Cleaning Validation for the 21st Century: Overview of New ISPE Cleaning Guide

by Andrew Walsh

Introduction

ISPE and representatives from the pharmaceutical industry have entered into a partnership to jointly develop a science- and risk-based approach for the prevention of cross contamination that will, on a case-by-case basis, determine the scope and degree of cleaning validation.

This new ISPE Guide, “Science and Risk-Based Cleaning Process Development and Validation,” will describe how to implement cleaning programs, using science- and risk-based approaches, in accordance with the new principles promulgated in ICH Q7 to Q10, FDA’s cGMPs for the 21st Century, FDA’s PAT Initiative, FDA’s Process Validation Guideline, as well as the statistical approaches of “Six Sigma” and “Operational Excellence.” The Guide will also describe how to implement cleaning programs that maintain compliance with FDA, EMEA, and MHLW regulatory expectations. A global team of cleaning, cleaning validation, quality assurance, toxicologists, and Six Sigma professionals representing API, clinical, pharmaceutical, and biological manufacturing, as well as FDA representatives has been assembled to develop this Guide.

Background

Cleaning validation is a required activity within the pharmaceutical, biological, nutritional supplement, and medical device industries. From both a regulatory and industry standpoint, cleaning validation is recognized as an important activity to establish that product cross contamination is controlled to ensure patient safety and product quality.

Cleaning validation is an ongoing activity within these cGxP compliant environments which necessitates the investment of significant resources and time. From a simple project management analysis, the time that would be required to perform cleaning validation runs for a non-dedicated facility with multiple products, pieces of equipment, and cleaning procedures can easily run into years. Considering that cleaning runs cannot be scheduled and performed every day and the need for supporting activities including method development, protocol development, laboratory analysis time, and report writing, cleaning validation can consume considerable time and resources.

Companies have made various efforts to reduce the amount of time and resources, such as dedicating equipment or converting to disposables. These strategies have other inefficiencies and costs associated with them. Even with such efforts, part of the reality has been that, for all intents and purposes, cleaning validation never seems to be completed. This emphasizes that a useful, effective, and efficient cleaning program cannot be developed without focusing efforts and resources where they provide the most value.

With appropriate cleaning development and risk assessments in place, a streamlined cleaning program may be readily developed that is both science-based and risk-based while ensuring patient safety and product quality.

Pharmaceutical manufacturing is in a dramatically revolutionary time in its history. There have been many new, and for this highly conservative industry, radical movements over the past few years from both regulators and within the industry itself. Examples coming from the FDA include “GMPs for the 21st Century,” “Quality by Design” (QbD), “Process Analytical Technology” (PAT), and the new Guideline on
Cleaning Validation

Process Validation. Globally, the new ICH guidelines, in particular Q7a to Q10, are another major force driving change in the industry. Movements within manufacturing itself include “Lean Manufacturing,” “Six Sigma,” and “Operational Excellence” (OpEx) that have grown out of the pressures to reduce costs and to better supply the market. Currently, all these “planets” are aligning to create a tide drawing the industry in a new direction toward science-based, risk-based, and cost effective approaches to ensuring patient safety and product quality during pharmaceutical development and manufacturing. As a critical manufacturing process, cleaning and its validation can benefit from all of these initiatives.

Cleaning, as with many things, has tended to be understood by the industry only 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 and as such, needed to be “validated” similar to process validation. At the same time, several legal decisions concerning cleaning were made during the resolution of the well known Barr Labs case that solidified this viewpoint. Consequently, a great deal of energy began to focus on the “validation” of cleaning procedures, but unfortunately not on the process of cleaning itself.

In many cases, companies set about “validating” cleaning procedures as they existed without questioning whether they 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 situation.

Cleaning validation took the traditional pre-approved protocol and three runs “process validation” approach. Because of the traditional “process validation” approach, the industry also struggled over how to set the required “predetermined acceptance limits.” Process validation was measured against predetermined specifications. This invoked the question: “What should the “predetermined acceptance criteria” for cleaning be?” This “process validation” approach was adopted without ever asking if three cleaning validation runs were appropriate or were predetermined acceptance criteria appropriate for cleaning validation or verification. Perhaps cleaning, which is considered a process, should be looked at and evaluated differently as is being suggested in the FDA’s new Process Validation Guideline.

This ISPE Guide will provide a new approach to meeting regulatory expectations for cleaning and offer a fresh perspective on approaches to cleaning and its validation based on science and risk.

Regulations and the Application of Current Guidance to Cleaning

The cleaning of manufacturing equipment, as a means to prevent cross contamination of pharmaceutical products, is a fundamental aspect of CGMPs. Cleaning, in and of itself, is a relatively simple process; yet, under the pressures of inspectional scrutiny and the reactionary programs created by industry to address regulatory concerns, the validation of cleaning has transformed into a complex, expensive, and time consuming activity. However, all of the industry forces mentioned above offer ways of making sensible changes in the areas of cleaning that would reduce the complexity, lower costs, and shorten the process while providing a high degree of assurance that cleaning has been effective. Before discussing how cleaning and its validation can be changed and improved, the goals of the regulations themselves and the Guidance should be examined.

Code of Federal Regulations

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.”

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.”

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.”

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. To alter the “identity,” “strength,” or “purity” of a product, 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 product quality. So one goal of a cleaning program is to verify that no gross contamination remains after cleaning and any process residues do not jeopardize the “safety” of the patient or “quality” of the next product.

ICH Q9 Guidance

Looking at the ICH Q9 guidance, it states two primary principles of quality risk management:

• The evaluation of the risk to quality should be based on scientific knowledge and ultimately, link to the protection of the patient.

• The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.
By applying these principles to cleaning, it is apparent that cleaning processes should have a risk assessment performed, using science, in the evaluation of the risks the cleaning processes may present to patient safety and product quality. The degree of any activities, such as cleaning development, cleaning validation, cleaning verification, monitoring, etc., should be driven by the level of risk presented. A precedent has already been set for this in the ISPE Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP).^5

cGMPs for the 21st Century Guidance
In the FDA guidance “Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach,” there are four principles with 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, the degree of any activities, such as cleaning development and cleaning validation, should be driven by the level of risk presented, and in addition, that the use of modern technology to implement these risk-based approaches is to be encouraged.

PAT Guidance
The FDA guidance “PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance” states:

• A desired goal of the PAT framework is to design and develop well understood processes that will consistently ensure a predefined quality at the end of the manufacturing process. Such 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 production cycle times by using on-, in-, and/or at-line measurements and controls.

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

Quality by Design
Although the Quality by Design initiative as described in the ICH Q8-Annex addresses product manufacturing processes, there are principles there that can be applied to cleaning processes as well, such as:

• Selecting an appropriate process.
• Identifying a Control Strategy (CS).
• A systematic evaluation, understanding, and refining of the process, including:
  - Identifying, through prior knowledge, experimentation, and risk assessment, the material attributes and process parameters that can have an effect on production Critical Quality Attributes (CQAs);
  - Determining the functional relationships that link material attributes and process parameters to product CQAs.
• Using enhanced process 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.

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

Process Validation: General Principles and Practices
The new Guide is intended to align process validation with the product lifecycle concept and with existing FDA guidance on ICH Q8-Q10 and also describe concepts that are directly applicable to cleaning and cleaning validation and the direction of this Guideline.

• Cleaning Process Design – Building and Capturing Process Knowledge and Understanding
  - Application of Design of Experiment
  - Multifactorial Interactions
  - Using Risk Analysis Tools to screen potential variables
• Cleaning Process Qualification
  - Use of statistical methods in analyzing all collected 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 new Process Validation Guideline provide a framework that closely matches the elements of this science- and risk-based guideline.

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.

Goals of Cleaning Based on Current Guidance

By compiling all the elements from the guidance and definitions above into a set of principles, a future vision of cleaning can be derived. This vision is comprised of five main themes: Science, Risk, Design, Validation, and Control. The goals for this Guide are as follows:

Science

An appropriate cleaning program should be based on state-of-the-art pharmaceutical science and design and develop well understood cleaning processes that will consistently ensure a predefined quality at the end of the cleaning process. Scientific knowledge and principles should be considered when defining a cleaning program including, but are not limited to:

- Develop process understanding.
- Identify, define, analyze, evaluate, control, and manage sources of variation - the sources of risk.
- Define, design, develop, optimize, control, and verify cleaning processes and cleaning assessment methodologies.
- Design and implementation of process analytical technologies.
- Describe, analyze, process, interpret, and evaluate information and data obtained from cleaning development and validation studies.

Risk

The cleaning process should have an evaluation of the risk to product quality based on scientific knowledge that focuses both industry and Agency attention on critical areas and ultimately links to patient safety and product quality. The level of risk presented by a cleaning process can be evaluated by considering the various factors associated with cleaning. Questions such as:

- What are the hazards associated with the process residues?
- Are there hazards associated with the cleaning process?
- How hard is it to clean the process residues?
- How effective is the cleaning process?
- Is it hard to detect process residue(s)?
- Can I see process residues below the safe limits?
- Can I visually inspect all of the equipment surfaces?

Based on the answers to these types of questions, the cleaning process can be assigned a position on the scale shown in Figure 1.

Design

For achieving the intended purpose(s) and desired quality objective(s) of cleaning processes, the cleaning processes and related activities shall be designed using scientific knowledge and principles. Such cleaning processes would be consistent with the basic tenet of “Quality by Design” and could reduce risks to patient safety, product quality, and regulatory concerns while improving efficiency. This should include a systematic evaluation, understanding, and refinement of the cleaning processes, including:

- identifying, through prior knowledge, experimentation, and risk assessment, the material attributes and cleaning process parameters (e.g., cleaning agents, product cleanability, raw materials, degradants, time, temperature, etc.) that can have an effect on cleaning Critical Quality Attributes
- determining the functional relationships that link material attributes and cleaning process parameters to cleaning CQAs through understanding of cleaning operating space and design space (e.g., Designed Experiments)
- using science and cleaning process knowledge and understanding for continual improvement of cleaning processes

Validation

Validation in this Guide includes validation and verification activities to ensure a capable cleaning process. Based on the level of risk, stage of development, or level of product understanding, cleaning processes should be subject to scaling levels of validation or verification with greater focus on products and/or processes that present higher risks. For example, cleaning processes for products that present little risk may be validated or verified using visual inspection alone. Also, for example, early stage products may involve higher levels of verification until increased product understanding indicates a low level of risk and a lower level of verification necessary.

Control

An appropriate control strategy should be established. This may include enhanced process understanding and adoption of new technologies in combination with quality risk management. An appropriate strategy may include real-time release of clean equipment using visual inspection, PAT, or real time modeling using multivariate analysis.

Application of Risk and Science to Cleaning

Cleaning Risk Assessment

The subject of “risk” in pharmaceutical manufacturing has
been discussed in ICH Q9 and ISPE’s Risk-MaPP Baseline Guide. Risk can be defined as:

\[
\text{Risk} = f (\text{Hazard, Exposure})
\]

where Risk is a function of the severity of a hazard and the level of exposure to that hazard.

For the purposes of cleaning, risk can be further defined as:

\[
\text{Risk} = f (\text{Hazard, Exposure, Detectability})
\]

or

\[
\text{Risk} = f (\text{Severity of Process Residues, Level of Process Residues, Detectability of Process Residues})
\]

For a reliable assessment of risk, it is imperative to have a scientific means (e.g., risk management tools) to identify the hazard presented by a product (e.g. API, degradants, intermediates), cleaning agent or bioburden/endotoxin, evaluate the ability of a cleaning process to remove process residues to levels that are acceptable and the ability to detect and quantify the presence of process residues after cleaning.

Risk analysis may be used to create a scientific rationale for cleaning validation. An evaluation of which process residues should be tested for is based on risk. Based on the level of risk, cleaning processes should be subject to scaling levels of validation or verification with greater focus on processes with higher risks. The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk posed by the cleaning process.

Cleaning Hazard Analysis

The FDA’s “Guide to Inspections Validation of Cleaning Processes” under the section on Acceptance Limits states, “The objective of the inspection is to ensure that the basis for any limits is scientifically justifiable.” Therefore, limits should be determined that are directly derived from an actual hazard that a process residue may pose.

The hazard presented by a process residue may be determined from a toxicological review performed by an individual(s) qualified to make that assessment, such as a toxicologist. This would involve a thorough review of all relevant toxicological data available for the compound under study. The pharmaceutical industry is unique in that extensive pre-clinical and clinical data on APIs is available to review. When these data are available, an Acceptable Daily Exposure (ADE) can be determined and used as a measure of the severity of hazard presented by the compound. The calculation of an ADE is a standard procedure of toxicology used for decades and is the basis of ISPE’s Risk-MaPP Guide. The ADE can be used to calculate a “Maximum Safe Carryover” to evaluate process residue data and determine the level of risk posed by the process residue. When an ADE is not available, such as for intermediates or compounds in early development, alternative approaches such as the “Threshold of Toxicological Concern” may be justified.9

The potential hazards presented by equipment design also should be considered. Equipment should be designed to facilitate cleaning, inspection, and monitoring.

Cleaning agents should be selected based on scientific principles and the level of hazard they pose. It is preferable that all cleaning agent components are found on the Generally Recognized As Safe (GRAS) lists. In the case the cleaning agent is not a GRAS material, the ADE can be used to calculate a “Maximum Safe Carryover” to evaluate process residue data and determine the level of risk posed by the process residue.

The hazard of possible bioburden from a previous product and the possibility of microbial proliferation during or after a cleaning process and the hazards this presents needs to be assessed as well. For example, the hazard(s) presented in holding equipment in a dirty state or clean state need to be addressed.

Cleaning Exposure

After the hazard of a compound has been identified and an ADE and corresponding “Maximum Safe Carryover” calculated, steps to minimize and evaluate the levels of possible exposure should be taken.

Prior to use, cleaning procedures should be subjected to risk assessments, e.g., Cleaning Failure Modes and Effects Analysis (FMEA/FMECA) or other risk management tools to minimize risk of failure, improve them, and make them more reliable and robust. If the severity of process residues, level of process residues, and detectability of process residues of the hazard can be measured and quantified, cleaning processes can then be evaluated by risk management tools. Based on the severity posed by process residues, the likelihood of process residues and the ability to detect process residues, a Risk Priority Number (RPN) can be determined for all cleaning process steps. Actions can then be taken to eliminate or reduce the risk of process residues.

Process residue data should be obtained during cleaning process development and statistically analyzed and compared to the “Maximum Safe Carryover” to evaluate the relative risk of cross-contamination. If risks are high, additional measures should be pursued and documented in the cleaning risk assessment. The higher the potential for contamination, the greater the level of effort and degree of documentation required to ensure product quality and patient safety. The lower the potential for contamination, the lower the level of effort and degree of documentation required. If risks cannot be reduced to acceptable levels, the equipment being cleaned should be either dedicated or disposable.

When the Risk Assessment indicates microbial contamination is a concern, such as for sterile equipment, equipment hold times etc., microbial data should be obtained and evaluated to determine what levels of exposure are presented. Microbial data can be evaluated in a manner similar to product residues. A scientifically based technique for evaluation has already been described.10,11 Where the risk assessment indicates microbial contamination is not a major or critical concern, such as for non-sterile equipment, obtaining microbial data may not be necessary.
Cleaning programs and cleaning master plans should be developed based on the results of hazard analyses and risk assessments.

**Cleaning Detection**

The ability to detect a hazard when it is present is an important factor in reducing risk. If a hazard can be seen or detected, steps can be immediately taken to remove or reduce the hazard before proceeding to manufacturing.

There are several methods of detecting process residues that are readily applicable to evaluation of cleaning processes and are appropriate for different levels of risk. Methods such as visual inspection, conductivity, total organic carbon analysis, and HPLC are typically used for cleaning validation studies.

Visual inspection is a powerful tool for cleaning validation and verification. Visual inspection allows the detection of contamination concentrated in small areas that could otherwise go undetected by sampling or other analyses. All cleaned accessible surfaces should be evaluated and certified clean through visual inspection. The limit of visual detection can be determined for the process residues of compounds. Visual standards (“coupons”) can then be created with specific levels of process residue deposited on them and used to certify inspectors. Extensive work has been done to demonstrate the applicability and validity of visual inspection. Visual inspection is most appropriate for products that pose low risks. (Note: Visual inspection may be used with products that pose higher risks if they are easily detected visually.)

Conductivity is another very sensitive tool for detecting the absence or presence of conductive (ionic or charged) compounds and is very useful in determining the presence of most cleaning agents and some products. Conductivity is most often used to determine the completion of Clean-in-Place (CIP) wash cycles. Conductivity is also most appropriate for products that pose low risks, but also can be used with higher risk products if scientifically justified.

Total Organic Carbon (TOC) analysis is another powerful tool for cleaning validation. TOC is a simple and rapid method that can detect low levels of process residues of most pharmaceutical compounds including those considered water-insoluble. TOC is a very easy method to develop and should be the first choice when swab samples are required. TOC is appropriate for cleaning processes that pose low to high risks.

HPLC is a very sensitive tool for detecting process residues and has been extensively used for cleaning validation studies. For process residues, these methods are normally product assay methods converted and validated for trace analysis. HPLC methods are very specific and can only give information on the specific process residue. HPLC should be the choice when methods such as visual inspection and TOC cannot be used. HPLC is most appropriate for cleaning processes that pose high risks that cannot be satisfactorily addressed by the previously described methods.

For validated cleaning processes, monitoring programs should be employed where risks are highest and should be PAT-based if possible. The use of online, inline, or at-line sensors to determine when cleaning is complete is encouraged. Analyses such as visual inspection, TOC, pH, and conductivity may be appropriate in a monitoring program.

In summary, for cleaning the parameters of hazard, exposure, and detectability can be mapped as shown in Table A.

**Summary**

The Guide described above will provide a framework for a scientific, risk-based approach to cleaning of products. The Guide will address how well established and accepted risk assessment methods can be used to develop health-based limits such as ADE and Maximum Safe Carry over (MSC) values.

This Guide will be applicable to the development and validation of cleaning processes for all health, medical, cosmetics, and consumer products, which includes pharmaceuticals (APIs, dosage forms, veterinary, biologics, and clinical supplies), dietary supplements, and medical devices.

**References**

1. International Congress on Harmonisation.

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**Table A.**

<table>
<thead>
<tr>
<th>Risk Parameter</th>
<th>Hazard</th>
<th>Occurrence</th>
<th>Detectability</th>
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<tbody>
<tr>
<td>Cleaning aspects</td>
<td>- API Residue - Cleaning Agent Residue - Microbial Growth - Degradants</td>
<td>- SOP Risk Assessment Training Program - Statistical Analysis of Swab Data - Risk Assessment Based on Data</td>
<td>- Visual Inspection - Online Sensors - At-line Sensors - Other Monitoring</td>
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### About the Author

**Andrew Walsh** is an Industry Professor at Stevens Institute of Technology in their Pharmaceutical Manufacturing Program where he teaches courses on validation and lean Six Sigma. In 2009, Walsh founded the Stevens Pharmaceutical Research Center (SPRC), a research lab focusing on Pharmaceutical manufacturing topics, such as cleaning process development, total organic carbon analysis and method development, visual inspection method development and automation of GMP systems. A current Chair of an international task team to write a cleaning Guide for ISPE and ASTM, he was one of the contributors to the ISPE Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP) Baseline® Guide. He has more than 20 years of diverse validation experience in pharmaceutical and biotech companies, including Johnson & Johnson, Schering-Plough, and Hoffmann-La Roche. Walsh has given numerous presentations over the past 15 years with IIR, Barnett, WorldPharm, IPA, IVT, and ISPE. He can be contacted by telephone: +1-201-216-5533 or email: andrew.walsh@stevens.edu.  

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