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CLEANING VALIDATION IN PHARMACEUTICAL INDUSTRIES

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ABSTRACT

In pharmaceutical industries, to ensure safety, efficacy and quality of subsequent batches of drug products,care must be taken to avoid cross-contamination, adulteration of drugs or drugs with other active ingredients, unintended compounds, contamination of microbiological origin or contamination by cleaning or sanitizing agents. Hence it becomes very necessary to validate cleaning procedures which strictly follow the guidelines and methods developed for the same. Cleaning is done to eliminate product and non-product contamination as ineffective cleaning can lead to adulterated and contaminated product. It includes different levels of cleaning, cleaning procedure, sampling procedure, cleaning agent selection etc to ensure the efficacy of cleaning procedures to ensure that the patients are not put at risk due to cross-contamination and ultimately result in better customer care and quality of product.

Keywords: Cleaning validation, cleaning procedure, level/ degree of cleaning, sampling technique.

INTRODUCTION

Validation is the documented act of establishing that any procedure, process, equipment, material, activity or system that has been followed leads to the expected results.

Validation can also be defined as documented evidence which provide a high degree of assurance that a particular process will constantly produce a product which will meet its preset specifications and quality attributes[1, 2].

Cleaning validation is a documented process that proves the effectiveness and consistency in cleaning pharmaceutical production equipment[3].

Equipment Validation and cleaning procedures are chiefly used in pharmaceutical industries to prevent cross contamination and adulteration of drug products hence is significantly important to be considered.

The main purpose of validating a cleaning process is to ensure compliance with federal and other standard regulations. The significance of carrying out such a validation process is the identification and rectification of major problems previously unanticipated, which could affect the safety, efficacy, or quality of subsequent batches of drug products produced in that equipment.

Importance and purpose of cleaning validation[4, 5]

Cleaning validation is

1. Not only required to comply with regulations, but also it is necessary to satisfy customer's requirements.
2. It ensures the safety, identity, purtiy, and strength of the product which are the basic prerequisites of cGMP (Current Good Manufacturing Practice).

3. It provides manufacturer with enough confidence that internal control is well established.

Areas of concern which affect one's ability to get a successful outcome and things needed to be considered when carrying out cleaning validation are given in Fig.1.

Objectives of cleaning validation

Equipment cleaning and cleaning validation in an Active Pharmaceutical Ingredient (API) area is needed to prevent contamination of a future batch with the previous batch material.

Cleaning validation in an API service isreally important as cross contaminationin one of the pharmaceutical dosage forms will increase the problem therefore it is suitable to perform at least three repeated and successful applications of the cleaning procedure in order to prove that the method is validated[7].

It is necessary to validate cleaningprocedures for the following reasons:

1. It is a prime customer requirement asit ensures the purity and safety of the product to be consumed.
2. It is a regulatory requirement in API (Active Pharmaceutical ingredient) productmanufacture.
3. It also confirms the quality of the processthrough an internal control andcompliance[8].

Contamination and Cross Contamination[1]

Generally cross contamination and contamination by a foreign material are of two types

1. 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 cause problems and may lower the final quality of product. Contamination of one batch of product with considerable level of residual active ingredient from a previous batch may causeapparent problem to consumer or patients from unintended contaminants.
2. The second type of contamination is by foreign material which may be bacterial in nature or could signify part of the equipment. Maintenance and storage condition may provide adventitious microorganisms with the opportunity to proliferate within processing equipment. This could result in clear problems for sterile products manufacture (production of high level of pyrogens, decreasing the assurance of sterility and purity obtained by equipment sterilization procedures etc.) It also possess serious problem for the manufacture of nonsterile dosage form particularly unpreserved products which support microbial growth[1].

Types and mechanism of contamination[9]

1. Cross contamination with active ingredient

One of the actual dangers in cross contamination of active ingredients is that, after contamination the outcome is a multiple active ingredient product instead of single active ingredient product. Depending on medical effects, the contamination may enhance the action or negate the action or contaminant may have an entirely different medical and health effects.

2. Microbiological contamination

This form of contamination is particularly disingenuousbecause the contamination may develop at any time, even after cleaning. A large contributing factor is the storage of equipment in a wet or damp condition. This provides a natural medium in which bacteria can grow easily.

3. Contamination by cleaning or sanitizing agents

Some pharmaceutical operations may find it unavoidable to use fairly toxic and hazardous materials for cleaning purpose for stubborn residues. This is especially true in the manufacture of active pharmaceutical ingredients (APIs). These materials represent a potential threat as contaminant of product. It seems obvious that one effective and best way of dealing with this potential problem is to use cleaning agents with the lowest possible toxicity that will still be efficient in removing the residue in the given cleaning situation. The same factors also apply to sanitizing agents used to wipe down cleaned equipments.

4. Contamination by miscellaneous other materials

Regardless of the usual expected or anticipated list of potential contamination in a pharmaceutical operation, several other less likely materials can also contaminate products. A partial list contains equipment parts for e.g. filling equipment,bristles from brushes used in packaging,excipients, paper filters, micron filters, fibers and rubber particles from gloves, cleaning aids such as brush bristles, cloth, and cotton fibers from rags and wiping materials, lubricantsetc[9].

Equipment characterization

Cleaning validation involves not only the removal of residues but also gives assurance and confidence that each and every piece of equipment associated with the process has been cleaned to desirable or acceptable levels. It is typically referred as train based approach. The equipment train is series of equipment by which the product or products move as they progress through the manufacturing process. In order to check that the equipment is cleanable or not it should be characterized in such a way that its design features are well known[1].

Cleaning Procedures[10]

Standard cleaning procedures for every piece of equipment and process should be prepared. It is important that the equipment design is figured out in detail in combination with the product residues which are to be removed, the available cleaning agents and cleaning techniques, when determining the most beneficial cleaning procedure for the equipment. Cleaning procedures should besufficiently and properly detailed to avoid the possibility of any inconsistencies during the cleaning process. Following parameters are being considered during cleaning procedures.

A. Equipment Parameters to be evaluated[10]

1. Identification of the equipment to be cleaned
2. 'Difficult to clean' areas
3. Property of materials
4. Ease of disassembly
5. Mobility

B. Residues to be cleaned

1. Cleaning limits
2. Solubility of the residues
3. Length of campaigns

C. Cleaning agent parameters to be evaluated

a) Preferable materials that are usually 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

1. Manual cleaning
2. CIP (Clean-in-place)
3. COP (Clean-out-of-place)
4. Semi automatic procedures
5. Automatic procedures
6. Time considerations
7. Number of cleaning cycles

Cleaning Agent selection[11]

Cleaning agents fall into several broad categories;

1. Water
2. Solvents
3. Commodity chemicals
4. Formulated cleaning agents

1. Water

It is the universal solvent. If water alone will efficaciously clean the product without undue time or physical effort to remove the residues, by all means water should be employedalone. For many, however the water alone requires an unacceptable increase in time to get the cleaning finished. So other approaches must be screened.

2. Solvent

These are basically applied in processes where solvent usage is already called for by the manufacturing process. For example, mother liquors are used as the solvents for cleaning of APIs. As the mother liquors is already known to dissolve the primary residue, there is little risk in using it for cleaning.

3. Commodity chemicals

Here, chemicals **s**uch as NaOH can be used for cleaning as well. Like their solvent counterparts, there can be hazard issues, effluent issues associated with these materials. Their typically high basicity or low acidity, however, often makes them helpful in inactivation processes. However these chemicals do not have the detergency of a formulated cleaning agent and they can be difficult to rinse, taking larger volumes of water to rinse free from systems than would a formulated cleaning agent.

4. Formulated cleaning agent

Is the largest class of cleaners. This category consists of solvent based formulations and aqueous formulations. Typically formulated cleaning agents can include one or more alkalinity or acidity sources, sequestrants, surfactants builders, chelants and either a solvent or water. For industrial uses, unlike consumer-use products, these materials are prepared to be low foaming and therefore are more easily rinsable and are appropriate for high delinquency or high turbulence cleaning.

Level / degree of Cleaning

Level 1 Cleaning

This is used between manufacturing of various batches of the same product. Example – In a manufacturing Campaign for Product X, there are 3 Batches to be manufactured as shown below. Batch A, Batch B, Batch C for a given equipment &/or equipment train, if batch A in the campaign is to be followed by Batch B in the campaign, then a level 1 cleaning is required.

Level 2 Cleaning

This level is used between manufacturing of different Batches of different Product and / or at the end of manufacturing operation even if same product is planned for the next operation.

The above two degree or level of cleaning varies from each other in terms of the degree of risk associated with it, acceptance limit, and degree of cleaning & method of verifying the cleaning process as shown in Table 1.

In addition the CEFIC-APIC (Europian Chemical Industry Council-Active Pharmaceutical Ingredients Committee)[13] guide to cleaning validation recommends three levels of cleaning that may be implemented. This approach is outlined in the table below, yet it should be mentioned that additional levels might be necessary depending on the nature of the process and requirement[14, 15]. Shown in Table 2.

Sampling Technique[17-24]

Generally there are three main types of sampling amongst whichthe most desirable is the direct method of sampling the surface of the equipment, other methods being used are swab sampling and rinse sampling.

1. Direct surface sampling

This technique involves the determination of the type of sampling material used and its impact on the test data to check the intervention of the sampling material with the test. Therefore, early in the validation programme, it is important to assure the sampling medium and solvent if they are satisfactory and be readily used.

Advantages of direct sampling

1. Areas hardest to clean and which are reasonably reachable can be evaluated
2. Leads to establish a level of contamination or residue per given surface area.
3. Residues that are "dried out" or are insoluble can be sampled by physical removal.

Disadvantages of direct sampling

1. There is no physical removal of the contaminant.
2. The rinsing solvent may not reach unapproachable or occluded part of equipment.
3. This method uses organic solvents for water insoluble materials.

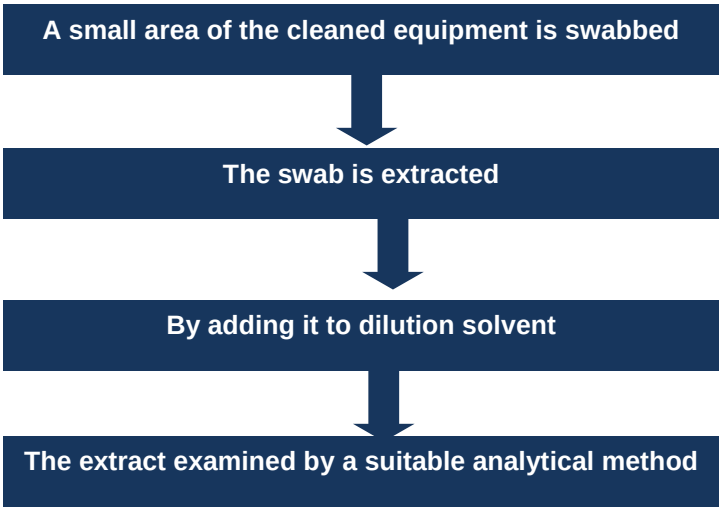
2. Swab sampling[17-24, 25, 26, 27]

After cleaning the equipment, product contact surfaces could be swabbed to assess surface cleanliness. Swabs used should be compatible with the active ingredients and should not interfere with the assays and results. They should not cause or result in any degradation of the compound. The solvent/(s) used for swabbing should supply good solubility for the compound and should not cause degradation (Fig. 2: Swab sampling).

Advantages of Swab Sampling

1. Dissolve and physically remove sample.
2. Adaptability to wide variety of surfaces.
3. Economically and widely available.
4. May allow sampling of a defined area.
5. Valid to active, microbial, and cleaning agent residues.

Method of swab sampling[29]



Limitations

1. An Invasive technique that may introduce fibers.
2. Results may be technique dependent.
3. Swab material and design can inhibit recovery and specificity of the method.
4. Evaluation of complex, complex and hard to reach areas difficult11-15, 30-33.

3. Rinse sampling[17-24, 25, 26, 27]

Sampling and testing of rinse samples for residual active ingredient is a commonly accepted method to evaluate cleanliness. This is a kind of convenient method in many cases

and requires control over the solvent used for rinsing, the contact time and the mixing involved. The solvent which is used should be chosen based on the solubility of the active ingredient and should either mimic a subsequent batch of product or at least provide enough solubility. (Fig. 3: Rinse sampling[29])

Advantages

1) Ease of sampling.
2) Evaluation of entire product contact surface.
3) Convenience of all equipment parts to the rinsing solvent.
4) Best fitted to sealed or large scale equipment and equipment which is not easily or regularly dis-assembled.

Limitations

1) Restricted information about actual surface cleanliness in some cases.
2) May reduce test sensitivity.
3) Residues may not be homogenously distributed.
4) Inability to detect location of residues.
5) Rinse volume is critical to assure accurate interpretation of results.
6) May be difficult to correctly define and control the areas sampled, therefore usually used for rinsing an entire piece of equipment, such as vessel[34, 35].

Testing methods

The basic requirements of the analytical methods should have the following principles

1. Testing method should have the ability to identify target substances at levels consistent with the acceptance criteria.
2. Testing method should have the ability to identify target substances in the presence of other materials that may also be present in the sample.
3. The testing analytical method should involve a calculation to convert the amount of residue identified in the sample to 100% if the recovery data generated shows a recovery out of the allowed range.

Analysis of cleaning validation samples

There are various analytical techniques available that can be used in cleaning validation[36].But selecting the appropriate analytical tool depends on a variety of factors[24-28]. The most important factor is to determine the specifications or parameters to be measured[37]. The limit should always be established before the selection of the analytical tool[38, 39].

Specific and non-specific methods

A specific method detects unique compounds in the presence of probable contaminants. Ex: HPLC.

Non-specific methods are those methods that identify any compound that produces a fixed response Ex: Total Organic Carbon (TOC), pH and conductivity.

Others[40-45]

1. Thin layer chromatography (TLC)

TLC is broadly used for the qualitative determination of surfactants.

2. Atomic absorption spectroscopy (AAS)

AAS (atomic absorption spectroscopy) is used for the determination of inorganic contaminants.

3. Bioluminescence

This is useful for biologicals. This type of analysis usually uses ATP-bioluminescence.

4. Optically simulated electron emission (OSEE)

In some cases the limits of residue are very less that they can't be detected by conventional methods. OSEE is a very sensitive method that can be used for both qualitative and quantitative manner aspect in this regard.

5. Portable mass spectrometer

Portable mass spectrometer can be used to find ultra sensitive measurements and identification of the residue.

Additional techniques

Apart from the above mentioned techniques the biopharmaceutical industries apply a wide range of techniques[46]. These include

1. Enzyme-Linked Immuno Sorbent Assay (ELISA)[47]
2. Limulus amaebocyte lysate (LAL) technique.

ELISA[48]

ELISA stands for enzyme-linked immune sorbent assay, also often referred to as enzyme immunoassay (EIA). An ELISA assay is usually performed in a multi-well plate (96- or 384-wells). The multi-well plate supplies the solid surface to immobilize the antigen. Immobilizations of the analytes promote separation of the antigen from the rest of the components in the sample. This attribute makes ELISA one of the easiest assays to perform on multiple samples simultaneously. (Fig. 4: Enzyme-linked immunosorbent Assay[49])

LAL (limulus amoebocyte lysate)[50]

The Limulus Amebocyte Lysate test is approved in international pharmacopeias as it is the method for identifying bacterial toxins/contamination both in the raw materials used for the synthesis of medicines and for the final products.
This test is also useful for the cosmetics industry and in food production as it is the method approved by the FDA (Food and Drug Administration) for the identification of pyrogens. (Fig.5: Limulus Amoebocyte lysate).

Validation report[51]

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

1. References to all the procedures that have been followed to clean the samples and tests.
2. Physical and analytical test results or references for the same, as well as any relevant observations.
3. Conclusions about the acceptability of the results, and the status of the procedures being validated.
4. Any approval or recommendation based on the results or relevant information obtained during the study including revalidation practices if applicable.
5. Review of any deviations from the protocol.
6. When it is not probable 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.
7. The report should conclude a pertinent level of verification subsequent to validation.

CONCLUSIONS/SUMMARY

A cleaning validation programme should be followedon a regular basis and whenever essential to ensure that each and every equipment and all the parts of equipments are cleaned. It should contain the assessment of equipment and products, assessment of the impact of a process on routine process, determination of an appropriate cleaning agent and method, determination of acceptance criteria for the residues, determination of a level of evaluation needed to validate the procedure, development of sampling and analytical methods for recovery. There should be acceptance criteria for the validation, different guidelines to be followed, compilation/collection and approval of the validation protocol, scope for the validation studies to be performed in harmony with the protocol, compilation and approvals of validation reports,documented studies, conclusions, recommendations and revalidation policy.

AUTHORS CONTRIBUTION

All the authors have contributed equally.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Table 1: Comparison between levels[12]

	Level 1	Level 2
Risk	Lowest	Highest
Acceptance limit	Highest	Lowest
Degree of cleaning	Less extensive	More extensive
Verification of cleaning	Visual inspection	Analytical testing

Table 2: CEFIC-APIC guide to cleaning validation[16]

Level	Thorough level of cleaning	Cleaning validation
2	Leftover of the previous product is critical. Cleaning required until predetermined stringent leftover limits are met.	Essential
1	Leftover of the previous product is less critical. Cleaning should reduce the potential leftover to a less stringent limit as required for level 2.	Increase from not required to necessary (Lower acceptable leftover limits)
0	Only gross cleaning if leftover of the previous product is not critical	Not required

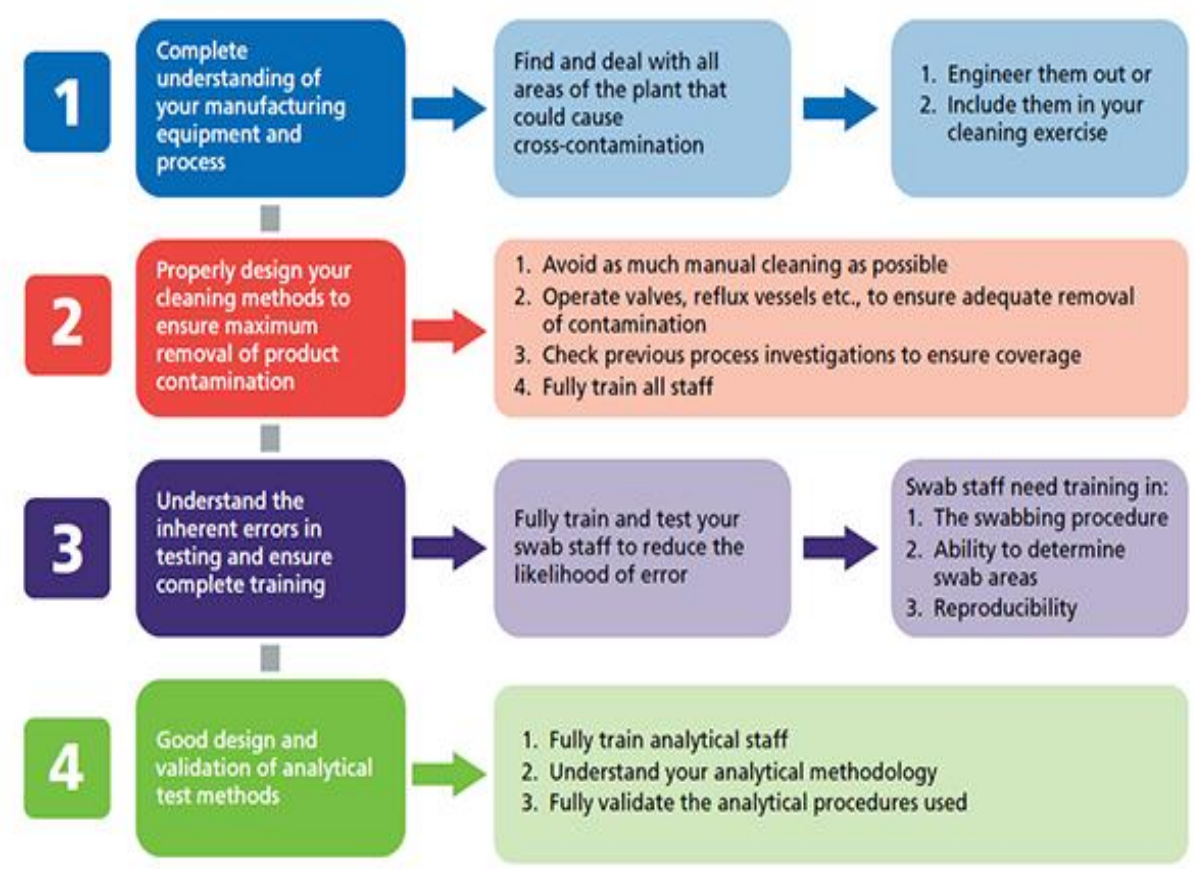

Fig. 1: Areas of concern to get a successful outcome[6]

Fig. 2: Swab sampling[28]

Fig. 3: Rinse sampling[29]

Fig. 4: Enzyme-linked immunosorbent Assay[49]

Fig. 5: Limulus Anmoebocytelysate[50]

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