

Developing A Science-, Risk-, & Statistics-Based Approach To Cleaning Process Development & Validation

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Cleaning manufacturing equipment to prevent cross contamination of pharmaceutical products is a fundamental aspect of GMPs. Validation of cleaning processes has been required within cGMP industries for a long time and is recognized as an important activity to establish that product cross contamination is controlled to ensure patient safety and product quality.



While cleaning, in and of itself, is a relatively simple process, the pressures of inspection scrutiny and the reactionary programs created by industry to address regulatory concerns have transformed the validation of cleaning into a complex, expensive, and time-consuming activity. From a simple project management analysis, the time that would be required to perform cleaning validation for a facility with multiple products, multiple pieces of equipment, and multiple cleaning procedures can easily run into years.

Figure 1 shows a very aggressive, and a clearly hard to accomplish, timeline for concurrently performing three runs for only three cleaning validations allowing only one day between runs and ignoring analysis time and other items. Despite this, the timeline is still six months.

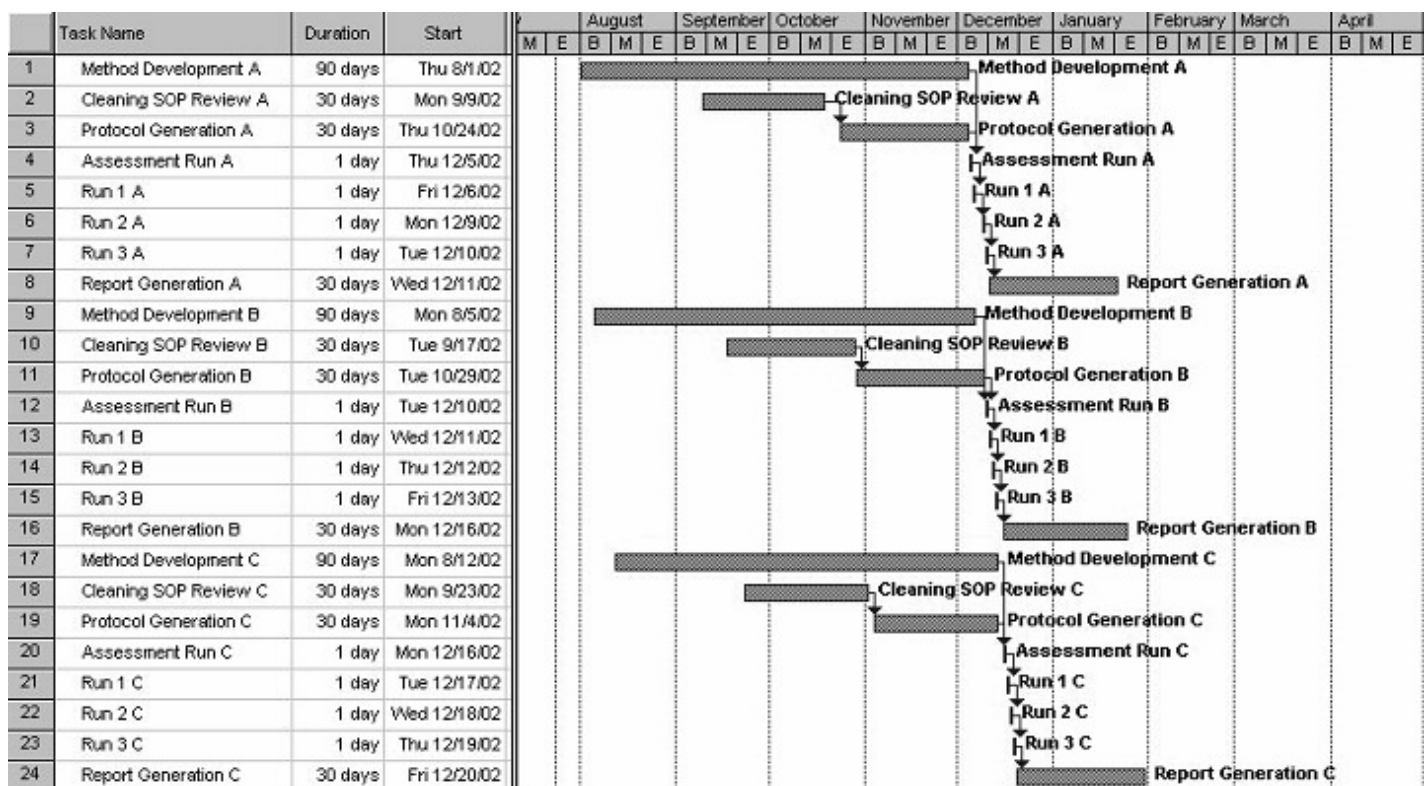


Figure 1: Hypothetical timeline for cleaning validation of three products

Considering that cleaning validation runs cannot be scheduled and performed every day and the need for method development, protocol development, laboratory analysis, and report writing, it is clear that cleaning validation consumes a considerable amount of resources.

Consequently, companies have made various efforts to reduce cleaning activities, such as dedicating equipment or converting to disposable items, but these strategies have their own inefficiencies and costs. Companies have also resorted to strategies such as product grouping, equipment grouping, matrixing, and bracketing to reduce the amount of cleaning they validate, sometimes without acceptable justification. Many companies today validate the cleaning of only one or two "hardest-to-clean" products, selecting them based on the solubility of the API or because the calculated limit is lowest, even though these may not be truly justifiable criteria. Even with such efforts, part of the reality has been that, for all intents and purposes, cleaning validation never seems to be completed. The EU guideline "Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use," Annex 15 outlines in Section 10 that for a worst case product approach a scientific rationale should be provided.² It also outlines criteria for determining the worst case, and these criteria may include solubility, cleanability, toxicity, and potency. This approach makes determining a worst case situation even more complex.

As with many things, the pharmaceutical industry has tended to understand cleaning almost entirely in its relation to regulatory expectations. In particular, cleaning has become closely associated with "process validation." In the late 80s/early 90s, the FDA, as well as other regulatory agencies, began to view cleaning as a process that needed to be validated.³ At the same time, several legal decisions concerning cleaning made during the resolution of the well-known Barr Labs case solidified this

viewpoint.⁴ Consequently, companies set about validating existing cleaning procedures without questioning whether the procedures were the most effective or optimal, or even if they were using an appropriate cleaning agent. The cleaning procedures that were subsequently validated may not have been the best choice for their situations.

Cleaning validation incorporates the traditional preapproved protocol, with predetermined acceptance criteria and a three-run process validation approach. Because of the traditional approach, the industry also struggled over how to set the required predetermined acceptance criteria. This process validation approach was adopted without ever asking if three cleaning validation runs and predetermined acceptance criteria were appropriate for the validation of cleaning. Based on that reason, Annex 15 also outlines in Section 10 that the cleaning procedure should be evaluated an appropriate number of times (based on a risk assessment) and meet the acceptance criteria in order to prove that the cleaning procedure is validated.

All these issues underscore the need for effective and efficient cleaning programs that focus efforts and resources where they provide the most value.

Since 2001, there have been many new, and for this highly conservative industry, radical movements from both regulators and within the industry itself. Examples coming from the FDA include “GMPs for the 21st Century,”⁵ quality by design (QbD),⁶ process analytical technology (PAT),⁷ and the agency’s 2011 guideline on process validation.⁸ Globally, the new International Conference on Harmonisation's guidelines, in particular Q8 and Q9,⁹ are major forces driving change in the industry. Movements within pharmaceutical manufacturing itself include lean manufacturing, Six Sigma, and operational excellence (OpEx), which have grown out of the pressures to reduce costs and to better supply the market. These “planets” have aligned to create a tide drawing the industry toward science-based, risk-based, statistics-based, and cost-effective approaches to ensuring patient safety and product quality during pharmaceutical development and manufacturing. As one of the critical processes in manufacturing, cleaning and its validation can benefit from all these initiatives.

The introduction of the acceptable daily exposure (ADE) in 2010 provided a tool that could be used for setting science-based acceptance criteria for the cleanliness of equipment.¹⁰ Several subsequent publications have revealed how replacing the traditional approaches to setting acceptance criteria with an approach based on the ADE leads to better patient safety and can reduce the validation effort for lower-risk situations,¹¹⁻¹⁴ and a recent publication discussed how an ADE-derived scale can be used to easily and visually evaluate the risks of cross contamination in manufacturing facilities, including for cleaning.¹⁵

Cleaning validation programs and master plans could benefit from a risk-based approach to their design and management. Cleaning procedures could benefit through a statistics-based QbD approach resulting in safer and more reliable procedures, and the analytical methods used in cleaning could benefit from PAT, resulting in faster turnaround of equipment. Many of the techniques used in lean manufacturing, Six Sigma, and operational excellence could be used to reduce the time and effort spent, improve the results obtained during cleaning validations, and

provide statistics-based means for evaluating and controlling cleaning processes. Perhaps even cleaning, which is certainly a process, should be looked at and evaluated in the manner being suggested in the FDA's 2011 process validation guidance; indeed, the FDA believes that this guidance is applicable to cleaning.¹⁶

The authors believe focusing industry efforts where the risks are high will increase patient safety and reducing efforts where the risks are low will ease the regulatory burden on industry and improve operational efficiencies overall.

Regulations And Current Guidance And Their Application To Cleaning

This section explores in more detail how the regulations and current guidance mentioned above provide direction on how to implement these approaches to cleaning.

The requirements in 21 CFR 211.67(a) state that *“Equipment and utensils shall 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 beyond the official or other established requirements.”*¹⁷

Similarly, 21 CFR 111.27(d) states *“You must maintain, clean, and sanitize, as necessary, all equipment, utensils, and any other contact surfaces used to manufacture, package, label, or hold components or dietary supplements.”*¹⁸

21 CFR 820.70(e) also states *“Contamination control. Each manufacturer shall establish and maintain procedures to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality.”*¹⁹

From these statements, several required elements of a cleaning program can be determined: the scope of cleaning, a required schedule for maintenance, and targets to achieve. In order to alter the “identity,” “strength,” or “purity” of a product, certainly gross contamination would be required. Such high levels should not be found after cleaning. However, in some cases, process residues below the order of gross contamination may still affect patient safety and possibly product quality. One goal of a cleaning program is to verify that no gross contamination remains after cleaning and that any residues that do remain do not jeopardize the safety of the patient or quality of the next product.

Now let's look at some of the many regulatory guidances that have come out since 2001. While some of them have some degree of application to cleaning, the two guidances that have the most applicability to cleaning are ICH Q9 and the FDA's 2011 process validation guidance.

ICH Q9 Guidance

ICH Q9 outlines basic principles and examples of tools for quality risk management that can be applied to pharmaceutical processes. In ICH Q9 we find two primary principles of quality risk management:⁹

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
- The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

If we apply these principles to cleaning, it is apparent that the risks the cleaning processes may present to patient safety and product quality should be **scientifically assessed**. The extent of any activities, such as cleaning development, cleaning verification, cleaning validation, monitoring, etc., should then be driven by **the level of risk** presented. The implementation of these principles offers serious potential for developing useful, effective, and efficient cleaning programs.

In fact, Annex II, "Potential Applications for Quality Risk Management," subsection 6, "Quality Risk Management as Part of Production" under Validation states, "To identify the scope and extent of verification, qualification and validation activities (e.g., analytical methods, processes, equipment and **cleaning methods**," which clearly encourages the use of ICH Q9 for developing a cleaning validation program. Annex II subsection II.4 "Quality Risk Management for Facilities, Equipment and Utilities" also states that ICH Q9 principles can be applied to setting "acceptable (specified) cleaning validation limits." A precedent for implementing ICH Q9, as it pertains to cleaning, has already been set for this in the International Society for Pharmaceutical Engineering's (ISPE) Risk-Based Manufacturing of Pharmaceutical Products (Risk-MaPP) Baseline® Guide.¹⁰ Figure 2 shows an overview of the ICH Q9 quality risk management process.

ICH Q9 Steps	Corresponding Cleaning Development and Validation Elements	
Risk Identification	Data collection	Identify possible cleaning process residues - API, cleaning agent, etc. Collect historical cleaning data and other knowledge Methods for detection of process residues
	Hazard identification	Determine ADEs for cleaning process residues Calculate maximum safe carryover Identify possible failure modes of cleaning process
Risk Analysis	FMEA (Initial)	
	Severity	Impact of cleaning process failure (e.g., toxicity, product quality)
	Exposure	Historical cleaning data and other cleaning knowledge Bench scale analysis (process residue characterization, cleanability, cleaning agent selection, critical process parameter determination, design of experiments, "design space" definition) Cleaning process robustness
	Detectability	Detectability of cleaning process residues
Risk Evaluation	Collection and evaluation of cleaning data Statistical evaluation of data (Cpk/Ppk) Margin of safety measurement Statistical process control limit determination	
Risk Reduction	Design of experiments Define the cleaning "designspace" Cleaning process optimization Training	
Risk Acceptance	FMEA (Final)	
	Severity	Impact of cleaning process failure (e.g., toxicity, product quality)
	Exposure	Process capability determination (Cpk/Ppk) Margin of safety measurement Statistical process control limit determination
	Detectability	Statistical process control charting Monitoring program / periodic evaluation Visual inspection PAT applications
Risk Review	Updates to ADEs based on new clinical/toxicological data Cleaning failure investigations New product introductions Cleaning process improvements Statistical process control charting Monitoring program / periodic evaluation	
Risk Communication	Facility cleaning risk assessment Hazard identification report ADE monographs Risk analysis of cleaning procedures Cleaning validation masterplan CV protocols CV reports Risk evaluation of cleaning procedures Cleaning control strategy Training records New product risk review	

(Note: FMEA is used as an example in this table. Other RA tools may be equally appropriate.)

Process Validation: General Principles And Practices

The FDA's process validation guidance⁸ aligns with the product life cycle concept and with existing FDA guidance on ICH Q8-Q10 and also describes concepts that are directly applicable to cleaning and cleaning validation. We can simply add "**cleaning**" to the elements of the process validation guidance as shown below.

- **Cleaning** Process Design — Building and capturing process knowledge and understanding
 - Application of design of experiment to **cleaning**
 - Multifactorial interactions
 - Using risk analysis tools to screen potential variables
- **Cleaning** Process Qualification
 - Use of statistical methods in analyzing all collected **cleaning** data
- Continued **Cleaning** Process Verification
 - Use of statistical process control techniques
- Continuous Improvement
 - Use of historical data (monitoring, etc.) or technological advances for improvement of **cleaning** processes

The elements of the process validation guideline can be easily worked into a framework for a science-, risk-, and statistics-based approach to cleaning. Table 2 shows how cleaning process development and validation maps to the FDA's process validation guidance.

Table 2: Map of FDA's Process Validation Guidance Elements to Cleaning

Process Validation Steps		Corresponding Cleaning Development and Validation Elements
Stage 1 - Process Design	Building and capturing process knowledge and understanding	Historical cleaning data and other cleaning knowledge Bench scale analysis (process residue characterization, cleanability, cleaning agent selection, critical process parameter determination) Design of experiments Define the cleaning "design space" Cleaning process optimization
	Establishing a strategy for process control	Process residue characterization, cleanability determination Cleaning agent selection Critical cleaning process parameters Risk analysis of cleaning procedures Level of cleaning necessary Risk analysis for master planning Product/equipment grouping strategies Cleaning control strategy Analytical method selection (Vis, TOC, etc.)
Stage 2 - Process Qualification	Design and qualification of utilities and equipment	Equipment design for cleanability Cleaning equipment design/qualification
	Process performance qualification	Cleaning process robustness Collection and evaluation of cleaning data Statistical evaluation of data (Cpk)
	PPQ protocol	Sampling strategy Analytical methods (Vis, TOC, HPLC, etc.) Hold Time Studies
	PPQ protocol execution and report	Process capability determination Margin of safety measurement Statistical process control limit determination
Stage 3 - Continued Process Verification		Statistical process control charting Monitoring program / periodic verification Visual inspection PAT applications New product risk review

cGMPs For The 21st Century Guidance

In the FDA guidance "Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach"⁵ we see four principles that have particular relevance to cleaning:

- Encourage the early adoption of new technological advances by the pharmaceutical industry.
- Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches, to all aspects of pharmaceutical production and quality assurance.
- Encourage implementation of risk-based approaches that focus both industry and agency attention on critical areas.
- Ensure that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science.

Applying these principles to cleaning, it follows that the extent of any activities, such as cleaning development and cleaning validation, should be driven by the level of risk presented and that the use of modern technology is encouraged.

PAT Guidance

The FDA guidance “PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance”⁷ states (again adding **cleaning**):

- A desired goal of the PAT framework is to design and develop well-understood **cleaning** processes that will consistently ensure a predefined quality at the end of the **cleaning** process. Such **cleaning** procedures would be consistent with the basic tenet of quality by design and could reduce risks to quality and regulatory concerns while improving efficiency.
- Reducing **cleaning** cycle times by using on-, in-, and/or at-line measurements and controls

In the PAT guidance we find that, as a process, cleaning should be designed, developed, and well understood, and the use of on-, in-, and at-line measurements and controls is encouraged.

Quality By Design

Although the quality by design initiative as described in ICH Q8-Annex 1 addresses product manufacturing processes, there are principles there that can be applied to cleaning processes as well, such as (once again adding **cleaning**):⁶

- Selecting an appropriate **cleaning** process.
- Identifying a **cleaning** control strategy (CS).
- A systematic evaluation, understanding and refining of the **cleaning** process, including:
 - Identifying, through e.g., prior knowledge, experimentation, and risk assessment, the material attributes and **cleaning** process parameters that can have an effect on **cleaning** critical quality attributes (CQAs);
 - Determining the functional relationships that link material attributes and **cleaning** process parameters to **cleaning** CQAs.
- Using the enhanced **cleaning** understanding in combination with quality risk management to establish an appropriate control strategy which can, for example, include a proposal for design space(s) and/or real-time release.

Using a systematic approach such as those described in the Q8-Annex 1 could enable continual improvement and innovation of cleaning processes without being locked into previously validated parameters and restricted by onerous change control procedures.

ICH Q7 Guidance

ICH Q7 Section 5.2.5 states that “Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified”.²⁰

Through the use of the word “justified,” this simple sentence implies that science-based approaches should be employed in setting acceptance criteria for cleaning development and cleaning validation. The risk-based approach to cleaning validation is further recommended in point 12.70:

"In general, cleaning validation should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to API quality."

Although ICH Q7 applies specifically to APIs, the concept that science-based and risk-based approaches should be employed in cleaning development and cleaning validation can be extended to all pharmaceuticals.

Annex 15 Of The EU GMP Guide

Annex 15 states that:²

“Limits for the carryover of product residues should be based on a toxicological evaluation to determine the product specific Permitted Daily Exposure (PDE) value¹. The justification for the selected PDE value should be documented in a risk assessment which includes all the supporting references”

¹ See EMA Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities

As in ICH Q7, the use of the word “justification” implies that science-based and risk-based approaches should be employed in setting acceptance criteria for cleaning development and cleaning validation. **Note:** Annex 15 is applicable to pharmaceutical products.

Operational Excellence And Six Sigma

Operational excellence can be defined as conducting business in a manner that satisfies customer demand, improves quality, and generates higher yields, faster throughput, and less waste. Six Sigma can be defined as a disciplined, data-driven approach and methodology for eliminating defects in any process.

These two approaches provide statistical tools to improve processes and increase quality. Since cleaning is a process that can be measured, these techniques can be effectively used to improve the cleaning process and enhance the safety and quality of pharmaceutical products.

Summary

The guidance discussed above can be applied to create a new approach to cleaning and cleaning validation that is based on science, risk, and statistics. It offers clear ways of making sensible changes in cleaning that would reduce the complexity, lower the costs, and shorten the process while providing an even higher probability that cleaning of pharmaceutical manufacturing equipment has

been effective. By implementing a truly science-based approach, such as the use of the ADE for risk analysis, with appropriate risk assessments, and with cleaning process development in place, a streamlined cleaning program may be readily developed that ensures patient safety and product quality while lightening the regulatory burden on industry.

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