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Cleaning Validation in Pharmaceutical Industry

Kalpana Zore[1], Sandhya Kadam[2], Dr. Vivekkumar Redasani[3]

Student[1], Assistant Professor[2], Principal[3]

Department of B. Pharmacy

YSPM'S Yashoda Technical Campus, Faculty of Pharmacy, Wadhe, Satara–415001

Corresponding Author's Email: *kalpanazore2020@gmail.com*

Abstract

The goal of this review is to establish the significance of cleaning validation in the pharmaceutical industry. Pharmaceutical product and active pharmaceutical ingredients (APIs) can be contaminated by other pharmaceutical products or APIs, by cleaning agents, by microorganisms or by other materials e.g. air borne particles, dust, lubricants, raw materials, intermediates, etc. Cleaning procedure is the process of assuring that cleaning procedures effectively remove the potentially dangerous substances from equipments. This can be minimized by proper cleaning of equipment, apparatus as well as the processing area. So it is necessary to validate the cleaning procedures to ensure safety, efficacy, quality of the subsequent batches of drug product and regulatory requirements in Pharmaceutical product manufacture. It briefly provides an overview on mechanism of contamination, cleaning mechanisms, cleaning agents, procedure of cleaning, and sampling techniques.

Keywords*: Cleaning validation, Objective of cleaning validation, cleaning mechanism, cleaning agent, cleaning validation program, cleaning methods, sampling technique. Revalidation*

INTRODUCTION

Validation is a term that first appeared in the United States in 1978.The concept of validation has expanded through the years to embrace a wide range of activities from analytical methods used for the quality control of drug substances and drug products to computerized systems for

clinical trials, labeling or process control. Validation is founded on, but not prescribed by regulatory requirements and is best viewed as an important and integral part of cGMP.1 Cleaning validation is documented evidence with a high degree of assurance that one can consistently clean a system or a piece of equipment to predetermined and acceptable limits.

The objectives of good manufacturing practices (GMP) include the prevention of possible contamination and cross contamination of pharmaceutical starting materials and products.[2]

Cleaning validation in a Manufacturing process has to be designed and carried out in a way that it prevent cross-contamination as much as possible. Since most pieces of equipment are being used to manufacture different products, cleaning procedure must be able to remove residues from equipment to an acceptable level.[3]

In pharmaceutical industry there is a great need of cleaning of equipment apparatus and processing area. Cleaning validation helps in analytical investigation of a cleaning procedure. The basic reason behind the process of good, effective, consistent cleanliness is to avoid contaminated substance of product made in the same equipment. The purpose is to provide high quality pharmaceutical products to our patients.[4]

Cleaning validation is documented evidence with a High degree of assurance that one can consistently clean a system or a piece of equipment to Predetermined and acceptable limits. The objectives of good manufacturing practices (GMP) include the Prevention of possible contamination and cross-Contamination of pharmaceutical starting materials and products. Pharmaceutical products can be contaminated by a variety of substances such as Contaminants associated with microbes, previous Products (both active pharmaceutical ingredients (API) and excipient residues), residues of cleaning Agents, airborne materials, such as dust and Particulate matter, lubricants. Adequate cleaning Procedures play an important role in preventing Contamination and cross-contamination. Validation Of cleaning methods provides documented evidence That an approved cleaning procedure will provide Clean equipment, suitable for its intended use.[5, 6]

DEFENITION [7, 8]

- To attain documented evidence, which provides a High degree of assurance that the Cleaning Procedure can effectively remove residues of a Product and a cleaning agent from the Manufacturing equipment, to a level that does not Raise patient safety concerns.
- Cleaning validation is a documented process that proves the effectiveness and consistency in cleaning A pharmaceutical production equipment
- Validations of equipment cleaning procedures are mainly used in pharmaceutical industries to prevent Cross contamination and adulteration of drug Products hence is critically important

OBJECTIVE OF CLEANING VALIDATION [9]

It is to prove that the equipment is consistently cleaned of product, detergent and microbial residues to an acceptable level, to prevent possible contamination &cross-contamination.

WHEN CLEANING VALIDATION IS TO BE PERFORMED?[9]

- It is not necessarily required for non-critical cleaning such as that which takes place between batches of the same product (or different lots of the same intermediate in a bulk process) or of floors, walls, the Outside vessels.
- It should be considered important in multi-product facilities and should be performed among outside vessels Equipment, sanitization procedures & garment washing.9
- Initial qualification of process/ equipment.[10]
- Critical change in a cleaning procedure.
- Critical change in formulation.
- Significant change in formulation.
- Change in a cleaning process.
- Change in a cleaning agent [10]

ADVANTAGE OF CLEANING VALIDATION [11]

- Assurance of quality & safety.
- Government regulations.
- Product integrity,
- Microbial integrity,

- Cross contamination integrity,
- Batch integrity,
- Equipment reuse,
- Reduction of quality costs.
- Making good business sense.
- Less down time, fewer batch failures and may Operate / clean more efficiently.

Contamination & Cross Contamination: [12]

Generally cross contamination and contamination by a foreign material are two types of Contamination. Cross contamination is usually through an active ingredient from one product carrying over into subsequent manufactured Product. However, carryover of other product Component such as excipients can also be Problematic and may degrade and final quality of Product. Contamination of one batch of product with significant level of residual active ingredient from a previous batch may pose obvious problem To consumer or patients from unintended Contaminants. Potential clinically significant synergistic Interaction between pharmacologically active Chemical is a real concern. Inert ingredients used in Drug product are generally recognized as safe for Human consumption and for routine use also. Maintenance and cleaning of equipment provide the potential for contamination with items such as Equipment parts and lubricant. Chemical cleaning Agent and piece of cleaning tools can cause Problems ranging from poor pharmaceutical Elegance to exceeding acceptable levels of Particulate matter in parenteral products to inadvertent inclusion of toxic compounds in the Product. In addition, some activities are adversely affected by trace contaminants and may exhibit Change in stability or bioavailability if exposed to Such contamination. The second type of contamination is by foreign Material these may be bacterial in nature or could represent part of the equipment. Maintenance, Cleaning, and storage condition may provide adventitious microorganisms with the opportunity To proliferate with in processing equipment. This could pose obvious problems for sterile products Manufacture (generation of high level of pyrogens, Decreasing the assurance of sterile achieved by Equipment sterilization procedures etc.) It also Possess serious problem for the manufacture on Nonsterile dosage form particularly unpreserved Products which support microbial growth.

CLEANING MECHANISM:[13, 14, 15, 16, 17, 18, 19]

Several basic mechanisms exist to remove residues from equipment; including Mechanical action refers to physical actions such as

- Brushing
- Scrubbing
- Pressurized water to remove particulates.

Dissolution: involves dissolving residues with a Suitable solvent. The most common and practical Solvent is water because of its advantages:

Water is non-toxic, cheap, does not leave residues, and is environment friendly. However, in some cases it may be preferable to use a Non-aqueous solvent or a combination of both Aqueous and non-aqueous solvents due to the Solubility characteristics of the materials. Alkaline or acidic solvents, for example, can enhance Dissolution of the materials and could be Advantageous.

Detergency: requires the use of surfactant, usually in an aqueous system. Detergents act in four different Ways**:**

- wetting agents
- solubilizers
- emulsifiers, and
- dispersants.

Usually detergents posses all these properties which Broaden their action.

Chemical reactions: Such as oxidation and hydrolysis in which the residues are chemically changed.

Example: Sodium Hypochlorite.

Cleaning is the process of removing an unwanted substance or contaminant from a manufacturing surface. There are a number of mechanisms that remove or assist in the removal of contaminants from equipment surfaces.13

The various cleaning mechanisms include:

Dispersion:

Dispersion involves the wetting followed by desegregation and then the formation of suspension of solid particles in water. This mechanism is like emulsification, difference is dispersion being used for cleaning of solid residues.14

Solubilization:

Solubilization is basically same as solubility the difference is it involves the addition of some substance to pure solvent to make the residue soluble, such as addition of surfactant to the purified water or pH modifier to make residue in the ionized or unionized hence soluble.15

Solubility:

Solubility here is the dissolution of the contaminant in a liquid medium or solvent. For instance some component (salt) might be soluble in water while other in hexane. However the rate of solubility, insoluble form left and solvent used for cleaning is considered in solubility.16

Emulsification:

This process basically involves the breaking an insoluble liquid residue into tiny droplets and then making those droplets suspended throughout the water or any other specific solvent.17

Hydrolysis:

This involves the cleavage of different bonds in an organic molecule. Hydrolysis is a very effective cleaning procedure because it converts the large water insoluble molecule into smaller water soluble molecule because the smaller molecule formed is slightly more polar but the resultant hydrolyzed residues might be either water soluble or solubilize at the pH of the cleaning solution. Thus after the hydrolysis cleaning with water or any other solvent with specific pH may be used.18

Oxidation:

Oxidation involves the cleavage of various organic bonds by the strong oxidizing agent such as sodium hypochlorite. The oxidants cleaves organic molecule at various linkages in the larger molecule which leads to small molecules that are more polar and increase the water

solubility of the degraded components. The effect is similar to that of hydrolysis, except that the phenomenon of oxidation is more universal (and less specific) than hydrolysis.19

Cleaning Agent: [20]

There is a variety of cleaning agent options available to pharmaceutical companies for their Cleaning processes. It may be a combination of detergent and water or other agent like chelating Agents. The properties of cleaning agents are given below;

1. It should not degrade the product.
2. It should be compatible with the equipment.
3. It should not cause environment hazardous.
4. Should not be a contaminant of subsequent product.
5. It should easily removable and easily available and non toxic.

Organic Solvents, including solvents such as acetone, methanol, and ethyl acetate, are most commonly used. Water serves as a solvent and a s a medium for other functional processes, including Hydrolysis, emulsification, and dispersion. “Surfactant” is short for “surface active agent. “ Surfactants used for cleaning generally have a Hydrophilic polar end and a lipophilic no polar end. The function of a surfactant is for wetting Surfaces (of both the residue and the surface to be cleaned), Solubilization, emulsification, and Dispersion. Chelants are products like EDTA (ethylenediaminetetraacetic acid), NTA (nitrilo triacetic acid), and certain polyphosphates (like sodium hexametaphosphate) that chelate or tie up certain metal ions In aqueous solution. Chelants can be important for any cleaning operation where hard water ions (calcium and magnesium) are present. The presence of chelants may also help remove trace amounts of iron from the system, thus reducing any tendency for a stainless steel system to rouge. Dispersants are generally charged, relatively low molecular weight polymers (such as Polyacrylates) that assist in suspending solids in water. They are generally used with surfactants, which assist in wetting of solid particles so that they can be effectively dispersed and carried away. Builders include a variety of alkaline salts, such as trisodium phosphate, sodium silicate, and Sodium carbonate. These builders serve to improve the detergency of surfactants.

Cleaning Agent selection [21,22]

Cleaning agents fall into several broad categories;

- Water.
- Solvents.
- Commodity chemicals.
- Formulated cleaning agents.

- **Water:** It is the universal solvent. If water alone will efficiently 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 unacceptable increase in time to get the cleaning finished. So other approaches must be screened.

- **Solvent:** These are basically applied in processes where solvent usage is already called for by the manufacturing process. For example, mother Liquors are used as the solvents for cleaning of APIs. As the mother liquor is already known to dissolve the primary residue, there is little risk in using it for cleaning.

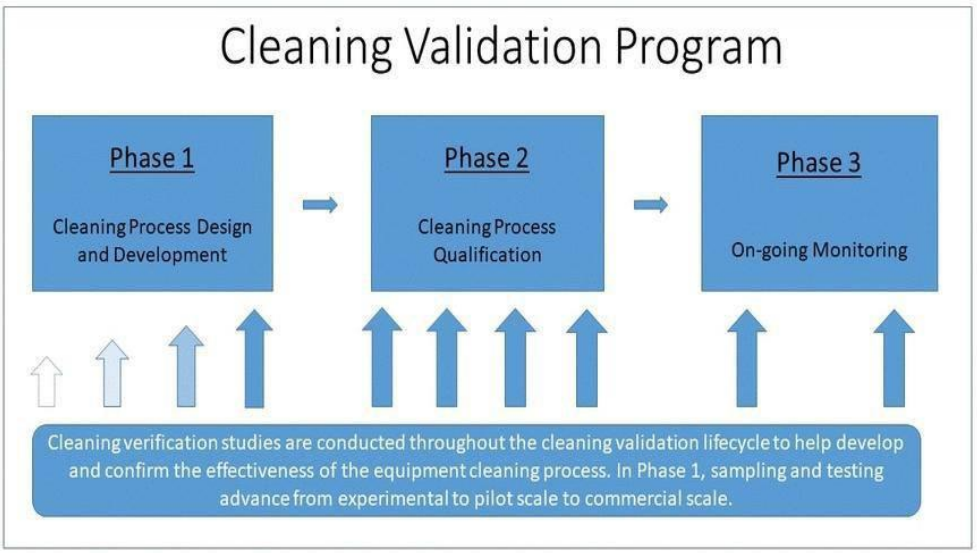
- **Commodity Chemicals:** Here, chemicals such as NaOH can be used for cleaning as well. Like their solvent counterparts, there can be Cleaning Issues, effluent issues associated with these materials. Their typically high Basicity or low acidity, however, often makes them helpful in inactivation Processes. However these chemicals do not have the detergency of a Formulated cleaning agent and they can be difficult to rinse, taking larger Volumes of water to rinse free from systems than would a formulated Cleaning agent.

- **Formulated Cleaning Agent:** Is the largest class of cleaners. This category consists of solvent based formulations and aqueous formulations. Typically Formulated cleaning agents can include one or more alkalinity or acidity Sources, sequestrants, 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 rinsable and Are appropriate for high delinquency or high turbulence cleaning (Lakshmana et al., 2010)21; (Agalico et al., 2008)22;

CLEANING VALIDATION PROGRAM [23,24,25,26,27,28,29,30]

- Selection of cleaning Level (Type).

- Selection of cleaning method.
- Selection of sampling method.
- Selection of Worst case related to the equipment.
- Selection of Worst case related to the product.
- Establishing the storage period after cleaning (hold time study).
- Selection of analytical method
- Documentation



SELECTION OF CLEANING LEVEL (TYPE)[23]

TYPE A: MINOR This type of cleaning take place Between two batches of same product or between Different strengths of the same product. For minor Cleaning, cleaning validation is not required, since Cross contamination is not an issue.

TYPE B: MAJOR This type of cleaning take place Between two products. In this case, validation of the effectiveness of the Cleaning procedure in removing residues to the required level is mandatory.

SELECTION OF CLEANING METHOD[24]

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

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.

Manual Cleaning Method

- Difficult to validate
- Most extensive and elaborate 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 SOP
- Training / Qualification of cleaning operator's

SELECTION OF SAMPLING METHOD [25]

Generally there are two types of sampling that are Accepted. The most desirable is the direct method of sampling the surface of the equipment, another Method being the use of rinse sampling.

Rinse samples (indirect method): This method is based on the analytical determination of a sample of the last rinsing solvent (generally Water) used in the cleaning procedure. The volume of solvent used for the last rinse must be known to Allow for the quantitative determination of the Contamination.

Advantages

- Ease of sampling.
- Evaluation of entire product contact surface.
- Accessibility of all equipment parts to the rinsing Solvent.
- Best fitted to sealed or large scale equipment and Equipment which is not easily or routinely disassembled.

Disadvantages

- No physical removal of the contaminant.
- The rinsing solvent may not reach inaccessible or occluded part of equipment.
- Use of organic solvents for water insoluble Materials.

Swab sampling: It is also known as direct surface sampling method. This method is based on the physical removal of Residue left over on a piece of equipment after it has been cleaned and dried. A swab wetted with a Solvent is rubbed over a previously determined Sample surface area to remove any potential residue, and thereafter extracted into a known volume of Solvent in which the contaminant active ingredient Residue is soluble. The amount of contaminant per Swab is then determined by an analytical method of adequate sensitivity.

Advantages

- Direct evaluation of surface contamination.
- Insoluble or poorly soluble substances may be physically removed from the equipment surfaces.
- Hard-to-clean but accessible areas are easily incorporated into the final evaluation.

Disadvantages

- Difficult to implement in large-scale manufacturing Equipment.
- Extrapolation of results obtained for a small sample Surface area to the whole product contact surface Area

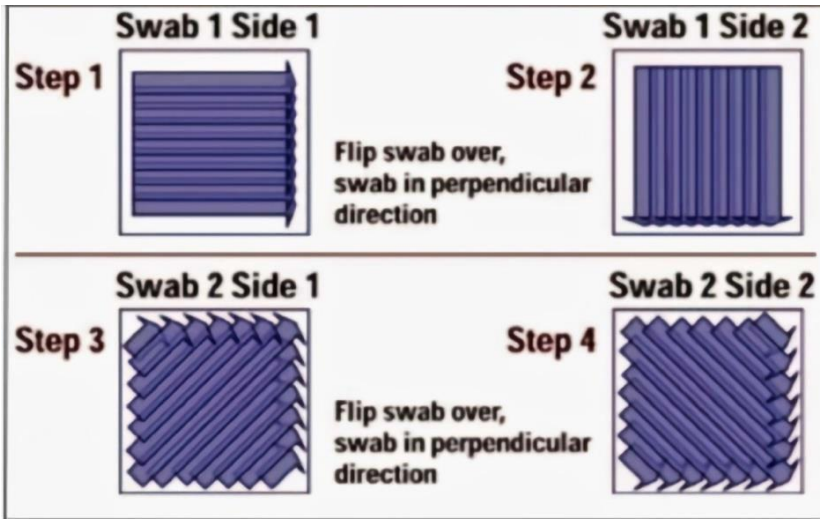


Figure: 1 Recommended direction's and motions of swabbing

Sampling Method Selected: Looking at the advantages and disadvantages of both The sampling methods swab sampling method was Selected. The cleaning procedure uses water as a Solvent and we have dosage forms having active Ingredient which is insoluble in water.

Sampling location and number of samples: 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 Take into consideration the equipment surface area, Design, shape, operating principle and construction Material.

Sample Surface Area: Sample surface areas usually vary from 25 sq.cm to 100 sq.cm.

Swab Recovery Study: A swab recovery study is performed to determine the ability of the swab to quantitatively remove the Contaminant from the surface sampled. Once the acceptance limit of cleaning validation is determined swab recovery study should be carried out. Product solutions of 50%, 100% and 150% of the Acceptable limit of area are prepared and spiked on the model surface equivalent to the swab surface Area. Surface is dried under gentle airflow. Surface Is sampled as per the standard swabbing technique, Which will be used for sampling. The swab is tested As per the Validated Analytical procedure.

Test result reported

% Recovered by the swab= ----------X 100

Known amount of product spiked

There should be evidence that samples are accurately recovered. For example, a recovery of > 80% is considered good, >50% reasonable and < 50% questionable. Recovery factor shall be taken into consideration while calculating the Acceptable limit for residue.

SELECTION OF WORST CASE RELATED TO THE EQUIPMENT:[26]

Bracketing by equipment should be done only when it is similar equipment, or the same equipment indifferent sizes (e.g. 300-L, 500-L and 1000-L tanks). An alternative approach may be to validate the Smallest and the largest sizes separately. The worst case for a group of equipment is represented by the equipment with the larger Product contact surface and the hardest-to-clean Locations.

SELECTION OF WORST CASE RELATED TO THE PRODUCT: [27]

Only one product out of a group of product Processed in a piece of equipment is selected for the Cleaning validation study, based on the lowest Solubility of the active ingredient and its therapeutic Dose.

ESTABLISHING THE STORAGE PERIOD AFTER CLEANING (HOLD TIME STUDY) :[28]

The objective for establishing time limit between Equipment cleaning and reuse is to ensure that the Equipment remains clean till the next use. This needs Demonstration that there is no microbial Proliferation in cleaned equipment during storage. For establishing the time limit, the equipment should Be dried. Initial swab samples for surface should be taken. Thereafter, the equipment should be Protected as prescribed in the SOP and stored in its designated area. Periodic samples of product contact Surface for microbiological contamination should be taken. (1st day, 2nd day, 3rd day etc.)Based on the data generated establish the Acceptable time limit.

SELECTION OF ANALYTICAL METHODS:[29]

1. There are many analytical techniques available that can be used in cleaning validation The Basic Requirements for the Analytical Method.
2. The sensitivity of the method shall be appropriate to the calculated contamination limit.
3. The method shall be practical and rapid, and, as Much as possible use instrumentation existing in the Company.
4. The method shall be validated in accordance with ICH, USP and EP requirements.
5. The analytical development shall include a Recovery study to challenge the sampling and

testing Methods.

SPECIFIC METHODS

- Chromatographic methods such as GC, HPLC Etc.
- Thin layer chromatography
- Specific ion meter of the above methods, chromatography methods Are the methods of choice, as they separate analytes, are highly specific, highly sensitive, and quantitative. But the methods are costly and time consuming.

NON-SPECIFIC METHODS:

- Spectrophotometric methods in the visible, Infrared, or UV ranges
- Total organic carbon (TOC)
- Other Methods

For monitoring cleaning procedure TOC method is Used. It offers at a moderate cost and in addition to Its rapidity, a detection capability down to the ppb Range.

DOCUMENTATION: [30]

1. Detailed cleaning procedure(s) are to be documented in SOPs.
2. A Cleaning Validation Protocol is required to define how the cleaning process will be validated.

It should include the following:

1. The objective of the validation process.
2. Responsibilities for performing and approving the validation study.
3. Description of the equipment to be used.
4. The interval between the end of production and the beginning of the cleaning procedure.
5. The number of lots of the same product, which could be manufactured during a Campaign before a full cleaning is done.
6. Detailed cleaning procedures to be used for each product, each manufacturing system or Each piece of equipment.

7. The number of cleaning cycles to be performed consecutively.
8. Any routine monitoring requirement.
9. Sampling procedures, including the rationale For why a certain sampling method is used.
10. Clearly defined sampling locations.
11. Data on recovery studies where appropriate.
12. Validated analytical methods including the Limit of detection and the limit of Quantization of those methods.• The acceptance criteria, including the Rationale for setting the specific limits;
13. Other products, processes, and equipment for which the planned validation is valid According to a “bracketing” concept.
14. Change Control/ Re-validation.

3. Depending upon the complexity of the system and cleaning processes, the amount of Documentation necessary for executing various Cleaning steps or procedures may vary.

4. When more complex cleaning procedures are required, it is important to document the critical Cleaning steps. In this regard, specific 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. However, for relatively simple cleaning operations, the mere Documentation that the 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 required. For example, when Variable residue levels are detected following Cleaning, particularly for a process that is believed to be acceptable, one must establish the effectiveness of the process and of the Operator performance. Appropriate evaluations must be made, and when operator performance is deemed a problem, more extensive Documentation (guidance) and training may be required.

6. A Final Validation Report should be prepared. The conclusions of this report should state if the Cleaning process has been validated successfully. Limitations that apply to the use of the validated Method should be defined (for example, the Analytical limit at which

7. Cleanliness can be determined). The report should be approved by management.

Revalidation Criteria: [31, 32]

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;

- Product has less solubility than the pre-Considered worst-case product.
- The new drug has low potency than the pre-Considered worst case product.
- The equipment is change or there is any major
- Modification, which can affect the contact surface Area.
- The cleaning agent or its concentration is changed.
- The cleaning procedure is changed.
- The procedure gets failed during routine Monitoring.

CONCLUSION

This review based article Concludes that cleaning validation is a documented Process that proves the effectiveness and Consistency in cleaning of pharmaceutical Equipment. It is necessary to have effective Cleaning program in place because of the Regulatory requirement. However, more Fundamental reason 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 Or a piece of equipment to predetermined and Acceptable limits. And this article primarily covers all aspects related to cleaning validation like Mechanism of cross contamination, different levels of cleaning, cleaning procedure, sampling Procedure, product grouping and equipment Characterization, cleaning agent selection, elements of cleaning validation.

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