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To Study On Validation In Pharmaceutical Industry: Cleaning Validation.

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ABSTRACT

In the pharmaceutical industry, ensuring the safety, efficacy and quality of subsequent drug collections .products, care should be taken to avoid contamination, drug abuse or drugs as well other active ingredients, unintentional compounds, contamination of microbiological origin or pollution by cleaning or sanitizing agents. It is therefore very necessary to be certified cleaning procedures strictly follow the guidelines and procedures designed for the same. Cleansing is done to eliminate product and non-product contamination as cleaning does not work leads to degraded and contaminated product. It includes different levels of cleaning, cleaning process, sample process, cleaning agent selection etc to ensure efficient cleaning efficiency procedures to ensure that patients are not exposed to the virus once and for all ultimately resulting in better customer care and product quality.

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

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INTRODUCTION

Verification is the written act of finding out that any process, process, tools, material, task or process that has been followed leads to the expected results. Verification can also be defined as written evidence that provides a high level of assurance that a particular process will always produce a product that will meet its specific specifications and quality attributes [1, 2]. Ensuring cleaning is a documented process that proves efficient and consistent in cleaning up pharmaceutical equipment [3]. Verification of machinery and cleaning processes are widely used in the pharmaceutical industry to prevent serious pollution and deterioration of drug products which is why it is so important to consider. The main purpose of ensuring a cleansing process is to ensure compliance with state and general laws. The importance of performing this process is to ensure the identification and repair of major previously unforeseen problems, which may affect the safety, efficiency, or quality of the next set of drug products produced in that product.

Importance and purpose of cleaning validation [4, 5]

Cleaning validation is

- It is not only necessary to comply with the regulations, but also to satisfy the needs of the customer.
- It ensures the safety, ownership, cleanliness, and strength of the product which are the basic requirements of cGMP (Current Good Production Practice).
- It provides the manufacturer with sufficient assurance that the internal controls are properly aligned. Concerns that affect a person's ability to achieve effective results and the things that need to be considered when performing a cleanup

Objectives of cleaning validation

Cleaning equipment and ensuring cleanliness in the area of Active Pharmaceutical Component (API) is required to prevent future mass contamination with the previous batch object. Ensuring cleanup in the API service is really important as contaminant contamination in one of the drug dosage forms will exacerbate the problem and therefore it is advisable to make at least three repetitive and effective cleanup applications to ensure a proven method [7]. It is necessary to confirm the cleaning procedures for the following reasons:

- It is a prime foremost customer requirement as it ensures the purity and safety of the product to be consumed.
- It is a precept requirement in API (Active Pharmaceutical ingredient) product manufacture.
- It also approves the quality of the process through an internal control and compliance[8] .

Contamination and Cross Contamination[1]

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

1. Contaminant contamination is usually an active ingredient from one product to the next manufactured product. However, carryover of other product components such as additives can also cause problems and reduce the final quality of the product. Contamination of a single product with a large amount of active ingredient residue from the previous collection may cause an obvious problem for the consumer or patients due to unintentional contamination.
2. The second type of contamination is foreign substances that may be viral in nature or may not be part of the tools. The storage and storage environment can provide microorganisms that do not have the opportunity to grow inside the processing equipment. This can lead to obvious problems with the production of sterile products (production of high levels of pyrogens, reduced fertility assurance and purity obtained by mechanical contraceptive procedures etc.) [1].

   It also possess serious problem for the manufacture of non sterile dosage form particularly unpreserved products which support microbial growth

Types and mechanism of contamination [9]

1. **Cross contamination with active ingredient** One of the real dangers of contaminating the active ingredients is that, after contamination the result becomes more active ingredient than one active product. Depending on the results of the treatment, pollution may improve the action or no doubt the action or pollution may have completely different medical and health effects.
2. **Microbiological contamination** This type of contamination is irrational, since contamination can develop at any time, even after cleaning. A major contributing factor is the maintenance of equipment in wet or wet conditions. This provides a natural environment in which germs can easily grow.
3. **Contamination by cleaning or sanitizing agents** Some medical services may find it inevitable to use toxic and dangerous substances to clean stubborn residues. This is especially true in the production of active pharmaceutical ingredients (APIs). These items represent a potential risk such as product contamination. It seems clear that one of the most effective and effective ways to deal with this problem is to use less toxic cleaning agents that may still be effective in removing the residue from a given cleaning condition. The same things apply to the sanitizing agents used to wipe clean materials.
4. **Contamination by miscellaneous other materials** In addition to the general expected or anticipated list of potential contamination in the pharmaceutical industry, a few other things that may be too small may contaminate products. The partial list contains mechanical components e.g. filling machines, brushes from used brushes, auxiliary materials, paper filters, micron filters, strips and rubber particles from gloves, cleaning supplies such as brushes, cloth, and cotton fibers from textiles and detergents, detergents.

Equipment characterization

Ensuring cleaning not only involves the removal of residues but also provides assurance and assurance that each piece of equipment associated with the process is cleaned to the desired or acceptable standards. It is often called the train-based route. A mechanical train is a series of machines in which a product or products go through as they go through the production process. To test whether a device is clean or not it should be noted in such a way that its design features are well known.

Cleaning Procedures [10]

Normal cleaning procedures for all pieces of equipment and procedures should be adjusted. It is important that the design of the equipment is carefully considered in accordance with the product residues to be removed, the available cleaning agents and cleaning techniques, when determining the most efficient cleaning process for tools. Cleaning procedures should be adequate and detailed to avoid any possible complications during cleaning. The following parameters are considered during cleaning.

Equipment Parameters to be evaluated [10]

- Identification of the equipment to be cleaned
- 'Difficult to clean' areas
- Property of materials
- Ease of disassembly
- Mobility

Residues to be cleaned

- Cleaning limits
- Solubility of the residues
- Length of campaigns

Cleaning agent parameters to be evaluated

- Preferable materials that are usually used in the process
- Detergents available (as a general guide, minimal use of detergents recommended unless absolutely required)

- Solubility properties
- Environmental considerations
- Health and safety considerations

Cleaning techniques to be evaluated

- Manual cleaning
- CIP (Clean-in-place)
- COP (Clean-out-of-place)
- Semi automatic procedures
- Automatic procedures
- Time considerations
- Number of cleaning cycles

Cleaning Agent selection[11]

Cleaning agents fall into several broad categories

- Water
- Solvents
- Commodity chemicals
- Formulated cleaning agents

Water It is a solvent that works all over the world. If water alone will purify the product successfully without undue time or physical effort to remove residues, water should definitely be taken care of. For many, however, water alone requires an unacceptable increase in time for cleaning to be completed. Therefore alternatives should be considered.

Solvent These are used primarily in processes where the use of solvent has already been called for the production process. For example, maternal alcohol is used as a solvent for cleaning APIs. Since alcoholic beverages are already known to dissolve the main residue, there is a small risk of using it for purification.

Commodity Chemicals Here, chemicals like NaOH can be used for cleaning as well. Like their smelter counterparts, there can be dangerous problems, problems of disposal associated with these substances. Their general high content or low acidity, however, often makes them useful in non-use processes. However these chemicals do not have a built-in cleaning agent and can be difficult to wash, taking a larger amount of water to wash them out of the systems than a combined cleaning agent.

Formulated cleaning agent It is the largest group of cleaners. This section contains solvent-based formulations as well as water composition. Formed cleaning agents can usually include one or more sources of alkalinity or acid, sequestrants, material builders, chelants and solvent or water. In industrial use, unlike the products used by consumers, these materials are designed to have a low foam and are therefore easy to clean and are suitable for high-grade sedation or anti-corrosion.

Level / degree of Cleaning

Level 1 Cleaning

This is used between the production of different collections of the same product. Example - In a Production X production campaign, there are 3 sets to be produced as shown below. Group A, Group B, Group C of donated goods and / or train equipment, if Group A in the campaign is to be followed by Group B in the campaign, then level 1 cleaning is required.

Level 2 Cleaning

This standard is used between the production of different sets of different Product and / or at the end of the production process even if the same product is scheduled for subsequent operation. The two degrees above or the degree of purification vary depending on the level of risk associated with it, the limit

of acceptance, and the degree of purification and the method of verifying the cleaning process. In addition the CEFIC-APIC (Europian Chemical Industry Council-Active Pharmaceutical Ingredients Committee) 13 purification certification recommends three levels of purification that can be used. This method is described in the table below, however it should be noted that additional standards may be required depending on the type of procedure and requirement [14, 15].

Sampling Technique [17 – 24]

There are usually three main types of samples among which the most desirable is the direct sampling method, the alternatives used for swab samples and cleaning samples.

Direct surface sampling This method involves determining the type of sample material used and its effect on the test data to determine the intervening of the sample material in the test. Therefore, at the beginning of the verification process, it is important to verify the sampling and solvent method if it is satisfactory and easy to use.

Advantages of direct sampling

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

Disadvantages of direct sampling

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

Swab sampling [17-25]

After cleaning the equipment, the product contact areas can be blown to check the hygiene of the area. Used swabs should be compatible with active ingredients and should not interfere with testing and results. They should not cause or cause any damage to the compound. The solvent / (s) used for the swab should provide good melting of the compound and should not cause deterioration (Fig. : Swab sampling).

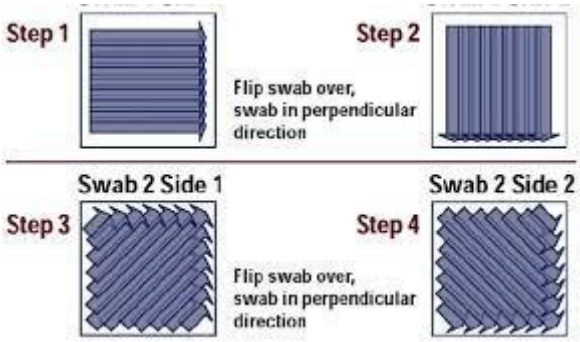

Figure 1: Swab sampling

Advantages of Swab Sampling

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

Limitations

- An Invasive technique that may introduce fibers.
- Results may be technique dependent.
- Swab material and design can inhibit recovery and specificity of the method.
- Evaluation of complex, complex and hard to reach areas difficult 11-15, 30-33.

Rinse sampling [17 – 24]

Sampling and testing of bath samples to find the remaining active ingredient is a commonly accepted method of hygiene testing. This is a simple method in most cases and requires control of the solvent used for bathing, contact time and the mixing involved. The solvent used should be selected based on the melting of the active ingredient and should mimic the following mass of product or at least provide adequate solubility.

Advantages

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

Limitations

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

Testing methods

The basic requirements of the analysis methods should be the following principles

- The assessment methodology should have the ability to identify targeted objects at levels consistent with acceptance criteria.
- The test method should have the ability to identify targeted objects where there are other potential items in the sample.
- The test analysis method should include the conversion value of the sample identified in the sample to 100% if the acquired acquisition data shows the acquisition within the allowed range.

Analysis of cleaning validation samples

There are various analytical techniques available that can be used in cleaning validation36 .But selecting the appropriate analytical tool depends on a variety of factors24-28. The most important factor is to determine the specifications or parameters to be measured37. The limit should always be established before the selection of the analytical tool.

Specific and non-specific methods

A particular method detects unique compounds before possible contamination. Example: HPLC. Indirect methods are those methods that identify any compound that produces a consistent response Ex: Total Organic Carbon (TOC), pH and conductivity.

Thin layer chromatography (TLC) TLC is widely used in determining the quality of surfactants.
Atomic absorption spectroscopy (AAS) AAS (atomic absorption spectroscopy) is used to determine inorganic contamination.
Bioluminescence This is useful for biology. This type of analysis usually uses ATP-bioluminescence.
Automatic electron emission (OSEE). In some cases the residual limits are so small that they cannot be obtained by conventional means. OSEE is a very sensitive method that can be used for both quality and volume in this regard.
Portable mass spectrometer A portable mass spectrometer spectrometer can be used to determine the most critical measurements and to identify fossils.

Additional techniques

Apart from the above mentioned techniques the biopharmaceutical industries apply a wide range of techniques46 . These include

- Enzyme-Linked Immuno Sorbent Assay (ELISA)
- Limulus amaebocyte lysate (LAL) technique.

ELISA48

ELISA represents the enzyme-linked immune sorbent assay, commonly referred to as the enzyme immunoassay (EIA). The ELISA test is usually performed on a multi-source plate (96- or 384 sources). The multi-source plate provides a solid surface to block the antigen. Analysts 'immobilizations promote antigen separation in all parts of the sample. This feature makes ELISA one of the easiest tests to perform on multiple samples at once.

LAL (limulus amoebocyte lysate)

Limulus Amebocyte Lysate testing has been approved by international pharmacopeias as a means of diagnosing bacterial / contaminant toxicity of both immature substances used in the combination of drugs and storage products. This test is also helpful in the cosmetics industry and in food production as it is the FDA (Food and Drug Administration)-approved method of identifying pyrogens.

Validation report

A verification report is essential to present results and conclusions as well as secure authorization for research. The report should include the following information

- References to all procedures that have been followed for sample cleaning and testing.
- Results of physical examination and analysis or similar indications, as well as any appropriate observations.
- Conclusions regarding the acceptance of results, and the status of validated processes.
- Any accreditation or recommendations based on the results or relevant information obtained during the study include re-certification procedures if applicable.
- Review of any protocol deviations.
- If it is not possible for other product groups to be made over a period of time, it is advisable to produce cluster reports until then.
- The report must contain the appropriate level of validation following the verification.

CONCLUSIONS

The cleaning process should be followed regularly and whenever necessary to ensure that everything and all parts of the equipment are cleaned. It should include equipment and product inspections, process impact assessments on routine process, proper cleaning agent and method, determination of residual acceptance process, determination of the level of testing required to validate the process, sample development and recovery analysis methods. There should be conditions for acceptance of certification, various guidelines to be followed, compilation / collection and approval of certification protocols, scope of certification studies to be done in accordance with protocol, compilation

and authorization of verification reports, written studies, conclusions. , recommendations and verification policy.

Figure 2: Cleaning Validation Steps

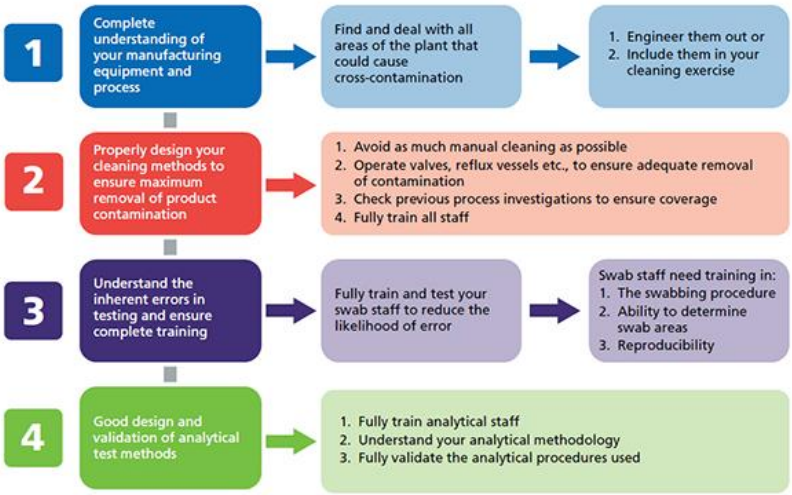

Figure 3: Steps Required Cleaning Validation

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