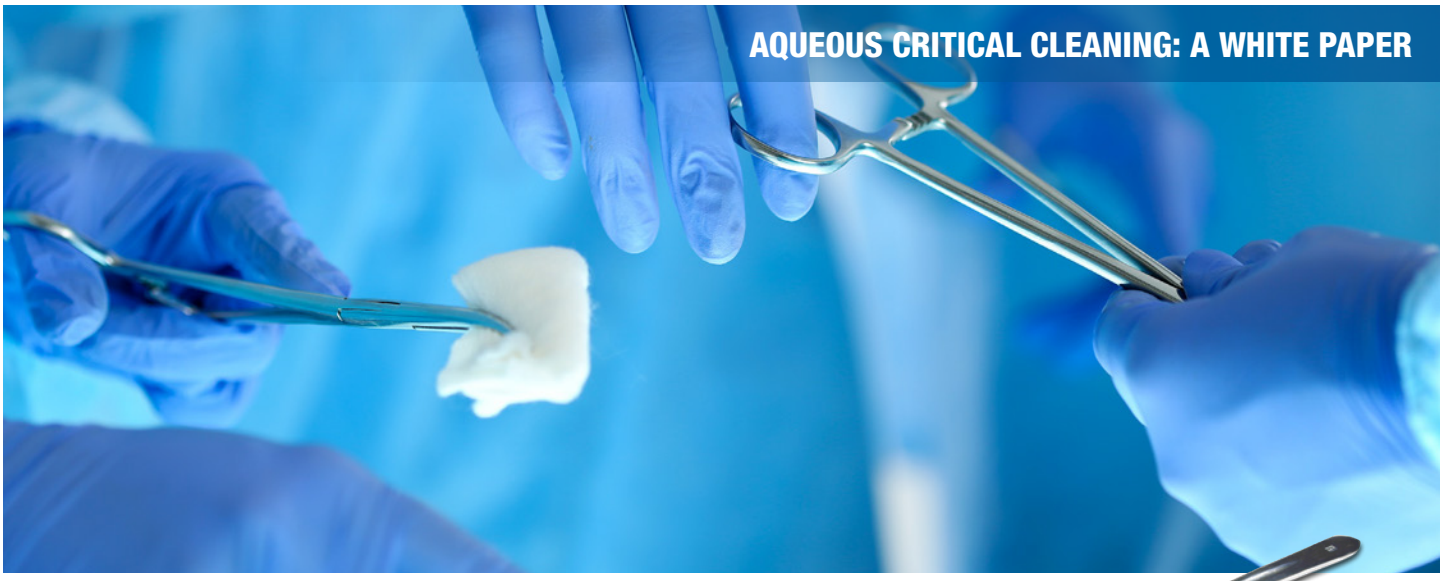


Cleaning Validation for Medical Device Manufacturing

Why Get Cleaning Validation Support From Your Cleaner Supplier?

Cleaning validation or verification is a necessary regulatory compliance step in medical device manufacturing and reprocessing. Support from the cleaner manufacturer can save time and money when establishing either cleaning validation or cleaning verification processes. This white paper outlines the basics of cleaning validation and how the cleaner manufacturer can help simplify and speed up the process, as well as support ongoing maintenance of the validated or verified state.

What Is Cleaning Validation?

Cleaning validation is documentation establishing that a cleaning process will consistently result in devices that are clean to a predetermined acceptable level of cleanliness. In the medical device manufacturing industry, cleaning validation is generally performed by examining the finished device itself rather than the equipment used to manufacture it.

In addition to cleaning validation, sterility validation is required for products sold sterile. Although sterility validation is beyond the scope of this paper, cleaning validation is important for any device sold sterile. (For more information about sterility validation, contact Alconox, Inc.)

Validation concerns vary across the industry and depend on the class of medical device. Devices are classified according to the nature of patient contact. Re-usable examining devices with incidental patient contact might be tested for function and, possibly, bioburden. Implantable medical devices with years of internal patient contact might also be tested for endotoxins, cytotoxicity, sterility, and proper device function.

The goal of validation is to prove that a system is functioning properly within established parameters to ensure product, patient, worker, and environmental safety. To achieve this, manufacturers typically have a validation committee with clearly defined

responsibilities, consisting of these members:

- **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 evaluates equipment data
- **R&D** — Performs recovery studies, validates and transfers methods, and selects new cleaners

The required cleaning validation documentation is specified in the relevant sections of the manufacturer's Validation Master Plan, including:

- The objective
- Background
- Equipment/reagents
- Responsibilities
- Product
- Procedures
- Residue acceptance limits, with rationale
- Analytical methods
- Sampling procedures and recovery
- Cleaning process design
- Data analysis
- Assumptions
- Change control/maintenance
- References

Before:
Blood dried onto scalpel handles is difficult to thoroughly remove.

After:
Soaking in TERGAZYME, followed by gentle cleaning, prepares surgical instruments for effective sterilization and prolongs instrument life.

All cleaning validation documents are subject to an FDA inspection process known as the Quality System Inspection Technique (QSIT), defined in the FDA "Guide to Inspections of Quality Systems" (FDA Center for Devices and Radiological Health [CDRH], August 1999). QSIT establishes a "top-down" approach for inspecting and managing these subsystems of a firm's overall quality system:

- Corrective and Preventive Actions
- Management Controls
- Production and Process Controls
- Facility and Equipment Controls
- Records, Documents and Change Controls
- Material Controls
- Design Controls

These subsystems must conform to current good manufacturing practice (cGMP) in accordance with the Quality System regulations (21 CFR Part 820). The ISO medical device quality equivalent is ISO 13485. The most relevant sections to critical cleaning and cleaning validation are listed below.

§820.3 Definitions

(p) *Manufacturing material* means any material or substance used in or used to facilitate the manufacturing process, a concomitant constituent, or a byproduct constituent produced during the manufacturing process, which is present in or on the finished device as a residue or impurity not by design or intent of the manufacturer.

§820.70 Production and process controls (ISO 13485:2003 6.3 + 6.4 + 7.1 + 7.5.1 + 7.5.2 + 8.2.3)

(e) *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.

(h) *Manufacturing material*. Where a manufacturing material could reasonably be expected to have an adverse effect on product quality, the manufacturer shall establish and maintain procedures for the use and removal of such manufacturing material to ensure that it is removed or limited to an amount that does not adversely affect the device's quality. The removal or reduction of such manufacturing material shall be documented.

§820.72 Inspection, measuring, and test equipment (ISO 13485:2003 7.6)

(a) *Control of inspection, measuring, and test equipment*. Each manufacturer shall ensure that all inspection, measuring, and test equipment, including mechanical, automated, or electronic inspection and test equipment, is suitable for its intended purposes and is capable of producing valid results. Each manufacturer shall establish and maintain procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained. The procedures shall

include provisions for handling, preservation, and storage of equipment, so that its accuracy and fitness for use are maintained. These activities shall be documented.

§820.75 Process validation
(ISO 13485:2003 6.3 + 6.4 + 7.1 + 7.5.1 + 7.5.2 + 8.2.3)

(a) Where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated with a high degree of assurance and approved according to established procedures. The validation activities and results, including the date and signature of the individual(s) approving the validation and where appropriate the major equipment validated, shall be documented.

Furthermore, the FDA has been supporting a risk-based approach for medical device process validations. These types of risk-based approaches would include something like a pFMEA (process failure mode engineering analysis). This is a quantitative way of evaluating risk that can be used as part of a design history file (DHF).

The need for cleaning validation or cleaning verification comes from cGMP required production and process controls, as well as design inputs and outputs. If cleaning verification is employed — commonly when small batches of devices are manufactured or re-use devices are being cleaned — then verification must be done every time cleaning is performed.

Cleaning verification is documented evidence that an individual cleaning event has produced a device that is acceptably clean. Verification tests may be performed as deemed appropriate by hazard analysis, and may include demonstrating:

- A 2–4 log reduction of bioburden
- Levels of less than 10 colony forming units (CFU) per device
- Less than 20 endotoxin units (EU) per device
- Chemical residues shown to be below limits affecting biocompatibility, function and toxicity

Cleaning verification is documented evidence that an individual cleaning event has produced a device that is acceptably clean.

TIR 30, SECTION 6, TABLE 6: TEST SOILS FOR REUSABLE DEVICES

Authors	Constituents of Soil	Device
AAMI TIR12 (Hucker's)	Peanut butter, evaporated milk, butter, flour, lard, dehydrated egg yolk, saline, printer's ink, blood	Not specified
Alfa and Jackson (2001)	ATS-B (bacteria, protein, carbohydrate, endotoxin, hemoglobin)	Flexible colonscope
Anderson and Nwoguh (1991)	*Klebsiella aerogenes*	Enteral feeding tubes
Bar, et al. (2001)	*Mycobacterium tuberculosis*	Bronchoscope
Chartier, et al. (2001)	Yeast extract, native human albumin, defibrinated native sheep blood, bovine serum, fibrin, Tween 80, water	Microplates
Donlan, et al. (2001)	*B. stearothermophilus* spores, *E. cloacae* biofilm	Needleless connectors to central venous catheters
Green, et al. (2001)	Oils, calf serum, albumin, gelatin, hog mucin, egg white	Microplates
Kozarek, et al. (2001)	*B. stearothermophilus* spores	Double-channel sphincterotomes
Merrit, et al. (2000a)	Bacteria, mammalian cells, albumin, bovine fibrin, bovine fibrogen	Microplates
Mostafa and Chackett (1976)	Radiolabeled human serum albumin	Surgical instruments
Orzechowski, et al. (2000)	Bovine albumin, mucin, fibrogen	Dental handpieces
Penna and Ferraz (2000)	*B. subtilis* in radioopaque iodine contrast, bovine blood with EDTA	Angiographic catheters, spinal needles
Pfeifer (1998a, 1998b)	Albumin, hemoglobin, fibrinogen, thrombin	Surgical instruments
Roth, et al. (1999b)	a) Radioactive marked macroalbumins b) *S. aureus, P. aeruginosa,* heparinized sheep blood, protamine	Biopsy forceps, papillotome, Dormia basket
Rowan and Anderson (1998)	*Bacillus cereus*	Infant feeding bottles
Schrimm, et al. (1994)	Radiolabeled marker macroalbumins	Tubular instruments
Verjat, et al. (1999)	Human albumin solution	Hemolysis glass tubes, surgical steel blades, ceramic penicylinders
Working group (1995)	Microorganisms in oleic acid-albumin-dextrose catalase	Endoscopes

Further testing should be done to show non-viable residuals may be removed. This could be done by applying soils such as those found in **TIR12, or TIR 30, Section 6, Table 6** (shown previous page). Examples of soils are Hucker's or ATS-B soils. Another example of a test to demonstrate removal of soil contamination is the ProFormance TOSI® (test object surgical instrument) cleaning challenge (see Healthmark Industries, 33671 Doreka, Fraser, MI 48026. www.hmark.com. Phone: 800.521.6224).

Validating the Use of a Cleaner

Validating the use of a cleaner requires demonstrating that the cleaning process removes any cleaner residues down to acceptable levels. This involves several steps:

- Identifying cleaner residues
- Selecting a residue detection method
- Choosing a sampling method
- Validating residue detection methods
- Constructing recovery studies
- Setting residue acceptance criteria
- Validating the cleaning process with the new cleaner, including:
  —design of experiments for optimal process
  —three consecutive cleaning trials
  —creating the validation report
- Writing procedures and training operators

To identify cleaner residues, you need to know the cleaner formulation. The cleaner supplier should be willing to disclose the ingredients of their cleaner under a non-disclosure agreement.

The validation is done on critical cleaning steps affecting the quality or safety of the final product or device. Validation is achieved by proving that a process operates within predetermined parameters. The performance qualification (PQ) portion of the validation should demonstrate at least three times that the cleaning process removes residues down to predetermined acceptable levels. Changing any significant part of the cleaning procedure, including the cleaner, mandates revalidation. This entails, at a minimum, first cleaning the new way, collecting data, then cleaning the prior way (validated) before using any equipment for manufacturing.

Identifying Cleaner Residues

To identify cleaner residues, you need to know the cleaner formulation. The cleaner supplier should be willing to disclose the ingredients of their cleaner under a non-disclosure agreement. Sometimes sufficient information about cleaner ingredients can be obtained from material safety data sheets (MSDS) and cleaning validation technical information supplied by the cleaner supplier. Ask your cleaner supplier which ingredients are likely to be the last to rinse away and which ingredients are best to analyze as a marker for the cleaner residue. After a residue marker is identified, a residue detection method can be selected and validated.

Selecting and Validating a Residue Detection Method

Selecting the appropriate detection method for cleaner residues begins with choosing a specific or non-specific methodology, according to the criteria shown in **Table 1**.

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) Ultra performance liquid chromatography (UPLC) Gas chromatography/mass spectroscopy (GC/MS) Titration Direct UV spectroscopy Assay Ion chromatography (IC)	Total organic carbon (TOC) pH levels Conductivity
Preferred for:	Initial validation Investigating failures or action levels	Broad detection of any residue Retesting to maintain a validated state Monitoring

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 information about a method, contact Alconox, Inc. technical support.

When performing a medical device cleaning validation, analytical methods for detecting detergent residues must be validated also.

The FDA often prefers use of specific methods, especially when investigating failures or action levels. Under specified usage conditions, these methods are proven specific at a 95 percent confidence level, without significant bias or interference from impurities, degredants, excipients, or other ingredients.

However, non-specific methods may be accepted, provided a scientific rationale for their use is determined. Non-specific methods are commonly used where the limit of quantitation is <50% of the residue acceptance levels and where the broad detection of any residue is desired.

When performing a medical device cleaning validation, analytical methods for detecting detergent residues must be validated also. **Table 2** lists a variety of appropriate residue detection methods for Alconox, Inc. detergents and cleaners.

The validation of the residue detection method may involve establishing accuracy, precision, linearity, reproducibility, selectivity, specificity (for specific methods), detection and/or quantitation limits, as well as robustness of the residue detection method. On request, Alconox, Inc. can supply analytical methods per Table 2 for use with the respective detergents.

TOC and other non-specific methods are

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.

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 subjective evaluations of various attributes. 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 analytes being tested.

When conducting a rinse extraction, to demonstrate exhaustive extraction, successive rinses must be studied to determine how much water or solvent is needed and for how long.

Choosing a Sampling Method

Residual cleaner can remain on device surfaces after cleaning. A sampling method needs to be established to sample for this. Available methods include:

- Rinse water sampling or solvent extraction
- Surface swabbing

Rinse water sampling requires taking a sample of equilibrated post-final rinse water or solvent recirculated over all device surfaces. When conducting a rinse extraction, to demonstrate exhaustive extraction, successive rinses must be studied to determine how much water or solvent is needed and for how long. Rinse samples should be correlated to a direct measuring technique such as swabbing.

Swab or wipe sampling for TOC involves a swab or wipe moistened with high-purity water such as water for infection (WFI) drawn over a defined area using a systematic, multi-pass technique, always moving from clean to dirty areas to avoid recontamination. Then the swab head is cut off or the wipe is placed in a pre-cleaned TOC, or other sample, vial. TOC analysis requires the use of very clean low background, water, swabs/wipes and sample vials.

Constructing Recovery Studies

Recovery studies use selected sampling and detection methods on residues that have been "spiked" on the device surfaces at known levels. Generally, spikes are set at 50, 100, and 150 percent of the acceptance criteria limit. This demonstrates and establishes 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 µg of residue were spiked on the surface and after swabbing or extracting the detection analysis yielded 90 µg, the calculated percent recovery would be 90%. For cleaning validation, any analytical results would have to be adjusted by this recovery factor. In this example, the resulting 90 µg per swabbed or sampled area needs to be interpreted as being actually 100 µg per swabbed or sampled area to adjust for the 90% recovery. If the area is the entire device, then a detection of 90 µg in the extraction fluid can be interpreted as 100 µg per device by the following equation:

Residue Detected / Per sampled area (or device) / % Recovery =
Adjusted Detected Residue

Solving for the example above, the equation would be:

90 µg Detected / Device / 90% Recovery =
100 µg / Device Detected Residue

Setting Residue Acceptance Criteria

Residue acceptance limits must be set for any residue according to its potential to affect the form, fit or function of the finished device in terms of biocompatibility, toxicity, or functionality. Typically, limits need to be set for contaminants such as process fluids, polishing compounds, mold releases, bioburden, and cleaning agents, as well as any degradation or new products resulting from reactions

or interactions with these compounds, fluids or cleaning agents and possibly endotoxins.

Any applicable historical data on residues from successful manufacturing processes can be used to set acceptable levels. For existing devices with a history of acceptable performance, the mean level of residue plus three standard deviations may be used.

For a new device, where no history is available, a study can be performed by cleaning and measuring the cleanliness of a series of predetermined and justified worst-case devices spiked with different residue amounts on the surface. The acceptability of this resulting worst-case cleanliness is established by biocompatibility studies, toxicology calculations, or clinical data. Clinical data can substantiate the functionality of the cleaned devices. If device performance is acceptable and toxicity acceptance criteria are not exceeded (assuming data are available to set toxicity-based limits), then this becomes the acceptance criteria level for the residue. If no toxicity data are available, then you rely on biocompatibility of the cleaned device and functional performance data alone. This type of approach is often used for process oils and particulates where no other toxicity or biocompatibility data may be available.

For a new device, where no history is available, a study can be performed by cleaning and measuring the cleanliness of a series of predetermined and justified worst-case devices spiked with different residue amounts on the surface.

For cleaning agents and process fluids, systemic toxicity-based limits or direct biocompatibility-based limits can be derived either by estimation using safety factors applied to known oral toxicity data or by directly using any known biocompatibility data. When relevant systemic toxicity data is not available for a cleaner, estimate the acceptable daily intake (ADI) from LD50 (lethal dose for 50 percent of the population by compatible route of exposure, depending on the device) and a conversion factor using the following equation:

$$\textbf{\textit{Acceptable Daily Intake}} = \frac{\textit{LD50 (mg/kg)} \times \textit{body weight (kg)}}{\textit{conversion factor}}$$

For example, consider a cleaner with an oral LD50 greater than 500 mg/kg. Acceptance criteria are to be set for a device with less than one week of patient exposure. A conversion safety factor of 10,000 is appropriate, and the resulting limit should not exceed acute biocompatibility limits such as irritation. Therefore, the calculation for a 70 kg adult is:

TABLE 4: ACCEPTABLE TOXICITY AND BIOCOMPATIBILITY EXPOSURE CONCENTRATIONS FOR ALCONOX, INC. DETERGENTS

Detergent Acceptable Exposure Concentration	Biocompatibility Factor	Results
LIQUINOX	**Oral Toxicity**	**LD50 appears >5000 mg/kg**
10.0 g/L LIQUINOX	Dermal irritation	Not a dermal irritant
0.1 mg/mL LIQUINOX	Dermal sensitization	Not a sensitizer
0.1 mg/mL LIQUINOX	Intracutaneous injection	No differences in response
0.1 mg/mL LIQUINOX	Systematic injection	Treated sites similar to control
0.1 mg/mL LIQUINOX	Cytotoxicity	Meets the requirements
CITRAJET	**Oral Toxicity**	**LD50 appears >5000 mg/kg**
0.1 mg/mL CITRAJET	Intracutaneous injection	Treated sites more irritated than control
0.1 mg/mL CITRAJET	Cytotoxicity	Meets the requirements
CITRANOX	**Oral Toxicity**	**LD50 appears >5000 mg/kg**
10.0 g/L CITRANOX	Dermal irritation	Not a dermal irritant
0.1 mg/mL CITRANOX	Dermal sensitization	Not a sensitizer
0.1 mg/mL CITRANOX	Intracutaneous injection	Treated sites more irritated than control
0.1 mg/mL CITRANOX	Systematic injection	Treated sites similar to control
0.1 mg/mL CITRANOX	Cytotoxicity	Meets the requirements

$$\textbf{ADI per Device} = \frac{500\ mg/kg \times 70\ kg}{10{,}000} = 3.5\ mg\ per\ device$$

Considering the surface area of the device, acceptable residue per square centimeter (sq cm) of device will depend on the size of devices. If the device has a surface of 100 sq cm, the surface residue limit for that detergent would be 35 micrograms per sq cm (3.5 mg/device ÷ 100 sq. cm). While a process requirement of visually clean might be more stringent, in this example, the detergent used is fairly non-toxic, the medical device has a relatively short contact time, and the resulting safety-based limit is fairly high.

When working with more toxic residues on implantable devices and others with greater exposure risk, conversion safety factors will be higher and the resulting acceptance limits therefore lower.

When working with more toxic residues on implantable devices and others with greater exposure risk, conversion safety factors will be higher and the resulting acceptance limits therefore lower. Conversion safety factors that are used to calculate acceptance limits from oral toxicity data when other systemic toxicity data is not available will vary from 100 to 100,000 depending on the type of device and duration of exposure. Higher risk devices have higher conversion factors. A more thorough discussion of conversion factors can be found in these articles:

Kramer, H. J., W.A. van den Ham, W. Slob, and M. N. Pieters. "Conversion Factors Estimating Indicative Chronic No-Observed-Adverse-Effect Levels from Short Term Toxicity Data." *Regulatory Toxicology and Pharmacology* 23 (1996): 249–255.

Conine, D.L., B. D. Naumann, and L. H. Hecker. "Setting Health-Based Residue Limits for Contaminants in Pharmaceuticals and Medical Devices." *Quality Assurance: Good Practice, Regulation, and Law* 1 no. 3 (1992): 171–180.

Layton, D. B., B. J. Mallon, D. H. Rosenblatt, and M. J. Small. "Deriving Allowable Daily Intakes for Systemic Toxicants Lacking Chronic Toxicity Data." *Regulatory Toxicology and Pharmacology* 7 (1987): 96–112 .

Of course, using conversion factors necessarily involves making conservative assumptions so as to minimize risk. The use of a conservative safety conversion factor will result in a very conservative low acceptance limit for residue. Acceptance limits can be more directly justified by using more direct biocompatibility systemic toxicity data rather than estimating toxicity with conversion factors. **Table 4** shows biocompatibility systemic toxicity data for Alconox, Inc. cleaners.

Using the tested concentrations of a detergent allows an acceptance limit to be set for the appropriate biocompatibility for the given device. The following equation can be used to calculate biocompatibility-based acceptance criteria:

$$\textbf{Biocompatibility Based Acceptance Criteria (µg/device)} = \textit{Acceptable Exposure Concentration (µg /mL)} \times \textit{Lowest Reasonable Volume of Extraction Body Fluid (mL/sq cm)} \times \textit{Surface Area of Device (sq cm)}$$

As shown in the equation above, to get the worst-case biocompatibility acceptance criteria, assume the lowest reasonable amount of available body fluid to extract the residue from the device. This is because a small volume of extraction fluid results in the highest concentration of residue being presented to the patient. When setting biocompatibility limits for dermal sensitization, intracutaneous injection, systemic injection, and cytotoxicity, the smallest reasonable amount of body fluid needs to be assumed.

For example, to determine a worst-case residue for LIQUINOX, assume 1 drop per square centimeter as the lowest reasonable amount of body fluid or (since 1 drop = 0.05 mL) 0.05 mL/sq cm of liquid that cannot exceed 0.1 mg/mL LIQUINOX (from Table 4) without exceeding the measured acceptable levels for the biocompatibility factors of dermal sensitization, intracutaneous injection, systemic injection or cytotoxicity. This means the 100 sq cm device could have 5 mL of liquid (100 sq cm X 0.05 mL/sq cm) in which case you would not want more than 0.5 mg of LIQUINOX (0.1 mg/mL X 5 mL) on the device. This translates to a biocompatibility-based limit of 0.5 mg LIQUINOX/100 sq cm = 5 µg LIQUINOX/sq cm, or 500 µg LIQUINOX/device.

Note that for an open wound or implantable devices, the amount of fluid contacting the device would reasonably be higher and the resulting biocompatibility acceptance limit for LIQUINOX would

be higher. For example, if you conservatively estimated the amount of body fluid available to extract LIQUINOX into a patient was 0.1 ml/sq cm, then the biocompatibility acceptance limit for LIQUINOX residue would be 100 sq cm/device X 0.1 mL fluid/sq cm X 0.1 mg LIQUINOX/mL fluid = 1 mg LIQUINOX/device; or 10 µg LIQUINOX/sq cm of device (1 mg/device ÷ 100 sq cm/device).

In summary, there are three approaches that can be used to set acceptance criteria for cleaning agent residues on medical devices:

1. Cleaning trials (and further sterilization, if applicable) that result in measured levels of cleanliness that pass biocompatibility, functionality, and possibly endotoxin and sterility requirements
2. Estimates of systemic toxicity using appropriate safety conversion factors
3. Actual biocompatibility data for the cleaner

You can calculate the theoretical surface concentration of cleaning agent residue if you know the TOC content of the cleaner.

Using Total Organic Carbon to Measure Residue Acceptance Criteria

Total organic carbon (TOC) is commonly used to determine if residue levels meet acceptance limits. You can calculate the theoretical surface concentration of cleaning agent residue if you know the TOC content of the cleaner. You assume a worst case where all the detected TOC derives from cleaner residue, then calculate the amount of cleaner residue that would yield that TOC reading.

First, take a TOC measurement by extracting residues from a device in high purity organic-free water. Next, use the resulting measurement to calculate cleanliness and simultaneously detect process oils and cleaning agent residues. **Table 5** shows the TOC contents for Alconox, Inc. cleaners.

Use the following equation to calculate how much detergent residue could be on a device surface, using the TOC content listed in Table 5:

$$\textit{Cleaner Residue (µg/device)} = \frac{\textit{TOC Reading (µg TOC/mL)} \times \textit{Device Extraction Volume (mL)}}{\textit{Cleaner TOC Content (\% TOC w/w)}}$$

For example, a TOC reading of 1 µg/mL determined for a device exhaustively extracted in 20 mL of high purity water would indicate a residue of 95 µg LIQUINOX/device (1 µg/mL x 20 mL ÷ 0.21). Using both the above examples of biocompatibility acceptance limits, this TOC reading would be acceptable because even in the worst case, the acceptance limit for LIQUINOX was 500 µg /device. Of course since some of the TOC likely comes from other sources, the actual amount of LIQUINOX is probably well below 95 µg/device — but because a non-specific analytical method for detection was used, it is assumed, for the purpose of determining if the acceptance criteria was met or not, that all the detected TOC is from LIQUINOX.

TABLE 5: TOTAL ORGANIC CARBON (TOC) CONTENT OF ALCONOX, INC. CLEANERS

ALCONOX	11% TOC w/w
LIQUINOX	21% TOC w/w
TERGAZYME	11% TOC w/w
ALCOJET	1.5% TOC w/w
ALCOTABS	10% TOC w/w
CITRANOX	17% TOC w/w
CITRAJET	14% TOC w/w
TERGAJET	10.5% TOC w/w
SOLUJET	6% TOC w/w
DETONOX	12% TOC w/w
KEYLAJET	3.6% TOC w/w
DETOJET	0.5% TOC w/w
DETERGENT 8	38% TOC w/w

Typically, TOC is used to detect other carbon-containing residues such as oils. If any of the other residues have lower TOC acceptance limits than the detergent, then you must meet the lowest of these other limits. Once you meet the lowest limit, assuming all the carbon was from the other residue, then you will also have met the detergent acceptance limit. For example, here's a comparison of the TOC limits for LIQUINOX and another oil:

Acceptance limits

- LIQUINOX: 500 µg/device
- Other oil: 600 µg/device

TOC content

- LIQUINOX: 19% (w/w) or 19 µg TOC/100 µg LIQUINOX
- Other oil: 15% (w/w) or 15 µg TOC/100 µg other oil

Calculated Cleaner Residues (TOC Limits)

- LIQUINOX: 95 µg TOC/device (500 µg LIQUINOX/device X 19 µg TOC /100 µg LIQUINOX)
- Other oil: 90 µg TOC/device (600 µg other oil/device X 15 µg TOC ÷ 100 µg other oil)

In this case, by meeting the 90 µg TOC/device limit (which corresponds to 600 µg other oil/device), you have also met the 500 µg LIQUINOX/device limit.

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 may be a part of a design history file. 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 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

Application Case History: Validation of Aqueous Critical Cleaning Used for Medical Devices Manufacturing

Alconox, Inc. frequently consults with manufacturers about their critical cleaning validation process. In one case, a leading manufacturer of implantable medical devices required specific technical support.

The company had over one million medical devices implanted in patients. The QA team sought an analytical method to detect cleaner detergent residues to validate their cleaning.

Alconox, Inc. technical staff recommended three different analytical methods, along with appropriate supporting documentation regarding the pros and cons of each method. Using the Alconox, Inc. input, the manufacturer selected the method that would work most specifically with their production processes and that could be validated the most quickly for their application.

Alconox, Inc. Provides Validation Support and Expertise for Every Product

Because Alconox, Inc. is a supplier to companies requiring exacting levels of quality control and technical service, each product is tested by lot number, with Certificates of Analysis available to end-users with quality control or regulatory-compliance requirements.

Support for regulatory-compliant cleaning validations includes lot number traceability of all cleaners and ingredients, cleaner toxicity and reactivity/degradation information, shelf-life testing, residue sampling, detection methods and written cleaning procedures.

As a leader in the field of critical cleaning, Alconox, Inc. can provide valuable consulting and information to medical device manufacturers — as well as to vendors, suppliers, and clients in many other industries who wish to establish cleaning validation methods and procedures. Contact Alconox Technical support for detection method details.

ALCONOX
Critical Cleaning Experts

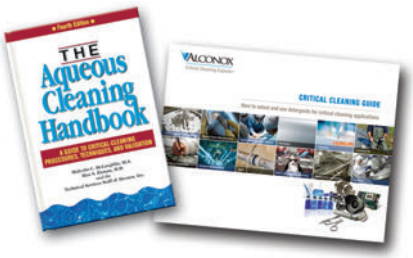
30 Glenn Street, Suite 309
White Plains, NY 10603 • USA

Get Validation Support or Help With Your Critical Cleaning Challenge

Alconox, Inc. has more than 70 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:

cleaning@alconox.com



Learn More About Critical Cleaning

Request a FREE copy of:

The Aqueous Cleaning Handbook
or
Critical Cleaning Guide

Try a Free Sample of Alconox, Inc. Detergents

Use our sample request form at alconox.com. Or call:

++914-948-4040

For questions or comments about this white paper, please contact Alconox, Inc. Technical Support at 914.948.4040 or cleaning@alconox.com