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Review Article

Cleaning Validation for the Pharmaceuticals, Biopharmaceuticals, Cosmetic and Neutraceuticals Industries

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Abstract

Cleaning and cleaning validation are two activities that have the largest opportunity to prevent patient risk by assuring that no cross-contamination can occur. Ineffective cleaning can lead to adulterated product, which may be from previous product batches, cleaning agent or other extraneous material introduced into generated by the process. Cleaning validation is becoming more and more important as we deals with potent, complicated drug substances and complex biotechnology products. This article will over all the element of cleaning validation.

Keywords: Validation, Cleaning Validation, Pharmaceuticals

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1. Introduction

Cleaning valdation: It 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.[2] The prime purpose of validating a cleaning process is to ensure compliance with federal and other standard regulations. The most important benefit of conducting such a validation work is the identification and correction of potential problems previously unsuspected, which could compromise the safety, efficacy or quality of subsequent batches of drug product produced within the equipment.[3]

History

Cleaning validation has come a long way since the days of the Barr Laboratories Court Case and since the first FDA guidelines referencing the subject of cleaning validation were published in 1991. At that time, the requirements for cleaning validation barely filled a single page of the Bulk Pharmaceutical Chemical and Biopharmaceutical guidance documents. Those documents were then expanded to create the Guide to Inspection of Cleaning Validations by FDA (first published in 1992 as a Mid-Atlantic Inspection Guidance, then reissued as an FDA guidance document in 1993). GMP

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regulations have their basis in cleaning validation. Beginning in 1906 with Upton Sinclair's "The Jungle," the people demanded that the government improve cleanliness practices in the processing of food giving rise to what we know of today as the cGMPs for both food and drugs. While cleaning has always been part of the GMP regulations. The GMPs that we follow today were predominantly written in 1978. References to cleaning and documentation associated with cleaning can be found throughout. As with many other areas of validation, however, there is no explicit reference to cleaning as a process to be validated. The GMPs that was challenged in the Barr Laboratories court case. In that decision, Judge Wolin ruled that cleaning did require treatment as a process and therefore required validation. In 1996 proposed revisions to the GMPs were drafted by the FDA; although not adopted, these revisions proposed to redefine the manufacturing process as beginning with a cleaning operation. When the FDA published "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach" in August of 2002, and reported on their progress in September 2004 and validation was reinforced in pharmaceutical manufacturing. Although risk-based decision-making in the establishment of scientific rationales was always a cornerstone of cleaning validation requirements, efforts have been renewed to ensure the incorporation of risk analysis documentation in cleaning programs.[1]

Objective

The objective of the cleaning validation is to verify the effectiveness of the cleaning procedure for removal of product residues, degradation products, preservatives, excipients, or cleaning agents as well as the control of potential microbial contaminants. It is necessary to Validate Cleaning procedures for the following reasons:

- Pharmaceutical products and API can be contaminated by other pharmaceutical products, cleaning agent & microbial contamination.
- It is regulatory requirement in pharmaceutical product manufacture the concern is the same-assurance that equipment is clean and that product quality and safety are maintained.
- It is also assure from an internal control and compliance point of view the quality of manufacture.
- To protect product integrity
- To reuse the equipment

Need for cleaning validation

To verify the effectiveness of cleaning procedures and to ensure no risks are associated with cross contamination of active ingredient or detergents.

WHY Cleaning Validation[4]

- Initial qualification of process/ equipment.
- Critical change in a cleaning procedure.
- Critical change in formulation.
- Significant change in formulation.
- Change in a cleaning process.
- Change in a cleaning agent.

Essential Programs that maintain the validated state and their required elements:

- Cleaning and testing, if any, to be conducted upon the introduction of new or repaired equipment

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- Monitoring of cleaning after validation completion
- Routinely conducted compliance initiatives on site that maintain quality and will affect the company's ability to maintain the validated state
- Failure investigation
- Change control
- Preventive maintenance
- Calibration
- Revalidation
- Important SOPs Governing Cleaning and Cleaning Validation
- Development of cleaning SOPs (especially for manual cleaning operations) Equipment cleaning and use logs
- Visual inspection requirements for cleaned equipment
- Equipment quarantine and release
- Equipment sampling procedures for cleaning assessments (e.g., swab, rinse, etc.).

Level of Cleaning: The level or degree of cleaning and validation required for the manufacturing process of drug substances mainly depends on:

- Usage of equipment (dedicated equipment or not)
- Manufacturing stages (early, intermediate or final step)
- The nature of the potential contaminants (solubility toxicity etc.)

In case of Drug Products: Different cleaning situation may arise during the manufacturing of drug products, such as;

a. Batch to batch changeover cleaning.

b. Product to product changeover cleaning

In case of non-dedicated drug product manufacturing facility, different cleaning procedures may exist depending on the manufacturing step and nature of the next manufacturing step to be followed in the same equipment. This results in two different levels of cleaning as explained below.

Level 1 Cleaning:

This is used between manufacturing of different batches of the same product.

Example – In a manufacturing Campaign for product A, there are 3 Batches to be manufactured as shown below.

Batch 1 Batch 2 Batch 3

For a given equipment &/or equipment train, if batch 1 in the campaign is to be followed by Batch 2 in the campaign, then a level 1 cleaning is required.

Level 2 Cleaning:

This is used between manufacturing of different Batches of different Product and / or at the end of manufacturing campaign even if same product is planned for the next campaign.

The above two degree or level of cleaning differs from each other in terms of the degree of risk associated with it, acceptance limit, degree of cleaning & method of verifying the cleaning process.

Table No. 1 Comparison Between levels

Factors	**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

In case of Drug Substance:

Different cleaning situation may arise during the manufacturing of drug products, such as:

- Batch to batch changeover cleaning

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- Changeover from early steps to intermediate of same product.
- Changeover from intermediate of one product to intermediate of another product.
- Changeover from intermediate of one product to final stage of another product.
- Changeover from one final product to another final product
- In case of non-dedicated drug substance manufacture

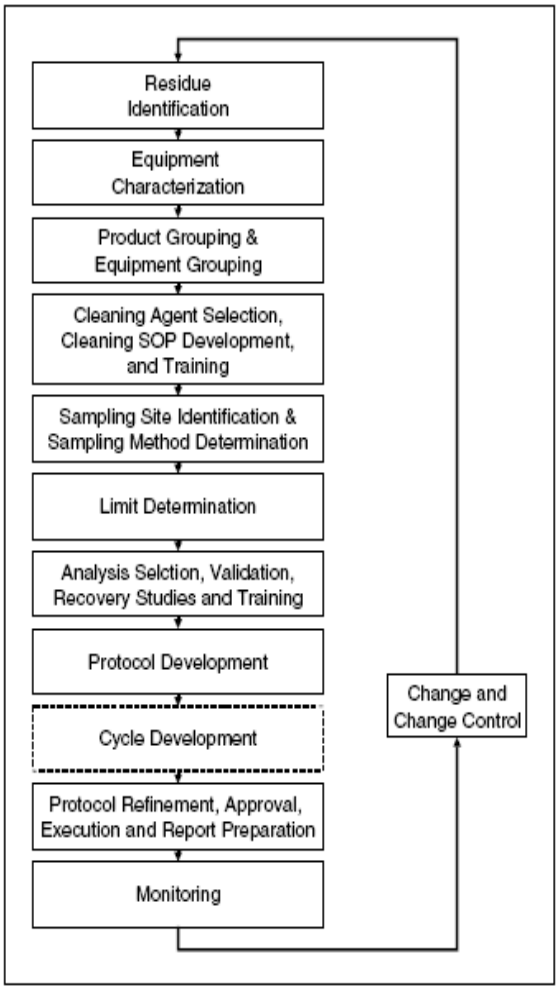


Figure No. 1 Cleaning validation process flow

CLEANING VALIDATON MASTER PLAN

Master Plan should[1]:

- Provide an overview of the site/facility/area that is governed by the Master Plan
- Provide an overview of the typical manufacturing process that are to be performed in the area and the dosage forms that are produced
- Provide an overview of the types of cleaning that are to be used (e.g., automated Clean-In-Place or Clean-Out-of-Place, semi-automated cleaning or manual cleaning)
- Provide the responsibilities of the various departments having a role in cleaning validation activities
- Provide the minimum requirements for the cleaning validation program, including:

Elements of Cleaning Validation:

1. Residue selection
2. Equipment characterization
3. Cleaning agent selection
4. Limits calculation
5. Product grouping
6. Equipment grouping
7. Cleaning procedure
8. Sampling
9. Analytical methods
10. Validation protocol
11. Validation report

Residue Identification: When performing cleaning validation there are a number of residues that must be considered:

1. API
2. Constituents of the cleaning agent
3. Preservatives
4. Precursors or starting materials
5. Intermediates
6. Processing aids
7. Media

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8. Buffer
9. Cellular debris or metabolites
10. Particulate
11. Bioburden
12. Endotoxin
13. Viral particles
14. TSE
15. Excipients
16. Colorants, dyes, flavors or fragrances
17. And many more.

If we have the advantage of using a nonspecific method for cleaning assessment (e.g., TOC, pH, conductivity), we may be able to use a single analytical method to look for all (or most) types of residues.In yet other instances, it is desirable to use a specific analytical method (e.g., HPLC, IMS, and, FTIR), which, by definition, requires that we select the residue(s) of interest to the cleaning validation.

Potential Residues:

a. Precursors of the drug substance.
b. By-products and/or degradation products of the drug substance.
c. Product from previous batch.
d. Solvents and other excipients employed during manufacturing process.
e. Microorganism
f. Cleaning agents and lubricants.

Equipment characterization

Cleaning validation involves not only the removal of residues but also gives assurance that each and every piece of equipment associated with the process has been cleaned to acceptable levels. It is typically referred as train based approach. The equipment train is series of equipment through which the product or products move as they progress through the manufacturing process. In order to asses that the equipment is cleanable or not it should be characterized in such a way that its design features are well known. Equipment characterization can assist cleaning validation initiatives in many ways:

- Promote more effective cleaning procedure by identifying cleaning challenges and ensuring that they are addressed in the cleaning methods employed.
- Identifying hard to clean locations and high risk locations in equipment for the purpose of sampling site selection.
- Target materials of construction that will be included in sampling recovery studies and those that will not be included.
- Isolate materials that will be disposed of at the end of a production process and/or will be dedicated to a single product.
- Verify that all materials of construction are compatible with the selected cleaning agents and temperature that will be used with the cleaning process
- Collect product contact and sample site surface areas for the purpose of calculating limits and results.
- Confirm similar geometries, capacities, and use of process equipment for the purpose of grouping that equipment.

Cleaning Agent Selection: All cleaning processes rely on the principle of TACT and WINS

TACT:

Time, Action, Concentration/Chemistry, Temperature or TACT are the process parameters that are required to be controlled in any cleaning process, whether manual, semi-automated or automated. Changes in one TACT parameter will cause a commensurate increase or decrease in the other parameters. In all cases, however, the correct balancing of the TACT parameters

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requires proper knowledge and understanding of WINS:

WINS:

Water, Individual, Nature of the Soil, Surface, WINS represents the parameters that affect the soil's removal from the surface and each parameter can affect your ability to apply TACT in a given situation. Cleaning chemistries fall into several broad categories[1]:

- Water
- Solvents
- Commodity chemicals
- Formulated cleaning agents

Current approaches in determining the acceptance limits for cleaning validation[9,10,11]:

Approach 1 (Dose criterion): Not more than 0.001 of minimum daily dose of any product will appear in the maximum daily dose of another product. Milligrams of active ingredient = I x K x M in product A permitted per J x L 4 inch2 swab area

I = 0.001 of the smallest strength of product A manufactured per day expressed as mg/day and based on the number of milligrams of active ingredient.

J = Maximum number of dosage units of product B per day

K = Number of dosage units per batch of final mixture of product B

L = Equipment surface in common between product A & B expressed as square inches.

M= 4 inch2/swab.

2. Approach 2 (10 ppm criterion): Any active ingredient can be present in a subsequently manufactured product at a maximum level of 10 ppm. Milligrams of active ingredient = R x S x U in product A permitted per T 4 inch2 swab area.

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

S = Number of kilograms per batch of final mixture of product B

T = Equipment surface in common between product A & B expressed as square inches.

U = 4 inch2/swab.

3. Approach 3 (Visually clean criterion): No quantity of residue should be visible on the equipment after cleaning procedures are performed.

Grouping of equipment[1,8]: All equipment must be:

- Used to produce products from the same product group
- Cleaned with the same cleaning agent
- Cleaned with the same cleaning method
- Equivalent in terms of position or role in the manufacturing process
- Similar functionality Similar design (e.g., **Product Grouping and Equipment Grouping:** It is a method by which products or equipment is considered to be similar or equivalent for the purpose of cleaning validation. When considering similar, a worst case area of the instrument or site is selected for demonstrating cleaning validation. When considering equivalent, any area of the instrument or site may be selected as representative of any other area of the instrument or site. Bracketing, a term that appear in EU GMP Annex on cleaning validation, has an equivalent meaning to grouping, although it may include an added burden for testing the extremes of population. Grouping may be used to simply prioritize cleaning validation studies or may be used to eliminate some of the numerous possible combinations of product and equipment studies that might otherwise need to be performed.

Grouping for products[1,8]: All products must be :

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- Manufactured on the same equipment group Cleaned with the same cleaning agent
- Cleaned with the same cleaning procedure Grouping considerations for products include: Similar patient risk levels (e.g., therapeutic indication, potency, toxicity for drugs/ devices/ nutraceuticals/ cosmetics)
- Similar formulations
- Similar manufacturing processes cleaning validation must always be carried out to meet the lowest limit of the entire product group.
- geometry, materials of construction, capacity)

Worst Case Rating:

- Solubility in subjected solvent
- Maximum Toxicity
- Minimum Therapeutic Dose
- Difficult to Clean
- Lowest Limit based on therapeutic dose / toxic data, batch sizes, surface areas, etc

Cleaning Procedures:

Standard cleaning procedure for each part of equipment and process should be prepared. It is important that the equipment design is evaluated in detail to remove the product residues. Following parameters are to be considered during cleaning procedures:

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 disassembly
5. Mobility

B. Residues to be cleaned

1. Cleaning limits
2. Solubility of the residues
3. Length of campaigns

C. Cleaning agent parameters to be evaluated

1. Preferable materials that are normally used in the process
2. Detergents available (as a general guide, minimal use of detergents recommended unless absolutely required)
3. Solubility properties
4. Environmental considerations
5. Health and safety considerations

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

Sampling Technique

Sampling sites was selected based on the difficult clean geometries of the equipment and these locations are inaccessible i.e. their inaccessibility makes them difficult to clean therefore, before choosing for sampling sites one must be conscious in selecting the desired sampling locations. Equipment is characterized into hot spots and critical sites. Hot spot is the location that is likely to become dirty during the manufacturing process and it is difficult to clean. Critical sites are those locations if remain dirty will certainly show disproportionate level of contamination to the next exhibit batch. The common sampling method employed in cleaning validation is rinse sampling, Direct surface sampling and swab sampling[5,6].

Direct surface sampling

It involves the determination of the type of sampling material used and its impact on the test data to check the interference of the sampling material with

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the test. Therefore, early in the validation programme, it is crucial to assure the sampling medium and solvent
if they are satisfactory and be readily used. It is done by using FTIR or photoelectron emission techniques. By employing these techniques, specific spectra obtained from residue remaining on the surface will directly measure the quality of the surface.

Advantages

- Areas hardest to clean and which are reasonably accessible can be evaluated,
- Residues that are "dried out" or are insoluble can be sampled by physical removal.
- Sampling and analysis will be taking place in one step and there will be no real loss of sampling system.

Swab Sampling

It usually requires materials which are absorptive & to physically wipe the surface and recover the analyte. Swabs used should be compatible with the active ingredients and should not interfere with the assay. They should not cause any degradation of the compound. The solvent used for swabbing should provide good solubility for the compound and should not encourage degradation.

Advantages

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

Limitation:

- An Invasive technique that may introduce fibers.
- Results may be technique dependent.
- Swab material and design may inhibit recovery and specificity of the method.
- Evaluation of large, complex and hard to reach areas difficult[12,13].

Rinse Sampling

Rinse sampling does not employ mechanical action on the surface and the sample is collected as a final rinse or rinse applied specifically for collecting a validation sample. Sampling and testing of rinse samples for residual active ingredient is a commonly adopted method to evaluate cleaniness. This is a fairly convenient method in many cases and requires control over the solvent used for rinsing, the contact time and the mixing involved. The solvent used should be selected based on the solubility of the active ingredient and should either simulate a subsequent batch of product or at least provide adequate solubility.

Advantages

- Adaptable to on-line monitoring
- Easy to sample
- Non-intrusive
- Applicable for actives, cleaning agents and excipients
- Allows sampling of a large surface area

Limitation

- Limited information about actual surface cleanliness in some cases.
- May lower test sensitivity.
- Residues may not be homogenously distributed.
- Inability to detect location of residues.
- Rinse volume is critical to ensure accurate interpretation of results.
- May be difficult to accurately define and control the areas sampled, therefore usually used for rinsing an entire piece of equipment, such as vessel.[10,11]

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Attributes	Swab	Rinse	Direct surface analysis	Coupon	Placebo
Physical sampling of surface	●	○	○	●	●
Robust technique (low technique dependency)	○	●	●	●	●
Non-invasive technique	○	●	○	●	●
Adaptable to hard to reach areas	○	●	○	○	●
Effective on flat surfaces	●	○	●	●	●
Effective on complex geometries	○	●	○	●	●
Controlled area sampling possible	●	○	●	●	○
Samples are homogeneous	●	○	○	●	○
Does not require prolonged contact time with surface	●	○	●	●	○
Adaptable to different solvents/materials for sample removal	●	●	N/A	●	●
Appropriate for online adaptation	○	●	●	○	●
No recovery study required	○	○	○	○	○
Frequency of use	High	High	Moderate	Low	Low

Key: ●, effective or low risk; ○, ineffective or high risk.

Table No. 2: Major Sampling Techniques and Their Attributes

Placebo Sampling

Placebo is recognized as both potential cleaning techniques and potential sampling techniques. Placebo material comprises of all typical excipients but not the active ingredient. And the placebo batches were passed through a same line so that it will have possibility to scrub of the clean system. The principle involved in placebo is that it is passed through the same pathway as the product therefore; it will have the possibility to scrub off residual product along those pathways. And it usually employed for measuring system cleanliness. It majorly depends on;

1. Excipients solubility in placebo.
2. Appropriate contact time of the placebo for collecting representative sample.
3. Coverage of the placebo in-process pathways ensures removal of the placebo from all equipment location.
4. Quantity of the placebo and residue being matched should be detectable range and the distribution of residue uniformly in the placebo ensures the detection of sample at any portion of the placebo.

Advantages

- Placebo contacts the same surfaces as the product
- Applicable for hard-to-reach surfaces
- Requires no additional sampling steps

Limitations

- Difficult to determine recovery (contaminants may not be evenly distributed in the placebo)
- Lowers analytical specificity and inhibits detect ability
- Takes longer and adds expense since equipment must be cleaned after the placebo run
- Placebos must be appropriate for each potential product
- Residues may not be homogenously distributed
- No direct measurement of residues on product contact surfaces

The preferred sampling method and the one considered as the most acceptable be regulatory authorities is the swabbing method.

ANALYTICAL TECHNIQUES

Choosing the appropriate analytical TECHNIQUE depends on a variety of factors. The most important factor is to determine the specifications or parameters to be measured. The limit should always be established prior to the selection of the analytical tool[14,15].

There are two methods:

- Specific method
- non-specific method

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Attribute	pH	Conductivity	Total organic carbon	HPLC	Ion mobility spectrometry	Direct surface FTIR
Nonspecific	○	○	○	●	●	●
Does NOT detect in the presence of solvents	●	●	○	●	●	●
Requires a soluble/ semi-soluble residue	○	○	○	●	●	●
Requires an ionizable residue	●	○	●	●	○	●
Is NOT typically rapid/real time	●	●	●	○	●	●
Does NOT typically have any on/at-line capability	●	●	●	○	●	●
Uses reagents/mobile phase/specialty gases	●	●	○	○	●	●
Requires special sample preparation	●	●	●	○	●	●

Key: ●, No (advantage); ○, yes (potential disadvantage).

Table No. 3: Comparison of Features of Typical Cleaning Validation Assay Methods

A specific method detects unique compounds in the presence of potential contaminants. Ex: HPLC. Non-specific methods are those methods that detect any compound that produces a certain response Ex: Total Organic Carbon (TOC), pH and conductivity.

Additional techniques

Apart from the above mentioned techniques the biopharmaceutical industry utilises a wide variety of techniques. TLC is widely used for the qualitative determination of surfactants. Atomic absorption spectroscopy is used for the determination of inorganic contaminants. Bio luminescence is useful for biologicals. This type of analysis usually uses ATP-bioluminescence. It also include Enzyme-Linked Immuno Sorbent Assay (ELISA) and Limulus[17,18].

VALIDATION PROTOCOLS

A Validation Protocol is necessary to define the specific items and activities that will constitute a cleaning validation study. It is advisable for companies to have drawn up a Master Validation plan indicating the overall Cleaning Validation strategy for the product range / equipment type / entire site. The protocol must be prepared prior to the initiation of the study and must either include or reference the documentation required to provide the following information:

- Background
- Purpose of the validation study
- Scope of the validation study
- Responsibilities for performing the validation study
- Sampling procedure to be used
- Testing method to be used
- Acceptance criteria
- Change control
- Approval of protocol before the study
- Deviations

VALIDATION REPORTS

A validation report is necessary to present the results and conclusions and secure approval of the study. The report should include the following:

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- Summary of or reference to the procedures used to clean, sample and test
- Physical and analytical test results or references for same, as well as any pertinent observations
- Conclusions regarding the acceptability of the results, and the status of the procedure(s) being validated
- Any recommendations based on the results or relevant information obtained during the study including revalidation practices if applicable.
- Approval of conclusions
- Review any deviations for the protocol that occurred.
- In cases where it is unlikely that further batches of the product will be manufactured for a period of time it is advisable to generate interim reports on a batch by batch basis until such time as the cleaning validation study has been completed.
- The report should conclude an appropriate level of verification subsequent to validation.

An effective cleaning validation maintenance programme [18,19]. When a minimum of three cleaning validation runs get completed and if the results meet the acceptance criteria, then the cleaning procedures would be demonstrated sufficiently and consistently to remove chemical and detergent residues from equipment surfaces during the study in order to meet the pre-established criteria. However, overtime and certain other factors can decrease the efficiency and consistency of the cleaning program. They are

1. Operator variability
2. Equipment aging and repair
3. Potential non representative results and monitoring programmes.
4. Changes to the product, equipment and process.

CONCLUSION

Form this review article it can be concluded that cleaning validation is a process of attaining and documenting sufficient evidence to proves the effectiveness of cleaning process. Cleaning is directly related to safety and purity of the pharmaceutical product therefore it becomes most important and primary activity. So, It is necessary to have effective cleaning program in place because of the regulatory requirement. this article covers all aspects related to cleaning validation like Residue selection, acceptance criteria for the validation, different levels of cleaning, cleaning procedure, sampling procedure, product grouping and equipment characterization, cleaning agent selection .

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