REVIEW ARTICLE ON CLEANING VALIDATION – AN IMPORTANT CONCEPT FOR QUALITY MANAGEMENT IN PHARMACEUTICAL INDUSTRY

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***Abstract*: Purpose of cleaning validation is becoming more significant as we deal with potent, complicated drug substances or product and complex biotechnology products. Pharmaceutical product and APIs can be contaminated by other pharmaceutical products or APIs, by some cleaning agents, any microorganisms or by other materials e.g. dust, lubricants, raw materials. Method Mainly cleaning is performed to remove or eliminate non-product contaminating material. In pharmaceutical industries, to ensure safety, efficacy and quality of drug products, care must be taken to avoid cross-contamination, adulteration of drugs or drugs with other active ingredients, contamination of microbiological origin or contamination by cleaning or sanitizing agents or product. It includes various levels of cleaning, cleaning procedure, sampling procedure, cleaning agent selection etc to ensure the efficacy of cleaning procedures to ensure that the patients are not put at risk due to cross-contamination.**

***key words:* Cleaning procedure, Cleaning Agent, level/ degree of cleaning, case study, Acceptance limits.**

I. INTRODUCTION [1] [2]

Cleaning Validation is the method used to assure that a cleaning process removes residues of the active pharmaceutical ingredients of the product manufactured in a piece of equipment, the cleaning agent utilized in the cleaning process and the microbial attributes[1]. All residues are eliminated to predetermined levels to ensure the quality of the next product manufactured is not compromised. It is a documented evidence with high degree of assurance that one can consistently clean a system or to predetermined and acceptable limits. Cleaning validation is primarily applicable to the cleaning of process manufacturing equipment in pharmaceutical industry. However essential reason is that to produce products that are as pure and free from contamination [2]. Moreover this article include some case study releted to this and some upcoming scope of cleaning validation.

VALIDATION [3]

Validation is documented evidence which provide a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attribute [3].

TYPES OF VALIDATION [4] [5]

1) Analytical validation
2) Equipment validation
3) Process validation
(a) Prospective validation
(b) Retrospective validation
(c) Concurrent validation
(d) Revalidation
4) Cleaning validation

1 Analytical Validation: - Analytical validation is an evaluation of a product quality assign through testing to demonstrate reliability is maintained throughout the product lifecycle and that the precision, accuracy, strength, purity and specification has not been compromised [4].

2 Equipment Validation:-Validation of equipments is known as qualification.

Equipment validation is divided into 3 types:-
(1) Installation Qualification (IQ)
(2) Operational Qualification (OQ)
(3) Performance Qualification (PQ) [4].

An IQ documents specific static assign of a facility or item to prove that the installation of the unit has been correctly performed and that the installation specifications of the manufacturer have been met all the criteria. After installation it must be ensured that the equipment can deliver operating ranges as specified in the purchase order [4]. This is known as OQ. The PQ's are concerned with proving that the process being investigated works as it is supposed to do [4].

3 Process Validation: Process validation is "A documented program which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes" [4]. Process validation is divided into different types as follows:

(a) Prospective validation:-It is defined as the establishment of documented evidence that a system does what it purports to do based on pre-planned protocol. This validation is usually carried out in prior to the introduction of new drugs and their manufacturing process [4] [5]. This approach to validation is normally consider whenever a new formula, process or facility must be validated before routine pharmaceutical formulation commences [4].

(b) Retrospective validation: It is defined as the establishment of documented evidence that a system does what it purports to do based on review and analysis of historical data [4]. This is achieved by the review of the historical manufacturing testing data to prove that the process has always persisted in control [4].

(c) Concurrent validation: It is similar to prospective, beside the operating firm will sell the product during the qualification runs, to the public at its market price [5] [4]. This validation involves in process monitoring of critical processing steps and product testing. It is the repetition of a validation process or a specific part of it. This is carried out when there is any change or replacement in formulation, equipment, and plant or site location [4] [5].

(d) Revalidation: Batch size and in the case of sequential batches that do not meet product and Process specifications [4].

4. Cleaning validation: Cleaning validation is documented evidence with high degree of assurance that one can consistently clean a system or piece of equipment to predetermined and acceptable limits [4]. Cleaning validation is primarily apply to the cleaning of process manufacturing equipment in pharmaceutical industry. It is necessary to have effective cleaning programs in any place because of the regulatory requirements [4].

CLEANING VALIDATION [6] [7]

Since the 90's, the Cleaning Validation was included in requirements of GMPs .Cleaning means to make any article, piece of equipment and area free from dirt, marks, or any unwanted matter [6][7]. In pharmaceutical industry there is a high need of cleaning of equipment apparatus in processing area and any testing areas [6] [7]. The inappropriate cleaning can lead to contamination and cross contamination. Pharmaceutical product can be contaminated by various materials such as residue of previously used API as a raw material, cleaning agents and dust particles [6]. The main purpose of it is GMP consist prevention of contamination and cross contamination of materials. Therefore a perfect cleaning method is required for avoiding the possibilities of contamination , and for this a validated program is required, this program is known as cleaning validation [6][7] . "Cleaning validation is a documented evidence which convince that cleaning of equipment, piece of equipment or system will obtain pre-determined and acceptable limits"[6] . Cleaning validation helps in analytical investigation of a cleaning procedure. The Purpose of cleaning validation is to verify the potency of the cleaning methods for removal of residues of a previous product, preservatives, or cleaning agents and microbial contaminants [6] [7]. Cleaning validation fulfills the requirement of regulatory bodies and maintains product quality and safety of purchaser [6] [7].

IMPORTANCE OF CLEANING VALIDATION [8] [9]

(1)Assurance of quality & safety (2) Government regulations (3) Product integrity,(4) Microbial integrity,(5)Cross contamination integrity, (6) Batch integrity,(7) Equipment reuse(8) Reduction of quality costs (9) Making good business sense.(10) Less down time, fewer batch failures and may operate / clean more efficiently.(11)Safety: Validation can also result in increased operator safety. Properly calibrated, validated instruments and gauge used to reduce accident and results in safety. (12) Better Customer quality: Through proper validation, market recall is avoided which results in better customer care and quality of the product. Not only required to comply with regulations, but also it is mandatory to satisfy customer's requirements. It make sure the safety, identity, purity, and strength of the product which are the basic prerequisites of cGMP (Current Good Manufacturing Practice). It provides manufacturer with enough confidence that internal control is well established.

OBJECTIVE OF CLEANING VALIDATION [10]

The objective of the cleaning validation is to verify the effectiveness of the cleaning procedure for exclusion of product residues, degradation products, preservatives, or cleaning agents as well as the control of potential microbial contaminants [10]. It is necessary to Validate Cleaning procedures for the following reasons: Pharmaceutical products and API can be contaminated by other pharmaceutical products, cleaning agent and microbial contamination [10]. It is regulatory requirement in pharmaceutical product manufacture the main concern is the same-assurance that equipment is clean. Also that products quality and safety are maintained [10]. It is also assure from an internal control and compliance point of view the quality of manufacture. (1) To protect product integrity (2) To reuse the equipment [10]

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WHY AND WHEN [11] [12] [13]

Why Cleaning Validation: To verify the effectiveness of cleaning procedures and to make sure no risks are associated with cross contamination of active ingredient detergents or sanitizer[11]. A validated process is the one which has been demonstrated to provide a highest degree of assurance that uniform batches will be produced that meet the required specifications [13].

When Cleaning Validation: 1. Initial qualification of process or equipment. 2. Change in a cleaning procedure.3.Critical change in formulation .4. Significant change in formulation. 5. Change in a cleaning methods. 6. Change in a cleaning agent [12] [13].

TYPE AND MECHANISM OF CONTAMINATION [14]

(1) Cross contamination with Active Ingredient: One of the actual risk in cross contamination of active ingredients is that, after contamination the result is a multiple active ingredient product instead of single active ingredient substances. Depending on medical

effects, the contamination may enhance the action or negate the action or contaminant may have an entirely different medical and health effects [14].

(2) Microbiological Contamination: This form of contamination is particularly disingenuous because the contamination may develop at any time, even after cleaning [14]. A large contributing factor is the storage of an equipment in a wet or damp condition. This provides a natural medium in which bacteria can grow easily [14].

(3) Contamination by cleaning or sanitizing Agents: Some pharmaceutical operations may find it unpreventable to use fairly toxic and hazardous materials for cleaning purpose for obstinate residues. This is especially true in the produce of active pharmaceutical ingredients (APIs). These materials represent a potential threat as a contaminant of product [14]. It seems obvious that one effective and best way of dealing with this potential problem is to use cleaning agents with the lowest possible toxicity that will still be well organized in removing the residue in the given cleaning situation [14]. The same factors also apply to sanitizing agents used to wipe down cleaned equipments [14]

(4) Contamination by miscellaneous other materials : Regardless of the usual expected or anticipated list of potential contamination in a pharmaceutical operation, several other less likely materials can also contaminate products [14] . A partial list contains an equipment parts for instance, filling equipment bristles from brushes used in packaging excipients, paper filters, micron filters, fibers rubber particles from gloves, cleaning materials such as brush bristles, and cotton fibers from rags and wiping materials, lubricants etc [14].

METHOD

CLEANING PROCEDURE [15]

Standard cleaning procedures for every piece of equipment and process should be prepared [15]. It is important that the equipment design is figured out in detail in combination with the product residues which are to be removed, the obtainable cleaning agents and cleaning techniques or method, when determining the most beneficial cleaning procedure for the equipment [15]. Cleaning procedures should be adequately and properly detailed to avoid the possibility of any unpredictability during the cleaning process [15]. Following parameters are being considered during cleaning procedures [15].

A. Equipment Parameters to be evaluated: (1) Identification of the equipment to be cleaned (2) Difficult to clean' areas (3) Property of materials (4) Ease of disassemble (5) Mobility

B. Residues to be cleaned: (1) Cleaning limits (2) Solubility of the residues (3) Length of campaigns [15]

C. Cleaning agent parameters to be evaluated: (1) Preferable materials that are usually used in the process (2) Solubility properties (3) Environmental considerations (4) Health and safety considerations [15]. (5) Detergents available (as a general guide, minor use of detergents recommended unless absolutely required) [15].

D. Cleaning techniques to be evaluated: (1) Manual cleaning (2) CIP (Clean-in-place) (3) COP (Clean-out-of-place) (4) Semi - automatic procedures (5) Automatic procedures (6) Time considerations (7) Number of cleaning cycles[15].

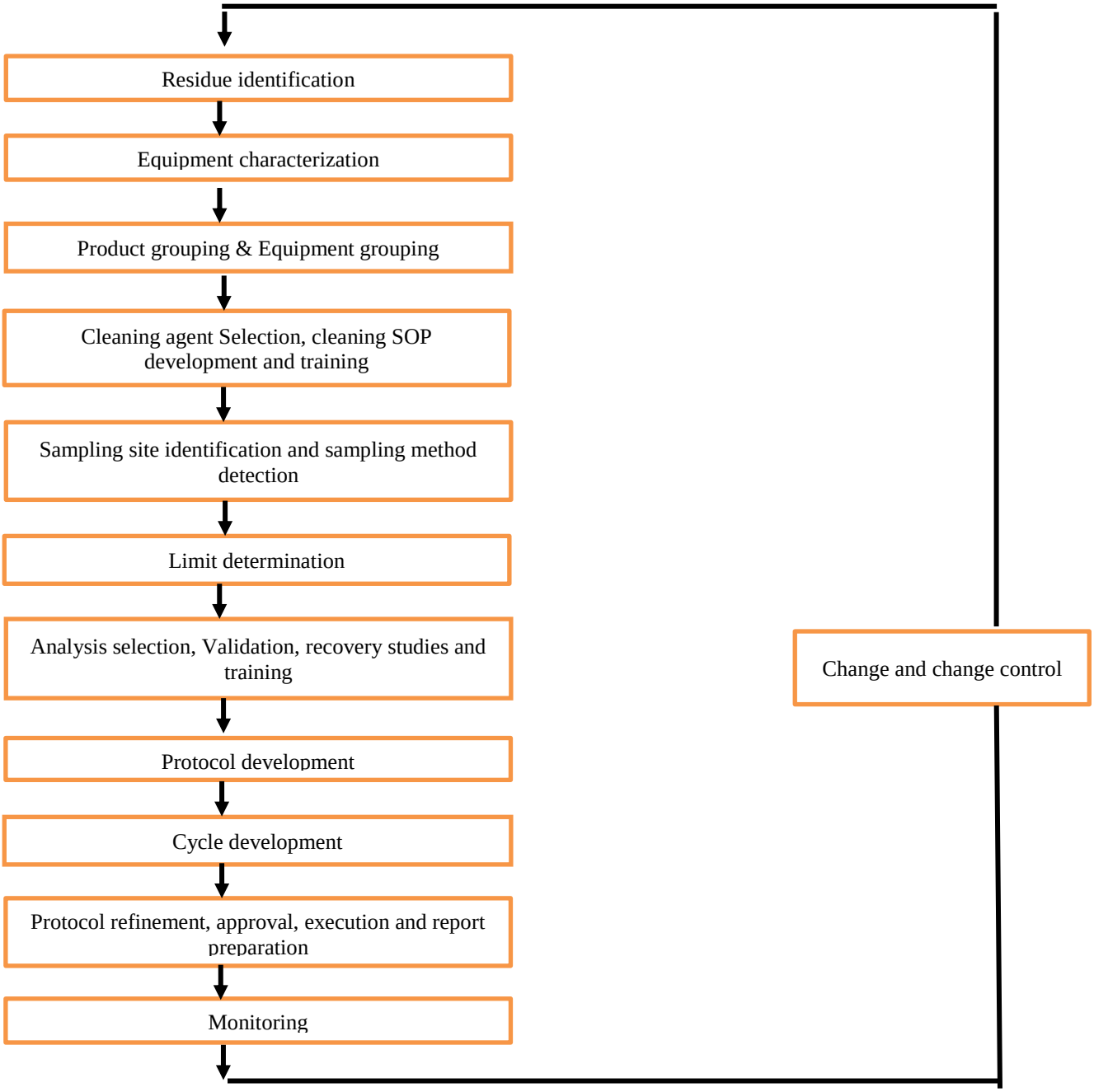

Fig 1: Cleaning validation process flow

CLEANING AGENT SELECTION [16] [17]

Cleaning agents fall into several broad categories; (1) Water (2) Solvents
(3) Commodity chemicals (4) Formulated cleaning agents.

(1)Water: It is the universal solvent. If water alone will effectively clean the product without undue time or physical effort to remove the residues, by all means water should be employed alone. For many, however the water alone requires an unsatisfactory increase in time to get the cleaning finished. So other approaches must be screened.

(2) Solvent: These are basically used in processes where solvent usage is already called for by the manufacturing process [16]. For example, mother liquors are used as the solvents for cleaning of Active Pharmaceutical Ingredients. As the mother liquors is already known to dissolve the primary residue, there is little risk in using for a cleaning.

(3) Commodity chemicals: Here, chemicals such as NaOH can be used for cleaning as well. Like their solvent counterparts, there can be danger issues, effluent issues associated with these materials [17]. Their typically high basicity or low acidity, however, often makes them helpful in inactivation processes [16] [17]. However these chemicals do not have the detergency of a formulated cleaning agent and they can be hard to rinse, taking larger volumes of water to rinse free from systems than would a formulated cleaning agent [16] [17].

(4) Formulated cleaning agent: Is the largest class of cleaners. This category consists of solvent based formulations and aqueous formulations [17]. Typically formulated cleaning agents can include one or more alkalinity or acidity sources, sequestrates, surfactants builders, chelants and either a solvent or water. For industrial uses, unlike consumer-use products, these materials are

prepared to be low foaming and therefore are more easily washable and are appropriate for high delinquency or high turbulence cleaning [16].

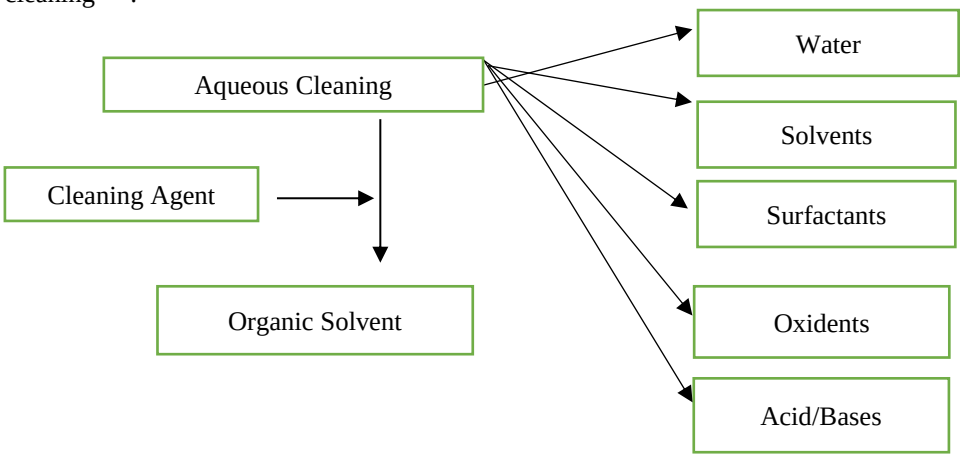

Fig 2: Cleaning Method

LEVEL /DEGREE OF CLEANING [18]

Level 1 Cleaning: This is used between manufacturing of different batches of the same product. Example – In a manufacturing Campaign for Product X, there are 3 Batches to be manufactured [18]. Batch A, Batch B, and Batch C for a given equipment &/or equipment train, if batch A in the campaign is to be followed by Batch B in the campaign, then a level 1 cleaning is required[18] .

Level 2 Cleaning: This level is used between manufacturing of different Batches of different Product and / or at the end of manufacturing operation even if same product is planned for the next operation [18]. The above two degree or level of cleaning varies from each other in terms of the degree of risk associated with it, acceptance limit, and degree of cleaning & method of verifying the cleaning process as shown in Table 1 [18]. In addition the CEFIC-APIC (Europian Chemical Industry Council-Active Pharmaceutical Ingredients Committee) guide to cleaning validation recommends three levels of cleaning that may be applied. This approach is outlined in the table below, yet it should be mentioned that additional levels might be necessary depending on the nature of the process and requirement shown in table 2 [18] .

Table 1 Comparison between levels

Factor	Level 1	Level 2
Risk	lowest	highest
Acceptance limit	Highest	Lowest
Degree of cleaning	Less extensive	More extensive
Verification of cleaning	Visual inspection	Analytical testing

Table 2 CEFIC-APIC guide to cleaning validation

Level	Thorough level of cleaning	Cleaning validation
2	Left over of the previous product is critical cleaning required until predetermine stringent left over limit are met	essential
1	Left over of the previous product is less critical cleaning should reduce the potential left over to a less stringent limit as required for level 2	Increase from not required to necessary
0	Only gross cleaning if left over of the previous product is not critical	Not required

SAMPLING TECHNIQUES [19] [20] [21] [22] [23]

Generally there are main three types of sampling. Amongst the most advantageous method is the direct method of sampling the surface of the equipment, other methods being used are swab sampling, rinse sampling and placebo sampling [19].

(1) Direct surface Sampling: This technique involves the determination of the type of the sampling material used and its impact on the test data to check the intervention of the sampling material with the test [19]. Therefore, early in the validation programme, it is essential to assure the sampling medium and the solvent if they are acceptable and be readily used [20].

Advantages of direct sampling: (1) Areas hardest to clean and which are reasonably reachable can be evaluated (2) Leads to establish a level of contamination or residue per given surface area. (3) Residues that are the "dried out" or are insoluble can be sampled by physical removal [21].

Disadvantages of direct sampling: (1) There is no physical removal of the contaminant. (2)The rinsing solvent may not reach unapproachable or occluded part of equipment. (3) This method uses organic solvents for the water insoluble materials [19].

Significance: completed by using FTIR or photoelectron emission technique.by using this technique spectra obtained from residue remaining on the surface will unswervingly quantity and quality of the surface.

(2) Swab sampling: After cleaning the equipment, product contact surfaces could be swabbed to assess surface cleanliness [21]. Swabs used should be compatible with the active ingredients and should be not interfere with the assays and results. They should not cause or result in any degradation of the compound [20] [21] .The solvents used for swabbing should supply good solubility for the compound and should not cause degradation [20].

Advantages of Swab Sampling: (1) Economically and widely available. (2) May allow sampling of a defined area. (3) Dissolve and physically remove sample. (4) Adaptability to wide variety of surfaces. (5) Valid to active, microbial, and cleaning agent residues [21].

Significance: It require materials which are absorptive & to physically wipe the surface and recover the analyte.

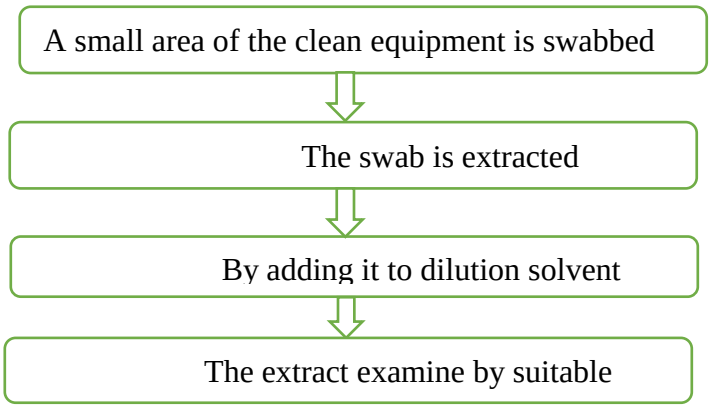

Fig 3: Method of swab sampling

Limitations: (1) Swab material and design can inhibit recovery and specificity of the method [19]. (2) Evaluation of complex, complex and hard to reach areas difficult [20] (3) An Invasive technique that may introduce fibers. (4) Results may be technique dependent [21].

(3) Rinse Sampling: Sampling and testing of washed samples for residual active ingredient is a commonly accepted method to evaluate cleanliness. This is a kind of convenient method in many cases and requires control over the solvent used for rinsing, the contact time and the mixing involved. The solvent which is used should be chosen based on the solubility of the active ingredient and should either mimic a subsequent batch of product or at least provide enough solubility [21].

Advantages: (1) Ease of sampling. (2) Evaluation of entire product contact surface. (3) Convenience of all equipment parts to the rinsing solvent. (4) Best fitted to sealed or large scale equipment and equipment which is not easily or regularly dis-assembled.

Limitations: (1) Restricted information about actual surface cleanliness in some cases. (2) Inability to detect location of residues. (3) Rinse volume is critical to assure accurate interpretation of results. (4) May reduce test sensitivity. (5) Residues may not be homogenously distributed. (6) May be difficult to correctly define and control the areas sampled, therefore usually used for rinsing an entire piece of equipment, such as vessel [21].

Significance: This Technique does not work mechanical action on the surface and the sample is composed as a final rinse**.**

(4) Placebo Sampling: Placebo is recognized as both potential cleaning techniques and potential sampling techniques [22]. Placebo ingredient comprises of all typical excipients but not the active ingredient. The principle involved in this it is passed through the same pathway as the product [22]. Therefore, it has the likelihood to scrub off residual product along those pathways. It is mainly depends on;

1. Solubility of active in placebo [23]
2. Appropriate contact time of the placebo for collecting respected sample.
3. Coverage of the placebo in process pathways to ensure removal of the placebo from all equipment location [23]
4. Quantity of the placebo and residue should be in detectable range and the distribution of residue uniformly in the placebo ensures the detection of sample in any portion of the placebo [23].

Significance: Placebo is documented as both potential cleaning method and potential sampling technique. Material comprise all typical excipient but not active ingredient.

(5) Coupon sampling: Coupons of the same materials of construction as the item to be cleaned can be affixed to the equipment, spiked with the product, subject to the cleaning procedures and then submitted to the laboratory for direct analysis and recovery studies [23].

Advantages: (1) Allows for direct surface sampling. (2) Useful in cleaning method development. (3) Reduced variability in recovery. (4) Useful in evaluation of equipment materials of construction.

Limitations: Coupon may not be representative of equipment contamination or cleaning as it is separate from primarily surface. (1) Invasive (2) Might interfere with the cleaning process.

ANALYTICALS METHOD [24]

The analytical methods should be validated before the cleaning validation is performed and the methods selected should be detect residuals or contaminants specific for the substances being assayed at suitable level of cleaning [24] .The detection limit for each analytical method should be sufficiently sensitive to detect the established suitable level of the residue or contaminants[24] .Some of

the analytical methods which can be used for the analysis of cleaning validation Samples include: (1) HPLC (2) GC (3) HPTLC (4) TOC (Total Organic Carbon) (5) UV spectroscopy (6) pH (7) Conductivity (8) ELISA[24]
These methods can be used alone or in combination depending upon the analysis required.
There are two analytical methods which are used to detect any compound [24].
1) Specific Method: This method detects a unique compound in the presence of potential contaminants. Examples are High liquid chromatography (HPLC), Atomic absorption, and other chromatographic methods [24].
2) Non-specific Method: This method detects any compound that produces a certain response. Examples are Total Organic Carbon (TOC), pH, Titration and Conductivity [24].

ESTABLISHMENTS OF LIMITS [25] [26] [27]
The rationale for selecting the limits for product residues should be logically depend on consideration of the materials involved and their therapeutic dose[25] [26] . The limit should be practical, achievable and verifiable. The rationale for the residue limit established should be logical [26] [27].Each situation should be assessed respectively. The approach for setting limits can be: **1)** Product specific cleaning validation for all types of products **2)** Grouping into product families and choosing a "worst case" product **3)** Grouping products according to risk, e.g. very soluble products, products with same potency, highly toxic or difficult to detect products [27].
Acceptance Criteria

Table 3 Acceptance Criteria

SR NO	Testing parameter	Acceptance criteria
1	Physical determination	The equipment should be visually clean i.e. no residue should be visible on equipment after cleaning
2	Chemical determination	a) NMT 0.1 % of the normal therapeutic dose of any product to appear in the maximum daily dose of the subsequent product. b) NMT 10 ppm of any product to appear in the next Product (basis for heavy metals in starting materials). c) For certain allergic ingredients, penicillins, cephalosporin's or Potent steroids and cytotoxic, the limit should be below the limit of detection by best available analytical methods.
3	Microbial contamination	Total aerobic counts a) NMT 10 cfu/100 ml by rinse method. b) NMT 5 cfu/25 cm2 by swab method.

DOCUMENTATION OF CLEANING VALIDATION [28] [29]
(1) Detailed cleaning procedure(s) are to be documented in SOPs [28]
(2) A Cleaning Validation Protocol is required to explain how the cleaning process will be validated it should include in the following The objective of the validation process: (a)Responsibilities for performing and approving the validation study, (b)Description of the equipment to be used (c)The interval between the end of production and the beginning of the cleaning procedure (d)The number of lots of the same product, which could be manufactured during a campaign before a full cleaning is done (e) Detailed cleaning procedures to be used for each product, each manufacturing system or each piece of equipment. (f) The number of cleaning cycle to be performed consecutively, (g) Any routine monitoring requirement.(h) Sampling procedures, including the rationale for why a certain sampling method is used (i) Clearly defined sampling locations [28] (j) Data on recovery studies where appropriate, (k)Validated analytical methods including the limit of detection and the limit of quantitation of those methods (l)The acceptance criteria, including the rationale for setting the specific limits [28] (m) Other products, processes, and equipment for which the planned validation is valid according to a "bracketing" concept (n)Change Control Re-validation[28].
(3) Depending upon the complexibility of the system and cleaning processes, the amount of documentation necessary for executing various cleaning steps or procedures may vary [28].
(4) When more complex cleaning procedures are required, it is important to document the critical cleaning steps [28]. In this regard, important documentation on the equipment itself which includes information about who cleaned it, when the cleaning was carried out, the product which was previously processed on the equipment being cleaned should be available[29]. However, for relatively simple cleaning operations, the mere documentation that overall cleaning process was performed might be sufficient.
(5) Other factors such as history of cleaning, residue levels found after cleaning, and variability of test results may also dictate the amount of documentation necessary. For example, when variable residue levels are detected following cleaning, particularly for process that is believed to be acceptable, one must be establish the essential of the process and of the operator performance [29]. Appropriate evaluations must be made, and when operator performance is deemed a problem, more extensive documentation (guidance) and training may be required [29]. A Final Validation Report should be prepared.
(6) The conclusions of this report should state if the cleaning process has been validated successfully. Limitations that apply to use of the validated method should be defined (for example, the analytical limit at which cleanliness can be determined). The report should be approved by management [29].

CASE STUDY

Case study 1: (POLYESTER SWAB) [30]

Case study 1 include the issue related to polyester swab than used in cleaning process in pharmaceutical industries. This issue raised by one pharmaceutical customer and according to his report company did testing and publish this article

Cleaning is the main concern in pharmaceutical industries, one small mistake can lead to the batch rejection as well as health of patients. When using swab for sampling care must be taken to ensure the product extracted from the swab themselves do not interfere with the sampling method. Sometimes materials extracted from the swabs can cover the presence of the contaminants collected from the equipment surface as they are detected in the same manner as the contaminant of interest. Recently such situation happened with pharmaceutical end user. They were using a competitor's polyester swab for cleaning validation, extracting the swabs with a solvent blend and analyzing the solvent extract using HPLC. In running a "blank" on the competitor's swabs (extracting clean swabs with the solvent blend and analyzing them by HPLC), they detected a peak in the chromatogram at the same wavelength of light as the product they were interested in measuring in the sample swabs used to clean the equipment. This peak inform that something was being extracted from the clean, unused swab that had a similar light absorption as the contaminant they were trying to be analyze. This blank signal was not consistent, so they could not simply subtract the blank amount from the amount determined for the swabs used in the analysis. They asked if we had a swab that would not have extractable products that would hinder with their analysis.

The common observation when using polyester swabs. Polyester fabric will contain extractable "oligomers" which are short chains of the ester molecule but much smaller than the polyester molecule. These oligomer contaminants are easily extracted from the polyester fibers by many of the solvents commonly used in such analyses. The oligomers that can be extracted will usually be different for swabs from different a manufacturer, reflecting different sources of the polyester material used in the swab construction, and different oligomers will have different light absorption wavelengths. In the present case the oligomers extracted from the competitor's polyester swab just happened to absorb light at the same wavelength as the contaminant for which the customer was testing, so the oligomer absorption interfered with the customer's analyses.

To solving this problem the consumer had a choice of trying a different swab from a different manufacturer or using a cleaner swab, which would aid in reducing the total amount of oligomer extractable in each sample. If a various manufacturer's swab is used it is likely the source of the polyester material used in the swab construction would be different and different oligomers would be extracted. These different oligomers may have a light absorption wavelength that would be different from the wavelength with which the consumer is worried, so there is no interference with the customer's analysis procedure. It is possible to use a specific cleaning procedure to temporarily minimize the amount of oligomer contamination in the competitor's swab, even though the offending peaks would return slowly over time, equiring repeated treatment of batches of swabs used in the analysis.

In summary such issues with the materials using sampling procedures occur frequently and must be taken into account when designing a cleaning validation procedure. The choice of materials used in the analysis can sometimes effect the accuracy of the analytical procedure and complicate the performance of the procedure.

Case study 2: (DEXAMETHASONE CREAM) [31]

In order to achieve a reliable degree of quality, the pharmaceutical industry needs to introduce a quality control system that includes cleaning validation of equipment. This study include cleaning validation on the dexamethasone cream production line. The case study involved evolution of the cleaning procedures for the dexamethasone cream.

If cleaning procedures are inadequate the next batch of product may contain API precursors, the active ingredient, solvents and other materials used in the manufacturing process, micro-organisms, as well as cleaning agents and machine lubricants. The cleaning process used to prevent such contamination from batch to batch must be shown to be effective in control of these contaminants from the previous production batch. Validation is achieved by swabbing or rinsing the process equipment and analyzing extracts of the swabs or rinse water for the contaminants of interest. Samples are collected at 13 points involving the reactor, the colloidal mill, the industrial blender, the mixer and the packaging machine, for each of the batches. Samples were collected for study of the residue of active ingredient, of detergent, and for microbiological analysis.

Cleaning was shown to be within the parameters (acceptable level = 9.95 µg/mL) for: residues of active ingredient, TOC, pH, conductivity and microbiological contamination. Similarly, microbial bioburden was < 25 CFU/swab the acceptable limit.

The method adopted to get rid of insoluble drug residue and microorganism from the cream and ointment production facility was successful. The method is simple as indicated by the results of the 3 cleaning cycles. It was thus concluded that the strategy adopted for cleaning validation was simple, efficient and capable of being applied to other kinds of pharmaceutical products.

Case Study 3: (CLEANING WATER SYSTEM CAPACITY) [32]

In order to achieve a reliable degree of quality, the pharmaceutical industry needs to introduce a quality control system that includes validation of the cleaning of equipment. This case study carried out by the Company that was performing manual cleaning for various pieces of process equipment.

Though manual cleaning was generally suitable for the nature of the company's operations, the company did experience variations in cleaning effectiveness in spite of its best intentions to standardize the cleaning procedures. The company tried to perform cleaning validation before addressing the sources of variability. When audited, this approach was not acceptable to the FDA, resulting in repeated observations.

The cleaning validation program received FDA's positive feedback only after company performed formal studies to investigate the variation in parameters such as high/low temperature, high/low pressure, and high/low flow rate of the cleaning water that was available in various shifts. The company was trying to standardize the cleaning procedures only by standardizing the duration of

various cleaning steps like pre-rinse time, detergent application time, detergent wash-off time, and final rinsing time without giving consideration .The variability in operating parameters of the cleaning water at different times of day.
This is an example of an approach where the company rushed to the cleaning validation (stage 2) before fully understanding and establishing the cleaning processes (stage 1).

SCOPE AND CHALLENGES OF CLEANING VALIDATION IN CIP SYSTEM [33] [34]

Scope and approaches of cleaning systems during clean in place systems, a comprehensive validation scheme supposed to be pursued which contains: Plan, Do, Check, Act (PDCA) methodology for obtaining ultimate results
The goal of cleaning validation is to establish and undertaken the dispensation or management of dealing apparatus should be sanitized and washed off time-after-time and, it is employed with cleaned of product, chemicals, microorganisms, to stop direct cross-contamination of hazards between the developed drug products. The EHEDG (Europian Hygienic Engineering and Design Group) guidelines which based on the concept of "Cleaning validation in the Food Industry- General Principles" are a brilliant resource to exploit when monitoring the CIP validation project charter.

CHALLENGES AND ADAPTABILITIES OF CLEANING VALIDATION [34]

A list of adequate machineries are used for examination and collection of data for uniform performance decisive factor, metrics which will be considered at each stages of following parameters like qualification of equipments, evaluation of hazards, sampling process, analytical techniques, CVP, cleaning validation report and its procedures etc. In execution of data's: Data is collected, according to fixed collection of methods, guidelines (in addition to health and safety) timeframe, as described in the project charter. In checking criteria's: the collected data is compiled and is compared with a sequential past records and also against performance and measurement criteria's. Any deficiencies can be addressed and retested prior to the CIP system can be validated. The cleaning validation master plan including policy components, diverse corrective and preventive actions are highly needed to facilitate and congregate the requisite standards. Ultimately these PDAC cycle acceptance limit, including its rationale, special cleaning validation protocols and adapted techniques are tremendously recommended for monitoring, absolute verification, and change control/revalidation performance. Now days CIP professionals are recommended in pharmaceuticals, biotechnology, and food industries that employ the rapid arrangement of data collections, comprehensive analysis of master plans, through efficient cleaning protocols. This methodology can emphasize about many zones for improvements in drug safety, environmental impact and satisfies level of "OEE". Eventually a documented report to be created once the CIP system has been productively and successfully validated as per the recommended FDA and ICH Q9 guidelines (Risk- Mapp baseline guide) which assign a science based limits for APIs .

CONCLUSION:

This review based article concluded that cleaning validation is a documented process that proves the effectiveness in cleaning of pharmaceutical equipment. It is requisite to have effective cleaning program in place because of the regulatory requirement. Cleaning validation programme should be followed on a regular basis and whenever it is essential to ensure that each and every equipment and all the parts of equipments are cleaned. More fundamental reason is that to produce products that as pure and free from contamination. And the main purpose of cleaning validation is to establish documented evidence with a high degree of assurance that one can consistently clean a system to predetermined and acceptable limits. This article covers all aspects related to cleaning validation like acceptance criteria for the validation, cleaning procedure, different levels of cleaning, sampling procedure, and cleaning agent selection.

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