INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com ISSN 2230 – 8407
Review Article

A REVIEW ON CONCEPT OF CLEANING VALIDATION IN PHARMACEUTICAL INDUSTRY

Kumar Satinder*, Shashikant, Prashar Bharat
Department of Pharmaceutical Sciences, Manav Bharti University, Solan (H.P) India

Article Received on: 09/04/12 Revised on: 21/05/12 Approved for publication: 09/06/12

*Email: skcrock87@yahoo.in

ABSTRACT
Pharmaceutical manufacturers must validate their cleaning process to ensure compliance with standard regulatory authorities. Manufacturing and cleaning equipment must be designed for effective and consistent cleaning to avoid cross-contamination and the cleaning processes must be verified as effective. This article provide introduction on cleaning validation and the associated regulations, level/degree of cleaning, approaches to cleaning validation, elements of cleaning validation, validation samples, acceptance criteria, validation protocols, validation reports.
KEYWORDS: Cleaning Validation, Validation Procedures, Sampling Procedures

INTRODUCTION

Cleaning validation is the process of assuring that cleaning procedures effectively remove the residue from manufacturing equipment/facilities below a predetermined level.[1]

Cleaning validation is primarily used for the cleaning of process manufacturing equipment in the pharmaceutical industries.[2] The main purpose of validating a cleaning process is to ensure compliance with standard regulatory authorities and 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.[3]

The term cleaning validation is to be used to describe the analytical investigation of a cleaning procedure or cycle. The validation protocols should reference background documentation relating to the rationale for "worst case" testing, where this is proposed. It should also explain the development of the acceptance criteria, including chemical and microbial specifications, limits of detection and the selection of sampling methods.[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]

Cleaning procedures are necessary to validate for the following reasons:

- Pharmaceutical products and API can be contaminated by other pharmaceutical products, cleaning agent & microbiological contamination.
- It is regulatory requirement in pharmaceutical product manufacture the concern is the same-assurance that equipment is clean and that product quality and safety are maintained.
- It is also assure from an internal control and compliance point of view the quality of manufacture. [1]

LEVEL/DEGREE OF CLEANING [1, 5, 6]

The level or degree of cleaning and validation mainly depends on

- The equipment usage (i.e. dedicated equipment or not)
- The stage of manufacture (early, intermediate or final step)
- The nature of the potential contamination (toxicity, solubility etc.)

APPROCHES TO CLEANING VALIDATION [6]

In order take lean approach to minimize validation requirements following points are taken into consideration:

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

Bracketing Procedure

The total manufacturing processes are grouped such as early steps, critical steps and API.

Each group of processes 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 of the trains made for the same purpose. The combination of substances in a train can be chosen based upon one or more the following strategies, or combinations of them.

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

Worst Case Rating

- Solubility in subjected solvent
- Maximum Toxicity
- Minimum Therapeutic Dose
- Difficult to Clean
- Lowest Limit based on therapeutic dose/toxic data, batch sizes, surface areas etc.

ELEMENTS OF CLEANING VALIDATION [1-3, 6-10]

1) Establishment of acceptance criteria

i) Chemical determination

Generally the residual Active Pharmaceutical Ingredient or intermediate, which is of greatest concern rather than reaction side products or residual impurities. There are a number of options available when determining acceptance criteria. Where either toxicological or therapeutic data if available than calculation A or B preferable. If data is not available for either of these calculations or if the result is more stringent calculation C should be used.

a) Limiting the level based on toxicity data

An Acceptance Daily Intake (ADI) is calculated with suitable safety factors applied and this is converted to the Maximum Allowable Carryover (MACO) to the API.

b) Pharmacological Dose Method

The philosophy is to reduce the levels of residual 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, which ties this philosophy to the acceptance criteria for the samples to be tested.

c) Limiting the level of product which could appear in the following products

Limits from 10ppm 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 unknowns material may be present in the product being tested)

ii) Physical determination

There should be provision during routine cleaning for a visual examination of the equipment, verifying that is free of visible residues. The validation protocol should include this requirement as an acceptance criterion. 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 products is deemed possible and presents a product quality risk.

2) Cleaning procedures

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

- Identification of the equipment to be cleaned
- Difficult to clean areas
- Property of materials
- Ease of disassembly
- Mobility

B. Residues to be cleaned

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

C. Cleaning agent parameters to be evaluated

- Preferable materials that are normally used in the process
- Detergents available (as a general guide, minimal use of detergents recommended 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)
- Semi automatic procedures
- Automatic procedures
- Time considerations
- Number of cleaning cycles

3) Sampling procedures

Generally there are two types of sampling that are accepted. The most desirable is the direct method of sampling the surface of the equipment, another method being the use of rinse sampling.

i) 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.

ii) Swab sampling: 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.

iii) Rinse sampling: 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.

4) Analytical methods

There are two analytical methods which are used to detect any compound.

i) Specific Method: This method detects a unique compound in the presence of potential contaminants. Examples are high performance liquid chromatography (HPLC), Ion chromatography, Atomic absorption, Capillary electrophoresis, and other chromatographic methods.

ii) Non-specific Method: This method detects any compound that produces a certain response. Examples are Total Organic Carbon (TOC), pH, Titration, and conductivity.

5) 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

6) 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 procedures 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.
- The report should conclude an appropriate level of verification subsequent to validation.

CHANGE CONTROL [2]

Validated cleaning procedures should be included in the change control program. This will ensure that any proposed changes are evaluated fully for their impact on the validated state of the procedure. Where deemed necessary, the proposed revised procedure may need to be validated prior to routine implementation.

CONCLUSION

The cleaning validation programme should be based on detailed cleaning procedures, a validation protocol, validated chemical and microbiological methods, a change control programme, a validation report and any auditing required to ensure compliance.

- Assess each situation on its merits.
- Scientific rationale must be developed
  i) Equipment selection
  ii) Contamination distribution
  iii) Significance of the contaminant
- In some situations "visually clean" may be all that is required.

ACKNOWELDGEMENT:

The Corresponding author would like to thank to my family, Dr. Bharat Prashar, Head of Department, Manav Bharti University, Solan (H.P) for his constant help, unflinching guidance, critical comments and helpful suggestions.

REFERENCES:

1. Cleaning Validation by balwant jadhav. Available from: http://www.authorstream.com/Presentation/bharatrbh-436837-cleaning-validation
2. Kumar VS, Sanjeev T, Sharma PK. Overview of cleaning validation in pharmaceutical manufacturing unit. IJARPB 2012; 1(2):154-164.
3. S. Lakshmana Prabu, T.N.K. Suriyaprakash. Cleaning Validation and its importance in Pharmaceutical Industry. Pharma Times 2010; 42(7):21-24.
4. Sami Power, Concept of Process Validation for Pharmaceutical Industry, Available from http://ezinearticles.com/Concept-of-Process-Validation-For-Pharmaceutical-Industry & id=2404112.
5. Cleaning Validation Acceptance Criterion 2009.
6. Ghosh A, Dey S. Overview of Cleaning Validation in Pharmaceutical Industry. International Journal of Pharmaceutical Quality Assurance 2010; 2(2):26-30.
7. APIC: Cleaning Validation in Active pharmaceutical Ingredient manufacturing plants: 1999; 3-7.
8. APIC: Guidance on aspects of cleaning validation in active pharmaceutical ingredient plants; 2000; 16-46.
9. Using Swabs for Cleaning Validation: A Review. Bioresearch online, 2003.
10. Patel Payal K, Patel NM and Patel PM. An Overview on Cleaning Validation. International Journal of Pharmaceutical & Biological Archives 2011; 2(5):1332-1336

Table 1: Level or degree of cleaning[1, 5, 6]

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 change over 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.