

CLEANING VALIDATION OF PHARMACEUTICAL DOSAGE FORMS**Gupta Mamta* and Bharkatiya Meenakshi**

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Article Received on
21 June 2015,Revised on 12 July 2015,
Accepted on 05 Aug 2015***Correspondence****For Author****Gupta Mamta**B.N. Institute of
Pharmaceutical Sciences,
Udaipur, Rajasthan, India.**ABSTRACT**

Cleaning validation is 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 extraneous material into subsequent product to a level which is below predetermined levels. Residue identification in a pharmaceutical manufacturing environment involves cleaner, primary ingredients, excipients, decomposition products and preservatives. The main purpose of cleaning validation is to prove the effectiveness and consistency of cleaning in a given pharmaceutical production equipment to prevent cross contamination

and adulteration of drug products with other active ingredients like unintended compounds or microbiological contamination, leading to prevent several serious problems. The basic mechanisms involved in removing the residues and contaminants from the equipment are mechanical action, dissolution, detergency and chemical reaction. Residual materials from the previous batch of the same product or from different product may be carried to the next batch of the product, which in-turn may alter the impurity profile of the subjected product. Selection of appropriate sampling to demonstrate that residues have been removed to an acceptable level is vital for the success of cleaning validation.

KEYWORDS: Contamination, cleaning validation, residue.**INTRODUCTION**

Cleaning validation refers to establishing documented evidence providing a high degree of assurance that a specific cleaning process will produce consistent and reproducible cleaning results that meet a predetermined level.^[1]

Cleaning validation is primarily applicable to the cleaning of process manufacturing equipment in the pharmaceutical industry. The focus of cleaning validation is those cleaned

surfaces that, if inadequately cleaned, could potentially contaminate the product subsequently manufactured in that same equipment.^[2]

Formulation and Mullen of Eli Lilly Company established a method for finding out cleaning acceptance criteria limit for a multi-drug facility in 1993. Pierre Rousseau introduced matrix approaches to the solved complex cleaning validation problems.^[3]

The most important benefit of conducting such a validation work is the identification and correction of potential problems previously unsuspected, which could compromise the safety, efficacy or quality of subsequent batches of drug product produced within the equipment.^[4]

Equipment cleaning validation in an API facility is extremely important as cross contamination in one of the pharmaceutical dosage forms, will multiply the problem. Therefore it is important to do a step-by-step evaluation of API process to determine the most practical and efficient way to monitor the effectiveness of the cleaning process.^[5]

The basic mechanisms involved in removing the residues and contaminants from the equipment are mechanical action, dissolution, detergency and chemical reaction.^[6]

- **Mechanical action**

It refers to the removal of residues and contaminants through physical actions such as brushing, scrubbing and using pressurized water.

- **Dissolution**

It involves dissolving the residues with a suitable solvent. The most common and practical solvent is water being non-toxic, economical, environment friendly and does not leave any residues. Alkaline and acidic solvents are sometimes preferred as it enhances the dissolution of the material, which are difficult to remove.

- **Detergency**

Detergent acts in four ways as wetting agent, solubilizer, emulsifier and dispersant in removing the residues and contaminants from the equipment.

- **Chemical reaction**

Oxidation and hydrolysis reaction chemically breaks the organic residues.

OBJECTIVE

“Equipment and utensils shall 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 beyond the official or other established requirements”.

The main objective of cleaning validation of equipment / utensils / components is to demonstrate sufficient documented evidence to ensure that the cleaning process can consistently remove residue of the subjected product below the established Acceptance Criteria.^[7]

It is necessary to Validate Cleaning procedures for the following reasons^[8]

- It is a customer requirement - it ensures the safety and purity of the product.
- It is a regulatory requirement in Active Pharmaceutical Ingredient product manufacture.
- It also assures from an internal control and compliance point of view the quality of the process.

TYPES OF CONTAMINATIONS**1. Cross contamination with active ingredients**

Contamination of one batch of product with significant levels of residual active ingredients from a previous batch cannot be tolerated. In addition to the obvious problems posed by subjecting consumers or patients to unintended contaminants, potential clinically significant synergistic interactions between pharmacologically active chemicals are a real concern.

2. Contamination with unintended materials or compounds

While inert ingredients used in drug products are generally recognised as safe or have been shown to be safe for human consumption, the routine use, maintenance and cleaning of equipments 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

Maintenance, cleaning and storage conditions may provide adventitious microorganisms with the opportunity to proliferate within the processing equipment.^[9]

POTENTIAL RESIDUES

Manufacturing of drug substances involves, in general, chemical &/or physical transformation through a series of processing steps. Equipment train / equipment &/or

ancillary system may be used for either multi product manufacturing or for dedicated individual products. The inadequate cleaning process/methods may lead to the fact that following residues may carry forward as contaminant in the next batch to be manufactured in the same equipment

- Precursors of the drug substance.
- By-products and/or degradation products of the drug substance
- Product from previous batch.
- Solvents and other excipients employed during manufacturing process.
- Microorganisms
- Cleaning agents and lubricants.^[10,11]

FDA REQUIREMENTS

- FDA expects firms to have written standard operating procedures (SOP) detailing the cleaning process used for various pieces of equipment.
- If firms have a specific cleaning process for cleaning between different batches of the same product and use a different process for cleaning between product changes, FDA expects the written procedures to address these different scenarios.
- If firms have one process for removing water-soluble residues and another process for non-water soluble residues, the written procedure should address both scenarios and make it clear when a given procedure is followed.
- It is required by the FDA, in the general validation procedure, that the personnel responsible for performing and approving the study should comply with the acceptance criteria and the revalidation data.
- FDA expects firms to prepare specific written validation protocols in advance for the studies to be performed on each manufacturing system or piece of equipment which should address such issues as sampling procedures, and analytical methods to be used including the sensitivity of those methods.
- It is expected that firms conduct the validation studies in accordance with the protocols and document the result of studies.
- Final validation report is to be approved by the regulatory board which states whether or not the cleaning process is valid.^[12]

CLEANING VALIDATION POLICY

The main focus of this document will be to describe equipment and ancillary equipment / process Cleaning Validation in an Active Pharmaceutical Ingredient manufacturing plant. However, it is appropriate to start by giving a brief introduction as to how the concept of Cleaning Validation should be approached in a facility.

It is advisable for Active Pharmaceutical Ingredient manufacturing facilities to hold an official Cleaning Validation Policy. Specific department responsibilities should be outlined in this and it should be approved by senior management. This policy should serve to provide a general guideline and direction for company personnel, regulatory authorities and customers as to how the company deals with areas associated with Cleaning Validation.

The policy should incorporate the following types of statements

- Definition of terms employed during validation i.e. rinse vs. flush vs. wash etc.
- A statement specifying what company policy is on validation of cleaning procedures related to equipment (including ancillary) and processes.
- Company policy re dedication of equipment in certain cases (if products are deemed too dangerous and / or highly active to manufacture on multi-product equipment).
- Analytical validation policy.
- The policy should also state the rational for the methods by which acceptance criteria is determined.
- Revalidation policy.^[13]

LEVELS/ DEGREE OF CLEANING VALIDATION

The level or degree of cleaning and validation required for the manufacturing process of drug substances mainly depends on:

- Usage of equipment (dedicated equipment or not)
- Manufacturing stages (early, intermediate or final step)
- The nature of the potential contaminants (solubility toxicity etc.)^[14]

Table 1: Level or degree of cleaning^[7, 9, 14]

Level	Attributes	Acceptance Criteria	Cleaning Validation
Level 0	i.e In campaign batch to batch.	Visual observation.	Not essential.
Level 1	1) Intermediates or final product to intermediate of another. 2) Early step to intermediate in product sequence.	General limit 500 ppm.	Progression between level 0 to level 2 depending on processes and nature of contaminant based on scientific region.
Level 2	1) Product changeover of equipment used in final step. 2) Intermediates of one batch to final step of another batch.	Based on TTD/Toxicity, 10 ppm whichever is lower.	Yes essential.

ELEMENTS OF CLEANING VALIDATION

1. Establishments of acceptance criteria

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 limits set should be practical, achievable and justifiable. In Active Pharmaceutical Ingredient manufacture there may be partial reactants and unwanted by-products which may not have been chemically identified. Therefore, it may be necessary to focus on by-products as well as the principle reactant. Companies should decide on which residue(s) to quantify based on sound scientific rational.

2. Cleaning procedures

Cleaning procedures should be sufficiently detailed to remove the possibility of any inconsistencies during the cleaning process.

A. Equipment parameters to be evaluated

- Identification of the equipment to be cleaned
- Difficult to clean areas
- Property of materials
- Ease of disassembly
- Fixed or not

B. Residues to be cleaned

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

C. Cleaning agent parameters to be evaluated

- Preferably materials that are normally used in the process
- Detergents available (as a general guide, minimize use of detergents unless absolutely required)
- Solubility properties
- Environmental considerations.
- Health and safety considerations

D. Cleaning techniques to be evaluated

- Manual cleaning
- CIP (Clean-in place)
- COP (clean-out-of-place)
- Semiautomatic
- Automatic
- Time considerations
- Number of cleaning cycles

E. Other requirements^[15]**3. Sampling Techniques**

The selection of either of these techniques must be consistent with sound scientific judgment and must support the objective of the study, which is to demonstrate that the amount of residual material in the equipment has been reduced to acceptable levels.

There are five known sampling methods

A. Swabbing (Or Direct Surface Sampling) Method

Swab sampling does not cover the entire equipment surface area therefore sites must be chosen with care. It is important that, as a minimum, the swab sites represents worst case locations on the equipment and that the result is then extrapolated to account for the total product contact surface area.

The following parameters should be considered while collecting swab samples

- Swab sampling should be done while wearing gloves.
- Area to be sampled should be described (sketched) and dimensions recorded.
- Applicable to API, microbial and cleaning agents.
- Swabbing can be done by going from more clean to less clean area, with strokes that are parallel and partially overlapping.
- Swabs should be moist but not saturated.
- Swabs should protect from contamination and stored in suitable condition to prevent degradation of residues, between sampling & testing.
- Moist swab pick up more material than dry swab but saturated will leave behind more material than moist.

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

Disadvantages

- Variation in results,
- Sampling errors may be frequent,
- Sampling technique difficult to standardized,
- Rubbing force varies from person to person,
- If solvent evaporate, it may influence the result,
- Swab can leave significant portion of fibers,
- Not suitable for many types of equipments because of complex design of equipment.^[11]

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 Method

- 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).
- It is important to ensure chosen solvent has appropriate recovery for residues being quantified.
- This method allows much greater ease of sampling than swabbing.
- A reduced no of samples are required to generate a carryover figure.

Advantages

- Adaptable to on-line monitoring
- Easy to sample
- Non-intrusive
- Less technique dependent than swabs
- Applicable for actives, cleaning agents and excipients
- Allows sampling of a large surface area
- Allows sampling of unique (e.g., porous) 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.^[16,17,18]

C. Placebo Sampling Method

- 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
- The preferred sampling method and the one considered as the most acceptable by regulatory authorities is the swabbing method^[19, 20]

D. Coupon sampling

Coupons of the same materials of construction as the item to be cleaned can be affixed to the equipment, spiked with the product, subject to the cleaning procedures and then submitted to the laboratory for direct analysis and recovery studies.

Advantages

- Allows for direct surface sampling.
- Useful in cleaning method development.
- Reduced variability in recovery.
- Useful in evaluation of equipment materials of construction.

Limitations

Coupon may not be representative of equipment contamination or cleaning as it is separate from primarily surface.

- Invasive
- Might interfere with the cleaning process.

E. Solvent sampling

This technique uses a solvent not normally employed in the cleaning process to maximize recovery residue.

Advantages

- Commonly used in bulk chemical facilities
- Applicable for actives, cleaning agents, excipients
- Less technique dependent than swabs.
- Usually affords more analytical specificity, less recovery loss than swabs.
- Allows sampling of a larger surface area.
- Allows sampling of porous and delicate surface
- Maximizes recovery to rinse.

Limitations

- May require operator protection and other safety and environmental protection measures.
- May require more than one sampling for broad spectrum analysis.
- Reduced physical sampling of the surface.
- May be difficult to accurately define the controlled area sampled, therefore usually used for rinsing an entire piece of equipment such as a vessel.
- May require the removal of solvent prior to equipment use for production.^[21,22,23]

Analytical Methods

Specific and non-specific are the two analytical methods used widely to detect any compound. The choice of using a specific or nonspecific 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.

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.

Non-specific method

- It detects any compound that produces a certain response.
- Some examples of nonspecific methods are Total Organic Carbon (TOC), pH, Titration, and, conductivity.
- It is always wise to choose the simplest technique that can be used to reach the desired goal.
- The basic requirement for the analytical method
- The sensitivity of the method shall be appropriate to the calculated contamination limit.
- The method shall be practical and rapid, and, as much as possible use instrumentation existing in the company.
- The method shall be validated in accordance with ICH, USP, EP requirements.
- The analytical development shall include a recovery study to challenge the sampling and testing methods.^[24, 25]

4. Validation Protocols

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 a Master Validation plan indicating the overall Cleaning Validation strategy for the product range / equipment type / entire site.

The protocol must be prepared prior to the initiation of the study and must either include or reference the documentation required to provide the following information:

- Background
- Purpose of the validation study
- Scope of the validation study
- Responsibilities for performing the validation study
- Sampling procedures to be used
- Testing methods to be used

- Acceptance criteria
- Change control
- Approval of protocol before the study
- Deviations

5. Validation Reports

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

- Summary of or reference to the procedures used to clean, sample and test
- Physical and analytical test results or references for same, as well as any pertinent observations
- Conclusions regarding the acceptability of the results, and the status of the procedure(s) being validated
- Any recommendations based on the results or relevant information obtained during the study including revalidation practices if applicable.
- Review of any deviations from the protocol.
- 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.
- The report should conclude an appropriate level of verification subsequent to validation²⁶.

6. Establishment of Limits

The fabricator's rationale for selecting limits for product residues should be logical and based on the materials involved and their therapeutic dose. The limits should be practical, achievable, and verifiable.

The approach for setting limits can be

- Product specific cleaning validation for all products;
- Grouping into product families and choosing a worst case product;
- Grouping by properties (e.g., solubility, potency, toxicity or formulation ingredients known to be difficult to clean);
- Setting limits on not allowing more than a certain fraction of carryover;
- Different safety factors for different dosage forms.

Carry-over of product residues should meet defined criteria for example the most stringent of the following criteria (i, ii, iii)

- i. NMT 0.1% of the normal therapeutic dose of any product to appear in the maximum daily dose of the following product;
- ii. NMT 10 ppm of any product to appear in another product;
- iii. No quantities of residue to be visible on the equipment after cleaning procedures are performed. Spiking studies should determine the concentration at which most active ingredients are visible.
- iv. For certain highly sensitizing or highly potent ingredients (such as penicillins, cephalosporin or potent steroids and cytotoxics), the limits should be below the limit of detection by best available analytical methods. In practice this may mean that dedicated plants are used for these products.^[27,28]

CONCLUSION

At the end of the article it can be concluded that to control the carryover of left over residue from previous batch to the next batch an effective, validated cleaning mechanism shall be in place. This shall contain a defined cleaning validation policy, different levels of cleaning depending on the criticality/ risk associated, approaches of cleaning validation and elements of cleaning validation.

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