IVT NETWORK
INSTITUTE OF VALIDATION TECHNOLOGY | an informa business
Unlimited Validation Knowledge Awaits...
Published on *IVT Network* (http://www.ivtnetwork.com)

CCF #2. Cleaning Terminology and Key Considerations

By **Paul L. Pluta**

Dec 23, 2021 8:00 am EST

Peer Reviewed

Critical Cleaning Forum (CCF) is an IVT feature that provides readers an opportunity to discuss information about cleaning, cleaning validation, and related topics. Cleaning to an appropriate quantitative level of cleanliness is a fundamental expectation in regulated industries. Cleaning is also essential in various non-regulated industries to accomplish acceptable product manufacturing. Cleaning is a process with a final “product” – a clean surface -- delivered by the process. Cleaning validation confirms the efficacy of the cleaning process and its defined elements. Readers have requested information about cleaning; any effort to increase the understanding and application of cleaning and cleaning validation in daily work performance will be useful to readers.

The multiple communication methods available through IVT will be utilized in CCF. Journal submissions for publication in the Journal of Validation Technology and Journal of GXP Compliance are invited. Blog discussions posted on the IVT Network are more informal and are also welcome. IVT “Voices in Validation” podcasts provide visual and verbal discussion by individuals and groups. Coupling written and podcast discussions have been effective methods of transmitting content and using multiple preferred learning methods. Please join us; CHF will be most successful when technical, validation, quality, engineering, and analytical communities participate in this endeavor. Please respond in the comments section below with ideas, suggestions, or topics for discussion.

INTRODUCTION

Cleaning in pharma, medical device, and associated industries is a complex topic with extensive subject content comprising multiple disciplines. Cleaning is required in many applications, and numerous specialized topics are relevant to cleaning. Often the range of topics in cleaning is overwhelming. Some personnel cannot understand differences in cleaning – critical cleaning vs. general cleaning. Some subject matter experts (SME's) have extensive expertise in certain aspects of cleaning but are not knowledgeable in all cleaning topics. This discussion begins an effort to organize the subject of cleaning, simplify content, emphasize most important considerations, and generally introduce a logical technical approach to cleaning and cleaning validation.

Objectives and Discussion Topics

The general objective of Critical Cleaning Forum (CCF) is to provide useful information to pharma and medical device cleaning professionals. This first discussion describes terminology and key topics for future discussion. Our focus is*critical cleaning*, key elements of*critical cleaning*, and supportive topics relevant to these key elements. A lifecycle approach to the cleaning validation process is also described – a comprehensive approach that includes design and development work, actual cleaning validation, and post validation follow-up. Cleaning content from non-pharma industry sources will also be included in future discussions; approaches and considerations used other industries may be also useful in pharma and medical device applications.

The following are topics for this CCF discussion:

- Cleaning terminology. Terminology, critical cleaning, and non-critical cleaning
- Cleaning basic topics. Surface to be cleaned; soil to be removed; the cleaning process to accomplish critical cleaning, and testing to evaluate cleaning validation
- Lifecycle approach to validation. Comprehensive approach to cleaning validation
- Example problems. Several example cleaning problems demonstrating misunderstandings of cleaning principles are described.

CLEANING TERMINOLOGY

Terminology is fundamental in any discussion. Cleaning and cleaning validation terminology suffer from numerous definitions, usages, parts of speech, slang use, and other applications of the words *clean* and *cleaning.* Everyone thinks they understand the meaning of these words. Perhaps it is this (mis)understanding that detracts from resolute performance of cleaning and cleaning validation. Managers comment that personnel "do whatever it takes" to clean equipment rather than explicitly following approved cleaning procedures – one of many common problems associated with cleaning performance (see example problems below). Cleaning practitioners describe *cleaning, critical cleaning, precision cleaning, lean cleaning, cleaning validation, cleaning process validation, critical cleaning validation, cleaning qualification, cleaning performance qualification, cleaning verification*, *cleaning procedure records, cleaning batch records,* and likely many other alternative wordings used in discussion. Some cleaning terms have multiple meanings; a*Cleaning Validation Master Plan* may describe a site program addressing all site cleaning validation or may discuss an individual cleaning validation project. Cleaning terminology is a problem.

Critical Cleaning

This discussion uses*critical cleaning* to describe cleaning and activities associated with cleaning validation in pharma and medical device regulated industries. Alconox (1) has generally described*critical cleaning* as follows:

> *"Critical cleaning refers to a very specific type of cleaning. It is where the cleaning itself impacts the value of the finished output from whatever residue/contaminant is being cleaned. Typically, some observation, measurement, or validation is done related to this. Critical cleaning in FDA, EU, cGMP, etc. regulated industries of components or substrates is the complete removal of undesirable contaminants to a desired preset level. This level will vary based on regulations and finished product requirements. It is normally the minimum level at which no adverse effects take place in a subsequent operation."*

Alconox has also published other technical literature (2) using*critical cleaning* terminology for multiple applications. Key in the above is that critical cleaning is a deliberate process that directly affects the value of the material being cleaned or of subsequent product or processing. By inference, non-critical or general cleaning is a separate and distinct type of cleaning that does not directly affect product or subsequent processing.

Some medical device companies use *critical cleaning* terminology to describe device cleaning. The *Handbook for Critical Cleaning* (3) has been a valuable cleaning resource for devices and other industry for many years. Some critical cleaning discussions identify critical steps in a cleaning process akin to critical process parameters in pharma Quality by Design (QbD), i.e., a critical cleaning step within a cleaning process sequence. Kanegsberg (4) and colleagues have identified industries requiring critical cleaning including electronics, aerospace, industrial metals, nanotechnology, food processing, paintings, and military applications. Contrast this with pharma companies who have historically used *cleaning* and *cleaning validation* -- n*ot critical cleaning* -- terminology in regular communication and documentation. FDA and other pharma regulatory guidances (5-6) also use *cleaning* and *cleaning validation* as their preferred wording.

Pharma and medical device cleaning and cleaning validation can logically be described as c*ritical cleaning.* Cleaning and cleaning validation in pharma certainly affect product value.*Critical cleaning* connotes a cautious, methodical, and deliberate activity with significant technical and business consequences if performed incorrectly – critical cleaning is distinctly separate from non-critical cleaning. Cleaning practitioners must understand the requirements for critical cleaning.

Elements of Critical Cleaning

The above definition leads to the identification of key topics in critical cleaning, i.e., what topics are investigated in the development of critical cleaning processes. Four primary elements are identified, the treatment of which helps to differentiate critical cleaning from non-critical cleaning:

- **Surface**. An identified surface to be cleaned. The composition, properties, and surface characteristics of the surface to be cleaned must be known and understood. A clean surface is the general objective of critical cleaning
- **Soil**. A specific unwanted soil to be removed. The composition and properties of the soil(s) must also be known and understood in critical cleaning
- **Process**. A detailed quantified procedure to accomplish cleaning must be developed and clearly documented. The cleaning process utilizes surface knowledge and soil knowledge for process development
- **Testing.**Analytical methods, functional tests, or other criteria to evaluate cleaning efficacy or levels of remaining soil is utilized in critical cleaning.

Contrast the above with typical practice in non-critical cleaning. Critical cleaning requires technical focus and understanding of each of the above elements; non-critical cleaning only superficially addresses these elements.

CLEANING BASIC TOPICS

The proposed critical cleaning definition above specifies four primary elements: Surfaces to be cleaned, soil to be removed, a specified cleaning process, and testing to evaluate cleaning performance including determination of residue levels as appropriate. These elements should generally describe essentially all applications of critical cleaning. Secondary topics relevant to each primary element that are specific to individual critical cleaning follow. These considerations exemplify the technical work relevant to critical cleaning.

Surfaces

A clean and appropriate surface is the ultimate objective of a critical cleaning process. The surface of interest may be equipment used in API, biotech, or product manufacturing, medical and surgical equipment, implanted polymeric devices, plastic and metal disposables, tissue for replacement, in-process subassemblies for subsequent manufacturing, and other materials. A clean surface is the “product” of the cleaning process.

Associated topics. Supportive considerations relative to surfaces include the following:

- **Surface composition.**Stainless steel, other metals, polymers, human or animal tissue, others
- **Surface area.** Product-contact surface area is needed for certain soil residue calculations
- **Equipment design.**Equipment design (angles, openings, curves) should facilitate cleaning of surfaces
- **Metal surfaces.**Surface finishes of metals and other materials may affect cleaning or analysis
- **Polymer surfaces.**Porosity and flexibility of polymers may have wide variation
- **Observation / lighting.**Surfaces being cleaned should be observable for evaluation.

Soil

Soil to be removed comprises undesirable matter or residue including API reactants, product active drug and formulation ingredients, metal fragments from processing, blood component residues, unwanted human or animal tissue, and so on. Understanding soil properties are vital to cleaning process development, cleaning agent selection, and to analytical method determination. Residual cleaning agent used in the cleaning process is also considered soil to be removed from the final clean surface.

Associated topics. Supportive topics for discussion relative to soils include the following:

- **Soil chemical properties.**Soil reactivity (hydrolysis, oxidation, and photolysis) must be known.
- **Soil physical properties.** Soil solubility (hydrophilic, hydrophobic), rate of dissolution, ionization, and other physical properties. Polymeric soils may be especially problematic.
- **Dirty hold time.** Time post manufacturing and start of cleaning. Soil properties may change degrade, dry, harden, polymerize) during hold time prior to cleaning
- **Campaign cleaning.** Cleaning of accumulated soil after multiple consecutive manufacturing processes
- **Calculation of target cleaning level.**Multiple calculation methods for residue level may be used
- **Uniform contamination surfaces.**Surfaces uniformly contaminated transfer residue to subsequent processing
- **Non-uniform contamination surfaces.** Certain equipment surfaces may transfer residue non-uniformly to subsequent processing.

Cleaning Process

The cleaning process comprises the sequence of integrated steps to accomplish cleaning of the surface of interest. The cleaning process is fundamentally simple – wash, rinse, and dry. The cleaning process may be automated, manual, or hybrid, and may utilize cleaning washers, ultrasonics, and other techniques.

Cleaning Agent. A cleaning agent may be utilized in the cleaning process to facilitate cleaning. Cleaning agents may include water, caustic chemicals such as sodium hydroxide and potassium hydroxide; acids (nitric, phosphoric, citric), non-aqueous solvents, soaps/surfactants, proprietary cleaning agents with multiple components, and other materials. Cleaning agent properties should be consistent with soil properties, materials or construction, and configuration of the surfaces to be cleaned.

Cleaning Process Parameters. Cleaning SME's often focus on cleaning process variables as themost critical element in cleaning; TACT, an acronym for**T**ime,**A**ction,**C**oncentration, and**T**emperature is often discussed. Listing of process variables does not address the complete "process" aspects of cleaning validation -- the lifecycle approach. A cleaning process must be consciously designed and developed, be validated to confirm efficacy, adequately documented, and then monitored to ensure continuing performance.

Associated topics. Supportive topics relative to the cleaning process include the following:

- **Cleaning agent selection and concentration used.** Technical basis for cleaning agent
- **Cleaning mechanism**. Dissolution, micelle solubilization, emulsification, physical dispersion, many others
- **Cleaning method.** CIP, COP, agitated immersion, static immersion, ultrasonic, others
- **Cleaning process parameters.** Time, temperature, spray rate, rinsing, drying, others
- **Cleaning agent compatibility with surfaces to be cleaned.** Certain polymers may react with cleaning agents, high pH, or low pH, proprietary components, others
- **Automated cleaning equipment validation.** Equipment must be validated
- **Clean equipment storage.** The cleaned equipment/device must be stored with protection from environmental dust
- **Cleaning process documentation.**Critical cleaning must be appropriately documented
- C**leaning process training.**Personnel performing cleaning processes must be trained; operator training is especially important in manual cleaning processes
- **Cleaning process safety.**Precautions needed for safe cleaning performance
- **Cleaning process environmental impact.**Cleaning waste disposal may have local environmental and atmospheric restrictions.

Testing

Test methods are developed to measure residue on surfaces after cleaning to determine the efficacy of the cleaning process. Tests adequate sensitivity will not be possible in certain situations. Functional testing may serve to evaluate critical cleaning.

Associated topics. Additional topics for discussion relative to testing include the following:

- **Soil analytic method validation.** Specific methods and non-specific methods
- **Cleaning agent analytical method validation.** Residual cleaning agent of components therein
- **Analytical method specificity and sensitivity.** Limit of quantitation and limit of detection
- **Residual soil recovery from surface.** Post-cleaning soil must be quantitatively recovered from surface for analytical determination
- **Sampling technique**. Swab sampling, rinse sampling, others
- **Training of sampling technicians.** Sampling technicians must demonstrate sampling technique competency; auxiliary equipment may be used in special sampling
- **In-line analytical testing.** Conductivity, pH, others.

LIFECYCLE APPROACH TO CRITICAL CLEANING VALIDATION

The lifecycle approach to cleaning validation utilizes the FDA lifecycle approach to manufacturing process validation. This approach to process validation was initially introduced in 2004 and formalized in a final FDA guidance in 2011 (7). FDA defined validation in this guidance as follows:

> *"Process validation is defined as 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 product. Process validation involves a series of activities taking place over the lifecycle of the product and process."*

Three stages are identified in the lifecycle approach. In brief:

- Stage 1– Process Design comprises all work conducted in advance of traditional validation. This includes R&D, development, pilot-scale trials, scale-up, and all other work to understand the formulation and process. Stage 1 activities may be simply described as*process understanding*.
- Stage 2– Process Qualification incudes actual performance of the commercial process by means of conformance lots. This stage*confirms* – note this key word -- the work of development to provide a validated process. Stage 2 may be simply described as*process validation*.
- Stage 3– Continued Process Verification comprises ongoing monitoring and maintenance of the manufacturing process throughout the entire product manufacturing life until product expiration. Stage 3 may be simply described as*process monitoring.*

The lifecycle approach to process validation emphasizes Stage 1 and Stage 3 activities – better planning, design, and development and better follow-up, monitoring, and maintenance. This approach differs significantly from the previous validation approach, i.e., emphasis on Stage 2 based on the 1987 FDA Guidance (8) in which successful manufacturing of three validation lots was essentially the complete story on validation. Since critical cleaning is also a process, its performance should generally follow validation lifecycle principles as proposed for manufacturing process validation (x). The Government of Canada Cleaning Validation Guide (GUI-0028) currently describes a lifecycle approach to cleaning validation (9). The above FDA definition may be directly modified to address critical cleaning and cleaning validation.

Critical Cleaning Elements

Critical cleaning work addressing surfaces, soil, cleaning process, and testing is conducted during stage 1 of the lifecycle approach to critical cleaning validation. Design and development work in these areas provide the technical basis for critical cleaning validation. Understanding surface characteristics and soil properties is vital to development of the cleaning process. Surface and soil knowledge is also vital to test method development and techniques in its performance. Critical cleaning is a process that must be addressed in the same manner as a manufacturing process, i.e., a lifecycle approach.

EXAMPLE PROBLEMS

Several example cleaning events demonstrate misunderstanding of the above fundamental considerations in cleaning. These events were described by multiple validation and quality managers from multiple companies – all established companies with ongoing site cleaning programs. Described problems include significant cleaning program design problems to individual personnel performance problems – all of which are significant in a site cleaning program.

Example #1. Cleaning Agent Incompatibility

Polymer parts in particle sizing equipment were being replaced by manufacturing operators. The manufacturing manager explained that these parts were examined every time the equipment was assembled. If particulate or surface roughness was observed on the surface of the parts, the parts were replaced. The production department maintained an inventory of these parts because replacement was needed on a regular basis. The polymer parts had direct product contact but contributed less than 1% of total product-contact surface area. Polymer material information indicated that the polymer was not compatible with the cleaning agent used for the equipment. Because the polymer was only a small percentage of the total surface area, material incompatibility was never addressed during development. Surface abrasion was eliminated when a new compatible cleaning agent was used.

Example #2. Equipment Part Changes

A change in equipment part materials was noted when reviewing equipment operation on a pharma packaging line. The white plastic chute on the tablet filling machine was now blue plastic. The packaging supervisor explained that the chute had become permanently stained with product residue, so he replaced the part with new plastic available in the maintenance shop. The original white plastic sheet was a significant size, was part of the equipment IQ, and would have been sampled for drug residue in cleaning validation; the blue plastic was a different material. The validation manager then visited the maintenance shop and found a container with numerous types of plastic, rubber, and other polymeric materials -- the “scrap bin” -- all of which were unlabeled and of unknown composition. The supervisor explained that when they needed to replace a plastic part, they obtained a plastic piece from the scrap bin and cut it to size.

Example #3. Pseudomonas Contamination

Pseudomonas contamination was detected in the tablets throughout the batch during routine microbiological release testing of the tablets. The source of the Pseudomonas contamination was ultimately found to be the elastomeric gasket which was part of the discharge valve assembly located at the bottom of the equipment. The cleaning procedure entailed a wash and clean-out of the V-blender without disassembly of the discharge valve. The rinse water was retained in the gasket of the discharge valve allowing the growth of Pseudomonas. The discharge valve on the bottom of the V-blender was not completely disassembled and dried for cleaning.

Pseudomonas was then consequently released from the wetted gasket and distributed through-out the batch when the final blend was discharged into drums.

Examples #4-5. Cleaning Validation "Improvements"

Cleaning Agent. A newly trained technician was manually cleaning a mixing tank. His supervisor asked about an unusually large volume of soap foam in the tank being cleaned. The technician responded that the tank was unusually dirty with process residue, so he added extra scoops of detergent to help with the cleaning. When the technician was reminded about using an exact amount of soap per the cleaning procedure directions, he responded that he followed directions, but also added extra soap – he believed what he did was a good thing! He exemplified "we do whatever it takes" to get the job done." Even though training was just conducted explaining the importance of following the exact directions in the cleaning method, the technician followed his usual method of cleaning – "doing whatever it takes."

New Solvent. The cleaning process for manufacturing equipment was being observed. The operator was carefully following the approved cleaning procedure as instructed. When cleaning of equipment gaskets was being performed, the operator left the equipment room with stained parts and returned shortly thereafter with clean white gaskets. When questioned, the operator explained that the approved cleaning procedure did not clean the gaskets; he went to the maintenance shop and used solvent stored in the solvent cabinet to clean the gaskets. Further investigation determined that the maintenance shop had a collection of organic solvents used to remove grease from equipment, and these solvents were used by operators whenever they had trouble cleaning equipment, floors, parts, or other applications. These solvents were not authorized in the approved cleaning procedure.

These examples demonstrate misunderstanding of the cleaning process and misunderstanding of compliance with process directions.

Examples #6-7. Passing Cleaning Validation

Multiple Washings

The validation manager was walking toward the production area to check on a cleaning project that was planned for that morning. Manufacturing equipment was to be swab-sampled. The validation manager inadvertently met the production manager who said "We are doing everything we can to pass the cleaning validation. I had three different people clean the equipment. With three different washings, they equipment should be clean and pass testing." Validation is addressed after one cleaning process – not done three times.

Extra Cleaning of Sampling Locations

Manual cleaning of equipment was being observed. Cleaning personnel utilized approved cleaning procedure documents for equipment and performed cleaning according to the written procedure. After the approved cleaning procedure was completed, the operators performed additional cleaning on swab-sampling locations. They had been instructed by management to do additional cleaning on sampling location to pass cleaning validation – like knowing the answers before the test was given.

Example #8. Active Drug Determination

Equipment used in manufacture of a polypeptide injection product was cleaned by use of an oxidizing agent. This cleaning agent completely destroyed the active drug molecule. Policy at the company was that analytical methods used in cleaning validation always tested for presence of the active drug – even though the active drug was chemically destroyed. Non-specific testing for presence of drug fragments or other remaining soil was not considered. Numerous arguments within the company debating this approach occurred; responsible analytical scientists vigorously defended their logic. Ultimately a regulatory inspector clearly stated that this approach was unacceptable.

Example #9. Worst-Case API

A company was using a product matrix approach to minimize repetition in cleaning validation. A worst-case API was identified based on lowest drug solubility in water. The cleaning process utilized an alkaline cleaning agent in a pH 12 cleaning liquid. The worst-case drug was very soluble in alkaline pH; selection of this drug as worst-case was technically incorrect. A different API with lowest solubility in pH 12 should have been selected for cleaning validation.

FUTURE CCF DISCUSSIONS

Future CCF discussions are planned to address topics identified within the four major elements of critical cleaning and across the range of products and processes. Pharma and medical device applications will be emphasized; contributions from practitioners outside pharma and medical device applications are most welcome. Blog posts and podcasts will be utilized to enhance and expand content. This series will succeed through contributions from cleaning practitioners in multiple applications and across multiple industries.

SUMMARY AND FINAL THOUGHTS

This discussion initiates an effort to simplify the subject of cleaning, organize subject content, emphasize most important considerations, and generally introduce a logical approach to technical cleaning. Three main points are emphasized.

1. **Cleaning is differentiated between*critical cleaning* and non-critical or general cleaning**. Key in this terminology is that critical cleaning directly affects the quality of a surface being cleaned or of a subsequent product or process. The work and consequences of critical cleaning are distinctly different than that of general cleaning. The focus in*critical cleaning* is technical knowledge and understanding of the cleaning process.
2. **Key elements of critical cleaning: Surface to be cleaned, soil to be removed, the cleaning process that removes the soil, and testing to evaluate cleaning**. These elements are universal in essentially all cleanings. Sometimes manufacturing equipment is cleaned and sometimes the actual manufactured device is cleaned; all identify surfaces, soil, process, and a method of testing. Each element requires supportive technical knowledge specific to the critical cleaning project.
3. **Lifecycle approach to cleaning validation.** Critical cleaning process validation is described in terms of a lifecycle approach in which the critical cleaning process is designed and developed, demonstrated in validation, and monitored. Most important in the lifecycle approach are Stage 1 in which the technical aspects of cleaning are understood, and Stage 3 in which the ongoing critical cleaning process is continually monitored to ensure successful performance. Actual cleaning validation is addressed in Stage 2. Critical cleaning is a process that should be addressed in the same manner as a manufacturing process.

REFERENCES

1. Alconox Tech Notes. What is Critical Cleaning? 1-4-20 https://technotes.alconox.com/industry/what-is-critical-cleaning/#:~:text=Critical%20cleaning%20in%20FDA%2C%20EU%2C%20cGMP%2C%20etc.%20regulated,adverse%20effects%2 . Accessed 12-15-21.
2. Alconox. Critical Cleaning Guide.https://www.alconox https://technotes.alconox.com/industry/what-is-critical-cleaning/#:~:text=Critical%20cleaning%20in%20FDA%2C%20EU%2C%20cGMP%2C%20etc.%20regulated,adverse% cleaning-guide-download. Accessed 12-15-21.
3. Handbook for CRITICAL CLEANING, second edition. Barbara Kanegsberg and Edward Konigsberg, editors. CRC Press, Taylor & Francis Group, Boca Raton, FL, 2011.
4. Kanegsberg, Barbara. Clean Critically: An Overview of Cleaning Applications, in Handbook for CRITICAL CLEANING, second edition. Barbara Kanegsberg and Edward Konigsberg, editors. CRC Press, Taylor & Francis Group, Boca Raton, FL, 2011.
5. FDA. Validation of Cleaning Processes (7/93).https://www.fda.gov/validation-cleaning-processes-793 . Accessed 12-15-21.
6. Gera, Vivek. Cleaning Validation Guidelines – A Complete List 2021. Leucine, 5-19-2021. https://www.leucinetech.com/post/cleaning-validation-guidelines. Accessed 12-15-21.
7. FDA. Process Validation. General Principles and Practices. January 2011. https://www.fda.gov/media/71021/download. Accessed 12-15-21.
8. FDA. Guideline on General Principles of Process Validation. May 1987.https://fda-consultant.com/provalid.html. Accessed 12-15-21.
9. Government of Canada. Cleaning validation guide (GUI-0028).https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/validation/cleaning-validation-guidelines-guide-0028/document.html. Accessed 12-15-21.

ACKNOWLEGEMENTS

Helpful discussions with Barbara Kanegsberg, Edward Kanegsberg, Paul Lopolito, and Rizwan Sharnez are gratefully appreciated**.**
