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Original Article

# An Overview on Cleaning Validation of API Manufacturing Plants.

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**Abstract**

In the manufacturing of the pharmaceutical products it is a must to reproduce consistently the desired quality of product .In the manufacturing of the pharmaceutical products it is a must to reproduce consistently the desired quality of product. 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 quality of the subjected product. An effective cleaning shall be in place to provide 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 level. This paper outlines the various aspects of the cleaning validation such as different types of contaminants, sampling procedures, analytical techniques and regulatory requirements are discussed in detail.

**Keywords:** Cleaning Procedure, Validation Procedure, Analytical technique.

## 1. Introduction

Cleaning validation is a documented process that proves the effectiveness and consistency in cleaning pharmaceutical production equipment. Validations of equipment cleaning procedures are mainly used in pharmaceutical industries to prevent cross contamination and adulteration of drug products hence is critically important. The prime purpose of validating a cleaning process is to ensure compliance with federal and other standard regulations. 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.

## Objective

The objectives of equipment cleaning and cleaning validation in an Active Pharmaceutical Ingredient (API) area are same as those in pharmaceutical production area. In both these areas efforts are necessary to prevent contamination of a future batch with the previous batch material. The cleaning of 'difficult to reach' surface is one of the most important consideration in equipment cleaning validation. 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.

It is necessary to validate cleaning procedures for the following reasons.

- It is a prime customer requirement since it ensures the purity and safety of the product.
- It is a regulatory requirement in Active Pharmaceutical Ingredient product Manufacture.
- It also assures the quality of the process through an internal control and Compliance.

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**Reasons for Cleaning Validation[3-6]**

Effective cleaning is a key to product quality assurance. Cleaning is performed to remove product and non-product containing materials. It is necessary to Validate cleaning procedures for the following reasons:

- 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.

**Different Types of Contaminants[7]**

The manufacturing of API and pharmaceutical products involves series of processing steps and use of various equipment's. Equipment's or ancillary systems may be used for manufacturing multiple product or single dedicated product. The inadequate cleaning process may leads to the fact that following residue may carry forward as contaminant in the next batch to be manufactured in the same equipment.

1. Precursors to the Active Pharmaceutical Ingredient
2. By-products and/or degradation products of the Active Pharmaceutical Ingredient
3. Contamination of one batch of product with significant levels of residual active ingredients from a previous batch
4. Microbiological contamination: Maintenance, cleaning and storage conditions may provide adventitious microorganisms with the opportunity to proliferate within the processing equipment.
5. Contamination with unintended materials or compounds such as Cleaning agents, lubricants etc.

**Bracketing and Worse Case[9, 10]**

The cleaning processes of multiple product use equipment in API facilities are subject to requirements for cleaning validation. The validation effort could be huge. In order to minimize the amount of validation required, a worst case approach for the validation can be used.

1. By means of a bracketing procedure the substances are grouped.
2. A worst case rating procedure is used to select the worst case in each group.
3. Validation of the worst case situation takes place. However, it is most importance that a documented scientific rational for the chosen worst cases exists.

It is recommended that at formal .worst case rating project is carried out, including studies to support the "worst case rating". When finalized, the results of the worst case rating shall give the priority of the validation efforts of the program. The worst case rating priority will then support a conclusion that the cleaning procedures are effective for all drug substances within the bracket, including those not individually tested.

**Bracketing Procedure**

The objective of a bracketing project, is for the company to demonstrate that it has a Scientific rationale for its worst case rating of the substances in the cleaning validation program. The first thing to do is to make groups and sub groups – which we will term .bracketing., from which worst cases will later be selected based on the results from the rating. The bracketing procedure should be included in a company policy, or an SOP or an equivalent document on cleaning validation.

**Worst Case Rating**

A worst case rating study will priorities existing drug substances, in a cleaning validation program, based on information on applicable criteria chosen by the company. Clean company chose the following criteria which are relevant to the molecule preparation in their facility (companies should evaluate individual Situations)

- Hardest to clean: experience from production
- Solubility in used solvent
- Highest toxicity
- Lowest therapeutic dose
- Lowest limit (based on therapeutic doses / tox data, batch sizes, surface areas etc.)
- Other scientific rationales

**Elements of Cleaning Validaaion[3-6, 8-11]**

This is followed by a more detailed view of the individual elements in this section.

- Establishment of acceptance criteria
- Sampling procedure and necessary validation of same
- Analytical method and its validation
- Validation protocol
- Validation report

**Establishment of acceptance criteria**

The Cleaning Validation should demonstrate that the procedure consistent 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 reactant. Companies should decide on which residue(s) to quantify based on sound scientific rational.

**i) Chemical determination**

In active pharmaceutical ingredient manufacture there may be partial reactants and unwanted by-products which may not have been chemically identified reactant. Companies should decide on which residue(s) to quantify based on sound scientific rational. There are a number of options available when determining acceptance criteria. Where either toxicological or therapeutic data if available then calculation A or B is preferable. If data is not available for either of these calculations or if the result is more stringent calculation C should be used.

*Limiting the level based on toxicity data*

An Acceptable Daily Intake (ADI) is calculated with suitable safety factors applied and this is converted to the maximum allowable.

*Pharmacology dose method*

The philosophy is to reduce the levels of residuals product in each piece of equipment such that no greater than 1/1000 of the normal therapeutic dose will be present per typical dose of the next product to be run in the equipment. The validation protocol should include a calculation.

*Limiting the level of products which could appear in the following product*

Limits from 1 0ppm up to 0.1% (based on the ICH impurity document which indicates that up to 0.1% of an individual unknown or 0.5% total.

**ii) Physical determination**

There should be provision during routine cleaning for a visual examination of the equipment, verifying that it is free of visible residues. The validation protocol should include this requirement as acceptance criteria. During validation, special attention should be given to areas that are 'hard to clean' (e.g. agitator shafts, thermo wells, discharge valves etc.) and areas that would be difficult to verify on a routine basis.

**iii) Microbiological determination**

Appropriate studies should be performed (e.g. swabs and/or rinse sampling) where the possibility of microbial contamination of subsequent product is deemed possible and presents a product quality risk. Whether or not CIP systems are used for cleaning of processing equipment, microbiological aspects of equipment cleaning should be considered. This consists largely of preventive measures rather than removal of contamination once it has occurred. There should be some documented evidence that routine cleaning and storage of equipment do not allow microbial proliferation. For example, equipment should be dried before storage, and under no circumstances should stagnant water be allowed to remain in equipment subsequent to cleaning operations. Time-frames for the storage of unclean equipment, prior to commencement of cleaning, as well as time frames and conditions for the storage of cleaned equipment should be established. The control of the bio-burden through adequate cleaning and storage of equipment is important to ensure that subsequent sterilization or sanitization procedures achieve the necessary assurance of sterility. This is also particularly important from the standpoint of the control of pyrogens in sterile processing since equipment sterilization processes may

not be adequate to achieve significant inactivation or removal of pyrogens.

**Current Approaches in Determining the Acceptance Limits[11]**

Acceptance limits for pharmaceutical manufacturing operation

1. Approach 1 (Dose criterion)

Not more than 0.001 of minimum daily dose of any product will appear in the maximum daily dose of another product.

Milligrams of active ingredient = I x K x M in product A permitted per J x L 4 inch2 swab area

I = 0.001 of the smallest strength of product A manufactured per day expressed as mg/day and based on the number of milligrams of active ingredient.

J = Maximum number of dosage units of product B per day

K = Number of dosage units per batch of final mixture of product B

L = Equipment surface in common between product A & B expressed as square inches.

M= 4 inch2/swab.

2. Approach 2 (10 ppm criterion)

Any active ingredient can be present in a subsequently manufactured product at a maximum level of 10 ppm.

Milligrams of active ingredient = R x S x U in product A permitted per T 4 inch2 swab area

R = 10mg active ingredient of product A in one kg of product B

S = Number of kilograms per batch of final mixture of product B

T = Equipment surface in common between product A & B expressed as square inches.

U = 4 inch2/swab.

3. Approach 3 (Visually clean criterion)

No quantity of residue should be visible on the equipment after cleaning procedures are performed.

**Cleaning Procedure[12]**

Standard cleaning procedures for each piece of equipment and process should be prepared. It is vital that the equipment design is evaluated in detail in conjunction with the product residues which are to be removed, the available cleaning agents and cleaning techniques, when determining the optimum cleaning procedure for the equipment. Cleaning procedures should be sufficiently detailed to remove the possibility of any inconsistencies during the cleaning process. Following parameters are to be considered during cleaning procedures.

*A. Equipment Parameters to be evaluated*

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*

1. Preferable materials that are normally used in the process
2. Detergents available (as a general guide, minimal use of detergents recommended unless absolutely required)
3. Solubility properties
4. Environmental considerations
5. 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

**Sampling Technique[13-19]**

The two methods of sampling generally employed are swab and / or rinse sampling these methods is shown be a scientifically sound method.

*1. Direct surface sampling*

It involves the determination of the type of sampling material used and its impact on the test data to check the interference of the sampling material with the test. Therefore,

early in the validation programme, it is crucial to assure the sampling medium and solvent if they are satisfactory and be readily used.
Advantages of direct sampling are that, areas hardest to clean and which are reasonably accessible can be evaluated, leading to establishing a level of contamination or residue per given surface area. Additionally, residues that are "dried out" or are insoluble can be sampled by physical removal.

*Swab*
After cleaning the equipment, product contact surfaces could be swabbed to evaluate surface cleanliness. Swabs used should be compatible with the active ingredients and should not interfere with the assay. They should not cause any degradation of the compound. The solvent used for swabbing should provide good solubility for the compound and should not encourage degradation.

*Rinse*
Sampling and testing of rinse samples for residual active ingredient is a commonly adopted method to evaluate cleanliness. This is a fairly convenient method in many cases and requires control over the solvent used for rinsing, the contact time and the mixing involved. The solvent used should be selected based on the solubility of the active ingredient and should either simulate a subsequent batch of product or at least provide adequate solubility.

A disadvantage of rinse samples is that the residue or contaminant may not be soluble or may be physically occluded in the equipment. An analogy that can be used is the "dirty pot." In the evaluation of cleaning of a dirty pot, particularly with dried out residue, one does not look at the rinse water to see that it is clean; one looks at the pot.

*Testing methods*
The basic requirements of the analytical methods should have the following criteria.

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

Various analytical techniques have been used for testing cleaning validation samples. Commonly used analytical tools for cleaning validation are mentioned in Table-1.
It includes both specific (e.g.HPLC) as well as non-specific methods (e.g.TOC, pH).Selection of suitable analytical method depends on various factors such as nature and type of analytes.

**Table 1.** Commonly used analytical tools for cleaning validation.

| **Traditional Analytical Methods** | **Modern analytical Techniques** |
|---|---|
| 1.Gravimetry<br>2.pH<br>3.Conductivity<br>4.Colourimetry<br>5.UV-spectroscopy | 1. Chromatographic techniques like HPTLC, HPLC and GC etc.<br>2.Total organic analysis(TOC)<br>3.Atomicabsorption spectroscopy<br>4.Charged aerosol detection(CAD)<br>5.Immuno assay: ELISA<br>6.Capillary electrophoresis.<br>7.Optically simulated electron emission(OSEE)<br>8.Portable mass spectrophotometer<br>9.Bioluminescence |

**Table 2.** Commonly used methods for some analytes.

| **Analytes** | **Analytical method** |
|---|---|
| Proteins | ELISA, HPLC, TOC |
| Organic compounds | TOC, HPLC, UV-VIS, TDS |
| Inorganic compounds | Conductivity, pH, TDS |
| Biological system | Vial cell analysis |

**Validation Protocol**

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. 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:

The objective of the study**,**

- What cleaning process is to be validated (indicating the product to be removed and the equipment from which it is to be removed)?
- If this study is to be employed to demonstrate the acceptability of the cleaning procedure for a group of products the rational for doing so should also be detailed here.
- The cleaning procedure to be validated should be identified i.e. cleaning agents, soakage times, equipment parameters, number of cleaning cycles etc.

A Cleaning Validation Protocol is required to define how the cleaning process will be validated. It should include the following:

The objective of the validation process,

- Responsibilities for performing and approving the validation study;
- Description of the equipment to be used;
- The interval between the end of production and the beginning of the cleaning procedure;
- The number of lots of the same product, which could be manufactured during a campaign before a full cleaning is done
- Detailed cleaning procedures to be used for each product, each manufacturing system or each piece of equipment;
- The number of cleaning cycles to be performed consecutively;
- Any routine monitoring requirement;
- Sampling procedures, including the rationale for why a certain sampling method is used;
- Clearly defined sampling locations;
- Data on recovery studies where appropriate;
- Validated analytical methods including the limit of detection and the limit of quantitation of those methods;
- The acceptance criteria, including the rationale for setting the specific limits;
- Other products, processes, and equipment for which the planned validation is valid according to a "bracketing" concept;
- Change Control/ Re-validation.

**Validation Report**

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.
- Approval of conclusions
- Review any deviations for the protocol that occurred.
- In cases where it is unlikely that further batches of the product will be manufactured for a period of time it is advisable to generate interim reports on a batch by batch basis until such time as the cleaning validation study has been completed. (Typically, in Active Pharmaceutical Ingredient Pharmaceutical manufacture, verification is deemed appropriate during development of the cleaning methods. Where products are manufactured infrequently, verification may be applied over a period of time until all measuring data has been collected for the Validation Report.)
- The report should conclude an appropriate level of verification subsequent to validation.

**Change Control/Revalidation[20]**

A change control system is in place to ensure that all changes that might impact the cleaning process are assessed and documented. Significant changes should follow satisfactory review and authorization of the documented change proposal through the change control procedure. Minor changes or changes having no direct impact on final or in-process product quality should be handled through the documentation system.

Changes which should require evaluation and likely re-validation include but not limited to:

- Changes in the cleaning procedure;
- Changes in the raw material sources;
- Changes in the formulation and/or process of products;
- New products;
- Changes in the formulation of detergents;
- New detergents;
- Modifications of equipment.

The cleaning process should be reassessed at defined intervals, and re-validated as necessary. Manual methods should be reassessed at more frequent intervals than clean-in-place (CIP) systems.

**Conclusion**

A cleaning validation programme 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 degree of evaluation required to validate the procedure, decisive on the residues to be tested based on solubility and toxicity, development of sampling and analytical methods for recovery and detection of residues. acceptance criteria for the validation, compilation and approval of the validation protocol, scope for the validation studies to be performed in accordance with the protocol, compilation and approvals of validation reports, documented studies, conclusions, recommendations and revalidation policy.

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