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Cleaning Validation In Pharmaceutical Industry

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ABSTRACT

In the manufacture of medicinal products and APIs, the cleaning of facilities and equipment is an important measure to avoid contamination and cross contamination. Cleaning validation is a documented process that proves the cleaning methods employed within a facility consistently control the cross contamination. Pharmaceutical manufacturers must validate their cleaning process to ensure compliance with cGMP regulations. In this article cleaning validation and cleaning validation program is discussed in brief.

Keywords: Cleaning, Cleaning Validation, Validation Protocol, Revalidation.

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INTRODUCTION

Cleaning validation is a documented process that proves the effectiveness and consistency in cleaning a pharmaceutical production equipment and that a specific cleaning process will produce consistent and reproducible cleaning results that meet a predetermined level.[1] 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. [2]

Objectives:

The objectives of equipment cleaning and cleaning validation in an Active Pharmaceutical Ingredient (API) area are same as those in pharmaceutical production area. In both these areas efforts are necessary to prevent contamination of a future batch with the previous batch material.

It is necessary to validate cleaning procedures for the following reasons

- Maintaining product integrity

  It includes preventing cross-contamination, in which one drug active from the product just cleaned becomes an unacceptable contaminant in the next drug product (with a different active) manufactured in the cleaned equipment.

- Equipment Reuse

  Most manufacturing equipment is stainless steel or glass lined and is relatively expensive. High capital costs require that the equipment be reused. Therefore, such equipment should be adequately cleaned (at least the product contact surfaces) in a validated process.

- Regulatory requirement

  To comply with regulatory requirement in that equipment is clean and that product quality and safety are maintained.

- Increased equipment utilization

  New equipment is often purchased to give greater flexibility in the manufacture of products. This sometimes means it is more complex in design, which may require more elaborate cleaning procedures to increase the equipment utilization.

- Assurance of cleaning

Both cleaning validation and cleaning verification are methods of showing that the cleaning of process equipment is performed adequately so as not to affect the safety or efficacy of the next drug product manufactured in the cleaned equipment.[3]

Background

The Barr Labs decision is regarded a s a critical case acknowledging the FDA's right to require that cleaning processes be validated. In that case, the FDA had identified problems at Barr Laboratories related (among other things) to Barr's cleaning practices. The FDA requested that Barr validate its cleaning procedures. Barr objected that validation of cleaning was not required by the cGMPs but still proceeded with a cleaning validation program. However, the FDA was dissatisfied with the extent of Barr's cleaning validation. In the US. v. Ban- Laboratories decision, the right of the FDA to require cleaning validation was upheld. The court also agreed that cleaning validation was not limited just to "major equipment"; companies also have to adequately describe the cleaning agents used. On the other hand, the court held that testing for residues of cleaning agents was not necessarily required, and one successful cleaning procedure may be "not insufficient" for cleaning validation. Clearly, the force of these last two points was lost in subsequent activities, since cleaning agent residues are generally of significant concern for the FDA, and the rule of three Process Qualification (PQ) runs for process validation generally applies to cleaning validation.[4]

At the time this case was being prosecuted, the FDA had issued its Biotechnology Inspection Guide, which called for the "validation of cleaning procedures for the processing of equipment," including the comment that this was "especially critical for a multiproduct facility." It was in this guide that the FDA first stated that residue limits must be "practical, achievable, and verifiable In July 1992, the Mid-Atlantic Region of the FDA published the Mid- Atlantic Region Inspection Guide: Cleaning Validation. This document covered in more detail the expectations for cleaning validation, including equipment design, SOPs and documentation, analytical methods, sampling procedures, limits, and detergents. This document was revised with a new introduction and minor wording changes in May 1993.

In July 1993, the official guidance document, Guide to Inspections of Validation of Cleaning Processes, was issued. It followed the same major topics as the earlier Mid-Atlantic guide but included significant changes in wording as related to the various topics. [5]

FDA'S Requirement

The FDA's guide to inspections, which "intended to cover equipment cleaning for chemical residues only," includes:

1. "FDA expects firms to have written procedures [Standard Operating Procedures (SOPs)] detailing the cleaning processes..."
2. "FDA expects firms to have written general procedures on how cleaning processes will be validated."
3. These procedures will "address who is responsible for performing and approving the validation study, the acceptance criteria, and when revalidation will be required."
4. "FDA expects firms to conduct the validation studies in accordance with the protocols and to document the results of studies."
5. Besides assuring chemical cleanliness, "the microbiological aspects of equipment cleaning should be considered. This consists largely of preventive measures…"
6. "Determine the specificity and sensitivity of the analytical method used to detect residuals or contaminants."
7. "The firm should challenge the analytical method in combination with the sampling method(s) used to show that contaminants can be recovered from the equipment surface and at what level..."
8. "Direct sampling (e.g., with swabs) is 'most desirable,' although rinse sampling may be satisfactory.[6]

Level / Degree of Cleaning

The manufacturing process of an Active Pharmaceutical Ingredient (API) typically consists of various chemical reaction and purification steps followed by physical changes. In general, early steps undergo further processing and purification and so potential carryover of the previous product would be removed.

The level of cleaning required in order to ensure that the API is free from unacceptable levels of contamination by previous substances varies depending on the step being cleaned and the next substance being manufactured in the same piece of equipment

It is recommended that at least three levels of cleaning in the production of a commercial product may be implemented. This approach is outlined in the table 1, however it should be mentioned that additional levels might be necessary depending on the nature of the process and requirements of individual companies but should always be based on risk assessment where the characteristics of the previous and subsequent products should be considered.[7]

Table 1: The APIC Guide to cleaning Validation

Level	Thoroughness of cleaning	Cleaning verification		
		Visual inspection	Analytical verification	Cleaning validation
2	Carryover of the previous product is critical. High risk.	Yes	Yes	Mandatory
1	Carryover of the previous product is less critical. Medium risk.	Yes	Yes	Recommended
0	Carryover of the previous product is not critic	Yes	No	No

Cleaning Agent

There are 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. It 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 nonpolar 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 a s trisodium phosphate, sodium silicate, and sodium carbonate. These builders serve to improve the detergency of surfactants.[7]

Cleaning Methods

Cleaning methods are usually differentiated based on the extent of disassembly required for the cleaned equipment and on the method of contacting the chemical cleaning agent with the surface to be cleaned.[8]

- CIP (clean-in-place)
- Agitated immersion
- Static immersion (soaking)
- Automated parts washing
- Ultrasonic cleaning
- High pressure spraying
- Manual cleaning

SAMPLING METHODS FOR CLEANING VALIDATION

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 and placebo sampling.

Direct 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 the test. Therefore, early in the validation programme, it is crucial to assure the sampling medium and solvent.

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.[9]

Swab sampling

A swab is a fibrous material that is used to wipe a surface to remove residues from the surface. The swab "head" (the fabric portion) is typically wetted with a solvent (water, an organic solvent, or a mixture), and then is wiped across a fixed surface area of the surface to be sampled, using a defined wiping motion. The residue is then extracted or desorbed from the swab head into a suitable solvent for subsequent analysis. 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.

Rinse Sampling

Rinse sampling involves using a liquid to cover the surfaces to be sampled. 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.[10]

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[11]

Table 2: Major Sampling Techniques and Their Attributes

Attributes	Swab	Rinse	Direct surface analysis	Placebo
Physical sampling of surface	✓	●	●	✓
Robust technique	●	✓	✓	✓
Adaptable to hard to reach areas	●	✓	●	✓
Effective on flat surfaces	✓	✓	✓	✓
Effective on complex geometries	●	✓	●	✓
Samples are homogeneous	✓	●	●	●
Non invasive technique	●	✓	●	✓
Adaptable to different solvents	✓	✓	●	✓
Frequency of use	High	High	Moderate	Low

✓ Effective ● Ineffective

CURRENT APPROACHES IN DETERMINING THE ACCEPTANCE LIMITS FOR CLEANING VALIDATION

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 x J x L

in product A permitted per

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.

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 x T

in product A permitted per

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.

Approach 3 (Visually clean criterion):

No quantity of residue should be visible on the equipment after cleaning procedures are performed.[12,13,]

TYPICAL ANALYTICAL PROCEDURES

There are many analytical techniques available that can be used in cleaning validation. But choosing the appropriate analytical tool 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.

The Basic Requirements for the Analytical Method.

1. The sensitivity of the method shall be appropriate to the calculated contamination limit.

2. The method shall be practical and rapid, and, as much as possible use instrumentation existing in the company.

3. The method shall be validated in accordance with ICH, USP and EP requirements.

There are two methods:

1. Specific method
2. non-specific method

Specific method

- It is a method that detects a unique compound in the presence of potential contaminants.
- Ex: HPLC. Non-specific methods are those methods that detect any compound that produces a certain response.

Non-specific method

- It detects any compound that produces a certain response.
- Some examples of nonspecific methods are Total Organic Carbon (TOC), pH, Titration, and, conductivity.
- The sensitivity of the method shall be appropriate to the calculated contamination limit.
- The method shall be practical and rapid, and, as much as possible use instrumentation existing in the company.
- The method shall be validated in accordance with ICH, USP, EP requirements.
- The analytical development shall include a recovery study to challenge the sampling and testing methods.[14]

High Performance Liquid Chromatography

HPLC involves injection of the sample into a chromatographic column, separation of the target species from other components in the sample, and then measurement of that target species as it exits the column by ultraviolet (UV) spectroscopy, conductivity, or ELSD (evaporative light-scattering detection). HPLC can generally be tweaked such that it is specific for the target species. The equipment is generally available in pharmaceutical facilities.

Total Organic Carbon (TOC)

TOC involves oxidation of the sample (by any of a variety of techniques) and measurement of the carbon dioxide generated by either infrared spectrometry or conductance. The method is generally considered nonspecific. TOC usually involves an assumption that all of the measured carbon is due to the target species, and the maximum possible level of the target species is calculated based on this assumption**.** TOC is becoming more widely used because it is an acceptable technique to replace for the oxidizable substances test for USP Purified Water and because of the possible degradation of actives due to the cleaning environment. For the latter reason, TOC is used commonly in the biotechnology industry for cleaning validation purposes.

Atomic Absorption

Atomic absorption is a specific method for metal ions. It can be utilized in the determination, for example, of sodium and/or potassium that may be present in cleaning formulations. This is not necessarily a common instrument in pharmaceutical analytical laboratories.

Ion Chromatography

Ion chromatography includes specific methods for both anions and cations in cleaning formulations. It can be used to measure both sodium and potassium a s cations, and different methods can be used to separate and measure anions, such a s the anions from acidic detergents (phosphates, citrates, glycolates) or builders (carbonates, gluconates, silicates, EDTA [ethylenediaminetetraacetic acid]). This is not necessarily a common instrument in pharmaceutical analytical laboratories, but it is becoming more widely used. [15]

Enzyme-Linked Immunosorbent Assay (ELISA)

ELISA is commonly used in the analysis of protein for the determination of actives. However, because proteins are usually degraded by the harsh conditions (temperature and pH) of the cleaning environment, ELISA has limited practical use for cleaning validation studies.

Titrations

Titrations can vary from alkalinity or acidity titrations, which can be used to give upper level estimates of cleaning agents present, to more specific titration procedures to measure components

of cleaning agents, such as titrations for chelants in cleaning agents. The laboratory equipment for these procedures is generally readily available.

Conductance

Conductivity measures a nonspecific property of ions in solution. It can be used as an upper limit estimate of the amount of an alkaline or an acid cleaning agent. Dilute solutions exhibit a linear behavior. If not available, the equipment can be purchased relatively inexpensively. Some companies have tried to use pH a s an estimate of residues of either an alkaline or an acidic cleaning agent. This should generally be discouraged. The measurement of pH in unbuffered systems around neutral is unreliable. In addition, the relationship between the level of cleaning agent and the pH is not a linear one. In such situations, it is preferred to use either conductivity or an acidity/alkalinity titration if a simple analytical procedure is desired for cleaning agent determination. pH can be a useful monitoring tool in that a high or low pH can indicate a system out of control. However, it is not a preferred technique for determining actual levels of alkaline or acidic residues.[16]

METHOD VALIDATION

Analytical methods used for measuring residues in cleaning validation protocols should themselves be validated. This validation usually means following standard industry practices for the validation of analytical methods, including evaluation of specificity, linearity, range, precision, accuracy, and LOD/LOQ.

Specificity

Specificity is a measure of the validity of the result based on expected interferences. In other words, one needs to confirm whether or not the method can unequivocally measure the target species in the presence of possible interferences. Methods such as HPLC are generally considered specific. For cleaning processes, this means that any HPLC procedure should be evaluated to see whether possible residues from the cleaning agent interfere with the assay. Interferences may include changes in retention time, peak height, or peak shape. If cleaning agents are found to interfere in an HPLC assay, the object should be to modify that assay such that the cleaning agent no longer interferes.

Range

Range is a series of values of the measured species or property over which the analytical procedure was evaluated. It is only necessary to assure that the procedure is valid over a range of expected values. For example, if the calculated acceptance limit for the analytical sample is X ppm, then one might want to evaluate a range from approximately 0.2X to 1 .OX. On the other hand, if expected results (perhaps based on prequalification studies) are to be in the 0.1X to 0.3X range, then validation of a range of 0.05X to 0.5X may be justified. Determining of the extent of a valid range for the assay

is a matter of risk assessment and will depend on the degree of confidence and expected consistency in any prequalification analytical studies

LOD / LOQ

LOD is the assay value at which it is still possible to say that the material is present, but it may be not possible to quantify with a specific value. LOD is typically estimated by several techniques. For example, for chromatographic techniques, LOD is estimated at three times the standard deviation of a baseline response. Values that are below the LOD are generally reported as < LOD. LOQ is the lowest assay value for which a reasonable confidence exists that the value is precise. For chromatographic procedures, the LOQ can be estimated as 10 times the standard deviation of the baseline noise. The LOQ can also be determined experimentally; as a practical matter, it can be considered the lower limit of the validated range of the assay.

Linearity

Linearity refers to the characteristic of the relationship of the measured property to the level of analyte present. Linearity is an indication that the measured signal is directly proportional to the concentration of the analyte over the range.

Accuracy

Accuracy refers to the trueness of the measurements to known values. This is determined by analyzing known standards. There is no "magic number" for acceptable accuracy. However, more accurate methods are preferred over less accurate methods.

Precision

Precision refers to the reproducibility of the method and is often measured by standard deviation. Simple precision is the reproducibility of the results in the same lab over a series of replicate assays using the same operator, the same equipment, and usually on the same day. Intermediate precision is the reproducibility of results in the same lab using different operators, different pieces of equipment, and generally done on different days.[17,18]

Validation protocols should contain [19]

1. Purpose of the validation study
2. Responsible person for validation study, like performer and approving authority
3. Full description of equipment to be used in cleaning which include list of equipment, make model, capacity
4. The cleaning cycle and their frequency for any equipment before and after use
5. Detailed list of all critical steps to be monitored

6. Selection of cleaning agent with all detail like solubility of material to be cleaned, safety product removal limit, minimum temperature and volume of cleaning agent
7. Detailed Sampling procedure
8. Type of sampler
9. Volume/quantity of sample
10. Containers for sample
11. Sampling location
12. Sample handling
13. Sample storage
14. Analytical testing procedure with LOD (limit of detection)
15. The rational acceptance criteria with margin of error and sampling efficiency
16. Change control
17. Approval of protocol before the study
18. Deviation

CHANGE CONTROL & REVALIDATION

Once the cleaning process is validated, it should be operated under change control procedures, and the validation should be confirmed on a regular basis. The cleaning validation master plan should specify that validated cleaning procedures are operated under change control. A change control system is in place to ensure that all changes that might impact the cleaning process are assessed and documented. Minor changes or changes having no direct impact on final or in-process product quality should be handled through the documentation system.

The revalidation is usually done on a regular basis, frequency should be specified in the cleaning validation master plan. On the specified frequency, all data related to the cleaning process should be evaluated. This may include the following information:

1. All change control done on the cleaning process
2. All change control on the manufacturing process of the product cleaned:
3. All monitoring data on the cleaning process
4. All QC (quality control) data on products made subsequent to the cleaning process
5. All QC data on the lots of cleaned product
6. The original report on the initial cleaning validation

It should be noted that before a full revalidation is performed, it is usually appropriate to investigate the cleaning process to determine what changes can be made to improve the consistency of that process.[20]

Validation Reports

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

- 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.
- If there is any deviation occurred then protocol is reviewed.[21]

Effective Cleaning Validation Maintenance

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

- Operator variability.
- Aging and repair of the equipment.
- Potential non representative results and monitoring programs.
- Changes to the product, equipment and process.[22]

CONCLUSION

From this review it can be concluded that cleaning validation is a process of attaining and documenting sufficient evidence to proves the effectiveness of cleaning process. The pharmaceutical industry should be free any contamination or cross contamination, it would be safe for the consumer. With the help of cleaning validation any department of pharmaceutical industry can achieve high

degree of assurance regarding the cleaning and it is necessary to have effective cleaning program in place because of the regulatory requirement.

REFERENCES

1. Prabu SL, Suriyaprakash TNK. Cleaning Validation And Its Importance In Pharmaceutical Industry. Pharm Times 2010; 42(7): 21-40.
2. Pankaj P. Chandratreya, Dr. Deenanath Jhade. Overview Of Cleaning Validation In Pharmaceutical Industry. J Harm Res Pharm 2018; 7(1): 34-42.
3. Mowafak Nassani. Cleaning Validation In The Pharmaceutical Industry. Institute Of Validation Technology 2005; 4(8): 42-47.
4. Destin A. Leblanc. Validated Cleaning Technologies For Pharmaceutical Manufacturing. Interpharrn /Crc, Boca Raton London New York Washington, D.C.: 2000.
5. Raj Pal Govind , Arya Rajeshwar Kamal Kant, Joshi Tanuj, Bisht Dheeraj. A Review On Cleaning Validation In Pharmaceutical Industry. J Drug Delivery & Thera 2018; 8(3): 138-146.
6. FDA, Guide To Inspections Of Validation Of Cleaning Process Division Of Investigations, Office Of Regional Operations & Office Regulatory Affairs. July 1993.
7. Active Pharmaceutical Ingredient Committee (APIC) Group Of EEFIC: Guide To Cleaning Validation In API Plants 1999; 3-7.
8. Fabio Geremia. Modern Cgmp Requirements For Cleaning Validation And Drugs Toxicological Evaluation. Acta Scien Pharma Sci 2019; 3(2):33-38
9. Pei Yang, Kim Burson, Debra Feder, Fraser Macdonald. Method Development Of Swab Sampling For Cleaning Validation Of A Residual Active Pharmaceutical Ingredient. Pharma Tech 2005: 84-94.
10. Anindya Ghosh, Sanjay Dey. Overview Of Cleaning Validation In Pharmaceutical Industry. Int J Pharma Quality Assurance 2010; 2(2): 26-30.
11. Kumar S. A Review On Concept Of Cleaning Validation In Pharmaceutical Industry. Int Res J Pharma Sci 2012; 3(7): 17-19.
12. Barbara Kanegsberg, Edward Kanegsberg. Handbook For Critical Cleaning Applications, Processes, And Controls. Crc Press Taylor & Francis Group; 2011: 119-161.
13. Leblanc Da. Establishing Scientifically Justified Acceptance Criteria For Cleaning Validation Of Finished Drug Products. Pharm Tech 1998; 22(10): 136-148.
14. Fourman Gl, Mullen Mv. Determining Cleaning Validation Acceptance Limits For Pharmaceutical Manufacturing Operations. Pharm Tech 1993: 54-60.

15. Andy Walsh. Cleaning Validation For The 21st Century: Acceptance Limits For Active Pharmaceutical Ingredients (Apis): Part I. Pharma Eng 2011: 74-84.
16. Kirsch Rb. Validation Of Analytical Methods Used In Pharmaceutical Cleaning Assessment And Validation. Pharma Tech 1998: 40-46.
17. USP 1995. United States Pharmacopeia, 23rd Ed. <1225> Validation Of Cornpendial Methods. Rockville,Md., USA: United States Pharmacopeial Convention :1982-1984.
18. Zahid Zaheer, Rana Zainuddin. Analytical Methods For Cleaning Validation. Der Pharmacia Lettre 2011; 3 (6): 232-239.
19. Chitra K, Murthy N. A Review Article On Cleaning Validation. Int J Pharm Sci Res 2013; 4(9): 3317-3327.
20. Code Of Federal Regulations Title 21, Volume 4, Section 211.67, 2006. http://www.fda.gov/cder/dmpq/cgmpregs.htm
21. Robert A Nash. Alfred H W: A Text Book Of Pharmaceutical Process Validation. Marcel Dekker, 3rd Edition; 2003: 500-541.
22. Hwang Rc. How To Establish An Effective Maintenance Program For Cleaning Validation. Pharm Tech 2000; 24(1): 62-72.