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A REVIEW ON CLEANING VALIDATION: CLEANING METHOD DEVELOPMENT

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ABSTRACT

Cleaning validation is a critical process in the pharmaceutical and biotechnology industries, ensuring that equipment and facilities are adequately cleaned to prevent cross-contamination and ensure product quality. This abstract discusses the importance of cleaning validation protocols, the methodologies employed, and the regulatory guidelines governing the process. It highlights key steps, including risk assessment, selection of appropriate cleaning agents, and the validation of cleaning procedures through analytical methods.Additionally, the abstract addresses the challenges faced during validation, such as variability in residue limits and the need continuous monitoring. Emphasizing a risk-based approach, this paper outlines best practices to achieve compliance with industry standards while safeguarding patient safety and product integrity. The findings underscore the necessity of robust cleaning validation as an integral part of quality assurance in manufacturing environments.

1.INTRODUCTION

Cleaning validation is an essential component of quality assurance in the pharmaceutical and biotechnology industries. It ensures that equipment and facilities are free from residues that could compromise product quality or patient safety. With increasing regulatory scrutiny and the complexity of modern manufacturing processes, effective cleaning validation protocols are critical to maintaining compliance with Good Manufacturing Practices (GMP). The primary goal of cleaning validation is to demonstrate that the cleaning process effectively removes residues, including active pharmaceutical ingredients (APIs), cleaning agents, and potential contaminants. This is particularly important in multi-product facilities, where the risk of cross-contamination is heightened. A validated cleaning process not only protects product integrity but also builds consumer trust in pharmaceutical products.This introduction outlines the key elements of a successful cleaning validation program, including risk assessment, selection of cleaning methods, and analytical techniques for residue detection. It emphasizes the need for a systematic approach that aligns with regulatory requirements and industry best practices, ensuring that all aspects of the cleaning process are thoroughly validated and documented. By implementing a robust cleaning validation strategy, manufacturers can mitigate risks, enhance operational efficiency, and ultimately contribute to improved patient outcomes.

2.CLEANING VALIDATION

- Cleaning means to make any article, piece of equipment and area free from dirt, marks, or any unwanted matter.In pharmaceutical industry there is a great need of cleaning of equipment apparatus and processing area. The improper cleaning can lead to contamination and cross contamination. Pharmaceutical products can be contaminated by various materials such as residue of previously used active pharmaceutical ingredients, raw material, cleaning agents and dust particles.

The main objective of GMP consists of prevention of contamination and cross contamination of materials. Therefore a perfect cleaning method is required for avoiding the possibilities of contamination and cross contamination, for this a validated program is required, this program is known as cleaning validation. “Cleaning validation is documented evidence which assures that cleaning of equipment, piece of equipment or system will obtain pre-determined and acceptable limits”. Cleaning validation helps in analytical investigation of a cleaning procedure. The Purpose of cleaning validation is to verify the efficacy of the cleaning methods for removal of residues of previous product, preservatives, or cleaning agents and microbial contaminants.
Cleaning validation fulfills the requirement of regulatory bodies and maintains product quality and safety of consumers

2.1ADVANTAGE OF CLEANING VALIDATION

• Assurance of quality & safety.

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Government regulations. Product integrity,
Microbial integrity,
Cross-contamination integrity,
Batch integrity,
Equipment reuse,
Reduction of quality costs
Importance and purpose of cleaning validation
Cleaning validation is Not only is it required to comply with regulations, but also it is necessary to satisfy customer's requirements.
It ensures the safety, identity, purity, and strength of the product which are the basic prerequisites of cGMP (Current Good Manufacturing Practice).
It provides manufacturers with enough confidence that internal control is well established

2.2TYPES OF CONTAMINATION

1. Cross contamination with active ingredient contamination of one batch of Product with significant levels of residual ingredient from previous batch can not be tolerated, in addation to the obvious problem posed by subjecting consumers of patients to unintended Contaminants potential Clinically significant Synergistic interaction between pharmacolo -gically active chemicals are a real concern
2. contamination with unintended materials or compounds. While inert ingredients used in drug Products crre generally recognized as safe for humon consumption the routine use maintenance and cleaning of equipment's Provide the potential contamination with such items and Chemical. As equipment parts, lubricant cleaning agents.
3. microbiological contamination maintenance cleaning and storage condition may provide aduentitious microorganisms. With the opportunity to proliferate within the processing equipment.

2.3TYPES Of VALIDATION

1. Process Validation: Confirms that manufacturing processes consistently yield products meeting predetermined specifications and quality attributes.
2. Cleaning Validation: Ensures that cleaning processes effectively remove residues from equipment to prevent cross-contamination.
3. Equipment validation in the pharmaceutical industry ensures that manufacturing and testing equipment consistently performs according to specifications and regulatory requirements. It typically involves several key components

2.4CLEANING VALIDATION PROTOCOL

1. The cleaning validation protocol include
2. The objective of validation process, responsibilities for performing and approving the validation stady
3. Description of the equipment to be used. W the interval between the end of production
4. The interval between the end of production and the beginning of the cleaning procedure
5. cleaning Procedure Cleaning Procedure to be used for each product and manufacturing sistem or piece of equipment
6. Analytical method including the limit of detection and the limit of quantitation of those methods or reference to them
7. when revalidation will be required

3.TYPES OF CLEANING

"Cleaning Type A" in a pharmaceutical context typically refers to a specific cleaning validation process designed to ensure that equipment used in manufacturing does not contaminate products with residues from previous processes.

1. Purpose

Prevent Cross-Contamination: Ensures that residues from one product do not affect another, particularly in multi-product facilities.
Regulatory Compliance: Meets regulatory standards set by agencies like the FDA and EMA.

1.Scope

Equipment and Surfaces: Involves cleaning of manufacturing equipment, containers, and surfaces that come into contact with products.
Cleaning Agents: Use of approved cleaning agents that do not leave harmful residues.
1. Cleaning Process
Pre-Cleaning Assessment: Evaluate the Cleaning Type B" in the pharmaceutical industry typically refers to a more stringent cleaning process compared to Cleaning Type A, often used for equipment that processes highly potent or sensitive products.

1.Purpose

Prevent Cross-Contamination: Particularly crucial for highly potent active pharmaceutical ingredients (APIs) and products.
Regulatory Compliance: Ensures adherence to strict regulations and guidelines set by regulatory agencies.
Scope
Equipment and Facilities: Focuses on cleaning equipment that handles potent compounds or sterile products, including tanks, mixers, and filling lines.
Cleaning Agents: Utilizes validated cleaning agents that effectively remove residues without leaving harmful traces.
Cleaning Process
Risk Assessment: Conduct a thorough risk assessment to identify potential contamination sources and define critical control points.
Detailed Cleaning Procedure: Develop comprehensive standard operating procedures (SOPs) that include:
Specific cleaning agents and concentrations.
Step-by-step cleaning instructions.
Recommended contact times and temperatures.

2. Validation
Cleaning Validation Studies: Perform rigorous validation to demonstrate the cleaning process effectively removes residues. This includes:

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Swab and Rinse Sampling: Collect samples from equipment surfaces and cleaning solutions.
Analytical Testing: Utilize techniques such as HPLC, LC-MS, or UV spectroscopy to quantify residues.
Acceptance Criteria: Establish stringent acceptance criteria based on product toxicity, permissible limits, and historical data.

3.Monitoring and Re-evaluation
Routine Monitoring: Implement ongoing monitoring of cleaning effectiveness, including periodic sampling and testing.
Change Control Procedures: Any modifications in equipment, cleaning agents, or processes require re-validation to ensure continued efficacy.equipment and identify potential residues.
Cleaning Procedure Development: Establish standardized procedures detailing the cleaning steps, agents used, and contact times.
Execution of Cleaning: Implement the cleaning procedure as per the defined protocol Validation Sampling and Testing: After cleaning, samples are taken to test for residual contaminants. Common techniques include:
Swab Sampling: Collecting samples from surfaces.
Rinse Sampling: Testing the cleaning solution used for rinsing.
Acceptance Criteria: Define acceptable limits for residual levels, often based on toxicological data or historical data.
Documentation: Detailed records of the cleaning process, including dates, personnel involved, and results of testing.
Monitoring and Re-evaluation Regular Reviews: Periodic re-evaluation of cleaning processes and validation to ensure continued efficacy and compliance.
Change Control: Any changes in products, equipment, or processes necessitate a re-validation of cleaning procedures.

4.CLEANING OF EQUIPMENT

• Instructions for Cleaning of Equipment: The equipment is cleaned with the help of the respective SOP of cleaning that particular equipment using a suitable nylon brush and cleansing agent. Then the cleansing agent is removed with potable/raw water and later rinsed with demineralized water. Compressed air or Clean dry lint-free cloth is used to dry the equipment. After completion of the cleaning activity, the "CLEANED" status label is then labeled by the production personnel and attached to the equipment after that the QA personnel shall verify only after inspecting the equipment visually for cleanliness. Line clearance of equipment should be made by visually examining the equipment and should be found satisfactory if not found then repeat the clean for the same.

There are two types of cleaning procedures for equipment used in manufacturing

Type A Cleaning Procedure for equipment Type B Cleaning Procedure for equipment

Type- A Cleaning Procedure For Equipment: All the parts of the equipment are dismantled and transferred to the washing area cleaned out of place (COP). In the washing area, the dismantled parts of equipment shall be cleaned with a cleansing agent (i.e. 0.5% w/w SLS) or other cleaning aids as per the procedure. Mentioned in their respective SOPs of cleaning of equipment. Equipment having non dismantled parts should be cleaned in place (CIP) as per their SOPs for cleaning. The washing/rinsing water sample should be collected after visual verification by production chemists and QA and then sent to Quality Control along with a sample request for determination of the residual drug and cleansing agent.

Type B cleaning for Equipment: It having some following conditions likei) Batch to the batch changeover of the same product having the same strength. ii) Same color and same flavor iii) Batch to batch changes over but from lower strength to higher strength. iv) After completion of the batch.
v) After minor breakdown vi) Cleaning is done after completion of preventive maintenance work if product contact parts are not contaminated, touched, or disturbed. vii) After any major breakdown where product contact parts are contaminated. viii) After completion of preventive maintenance work.
Type B cleaning procedure for equipment: All gross accumulations from equipment and area are removed. Then the equipment should be cleaned without dismantling and dust from the previous product is removed with the help of a vacuum cleaner. Then equipment shall be mopped with a clean moist lint-free cloth (moist with demineralized water) and later with a clean dry cloth.

5.CLEANING VALIDATION PROGRAM

a. Selection of cleaning Level (Type)
b. Selection of cleaning method
c. Selection of sampling method d) Selection of the scientific basis for the contamination limit
d. Selection of defeat case related to the equipment Selection of defeat case related to the product
e. stablishing the storage period after cleaning
f. Selection of analytical method

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6.SELECTION OF CLEANING METHOD

1. Manual cleaning
2. Semi-automatic procedures
3. Automatic procedures
4. CIP (Clean-in-place)
5. COP (Clean-out-of-place)

6.1MANUAL CLEANING METHOD

- It is difficult to validate.
- For this detailed cleaning procedures are necessary, • A high-quality training program is essential.
- The risk which is involved in manual cleaning process are as follows: Proper washroom design with drying, protection, and storage requirements
- Detailed cleaning SOPs are required. Training of cleaning operators is mandatory.

6.2CLEAN-IN-PLACE (CIP) METHOD

- Equipment cleaning is performed in place without disassembling
- The process of cleaning is controlled manually or by an automatic program
- It is a very reproducible cleaning method.
- Can be validated readily.

6.3CLEAN-OUT-OF-PLACE (COP) METHOD

Disassembled parts of the equipment are cleaned or the process of cleaning is performed in a central washing machine.

The washing machine also needs validation like ultrasonic activity, cycle time, temperature, cleaning operation sequence, detergent quantity dispensed, etc.

6.4 CLEANING PROCEDURES

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 be sufficiently and properly detailed to avoid the possibility of any inconsistencies during the cleaning process. Following parameters are being considered during cleaning procedures.

6.5EQUIPMENT PARAMETERS To Be Evaluated

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

RESIDUES TO BE CLEANED

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

7.CLEANING AGENT PARAMETERS TO BE EVALUATED

1. Preferable materials that are usually used in the process.

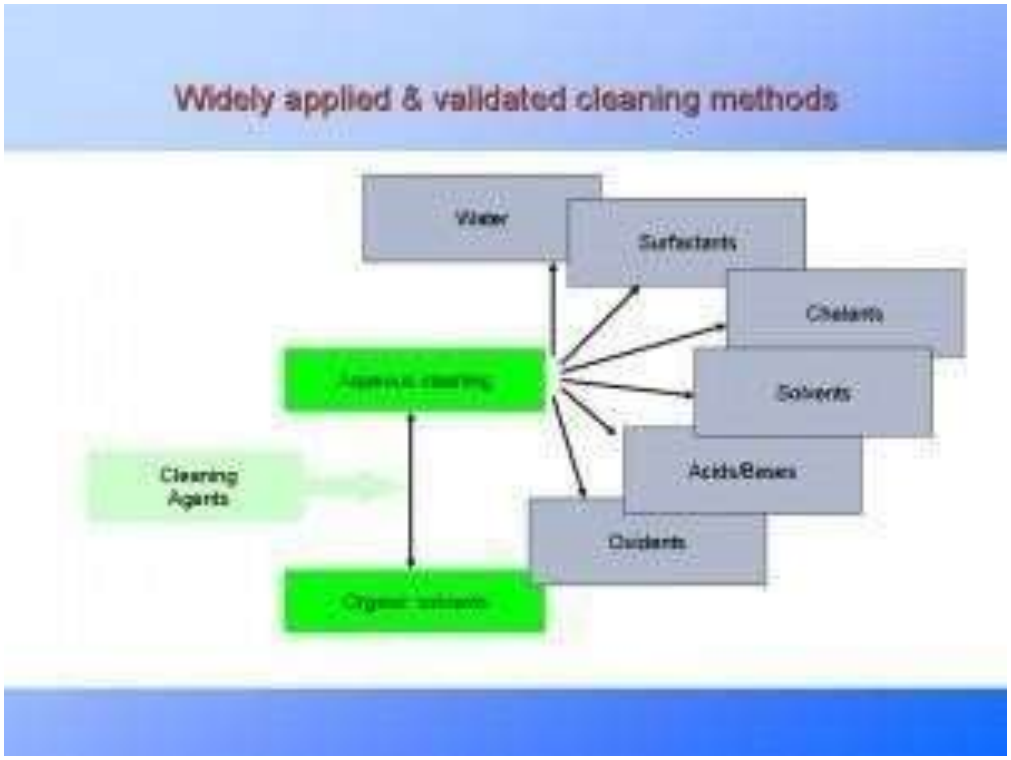
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2. Detergents available (as a general guide, minimal use of detergents recommended unless absolutely required).
3. Solubinty properties
4. Envuonmental considerations
5. ealth and safety considerations.

8.CLEANING AGENT SELECTION

Cleaning agents fall into several broad categories,

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



- Water: It is the universal solvent. If water alone will efficiently clean the product without undue time or physical effort to remove the residues, by all means water should be employed alone. For many, however, the water alone requires an unacceptable increase in time to get the cleaning finished. So other approaches must be screened.
- 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 liquor is already known to dissolve the primary residue. There is little risk in using it for cleaning
- Commodity Chemicals Here, chemicals such 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.
- 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

9.EVALUATION OF CLEANING

- Visual Cleaning Test: All parts of equipment that are in direct contact and Clen-contact with products should be visually checked and verified for cleanliness. Spiking Test: This test validates that equipment has been thoroughly
- Cleaned, no residue should be visible in a volatile solvent, a diluted series of the worst case is prepared and applied to the test equipment surface, which is similar to the sample surface (eg. 25 cm^2). The active compute quantity should be evenly dispersed on the test equipment's surface, test should be carmed out with various concentrations while simulating the identical test conditions with an approximate volume. After that, the solvents are evaporated and compared to the test surfaces of the equipment to determine the visual limit of detection. However, light intensity, surface properties, and operator or operator-initiated method handling can all influence this limit.

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- Bracketing or Worst Case Rating in the pharmaceutical industry, when we are dealing with two or more similar products and the same process is being used, there is no requirement to validate individual equipment for the same product, to minimize the number of the validation; a single study is taken into consideration for the worst-case or bracketing approach of validation is used. This approach is based on a scientific rationale with appropriate justification. First, the grouping of substances/ products or equipment is done for similar products manufactured in the same equipment.

Substances can be grouped as follows

1. Grouping by Product: The formulations are grouped based on the dosage form for example if a company has 5 tablet formulations, 5 ointment formulations, and 5 liquid formulations. They are categorized into 3 groups, these groups can be further classified into subgroups like tablets can be classified into 2 subgroups based on the manufacturing procedure Likewise, ointment and liquid formulation can also be classified into subgroups. After establishing formulations, the group and subgroups worst case' of each group is determined.

2. Grouping by Substances: The products are grouped or categorized as they are produced in the same train substances with the same cleaning procedure. Then they are categorized into subgroups as they are produced in the same train substances with very low therapeutic dose and/or low batch sizes or with very low/high acceptable daily exposure (Then subgroups to be formed based on the cleaning process). Once the product groups have been established the next step is determining the 'worst case representative of each group and cleaning validation of the same.

10.ANALYSIS OF CLEANING VALIDATION SAMPLES

There are various analytical techniques available that can be used in cleaning validation (Heinig et all, 1998)20, But selecting the appropriate analytical tool depends on a variety of factors (Maurya, 2016); (Govind et al., 2018)21; (Nassani, 2005)22; (Yang et al., 2009)23. The most important factor is to determine the specifications or parameters to be measured (Kaiser et al., 1999124. The limit should always be established before the selection of the analytical tool (LeBlanc, 1998)25;(Fourman et al., 1993)26 Specific and non-specific methods: A specific method detects unique compounds in the presence of probable contaminants. Ex: HPLC. Non-specific methods: These are those methods that identify any compound that produces a fixed response Ex: Total Organic Carbon (TOC), pH and conductivity.

Others Techniques includes;

Thin layer chromatography (TLC): TLC is broadly used for the qualitative of surfactants Atomic absorption spectroscopy (AAS): AAS (atomic absorption spectroscopy) is used for the determination of inorganic contaminants.

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

Optically stimulated electron emission (OSEE): In some cases the limits of residue are so low that they can't be detected by conventional methods. OSEE is a very sensitive method that can be used in both qualitative and quantitative manner in this regard.

Portable mass spectrometer: Portable mass spectrometer can be used to find ultra sensitive measurements and identification of the residue (Bosdorf et al., 1996)27; (Read, 1985)2; (Henrich, 1992)29; (Raghavan et al.), 2000)30; (Davidson et al., 1999)

Additional Techniques: Apart from the above mentioned techniques the biopharmaceutical industries apply a wide range of techniques These includes:

Enzyme-Linked Immunosorbent Assay (ELISA)

Limulus amebocyte lysate (LAL) technique 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. The Limulus Amebocyte Lysate test is approved in international pharmacopoeias 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 .

11.THE REGULATORY BASIS FOR PROCESS VALIDATION

FDA regulatory experts established that there was a legal foundation for needing process validation once the concept of being able to forecast process performance to fulfil user needs arose. The ultimate legal authority is Section 501(a)(2)(B) of the FD&C Act, which states that a drug is deemed to be adulterated if the methods used in, or the controls utilised in its manufacture, processing, packing, or storage do not comply with CGMP, or were not managed or administered in accordance with CGMP. It must be guaranteed that the medicine will meet the act's safety criteria, as well as that it will have the identity, strength, and quality and purity qualities that it purported or was represented to have. Because active pharmaceutical ingredients are likewise considered medications under the act. that provision of the act establishes the foundation for process validation requirements for both finished pharmaceuticals and active pharmaceutical components. The 21 CFR 210 and 211 CGMP standards for finished pharmaceuticals were created to enforce the act's obligations. Despite the lack of a definition under these regulations.

11.1APPROACH TO PROCESS VALIDATION

Stage 1: Process Design: During this stage, knowledge gained from development and scale-up activities is used to define a commercial manufacturing process.

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Stage 2: Process Qualification: During this stage, the method design is estimated to see if the process can be replicated and turned into a viable product.
Stage 3: Ongoing Process Verification: Throughout ordinary production, constant assurance is received that the process is under control.



12.CONCLUSION

Validation is the most commonly used term in the fields of medication research, manufacturing, and completed product specification. For the industry. Consistency and reliability of a verified process to deliver a quality product are critical. Quality assurance procedures must be utilised throughout the manufacturing process, not only at the end, to ensure that the product is of highQuality. Process validation entails a series of activities that take place throughout the product and process lifecycle.From the study, it can be stated that with the help of cleaning validation any department of the pharmaceutical industry can achieve a high degree of assurance regarding the cleaning, with this we can minimize any kind of contamination or cross-contamination which may be any residue of the previous

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