EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 4
202-208
Year: 2019

REVIEW ON: RECENT TRENDS IN PHARMACEUTICAL CLEANING VALIDATION

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Article Received on 11/02/2019 **Article Revised on 03/03/2019** **Article Accepted on 25/03/2019**

ABSTRACT
Pharmaceutical industries are the of the essence section of health-care system. Enclose control more of cross contamination plays an chief role in order to maintain the quality of products in the manufacturing of the pharmaceuticals. The validation of cleaning course of action in the manufacturing of pharmaceutical products must ensure falling in line with cGMP. This review is paying attention on cleaning validation, CVMP, validation procedure, cleaning validation protocol and report, cleaning acceptance criteria, terminologies related to cleaning, sampling procedure, cleaning agent, worst case.

KEYWORDS: Cleaning validation, Cross Contamination, Worst case, Acceptance Criteria.

INTRODUCTION

A course of provide documentary evidence with high degree of assurance that the cleaning method employed with the facility consistently controls prospective carryover of product, cleaning agent and unconnected material into consequent product to a level which is below encoded level. By implement right cleaning process, contamination or cross contaminations know how to be banned. Contamination or cross contamination my cause by various factors such as cleaning agent, previous product, other environmental contaminants or dust particles, to prevent such contamination cleaning validation planned in necessary. The prime purpose of cleaning validation process in various manufacturing process is to identification and proving corrective actions of potential problems that are previously unsuspected. Cleaning validation is primarily employed for cleaning of equipment and area used for manufacturing of dosage forms. The prime objective of cleaning validation is to meet with the regulatory guidelines i.e. regulatory compliance. The United State Food and Drug administration issued its steer to inspections by heading "validation of cleaning process" during 1993. An improved awareness has been ready from that point in cleaning processes in pharmaceutical manufacturing environments.[1-7]

PURPOSE

- To prevent contamination and cross contamination.
- To get quality product.
- To comply with the regulatory agencies.[2-4,7]

ADVANTAGES

- Assurance of Safety and quality
- Product integrity
- Microbial integrity
- Cross contamination integrity
- Batch integrity
- Equipment reuse
- Reduction of quality cost
- Making excellent business sense
- Government regulations

WHEN CLEANING VALIDATION IS CONDUCTED

- Change in cleaning process
- Change in cleaning agent
- Addition of new product if it impact on worst case
- Change in minimum batch size
- Change in highest surface area of equipment chain.[2-4,7]

TERMINOLOGIES RELATED TO CLEANING VALIDATION

Cleaning validation: - A process of providing documentary evidence with high degree of assurance that the cleaning method employed with the facility consistently controls potential carryover of product, cleaning agent and extraneous material into subsequent product to a level which is below predetermined level.

Cleaning verification:- The process of providing documented evidence that the cleaning method employed with the facility controls potential carryover of product,

cleaning agent, and extraneous material into subsequent product to a level which is below predetermined level.

cVMP:- Document that summarizes the firm's/ manufacturing site's overall philosophy, intentions and approach to be used for establishing performance adequacy of the cleaning process.

Cleaning validation protocol:- A document describing strategy and procedure for conducting and recording the test and results of cleaning on manufacturing/ process equipments to confirm and to demonstrate that the cleaning process is capable of removing residue of the product or material used in the manufacturing equipment below the defined limit.

Cleaning validation report: - A document which includes assessment, evaluation and conclusion of cleaning validation study results conducted as prescribed in the cleaning validation protocol.

Cleaning process: - A process of removing contaminant from the process equipment such that equipment can be safely used for subsequent product manufacture.

Cleaning agent:- The solution or solvent used in cleaning process. Examples of cleaning agents are water, organic solvents, etc.

Acceptance criteria:- Numerical limits, ranges or other suitable measures for acceptance of test results.

Acceptable daily exposure: - A dose that is unlikely to cause an adverse effect if an individual is exposed, by any route, at or below this dose every day for a lifetime.

No observed adverse effect level (NOAEL):- The dose in toxicological study which produces no adverse effect.[3,4,7,8]

SELECTION OF CLEANING LEVELS

Type A: Such types of cleaning are employed between different strength of same formulations or two batches of same formulations. For such types of clean-up, cleaning justification is not compulsory, as cross contamination is not a matter.

Type B: Such types of cleaning are employed for different formulations. In such cases, validation of the efficacy of the cleaning procedure is remove residue to the necessary level is obligatory.

SELECTION OF CLEANING METHOD

- Manual Cleaning
- Semi-automatic cleaning
- Automatic cleaning
- Clean in place (CIP)
- Clean out of place(COP)

Clean in place

- Without disassembling equipment is cleaned in place
- Controlled of Cleaning process could be manually or by an computerized system.
- Reliable and reproducible cleaning process.
- Can be validated willingly.
- Difficult to inspect visually all components as a closed system

Clean out of place

- By utilizing central washing machine disassembled equipments is cleaned.
- Washing machine should be validated in accordance with the temperature, cleaning operation sequence, ultrasonic activity, run time, detergent quantity dispensed

POTENTIAL CONTAMINANTS

1. Air born particulate stuff
2. Dirt
3. Lubricants
4. Product deposit
5. breakdown deposit
6. Cleaning agents
7. Microorganisms and endotoxins
8. Operator interface
9. Previous product
10. Other materials used in process of manufacturing

NEED OF CENTER OF ATTENTION OF REGULATORY AGENCIES ON CLEANING VALIDATION

In the course of manufacture of medicinal products the cleaning of equipments and facilities is an vital assess to avoid contamination and cross contamination.

Among the regulation of GMP cleaning is performed and documented according to the described procedures.

Outlook from regulatory –

a) Traditionally, cleaning efficacy was over and over again monitor just visually.
b) Though, residues of API's excipients, degradation are gradually more an matter in examination and audits.

CLEANING VALIDATION AND VERIFICATION STUDY

Once the validation study has been completed successfully for three consecutive cleaning cycles for worst case, the cleaning procedure of equipment may be considered qualified/ validated for specific cleaning method, product residue and items of equipments. The observations of the validation study are documented in the cleaning validation report produced by the validation team.[2,4,6,7]

PROCEDURE FOR CLEANING

Cleaning validation activity shall be performed in two stages as cleaning process validation and maintenance of validated state.

A. **Cleaning process validation:-**Confirming that the cleaning process is capable of removing the previous product residue, cleaning agent and other environmental contaminants to pre-defined desired level.

B. **Maintenance of validated state: -** Assure that during routine cleaning, the validated process remain in state of control.[2,4-7]

A. CLEANING PROCESS VALIDATION

The cleaning procedure which is normally includes dislodgement of the adhering residues using appropriate cleaning agent and cleaning methodology.

The cleaning procedure for equipment that comes in contact with the product like Rapid mixture granulator, Dryer, Compression & Coating machine, etc is cleaned as per procedure and same is used for documentation of cleaning process.

CURRENT APPROACHES IN DETERMINING THE ACCEPTANCE LIMITS FOR CLEANING VALIDATION

Approach 1 (Dose Criterion):- NMT 0.001 of minimum daily dose of any product will appear in the maximum daily dose of another product. Milli grams of active ingredient = 1xKxM in product A permitted per J x L 4inch 2 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.
L = Equipment surface in common between product A & B expressed as square inches.
J = Maximum number of dosage units of product B per day
M = 4 inch2/swab
K = Number of dosage units per batch of final mixture of product B.[9-11]

10ppm criteria (Approach 2):- Some active pharmaceutical ingredient can be there in a next manufactured product at a maximum level of 10 ppm. Active ingredients (Milligrams) = R x S x U in a product A permitted per T 4 inch 2 /swab area.
R = Active ingredient of product A (10 mg) in one kg of product B.
U = 4 $inch^2$/wipe down
T = Surface of equipment in ordinary between product A & B spoken as square inches.
S = kilograms per batch of final mixture of product B.[9-11]

Visually clean Criterion (Approach 3):- On the equipment there should not be any residue after cleaning procedures are perform.[9-11]

MACO (Approach 4):- Maximum allowable carryover (MACO) of the molecule can be derived by using acceptable daily exposure (ADE mg/Day) of molecule. Health based exposure limit such as ADE are derived by dividing NOAEL/NOEL/LOAEL for critical effect (after adjusting of body weight) by adjustment factor to extrapolate to the true no effect level in subpopulation of interest. In case of unavailability of NOAEL/NOEL/LOAEL values, ADE can be derived from therapeutic daily dose (TDD).[9-11]

a. Cleaning process validation approach

1. Identification of worst case molecule:- Worst case molecule for cleaning validation may be selected based on solubility, cleanability, toxicity and potency of molecule.

b. Establishment of MACO

1. Maximum allowable carryover (MACO) of the substance can be resultant by means of acceptable daily exposure (ADE mg/Day) of molecule. Health based exposure limit such as ADE are derived by dividing NOAEL/NOEL/LOAEL for critical effect (after adjusting of body weight) by adjustment factor to extrapolate to the true no effect level in subpopulation of interest. In case of unavailability of NOAEL/NOEL/LOAEL values, ADE can be derived from therapeutic daily dose (TDD).[5-7]

c. MACO calculations for drug product

1. MACO based on ADE criteria:- MACO of previous product (A) in next product (B) can be calculated as

$$\text{MACO in mg} = \frac{ADE_A \times MBS_B}{TDD_{(max)}}$$

Where:

- ADE- Acceptable Daily Exposure in previous product
- MBS- Minimum batch size of next product
- TDD- therapeutic daily dose of next product

II. MACO is also derived by considering product change over form one product to any other product produced in the same facility and same equipment.
III. Considering product A, B, C, and D in same facility and same equipment.[2,5-7,12,13]

PRODUCT	TDD mg	MBS Kg	ADE mg/day
A	15	6	30
B	25	9	35
C	60	11	25
D	90	15	260

Calculate MACO for each combination		MACO Criteria	Subsequent product			
			A	B	C	D
Previous Product	A	MACO based on ADE criteria in mg/day		10800000	5500000	5000000
	B	MACO based on ADE criteria in mg/day	14000000		6416666.7	5833333.3
	C	MACO based on ADE criteria in mg/day	10000000	9000000		4166666.7
	D	MACO based on ADE criteria in mg/day	104000000	93600000	47666667	

d. Acceptance criteria for swab and rinse sampling

a. **Swab sampling** :- Swab sampling location of the equipments is decided and discuss in cleaning validation protocol with appropriate justification.[5,6,12-14]

$$\text{Swab sampling} = \frac{\text{MACO x 0.75 x SA x 1000}}{\text{TSA}}$$

Where,

- MACO – Maximum allowable carryover
- 0.75 – Recovery factor
- SA - Swabbed area m^2/$inch^2$
- 1000 – Conversion factor for mcg
- TSA – Total surface area m^2/$inch^2$

b. **Rinse sample: -** The acceptance criteria obtained for swab can be considered as acceptance criteria for rinse sample converting it into ppm. The acceptance criteria obtained for swab can be considered for calculation of rinsing agent quantity.[2,5,6,13,14]

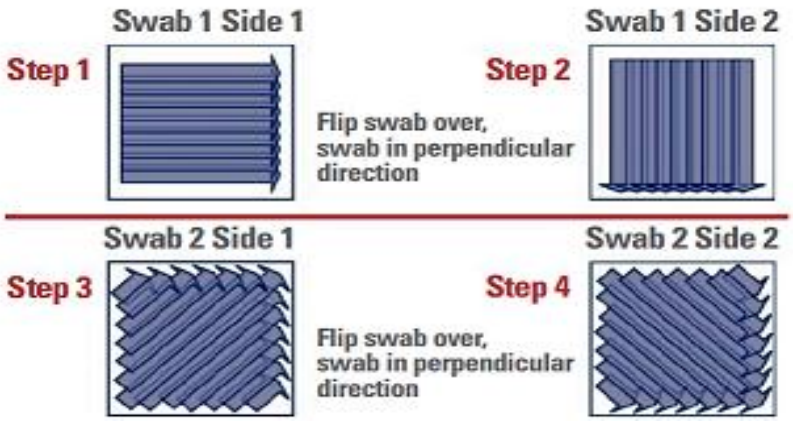
$$V_{liter} = \frac{\text{MACO x SA}_{(Equipment)} \text{x Rf}}{\text{L x TSA}}$$

Where,

- MACO – Maximum allowable carryover
- SA- surface area of sampling
- Rf – Recovery factor (0.75)
- L – target rinse limit in ppm
- TSA – Total surface area m^2/$inch^2$

V. Microbial swab sampling:- Microbial aspects is considered during the cleaning validation where water is used as cleaning agent. After cleaning of equipment microbial swab sampling is done from the designated sampling location as per protocol and by using site specific standard procedure.

a. Acceptance criteria:- For microbial swab sampling the acceptance criteria NMT 2cfu/cm^2.[2,5,6,12]



❖ **Equipment**

o All product contact parts of the major and minor equipments which are used in the manufacturing and packing are made up of SS316, hence those parts of the equipments are non-reactive, non-additive and non-adsorptive with the process and product material that comes in contact with it.

- Equipments are design in such a way that all contact parts surface are assessable for cleaning and rising adequately.
- Teepol solution (0.2% v/v) is used as cleaning agent and defied volume for cleaning is taken as per standard operating procedure.
- Cleaned equipment can be hold up to 6 days and uncleaned equipments may be hold up to 48 hours, if equipment is not used within validated state then such equipments are re-cleaned before taking it for manufacturing.[5,15] [6]

SAMPLING METHODOLOGY

Depending on type of equipment rinse sample and swab sample is collected.

A. Rinse sample

a. The cleaning agent or its vapor during reflux/boiling can wet the entire surface of equipment and easy to collect rinse. Swan sampling is not possible (uneven surface, small opening, piping, round surface, out of reach, etc.). Thus rinse sample technique to be used in case of tanks / vessels, pots, pipelines. It usually requires materials which are absorptive and to physically wide the surface and recover the analyte. Swab used should be compatible with active ingredients and should not interfere with the assay. They should not cause not cause any degradation of the compound. The solvent used for the swabbing should provide good solubility for the compound and should not encourage degradation.[5-7,14,16,17]

Advantages

- Dissolved and physically remove sample
- Adaptability to wide variety of surfaces
- Economically and widely available
- May allow a sampling of defined area
- Applicable to active, microbial and cleaning agent residues.

B. Swab sample

a. Swab sample is used when

➢ Collection of cleaning agent is not possible like (Rapid mixture granulator, Dryer, Compression & Coating machine, sifters, etc). Location of swab sample can be taken from equipment to ensure proper evaluation of cleaning. Selection of location of swab sample is done in such way that,

- Surface is extensively in contact with product
- Includes difficult to clean area
- It is representative of equipment surface
- The sample is accessible for sampling.

➢ Trained personnel is performed the sampling and forward the samples to quality control department for analysis.

➢ After completion of cleaning process tae swab sample from those sampling points which are predefined in cleaning validation protocol. Approximate 100 sq.cm swabbing is done in across surface applying the swab in vertical direction and after rotating it 90^{o} in horizontal direction.

➢ After swab sampling analyzed the sample as per pre-specified testing specification for the target API.

➢ Swab Sampling Procedure:-

- Wear cleaned hand gloves and take swab sample.
- Take required quantity of cleaning agent on closed beaker.
- Swab preferably in 4 x 4 inch (10cm x 10cm) surface area of equipment using flexible template from predefined location.
- If the surface area of the equipment of is less than 4 x 4 inch then consider the swab area which is feasible to swab and selected area is applied in calculation.
- In case of microbial swab sampling, the swab area is considered as 5cm x 5cm (i.e. 25cm^{2})
- Dip the swab in the beaker containing solvent and squeeze the swab to discharge the residues.
- Swabbing is done using horizontal and vertical strokes in specified area as mentioned in diagram.[4,6,7,12,14,16,17]

B. MAINTAINANCE OF CLEANING VALIDATION

Ongoing monitoring ensures the continued compliance and maintenance of monitoring involves the following:

a. **Routing Monitoring: -** Routing monitoring includes visual examination after each cleaning process during product change over and ensure there shall be any residue left over in the equipment.

b. **Periodic Testing: -** Cleaning verification is done quarterly for the validated processes in the respective area to ensure that the cleaning process is in validation state.

- If any sample fails to meet the acceptance criteria during validation / periodic review, the investigation is performed, documented and accordingly quality assessment is performed to verify the impact on validated status.[5,18]

NUMBER OF CLEANING CYCLES/ RUNS FOR CLEANING VALIDATION STUDY

- Three consecutive runs of worst case product is considered in cleaning validation, if three consecutive runs are not feasible, then three cleaning verification cycles for each product is considered

performed till cleaning validation on worst case product.

- Cleaning procedure is considered as validated, if each cleaning cycle/ run complies with the acceptance criteria.[5-7,15,18]

CLEANING VALIDATION/ VERIFICATION DOCUMENTATION

A. Cleaning Validation Protocol :- A document describing strategy and procedure for conducting and recording the test and results of cleaning on manufacturing/ process equipments to confirm and to demonstrate that the cleaning process is capable of removing residue of the product or material used in the manufacturing equipment below the defined limit.

Cleaning validation protocol must include:-

- Objective
- Scope
- Introduction
- Planning validation approach
- Method of execution
- Responsibilities
- Cleaning process details related to the processing area, process equipments, process description and process parameters
- Equipment matrix
- Selection of cleaning agent
- Calculations of acceptance criteria
- Sampling method and sampling locations of equipments.[2,5,7,18,19]

B. **Cleaning validation Report: -** A document which includes assessment, evaluation and conclusion of cleaning validation study results conducted as prescribed in the cleaning validation protocol.

Cleaning validation report must include: -

- Product batch detail
- Confirmation of cleaning procedure used
- Analytical results from cleaning assessments
- Confirmation of locations used for cleaning assessments
- Assessments of results against acceptance criteria.[2,5-7,18,19]

REVALIDATION

Revalidation of the cleaning procedure is evaluated in or more of following conditions:-

- Change in cleaning process
- Change in cleaning agent
- Addition of new product if it impact on worst case
- Change in minimum batch size
- Change in highest surface area of equipment chain
- Any change or modification that has impact on efficiency of cleaning process.[5-7,18]

CVMP

Cleaning validation master plan is to afford document authentication that the standard cleaning procedure used to clean equipments that is appropriate for processing medicinal products manufactured and cover up equipments used for manufacturing of pharmaceutical products to guarantee removal of contaminants related with former product, residue of cleaning agents as well along with manage of microbial load.

Cleaning validation master plan is a elevated depth document which establish a extensive arrangement for a complete cleaning validation project and is used as direction document to the cleaning validation project team for general guidance, resource and technical planning.

Cleaning validation master planned is prepared for manufacturing plant/ facility/ block/ site engaged in manufacturing of finished dosage forms.[5-7,18]

CONCLUSION

There is virtually unfeasible to establish that production equipment is “clean” at the point of 100%. on the other hand, it is achievable to confirm that the traces of active product left over spread from beginning to end the equipment parts are contained by an acceptable limit and that we are accomplished of detecting and quantifying these trace levels. A cleaning validation program be supposed to surround the assessment of equipment and products, assessment of the bang of a process on routine process, fortitude of an correct cleaning agent and method, fortitude of acceptance criteria for the residues, fortitude of a degree of estimate required to validate the procedure, This article be full of a defined cleaning validation course.

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