primarily applicable to the cleaning of process manufacturing equipment in pharmaceutical industry. It is necessary to have effective cleaning programs in place because of regulatory requirements.

However more fundamental reason is that to produce products that are as pure and free from contamination to extent that is possible and feasible 2 .

Why Cleaning Validation is required : To verify the effectiveness of cleaning procedures and to ensure no risks are associated with cross contamination of active ingredient, detergents and microbes.

When Cleaning Validation is performed :

1. Initial qualification of process/ equipment.

2. Critical change in a cleaning procedure.

3. Critical change in formulation.

4. Significant change in formulation.

5. Change in a cleaning process.

6. Change in a cleaning agent 3 .

Advantages of Cleaning Validation:

1. **Safety**: Validation can also result in increased operator safety. Properly calibrated, validated instruments and gauge used to reduce accident and results in safety.

2. **Better Customer quality**: Through proper validation, market recall is avoided which results in better customer care and quality of the product.

Contamination & Cross Contamination

Generally cross contamination and contamination by a foreign material are two types of contamination. Cross contamination is usually through an active ingredient from one product carrying over into subsequent manufactured product. However, carryover of other product component such as excipients can also be problematic and may degrade the final quality of product. Contamination of one batch of product with significant level of residual active ingredient from a previous batch may lead to the risk to consumer or patients from unintended contaminants.

Potential clinically significant synergistic interaction between pharmacologically active chemical is a real concern. Inert ingredients used in drug product are generally recognized as safe for human consumption and for routine use also. Maintenance and cleaning of equipment provide the potential risk of contamination from equipment parts and lubricant.

Cleaning agent and piece of cleaning tools can cause 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. In addition, some activities are adversely affected by trace contaminants and may exhibit change in stability or bioavailability if exposed to such contamination.

The second type of contamination is by foreign material these may be bacterial in nature or could represent part of the equipment. Maintenance, cleaning, and storage condition may provide adventitious microorganisms with the opportunity to proliferate with in processing equipment. This could pose obvious problems for sterile products manufacture (generation of high level of pyrogens, decreasing the assurance of sterile achieved by equipment sterilization procedures etc.) It also possess serious problem for the manufacture on non-sterile dosage form particularly unpreserved products which support microbial growth 5.

1. **Cross contamination with active ingredient**: One of the real risks in cross contamination of product is that by being contaminated by previous product active ingredients resulting in a multiple ingredient product instead of single active ingredient. Depending on therapeutic effects, the contamination may enhance the action or work against the therapeutic action or contaminant may have an entirely different therapeutic effects.

2. **Microbiological contamination**: This form of contamination is particularly dangerous because the contamination may develop at any time even after cleaning. A major contributing factor is the storage of equipment in a wet condition. This provides a natural medium in which bacteria /fungus can grow and may lead to serious health issues.

3. **Contamination by cleaning or sanitizing agents**: Some pharmaceutical operations may find it necessary to use detergents for cleaning purpose for stubborn residues. This is particularly true in the manufacture of active pharmaceutical ingredients (APIs). As such, these materials represent a potential threat as contaminants. It seems obvious that one effective way of dealing with this potential problem is to use cleaning agents with the lowest toxicity that will still be effective in removing the residue in the given cleaning situation. The same factors also apply to sanitizing agents used to wipe down cleaned equipment.

Equipment characterization: Cleaning validation involves not only the removal of residues but also gives assurance that each and

every piece of equipment associated with the process has been cleaned to acceptable levels. It is typically referred as train based approach. The equipment train is series of equipment through which the product or products move as they progress through the manufacturing process. In order to asses that the equipment is cleanable or not it should be characterized in such a way that its design features are well known. Equipment characterization can assist cleaning validation initiatives in many ways.

1. Promote more effective cleaning procedure by identifying cleaning challenges and ensuring that they are addressed in the cleaning methods employed.
2. Identifying hard to clean locations and high risk locations in equipment for the purpose of sampling site selection.
3. Target materials of construction that will be included in sampling recovery studies and those that will not be included.
4. Isolate materials that will be disposed of at the end of a production process and/or will be dedicated to a single product.
5. Verify that all materials of construction are compatible with the selected cleaning agents and temperature that will be used with the cleaning process.
6. Collect product contact and sample site surface areas for the purpose of calculating limits and results.
7. Confirm similar geometries, capacities, and use of process equipment for the purpose of grouping that equipment

Product Grouping and Equipment Grouping:

Grouping, sometimes also called as a family approach. It is a method by which products or equipment is considered to be similar or equivalent for the purpose of cleaning validation. When considering similar, a worst case molecule of the group is selected for performing cleaning validation. When considering equivalent, any molecule of the family may be selected as representative of any other member.

Bracketing- is a term that appear in EU GMP Annex on cleaning validation, has an equivalent meaning to grouping, although it may included as an added burden for testing the extremes of all equipment. Grouping may also 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 perform.

When grouping products, all products must be

1. Manufacture on the same equipment group.

2. Cleaned with the same cleaning agent.

3. Cleaned with the same cleaning procedure

Grouping considerations for products include:

1. Similar therapeutic actions, route of administration, potency, toxicity for drug.

2. Similar formulations

3. Similar manufacturing process.

Cleaning validation must always be carried out to meet lowest limit of the entire product group. When grouping equipment, all equipment must be:

1. Used to produce products from the same product group.

2. Cleaned with the same cleaning agent.

3. Cleaned with the same cleaning method

Cleaning Agent selection:

Cleaning Agent fall into several broad categories;

1. Water

2. Solvents

3. Commodity chemicals

4. Formulated cleaning agents

Sampling Techniques:

Sampling sites selected should be based on the difficult clean , seam, hard to reach & inspect locations on the equipment and these locations are inaccessible i.e. their accessibility makes them difficult to clean therefore, before choosing for sampling sites one must be conscious in selecting the desired locations.

An example of hot spot is bottom of an agitator or discharge port inside an rapid mixer granulator that become soiled during the manufacturing process and proves to be difficult to be cleaned during the cleaning process. Before selecting

sample sites one must evaluate a variety of locations

The common sampling method employed in cleaning validation is rinse sampling and swab sampling.

Swab Sampling direct method:

This method of sampling is the most commonly used and involves taking an inert material (e.g. cotton wool) on the end of a probe (referred to as "swab") and rubbing it methodically across a surface. The swabs are added to the dilution solvent and these
solvents are analyzed by suitable analytical instruments for the presence of residue of
previous products per given area. i.e. 25-100 square cm.

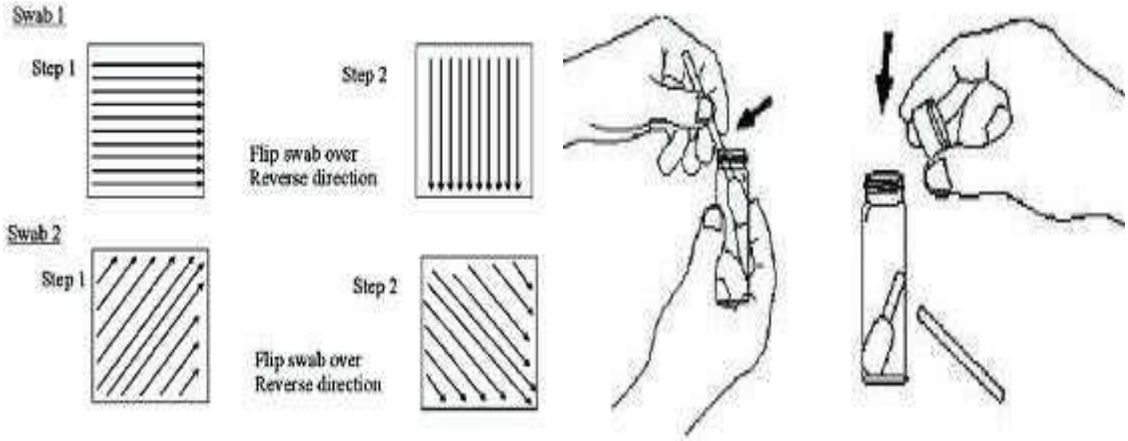

Figure 1-Direct swab sampling technique

Rinse samples (Indirect method):

In this method, a measured area of clean surface is rinsed with solvent and the solvent is collected and tested for traces of contaminants. This method allows sampling of a large surface, of areas that are inaccessible or that cannot be routinely disassembled and provides an overall picture. It is also suitable for checking the residue of cleaning agents, e.g. detergents. Rinse sampling method should be used in combination with other sampling methods such as surface sampling. There should be evidence that samples are accurately recovered. ISPE suggests 0.5m-lml per sq.cm as rinse volume.

Strategy on Cleaning Validation Studies: Basic elements of cleaning validation study includes

1. Evaluating of new product/equipment
2. Determination of limit and reporting.
3. Cleaning procedures.
4. Analytical method and its Validation

Evaluating of new product/equipment

For new product: In case there are more than one API for the new product, each API shall be evaluated for the below detailed parameters and based on the evaluation one API shall be selected as worst case product

1. **Therapeutic Dose for the product:** The product having minimum therapeutic daily dose can be considered as worst case product.
2. **Solubility of the API:** Product having least solubility in water and higher strength can be considered as worst case product on basis of solubility.
3. **HBEL / ADE/ PDE values :** The Permitted Daily Exposure (PDE) represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime. Consideration should be given to the product (API) having the minimum PDE values.

Thus a combination of these above three should be considered as a worst case.

Determination of Limit and Result reporting:

1. Calculation of MACO for Product is given by the formula:

a. By dose criteria:

NMT 1/1000th dose of any product shall appear in the maximum daily dose of another product manufactured subsequently.

MACO by therapeutic dose criteria by considering 0.1% safety factor

$$\text{Limit (mcg)} = \frac{1 \times \text{Minimum Therapeutic dose of product A (mg)} \times \text{Minimum batch size of next product B (in units)}}{1000 \times \text{Maximum daily dose of next product B (in units)}}$$

Converting the MACO values to per swab limit

$$\text{Mcg per swab} = \frac{\text{MACO X swab surface area (i.e. 25 cm}^2\text{ or 100 cm}^2\text{)}}{\text{Shared surface area between the product A \& B in cm}^2}$$

MACO by 10 ppm as acceptance criteria

The quantity equivalent to 10 mg/L of the batch size is considered as the acceptance criteria for the acceptance criteria as 10 ppm.

Limit (mcg) = 10 PPM x Minimum batch size of next product B (in Kg) x 10^6

Converting the MACO values to per swab limit

$$= \frac{\text{MACO X swab surface area (i.e. 25 cm}^2\text{ or 100 cm}^2\text{)}}{\text{Shared surface area between the product A \& B in cm}^2}$$

MACO by PDE values

$$\text{Limit (mcg)} = \frac{\text{Minimum PDE values of product A} \times \text{Minimum batch size of next product B (in kg)} \times 10^6}{\text{Maximum daily dose of next product B (in mg)}}$$

Converting the MACO values to per swab limit

$$\text{mcg per swab} = \frac{\text{MACO X swab surface area (i.e. 25 cm}^2\text{ or 100 cm}^2\text{)}}{\text{Shared surface area between the product A \& B in cm2}}$$

Cleaning Procedures: Standard cleaning procedures for each piece of equipment and process should be prepared. It is vital that the equipment design is evaluated in detail in conjunction with the product residues which are to be removed, the available cleaning agents and cleaning techniques, when determining the optimum cleaning procedure for the equipment.

Cleaning procedure should be sufficiently detailed to remove the possibility of any inconsistencies during the cleaning process. Following parameters are to be considered during cleaning procedures.

Equipment Parameters to be evaluated include

a. Identification of the equipment to be cleaned

b. Difficult to clean areas.

c. Property of materials.

d. Ease of disassembly.

e. Mobility.

B. Residues to be cleaned

a. Cleaning limits

b. Solubility of the residues.

c. Length of campaigns

C. Cleaning agent parameters to be evaluated

a. Preferable materials that are normally used in the process.

b. Detergents available (as a general guide, minimal use of detergents recommended unless absolutely required).

c. Solubility properties.

d. Environmental considerations

e. Health and safety considerations.

D. Cleaning techniques to be evaluated

Manual cleaning.

b. CIP (Clean-in- Place)

c. COP (Clean out of place)

Testing Methods: The basic requirements of the analytical methods should have the following criteria.

a. Testing method should have the ability to detect target substances at levels consistent with the acceptance criteria.

b. Testing method should have the ability to detect target substances in the presence of other materials that may also be present in the sample.

c. The testing analytical method should include a calculation to convert the amount of residue detected in the sample to 100% if the recovery data generated indicates a recovery outside the allowed range.

Analyzing cleaning Validation samples: There are many analytical techniques available in cleaning validation. But choosing the appropriate analytical tool 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. **Specific and non-specific methods:** A specific method detects unique compounds in the presence of potential contaminants e.g. HPLC. Nonspecific methods are those methods that detect any compounds that products a certain response e.g. Total organic carbon, pH and conductivity

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

a. Reference to all the procedures followed to clean the samples and tests.

b. Physically and analytical test results or reference for the same, as well as any pertinent observations.

c. Conclusion regarding the acceptability of the results, and the status of the procedures being validated.

d. Any recommendation based on the results or relevant information obtained during the study including revalidation practices if applicable.

e. Review of any deviations from the protocol.

f. When it is unlikely that further batches of the product will be manufactured for a period of time. It is advisable to generate reports on a batch by batch basis until such time.

g. The report should conclude an appropriate level of verification subsequent to validation 14

h. The report should include the trending of cleaning variable factors such as operator variability such as shift change, cleaning performed by different operators, time of cleaning, temperature and pressure of cleaning of water.

Conclusion:

This review based article concludes that cleaning validation is a documented process that proves the effectiveness and consistency in cleaning of pharmaceutical equipment. It is necessary to have effective cleaning program in place because of the regulatory requirement. However, more fundamental reason is to produce products that free from contamination and the main purpose 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 cross contamination, different levels of cleaning, cleaning procedure, sampling procedure, product grouping and equipment characterization, cleaning agent selection, elements of cleaning validation.

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