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Validating Cleaning Methods in Pharmaceutical Industries

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ABSTRACT

In the pharmaceutical industry, cleaning is a vital area that needs special focus before, during, and after any batch of manufacturing to prevent contamination and cross-contamination of the product(s). Cleaning validation refers to that something has been cleaned and that the contamination levels have been reduced to a certain ratio or below a certain target level. The main aim of cleaning validation is to assure documented evidence that a cleaning procedure has and will consistently remove all possible contamination for chemical, detergent, and microbial load to an acceptable limit. Contaminant of different type i.e. active ingredient, by-product or excipients, dust particle, residual of cleaning agent, residual of rinse water as well as microbial contamination is also of concern. This article highlights cleaning validation as a basic requirement for pharmaceutical products with an emphasis on acceptance criteria, sampling, worst-case analysis during cleaning validation.

1. Introduction

Cleaning means to make any surface, article, piece of equipment free from dirt, external particle, any residual chemicals, resting or multiplying microbes, and any unwanted matter that might be present in any part of pharmaceutical equipment or machinery, unintendedly. In pharmaceutical industries, there is a high demand for cleaning of pharmaceutical equipment and processing area so that the carryover of this unwanted matter can be minimized and kept well within limits. Wrong, irregular, unwarranted, or improper cleaning can lead to various problems from contamination to cross-contamination which will ultimately lead to adulterated products and can alter the overall pharmacological action of the product [1].

Cleaning validation implies the process adapted for cleaning and the result that has been shown to produce a reproducible, acceptable result even under the worst operating conditions. It is a documented evidence or method used to give a high level of assurance that a cleaning procedure will consistently remove residues of the active pharmaceutical ingredient of the product manufactured in a part of the equipment of either the same product or different product, excipients, cleaning material used in the cleaning process, dust particle and microbial load [2]. All the said residues are to be removed to a predetermined level to ensure that the quality of the subsequent products to be manufactured in the equipment is not compromised by the residues or waste of the previous products [3]. Cleaning validation and cleaning procedures coexist but are two separate operations and none of them is complete in absence of another. Cleaning validation and cleaning procedure are crucial as they prevent all possible contamination and cross-contamination to a minimum accepted level to ensure the safety of the drug manufactured for the patient [4].

Since cleaning validation gives a high degree of assurance that a cleaning procedure will systematically remove residues of the active ingredient, chemical agent, used detergent and microbial attribute, the understanding of cleaning validation should not be limited and misunderstood as removal of microbial load only, rather a combination of all the aspects in totality [5]. The presence of a low or limited level of microorganism is acceptable, however, certain microorganisms need to be completely removed as their presence is unacceptable in any case due to the level of pharmacological hazard that can occur in addition to the compromise with quality if they are in any percentage residing on the equipment. Different cleaning procedures are adopted for different equipment in different manufacturing units. As a result, residue contamination microbial studies are well included in cleaning validation [6]

to evaluate these microbiological risks. Hence, a complete and appropriate microbiological sampling strategy is required. Since microorganism is not introduced into the system, the emphasis for sampling is essential. This stands opposite to chemical validation wherein the equipment is introduced to chemicals (in terms of Active Chemical Ingredients and excipients) [7] and or cleaning agents as new chemicals while testing out the cleaning efficiency [8]. Therefore, it should be illustrious that the microbial attributes should not be given the same consideration as chemical residues meaning that microbial residue should not be based on a reduction to the minimum or acceptable low limits. Nevertheless, some products are contaminated even with a minute quantity of microorganisms naturally and for such products, the manufacturing equipment is required to be sanitized or sterilized. Sanitization and sterilization are separate from cleaning procedures, though [9].

Broadly, two types of contamination exist as far as pharmaceutical products are concerned. One is the cross-contamination in which one of the products as the active ingredient gets transferred to the next product. Carryover of excipients and dyes can also be problematic. On the flip side, the other type of contamination is contamination by foreign materials like microbial contamination and or incorporation of equipment parts like gasket or linings such as glass, plastic, lubricants, fiber, wipes, etc. The primary reason for cleaning validation is to have good, consistent, and effective cleaning procedures to prevent contamination of the following product [10] The total purpose of cleaning validation is to provide a pharmaceutical product with high quality that conforms with the standard of current Good Manufacturing Practice (cGMP) and to deliver the highest quality and pharmaceutical product to the patient. Cleaning validation should not engross on the satisfaction of the regulations only but also focus on the safety of the patient which should be the primary objectives [11]. To this effect, for giving the apt guidance, various international bodies have given their guidelines elaborately on this, like, GMP, ICH (International Council for Harmonization), TGA (Therapeutic Goods Administration), USFDA (US Food and Drug Administration), and the likes. The purpose of this article is to look into the whole element of cleaning validation and concentrate on the current cleaning procedure based on cGMPs and FDA regulations.

2. Requirement

The FDA requirement of cleaning the equipment before use is more than 65 years old practice in the pharmaceutical industry. In 1963, a GMP regulation was passed (part 133.4) stating that "*Equipment shall be properly maintained in a clean and orderly manner before*

and after a manufactured batch". However, the same section on equipment cleaning was included in the 1978 cGMP regulation [12]. These regulations are set out by both the FDA and EMA (European Medicine Agency) for the sole purpose of helping multipurpose industries in preventing contamination and cross-contamination by explaining different aspects of cleaning validation and to ensure the quality and safety of the pharmaceutical product for the amelioration of patient [4]. These guidelines insist on the basic requirements enlisted as under.

i. Generally written procedures or SOPs (Standard Operating Procedure) are to be made available explaining how the process is carried and its validation.

ii. The industry needs to identify the skills and or trained person responsible for executing such procedure and consenting on validation study, acceptance criteria, and the subsequent requirement of re-validation as per the requirement [9].

iii. FDA also expects industries or firm to have a written validation protocol for the studies to be performed on each manufacturing system or piece of equipment which will address issues as sampling procedure, analytical method to be use and sensitivity of these methods.

iv. Food and Drugs Administration also expect the firm to carry out a validation procedure based on this protocol and document the study results.

v.FDA expects a final report of validation protocols which is approved by the management that a said cleaning process is valid or not and the conclusion of the result should include that the residues are reduced to the accepted limit.

vi. At least 3 consecutive cleaning procedures should be performed and shown a successful result that a method is validated.

3. Cleaning Validation Protocol

A cleaning validation protocol refers to a written plan explaining the process to be validated and the way it is going to be carried out. In general, validation protocols are a sub-part of the Master Plan of Cleaning Validation [13].

3.1 Responsibilities

3.1.1 Production Supervisor

i. The production supervisor should ensure that the cleaning of production equipment is carried out following the written procedure as in the SOP (Standard Operating Procedure).

ii. To train the personnel associated with the manufacturing and cleaning process periodically on how to carry out the cleaning procedures, particularly sampling and monitor them throughout the execution.

3.1.2 Quality Control (QC) Department

The head of the quality control department is responsible for validating cleaning methods used pre and post-production of a batch.

i. **Microbiology Department:** This department is responsible for validating the method used in the analysis of microbes or microbial contamination.

ii. **Quality Assurance:** They are responsible for writing the validation protocol and report. Also, the QA department supervises and ensures that the protocol is duly followed.

3.1.3 Production Manager

The Production Manager is to check the written protocols and the final report provided.

i. **Engineering Overseer:** He is responsible for supporting the personnel on working of the equipment during the cleaning procedures of the equipment.

4. Scheme of Action

Frequently conducted activities performed on the production site help maintain the quality and give the company ability to remain validated under the following heads.

i. Cleaning and testing to be conducted on any new or repaired equipment.

ii. Failure investigation to be done to detect any failure that might compromise the quality of the product.

iii. Change control is done to manage any changes that might arise during production and it is also used to ensure that no undesired changes are done, which are not documented in the SOP.

iv. Preventive maintenance is yet another check done on the equipment while working to reduce the likelihood of equipment failure.

v.Calibration of the equipment and instrument periodically.

vi. Re-validation as and when required.

vii. Important SOPs covering cleaning and cleaning validation are revised from time to time.

viii. Visual inspection of the practical methodology followed and its resemblance with the SOP.

ix. Equipment quarantine and release [3].

5. Procedure to Validate Cleaning

It becomes crucial in the preparation of a standard procedure for cleaning to study and evaluate the design of the equipment in detail. This will give the company ability to modify the SOPs about hard-to-reach areas of the equipment and facilitate the better removal of the residues of the product last manufactured in the equipment. The discussion beneath gives a better view of the factor(s) that need special attention.

5.1 Equipment Parameters

A deep study and understanding of the make and the parts of any pharmaceutical equipment and or vessel or container used for manufacturing is of utmost importance while designing the cleaning procedure for the same. Also, the nature of the product being manufactured, particularly, the active pharmaceutical agent holds the main attention. Hereafter, a detailed discourse is given on the parameters to be considered during the preparation of a cleaning procedure for equipment.

a.General study and identification of the equipment

b.Identification of difficult to access location which is difficult to clean

c. The material used for the construction of equipment and hence the selection of the cleaning agent.

d. If there is a provision to dismantle the equipment

e. Portability of the equipment and hence the ease of cleaning

5.1.1 Residues to Be Cleaned

a. The acceptable limit of the residues, both, the product remnants and the cleaning agent.

b. Water Solubility. This will determine the ease of cleaning.

c. Periodic intervals of cleaning

5.1.2 Cleaning Agent to be selected and used

a. The cleaning agent needs to be inert and least interactive.

b. Water solubility is to be high.

c. Detergent to be used only when necessary.

d. The interference and safety issue to be analysed.

e. Effect of the cleaning agent on both human and environment to be assessed.

5.1.3 Cleaning Techniques to be Considered and Evaluated

a. Manual cleaning

b. Automatic procedure

c. Semiautomatic procedure

d. Cleaning in place (CIP)

e. Cleaning out of place (COP)

f. Cleaning circles

g. Cleaning span

5.1.4 Determination of Active Residues

a. After the manufacturing process is completed, utmost care is to be taken to ensure that proper cleaning is carried out by the trained personnel.

b. The production supervisor physically visualizes the equipment to make sure it is clean and document the procedure followed with initials, date, and time.

c. The following step is to determine the presence of active residues, if any, *via* the following steps [14].

i. The surface of the clean equipment is rubbed with a swab test kit saturated with water or methanol.

ii. The swab cotton is then transferred into a vial and the vial is closed and refrigerated for not more than 24 hours.

iii. Then the sample is sent to the quality control department for analysis using a validated method.

5.1.5 Determination of Detergent Residues

The level of detergent residues are determined by the following steps

a. The clean equipment is washed down with purified water.

b. Collected the final rinse in a clean amber glass bottle approximately 500 ml in quantity

c. The collected sample is analyzed by the QC department for chemical and microbial remnants [5].

5.2 Sampling

Usually, in cleaning validation, there are two methods of sampling, namely Direct Surface Method (*Swab Method*) and Indirect Method (*Rinse Method*).

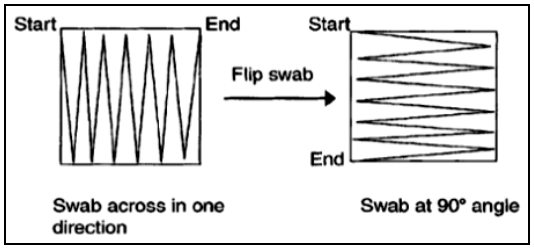

Fig. No. 1: Swabbing Technique adapted

5.2.1 Direct Surface Method or Swab Method

The swab method, as depicted in Figure 1, also called a direct method is the most widely used method of sampling invalidating a cleaning procedure. This method involves the use of nonreactive or inert material like cotton or wool while placing it on a template of a probe called a swab, rubbed the cotton on the defined surface of the clean equipment.

These swabs are transferred into dilution solvent to be analyzed using a validated analytical method for detection of the active residues of the previous product per given area in a square inch. The location from which the sample to be taken e.g. (walls, fitting, tanks, etc.) and the composition of the equipment should be put into consideration i.e. (glass, steel) in addition to the places that are difficult to reach and clean are to be identified. For microbial contamination sampling, a similar method is adapted, wherein each step carried is out aseptically and the material used is sterilized [4].

5.2.2 Indirect Method or Rinse Method

This method is explicitly used for the determination of detergent residues by rinsing a predetermined area of the equipment with purified water and the final rinse was then collected and handed over to personnel in the quality control department for analysis. This method holds the advantage of analyzing the larger surface area of the equipment and is also used in the detection of active residues for those areas that are inaccessible by the swap method. Rinse sampling is used in combination with surface sampling and strong evidence is provided to show that the samples are recovered accurately, where the recovery is rated as more than 80% as ‘good’, more than 50% as ‘reasonable’, and less than 50% as ‘questionable’.

6. Analytical Method

Analysis of the samples of the rinse collected post-cleaning of the utensils and equipment is usually done by the quality control department to quantify the degree of chemical residuum. The analytical methods used are evaluated and validated following the International Council of Harmonization (ICH), US Food and Drug Administration (US-FDA), and European Medical Agency (EMA) before the commencement of cleaning validation as per the requirement of the industry. This validated method(s) enables the detection of the residues to the accepted limit including recovery study. Some of the conventional instruments and methods employed include UV-spectroscopy, high-performance liquid chromatography (HPLC), high-performance thin-layer chromatography (HPTLC), gas chromatography (GC), enzyme-linked immunoassay (ELISA), conductivity, and the likes. These methods can be used alone or in combination with another depending on the residues to be analyzed [15].

6.1 Levels or Degree of Cleaning

The level or degree of cleaning validation required depends on the undermentioned factors

i. Nature of the contaminant (solubility, toxicity)

ii. Usage of equipment (dedicated equipment or not)

iii. Manufacturing stages (initial, intermediate, or final stage)

iv. Batch to batch change over

v. Product to product change over

In the case of potent or antibiotic drug product(s), special care has to be taken to ensure the cleanliness of the used equipment and container for the manufacturing process [17].

Dedicated equipment is those which are specific to a particular product or step while non-dedicated equipment is multipurpose equipment used for different step and product. When non-dedicated equipment is used, different cleaning procedures are incorporated depending on the steps and the nature of the product to be manufactured.

The cleaning needs for multi-use equipment must necessarily be more stringent than for a dedicated plant, but even this has to be treated to ensure that subsequent batches of the

product do not fail to meet the set specifications for purity, safety, and potency. Non-dedicated equipment results in two levels or degrees of cleaning as indicated hereafter.

6.1.1 Level 1 Cleaning

This is used in the manufacture of different batches of the same product. This can be illustrated by taking the example of the manufacture of 4 subsequent batches of paracetamol, say, batch 1, batch 2, batch 3, and batch 4; then, if the manufacture of batch 1 is followed by batch 2 in the same equipment level 1 cleaning is to be followed, which is not so rigorous [3].

6.1.2 Level 2 Cleaning

This level of cleaning is used for the equipment used in the manufacture of different products of different batches or at the end of the manufacturing stage even if the same product is planned for the next batch. The above levels of cleaning, level 1 and level 2, differ from each other in terms of their risk association, acceptance limit, degree of cleaning, and even the method of verifying the effectiveness of cleaning [16].

7. Worst Case

Cleaning validation is a lengthy process and consumes a lot of time. Pharmaceutical industries manufacture several products and many of the equipment is used in the common facility of the production area. As a result, validating the cleaning procedure becomes crucial and tedious. Hence, to justifying and reduce the burden of repeating many procedures adapted while fabricating each product to product change over, the grouping method is embraced. This method is alternatively known as the *worst-case analysis* or *bracketing method* in which some products and or equipment are considered similar for cleaning [17]. The grouping method considers the following

i. All products manufactured on the same equipment

ii. All the equipment cleaned with the same cleaning agent

iii. All equipment was cleaned with the same cleaning procedure [18].

This methods also include that the equipment can be segregated under the following heads, namely,

Grouping By Product

In this, the bracketing of the product is done based on their dosage. For instance, if a company manufactures six tablets, six liquid preparations, six ointments, then, the company will divide them into 3 groups based on their dosage form. Further, a division can be made based on the subcategories, that is, the tablet can be subdivided based on the process of their production i.e. those produce by wet granulation and those produced by dry granulation and the like. This categorization helps after the grouping then the worst case is determined for each group [19].

Grouping By Substance

Products using the same equipment and have similar cleaning procedures are grouped under a single head and then the worst-case analysis is conducted for each group.

7.1.1 Worst Case Analysis

The worst-case analysis is the name given to a procedure in which the worst outcome imaginable from each group is determined to protect the cleaning validation procedure based on the solubility of the product in water. Some of the things to be considered while selecting the worst-case analysis.

i. Solubility factor

ii. The product that is hard to clean

iii. Lowest therapeutic dose

iv. Occupation factor [20]

7.1.2 Acceptance Criteria

According to the definition of cleaning validation, it should give an assurance or confirmation that a cleaning procedure consistently removes residues of active pharmaceutical or microbial contamination to the accepted limit. The limit should practically be achievable and justifiable and the cleaning process itself should not leave a remaining cleaning detergent used. This is called the acceptance criteria [21]. During manufacturing of a product, care is taken to

chemically identify any additives or by-product(s), to avoid contamination of both active and by-product.

7.1.3 Testing Parameters

7.1.3.1 Physical Testing

In cleaning validation, physical or visual checking of the equipment by the production personnel is included as part of the acceptance criteria. This is done to make sure that there is no visually detected remaining residue on the production equipment and also a place that is hard to clean should be given due consideration [22].

7.1.3.2 Microbial Testing

There is no specific microbial testing limit prescribed by the regulatory agencies. This is because the acceptable limit differs for microbial contamination and can only be decided through risk assessment and cleaning of sterile equipment concerning non-sterile equipment. For the sterile cleaning process, the acceptable limit depends on the number of microbes and the threat they pose to the equipment which in turn depends on the number and species of the microbes e.g. the threat of spore-forming bacterial is higher than non-spore bacteria [6].

On the contrary, for non-sterile processes, the Scott Docherty formula is used to determine the quantity or number of microbes that can maximum be allowed in the finished product. This formula was devised in 1999 using a similar approach for determining chemical residues. Using a similar approach Docherty realized that quite several solid dosage forms have a USP limit of <1000 CFU/grams (colony-forming unit/grams). Docherty considered a finished product limit of 1000 CFU/grams calculating backward. He found out how many microorganisms/cm^2 should be on the surface of the manufacturing equipment to result in 100 CF/gram in the finished product. [(vii)]

7.1.4 Approach Of Acceptance Criteria

Some of the approaches used in the determination of acceptance criteria are discussed below.

7.1.4.1 Approach 1 (Dose Criterion)

While setting the limits with 'dose' as the base criteria, it is established that not more than 0.001 mg/day of the minimum daily dose of any Product - A ought to appear in the maximum daily dose of another Product - B.

Dr. Hall came up with a proposal which has been adapted for several pharmaceutical products that are set as guidance in the industrial documents given by

NOEL (No Observed Effect Level) is the amount of drug in mg that does not have any effect on human health.

$$NOEL = LD_{50} \times 70\ kg/2000 \quad \text{.....(i)}$$

where,

LD_{50} = Lethal Dose for 50% of the animal population in the study
NOEL = No observed effect level
70 Kg = Average adult dose
2000 = Constant

Now, NOEL is used to calculate Maximum Allowable Carry Over (MACO).

$$MACO\ (L1) = NOEL(A) \times MBS/SF \times TDD(B) \quad \text{.....(ii)}$$

Where,

NOEL = No observed effect level
MBS = Maximum batch size
TDD = Total daily dose
SF = Safety factor
(A) = Previous product
(B) = Incoming Product

7.1.4.2 Approach 2 (10 ppm criteria)

No active ingredient should be present in the next product more than 10 ppm.

Milligrams of active ingredient = R x S x M of Product-A permitted per L *……(iii)*

Where,

R = 10 mg active ingredient of Product - A in one kg of Product - B

S = Number of kilograms per batch of the final mixture of Product – B

L = Common equipment surface area between Product-A & Product-B expressed as sq. inches.

M = 4 inch^2/swab [23].

$$\text{MACO (L1)} = \frac{\text{Minimum therapeutic dose of product A} \times \text{Safety Factor}}{\text{Maximum daily dose of product B}} \quad \text{.....(iv)}$$

Where,

L1 = 10 mg of product A per Kg of product B

MACO limit of product A into the total batch size of Product B (L2) is calculated as per the formula

$$L2 = L1 \times \textit{minimum batch size of product B} \quad \text{.....(v)}$$

MACO limit of product A per sq cm surface area (*L3*) can be calculated by using the following formula

$$L3 = \frac{L2}{\textit{Cumulative contact surface area between the product and the equipment}} \quad \text{.....(vi)}$$

MACO limit of product A per swab area (L4) shall be calculated as per the following formula

$$L4 = L3 \times \textit{swab area } (cm^2) \quad \text{.....(vii)}$$

MACO limit of product A per rinse (L4) shall be calculated as per the following formula

$$L4\ (rinse) = \frac{\text{L3} \times \text{area rinsed}}{\text{amount of rinsing solvent}} \quad \text{.....(viii)}$$

7.1.4.3 Approach 3 (Visual Criteria)

According to visual criteria, no amount of the active ingredient or by the product is permitted to be present on the surface of the equipment after performing of cleaning procedure. The requirements for this approach are that the validated cleaning procedure is to be implemented in addition to the fact that equipment and place should be well equipped with suitable light to permit physical visualization. Therefore, the visual cleanliness of the equipment must be checked and verified after cleaning.

7.1.4.4 Calculation Based on Therapeutic Dose

Here the maximum acceptable carry over (MACO) is calculated based on Acceptable Daily Exposure (ADE) or Permitted Daily Exposure (PDE) the MACO is calculated by the calculation of your acceptable carryover based on the calculation of ADE or PDE of the previous product into the next product [24]. The formula is given as [25]

$$ADE = \frac{NOAEL \times BW}{UF_C \times MF \times PK} \quad \text{.....(ix)}$$

$$PDE = \frac{NOAEL \times BW}{F1 \times F2 \times F3 \times F4 \times F5} \quad \text{.....(x)}$$

Based on the result of ADE or PDE, MACO can be calculated using the following formula

$$\text{MACO} = \frac{\text{ADE/PDE}_{\text{previous}}}{\text{TDD}_{\text{next}}} \times \text{MBS}_{\text{next}} \quad \text{.....(xii)}$$

Where

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

ADE = Acceptable Daily Exposure (mg/day)

PDE = Permitted Daily Exposure (mg/day)

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

BW = Weight of an average adult (e.g. 70 kg)

MF = Modifying Factor: a factor to address uncertainties not covered by the other factors

F1 to F5 = Adjustment factors to account for uncertainties

TDD next = Standard Therapeutic Daily Dose for the next product (mg/day)

PK = Pharmacokinetic Adjustment

MBS next = Minimum batch size for the next product(s) (where MACO can end up) (mg) [13]

7.1.4.5 Acceptance criteria based on LD_{50}

This method of calculation is applicable when no other data is available (e.g. ADE, OEL, TDD) but LD_{50} (e.g. chemicals, intermediates, detergents), then MACO can be based upon LD_{50} data.

7.2 Microbiological Testing

Microbiological test samples should be removed according to the standard procedure laid by various regulatory agencies. Hard to reach places of the equipment are identified also for swab collection. If there is no standard operating procedure in place, a detailed written description of the process and sampling technique is laid for the quality assurance sampler [26]. All sampling details (swab, rinse, and microbiological) are to be referenced and later sent to the quality control department for analysis. Any relevant sample transfer conditions are to be kept noted.

8. Hold Time for Cleaning

The duration between the termination of cleaning and the initiation of the next manufacturing operation is technically called Clean Hold Time. On the flip side, as to hold time increases, dirt accumulated on equipment as a part of natural phenomenon gets sticky and again cleaning becomes necessary, especially for the hard to clean areas. So hold time for cleaning becomes critical. Usually, the clean hold time for any equipment should not be more than 72 hrs and for cleaned equipment, it should not be 120 hrs from the date of cleaning off that equipment.

8.1 Clean Hold Time and Dirty Hold Time

The time-lapse between cleaning the equipment and its reuse, before extra cleaning, is referred to as Clean Hold Time (CHT). Ideally, this should be included as part of the validation of cleaning procedures. The period before cleaning equipment after use is commonly called Dirty Hold Time (DHT). Attention is paid to check that routine cleaning and storage of equipment does not give a chance for the potential buildup of degradation products that may not be removed by the standard cleaning procedure [27]. Also, the potential for microbial contamination of equipment and ensuring that these potential risks are properly assessed and controlled is to be taken into consideration.

Conclusion

The main objective of pharmaceutical industries is to provide a pharmaceutical product exhibiting supreme pharmacological activities and free from any harmful contaminant that may render such product unhealthy or adulterated. Since it is next to impossible to prove that production equipment is "clean" at the level of 100% practically, cleaning validation is one of the most important processes while switching over from one product to another. A cleaning validation program comprises of the assessment of equipment and products, assessment of the impact of a process on the routine process, determination of an appropriate cleaning agent and method, determination of acceptance criteria for the residues, determination of a degree of the evaluation required to validate the procedure for chemical and microbial minimal load discretely. Surface area calculations should be performed, verified, and kept in a file for all equipment evaluated (photos may be incorporated into the protocol to ensure samples are taken from the correct position). Worst case result when recorded is less than the limit of detection for the test being performed, the value denoting the limit of detection should be used to perform the calculations.

The worth of validating the cleaning method in a pharmaceutical industry establishes why it is an essential and a regulatory requirement after the manufacture of a batch of medicines. One must be aware of the potential sources of chemical (pharmaceutical ingredient, excipients and or cleaning agents) and microbial contaminants so that master validating plan can be modulated in accordance. As well as the initial cleaning validation, monitoring should be an on-going process. This means regular reviews of cleaning parameters and periodic sampling (which can take the form of re-validation exercises) has to be well maintained as a

part of necessary documentation and prescript. Thus it becomes necessary to assure that cleaning remains consistent over time (accounting for variables like changes in personnel, training a person, alteration of equipment, abrasions on surface and so on; some of these variables will change with manual cleaning steps). When a new disinfectant is introduced for the sanitization of a clean-room, a manufacturing room, a filling or packing room, quarantine or store area, environmental monitoring needs to be conducted as part of monitoring process so that the permissible limits are met. Continuous reassessment is a required as part of an on-going environmental monitoring program and yet cleaning validation is too often seen as a stand-alone activity. In a nutshell, chemical and microbiological panorama of cleaning can readily be captured within the spectrum of cleaning validation approach.

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