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A REVIEW ON CLEANING VALIDATION IN PHARMACEUTICAL INDUSTRY

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ABSTRACT

In pharmaceutical industry there are some possibilities of contamination and cross contamination because of improper cleaning of equipment, apparatus, processing area or the starting material, this can lead to severe hazards, therefore in pharmaceutical industry we can't afford any contamination as well as cross contamination. This can be minimized by proper cleaning of equipment, apparatus as well as the processing area. TheIndustry wants to achieve these main goals with the help of GMP. This review focused on the different types of cleaning process adapted by pharmaceutical industry, how the process of cleaning validation is done. In the cleaning validation different critical parameter, factor, material and critical process are monitored and validated so that the cleaning consistency can be achieved and documented accordingly.

Keywords: Cleaning validation, contamination, clean in place, clean out of place, swab sampling, worst case

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INTRODUCTION

Cleaning means to make any article, piece of equipment and area free from dirt, marks, or any unwanted matter. In pharmaceutical industry there is a great need of cleaning of equipment apparatus and processing area. The improper cleaning can lead to contamination and cross contamination. Pharmaceutical product can be contaminated by various materials such as residue of previously used active pharmaceutical ingredient, raw material, cleaning agents and dust particles. The main objective of GMP consist prevention of contamination and cross contamination of materials. Therefore a perfect cleaning method is required for avoiding the possibilities of contamination and cross contamination, for this a validated program is required, this program is known as cleaning validation. "Cleaning validation is documented evidence which assure that cleaning of equipment, piece of equipment or system will obtain pre-determined and acceptable limits". Cleaning validation helps in analytical investigation of a cleaning procedure. The Purpose of cleaning validation is to verify the efficacy of the cleaning methods for removal of residues of previous product, preservatives, or cleaning agents and microbial contaminants. [1, 2] Cleaning validation fulfills the requirement of regulatory bodies and maintains product quality and safety of consumer.

When Cleaning Validation is require

- When one is establishing initial qualification of cleaning method and equipment.
- If there are some major change in a cleaning method are being adopted.
- If there is a major change in master formula.
- If the cleaning substance is changed.

Cleaning Validation protocols [2, 3, 4, 5, 6,7,8,9, 10]

In the cleaning protocol the cleaning validation should be well described, the validation protocol defines all the critical method/ process, equipment, personnel and area

that can affect the effective cleaning. So a master validation plan should be prepared, that will guide the cleaning validation step by step. While preparing cleaning validation protocol some points should be considered.

1. Disassembling of equipments,
2. The pre-cleaning method which is to be used
3. A complete detail of cleaning agent which include the concentration, volume of cleaning agent required.
4. The flow rate, pressure, rinsing time and rinsing frequency should be given.
5. Complexity and designing of equipment
6. Training schedule of personnel's

Validation protocols should contain[1, 2, 3, 4]

a) Purpose of the validation study
b) Responsible person for validation study, like performer and approving authority
c) Full description of equipment to be used in cleaning which include list of equipment, make model, capacity
d) The cleaning cycle and their frequency for any equipment before and after use
e) Detailed list of all critical steps to be monitored
f) Selection of cleaning agent with all detail like solubility of material to be cleaned, safety , product removal limit, minimum temperature and volume of cleaning agent
g) Detailed Sampling procedure
h) Type of sampler
i) Volume/quantity of sample
j) Containers for sample
k) Sampling location
l) Sample handling
m) Sample storage
n) Analytical testing procedure with LOD (limit of detection)
o) The rational acceptance criteria with margin of error and sampling efficiency
p) Change control
q) Approval of protocol before the study
r) Deviation

Cleaning agent [10]

Cleaning agent is used for cleaning purpose; it may be a combination of detergent and water or other agent like chelating agents. It should have high solubility towards the product to be removed. The properties of cleaning agents are given below

a) It should not degrade the product.
b) It should be compatible with the equipment.
c) It should not cause environment hazardous.
d) It should not be a contaminant of subsequent product.
e) It should easily removable and easily available and non toxic.

Some example of solvent given below-

1. Water is universal solvent which is used in combination with surfactants
2. Organic solvent like acetone, methanol, ethyl acetate are also used
3. We can use aqueous solution of sodium lauryl sulphate or sodium dodecyl sulfate
4. The chelants solvents can also be used (ethylene diamine tetra acetic acid, nitrilo tri acetic acid, sodium hexa meta phosphate /base sodium hydroxide, potassium hydroxide)
5. We can also use some acid for example glycolic acid, citric acid etc.
6. The oxidant can also be used for example sodium hypochlorite, hydrogen peroxide

Personnel for cleaning

Personnel involving in cleaning procedure should be trained. Training should be recorded. The person should have suitable working clothing to prevent spreading the particles and dust. The direct contact between personnel and products should beavoided. [(1, 2)]

Design and construction:[3]

The buildings should be designed to minimize the potential contamination whether it is a cross contamination or microbiological. Therefore the designing and location of buildings and facilities should be constructed to facilitate the easy cleaning and easy maintenance. All parts of the equipment and area can be easily washable to minimize or reduce the chances of deposition of contaminants on broken parts, groves and open joints of equipments. The methods, critical parameter like cleaning frequency and number of cleaning cycles and cleaning procedure must be validated.

Cleaning Validation Program [4, 5, 10]

a) Selection of cleaning Level (Type)
b) Selection of cleaning method
c) Selection of sampling method
d) Selection of scientific basis for the contamination limit (acceptance criteria)
e) Selection of Worst case related to the equipment
f) Selection of Worst case related to the product
g) Establishing the storage period after cleaning (hold time study)
h) Selection of analytical method

i) Documentation

Selection of Cleaning Method [10]

1. Manual cleaning
2. Semi-automatic procedures
3. Automatic procedures
4. CIP (Clean-in-place)
5. COP (Clean-out-of-place)

Manual Cleaning Method

- It is difficult to validate
- For this extensive and detailed cleaning procedures are required
- A high quality and extensive training program is required

The risk involved in manual cleaning processes is taken care of with following:

- Proper washroom design with drying, protection and storage requirement.
- Detailed cleaning SOPs are required
- Training / Qualification of cleaning operators is required

Clean-In-Place (CIP) Method

- Cleaning of the equipment is performed in place without disassembling
- 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) Method

- 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, detergent quantity dispensed etc.

Evaluation of cleaning: [2]

Visual Cleaning Test

All parts of equipment which are in direct contact and non-contact with products should visually check and verified for cleanliness.

Spiking test

This test verifies the cleaning of equipment visibly, there should be no residue. A diluted series of the worst case are made in volatile solvent and applied on surface of test equipment, which is similar to the sample surface (e.g. 25 cm^2). The active ingredient quantity should be distributed uniformly on surface of test equipment; the test should be performed by using different concentrations and also mimicking the same test conditions using approximate volume. The solvents are then evaporated to determinethe visual limit of detection by comparingwith the test surfaces of equipment. But this limit can be affected by light intensity, surface characteristics, and method handling by operators' or operator itself. Therefore all the condition related to the test should properly match with the validation studies conditions. This test is not performed for the materials, which are Generally Recognized as Safe (GRAS).

Bracketing or Worst Case Rating[11]

In pharmaceutical industry, when we are dealing with two or more similar product and same process is being used, there is no need to validate individual equipment for the similar product, to minimize the number of validation; a single study considering the worst case or bracketing approach of validation is used.

This approach is based on scientific rationale with appropriate justification. First the grouping of substances/ products or equipment is done for similar product manufactured in same equipment.

Substances can be grouped as follows

Grouping by Product:

The formulations are grouped on the basis of the dosage form for example if a company has 5 tablet formulations, 5 ointment formulations and 5 liquid formulations. They are categorized in 3 groups; these groups can be further classified in subgroups like tablet can be classified into 2 subgroups on the basis of the manufacturing procedure (out of 5 products 3 by dry granulation and 2 by wet granulation). Likewise ointment and liquid formulation can also be classified in sub groups. After establishing formulations group and subgroups 'worst case' of each group is determined.

Grouping by Substances:

The product are grouped or categorized as they are produced in the same train substances with the same cleaning procedure. Then they categorized in subgroup as they produced in the same train substances with very low therapeutic dose and/or low batch sizes or with very low/high acceptable daily exposure (Then sub groups to be formed based on cleaning process). Once the product groups have been established the next step is determined the 'worst case' representative of each group and cleaning validation of the same. Same cleaning process is performed using same cleaning agent and other parameters, and thena worst case rating procedure is used to select the worst case, which includes:

1) The product hardest to clean (easy, difficult or medium)
2) Solubility in used solvent (soluble, very soluble, sparingly soluble or slightly soluble),
3) Lowest acceptable daily exposure (maximum limit of drug bearable by patient on daily basis)
4) Lowest therapeutic dose are considered as worst case with in group.

Cleaning Of Equipment: [5, 7, 9]

There are two types of cleaning procedure for equipment used in manufacturing.

A. Type A Cleaning Procedure for equipment
B. Type B Cleaning Procedure for equipment

Type A Cleaning Procedure For Equipment

All the parts of equipment are dismantledand transferred to washing area cleaned out of place (COP). In washing area the dismantled parts of equipment shall be cleaned with cleansing agent (i.e. 0.5% w/w SLS) or other cleaning aids as per procedure mentioned in their respective SOPs of cleaning of equipment. The non-dismantle part of the equipment should be cleaned in place (CIP) as per their respective SOPs for cleaning. The washing/rinsing water sample should be collected after visually verification by production chemists and QA and the send to Quality Control along with sample request for determination of residual drug and cleansing agent.

Type B cleaning for equipment is applied in the following conditions.

i) Batch to batch changeover of the same product having same strength.
ii) Same color and same flavor
iii) Batch to batch change over but from lower strength to higher strength.
iv) After completion of the batch.
v) After any minor breakdown, where product contact parts are not disturbed.
vi) Cleaning done after completion of preventive maintenance work if product contact parts are not contaminated, touched and disturbed.
vii) After any major break down where product contact parts are contaminated.
viii) After completion of preventive maintenance work If product contact parts are disturbed/ contaminated.

Type B cleaning procedure for equipment

All gross accumulations from equipment and area are removed. Then the equipment should be cleaned without dismantling and dust of previous product is removed with the help of vacuum cleaner. Then equipment shall be mopped with clean moist lint free cloth (moist with de-mineralized water) and later with clean dry cloth.

Instructions for Cleaning of Equipment's

The equipment is cleaned with help of respective SOPs of cleaning of that particular equipment using suitable nylon brush and cleansing agent. Then the cleansing agent is removed with potable/raw water and later rinsed with de-mineralized water. Clean dry lint free cloth or compressed air is used to dry the equipment. After completion of cleaning activity, the "CLEANED" status labels is then labeled by the production personnel and attached on equipment after that the QA personnel shall verified only after inspecting the equipment visually for cleanliness. Line clearance of equipment should be made by visually examine the equipment and should be found satisfactory if not found then repeat the clean for same.

Hold Time for Cleaning [5, 6, 7, 12]

Clean Hold Time is time duration between the completion of cleaning and the initiation of the next manufacturing operation. If hold time is not determined the cleaning of equipment vary from standard procedure and harder to clean, because the dirt on equipment becoming sticky as hold time increases. So hold time for cleaning must be evaluated.

Generally the Clean hold time for unclean should not be more than 72 hrs and for cleaned equipment it should not be 120 hrs from the date of cleaning of that equipment.

Cleaning of Area [9]

The area shall be cleaned according to the following types:

Type A cleaning for area

The whole room from ceiling to walls progressing to downwards including pallets, trolleys SOPs stand, accessories box weighing balance, air handling unit (AHU) supply/return grilles switchboards, utility pendants should be cleaned by using the vacuum cleaner and wiped with vacuum cleaner. Then the waste materials are collected, put into suitable poly bags and tied up, then accordingly labeled and sent to the scrap area. The entire room is cleaned with potable water and rinsed with de-mineralized water, and then dry duster is applied, and cleaned with disinfectant solution using wet duster or lint free cloths. All item present in room are mopped with dry duster and then with wet duster using disinfectant solution. The drain points are cleaned and sufficient volume of disinfectant is poured. The whole cleaning activity should be recorded in the cleaning record log book and specific log book of item present in the room.

Type B cleaning for area

All the dust and gross accumulations from equipment and area removed**.** Then the waste material is collected and put in suitable poly bags then tied up, labeled and sent to scrap area. The dust from the whole room from ceiling to walls progressing to downwards including pallets, trolleys SOP stand accessories box weighing balance air handling unit (AHU) supply/return grilles switchboards is removed using the vacuum cleaner and wiped with vacuum cleaner. The waste material is then collected, put into suitable poly bags, tied up, labeled and then sent to scrap area. All item present in room are mopped with dry duster and then with wet duster using disinfectant solution**.** The drain points are cleaned and sufficient volume of disinfectant is poured. The whole cleaning activity should be recorded in the cleaning record log book and specific log book of item present in the room.

Cleaning record

Cleaning activity should be recorded in approved log book for cleaning of equipment; room and specific log book of item present in that particular room are then signed with date by the operator and person responsible for that area.

Sampling techniques [13]

Sampling techniques can be used for collecting the samples from the equipment

1. Rinse Sampling.
2. Swab Sampling.

Swab sampling

1. Swab sampling is used to determine previous product residue.
2. Microbial Analysis of Swab Samples

A) Swab sampling to determine previous product residue [6, 14,15]

It is also known as direct surface sampling method. This method is based on the physical removal of residue left over a piece of equipment after it has been cleaned and dried. A swab with a solvent is applied over a surface to remove any residue, and extracted into a known volume of solvent in which the contaminant active ingredient residue is soluble. The amount of contaminant per swab is then analyzed by an analytical method of high sensitivity.

Advantages of swab sampling

1. It physically removes insoluble or poorly soluble substances from the equipment surfaces.
2. It is direct evaluation of equipment surface contamination.
3. Adaptable to wide variety of surfaces.
4. Economical and widely available.

Disadvantages of swab sampling

1. This techniquemay introduce fibers.
2. It is technique dependent of sampler.
3. Difficult to implement in complex and large vessels, pipes, valves etc.

Swab sampling:

Sampling Location and Number of Samples [10, 14]

The sample locations are dictated by worst-case conditions. The equipment's hard to clean locations are identified based on cleaning experience and the design of equipment. The number of samples should be taken into consideration, the equipment surface area, design, shape, operating principle and construction material.

Sample Surface Area [16]

The swab sampling technique is used wherever swabbing of equipment surface area is accessible. After unloading final rinse from the equipment, the swab samples are collected from the selected critical areas where the possibilities of contamination are more. The fixed quantity of disorbent is taken to collect the swab sample (Disorbent used for swab sampling shall be the cleaning agent in final rinse). The swab samples arecollectedwith the help of swab sampler from the equipment surface area (25-100 sq.cm) and dip in to the disorbent. The swabs are collected in sample bottle from all the critical sampling points and send for analysis.

Swab sampler should-

1. Swab should be compatible with the product.
2. It should allow extraction of the compound for analysis.
3. Swab should not release fibers

Fixing limits for sample:

Limit in Swab analysis:

$$S = \frac{\text{MAC x RF x 1000}}{TSA \text{ x } DV} \qquad \text{eq.1}$$

S = Allowable limit in Swab sample
MAC = Maximum Allowable Carryover
RF = Recovery Factor
1000 = Conversion Factor in to PPM
SA = Swabbed area for individual equipment.
TSA = Total shared surface area of non-dedicated Equipment.
DV = Disorbent volume.

RF: Recovery factor

The recovery of the extraction process is validated by spiking the analyte at known concentration to determine the recovery. The recommended recovery is 80%, less than 80% is needs justification. Piece of the equipment use to study recovery factor should be same material of construction of equipment used for the process.There should be evidence that samples are accurately recovered.

For example, a recovery of >80% is considered good, > 50% reasonable and< 50% questionable.

% recovered by the swab

$$= \frac{\textbf{Test result reported x 1000}}{\textbf{Known amount of product spiked}} \qquad \text{eq.2}$$

b) Microbial Analysis of Swab Samples from Equipment Surface in Production Area [17]

The method of analysis of swab sample for total microbial count, yeast mold count and pathogens is given below.

Total Microbial Count:

Swabbing/ Sampling Method of a 10cmx10cm Flat Surface (100cm^2) [18]

The swab is aseptically moistened for not more than 2 hours prior to use by a technician in a bio-safety chamber. The swab is aseptically removed from the plastic applicator tube with taking care to not touch with the shaft or the swab tip, the plastic tube is kept such a way that it remains clean and sterile.The swab with the sterile diluents pressed against the side of the diluents bottle to remove the excess diluents, leaving the swab moist, not saturated and then the swab is placed aseptically to the plastic applicator tube.

Procedure for Microbiology Swabbing Method [14]

The production chemist/QC personnel remove the swab aseptically from the plastic applicator tube, without touching the shaft or the swab tip and also the plastic tube is kept clean, sterile and handled as little as possible. A 10cm^{2}nylon template previously wiped with 70% isopropyl alcohol is placed over the area to be sampled, to ensure that the correct surface area is

swabbed. The moistened swab is placed on the test site and sampled across the entire selected surface. The swab should be hold at a slight angle to the surface and slight pressure is applied. The angle and pressure should be such as to allow as much contact between the swab head and surface as possible, without damaging the swab. The surface should be sampled using parallel strokes from right to left (horizontally) from top to bottom of sampling area, rolling the swab approximately 180^0 in a clockwise direction, ensuring the previously swabbed area is slightly overlapped. It should be ensured that the entire surface of the swab head comes into contact with the surface. This procedure is then repeated same vertically, i.e. at 90^0 to the initial swabbing. Then repeated diagonally, i.e. at 45^0 to the initial swabbing, the swab is then returned aseptically to the plastic applicator tube for QC/Microbiology laboratory for further processing.

Swabbing/ Sampling Method of an Irregular Surface [15]

Swab samples are assigned a unique sample number in QC. 4 sterile Petri dishes are taken and 1 ml of the sample is taken into each Petridis. In two Petridis, 20 ml of sterile, molten soybean casein digest agar is added and cooled to 40-45ºC and allowed to set. Then in remaining two Petri dishes, 20 ml of sterile, molten sabourauds and agar is added and cooled to 40-45ºC and allowedset. The soybean casein digest agar plates are incubatedat 30-35ºC for 5 days and sabourauds-agar plates also incubated at 20-25ºC for5 days.After the incubation period, the numbers of colonies arecounted.

Yeast and Mold Count:

For determination of yeast and mold count the previous method for total microbial count is followed except the medium. In this case sterile, molten potato dextrose agar is used.

Test for E. coli:

1ml of the sample in 5ml of sterile nutrient broth is incubated at 37ºC for 24 hrs(enrichment culture I), 1ml of this, is transferred to a sterile tube containing 5ml of MacConkeys broth and an inverted Durham tube, and incubate for 48 hrs at 35-37ºC . If the tube do not turns yellow and gas bubbles are not seen in the Durham tube this shows absence of E. coli., if this happens this shows presence of E. coli., then the secondary testcarried out in which 1ml of sample is added tube (a) containing 5ml of MacConkeys broth and an inverted Durham tube and tube (b) containing 5ml of peptone water, both the tubes are incubated for 24 hours at 43.5-44.5 º, and tube (a) observed for acid and gas production and tube (b) for indole. For indole testing 0.5ml Kovac's reagent added and shaken well and allowed to stand for one minute, if a red color layer is observed it indicate presence if E. coli.

Test for Salmonella:

1ml of enrichment culture-I is transferred to two sterile test tubes, each tube contains 10ml Selenite F broth and Tetrathionate Brilliant Green Bile Broth,then the tubes are incubated at 37ºC for 24 hrs. Then a loopful of the contents taken from tube and transferred to any two of the following media (1) Brilliant Green Agar (2) Bismuth Sulphite Agar, (3) Xylose Lysine Deoxycholate Agar, (4) Deoxycholate Citrate Agar, and incubated at 35-37ºC for 24 hrs, the presence of Salmonella colony is observed, if there is no colonies then test is complies for absence of Salmonella.

Test for *Staphylococcus aureus*:

1ml of the sample was taken to 100 ml of sterile Soybean Casein Digest Medium (enrichment culture II) and incubated at 35-37ºC for 24 hrs. Then a loopful of enrichment culture II transferred to sterile pre-incubated plates of Vogel Johnson agar, mannitol salt agar and Baird Parker agar and then observed for colonies of S. aureus. If there is presence of colonies the coagulase tests is done for confirmation of S. aureus. In this test, a colonytransferredinto a tube having 0.5 ml of mammalian plasma and incubated on water bath at 37ºC for 24 hrs. Ifthe coagulation occurs, this shows the presence of S. aureus.

Test for Pseudomonas aeroginosa:

A loopful of enrichment Culture II is streaked out and transferred to a pre-incubated plate of sterile cetrimide agar and incubated for 24 hrs at 35-37ºC and the presence of colonies is observed, if there colonies are seen, then confirmation pigment test is carried out. For this a colony is taken out on sterile Petri dish of pseudomonas agar for detection of fluorescein and pyocyanin. The Petri dish is incubated at 33-37ºC for minimum 3days. The Petri dish are then examined under UV light and looked for colonies, To detect oxidase, 2–3 drops of fresh prepared solution of 1% N, N, N1, N1-tetra methyl-4 –phenylene diamine dihydro chloride placed on a filter paper and smear with the suspect colony. If the pink color changed to purple, which assure the presence of pseudomonas aeroginosa.

Swab Recovery [19]

The swab is placed into bio-safety cabinet, a sterile tube containing 2mL sterile saline. The handle of swab isaseptically broken. Then the tube is vortexed at high speed for 2 minutes, and after this 1ml is transferred to a sterile Petri dish, 20ml molten TSA media is added to the Petri dish, and properly mixed with sample. TSA is cooled, solidified, inverted and then incubated at 30-35^0C for 5 days. The number of colony forming unit are counted and recoded, with the help of Colony Counter. 0.5ml of the liquid of vortexed tube is added to 9ml of TSB in a sterile tube and incubate (enrichment step) at 30-35^0C for 5 days. After incubation, 0.1ml of the broth is streaked onto pseudomonas-CFC selective agar plates and MacConkey agar plates to find out the presence/absence of coliforms/pseudomonas. The pseudomonas-CFC agar plates is incubated at 20-25^0C for 48 hrs, the grown colonies are suspected as pseudomonas spp. and then counted and confirmedby using Gram staining and Vitek-II system. The MacConkey agar plates are incubated at 37 ± 1^0C for 48 hrs, the grown colonies are suspected as coliforms and are counted and confirmed by using Gram staining and Vitek-II system.

Swab Negative Control

The negative control is prepared by inoculatinga separate swab directly with the sterile diluents with the same volume (0.1ml) asused to moisten the test swab and the test is performed as similar to test swab.

Acceptance criteria [14, 15]

a) Absence of Coliforms and Pseudomonads

b) The total microbial count should not be more than 100 CFU/100 cm^2, fungi count should not be more than 10 CFU/100 cm^2 and pathogens should be absent

Rinse sampling: [19, 20]

The rinse sampling technique is used for large vessels, hoses etc., (reactors, pumps, big equipment etc.). The entire equipment surface area rinsed with fixed quantity of the cleaning agent. The cleaned and dried sample bottle is taken and the sample is collect from the equipment.

Advantages of rinse sampling

a) Easy to sampling

b) Allows sampling of a large surface area and porous area.

Disadvantages of rinse sampling

a) Residues may not be distributed homogeneously.
b) Inability to detect location of residues.
c) Rinse volume is critical to ensure interpretation of results.
d) Insolubility of residues and residues
e) Physically occluded in the equipment

Limit in rinse sample: [19, 20]

$$S = \frac{MAC \times RF \times 1000}{V}$$ eq.3

Here:
S = Allowable Limit in Rinse Sample in PPM.
MAC = Maximum Allowable Carryover
RF = Recovery Factor.
V = Volume of solvent used for final rinse for all equipment

Calculation of Acceptance Criteria [21, 22, 23]

a) Health-based data

b) LD_{50}

c) Therapeutic Daily Dose

d) General Limit as acceptance criteria

a) Health-based data

$$ADE = \frac{NOAEL \times BW}{UFc \times MF \times PK}$$ eq.4

$$MACO = \frac{ADE_{previous} \times MBS_{next}}{TDD_{next}}$$ eq.5

MACO-Maximum Allowable Carryover: amount from the previous product into next product (mg)

ADE-Acceptable Daily Exposure (mg/day)

NOAEL -No Observed Adverse Effect Level (mg/kg/day)

BW -Is the weight of an average adult (e.g. 70 kg)

MF- Modifying Factor: factor -uncertainties not covered by the other factors

PK- Pharmacokinetic Adjustments

UFc- Composite Uncertainty Factor: factors which reflects the inter individual variability, interspecies differences, sub-chronic-to-chronic extrapolation.

TDD_{next} - Standard Therapeutic Daily Dose of next product (mg/day)

MBS_{next} Minimum batch size of next product(s) (where MACO can end up) (mg)

b) Based on LD_{50}

NOEL number (No Observable Effect Level) can be use for to determine MACO.

$$NOEL = \frac{LD_{50} \times BW}{2000}$$ eq.6

From the NOEL number a MACO can be calculated according to:

MACO Maximum Allowance Carryover: acceptable transferred amount from the previous product into your next product (mg)

$$MACO = \frac{NOEL_{previous} \times MBS_{next}}{SF_{next} \times TDD_{next}}$$ eq.7

BW is the weight of an average adult

2000 2000 is an empirical constant

$NOEL_{previous}$ No Observed Effect Level (mg/day)

LD50 Lethal Dose 50 in mg/kg animal.

TDD_{next} Standard Therapeutic Daily Dose of the next product (mg/day)

MBS_{next} Minimum batch size of the next product (s)

SF_{next} Safety factor

c) Based on Therapeutic Daily Dose

Apply when we have limited toxicity data.

Maximum Allowable Carryover (MACO).

$$MACO = \frac{TDD_{previous} \times MBS_{next}}{SF_{next} \times TDD_{next}}$$ eq. 8

MACO Maximum Allowance Carryover (mg)

TDD_{next} Standard Therapeutic Daily Dose of the next product (mg/day)

MBS_{next} Minimum batch size of the next product(s) (where MACO can end up (mg

$TDD_{previous}$ Standard Therapeutic Daily Dose of the investigated product

SF Safety factor

Safety factors:

Topical 10 – 100

Oral products 100 – 1000

Parenterals1000 – 10 000

d) General Limit as acceptance criteria

Upper limit for the maximum conc. (MAXCONC) of a contaminating product.

$$\mathbf{MACO_{ppm} = MAXCONx\ MBS}$$

eq.9

MBS Minimum batch size of the next product(s)

MACOppm Maximum Allowable Carryover:

MAXCONC maximum allowed conc. (kg/kg or ppm) of previous product in the next batch.

Analytical Method Selection [24]

There various analytical method are available which can used in validation of cleaning process

1. The Analytical Method is selected on the following basis.
2. The method should be highly sensitive to calculate the contamination limit.
3. It should be fast and practically performable, with in house instrument
4. A validated analytical method in accordance to ICH, USP and EP should be used.

Specific Method

In specific method we can use the chromatographic technique to analyze the residue or contamination because they arehighly specific, sensitive, and also quantitative method. These methods are very expensive and tedious.For example gas chromatography, High Performance Liquid ChromatographyTLC,etc. Chromatographic methods are the methods of choice.

Non-Specific Method

In specific method UV/visible spectrophotometric or infrared spectrophotometric methods are used the visible. The cleaning procedure is monitored by usingtotal organic count(TOC) method. It is cost effective and rapid;it has lowest detection limit (parts per billion).

Documentation

The whole cleaning procedure is then documented.These documents include validation protocol, SOPs, reports. The cleaning process is complextherefore the number of document may vary; all the critical steps in cleaning are documented. The document should carry detailed information about cleaning of equipment, which includesthe person who will clean it, cleaning schedule, previously used product, cleaninghistory, limits of residue after cleaning, test results and acceptable limits. The operator performance and effectiveness of the process is evaluatedand if theperformance of operator is not upto the mark, for this guidelines and training schedule are required and documented. Then final validation reportis prepared. In this report it is also statedweather the cleaning process is validated successfully or not. Thenthe management finally approves the report.

Revalidation Criteria [25, 26]

A close view is placed to ensure that some changes can affect the whole cleaning process are identified and recorded**.** The changes are reviewed; if they have significant effect then the change proposal is made through the change control procedure, which is documented and authorized. If the change is minor or it has no direct effect on quality of the final product may be handled only by the documentation. Revalidation is necessary when;

1. The product has less solubility than the pre-considered worst-case product.
2. The new drug has low potency than the pre-considered worst case product.
3. The equipment is change or there is any major modification, which can affect the contact surface area.
4. The cleaning agent or its concentration is changed.
5. The cleaning procedure is changed.
6. The procedure gets failed during routine monitoring.

Validation Reports

The validation report is then prepared which contains the result, conclusion and secured approval of the study.

The validation report includes the following:

1. The references/summary of the method used for cleaning, sample and test.
2. The analytical, physical and other observations of test result or reference.
3. The final conclusion with respect to acceptability of the results, and the status of the procedure(s) being validated.
4. If there is any a recommendation given on the basis of the result or information obtained during the study for example revalidation of process.
5. Approval of conclusion.
6. If there is any deviation occurred then protocol is reviewed.

FDA Requirements [27]

1. FDA requires, firm should have written SOPs with detailed cleaning procedure being used for different pieces of equipment.
2. If firm is using specific cleaning procedure for cleaning between two different batches of the same product and uses a different process for cleaning between product changes, FDA requires the written procedures to address these different scenarios.
3. The firms should have a clear written procedure to remove water soluble and water insoluble residue.
4. FDA requires the personnel responsible for performing and approving the study should comply with the acceptance criteria and the revalidation data.

5. FDA require, firms should have a validation protocols in written before performing the cleaning validation for each manufacturing machine or piece of equipment also carry the sampling procedures, and analytical methods to be used including the sensitivity of those methods.
6. The firm has to conduct the validation according to the protocols and the results should be documented.
7. The regulatory board has to approve the final validation, this express that the cleaning procedure is validated or not.

CONCLUSION

The pharmaceutical industry should be free any contaminationor cross contamination, it would be safe for the consumer. With the help of cleaning validation any department of pharmaceutical industry can achieve high degree of assurance regarding the cleaning, with this we can minimize any kind of contaminationor cross contaminationwhich ismay be any residue of previous product, substance of machine or any microbial contamination.

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