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A REVIEW ARTICLE ON CLEANING VALIDATION

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ABSTRACT: 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 particle, dust, lubricants, raw materials, intermediates. Mainly cleaning is performed to remove product and non-product contaminating material. 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. In many cases, the same equipment may be used for processing different products. To avoid contamination source or facility configuration there is a need to ensure that cleaning procedure must strictly follow carefully established and validated method of execution.

INTRODUCTION: 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 attributes [1].

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. Cleaning validation is primarily applicable to the cleaning of process manufacturing equipment in pharmaceutical industry. It is necessary to have effective cleaning programs in place because of regulatory requirements.

However more fundamental reason is that to produce products that are as pure and free from contamination to extent that is possible and feasible [2].

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Why Cleaning Validation: To verify the effectiveness of cleaning procedures and to ensure no risks are associated with cross contamination of active ingredient or detergents/sanitizer.

When Cleaning Validation:

1. Initial qualification of process/ equipment.
2. Critical change in a cleaning procedure.
3. Critical change in formulation.
4. Significant change in formulation.
5. Change in a cleaning process.
6. Change in a cleaning agent [3].

Advantages of Cleaning Validation:

1. **Safety:** Validation can also result in increased operator safety. Properly calibrated, validated instruments and gauge used to reduce accident and results in safety.

2. **Better Customer quality:** Through proper validation, market recall is avoided which results in better customer care and quality of the product [4].

Contamination & Cross Contamination: 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 [5].

Mechanism of Contamination:

1. **Cross contamination with active ingredient:** One of the real dangers in cross contamination of active ingredients is that by being contaminated results in a multiple ingredient product instead of single active ingredient. Depending on medical effects, the contamination may enhance the action or negate the action or contaminant may have an entirely different medical effects.

2. **Microbiological contamination:** This form of contamination is particularly insidious because the contamination may develop at any time, even after cleaning. A major contributing factor is the storage of equipment in a wet condition. This provides a natural medium in which bacteria can grow.

3. **Contamination by cleaning or sanitizing agents:** Some pharmaceutical operations may find it necessary to use fairly toxic materials for cleaning purpose for stubborn residues. This is particularly true in the manufacture of active pharmaceutical ingredients (APIs). As such, these materials represent a potential threat as contaminants. It seems obvious that one effective way of dealing with this potential problem is to use cleaning agents with the lowest toxicity that will still be effective in removing the residue in the given cleaning situation. The same factors also apply to sanitizing agents used to wipe down cleaned equipment.

4. **Contamination by miscellaneous other materials:** In addition to the usual expected or anticipated list of potential contamination in a pharmaceutical operation, many other less likely materials can also contaminate products. A partial list includes equipment parts such as excipients, bristles from brushes used in packaging filling equipment, paper filters, micron filters, fibers and rubber particles from gloves, cleaning aids such as brush bristles, cloth, and cotton fibers from rags and wiping materials, lubricants. [6]

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:

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

Note: When performing correctly, equipment characterization is the process whereby it catalogues the features and attributes of equipment, thereby ensuring that equipment can be cleaned reliably and reproducibly.

Product Grouping and Equipment Grouping: Grouping, sometimes also called as a family approach. 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 member of the family is selected for demonstrating cleaning validation. When considering equivalent, any member of the family may be selected as representative of any other member.

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 also 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 perform. When grouping products, all products must be:

1. Manufacture on the same equipment group.
2. Cleaned with the same cleaning agent.
3. Cleaned with the same cleaning procedure.

Grouping considerations for products include:

1. Similar patient risk levels (e.g. therapeutic indication, patient population route of administration, potency, toxicity for drugs/devices/nutraceuticals/ cosmetics or in case of *in-vitro* diagnostics used, such as so called health and safety products)
2. Similar formulations.
3. Similar manufacturing process.

Cleaning validation must always be carried out to meet lowest limit of the entire product group. When grouping equipment, all equipment must be:

1. Used to produce products from the same product group.
2. Cleaned with the same cleaning agent.
3. Cleaned with the same cleaning method.

Grouping considerations for equipment include:

1. Equivalent in terms of position or role in the manufacturing process.
2. Similar functionality.
3. Similar design.

Cleaning Agent selection: Cleaning chemistries 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 employ water alone. For many, however the water alone requires an unacceptable increase in time to get the cleaning accomplished. For these individuals, one of the other approaches must be sought.

2. **Solvent:** These are typically applied in processes where solvent usage is already called for by the manufacturing process. For example, mother liquors are typically used as the solvents for cleaning of APIs. As the mother liquors is already known to dissolve the primary residue, there is little risk in employing if for cleaning.

3. **Commodity chemicals:** In this, chemicals **s**uch as NaOH can be used for cleaning as well. Like their solvent counterparts, there may be hazard issues, effluent issues associated with these materials. Their typically high alkalinity or low acidity, however, often makes them helpful in inactivation processes. However these chemicals lack the detergency of a formulated cleaning agent and they may be difficult to rinse, taking larger volumes of water to rinse free from systems than would a formulated cleaning agent.

4. **Formulated cleaning agent** is the largest class of cleaners. This category includes solvent based formulations and aqueous formulations. Typically formulated cleaning agents can include one or more alkalinity or acidity sources, surfactants builders, sequestrants, chelants and either a solvent or water. For industrial applications, unlike consumer-use products, these materials are formulated to be low foaming and therefore are more readily rinsable and are appropriate for high impingement or high turbulence cleaning [7].

Sampling Techniques: 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.

An example of hot spot is bottom of an agitator or instrument port inside a vessel that become soiled during the manufacturing process and proves to be difficult to clean during the cleaning process. Before selecting sample sites one must evaluate a variety of locations i.e. hot spots and critical sites. The number of sample locations selected for individual equipment was based on the same consideration that was mentioned in sampling location selection i.e. difficult to clean geometries, representative location were disproportionately contaminate the portion of the next batch. Besides sampling sites and sample locations selected was influenced by:

1. Material of construction
2. Over all scale of the piece of equipment.

E.g. in a fluid bed granulator which is of nearly two stories tall may find difficulties to coverage side to side and top and bottom. To ensure adequate cleaning sample locations are preferred on the side wall of this equipment despite the fact that the sidewall is made up of the same material of construction and may not find difficult to clean.

The common sampling method employed in cleaning validation is rinse sampling and swab sampling.

A. **Swab Sampling:** It usually requires materials which are absorptive & to physically wipe the surface and recover the analyte. Because the need to physically wipe the surface was the preferred method that is readily accessible to human hand or arm.

Advantages of Swab Sampling:

1. Dissolve and physically remove sample.
2. Adaptability to wide variety of surfaces.
3. Economically and widely available.

4. May allow sampling of a defined area.
5. Applicable to active, microbial, and cleaning agent residues.

Limitation

1. An Invasive technique that may introduce fibers.
2. Results may be technique dependent.
3. Swab material and design may inhibit recovery and specificity of the method.
4. Evaluation of large, complex and hard to reach areas difficult [2, 8].

B. **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.

Limitation:

1. Limited information about actual surface cleanliness in some cases.
2. May lower test sensitivity.
3. Residues may not be homogenously distributed.
4. Inability to detect location of residues.
5. Rinse volume is critical to ensure accurate interpretation of results.
6. May be difficult to accurately define and control the areas sampled, therefore usually used for rinsing an entire piece of equipment, such as vessel. [8, 9]

C. **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.

D. **Direct Sampling:** 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. The advantage of using these techniques is that sampling and analysis will be taking place in one step and there will be no real loss of sampling system. Where as in swab sampling direct analysis of the surface is limited to the area that are accessible for inspection [7].

Level 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 process and purification and so potential carryover of the previous product would be removed. It is required in order to ensure that the API is free from unacceptable levels of contamination by previous substances. And it varies depending on the step being cleaned and next substance being manufactured in the same piece of equipment train.

API's and related intermediate are often produced in multipurpose equipment with frequent product changes which results in a high amount of cleaning [10].

The degree or level of cleaning and validation required for process in API manufacturing depends largely on:

1. The equipment usage (i.e. dedicated equipment or not)
2. The stage of manufacture (early, intermediate or final step)
3. The nature of the potential contaminants (toxicity, solubility etc) [11, 12]

The CEFIC-APIC guide to cleaning validation recommends three levels of cleaning that may be implemented. This approach is outlined in the table below, however it should be mentioned that additional levels might be necessary depending on the nature of the process and requirement.

Level	Thorough of Cleaning	Cleaning validation
2	Carryover of the previous product is critical. Cleaning required until predetermined stringent carryover limits are met.	Essential
1	Carryover of the previous product is less critical. Cleaning should reduce the potential carryover to a less stringent limit as required for level 2.	Increase from not required to necessary (Lower acceptable carryover limits)
0	Only gross cleaning if carryover of the previous product is not critical	Not required

Documentation: A Cleaning Validation protocol 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 procedures.
5. Cleaning procedures to be used for each product, each manufacturing system or each piece of equipment.
6. The number of cleaning cycle to be performed consecutively.
7. Any routine monitoring equipment.
8. Sampling procedures, including the rationale for why a certain sampling method is used.
9. Clearly defined sampling locations.
10. Data on recovery studies where appropriate.
11. Analytical methods including the limit of detection and the limit of quantitation.
12. The acceptance criteria, including the rationale for setting the specific limits.

- The cleaning validation protocol should be formally approved by the plant Management, to ensure that aspects relating to the work defined in the protocol, for example personnel resources, are known and accepted by the management. Quality assurance should involve in the approval of protocol and reports.
- A final Validation report should be prepared. The conclusions of this report should state that the cleaning process has been validated successfully. Limitations that apply to the use of the validated method should be defined. The report should be approved by the plant management.
- The cleaning process should be documented in an SOP.
- Records of cleaning activity should include:
  a. The area or piece of equipment cleaned;
  b. The person who carried out the cleaning;
  c. When the cleaning was carried out;
  d. The SOP defining the cleaning process; and
  e. The product, which was previously processed on the equipment being cleaned.
- The cleaning record should be signed by the operator who performed the cleaning activity [13].

Cleaning Validation procedure:

1. Cleaning validation studies are carried out to provide a documented evidence and actual experimental data that the procedure being followed for cleaning of equipment and accessories is effective and removes all residues of previous upto a predetermined acceptance level, thereby avoiding the risk of cross contamination.

2. Cleaning validation studies conducted shall be carried to determine the leftover residue of active ingredient for traces of cleaning agent and microbiology status of cleaned equipments.

Strategy on Cleaning Validation Studies: Basic elements of cleaning validation study includes

1. Evaluating of new product/equipment
2. Determination of limit and reporting.
3. Cleaning procedures.
4. Analytical method and its Validation

1. Evaluating of new product/equipment

For new product: In case there are more than one API for the new product, each API shall be evaluated for the below detailed parameters and based on the evaluation one API shall be selected as worst case product

a. **Batch size of the product:** The product which has minimum batch size should be considered as worst case product, which makes the acceptance criteria more stringent.

b. **Based on Label Claim of API:** The Product with highest strength can be considered as worst case product.

c. **Dose for the product:** The product having maximum daily dose can be considered as worst case product.

d. **Solubility of the API:** Product having least solubility in water and higher strength can be considered as worst case product on basis of solubility.

Group	Included descriptive terms	Appropriate quantities of Solvent by volume for 1 part of solute by weight
1	Very soluble Freely soluble	Less than 1 Part From 1 to 10 Parts
2	Soluble Sparingly soluble	From 10 to 30 parts From 30 to 100 Parts
3	Slightly soluble Very slightly soluble Practically insoluble	From 100 to 1000 parts From 1000 to 10000 parts More than 10000 Parts

e. **Based on Therapeutic Potency:** The most Potent product can be considered as the worst case product on the basis of therapeutic potency.

f. **For new equipment:** When new product is identified as worst case, the total surface area for the equipment shall be arrived by identifying the equipment used for manufacturing.

Determination of Limit and Result reporting:

1. **Calculation of MAC for Product is given by the formula:**

a. By dose criteria: NMT 1/1000th dose of any product shall appear in the maximum daily dose of another product manufactured subsequently.

$$MAC = \frac{STD \times SBS \times SF}{LDD}$$

MAC = Maximum allowable carryover in mg; STD = Single Therapeutic dose of previous; SBS = Smallest batch size of next product to be manufactured in mg; SF = Safety factor; LDD = Largest daily dose of next product in mg;

Or

b. 10 ppm criteria: 10 ppm of any product residue shall appear in another product manufactured subsequently.

$$MAC\ (mg) = 10\ ppm \times SBS$$

SBS = Smallest batch size of next product to be manufactured in mg.

Cleaning Procedures: Standard cleaning procedures for each piece of equipment and process should be prepared. It is vital that the equipment design is evaluated in detail in conjunction with the product residues which are to be removed, the available cleaning agents and cleaning techniques, when determining the optimum cleaning procedure for the equipment.

Cleaning procedure should be sufficiently detailed to remove the possibility of any inconsistencies during the cleaning process. Following parameters are to be considered during cleaning procedures.

A. Equipment Parameters to be evaluated include

a. Identification of the equipment to be cleaned

b. Difficult to clean areas.

c. Property of materials.

d. Ease of disassembly.

e. Mobility.

B. Residues to be cleaned

a. Cleaning limits

b. Solubility of the residues.

c. Length of campaigns

C. Cleaning agent parameters to be evaluated

a. Preferable materials that are normally used in the process.

b. Detergents available (as a general guide, minimal use of detergents recommended unless absolutely required).

c. Solubility properties.

d. Environmental considerations

e. Health and safety considerations.

D. Cleaning techniques to be evaluated

a. Manual cleaning.

b. CIP (Clean-in- Place)

c. COP (Clean out of place)

d. Semi-automatic procedures

e. Automatic procedures

f. Time considerations.

g. Number of cleaning cycles.

Testing Methods: The basic requirements of the analytical methods should have the following criteria.

a. Testing method should have the ability to detect target substances at levels consistent with the acceptance criteria.

b. Testing method should have the ability to detect target substances in the presence of other materials that may also be present in the sample.

c. The testing analytical method should include a calculation to convert the amount of residue detected in the sample to 100% if the recovery data generated indicates a recovery outside the allowed range.

Analyzing cleaning Validation samples: There are many analytical techniques available 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.

Specific and non-specific methods: A specific method detects unique compounds in the presence of potential contaminants e.g. HPLC. Nonspecific methods are those methods that detect any compounds that products a certain response e.g. Total organic carbon, pH and conductivity.

A. **High Performance Liquid Chromatography:** Almost every pharmaceutical company has an HPLC instrument, utilizing a variety of detector. These include UV, Fluorescence, Electrochemical, Refractive Index, Conductivity, Evaporate Light Scattering Detector and many others.

The vast majority of techniques described in the literature are for the determination of surfactants in concentrated products.

B. Therefore, the limits of quantitation and the limit of detection are rather high. Analysis of anionic and cationic surfactants is done by HPLC and Capillary electrophoresis whereas amphoteric surfactants are analyzed by HPLC.

C. **Capillary Electrophoresis:** Capillary electrophoresis can be used for many different types of analysis, viz., separation, detection and determination of sodium lauryl sulphate in cationic, anionic and non-ionic surfactants. Another technique known as Micellar electro kinetic capillary chromatography is used for the separation of non-ionic alkyl phenol polyoxy ethylene type surfactants.

D. **Total organic carbon:** It is used widely in the pharmaceutical industries for various purposes. TOC is determined by the oxidation of an organic compound into carbon dioxide. The oxidation can occur through a number of mechanisms depending on the instrument being used. TOC is used for the analysis of detergents, endotoxins, biological media and poly ethylene glycol.

E. **Ion Chromatography:** Ion chromatography can be used for the analysis of inorganic, organic and surfactants present in the cleaners. Most cleaners contain sodium and/or potassium. The ion chromatography detection technique of suppressed conductivity is more sensitive to potassium ions than to sodium ions. Very low levels of cleaning agents can be detected by using this technique.

F. Others

1. Thin layer chromatography: TLC is widely used for the qualitative determination of surfactants.

2. Atomic absorption spectroscopy: AAS is used for the determination of inorganic contaminants.

3. Bio luminescence: It is useful for biologicals. This type of analysis usually uses ATP-bioluminescence.

G. **Optically simulated electron emission:** In some cases the limits of residue are very less that they can't be detected by conventional methods. OSEE is a very sensitive method that can be used for both qualitative and quantitative manner in this regard.

H. **Portable mass spectrometer:** Portable mass spectrometer can be used to detect ultra-sensitive measurements and identification of the residue.

I. **Additional techniques:** Apart from the above mentioned techniques, Biopharmaceutical industry utilizes a wide variety of techniques include ELISA and LAL technique.

Method Validation: It is very important to scientifically establish the residue limit prior to choosing the method of analysis. This includes the limit in the analytical sample and the limit in the next product. This will ensure the ability of the chosen method to detect and quantitated the limit present.

Once the technique for analysis has been chosen, it is very important to validate the method used. The validation of a method is very different from validation of recovery. A validated method is one that is rugged and robust enough to measure the residual limit established, whereas, the validation of a recovery helps to determine the amount that can be recovered from a surface.

Data analysis for estimating possible contamination: To support the cleaning validation study, an appropriate analytical method must be developed to product at a sensitivity level, at least equal to that of the acceptable residual level. For each analytical method, values defined as 'minimum quantifiable quantity' (MQQ) and non-detectable (ND) are applied. A test result greater than or equal to the MQQ is considered reliable, whereas if it lies between ND and MQQ it is considered unreliable. Therefore values reported as ND or between ND and MQQ can be manipulated to apply for the possible contamination.

Difficulty in cleaning the equipment: The most difficult to clean pieces of equipment require the most intensive monitoring schedule. Easier to clean pieces require a moderate monitoring schedule.

Difficulty in cleaning the product and equipment:

It is divided into three groups based on the degree of difficulty in cleaning the product and equipment.

a. Most difficult to clean product and equipments requires the most intensive monitoring schedule.

b. Easier to clean product and equipment that requires a moderate monitoring schedule.

c. Easier to clean product and equipment that requires only periodic monitoring.

The monitoring program provides a mechanism to verify the capability of the cleaning procedures, the efficiency of the training program and the effectiveness of the equipment maintenance program.

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

a. Reference to all the procedures followed to clean the samples and tests.

b. Physically and analytical test results or reference for the same, as well as any pertinent observations.

c. Conclusion regarding the acceptability of the results, and the status of the procedures being validated.

d. Any recommendation based on the results or relevant information obtained during the study including revalidation practices if applicable.

e. Review of any deviations from the protocol.

f. When it is unlikely that further batches of the product will be manufactured for a period of time. It is advisable to generate reports on a batch by batch basis until such time.

g. The report should conclude an appropriate level of verification subsequent to validation [14].

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.

REFERENCES:

1. Amit Kailaschand M. Process validation of cephalosporin antibiotics cefuroxime axetil 500 mg tablets. Karnataka: Rajiv Gandhi University of Health Sciences; 2011.
2. Kumar V S, Sanjeev T: Overview of cleaning validation in pharmaceutical manufacturing unit. International Journal of Advanced Research in Pharmaceutical & Bio sciences. 2012; 1(2): 154-164.
3. Robert Fredrick: The Basic Facts of Cleaning Validation. Canada: Pharmainfo.net; 2004. Available from http://www.pharmainfo.net/reviews/basic-facts-cleaning-validation
4. Patel Hiren Popatbhai *et al*: Process validation of Benzepril HCL 5 mg tablet. International Research Journal of Pharmaceutical and applied sciences 2012; 2(4): 1-16.
5. Kathiresan K: Cleaning validation of acetaminophen tablets. Rasayan Journal 2010; 3(3): 503-506.
6. Robert A Nash. Alfred H W: A Text Book of Pharmaceutical Process Validation. Marcel Dekker, 3rd Edition 2003: 793-820.
7. Agallaco J. Frederick Carelton J: A Text Book of Validation of Pharmaceutical Process. Spring Publisher, 3rd Edition 2008: 525-565.
8. Bodavula Samba Siva Rao: Cleaning validation of albendazole tablet 400 mg. Pharma Innovations. 2012; 1(4): 76-94.
9. Kumar S: A review on concept of cleaning validation in pharmaceutical Industry. International Research Journal of Pharmaceutical Sciences 2012: 3(7): 17-19.
10. Active Pharmaceutical Ingredient Committee (APIC) group of EEFIC: Guide to cleaning

validation in API plants. APIC Publications 1999; 2-23.
11. Health product and food branch inspectorate: Cleaning validation guidelines 2008; 1-16.
12. Sanjay Dey, Anindya G: Overview of cleaning validation in pharmaceutical industry. Indian Journal of Pharmaceutical Quality Assurance 2010; 2(2): 26-30.
13. PIC/S document PI 006-3: Preparation of Validation Master Plan Installation and Operational Qualification Non- Sterile Process Validation Cleaning Validation. A Regulatory Guideline 2013; 9-11.
14. Lakshmana P: Cleaning validation and its importance in Pharmaceutical Industry. Pharma Times 2010; 42(07): 21-25.

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