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Review Article
ABHI Publications since 2013
International Journal of Pharmacy and Engineering (IJPE)
ISSN 2320-849X

A REVIEW ON CLEANING VALIDATION IN PHARMACEUTICAL INDUSTRY

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ABSTRACT

In pharmaceutical product manufacturing, it is most important to reproduce consistently the desired quality product. The current Good Manufacturing Practice (cGMP) regulations recognize that cleaning is a critical issue to ensure product quality. For maintaining the quality of the product, the cross contamination of a drugsare playing very important role. The manufacturing of pharmaceutical product involves series of processing steps and variousequipments use. For processing of different product many times same equipments may be used. Product residue from the previous batch of same or different product may be carried to the next batch of the product, which in-turn may alter the quality of subjected product. An effective and consistent cleaning shall be in place to provide documented evidence that the cleaning methods employed within a facility consistently control potential carryover of product including intermediates and impurities, cleaning agents and extraneous material into subsequent product to a level which is below predetermined level. The validation process gives the documented evidence of the consistent performance of cleaning process. It ensures safety, efficacy, purity and quality of the drug product. In this article the various aspect of cleaning validation such as regulatory requirements, cleaning validation approaches, types of contaminants, selection of cleaning methods,determining the acceptance limits, sampling methods, analytical technique, cleaning validation protocol and report in detail.

Keywords: Cleaning Validation, Equipment, Efficacy, Protocol.

INTRODUCTION

Cleaning and decontamination is one of the major and critical activities in pharmaceutical operation. The four basic requirement of cGMP are **Identity, Safety, Strength, Purity**. The concept of purity is directly related to the cleaning operation [1].The process of providing documented evidence that the cleaning methods employed within a facility consistently controls potential carryover of product (including intermediates and impurities), cleaning agents and extraneousmaterial into subsequent product to a level which is below predetermined levels [2].Cleaning validation is primarily used for the cleaning of process manufacturing equipment in the pharmaceutical industries [3].The basic reason for having good, effective, consistent cleaningprocedures is toprevent the contamination ofproducts made subsequently in the sameequipment. The goal is to provide pharmaceuticalproducts of the highest quality to our patients. Thisis the basic regulatory requirement as well as thegoal of all of those suppliers of products andservices [4].

OBJECTIVE

The objective of the cleaning validation is to verify the effectiveness of the cleaning procedure for removal of product residues, degradation products, preservatives, excipients, and/or cleaning agents as well as the control of potential microbial contaminants. In addition one need to ensure there is no risk associated with cross contamination of active ingredients. Cleaning procedures must strictly follow carefully established and validated methods [2].

It is necessary to validate cleaning procedure for the following point reasons[2]:

1) It is a customer requirement- it ensures the purity and safety of the product.
2) It is a regulatory requirement in Active Pharmaceutical Ingredient (API) product.
3) It also assures from an internal control and compliance point of view the qualityof the process.

REGULATORY REQUIREMENTS FOR CLEANING VALIDATION

The Food and Drug Administration of United State establishes the regulations and policies relating to the pharmaceutical grade products distributed commercially in United States. These regulations are called Current Good Manufacturing Practices (cGMP) and are classified in Title 21, Part 211 of the Code of Federal Regulation (CFR). The applicable laws at this time are

general and somewhat vague, and are centered around 21 CFR 211.67 that states: "Equipment and utensils be cleaned, maintained and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality or purity of the drug product" [4].

According to this law each and every pharmaceutical and food industry should followthe cleaning validation programmed to avoid malfunctioning, contamination and cross contaminationof finished product.

NEED OF THE STUDY

Pharmaceutical product can be contaminated by variety of substances such as contaminants associated with microbes, previous products (both active pharmaceutical ingredients (API) and excipient residues), residue of cleaning agent, airborne materials, such as dust and particulate matter, lubricants and ancillary materials, such as disinfectant, and decomposition residue from:

- Product residue breakdown occasioned by, e.g. the use of strong acids and alkalis during the cleaning process; and
- Breakdown procedures of the detergents and alkalis that may be used as part of the cleaning process.

Adequate cleaning procedures play an important role in preventing contamination and cross contamination. Validation of cleaning method provides documented evidence that an approved cleaning procedure will provide clean equipment, suitable for its indeed use[4]. In 1937 improper preparation of "Elixir of Sulphanilamide" cause mass poisoning in United States become responsible for death of around 100 people. This leads to broadening the existing legislation on cleaning validation [5,6].

APPROCHES FOR CLEANING VALIDATION [3,7]

For minimize validation requirements following points are taken into consideration

- By adopting bracketing procedure the substance are grouped.
- A worst case scenario rating is used to select the worst case in each group.
- Validation of worst case.

A. Bracketing procedure

The total manufacturing process is grouped such as early step, critical step and API. Each group of process is further grouped as per equipment usage similarities. All the processes are then divided as per the solubility and worst case scenario rating is made. If two or more equipment trains are used for a given manufacturing process, a choice made for the same purpose. The combination of substance in a train can be chose based upon one or more the following strategies, or combination of them.

- Substances with the same cleaning procedure produce in the same train.
- Substance with low therapeutic daily dose/ low batch size (and the opposite), produce in the same train.
- Non toxic substances produce in the same train
- Substance with high solubility produce in the same train

B. Worst case rating

- Solubility in subjected solvent
- Maximum toxicity
- Minimum therapeutic dose
- Difficult to clean
- Lowest limit base on therapeutic dose/toxic data, batch size, surface area etc.

CONTAMINATIONS [8,9]

Contamination is a condition in which the product contains any material that is not intended to present and not listed in a current formulation as an ingredients.

Types of contaminations

1. Cross contamination with active ingredients.

Cross contamination with active ingredients may cause potential higher level of synergistic interactions between pharmacologically active chemicalsand it causes unintended pharmacological activity. So contamination of one batch of product with residue of active ingredient of different batch or previous batch should not be tolerated if the residue is more than that of acceptance limit.

2. Contamination with Unintended Materials or Compounds.

Whenever inert ingredients used in drug products are generally recognized as safe or have been shown to be safe for human consumption, the routine use, maintenance and cleaning of equipment's provide the potential contamination with such items as equipment parts, lubricants, chemical cleaning agents and pieces of cleaning tools such as brushes and rags.

3. Microbiological Contamination.

The processing equipments is not properly maintained, clean and stored then there is a chance of microbial growth in that equipments.

SELECTION OF CLEANING METHOD[9,10]

A. Clean in Place (CIP)

Clean in place is an automated system that consists of a recirculation system that uses various tanks and return system such as return pump. Equipment cleaning is performed in place without disassembly. A system of piping delivers the cleaning solution to the equipment and return to a recirculation tank. Cleaning process may be done by manually or by an automated program. The equipment utilizes spraying devices to provide coverage and physical impingement of the cleaning solution on equipment surfaces. These systems are commonly used to clean large piece of equipment such as manufacturing tank, filtration tank.

B. Clean out of place Method (COP)

Clean out of place, in which equipment include such item such as wash tank used to clean small part or parts removed from large equipment's. It usually has some sort of automated or program control system. Cleaning of this equipment may also be performed in a central washing machine or a dishwasher type cabinet. This type of cleaning is also known as closed system cleaning.

C. Manual cleaning.

The manual cleaning method is done by scrubbing/or wiping by the operator and validation of this method is most difficult. A high quality and extensive cleaning program is required. Some consideration of manual cleaning includes

- Trained and experience working staff.
- Product diversity
- Risk of failure of cleaning equipment's

CURRENT APPROACHES IN DETERMINING THE ACCEPTANCE LIMITS FOR CLEANING VALIDATION[8, 10-12]

The Cleaning Validation should demonstrate that the procedure consistently removes residues of the substance previously manufactured down to levels that are acceptable and that the cleaning procedure itself does not contribute unacceptable levels of residual materials to the equipment. The limit should be practical, achievable and justifiable.

A. Dose criteria approach

NMT 0.1% of normal therapeutic dose of any product to be appear in the maximum daily dose of the next product.

$$MAR = \frac{TDD_{previous} \times MBS}{SF \times TDD_{Next}}$$

Where

MAR : Maximum allowable residue
TTD Prev. : Standard therapeutics dose of the daily dose of the previous product
TDD Next : Standard therapeutics dose of the daily dose of the previous product
MBS : Minimum batch size of the next product
SF : Safety factor (normally 1000 is used)

B. 10 ppm Criteria

NMT 10 ppm of any product to appear in another product.

$$\text{Milligrams of active ingredient In product A permitted per 4 inch2 swab area} = \frac{R \times S \times U}{T}$$

Where,

R:10mg active ingredient of product A in one kg of product B
S: Number of kilograms per batch of finalmixture of product B
T: Equipment surface in common between product A & B expressed as square inches.
U: 4 $inch^2$/swab.

C. Visually clean criterion

- **Visual Inspection**

Equipments were cleaned using purified water and after cleaning, equipments were visually checked for presence of residues.

- **Acceptance Criteria for Visual Inspection**

No quantity of residue should be visible on equipment after cleaning procedure. Spiking studies of drugs have been determined using 100 mcg of drugs in which most products are visible.

SELECTION OF SAMPLING METHODS [3, 5, 10, 12]

For all the methods the sampling point must be fixed in a manner that the true contamination of the equipment will be reflected. A combination of rinse sampling and swabbing is the effective method. Sampling methods for cleaning validation are as follows are as follows,

A. Swab Sampling

This method is based on the physical removal of residue left on a piece of equipment after it has been cleaned and dried. A swab wetted with a solvent is rubbed over a previously determined sample surface area to remove any potential residue, and thereafter extracted into a known volume of solvent in which the contaminant active ingredient residue is soluble. The amount of contaminant per swab is then determined by an analytical method of adequate sensitivity.

Advantages

- Dissolves and physically removes sample
- Adaptable to a wide variety of surfaces
- Economical and widely available
- May allow sampling of a defined area
- Applicable to active, microbial, and cleaning agent residues.

Limitations

- An invasive technique that may introduce fibers
- Results may be technique dependent
- Swab material and design may inhibit recovery and specificity of the method
- Evaluation of large, complex and hard to reach areas difficult (e.g., crevices, pipes, valves, large vessels)

B. Rinse Sampling

This method is based on the analytical determination of a sample of the last rinsing solvent (generally water) used in the cleaning procedure. The volume of solvent used for the last rinse must be known to allow for the quantitative determination of the contamination. Thus, collection

of rinse samples should consider location, timing, and volume. It is important to ensure chosen solvent has appropriate recovery for residues being quantified. The solvent rinse occurs after cleaning has been completed. This method is not as direct as swabbing but will cover the entire surface area (and parts inaccessible to swabs).

Advantages

- Adaptable to on-line monitoring
- Easy to sample
- Non-intrusive
- Allows sampling of a large surface area
- Allows sampling of unique surfaces

Limitations

- Limited information about actual surface cleanliness in some cases
- May lower test sensitivity
- Residues may not be homogeneously distributed
- Inability to detect location of residues
- Rinse volume is critical to ensure accurate interpretation of results
- Sampling methodology must be defined since rinse sampling method and location can influence results
- May be difficult to accurately define and control the areas sampled, therefore usually used for rinsing an entire piece of equipment, such as a vessel
- Reduced physical sampling of the surface

C. Placebo Sampling

Placebo sampling can be used to detect residues on equipment through the processing of a placebo batch subsequent to the cleaning process. It is appropriate for active residue, cleaning agent, particulates and microbial testing. Placebos are used primarily to demonstrate the lack of carryover to the next product. The placebo should mimic product attributes. The equipment characteristics also impact the choice of the placebo batch size.

Advantages

- Placebo contacts the same surfaces as the product
- Applicable for hard-to-reach surfaces

- Requires no additional sampling steps

Limitations

- Difficult to determine recovery (contaminants may not be evenly distributed in the placebo)
- Lowers analytical specificity and inhibits detect ability
- Takes longer and adds expense since equipment must be cleaned after the placebo run
- Placebos must be appropriate for each potential product
- Residues may not be homogenously distributed
- No direct measurement of residues on product contact surfaces
- No direct measurement of residues on product contact surfaces

METHOD OF ANALYSIS [3, 8, 13]

The analytical method should be validated. The analytical methods used must be specific towards the residual or contaminants. The analytical methods used should have predetermined specificity and sensitivity. If level of contamination or residue are not detected, it does not mean that there is no residual contaminant present after cleaning, it means that the level of contaminant greater than the sensitivity or detection limit of the analytical method are not present in the sample.

There are many analytical techniques available but selection of appropriate tool depends on the parameter to be measured. Analytical methods are categories into Specific and non-specific to detect any compound. The choice of using a specific or non specific method can be difficult. If a drug active is highly toxic, a specific method is always recommended. Chromatographic methods are preferred for cleaning validation studies because of their sensitivity, specificity, and ability to quantify

A. Specific method

It is a method that detects a unique compound in the presence of potential contaminants. Some examples of specific methods are high performance liquid chromatography (HPLC), Ion chromatography, Atomic absorption, Capillary electrophoresis, and other chromatographic methods.

B. Non-specific method

It detects any compound that produces a certain response. Some examples of non specific methods are Total Organic Carbon (TOC), pH, Titration, and conductivity.

VALIDATION PROTOCOL [3, 14]

A validation protocol is necessary to define the specific items and activities that will constitute a cleaning validation study. It is advisable for companies to have drawn up master validation plan indicating the overall cleaning validation strategies for the product range/equipment type/entire site.The protocol must be prepared prior to the initiation of the study must either include or reference the documentation required providing the following information:

- Background
- Purpose of the validation study
- Scope of the validation study
- Responsibilities for performing the validation study
- Sampling procedure to be used
- Testing method to be used
- Acceptance criteria
- Change control
- Approval of protocol before the study
- Deviations

VALIDATION REPORT [3, 14]

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

- Conclusion regarding the acceptability of results, and the status of the procedures being validated.
- Any recommendation based on the results relevant information obtain during the study including revalidation practices if applicable
- Approval of conclusion
- Review any deviation for the protocol that occurred.
- The report should conclude an appropriate level of verification subsequent to validation.

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