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CLEANING VALIDATION IN PHARMACEUTICAL INDUSTRIES

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INTRODUCTION, PRINCIPLE AND OBJECTIVE:

Cleaning Validation is the methodology used to assure that a cleaning process removes residues of the active pharmaceutical ingredients of the product manufactured in a piece of equipment, the cleaning aids utilized in the cleaning process and the microbial attributes. All residues are removed to predetermined levels to ensure the quality of the next product manufactured is not compromised by waste from the previous product.

Pharmaceutical products can be contaminated by a variety of substances such as contaminants associated with microbes, active pharmaceutical ingredients (API) and excipient residues of previous products, residues of cleaning agents, airborne materials such as dust and particulate matter, lubricants and ancillary material, such as disinfectants, and decomposition residues from:

- Product residue breakdown occasioned by. e.g. the use of strong acids and alkalis during the cleaning process and
- Breakdown products of the detergents, acids and alkalis that may be used as part of the cleaning process.

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

Cleaning validation is documented evidence which provide high degree of assurance that an approved cleaning procedure will provide equipment that is suitable for processing of pharmaceutical products or API.

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REGULATORY REQUIREMENTS FOR CLEANING VALIDATION:

The FDA (Food and Drug Administration) establishes the regulations and policies relating to pharmaceutical grade products distributed commercially in United States. These regulations are called current Good Manufacturing Practices (cGMP) and are classified in Title 21, part 211 of the Code of

Federal Regulation (CFR). The applicable laws at this time are general and somewhat vague, and are centered around 21 CFR 211.67 that states: "Equipment and utensils be cleaned, maintained and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality or purity of the drug product". According to this law each and every pharmaceutical and food industry should follow the cleaning validation program to avoid malfunctioning, contamination and cross contamination of finished product.

CLEANING VALIDATION PROGRAM:

Equipment cleaning validation may be performed concurrently with actual production steps during process development and manufacturing. Validation program should be continued through full scale commercial production. The concept "Test-Until-Clean" should be applied. This concept involves cleaning, sampling and testing with repetition of this sequence until an acceptable residue limit is attained.

A validation program generally encompasses at least three consecutive successful replicate to establish that the procedure is reproducibly effective.

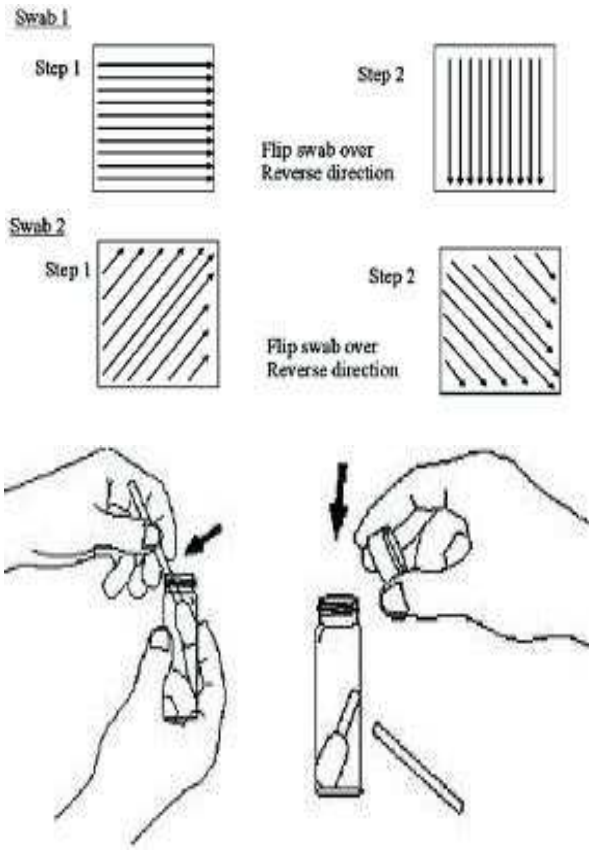
If the equipment of the similar size, design and construction is cleaned by the same procedure, studies need not be conducted on each unit as long as a total of three successful replicates are done on similar piece of equipment; this concept is known as equipment grouping.

SAMPLING PROCEURE:

There are two methods of sampling.

1. Direct surface sampling (swab method):

This method of sampling is the most commonly used and involves taking an inert material (e.g. cotton wool) on the end of a probe (referred to as "swab") and rubbing it methodically across a surface. The swabs are added to the dilution solvent and these solvents are analyzed by suitable analytical instruments for the presence of residue of previous products per given area. i.e. 60-100 square inch.



The location from which the sample is taken should take into consideration the composition of the equipment (e.g. glass or steel) and the location (e.g. blades, tank walls or fittings). Worst case location should be considered. Critical areas, i.e. those hardest to clean, should be identified, particularly in large systems that employ semi automatic or fully automatic clean-in-place systems.

For determination of the microbiological contamination on surfaces is to use sterile cotton swabs moistened with sterile peptone water, water for injection, or phosphate buffer. Using sterile forceps and aseptic technique, a predetermined area is wiped with a sterile swab. The swab is then aseptically transferred to a sterile tube containing a

suitable diluent. The tube is then agitated to suspend any viable microorganisms and aliquots are placed in a semisolid medium to obtain quantitative results.

2. Rinse samples (Indirect method):

In this method, a measured area of clean surface is rinsed or washed with solvent and the solvent is collected and tested for traces of contaminants.

This method allows sampling of a large surface, of areas that are inaccessible or that cannot be routinely disassembled and provides an overall picture. It is also suitable for checking the residue of cleaning agents, e.g. detergents.

Rinse sampling method should be used in combination with other sampling methods such as surface sampling. There should be evidence that samples are accurately recovered. For example a recovery of > 80% is considered good, > 50% reasonable and < 50% questionable.

DETERGENTS:

The efficiency of cleaning procedures for the removal of detergent residues should be evaluated. Acceptable limits should be defined for levels of detergent after cleaning. Ideally, there should be no residues detected. The possibility of detergent breakdown should be considered when validating cleaning procedures. Detergents that have persistent residues such as cationic detergents which adhere very strongly to glass and are difficult to remove, should be avoided where possible.

The composition of detergents should be known to the manufacturer. If such information is not available, alternative detergents should be selected whose composition can be defined. The manufacturer should ensure that he is notified by the detergent supplier of any critical changes in the formulation of the detergent.

ANALYTICAL METHODS:

The analytical methods should be validated before the cleaning validation is performed and the methods chosen should detect residuals or contaminants specific for the substances being assayed at an appropriate level of cleanliness (sensitivity).

The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminants.

Some of the analytical methods which can be used for the analysis of cleaning validation samples include:

- HPLC
- GC
- HPTLC
- TOC
- UV spectroscopy
- pH
- Conductivity
- ELISA

These methods can be used alone or in combination depending upon the analysis required.

ESTABLISHMENT OF LIMITS:

The rationale for selecting limits for product residues should be logically based on a consideration of the materials involved and their therapeutic dose. The limit should be practical, achievable and verifiable.

The approach for setting limits can be:

- Product specific cleaning validation for all products
- Grouping into product families and choosing a “worst case” product
- Grouping products according to risk, e.g. very soluble products, products with similar potency, highly toxic or difficult to detect products.

ACCEPTANCE CRITERIA:

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

CALCULATION OF THE MAXIMUM ALLOWABLE CARRY OVER (MACO):

For the calculation by considering 0.1% safety factor

$$\text{Limit (mg)} = \frac{Daily\ therapeutic\ dose\ of\ product\ A\ (in\ mg)}{1000} \times \frac{Minimum\ batch\ size\ of\ product\ B\ (in\ mg)}{Max.qaily\ therapeutic\ dose\ of\ product\ B\ (in\ mg)}$$

Where,

Product A = Product manufactured before cleaning

Product B = Next product after cleaning

For considering 10 ppm as acceptance criteria

The quantity equivalent to 10 mg/L of the batch size is considered as the acceptance criteria for the acceptance criteria as 10 ppm.

Calculation of acceptance criteria for Swab samples

$$\text{Limit (PPM)} = MACO \times \frac{1000}{C} \times \frac{D}{V}$$

Where,

C = Cumulative surface area of the equipments used (in cm^2)

V = Volume of solvent used to dispense swab

D = Swabbed surface area in cm^2

1000 is the multiplication factor to convert value in mcg from mg

Calculation of acceptance criteria for Rinse samples

$$\text{Limit (PPM)} = MACO \times \frac{1000}{C} \times \frac{1}{V}$$

Where,

C = Cumulative surface area of the equipments used (in cm^2)

V = Volume of solvent used for rinse of the same in mL/cm^2 of equipment

1000 is the multiplication factor to convert value in mcg from mg

Calculation of Recovery factor

% recovery shall not be less than 75% unless otherwise specified and justified in individual protocol of analytical method validation.

Recovery factor shall be calculated as follows:

$$\text{Recovery factor} = \frac{100}{\%\ Recovery}$$

Calculation of worst case

$$\text{Worst case} = \frac{Smallest\ batch\ size}{Larest\ daily\ dose}$$

Revalidation of cleaning procedure

Revalidation of cleaning procedure is required if any of the following occur:

- Cleaning procedure is changed
- Raw materials are changed
- Change in formulation
- New detergent
- Change in analytical method for determination of residue
- Major non-traceable contamination occurrence
- Failure during cleaning verification/validation

Revalidation of cleaning procedure shall be performed on a minimum of three cleaning cycles.

REFERENCES:

1) The validation of cleaning processes, Pharmaceutical Technology – S.W. Harder
2) Cleaning Validation: An overall perspective – Jenkins M, Vanderweilen AJ
3) ICH: Good Manufacturing Practice guideline for Active Pharmaceutical Ingredients.
4) Pharmaceutical Quality Assurance: Cleaning Validation – Manohar A. Potdar
5) Determining cleaning validation limits for pharmaceutical manufacturing operations, Pharmaceutical Technology – Fourman, G.L. and Mullen, M.V.
6) Points to consider in the validation of equipment cleaning procedures, Journal of Parenteral science and Technology - James Agalloco
7) Process Analytical Technology and Cleaning – Verghese, G. and Lopolito, P.
8) Cleaning Technology for Pharmaceutical Manufacturing – LeBlanc, Destin A. et al.

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