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CLEANING VALIDATION: IMPORTANT ASPECT IN PHARMACEUTICAL INDUSTRY

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ABSTRACT

The objective of cleaning and sanitization in pharmaceutical industry is to ensure that product is not cross contaminated with cleaning agent and manufactured product. Residue behind affect the quality of the finished product. Cleaning validation is documented proof that a particular pharmaceutical facility consistently and effectively cleans a system or equipment item. Cleaning validation program is required by regulation of GMP and enforced by U.S Food and Drug Administration. This review intent the importance of cleaning validation in pharmaceutical industry, various regulatory requirements, types of sampling, residual detection method and their acceptance criteria.

Key words: *GMP, WHO, API, cleaning validation etc.*

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INTRODUCTION

The cleaning processes used in pharmaceutical operations have achieved an increasing emphasis in the past decade both by the regulatory agencies and industry itself. At this time it is generally regarded as just as critical to have effective cleaning processes as to have consistent, validated manufacturing processes. The basic reason for having good, effective, consistent cleaning procedures is to prevent the contamination of products made subsequently in the same equipment. The goal is to provide pharmaceutical products of the highest quality to our patients. This is the basic regulatory requirement as well as the goal of all of those suppliers of products and services. [1]

Cleaning continuum is concept advocated by the Klenzaid G.M.P academy and can be defined as “an international organizational model which helps to draft the operational details of specific cleaning validation programme”. The cleaning validation is highly complex process and it refers to cleaning activities viz.

- Establishing critical parameters.[2]
- Developing grouping philosophies.

- Establishing the scientific rationale for cleaning programme.
- Determining the process, equipment and products that represent the greatest concern.
- Establishing the criticality of cleaning limits and methods.

PRINCIPLE AND NEED OF CLEANING VALIDATION [3]

1. The objective of good manufacturing practices (GMP) includes the prevention of possible contamination and cross contamination of pharmaceutical starting material and product by cleaning validation.
2. Pharmaceutical product can be contaminated by variety of substances such as contaminants associated with microbes, previous products (both active pharmaceutical ingredients (API) and excipient residues),residue of cleaning agent, airborne materials, such as dust and particulate matter, lubricants and ancillary materials, such as disinfectant, and decomposition residue from:
    - Product residue breakdown occasioned by, e.g. the use of strong acids and alkalis during the cleaning process; and
    - Breakdown procedures of the detergents and alkalis that may be used as part of the cleaning process.
3. Adequate cleaning procedures play an important role in preventing contamination and cross contamination. Validation of cleaning method provides documented evidence that an approved cleaning procedure will provide clean equipment, suitable for it's indeed use.
4. 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.
5. Cleaning validation is not necessarily required for non-critical cleaning such as that which takes place between batches of the same product (or different lots of the same intermediate in bulk process),or of floors, walls, the outside of vessels, and following some intermediate steps.
6. Cleaning validation should be considered important in multiproduct facilities and should be performed among others, for equipment, sanitization procedures and garment laundering.

REGULATORY REQUIREMENTS FOR CLEANING VALIDATION

The Food and Drug Administration establishes the regulations and policies relating o pharmaceutical grade products distributed commercially in United States. These regulations are called current Good Manufacturing Practices 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 around21 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".[4]

According to this law each and every pharmaceutical and food industry should follow the cleaning validation programme to avoid malfunctioning, contamination and cross-contamination of finished product.

TYPES OF CONTAMINANTS [5]

The manufacturing of API and pharmaceutical products involves series of processing steps and use of various equipments. Equipments or ancillary systems may be used for manufacturing multiple product or single dedicated product. The

inadequate cleaning process may leads to the fact that following residue may carry forward as contaminant in the next batch to be manufactured in the same equipment.

1. Precursors to the Active Pharmaceutical Ingredient
2. By-products and/or degradation products of the Active Pharmaceutical Ingredient
3. Contamination of one batch of product with significant levels of residual active ingredients from a previous batch
4. Microbiological contamination: Maintenance, cleaning and storage conditions may provide adventitious microorganisms with the opportunity to proliferate within the processing equipment.
5. Contamination with unintended materials or compounds such as Cleaning agents, lubricants , surfactant etc.

SAMPLING METHOD USED IN CLEANING [6-8]

Equipment should normally be cleaned as soon as possible after use. This may be especially important for operations with topical products, suspensions and bulk drug or where the drying of residues will directly affect the efficiency of a cleaning procedure. Two methods of sampling are considered to be acceptable. These are direct surface sampling and rinse samples. A combination of the two methods is generally the most desirable. The practice of resampling should not be used before or during cleaning and operations and is acceptable only in rare cases. Constant retesting and resampling can show that the cleaning process is not validated because these retests actually document the presence of unacceptable residue and contaminants resulting from an ineffective cleaning process.

a) Direct surface sampling (direct method)

I. 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 a "swab") and rubbing it methodically across a surface. The type of sampling material used and its potential impact on the test data is important as the sampling material may interfere with the test. (For example, the adhesive used in swabs has been found to interfere with the analysis of samples.)
II. Factors that should be considered include the supplier of the swab, area swabbed, number of swabs used, whether they are wet or dry swabs, swab handling and swabbing technique.
III. 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 locations should be considered. The protocol should identify the sampling locations.
IV. 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. The sampling medium and solvent used should be appropriate to the task.

b) Rinse samples (indirect method)

I. This method allows sampling of a large surface, of areas that are inaccessible or that cannot be routinely disassembled and provides an overall picture. Rinse samples may give sufficient evidence of adequate cleaning where accessibility of equipment parts can preclude direct surface sampling, and may be useful for checking for residues of cleaning agents, e.g. detergents.
II. Rinse samples should be used in combination with other sampling methods such as surface sampling.
III. There should be evidence that samples are accurately recovered. For example, a recovery of >80% is considered good, >50% reasonable and <50% questionable.

ANALYSING CLEANING SAMPLE

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.

a. High performance Liquid Chromatography

The High performance Liquid Chromatography technique is widely used in the analyzing of cleaning sample . The process have applied to a wide variety of natural product such as nucleic acid, urine, serum, carbohydrates, lipid, amino acid, bile salt, and manufactured product such as pharmaceuticals, pesticides, surfactant and antioxidants.[9]

b. TOC

One analytical technique that provides an excellent mean of conducting whole detergent product analysis is that referred to as Total Organic Carbon analysis. Using this technique, organic compound are oxidized to CO_2 which is then quantitated, typically by non-dispersive infrared absorption or conductivity. TOC analysis is non-specific and offers low detection limits, potentially down to low non-specific and offers low detection limit, potentially down to low parts per billion levels. Further more, TOC analysis is theoretically capable of quantitating any carbon containing compound.[10]

c. FTIR Spectroscopy

A systematic procedure was described recently by Smith. He used FTIR spectroscopy to identify the component of a formulated cleaning agent that was the last to rinse from stainless steel and borosilicate glass surfaces.[11,12]

d. 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.[13]

ANALYTICAL METHOD VALIDATION[14]

The analytical method should be validated before the cleaning validation is performed. The method chosen should detect residuals or contaminants specific for the substance being assayed at an appropriate level of cleanliness. The validation of analytical method should include appropriate:

- Precision
- Linearity
- Selectivity
- Limit of Detection
- Limit of Quantitation
- Robustness
- Ruggedness

ESTABLISHING ACCEPTABLE LIMITS[15-16]

I. The limit-setting approach can be product-specific group products into families and choose a worst case product, Group products into groups according to risk, e.g. very soluble products, products with similar potency, highly toxic, or difficult to detect products, use different safety factors for different dosage forms based on physiological response (this method is essential for potent materials).

II. Limits may be expressed as a concentration in a subsequent product (ppm), limit per surface area (mcg/cm2), or in rinse water as ppm.

III. The sensitivity of the analytical methods should be defined to enable reasonable limits to be set.

IV. The rationale for selecting limits for carry-over of product residues should meet defined criteria.

V. The three most commonly used criteria are:

a. Visually clean. (No residue should be visible on equipment after cleaning.) Spiking studies should determine the concentration

at which most active ingredients are visible. This criterion may not be

b. suitable for high-potency, low-dosage drugs; no more than 10 ppm of one product will appear in another product (basis for heavy metals in starting materials); and
c. no more than 0.1% of the normal therapeutic dose of one

CALCULATIONS FOR SWAB SAMPLING

Total residue =

$$\frac{\text{Residue detected by analytical method}}{\text{Square inch of swabbed area}} \times \text{total surface area of equipment}$$

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