Implementation of Cleaning Validation Program in Formulation Manufacturing Plant

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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, with residues from previous product batches, cleaning agent or other extraneous material introduced into or generated by the process. Cleaning validation is becoming more and more important as we deal with potent, complicated drug substances and complex biotechnology products. This article will cover all the elements of cleaning validation.

Index Terms — Validation, Cleaning Validation, Pharmaceuticals

I. INTRODUCTION

Cleaning validation: 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]. 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 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 were 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, 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 also provides assurance from an internal control and compliance point of view 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]: Cleaning validation is also required for Initial qualification of process/ equipment; Critical change in cleaning procedure; Critical change in formulation; Change in cleaning process; Change in cleaning agent.

Essential Programs that maintain the validated state and their required elements:
 Routinely conducted compliance initiatives on site that maintain quality and affect the company’s ability to maintain the validated state are as follows. Cleaning and testing, if any, must be conducted upon the introduction of new or repaired equipment. Monitoring of cleaning after validation completion is essential to ensure validated state. Other important programs are 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 procedures; 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)

In case of Drug Products: Different cleaning situations 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 – level 1 cleaning - Batch 2 – level 1 cleaning - 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 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 degrees or levels of cleaning differ 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 1: Comparison between cleaning levels

| Factors         | Level 1 | Level 2 |
|-----------------|---------|---------|
| Risk            | Low     | High    |
| Acceptance limit| High    | Low     |
| Degree of cleaning | Minimal | Extensive |
| Verification of cleaning | Visual inspection | Analytical testing |

II. CLEANING VALIDATION 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 processes 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 and provide the minimum requirements for the cleaning validation program. The process flow is described in Figure 1 below.
III. WINS (17):
Water, Individual, Nature of the Soil (or residue), Surface. WINS represents the parameters that affect the residue’s removal from the surface and each parameter can affect one’s ability to apply TACT variables (Time, Action, Chemistry, Temperature) in a given cleaning situation.

Time denotes the contact time of residue on the equipment surface. Action refers to the act of cleaning, mainly soaking & brushing using the cleaning agent (for manual cleaning) and agitation (for automated cleaning). Chemistry refers to the selected type of cleaning agent, which will determine the effectiveness of the cleaning process. Temperature of the solvent or water can have an effect on the cleaning process. These factors impact the residue’s removal from equipment surface (WINS).

Cleaning chemistries fall into several broad categories:

❖ Water
❖ Solvents
❖ Commodity chemicals like alkalis (NaOH)
❖ Formulated cleaning agents (such as Teepol, Labolin, manufactured by leading companies)

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

1. 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.

   Maximum allowable carry-over of product A per 10 sq.cm swab area = \( \frac{A \times B \times C \times RF}{D \times E} \)

   \( A = 0.001 \ (1/1000^{th}) \) of the lowest strength of product A manufactured (in milligrams of active)

   \( B = \) Number of dosage units per batch of product B

   \( D = \) Maximum number of dosage units of product B per day

   \( E = \) Equipment surface in common between product A & B in square centimeters

   \( C = \) Swab area (10 sq.cm)

   \( RF = \) Recovery Factor (75% i.e., 75/100 =0.75)

2. Approach 2 (10 ppm criterion):
No more than 10 ppm of a product will appear in another product.

   Maximum allowable carry-over of product A per 10 sq.cm swab area = \( \frac{A \times B \times C}{E} \)

   \( A = 10\text{mg} \) active ingredient of product A in one kg of product B

   \( B = \) Number of kilograms per batch of final mixture of product B

   \( E = \) Equipment surface in common between product A & B in square centimeters

   \( C = \) Swab area (10 sq.cm)

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

Product Grouping and Equipment Grouping:

Grouping of equipment [1, 8]:

All equipment must be used to produce products from the same product group, additionally must be 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., It is a method by which similar or equivalent equipment are grouped for the purpose of cleaning validation. When considering similar equipment, a worst-case area of the equipment or site is selected for demonstrating cleaning validation. When considering equivalent equipment, any area of the equipment or site may be selected as representative of any other area of the equipment or site. Bracketing, a term that appears 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: 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)

IV. WORST CASE RATING

In facilities with a very large number of products manufactured using common equipment, quantum of cleaning validation studies can be reduced and need for frequent re-validation may be avoided by identifying the worst-case soil (residue for cleaning). During the validation, limits are set at low levels such that potential for re-validation can be reduced. A worst-case product may be chosen for cleaning based on solubility in subjected solvent. Other considerations include:

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

V. 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 before preparation of the cleaning procedure to ensure removal of product residues. Following parameters are to be considered during cleaning procedure preparation:

A. Equipment Parameters to be evaluated

1. Identification of the equipment to be cleaned
2. ‘Difficult to clean’ locations
3. Material of construction
4. Whether equipment can be dismantled
5. Portability of the equipment

B. Residues to be cleaned

1. Acceptable cleaning levels
2. Solubility of the residues
3. Intervals between cleaning

C. Cleaning agent parameters to be evaluated

1. Preferably materials that do not affect the process
2. Detergents available (as a general guide, minimize use of detergents unless absolutely necessary)
3. Solubility in water
4. Effect on environment
5. Effect on human health and safety

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. Cleaning duration
7. Cleaning cycles required

VI. SAMPLING TECHNIQUES

Sampling sites are selected based on the difficult to clean geometries of the equipment and these locations are inaccessible i.e., their inaccessibility makes them difficult to clean. Therefore, before choosing sampling sites one must be conscious in selecting the required 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 which if remain dirty will certainly result in disproportionate level of contamination to the next exhibit batch. The common
sampling methods employed in cleaning validation are indirect or rinse sampling and direct surface sampling or swab sampling [5, 6].

**Direct surface sampling**

Direct sampling depends on the type of sampling material used and its impact on the test data to check interference of the sampling material with the test. Therefore, early in the validation program or during development studies, it is crucial to assure that the sampling material and solvent are satisfactory and be readily used.

**Advantages**
- Areas hardest to clean and which are reasonably accessible can be evaluated,
- Physical removal of residues that are “dried out” or are insoluble.
- 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.
- Adaptable to different types of surfaces.
- Swabs are economical and commonly available
- Permits sampling of a specific defined area.
- Applicable to active, microbial, and cleaning agent residues.

Normally used in conjunction with specific analytical techniques like HPLC

**Limitation:**
- An invasive technique that may introduce fibers.
- Results may be dependent on individual technique.
- Swab material and design may affect recovery and specificity of the method.
- Sampling of large, complex and hard to reach areas difficult [12,13].

**Rinse Sampling**

This does not involve sampling the equipment and does not employ mechanical action on the surface. The sample is collected indirectly as a final rinse or rinse applied specifically for cleaning validation. Sampling and testing of rinse samples for residual active ingredient is a commonly adopted method to evaluate cleanliness. 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 provide adequate solubility. Absence of absence of residual product or contaminants in the rinse solvent would infer the absence on equipment surface.

**Advantages**
- Adaptable to on-line monitoring
- Permits easy sampling
- Non-invasive technique
- Permits sampling of a large surface area.

It is normally used in conjunction with non-specific methods like TOC, conductivity or pH measurement.

**Limitation**
- Limited information about actual surface cleanliness in some cases.
- May lower test sensitivity.
- Solvent may not cover all areas or residues may not be homogenously distributed.
- Difficult to detect location of residues in large equipment
- Volume of rinse is critical to ensure accurate interpretation of results.
- May be difficult to accurately define and control the areas sampled, hence normally used for rinsing single piece of equipment, such as vessel. [10,11]

**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 are passed through the same line so as to scrub the equipment clean. The principle involved in placebo is that it is passed through the same pathway as the product. Therefore, it has the likelihood to scrub off residual product along those pathways. It is usually employed for measuring system cleanliness and mainly depends on:

1. Solubility of active in placebo.
2. Appropriate contact time of the placebo for collecting representative sample.
3. Coverage of the placebo in process pathways to ensure removal of the placebo from all equipment location.
4. Quantity of the placebo and residue should be in detectable range and the distribution of residue uniformly in the placebo ensures the detection of sample in any portion of the placebo

**Coupon Sampling**

This is used very rarely.

A comparative evaluation of commonly used sampling techniques is provided in Table 2 below.

| Attributes                              | Swab | Rinse | Direct | Placebo |
|----------------------------------------|------|-------|--------|---------|
| Physical sampling of equipment surface | ✓    | x     | x      | ✓       |
| Technique dependent                    | ✓    | x     | ✓      | ✗       |
| Invasive technique                     | ✓    | x     | ✗      | ✓       |
| Sampling of difficult to clean areas   | ✓    | ✓     | ✗      | ✓       |
| Sampling of defined areas              | ✓    | x     | ✓      | ✗       |
| Homogeneity of samples                 | ✓    | x     | ✗      | ✓       |
| Prolonged contact with equipment surface| ✗   | ✓     | ✗      | ✗       |
| Suitability for online monitoring      | ✗   | ✓     | ✓      | ✗       |
| Usage                                  | High | High  | Moderate | Low   |

Key: ✓: indicates suitability for use; ✗: not suitable

**VII. 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].

Analytical methods are of two types: Specific method, non-specific method

**VIII. VALIDATION PROTOCOL**

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 available a Master Validation Plan indicating the overall Cleaning Validation strategy for the product range / equipment type / entire site. The protocol must be prepared and approved prior to the initiation of the study and must either include or reference the documentation required to provide the following information:

- Specific Background, Purpose of the validation study, Scope of the validation study
- Responsibilities for performing the validation study
- Sampling procedure to be used and testing method to be used
- Acceptance criteria, Change control requirements, Deviations during the study

**IX. VALIDATION REPORT**
A validation report is necessary to present the results and conclusions and provide approval of the study. The report should include the following:

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 requirements, if applicable; approval of conclusions; Review of any deviations 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.

Subsequent to validation, an appropriate level of verification is required for routine operations.

X. CONCLUSION

Form this review article it can be concluded that cleaning validation is a process of attaining and documenting sufficient evidence to prove the effectiveness of cleaning process. Cleaning is directly related to safety and purity of the pharmaceutical product therefore it is an important and primary activity. Hence, 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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