



AQUEOUS CRITICAL CLEANING: A WHITE PAPER

CLEANING VALIDATION FOR PHARMACEUTICAL MANUFACTURING

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Why get Cleaning Validation Support from the Cleaner Supplier?

Cleaning validation is a necessary and time consuming part of manufacturing pharmaceuticals. The validation process can be expedited and cost of validation can be lowered if the cleaner supplier can provide support, allowing for pharmaceuticals to get to market faster and at a lower cost. This paper outlines the basics of cleaning validation, as well as discussing the kinds of support services you should seek from your supplier of critical cleaning products in order to optimize your cleaning validation process.

What Is Cleaning Validation?

Cleaning validation is a requirement in industries such as pharmaceutical manufacturing which adhere to Good Manufacturing Practice (GMP) and Quality Systems Regulations (QSR), and is specific to the cleaning method and cleaner employed.

Simply stated, validation is a documented guarantee that cleaning can be performed reliably and repeatedly to satisfy a predetermined level of cleanliness. Validation is achieved by demonstrating at least three times that the cleaning process removes residues down to acceptable levels. Testing for acceptable residues includes:

- Residue identification
- Residue detection method selection
- Sampling method selection
- Setting residue acceptance criteria
- Methods validation and recovery studies
- Writing a procedure and training operators

After establishing three or more times that a process can be repeated reliably to remove residues down to acceptable levels, a program can be implemented to maintain the state of validation where only periodical retesting is required. Changing any part of the cleaning procedure, including the cleaner, mandates revalidation. This entails first cleaning the new cleaners or methods, collecting data, and then cleaning the equipment with the prior validated process before using the equipment. These previously validated steps need to be followed until the new procedure is fully validated.



Generally, process validation is comprised of three parts: Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) of manufacturing equipment and operations. Cleaning validation can be incorporated in part in to the PQ process. Cleaning validation is done when it's impractical to verify cleaning on 100% of the production equipment used in high-volume manufacturing operations. Larger-volume manufacturing, such as in the pharmaceutical industry, therefore relies upon validation, which is performed on critical cleaning steps effecting the quality or safety of the final product.

This procedure begins with a validation "Master Plan" which typically includes:

- The objective
- Responsibilities of validation committee members
- Equipment/product/procedures
- Test acceptance limits
- Analytical methods
- Sampling procedures and recovery
- Cleaning process design
- Data analysis
- Assumptions
- Change control/maintenance
- References

Cleaning validation in the US is under the FDA's jurisdiction, which employs a risk-based approach emphasizing quality systems inspections. Whether the validation's objective is ensuring product, worker, or environmental safety while controlling the risk of cross-contamination, it must comply with FDA standards, and is typically under the auspices of a designated "validation committee" with clearly-defined responsibilities. Such a team usually comprises:

- **Validation Specialist** - writes and coordinates the procedure
- **Manufacturing** - writes SOPs and provides training
- **Quality Assurance/Control** - approves and implements analytical methods
- **Engineering**- communicates changes and equipment data
- **R&D** - performs recovery studies, validate methods, transfer methods, and selects new cleaners

In pharmaceutical manufacturing, the quality subsystems inspected by the FDA under The Drug Manufacturing Inspection Program (US FDA Center for Drug Evaluation and Research CDER 7356.002) include: production systems; facilities and equipment systems; packaging and labeling systems; materials systems; and laboratory control systems.

Simplify Validation Using a Worst Case Matrix

To simplify validations, it is recommended that a matrix of worst case equipment to clean and worst case residues to remove be created. Start by first assembling an equipment matrix and residue matrix that defines all shared and dedicated equipment with what residues they are exposed to. By conducting testing, it is possible to identify and document a “worst case”, for the most difficult to clean equipment and residues. Then perform a complete validation on these worst-case equipment and residues, which in turn will serve to validate the process for easier-to-clean equipment and easier-to-clean residues. Typically groups of worst case situations are established with one piece of equipment representing a group of similar or easier-to-clean equipment, just as residues are grouped by cleaning with one residue representing a group of similar or easier-to-clean residues.

It’s important to validate a “worst case” scenario and justify its choice. The rationale for why a piece of equipment or residue was determined to be worst case needs to be documented. The worst case is usually based on a variety of factors including: product solubility in cleaner; toxicity of the products or respective degraded products being cleaned; dose sizes and normal therapeutic dose size (smaller may be more critical to validate); hardest-to-clean equipment; and worst interactions with the upcoming batch to be cleaned. Whenever a new residue or piece of equipment is used, an evaluation needs to be made if it can be added to an existing group or if it represents a new worst case that will require a new validation.

Identifying Residue and Selecting a Detection Method

Before you start identifying residues, first you have to assemble a list of all the possible residues that could be left on critical manufacturing surfaces as a result of the cleaning process: including cleaners, primary ingredients, excipients, decomposition products, and preservatives. Once you have your list of residues, you need to have a detection method for those residues.

For cleaner residues, selecting the proper detection method involves choosing a specific or non-specific methodology. Specific methods test for an individual ingredient include high-performance liquid chromatography (HPLC); ion selective electrodes; flame photometry; derivative UV spectroscopy; enzymatic detection; and titration. On the other hand, non-specific methods such as total organic carbon (TOC), pH levels, and conductivity test for the presence of a blend of ingredients. While the FDA often prefers use of specific methods, non-specific methods may be accepted provided a scientific rationale for their use is determined. Specific methods are also preferred when investigating failures or action levels. Sometimes a broad non-specific method is used for monitoring, and specific methods are used for investigating when the non-specific method exceeds acceptance criteria or internal action limits. Sometimes a specific

method is used for an initial validation, and then correlated with a non-specific method which is then later used for retesting to maintain a validated state of manufacturing.

Selecting a Sampling Method

When sampling for critical cleaners used in the production of pharmaceutical products, several sampling methods are available including rinse water sampling, swabbing surfaces, coupon sampling, and placebo sampling. Rinse water sampling is done when sampling large pieces of equipment or runs of piping. In this regard, a sample is taken of an equilibrated post-final rinse that's been re-circulated over all surfaces. Such samples should be correlated to a direct measuring technique like swabbing in order to assure that residues are being adequately detected and not simply sitting on the surface and not being dissolved into the equilibrated rinse water. Swab or wipe sampling is done to directly measure and remove residues from surfaces for analysis. To do this, a swab or wipe is moistened with high-purity water (WFI) that's drawn over a defined area using a systematic, multi-pass technique, always moving from clean to dirty areas to avoid recontamination. If TOC analysis is being done, then the swab head is cut off and placed in a pre-cleaned TOC vial. TOC analysis requires the use of very clean low background swabs/wipes and sample vials. Coupon sampling utilizes a coupon placed inside a piece of equipment or removable piece of actual pipe that's dipped into WFI to extract residues for analysis. Placebo testing is performed using placebo products and analyzing for residues from the previous batch.

Setting Residue Acceptance Criteria

Pharmaceutical product manufacturing requires the identification of potential residues including limits for the active drug, excipients, degradation products, cleaning agents, bioburden and endotoxins and setting acceptable residue limits for them. Determining acceptable levels of each residue must take into account how the residue will affect the next product ingredient to contact that equipment or processing surface during production. Residue levels must maintain pharmacological safety and stability while avoiding toxicity or contamination of the product that follows. Typically, limits are set for visual, chemical, and microbiological residues.

Cleaning agent limits are generally covered under chemical limits, which can be expressed as a maximum concentration in the next product (ug/ml), amount per surface area (ug/cm²), amount in a swab sample (ug or ug/ml), maximum carry-over in a train (mg or g), or concentration in equilibrated rinse water (ug/ml). A calculated safety-based acceptance limit should be determined, and a lower internal action level plus a lower process control level based on actual manufacturing and measuring experience, may also be desirable.

Cleaning agent safety-based limits are most often calculated from a safety factor of an acceptable daily intake (ADI), a reduction (1/1000 or more) of an LD50, preferably by the same route of administration or reproductive hazard levels. If the calculated limit is

equal to or greater than a 10 ppm carry-over to the next batch, the safety-based limit can be set to that level as well.

The following equation can be used to calculate the safety-based limit in mg/cm² or mg/ml of cleaner residue on just-cleaned equipment:

<p style="text-align: center;">Safety Based Limit: Limit(mg/cm² or L) = [ADI carry-over, see below(mg) X Smallest Next Batch(kg)]/[Size of Shared Equipment (cm² or L) X Biggest Daily Dose of Next Batch(kg)]</p> <p style="text-align: center;">Acceptable Daily Intake: ADI carry-over(mg) = [LD50 by administration route(mg/kg) X body weight(kg) X (1/10,000 or 1/1,000)]*</p>
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* - a conversion safety factor

For a comparison calculation of limit based on no more than 10ppm carry-over:

<p style="text-align: center;">10 ppm Carryover Limit: Limit (mg/cm²) = [10mg residue on just-cleaned surface X Next Batch Size (kg or L)]/[1(kg or L) of Next Product X Size shared equipment(cm² or L)]</p>

It's important to note that, for many residues, a visual detection limit can be validated on the order of 1-4ug/ cm², and that the possibility exists for the visually clean criteria to be the most stringent criteria. For example, for a cleaner with a rat oral LD50 over 5000 mg/kg, the ADI calculation using a 70 kg person and a safety factor of 1,000 gives a result of 350 mg (5000 mg/kg x 70kg/1,000). In a 2,000kg mixer where the next smallest batch of 1,000kg, the area of the mixer and equipment used in the next batch is 100,000 cm², and the daily dose of the next product is 0.005kg: the calculated residual acceptance criteria is 700 mg/ cm² (350mg x 1,000 kg/(100,000 cm² x 0.005 kg). Comparatively, the 10ppm in next batch limit gives acceptance criteria of 100 ug/ cm² (10 mg x 1,000 kg/ (1 kg x 100,000 cm²) x 1,000 ug/mg. In this case, if the ability to detect visually to 4 ug/ cm² is demonstrated, then a visually clean surface will be the most stringent acceptance criteria for residues.

In this example, the desire is to avoid more than 350 mg of residue in a daily dose of the next product. For small final filling equipment such as filling needs for vials, or tablet punches and dies, it may be necessary to do separate residue studies on the filling needles or punches to ensure that less than required residue remained, on that particular

equipment, to contaminate the first few bottles or tablets of the next batch with a residue of 350 mg/daily dose.

If the safety-based limit is set at 100 mg/ cm², it can be expressed as a rinse water concentration of 100 mg/L in a post-final rinse using 100L of rinse water recirculated to equilibrium (0.1 mg/ cm² x 100,000 cm²/100 L). The same limit could be expressed as 6.25ug/ml or ppm total organic carbon (TOC) in a sample for a residue that is 10% TOC by weight in a 20 ml swab sample from a 25cm² swab area where 50% recovery has been established [(25 cm² x 100 ug/ cm²) x 50% recovery] x 10% TOC/20 ml. The same safety limit can be expressed several different ways.

Validating of Residue Detection Methods and Implementing Recovery Studies

Recovery studies consist of using the sampling and detection methods on a known spiked surface at representative levels of residue. Generally, spikes are set at 50-, 100-, and 150-percent of the acceptable limit. This help to illustrate linearity with documented percent recovery as analyzed, and helps determine the limits of detection and quantitation. Ideally, the expected values and limits should be multiples of the limits of quantitation. The percent recovery is used to correlate amount detected with the amount of assumed surface residue found acceptable.

For example, if 100 ug of residue was spiked on the surface, and after swabbing, extracting, and analyzing only 90 ug was detected, you have 90 percent recovery. For cleaning validation, any results would have to be adjusted by this recovery factor. In this example, the resulting 90 ug per swabbed area needs to be interpreted as actually being 100 ug per swabbed area to adjust for the 90 percent recovery.

When the solubility or rinseability post-drying of a particular critical cleaning detergent ingredient is in question, a rinseability profile detailing complete rinsing should be done. If the chosen analytical detection method is sensitive to only one ingredient in the cleaner, document that all ingredients rinse at the same rate, or that the ingredient being tested for is the last to rinse away. If neither explanation can be demonstrated, a rationale outlining support for one or both must be provided.

In the case of surfactants in cleaners, one can justify analyzing for surfactant residues as a marker for the entire surfactant formulation because as surfactants they are attracted to the solution surface interface and will theoretically be the last material to rinse away out of otherwise readily water soluble ingredients in the detergent or cleaner.

In some cases, bioburden/endotoxin levels may need to be validated. Because this takes longer, performing this process separately from the cleaning validation procedure is recommended.

CLEANER RESIDUE DETECTION METHODS

When performing a pharmaceutical cleaning validation, a company must have a validated analytical method for detecting detergent residue. The table below (Table A) lists a variety of residue detection methods that can be used for the cleaning validation for cleaners manufactured by Alconox, Inc.

The choice here varies from selective methods to non-specific ones such as total organic carbon (TOC). Selective methods are those proven specific at a 95 percent confidence level, under specified usage conditions, without significant bias or interference from impurities, degredants, excipients, or other ingredients.

TABLE A: DIRECTORY OF CLEANER RESIDUE DETECTION METHODS FOR ALCONOX, INC. CLEANERS									
Alconox brand Cleaner	Anionic Surfactant by HPLC	Nonionic Surfactant by Deriv. UV-Vis	Direct UV/Vis	Phosphate by Titration	Enzyme by Assay	Organic Carbon by TOC	Conductivity	Citric Acid by HPLC, UV, or Assay	Potassium by flame or IC
Alconox	X		X	X		X	X		
Liquinox	X	X	X			X	X		X
Tergazyme	X		X	X	X	X	X		
Alcojet				X		X	X		
Alcotabs	X		X			X	X		
Detojet				X			X		X
Detergent 8						X			
Citranox	X	X	X			X	X	X	
Luminox						X			
Citrajet						X		X	
Solujet						X	X	X	
Tergajet						X	X	X	

TOC and other non-specified methods are commonly used where the limits of detection and quantitation are well below residue acceptance levels. Table B reviews method validation requirements:

TABLE B: ANALYTICAL RESIDUE DETECTION METHOD VALIDATION CONDITIONS

Method	Accuracy	Precision	Linearity	Reproducibility	Selectivity	Specificity	LOD	LOQ	Ruggedness
HPLC	X	X	X	X	X	X	X	X	X
TLC	X	X	X	X	X	X	X	X	X
IC	X	X		X	X	X	X	X	X
Wet	X	X	X	X	X	X	X	X	X
UV-vis	X	X	X	X	X	X	X	X	X
TOC	X	X	X	X			X	X	X

HPLC- High performance liquid chromatography, TLC- Thin Layer Chromatography, IC- Ion Chromatography, UV-vis – ultraviolet visible spectroscopy, TOC – total organic carbon, Wet – wet titrations and assays

Example of a Typical Application: Aqueous Critical Cleaning Used For Pharmaceutical Product Manufacturing

Frequently, Alconox, Inc. provides technical support to help the product manufacturing units of pharmaceutical companies meet their critical cleaning demands. In one such case, the bio-pharmaceutical subsidiary of a large global healthcare company had already selected Alconox’s Liquinox® brand as their cleaner. However, the pharmaceutical product development group was having trouble getting linearity in a Total Organic Carbon (TOC) detection method when using the Liquinox® cleaner.

The Alconox technical support team suggested changes in the pharmaceutical company’s sample handling procedures.

The Alconox recommendations improved the manufacturer’s linear recovery of low concentrations of surfactants, as well as explained and corrected for the results the manufacturing team had been experiencing. The changes allowed the group to complete their method detection validation.



Alconox Provides Expertise in Validation Support

Alconox, Inc. supplies the best brands of aqueous cleaner to company's requiring exacting levels of quality control and technical service. Support for regulatory-compliant cleaning validations includes lot number traceability of all cleaners and ingredients, cleaner toxicity and reactivity/degradation information, residue sampling, detection methods and written cleaning procedures. To help meet quality control and regulatory compliance requirements required, each Alconox product has downloadable Certificate of Analysis, technical bulletin, MSDS, method detection references, and trace analysis.

As a leader in its field, Alconox can provide valuable consultant services to manufacturers of pharmaceutical products — as well as vendors, suppliers, and clients in many other industries — who wish to establish cleaning validation methods and procedures.

For Alconox, Inc Validation Support, please contact:

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For Additional Help with Your Critical Cleaning Challenge

Alconox, Inc has 60 + years in developing aqueous cleaning solutions for pharmaceutical manufacturing and is able to help solve critical cleaning challenges.

Please contact the Critical Cleaning Experts at Alconox Validation Support or Alconox Cleaning Verification Lab for assistance.

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For cleaning verification, cleaning chemistry identification and initial process condition recommendations for a given cleaning procedure, please contact the cleaning lab for consideration to be included in a study.
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