Cleaning Validation for Pharmaceutical Manufacturing

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 the cost reduced if the cleaner supplier can provide support — ultimately allowing pharmaceuticals to get to market faster and at a lower cost. This paper outlines the basics of cleaning validation and discusses the support services you should seek from your critical cleaning products supplier to optimize your cleaning validation process.

What Is Cleaning Validation?

Cleaning validation is a requirement in industries such as pharmaceutical manufacturing that adhere to current Good Manufacturing Practice (cGMP) and Quality Systems Regulations (QSR). It 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 consistently that the cleaning process removes residues to acceptable levels. Testing for acceptable residues includes:

- Residue identification
- Residue detection and quantitation method selection
- Sampling method selection
- Setting residue acceptance criteria
- Method validation and recovery studies
- Writing procedures and training operators

After establishing that a process can be repeated reliably to remove residues to acceptable levels, a program can be implemented to maintain the state of validation so that only periodical retesting is required.

Changing any part of the cleaning procedure — including the cleaner — often mandates revalidation. This entails first cleaning with the new cleaners or methods, collecting data, and then cleaning the equipment with the prior validated process before using the equipment. The previously validated steps need to

be followed until the new procedure is fully validated.

Generally, process validation comprises four parts:

1. Design Qualification (DQ)
2. Installation Qualification (IQ)
3. Operational Qualification (OQ)
4. Performance Qualification (PQ) of manufacturing equipment and operations

Cleaning validation is done when it's impractical or impossible to verify cleaning on all — literally 100 percent — of the production equipment used in high-volume manufacturing operations. Instead, large-volume pharmaceutical manufacturers rely on validated critical cleaning at steps affecting the quality or safety of the final product.

The validation procedure begins with a 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 United States is under FDA jurisdiction, which employs a risk-based approach emphasizing quality systems inspections.

Cleaning validation in the United States is under FDA jurisdiction, which employs a risk-based approach emphasizing quality systems inspections. Whether the validation 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. The committee usually consists of members such as these:

- **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, validates and transfers 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
- Laboratory control systems.

Simplify Validation Using a Worst-Case Matrix

To simplify validations, create a matrix of worst-case equipment to clean and worst-case residues to remove. This can be done in two steps:

Step 1: Develop an equipment matrix and residue matrix that defines all shared and dedicated equipment by the residues they are exposed to. Specifically, you'll need to conduct tests to identify and document a worst case for the most difficult-to-clean equipment and residues. Identify groups or families of worst-case situations with one piece of equipment representing a group of similar or easier-to-clean equipment. Residues can also be grouped with one residue representing a group of similar or easier-to-clean residues.

Step 2: Perform complete validations on the worst-case equipment and residues. These will serve to validate the process for easier-to-clean equipment and 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
- Worst interactions with the upcoming batch to be cleaned

Whenever a new residue or piece of equipment is used, evaluate whether 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 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, according to the criteria shown in **Table 1**.

While the FDA often prefers the use of specific methods, non-specific methods may be accepted, provided a scientific rationale for their use is determined.

Selecting a Sampling Method

Several methods are available to sample for critical cleaners used in the production of pharmaceutical products, including:

- Rinse water sampling
- Swab or wipe sampling
- Coupon sampling
- Placebo sampling
- Direct analysis

Rinse water sampling is done when sampling large pieces of equipment or runs of piping. 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 to assure that residues are being adequately detected and not simply sitting on the surface without dissolving 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 moistened with high-purity water (WFI) is drawn over a defined area using a systematic multi-pass technique — always moving from clean to dirty areas to avoid recontamination. If total organic carbon (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 uses a WFI-dipped coupon placed inside a piece of equipment or removable piece of actual pipe to extract residues for analysis.

Placebo testing is performed using placebo products and analyzing for residues from the previous batch.

Direct analysis may be performed by an instrument that takes residual readings directly from the surface of manufacturing equipment. A handheld FTIR is an example of this type of equipment.

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.

Setting Residue Acceptance Criteria

Pharmaceutical product manufacturing requires identifying and setting acceptable residue limits for potential residues, including:

- Limits for the active drug
- Excipients
- Degradation products
- Cleaning agents
- Bioburden
- Endotoxins

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 in any of the following ways:

- Maximum concentration in the next product (µg/ml)
- Amount per surface area (µg/cm^2)
- Amount in a swab sample (µg or µg/ml)
- Maximum carry-over in a train (mg or g),
- Concentration in equilibrated rinse water (µg/ml)

A calculated safety-based acceptance limit should be determined. A lower internal action level, plus a lower process control level based on actual manufacturing and measuring experience, may also be desirable.

TABLE 1: SELECTING THE PROPER CLEANER RESIDUE DETECTION METHOD

	Specific	Non-specific
Tests for:	Individual ingredient	Blend of ingredients
Methods:	High-performance liquid chromatography (HPLC) Ion selective electrodes Derivative UV spectroscopy Enzymatic detection Titration Direct analysis GC/FID or GC/MS ICP	Total organic carbon (TOC) pH levels Conductivity
Preferred for:	Initial validation Investigating failures or action levels	Retesting to maintain a validated state Monitoring

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/cm^2 or mg/ml of cleaner residue on just-cleaned equipment:

Safety Based Limit:

$$\textbf{Limit (mg/cm}^2\textbf{ or L)} = \frac{\text{ADI carry-over (mg)* x Smallest next batch (kg)}}{\text{Size of shared equipment (cm}^2\text{ or L) x Biggest daily dose of next batch (kg)}}$$

*Acceptable Daily Intake:

$$\textbf{ADI carry-over (mg)} = \text{LD50 by administration route (mg/kg) x body weight (kg) x (1/10,000 or 1/1,000)}^{\dagger}$$

† a conversion safety factor

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

10 ppm Carryover Limit:

$$\textbf{Limit (mg/cm}^2\textbf{)} = \frac{\text{10 mg residue on just-cleaned surface x Next batch size (kg or L)}}{\text{1 (kg or L) of next product x Size shared equipment (cm}^2\text{ or L)}}$$

It's important to note, for many residues a visual detection limit can be validated on the order of 1–4 µg/cm^2, and the possibility exists for the visually clean criteria to be the most stringent criteria.

For example, let's look at a cleaner with a rat oral LD50 of 5000 mg/kg. The ADI calculation using a 70 kg person and a safety factor of 1,000 produces a result of 350 mg (5000 mg/kg x 70 kg/1,000). So, our goal is to avoid more than 350 mg of residue in a daily dose of the next product.

Assume the following about the next batch: a 2,000 kg mixer, next smallest batch of 1,000 kg, 100,000 cm^2 shared area of mixer and filling equipment, and daily dose of 0.005 kg. Given that, the calculated residual acceptance criteria is 700 mg/cm^2 (350 mg x 1,000 kg/(100,000 cm^2 x 0.005 kg). Comparatively, the 10 ppm in next batch limit gives acceptance criteria of 100 µg/cm^2 (10 mg x 1,000 kg/(1 kg x 100,000 cm^2) x 1,000 µg/mg. In this case, if the ability to detect visually to 4 µg/cm^2 is demonstrated, then a visually clean surface will be the most stringent acceptance criteria for residues.

Small final filling equipment such as tablet punches and dies or filling needles for vials may require separate residue studies to prevent the punches or needles themselves from contaminating the first few bottles or tablets of the next batch.

If the safety-based limit is set at 100 mg/cm^2, it can be expressed as a rinse water concentration of 100 mg/L in a post-final rinse using 100 L of rinse water recirculated to equilibrium (0.1 mg/cm^2 x 100,000 cm^2/100 L). The same limit could be expressed as 6.25 µg/ml or ppm TOC in a sample for a residue that is 10% TOC by weight in a 20 ml swab sample from a 25 cm^2 swab area where 50% recovery has been established (25 cm^2 x 100 µg/cm^2) x 50% recovery x 10% TOC/20 ml. The same safety limit can be expressed several different ways.

Establishing the acceptable daily exposure (ADE) for a compound is a relatively new method for setting cleaning validation and cross contamination limits in pharmaceutical manufacturing facilities. Defined by the ISPE as a dose that is unlikely to cause an adverse effect, even if exposure occurs every day for a lifetime, the ADE is protective of all populations by all routes of administration. ADEs are determined by qualified industrial hygienists and toxicologists using all available toxicology and safety data. Once established, the ADE provides the basis for the maximum allowable carryover (MACO), as shown by following equations.

Acceptable Daily Exposure

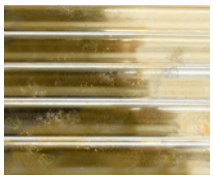
$$\textbf{ADE} = \frac{\text{NOAEL x BW}}{\text{UFc x MF x PK}}$$

Maximum Allowable Carryover

$$\textbf{MACO} = \frac{\text{ADEprevious x MBSnext}}{\text{TDDnext}}$$

Definitions

ADE	Acceptable daily exposure (mg/day)
BW	Body weight of an average adult (e.g. 70 kg)
MACO	Maximum allowable carryover; the acceptable transferred amount from the previous product into the next product (mg)
MBSnext	Minimum batch size for the next product(s) (mg)
MF	Modifying factor; a factor to address uncertainties not covered by the other factors
NOAEL	No observed adverse effect level (mg/kg/day)
PK	Pharmacokinetic adjustments



Before:
Coating residue from pharmaceutical tablet presses and packaging equipment can be tough to clean.

After:
Tablet presses and packaging equipment cleaned with CITRANOX meet stringent pharmaceutical cleaning validation standards.

TDDnext Standard therapeutic daily dose for the next product (mg/day)

UFc Composite uncertainty factor; the combination of factors which reflects the inter-individual variability, interspecies differences, subchronic-to-chronic extrapolation, LOEL-to-NOEL extrapolation, database completeness

Validating 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 percent, 100 percent, and 150 percent of the acceptable limit. This helps 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 the amount detected with the amount of assumed surface residue found acceptable.

For example, if 100 µg of residue was spiked on the surface, and after swabbing, extracting and analyzing only 90 µg 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 µg per swabbed area needs to be interpreted as actually being 100 µg per swabbed area to adjust for the 90 percent recovery.

When the post-drying solubility or rinseability 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.

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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 out of otherwise readily water-soluble ingredients in the detergent or cleaner. If there is no surfactant to be analyzed — either because no surfactant is present, or the surfactant is not a good marker due to stability — then other markers may be chosen.

In some cases, bioburden/endotoxin levels may need to be validated. Validation of biologics exceeds the scope of cleaning validations.

Cleaner Residue Detection Methods

When performing a pharmaceutical cleaning validation, analytical methods for detecting detergent residues must be validated also. **Table 2** (below) lists a variety of residue detection methods for the validation of Alconox Inc. detergents and cleaners.

The available choices vary from selective to non-specific methods such as TOC. Selective methods are those proven specific at a 95 percent confidence level, under specified usage conditions, without significant

TABLE 2: CLEANER RESIDUE DETECTION METHODS FOR ALCONOX INC. CLEANERS

Alconox Inc. Brand Cleaner	Anionic Surfactant by HPLC	EDTA by HPLC	Direct UV/Vis	Phosphate by Titration and IC	Enzyme by Assay	Organic Carbon by TOC	Conductivity	Organic Acid by HPLC, UV, or Assay	Potassium by flame or IC
ALCONOX	●	●	●	●		●	●		
LIQUINOX	●		●			●	●	●	
TERGAZYME	●	●	●	●	●	●	●		
ALCOJET		●		●		●	●		
ALCOTABS	●	●	●	●		●	●	●	
DETOJET				●		●	●	●	●
DETERGENT 8						●	●		
CITRANOX	●		●			●	●	●	
LUMINOX						●		●	
CITRAJET						●		●	
SOLUJET						●	●	●	●
TERGAJET		●				●	●	●	
DETONOX	●	●	●	●		●	●		●
KEYLAJET		●		●		●	●	●	●

For detection method details contact Alconox Inc. technical support.

TABLE 3: DATA ELEMENTS REQUIRED FOR VALIDATION

Analytical Performance Characteristics	Category I	Category II		Category III	Category IV
		Quantitative	Limit Tests		
Accuracy	Yes	Yes	*	*	No
Precision	Yes	Yes	No	Yes	No
Specificity	Yes	Yes	Yes	*	Yes
Detection Limit	No	No	Yes	*	No
Quantitation Limit	No	Yes	No	*	No
Linearity	Yes	Yes	No	*	No
Range	Yes	Yes	*	*	No

* May be required, depending on the nature of the specific test.

bias or interference from impurities, degredants, excipients or other ingredients.

TOC and other non-specific methods are commonly used where the limits of detection and quantitation are well below residue acceptance levels. USP chapter <1225>, Validation of Compendial Procedures, provides information about validating compendial analytical procedures ranging from exacting analytical determinations to limit tests. Within this range, tests are categorized as follows:

- **Category I** — Analytical procedures for quantitation of major components of bulk drug substances or active ingredients (including preservatives) in finished pharmaceutical products.
- **Category II** — Analytical procedures for determination of impurities in bulk drug substances or degradation compounds in finished pharmaceutical products. These procedures include quantitative assays and limit tests.
- **Category III** — Analytical procedures for determination of performance characteristics such as dissolution, drug release, and others.
- **Category IV** — Identification tests.

Table 3 shows the analyte being tested.

The Alconox Inc. recommendations improved the linear recovery of low concentrations of surfactants, and explained and corrected for the results the manufacturing team had been getting.

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

Alconox Inc. frequently provides technical support to help pharmaceutical companies' product manufacturing units meet their critical cleaning requirements. In one case, the bio-pharmaceutical subsidiary of a large global healthcare company had already selected Alconox Inc. LIQUINOX® brand liquid detergent as their cleaner. However, the pharmaceutical product development group was having trouble achieving linearity in a TOC detection method when using LIQUINOX cleaner.

The Alconox Inc. technical support team suggested changes in the company's sample handling procedures.

The Alconox Inc. recommendations improved the linear recovery of low concentrations of surfactants, and explained and corrected for the results the manufacturing team had been getting. The changes made it possible for the group to complete their method detection validation.

Writing Procedures and Training Operators

In addition to the cleaning validation, written procedures should include:

- Assignment of responsibilities
- Equipment disassembly and monitoring procedures
- Cleaning conditions
- List of consumables and equipment
- Scope of procedure
- Documentation requirements
- Labeling instructions for in-process and cleaned equipment that state cleaning expiration date, post-cleaning inspection, storage conditions and inspection requirements prior to next use

Operators must then be trained and certified in the procedures, and receive regular appropriate retraining.

Final Validation Report

The final validation report also includes a section dealing with cleaning process design. It references the standard operating procedures (SOPs) or work instructions (WI) and their evaluation. Also, there is a section of data analysis providing statistical justification for conclusions reached. A defined procedure for revalidating an altered validated process is included and should describe approval and review processes required when making specific types of alterations. Whenever any aspect is changed — for example, hardest-to-clean or most-toxic worst cases — a list of constraints and assumptions should be developed for review. This may be a part of the validation itself, or part of a design history file (DHF). Additionally, provisions for emergency changes are established.

The final section of the validation report should provide references to any standard methods, journal articles, or government documents that were used.

Revalidation is required whenever a major change is made. The level of revalidation may be covered in a Master Validation Plan. This is typically required when the cleaner is changed. The validated processes are often reviewed during annual product review (APR), providing an opportunity to determine whether all minor changes made since the previous review amount to significant changes that exceed assumptions and need revalidation. It may be appropriate to continue an old cleaning operation while phasing in a new one, and it is important to monitor the new process to prove it produces the same validated results.

It may be appropriate to continue an old cleaning operation while phasing in a new one and it is important to monitor the new process to prove it produces the same validated results it is replacing.

Cleaning Supplier Validation Support

When selecting an aqueous cleaner for cGMP manufacturing where a cleaning validation is required, consider both the efficacy of the cleaner and the ability of its manufacturer to support validation efforts.

The chosen critical cleaner manufacturer should provide:

- Lot traceability of cleaners
- Certificates of Analysis
- Consistent manufacturing
- Cleaner selection consulting
- Ingredient disclosures under confidentiality
- Cooperation on audits and quality questionnaires
- Ingredient toxicity data
- Ingredient reactivity information to help determine degradations and interactions
- Cleaner shelf life data
- Residue sampling and detection method information
- Acceptance limits and recovery data
- Residue detection methods validation information
- Assistance with written cleaning procedures

Alconox Inc. Provides Validation Support for Every Product

Pharmaceutical companies requiring exacting levels of quality control and technical service choose Alconox Inc. cleaners for performance and support.

To help meet quality control and regulatory compliance requirements, each Alconox Inc. product has a downloadable Certificate of Analysis, technical bulletin, SDS, method detection references, and trace analysis.

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. For analytical detection method details contact Alconox Inc. technical support.

In addition, Alconox Inc. can provide expert consultative services to pharmaceutical manufacturers, vendors and suppliers who wish to establish cleaning validation methods and procedures. The same services are also available to the healthcare, veterinary, medical device manufacturing, cosmetics and other industries.

ALCONOX
Critical Cleaning Experts

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Get Validation Support or Help With Your Critical Cleaning Challenge

Alconox Inc. has more than 75 years' experience developing aqueous cleaning solutions for pharmaceutical manufacturing. Let us help solve your next critical cleaning challenge.

Please contact Alconox Inc. for expert validation support or verification laboratory services:

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