Available online on www.ijpqa.com
International Journal of Pharmaceutical Quality Assurance 2016; 7(2); 29-34

ISSN 0975 9506

Research Article

Establishing A Cleaning Method Validation Programme of Solid Dosage form of A Finished Drug Product

Md Semimul Akhtar*, Shailendra Kumar Verma

SRMSCET (Pharmacy), Bareilly, U.P., India

Available Online:1st April, 2016

ABSTRACT
Cleaning validation proved the effectiveness of the cleaning procedures used for cleaning product contact equipment. These can be accomplished by analyzing swab and / or rinse samples for chemical residues. The approach evaluates overall cleaning requirement of the product range and concentrates the validation effort to develop 'Worst Case' situation, where common cleaning procedures are followed for similar type (Operating Principle and Capacity) of equipment Rationale for the residue limit established should be scientific, logical and based upon knowledge of the material. As per the guide to inspections of Validation of Cleaning Processes the limits should be "practical, achievable and verifiable". The limit is often based on allowing not more than a fraction of a therapeutic dose to be present in a subsequent product. The fraction in this case is called as a "Safety factor". The degree of risk may be different for different dosage forms. The final conclusion has been drawn on the basis of the results obtained during execution of the cleaning validation on solid dosage forms. Altogether three consecutive batches of Librium 10 Tablets (Clordiazepoxide 10 mg) were taken under cleaning validation study to prove the effectiveness and consistency of the pre-established standard equipment cleaning procedures. All the results were evaluated against the acceptance criteria mentioned in Cleaning Validation Master Plan, i.e. NMT 10 ppm and NMT 100 ppm for residue limits of direct contact surfaces and non contact surfaces.

Keywords: Worst Case, Safety factor, NTP, ppm, CVMP.

INTRODUCTION

The Code of Federal Regulation (CFR) states in section 211.67, equipment cleaning and maintenance, "written procedure shall be established and followed for cleaning and maintenance of equipment, including utensils, use in the manufacture, processing, packing or holding of drug product". Cleaning validation proved the effectiveness of the cleaning procedures used for cleaning product contact equipment. These can be accomplished by analyzing swab and / or rinse samples for chemical residues. Validation usually consists of three consecutive runs. Additionally, for injectable products, microbial monitoring should be included as per the cleaning validation program. It provides an overview of multi product manufacturing procedures included in this section is an analysis of the risk to benefit scenarios associated with the various form of product manufacturing. Analysis of change over programs, equipment considerations and material transport as they are affected by multi product manufacturing strategies is also included. Cleaning validation is the methodology use to assure that a cleaning process remove residues of the active pharmaceutical ingredients (API) of the product manufactured in a piece of equipment, the cleaning aids utilized in the cleaning process and the microbial attributes. All residues are removed to predetermined levels to ensure the quality of the next product manufactured is not compromised. What is cleaning validation? It is documented evidence with a high degree of assurance that one can consistently clean a system or a piece of equipment to predetermined and acceptable limits.
Why cleaning validation? To verify the effectiveness of cleaning procedure and to ensure no risks are associated with cross contamination of active ingredients or detergents/sanitizer.
When cleaning validation?
Initial qualification of process/equipment.
Critical change in a cleaning procedure.
Critical change in formulation.
Significantly change in equipment.
Change in a cleaning process.
Change in a cleaning agent.
This Cleaning Validation Master Plan addresses the activities and documentation required to provide high degree of assurance that once cleaning method (procedures) are validated, shall be adhered for cleaning of process equipments, utensils, components and areas to ensure that the subsequent manufactured product is free from previous product residue and conform that the product is safe and complied with predetermined quality parameters.

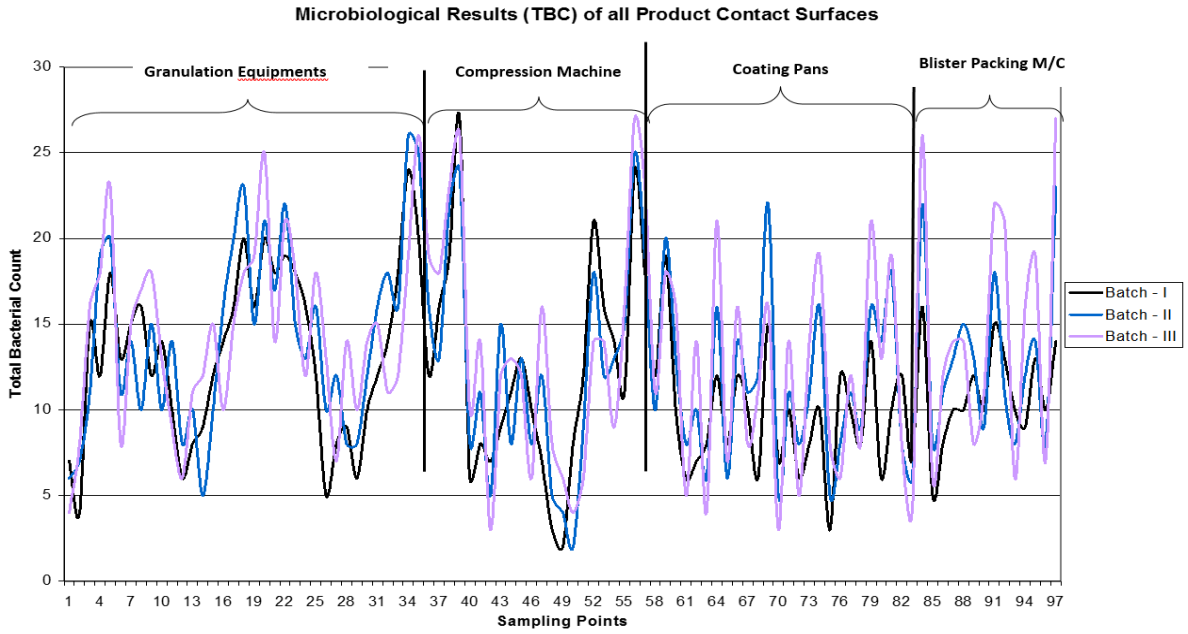
METHODS AND DISCUSSION

Cleaning Validation Master Plan
Objective

*Author for Correspondence

Table 1:

Product Equipment Contact Surface	Microbiological bioburden, cfu / 100 cm^2			Corrective Action
	Total plate count	Mold and Yeast	Fungi	
Alert Level	Less than or equal to 50	Less than or equal to 35	Should be absent.	* No action required
Action Level	Less than or equal to 100	Less than or equal to 50	Should be absent.	Investigate possible causes. Perform re-cleaning. Perform extra microbial testing
Limit	Less than or equal to 200	Less than or equal to 100	Should be absent.	Investigate possible causes. Perform re-cleaning and re-sampling. Finished product testing for microbial contamination with speciation if positive.



The objective of Cleaning Validation Master plan of equipment, utensils, components and areas is to establish sufficient documented evidence to assure that, cleaning procedures can repeatedly and reproducibly remove residue of the subjected product within established acceptance limit. The acceptance limit is maximum allowable quantity of product residue, which does not affect quality and safety of the subsequent product to be manufactured, by using same equipment and facility. To establish acceptable time limit for storage of cleaned equipment, utensils and components after cleaning.Equipment are not expected to be free from all microorganisms, particularly when the final stage in cleaning does not involve final rinsing with sterile water for injection. The objective shall be to demonstrate that there is no microbial proliferation in equipments during storage.

Scope

This Cleaning Validation Master Plan is applicable to the manufacturing of Tablets, Capsules, Soft gelatin capsules and Liquid orals.On introduction of new equipment/ product, it shall be re-evaluated with the guidelines provided in cleaning validation master plan for determination of requirement of cleaning validation.

Validation Strategy

In order to avoid potential risk of cross contamination, cleaning validation shall cover the following areas-

Dispensing Area: Equipment and area shall be covered during cleaning validation process to establish the cleaning procedure to be followed.

Manufacturing Area: Manufacturing areas are defined as

Tablets.

Capsules

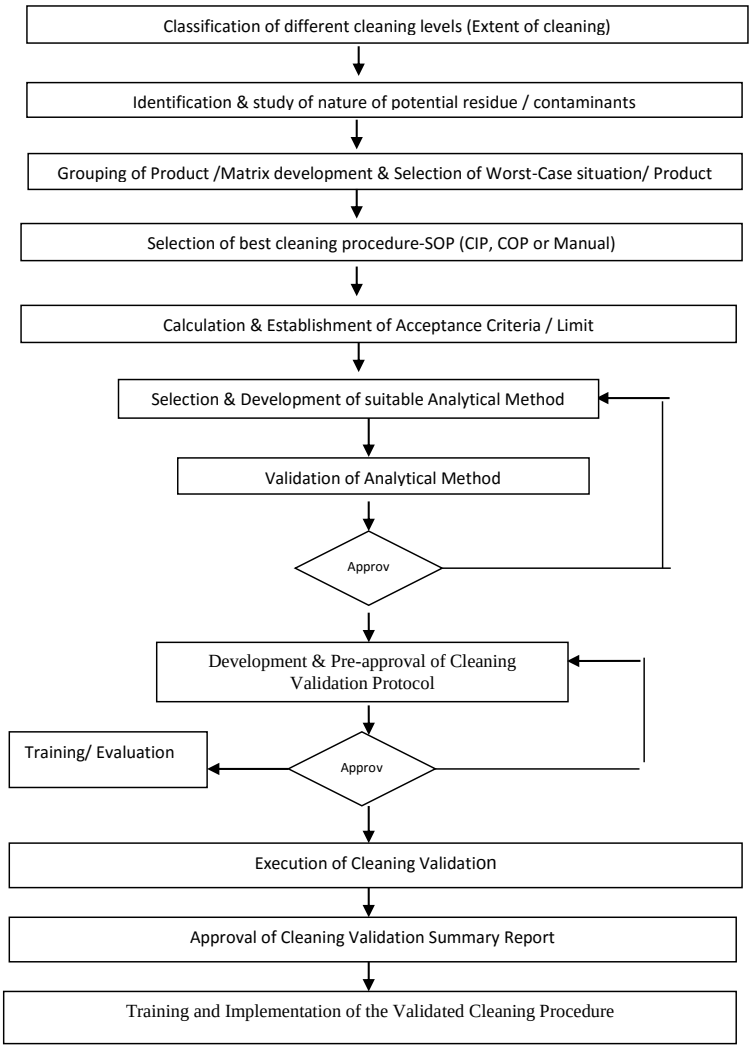
Liquid Oral

Soft Gelatin

Areas along with equipment shall be covered during cleaning validation process

Validation Approach

Product/Equipments Grouping (Bracketing)



Cleaning Validation Cycle*- The flow chart of development of cleaning validation for any particular product / equipment.*

The approach evaluates overall cleaning requirement of the product range and concentrates the validation effort to develop 'Worst Case' situation, where common cleaning procedures are followed for similar type (Operating Principle and Capacity) of equipment.

The 'Worst Case' is considered on the basis of following factors-

Physical characteristic i.e. Solubility, Clean ability.

Therapeutic Dose of the Product.

Concentration of Active Ingredient.

Equipment combination (Equipment Train).

In this approach cleaning validation of each equipment train shall be performed based upon the worst-case product selected for that equipment train.

Selection of Cleaning Procedure

There are following three types of cleaning methods utilized in the drug product manufacturing facilities

Clean-In-Place (CIP)

Cleaning of the equipment is performed in place without disassembling and transferring to the washing area which is also defined as In Situ Cleaning.

Cleaning process may be controlled manually or by an automated program.

Very consistent and reproducible cleaning method.

Can be validated readily.

Being a closed system visual inspection of all components is difficult.

Clean-Out-Of-Place (COP)

Cleaning of disassembled equipment is performed in a central washing machine.

The washing machine also requires validation such as the temperature, ultrasonic activity, cycle time, cleaning operation sequence, water quantity, detergent quantity dispensed etc.

Manual Cleaning

Difficult to clean.

Most extensive and elaborate cleaning procedures are required.

A high quality and extensive training program is required.

Following were taken into consideration for selecting manual cleaning method.

Mopping.

Hot air drying.

"Seeing is Believing"

Product diversity

Risk of failure of cleaning equipments

Validation of automated cleaning equipments

Trained and experienced working staff

Selection of Analytical Method

The development and validation of analytical procedures for detection of residue in cleaning validation sample requires the selection of appropriate analytical methods.

Method must be selected carefully for the specific situation; a non-specific analytical method may lead to false analytical results.

Specific Analytical Test Methods

Chromatographic technique may be appropriate for active ingredients, as they are sensitive and specific. Consideration should be given to the presence of degradation products and other related substances, which may have an adverse effect on the next product manufactured. Following are some of the specific analytical methods, which are commonly used for cleaning validation.

UV spectrophotometry
HPLC
GC
HPTLC
Atomic absorption spectrophotometric method
Flurometry
Flame photometry

Non-Specific Analytical Test Methods

Although it is expected to follow specific analytical test methods for the cleaning samples, but many of the non-specific methods such as visual, pH, conductivity and TOC are simple, fast and still provide valuable information related to the level of cleaning and presence of any contaminant. Due to these properties these methods can be effectively used for evaluation of cleaning and on-line monitoring application. Following are some of the non-specific analytical methods, which are commonly used for cleaning verification.

Visual examination
Gravimetric analysis
pH
Conductivity
Microscopy
Titration
Total Organic Carbon. (TOC)

Evaluation of Cleaning Procedures

The effectiveness of cleaning procedures shall be evaluated by following methods.

Visual Inspection
Swab sampling
Rinse Sample (Wherever applicable)

Visual Inspection

Easy and preferred pre-sampling criteria
Qualitative and subjective
Difficult to inspect certain location
Results vary from inspector to inspector, difficult to validate

Direct Surface (Swab) Sampling Method

Strongly preferred method, as some residues may need a mechanical or physical action to remove from the surface.

Not suitable for the equipment, which are difficult to access, such as inner surface of the hoses, transfer lines, small intricate instruments (as micronizers), sieves/screens, dosators and brushes.

The sampling medium and solvent used for extraction of residue (from the sampling medium) may interfere with the analytical test.

Rinse Sampling Method

Large surface area can be sampled.

Strongly preferred method for difficult to access equipment.

May indicate false result when, the residue need mechanical or physical action to remove from the surface. For example when the contaminant is not soluble or occluded in the equipment.

The residue can be diluted below the level of detection, if large rinse volumes are used.

Acceptance Criteria

Establishment of limit for maximum allowable carry-over for previous product residue

Rationale for the residue limit established should be scientific, logical and based upon knowledge of the material. As per the guide to inspections of Validation of Cleaning Processes the limits should be "practical, achievable and verifiable".

A quantitative limit should be based on one or more of the following:

Therapeutic dose.
Difficulty of cleaning.
Use/ Application of the product.
Nature of other products manufactured in the equipment

Limit calculation on the basis of smallest therapeutic dose (Dose Criterion)

The limit is often based on allowing not more than a fraction of a therapeutic dose to be present in a subsequent product. The fraction in this case is called as a "Safety factor". The degree of risk may be different for different dosage forms.

Normally accepted Safety Factor for Oral Dosage Forms (Tablets, Capsules & Liquid Orals) is 1/1000

All of these factors mentioned previously are usually summarized in an equation, which may take the following general form:

$$MAR = \frac{STD \times SBS \times SF}{MDD}$$

Where,

MAR	Maximum Allowable Residue
STD	Smallest Therapeutic Dose amongst all products manufactured in equipment train (Product A) i.e. single strength (mg/unit dose)
SBS	Smallest batch size of any subsequent product to be manufactured in the same equipment train (Product B). i.e. No. of dosage unit/batch.
SF	Safety Factor i.e. 1/1000 for Tablets, Capsules and Liquid Orals
MDD	Maximum Daily Dose of any product to be manufactured in the same equipment train.

Limit calculation on the basis of 10 ppm criterion

MAR shall be calculated on the basis of default limit "10 ppm" criterion according to below formula.

$$MAR = 10 \times SBS$$

Where,

MAR	Maximum Allowable Residue

SBS Smallest batch size of any subsequent product to be manufactured in the same equipment train (Product B). i.e. Kg /Ltrs. Of batch.

Limit calculation on the basis of equipment surface area

Once the Maximum Allowable Residue limit in subsequent product is calculated based on the "Dose" & "10 ppm" criterion, it is practical and logical to determine the limit in terms of active ingredient contamination level per surface area of individual equipment of same equipment train.

MAR limit for the total swab area sampled collectively can be calculated as follows

MAR limit for the sampled surface =

$$\frac{\text{No. of swab samples x Swab Area}}{\text{Shared Equipment Surface Area}} \times \text{MAR Limit}^*$$

* Lower value of "Dose" & "10 ppm" Criterion

Either the limit can be calculated in terms of the total swabbed area or per swab.

Microbiological Test

Swab samples to be collected from product contact surface area immediately after completion of cleaning activities and after specified hold time period for total aerobic microbial count. The limits for the microbiological bioburden criteria for product contact surface are presented below.

RESULTS

Graphical Representation

CONCLUSION

The Final Conclusion has been drawn on the basis of the results obtained during execution of the cleaning validation on solid dosage forms. Altogether three consecutive batches of Librium 10 Tablets (Clordiazepoxide 10 mg) were taken under cleaning validation study to prove the effectiveness and consistency of the pre-established standard equipment cleaning procedures. Only product to product change over (B- type cleaning) cleaning method has been validated. All the qualification studies, calibrations and analytical method validation have been conducted prior to this cleaning validation as a prerequisite. All the results were evaluated against the acceptance criteria mentioned in Cleaning Validation Master Plan, i.e. NMT 10 ppm and NMT 100 ppm for residue limits of direct contact surfaces and non contact surfaces, respectively. The microbiological acceptance criteria are NMT 30 cfu/plate and NMT 100 cfu/plate for swab samples and rinse samples, respectively. By thorough compilation of the obtained results, we can conclude that chemical residue and microbiological contamination are well under pre-determined acceptance criteria. The chemical residues of Chlordiazepoxide at all product contact equipment surfaces (critical equipment sufaces) were lies below 10 ppm. The highest chemical residue of 9.94 ppm was observed at Feed Bowl– I in Sifter which is still satisfy the 10 ppm criteria. This particular point can be considered as the hot spot of the entire equipment train and shall be subjected to routine verification of post cleaning inspection. On the other hand, all collected samples satisfy the microbiological criteria and no sample fails to achieve the desired cleanliness. The three times repetition of the same results indicates the consistency of the existing cleaning method for achieving expected cleanliness. The worst case approach intensifies the ruggedness of the cleaning method. This risk based study also take care the safety of the products manufactured in this multi product manufacturing facility. This cleaning method validation meets all criteria to satisfy the regulatory requirements on its part.

REFERENCES

1. Points to consider for cleaning validation, PDA Journal of Pharmaceutical Science and Technology, volume 52, November – December 1998 Supplement.
2. Human Drugs CGMP Notes, volume 5, Number 3, September 1997.
3. Equipment Cleaning and Maintenance, CFR 21, Part 211, Subpart 211.67.
4. Good Manufacturing Practices for Active Pharmaceutical Ingredients, ICH Q7A 2000.
5. Guide to Inspection of Validation of Cleaning Procedures, US FDA, 1993.
6. Guide to Inspection of Bulk Pharmaceutical Chemicals, US FDA 1994.
7. Rules and Guidance for Pharmaceutical Manufacturers and Distributors, MCA.
8. validation of Bulk Pharmaceutical Chemicals, by Danial Harpaz and Ira R. Berry, Interpharm press Inc. Illinois, 1997.
9. Rinse Sampling for Cleaning Validation Studies, Pharmaceutical Technology, 22(5), 66 – 74, 1998.
10. Indian Pharmacopoeia 1996 volume I and volume II
11. British Pharmacopoeia 2005 volume I and volume II
12. Current index of Medical Specialities (CIMS), July-2006
13. Food and Drug Administration, "Guide to inspection of validation of cleaning processes," (FDA, Rockville, MD, July 1993).
14. G.M. chudzik, "General guide to Recovery studies using Swab Sampling Methods for cleaning validation", J. Validation technol.5 (1), 77-81 (1998).
15. R.J. Forsyth and D.V. Haynes, "Cleaning Validation in a Pharmaceutical Research Facility", Pharm.Technol.22 (9), 104-112 (1998).
16. J.A. Thomas, "A Cleaning Validation Master Plan for Oral Solid Dose Pharmaceutical Manufacturing equipment", J. Validation Technol.6 (2), 522-530 (2000).
17. PDA Technical Report No. 29, "Points to consider for cleaning validation" PDA J. Pharm. Sci. and Tech, 52 (6), 1-23 (1998).
18. G.L. Fourman and M.V. Mullen, "Determining Cleaning Validation Acceptance Limits for Pharmaceutical Manufacturing Operation," Pharma.Technol.17(4), 54-60 (1998
19. D.A. Le Blance, "Establishing Scientifically Justified Acceptance Criteria for Cleaning Validation of Finished Drug Product," Pharm. Technol.2 (10), 136-148 (1998).

20. J. Agalloco, "Points to consider in the validation of equipments cleaning procedure", Journal of Parenteral Science and Technology, vol. 46 No.5, September 1992.
21. R. Baffi, et at., PDA Questionaire July 11, 1988, "A Total organic carbon Analysis Method for validating cleaning between products in Bio Pharmaceutical Manufacturing", Journal of Parenteral Science and Technology, January/February, 1991.
22. S.W. Harder, "The validation of cleaning procedures", Pharmaceutical Technology, May 1984.
23. D.W. Layton et al., "Deriving Allowable Daily intake for systemic Toxicants Lacking chronic Toxic Data". Regulatory Toxicology and Pharmacology 7, 96-112, 1987.
24. PMA, "Validation Concepts for Cleaning Method Associated with Manufacture of Drug Products," 1986.