ISSN 0976 – 3333

Available Online at www.ijpba.info

**International Journal of Pharmaceutical & Biological Archives 2011; 2(5):1332-1336**

***REVIEW ARTICLE***

# An Overview on Cleaning Validation

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Received 22 Jun 2011; Revised 27 Sep 2011; Accepted 01 Oct 2011

**ABSTRACT**

Pharmaceuticals can be contaminated by potentially dangerous substances. Essential to establish adequate cleaning procedures. Cleaning procedure is the process of assuring that cleaning procedures effectively remove the potentially dangerous substances from equipment or facility below predetermined level.

**Key words:** Validation protocol, Rinse, Swab.

## INTRODUCTION

Validation: "The process of providing documented evidences, that provides a high degree of assurance that specific process, method, will consistently produce a result with pre – determine acceptance criteria".

Cleaning validation: "Cleaning validation is the process of assuring that cleaning procedures effectively remove the residue from Manufacturing equipment / facilities below a predetermined level".

### Cleaning Validation in Active Pharmaceutical Ingredient Manufacturing Plants

**Objective:**

The intention of this has been to define a comprehensive approach to the Validation of Cleaning procedures in Active Pharmaceutical Ingredient manufacturing facilities.

Cleaning Validation in the context of Active Pharmaceutical Ingredient manufacture may be defined as:

The process of providing documented evidence that the process of providing documented that the cleaning methods employ within facility consistently control potential carryover of product, cleaning agents and extraneous material in to subsequent product to a level which is below predetermined levels.

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 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.

**Scope:**

This will serve to;

- Define the basic concepts and terms associated with cleaning validation in the active pharmaceutical ingredient industry.
- Serve as a guide from which master plans, protocols and reports may be complied.

General validation principles and a glossary of terms also relevant to cleaning validation are detailed in the CEFIC/EFPIA guide entitled 'Good manufacturing practices for active pharmaceutical ingredient manufacturers'.

It applies sterile API's only up to the point where the API is rendered sterile.

**Potential residues:**

The active pharmaceutical ingredients industry involves (in general) the manufacture of Active Pharmaceutical Ingredients by both chemical and physical means through a series of multiple step processes. Plants or individual pieces of equipment, including ancillary equipment, may be used in multi-product manufacture or dedicated to individual products.

The result of inadequate cleaning procedures is that any of a number of contaminants may be present in the next batch manufactured on the equipment such as:

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- Precursors to the active pharmaceutical.
- By- products and/or degradation products of the active pharmaceutical ingredient.
- The previous product.
- Solvents and other materials employed during the manufacturing process.
- Micro-organisms.

**Cleaning validation on policy:**

The main focus of this will be to describe 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 concepts of cleaning validation should be approached in a facility.

It is advisable for active pharmaceutical ingredient manufacturing facility 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.

**Elements of cleaning validation:**

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.

**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.

**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.

**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.

- **Cleaning procedures**

Written cleaning procedures for each piece of equipment and process1 must be prepared. It is vital that the equipment design is evaluated in detail in conjunction with the product residues to be removed, the available cleaning agents and cleaning techniques when determining the optimum cleaning procedure for the equipment.

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 etc

Residues to be cleaned

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

Cleaning agent parameters to be evaluated

- Preferably materials that are normally used in the process.
- Solubility property.
- Environmental consideration
- Health and safety consideration etc

Cleaning techniques to be evaluated

- Manual cleaning
- CIP (clean in place)
- COP (clean out of place)
- Semi automatic.
- Time considerations.
- Number of cleaning cycles.

- **Sampling**

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

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 level.

Each method describe brief in below:

- **Swab:**

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 represent worst case locations on the equipment and that the result is then extrapolated to account for the total product contact surface area this calculation makes it possible to make a worst case determination of potential carryover into subsequent product. Due to the nature of this method which employs physical forces as well as chemical forces it may be necessary to perform sampling technique evaluation. Swabbing efficiency (% recovery) for the swabbing method must be determined.

- **Rinse:**

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 qualified.

This method allows much greater ease of sampling than swabbing.

- **Analytical methods:**

In order for the analytical testing of the cleaning validation samples (swabs or rinses) to yield meaningful results, the analytical methods used should be validated. This should be documented.

The basic requirements are:

- ✓ The ability to detect the target substance(s) at levels consistent with the acceptance criteria.
- ✓ The ability to detect the target substance(s) in the presence of other materials that may also be present in the sample (selectivity)
- ✓ The 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 of an allowed range.

- **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.

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.

- **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:

- ✓ 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.
- ✓ 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.)

**Cleaning Validation Methods for Equipments:**

- ✓ Manual
- ✓ Semi automated
- ✓ Fully automated.

The two common cleaning procedures are,

1. Manual cleaning

2. Automated cleaning procedures such as CIP (Cleaning in Place)

| **Manual Cleaning Sequence** | **CIP Cleaning Sequence** |
|---|---|
| Dismantle the parts of equipment to be cleaned | Pre-wash the parts in tap water |
| Pre-wash the parts with tap water | Wash the pre-washed parts with cleaning solution |
| Wash the pre-washed parts with cleaning solution | Blow out using compressed air |
| Rinse the parts in tap water | Rinse the parts with tap water |
| Rinse now with purified water | Final rinse using purified water |
| Dry the parts using hot air | Blow out using compressed air |
| Visual inspection is done to check whether the equipment is clean | Drying using hot and compressed air |
| Reassemble the parts finally | |

In all cases cleaning procedure must prove to be effective, consistent and reproducible.

FDA recommends (CIP) should be used to clean process equipment and storage vessels in order to reproduce exactly the same procedure each time (FDA, March 1998).

With manual procedure one must rely on the operator skills and thorough training of the operator is necessary to avoid variability in performance. However in some instances, it may be more practical to use only manual procedures.

**Cleaning Validation Protocol**

Should include:

- ✓ Interval between end of production and cleaning, and commencement of cleaning procedure
- ✓ Cleaning procedures to be used
- ✓ Any routine monitoring equipment used
- ✓ Number of cleaning cycles performed consecutively
- ✓ Sampling procedures used and rationale
- ✓ Sampling locations (clearly defined)
- ✓ The manufacturer needs a cleaning validation strategy

**CONCLUSION:**

The manufacturer needs a cleaning validation strategy

- ✓ Assess each situation on its merits
- ✓ Scientific rationale must be developed
  - o equipment selection
  - o contamination distribution
  - o significance of the contaminant
- ✓ "Visually clean" may be all that is required

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