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Published on *IVT Network* (http://www.ivtnetwork.com)

Lifecycle Approach Application to Cleaning Validation

By **Parveen Bhandola, Ph.D.** **Dec 1, 2015 8:00 am EST**

Peer Reviewed: Cleaning Validation

ABSTRACT

This discussion addresses the application of the lifecycle approach to cleaning validation. It is intended to help in the development of compliant, effective, and efficient cleaning validation processes and programs following a structured lifecycle approach. The distinction between "cleaning process" and "cleaning program" is discussed. The cleaning process is the actual performance of cleaning of the manufacturing equipment. The cleaning program encompasses all individual activities and systems supportive to the cleaning process. A listing of "WH" family questions – WHat, WHy WHen, WHere, and HoW that specifically address cleaning validation considerations is provided. A definition of cleaning validation based on the 2011 FDA definition for process validation is proposed. Cleaning validation activities are described in terms of the FDA lifecycle approach to process validation. Effective cleaning validation is not only a regulatory requirement, but it also makes a good business sense by preventing failures of the cleaning process that in turn result in economic losses including lost time, materials, and manpower, as well as the cost of investigations and documentation associated with these failures. Cleaning validation failures are detrimental to the manufacturer's reputation amongst patients and medical professionals as well as potentially causing regulatory action against the manufacturers. Several case studies are also presented.

INTRODUCTION

Cleaning Validation is a legally enforceable cGMP regulatory requirement per 21 CFR part 210 [1] that plays a crucial role in quality systems in life science industries. With ever-increasing concerns about cross-contamination, FDA inspections have recently enhanced their scrutiny of the strategy and approach that firms take in developing their cleaning validation protocols and programs. The FDA expects firms to base their cleaning validation activities on principles associated with the lifecycle approach. The science-based and risk-based lifecycle approach to manufacturing process validation described in FDA's "Guidance for Industry – Process Validation: General Principles and Practices (January 2011)" [2] is also directly applicable to cleaning validation. The lifecycle approach for cleaning validation is also consistent with FDA/ICH's guidance "Q8 (R2) Pharmaceutical Development" [3], "Q9 Quality Risk Management" [4], and "Q10 Pharmaceutical Quality System [5]. This approach has constantly been evolving over the years, and it very well reflects the FDA's current thinking about its applicability to the cleaning validation. All of the aforementioned documents are applicable and build on FDA "Guide to Inspections: Validation of Cleaning Procedures (7/93)" [6], the general regulatory expectations for cleaning validation.

This paper addresses the application of lifecycle approach to cleaning validation. It is intended to help in the development of compliant, effective, and efficient cleaning validation processes and programs according to the current regulatory expectations.

DEFINITIONS

Before addressing the FDA regulatory requirements and expectations for application of lifecycle approach to cleaning validation, discussion of “cleaning process” and “cleaning program” is warranted.

Cleaning Process

The cleaning process is the actual performance of cleaning of the manufacturing equipment. The cleaning process must reliably reduce levels of all potential contaminants on product-contact surfaces including previous product residues, cleaning agent residues, and the microbial contaminants to acceptable limits. The 100% removal of all contaminants is generally not practically possible and is not even required. Modern and highly sensitive analytical methods will always be able to find some level of contaminant. Criticality of residual limits of contaminants should be determined on a case-by-case basis for each situation, and the acceptable safe limits of the residues remaining after cleaning should be determined using a science-based and risk-based approach.

Cleaning procedures may be broadly categorized into two types: COP (Clean out-of-place) and CIP (Clean-in-place). In COP, the equipment is disassembled, or as such moved to a designated cleaning area, cleaned, dried, returned to the original location, assembled, and returned to service. CIP generally involves cleaning of the large installed equipment such as mixing tanks, dryers, and pipelines by circulating CIP solutions in the equipment. Hybrid cleaning processes are also possible, *i.e.,* equipment may be partially disassembled and parts cleaned COP while the major equipment structure is cleaned CIP. COP is the original and traditional cleaning process. CIP subsequently evolved to automate cleaning and reduce the cleaning time, minimizing variation, and reducing use of resources including water, cleaning agent, energy, and personnel. Basic cleaning procedures including pre-rinse, wash, post-rinse and final rinse/sanitization remain essentially the same for both the COP and CIP. Manual COP cleaning processes are generally more difficult to standardize due to numerous sources of variability inherently associated with manual cleaning. The strength and reliability of both the COP and CIP cleaning methods lie in identifying, evaluating, and controlling sources of variation – an extremely critical step before proceeding with the cleaning validation. Further, measuring residual contamination by appropriate and validated analytical methods must be carefully addressed. Documentation of all the above is essential.

Cleaning Program

The cleaning program encompasses all individual activities and systems supportive to the cleaning process. The cleaning program is aimed at identifying, evaluating, and controlling various factors to prevent cross-contamination. Analytical methods for measurement of residual contamination must be developed. Documentation of these activities is vital. Inter-disciplinary participation is essential for developing scientifically-sound cleaning programs. A well-developed cleaning program includes the procedures and data recording sheets (forms) that are able to address all of the following “WH” family questions (not a comprehensive list):

- **WH**AT to clean?
- **WH**Y to clean?
- **H**O**W** to clean?
- **H**O**W** to train for cleaning?
- **H**O**W** to document?
- **WH**EN to clean?
- **WH**O to clean?
- **WH**AT residues to measure?
- **WH**AT are worst- case residues?
- **H**O**W** are worst- case residues determined?
- **WH**AT is recovery percentage of residues from surfaces?
- **H**O**W** to measure residues?
- **WH**ERE to sample residues?
- **H**O**W** to train for sampling residues?
- **H**O**W** are sampling locations determined?
- **WH**AT is acceptable delay before starting cleaning (dirty hold time)?
- **WH**ERE is clean equipment stored?
- **H**O**W** long can clean equipment be stored (clean hold time)?

The objective of the cleaning program is to developspecific systems and controls to effectively prevent cross-contamination. The following are considerations associated with this objective:

- Facility: Dedicated to a single product or a multi-product facility
- Nature of processes: Sterile or non-sterile
- Facility design: Air handling system design, materials/personnel flow pattern, barriers and isolators
- Dosage form type: Solid, semi-solid, liquid or gel
- Residue type: Hydrophilic, hydrophobic, mixed composition, soluble, insoluble, rate of solubility, other considerations.
- Process equipment: Dedicated, shared, single-use
- Method of cleaning: Mechanized cleaning equipment with automatic or semi-automatic controls or manual cleaning.

CLEANING VALIDATION

Cleaning validation may be defined as follows:

The collection and evaluation of the cleaning data, from the cleaning process design stage through routine repeatable cleaning during commercial production, to provide documented assurance that the cleaning procedures are effective in reliably, reproducibly, and consistently reducing the levels of all contaminants including the previous product residues, cleaning agent residues, and the microbial contaminants to levels below the acceptable safe limits.

This definition of cleaning validation is based upon the FDA's current process validation guidance [2] which defines the process validation as follows:

"The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products."

It is noteworthy that the word "manufacturing" is missing from this definition, which implies a potential applicable to other processes including the cleaning validation.

Critical Aspects of the Cleaning Validation Definition

The critical aspects of the cleaning validation definition derived from the FDA Process Validation Guidance are the following:

"**Collection and evaluation of cleaning data...**" Cleaning validation must be science-based and data-driven.

"…f**rom the cleaning process design stage through routine repeatable cleaning during commercial production.**" The entire cleaning process must be addressed from design and development through monitoring and maintenance of the cleaning process, i.e., the lifecycle approach.

"…routine repeatable cleaning…" The cleaning procedure must be a defined cleaning procedure that is performed repeatably throughout the commercial lifecycle of the process. The process is repeatable – same input into cleaning.

"…documented assurance…" All aspects of the cleaning process must be documented. This includes supportive documentation.

"…effective in reliably, reproducibly, and consistently reducing the levels of all contaminants…" All residues must be considered. The process must be robust and reliable. The consistency of the process throughout the entire lifecycle of the product and process must be monitored and maintained. The outcome is repeatable – same output of the cleaning process. A cleaning process can be consistently repeatable and reproducible only if there is absence of significant sources of unknown and uncontrolled variability in the process.

PROCESS VALIDATION LIFECYCLE APPROACH – APPLICATION TO CLEANING VALIDATION

The lifecycle approach as stated in the FDA Process Validation Guidance when applied to the cleaning validation considers the cleaning validation as a continuous process having the following three distinct phases:

Stage 1: Design and Development of the Cleaning Process

Stage 2: Cleaning Validation including Process Performance Qualification

Stage 3: Continued Process Verification of the Cleaning Process

Stage 1: Design and Development of Cleaning Process

Stage 1 involves the design, development, and implementation of a cleaning validation process for removal of specific process residues. It further includes general and site level cleaning program considerations applicable to other cleaning processes conducted in the facility. These considerations are supportive to the specific cleaning process. The foundation of cleaning validation is laid in this stage. Main focus of this stage is on generating the cleaning process knowledge and understanding through well-designed and documented studies. These include understanding the properties of specific residues to be cleaned, cleaning cycle development, identification and control of potential variables, and ultimately providing assurance that the cleaning process remain in a state of control. These development activities should guide the development of cleaning programs and procedures. An effective process design is essential for developing a cleaning process capable of reliably and reproducibly producing the expected results. Main objectives of Stage 1 include the following:

- Develop equipment-specific cleaning procedures for product-contact surfaces. This should also consider procedures to clean the associated manufacturing area, equipment cleaning area, and areas that support the manufacturing and cleaning process.
- Develop procedures for cleaning between batches of the same product as well as for the cleaning to be performed at product change-overs.
- Assess the capability of environmental controls for suitability to prevent cross-contamination; for example, the adequacy of dust control systems.
- Select cleaning agent(s) and develop cleaning cycles.
- Develop the cleaning process and perform the cleaning cycle optimization to establish scientific knowledge and data to define the cleaning process for routine manufacturing use.
- Identify sources of process-related, equipment-related and personnel-related variability and develop a control strategy. See Case Study 1 for an example of variation in the cleaning process due to cleaning water system capacity.
- Identify the most-difficult-to-clean parts of the process equipment. See Case Studies 2 and 3.
- Ensure through procedural controls that the gaskets, hoses, filter bags, and similar equipment that are product-dedicated.
- Develop product-specific analytical methods for residues or utilize non-specific analytical methods as necessary.
- Perform swab recovery studies for all materials of construction (MOC) for the product-contact equipment parts.
- Toxicity of residues and analytical method development to appropriate levels of sensitivity.
- Develop a worst-case matrix for products that may be grouped for cleaning validation. See Case Study 4.
- Document all studies in support of the above.

Stage 1 also involves identifying and controlling the sources of variability in the cleaning process. Variability may be caused by variations in:

- Materials. For example, variation in cleaning agent concentration, water temperature
- Equipment. For example, reduction in the surface smoothness of product contact areas as well as reduction in efficiency of the cleaning equipment over a period of time
- Environment. For example, varying level of dust generation in the manufacturing area
- Process controls. For example, variation in the pressure of the water used for manual cleaning
- Personnel. For example, newly trained and experienced operators, day shift/night shift operators, and physical strength of operators.

Cleaning Process and Cleaning Program. Since process understanding is the foundation of cleaning validation, cleaning processes must be specifically developed for each specific API / product. A universal fit for cleaning validation cannot be expected except in unique situations, e.g., cleaning of highly water soluble formulations in large volume parenteral solutions. Insufficient understanding about the cleaning process is perhaps the most common cause of the failing or ineffective cleaning validation. Much of what is described in Stage 1 above is part of the site cleaning program applicable to other product cleaning validation conducted at the site. Again, all studies and cleaning program policies described above must be documented, and documents must be readily available for audit.

Stage 2: Cleaning Validation including Process Performance Qualification

Stage 2 activities demonstrate the successful completion of Stage 1 objectives. Stage 2 involves developing the cleaning validation protocol including acceptance criteria for the residue limits based on scientifically sound principles. The cleaning validation protocol, which is synonymous with Process Performance Qualification (PPQ), is executed during this stage. Cleaning validation is performed under cGMP conditions with the purpose of demonstrating controls over the cleaning process conducted during routine operations. Demonstration of controls should include variability that may be caused by operator-to-operator, shift-to-shift, and equipment-to-equipment (for similar equipment) variations; shift changeovers as well as the effects of breaks or time lags during various stages of the cleaning process. Specified sampling and acceptance criteria for residue limits must be soundly based and justified.

Cleaning validation is performed under routine commercial manufacturing conditions by the operators trained for the commercial process. These operators must also be trained in executing the cleaning process. Cleaning equipment and the utilities used in cleaning must be qualified before executing the cleaning validation protocol. Analytical methods used to measure residues must also be validated before executing the cleaning protocol.

Stage 3: Continued Process Verification of the Cleaning Process

The objective of the Stage 3 is to provide ongoing assurance that the Cleaning Validation continues to remain under a state of control throughout the entirety of commercial operations during the product life. This stage involves monitoring of the critical cleaning process parameters during routine manufacturing operations. It is aimed at detecting the process drifts and evaluating the unplanned and unexpected process variability that almost invariably creeps into the system in spite of having well-developed change control systems in place. Stage 3 involves performing periodic evaluation of the collective impact of individual changes implemented based on individual change assessments. Periodic evaluation of the executed CAPA's is also performed during this stage. Application of Statistical Process Control (SPC) techniques such as Control Charts for tracking the critical control parameters is a powerful tool for effectively implementing the Continued Process Verification. Occurrences requiring re-cleaning dirty equipment, deviations to the validated process, and other non-conformances are reviewed and evaluated as part of Stage 3 activities.

It is essential to understand the nature, source, and extent of variability in the cleaning process besides understanding the impact of variability on effectiveness of the cleaning process. Some degree of variability is inherently present in any cleaning process, and it is crucial to develop a strategy to optimally control the variability to provide assurance that the cleaning process remains consistent and reproducible during routine use. This process of developing an understanding and the mechanism of controlling the variability begins at the initial stages of the cleaning validation lifecycle and is ongoing as the process is used. Stage 3 never ends unless the product is discontinued.

Implementation of the lifecycle approach facilitates adoption of new technologies and making continuous improvements based upon the continuous increase in the level of process understanding. In fact, efforts to enhance process understanding should never stop as there is no finishing line in the race of process understanding.

FINAL THOUGHTS

From the lifecycle perspective, cleaning validation is not a one-time event starting and finishing with the execution of cleaning validation protocol. Cleaning validation is a continuous process consisting of three distinct stages. Stage 1 (Design and Development) is followed by Stage 2 (Cleaning Validation or PPQ) followed by Stage 3 (Continuous Process Verification). The lifecycle approach for cleaning validation facilitates implementing improvements essentially by making changes based on the process understanding gained during all three stages in the cleaning validation process. Success of each stage of cleaning validation depends on the success of the preceding stage. The overall cleaning validation can be successful only if it

is successful throughout the lifecycle.

Effective cleaning validation is not only a regulatory requirement, but it also makes a good business sense by preventing failures of the cleaning process. Effective cleaning validation is a key component of ensuring ongoing product quality. Cleaning process failures can result in huge economic losses in terms of the lost materials, time, and manpower as well as the cost of investigations and documentation associated with these failures. Failures may be highly detrimental to the manufacturer's reputation amongst patients and medical professionals as well as potentially causing regulatory action against the manufacturers. Cleaning validation can neither succeed in meeting the regulatory requirements nor in achieving business goals unless it is based on a thorough and complete approach including science and risk-based considerations. The lifecycle approach, comprising stages process design and development, reliable demonstration of cleaning validation, and ongoing monitoring and maintenance of the cleaning process, provides a structured approach for successful cleaning validation.

REFERENCES

1. FDA. Title 21 – Food and Drugs, Part 211, Current Good Manufacturing Practice for Finished Pharmaceuticals
2. FDA. Process Validation: General Principles and Practices, Guidance for Industry (January 2011)
3. FDA/ICH. Q8(R2) Pharmaceutical Development, Guidance for Industry (November 2009)
4. FDA/ICH. Q9 Quality Risk Management, Guidance for Industry (June 2006).
5. FDA/ICH. Q10 Pharmaceutical Quality Systems, Guidance for Industry (May 2007)
6. FDA. Guide to Inspections: Validation of Cleaning Procedures, Inspection Guide (7/93)

CASE STUDY 1: CLEANING WATER SYSTEM CAPACITY

Company A was performing manual cleaning for various pieces of process equipment. Though manual cleaning was generally considered suitable for the nature of the company's operations, the company did experience considerable variations in cleaning effectiveness in spite of its best intentions to standardize the cleaning procedures. The company tried to perform cleaning validation before addressing the sources of variability. When audited, this approach was not acceptable to the FDA, resulting in repeated 483 observations. The cleaning validation program eventually received FDA's positive feedback only after the company performed formal studies to investigate the ranges of variation in parameters such as high/low temperature, high/low pressure, and high/low flow rate of the cleaning water that was available in various shifts. Variation in cleaning water parameters was caused by the factors such as varying levels of demand for the cleaning water in various shifts. The company was initially trying to standardize the cleaning procedures only by standardizing the duration of various cleaning steps like pre-rinse time, detergent application time, detergent wash-off time, and final rinsing time without giving consideration to the variability in operating parameters of the cleaning water at different times of day. This is a clear example of an approach where the company rushed to the cleaning validation (stage 2) before fully understanding and establishing the cleaning processes (stage 1).

CASE STUDY 2: SPECIAL CLEANING EQUIPMENT

Company B cleaning validation program came under FDA's scrutiny due to repeated failures of the swab test results for a particular part of a piece of equipment during periodic cleaning verifications (stage 3) performed after completing the cleaning validation (stage 2). The issuance of an FDA-483 observation was averted by the company's proactive approach. The company conducted very thorough investigation into the likely causes of the swab test failures for that particular part of the equipment. It was discovered that scrubbing tools specified in the cleaning procedure were inadequate. The equipment part had an intricate interior surface that required a flexible scrubbing tool for thorough contact with the problematic surface. The company procured the proper scrubbing tool specifically for cleaning that part of the equipment, and revised the cleaning procedure instructions to reflect use of the new tool. Thereafter, the swab test results for that part of the equipment piece never failed. FDA accepted this approach -- and an FDA-483 observation was averted.

CASE STUDY 3: WORST-CASE SAMPLING LOCATIONS ON EQUIPMENT

Company C cleaning validation program was not consistent regarding the location of swab samples taken on equipment. Each validation protocol directed that “worst- case locations on equipment be sampled.” However, the selection of worst- case samples was not specified and was left to the discretion of the sampling technician. The technician had no basis for selection, and different sampling technicians selected different locations for sampling on the same piece of equipment. Every cleaning validation was different even though manufacturing processes were the same and residues were similar. Explaining why the same equipment had different worst-case sampling locations, including having no basis for selection of sampling locations except operator discretion, would have been difficult to explain in a regulatory audit.

A program to identify and standardize worst- case locations on equipment was initiated. A specified sequence of activities were implemented to determine worst-case locations. These included engineering analysis of equipment, areas of high accumulation of residues, operator input regarding most difficult to clean locations, ability to evaluate cleanliness, and other considerations. All information was documented and used to clearly identify worst-case sampling locations. Digital pictures were prepared indicating exact locations to be sampled by cleaning technicians. Sampling pages were then incorporated into all cleaning validation protocols. This activity resulted in standardized sampling for all protocols based on a thorough and defendable identification worst-case sampling locations.

CASE STUDY 4: SELECTION OF WORST-CASE API FOR CLEANING MATRIX

Company D was audited regarding the selection of worst- case API and product for cleaning validation. Their approach was critical for the cleaning validation program. Cleaning validation of the selected the worst-case API and associated product was used to justify not performing cleaning validation on other products. The selection of the worst-case API was based on USP listing of aqueous solubility of the API. The API with the lowest solubility in water was selected as the worst-case API, and cleaning validation was completed on that product. The cleaning procedures for all other products at the site were then considered to be acceptable because cleaning of the worst-case product was demonstrated to be validated. The auditor rejected this approach for multiple reasons. The company had several cleaning procedures utilizing different cleaning agents. Several of these methods used alkaline cleaning agents which had no relationship to solubility in water. The solubility properties of the various API’s in products at the site were also pH-dependent, again discrediting the use of water-solubility as the sole determinant of worst-case API. Several products contained polymeric excipients which resisted cleaning and were identified by manufacturing personnel as being very difficult to clean. There was no consideration of API dosage or toxicity in determining the worst-case compound.

The company initiated a program to revise their worst-case approach to cleaning. Products were grouped according to the cleaning method used for cleaning. Worst- case API and products were evaluated by multiple criteria including solubility in the cleaning agent, toxicity, difficulty to clean, and other considerations. Six groupings were ultimately determined, and the worst-case API / product was identified for each group. Cleaning validation was then completed on each worst-case API / product identified representing the identified group.
