

Alconox, Inc. Cleaning Validation References Table of Contents

	<u>Page</u>
<u>Pharmaceutical Cleaning Validation</u>	2
Identifying Residues	4
Selecting a Residue Detection Method	4
Selecting a Sampling Method	4
Setting Residue Limit Acceptance Criteria	5
Validating Methods and Implementing Recovery Studies	5
Writing Procedures and Training	5
Directory of Methods for Each Detergent	5
<u>Medical Device Cleaning Validation</u>	7
Identifying Residues	9
Selecting a Residue Detection Method	9
Selecting a Sampling Method	9
Setting Residue Limit Acceptance Criteria	10
Validating Methods and Implementing Recovery Studies	10
Writing Procedures and Training	10
Directory of Methods for Each Detergent	10

PHARMACEUTICAL CLEANING VALIDATION REFERENCES



Pharmaceutical Cleaning Validation Method References for Alconox, Inc. Detergents

A cleaning validation involves testing for acceptable residues on pharmaceutical manufacturing or medical device surfaces. The validation involves:

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

This procedure is used to document acceptable residues 3 or more times and then a rational monitoring program to maintain a validated state is put in place. If you are changing any part of your procedure or cleaner, first clean the new way, collect data and then clean the old way before using any equipment while you are in the process of validating the new procedure.



Residue identification—in a pharmaceutical manufacturing environment involves; the cleaner, primary ingredients, excipients, decomposition products, and preservatives. This document is intended to help with the cleaner residue identification.

Residue detection method selection—for cleaners can involve specific methods for specific cleaner ingredients such as; high performance liquid chromatography (HPLC), ion selective electrodes, flame photometry, derivative UV spectroscopy, enzymatic detection and titration, or it can involve non-specific methods that detect the presence of a blend of ingredients such as: total organic carbon, pH, and conductivity. The FDA prefers specific methods, but will accept non-specific methods with adequate rationales for their use. For investigations of failures or action levels, a specific method is usually preferable. The later section of this document lists references to several methods for each cleaner brand.

Sampling method selection—for cleaners involves choosing between rinse water sampling, swabbing surfaces, coupon sampling, or placebo sampling. Rinse water sampling involves taking a sample of an equilibrated post-final rinse that has been recirculated over all surfaces. Rinse samples should be correlated to a direct measuring technique such as swabbing. Swabbing involves using wipe or swab that is moistened with high purity water (WFI) that is typically wiped over a defined area in a systematic multi-pass way always going from clean to dirty areas to avoid recontamination - ie. 10 side by side strokes vertically, 10 horizontally and 10 each with the flip side of the swab in each diagonal direction. For TOC analysis very clean low background swabs or wipes and sample vials such should be used. The Texwipe large Alpha Swab 714A or 761 have been used, these are available in kits with clean sample containers. Quartz glass fiber filter papers have been used successfully. Coupon sampling involves the use of a coupons or an actual removable piece of pipe that is dipped into high purity water to extract residues for analysis. Placebo testing involves using placebo product and analyzing for residues from the previous batch.

Setting residue acceptance criteria—in pharmaceutical and medical device manufacturing requires setting residue acceptance levels for potential residues such as the active drug, excipients, degradation products, cleaning agents, bioburden and endotoxins. These

levels are determined based on potential pharmacological, safety, toxicity, stability, and contamination effects on the next product using that surface or equipment. Limits are typically set for visual, chemical, and microbiological residues.

The cleaning agent limits are generally covered under chemical criteria. Chemical limits 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 carryover in a train (mg or g), or concentration in equilibrated rinse water (ug/ml). You should have a calculated safety based acceptance limit, and you can have a lower internal action level, and a lower process control level based on actual manufacturing and measuring experience.

Cleaning agent safety based limits are typically calculated from a safety factor of an acceptable daily intake (ADI), a (1/1000 or more) reduction of an LD50 preferably by the same route of administration, or reproductive hazard levels. If the calculated limit is found to be higher than a less than 10 ppm carryover to the next batch, then the limit can be set to the more stringent 10 ppm carryover level for the safety based limit.

Calculated safety based limit in mg/cm² or mg/ml of cleaner residue on a just cleaned equipment:

$$\text{Limit (mg/cm}^2 \text{ or L)} = \text{ADI carryover} - \text{see below (mg)} \times \text{Smallest Next Batch (kg)} \\ \text{Size of Shared Equipment (cm}^2 \text{ or L)} \times \text{Biggest Daily Dose or of Next Batch (kg)}$$

$$\text{ADI carryover (mg)} = \text{LD50 by administration route (mg/kg)} \times \text{body weight (kg)} \\ \times (1/10,000 \text{ or } 1/1000^*)$$

Comparison calculation of limit based on no more than 10 ppm carryover:

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

Note that for many residues you can validate a visual detection limit on the order of 1-4 ug/cm². It is possible that the visually clean criteria will be the most stringent criteria.

Example with a cleaner that has an rat oral LD50 of over 5 g/kg, the ADI calculation using a 70 kg person and a safety factor of 1000 gives a result of 350mg (5 g/kg X 70 kg / 1000). The calculated residual acceptance limit for a 2000 kg mixer and line where there might be a next smallest batch of 1000 kg, and the area of the mixer and filling equipment which is all used in the next batch is 100,000 cm² and the daily dose of the next product is 0.005

kg results in a calculated residual acceptance criteria of 700 mg/cm² (350 mg X 1000 kg / (100,000 cm² X 0.005 kg). By comparison, the 10 ppm in next batch limit gives an acceptance criteria of 100 ug /cm² (10 mg X 1000 kg / (1 kg X 100,000 cm²) X 1000ug/mg. In this case, it is likely that you will be able to show that you can visually detect down to 4 ug/cm² and since you need to have a visually clean surface, your most stringent acceptance criteria will be the visual limit.

Note that in this example you are trying to avoid getting more than 350 mg of residue in a daily dose of the next product. In the case of small final filling equipment such as filling needles for vials or tablet punches and dies, you might need to do separate residue studies on the filling needles or punches to be sure that there was not enough residue just on that 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 in this example is set at 100 ug/cm². Then this limit can be expressed as a rinse water concentration of 100 mg/L in a post final rinse using 100 L of recirculated to equilibrium rinse water (0.1 mg/cm² X 100,000 cm²/100 L). This same limit could be expressed as 6.25 ug/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 25 cm² 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.

The methods validation and recovery study—is the use of the sampling and detection method on known spiked surfaces at representative levels, typically spiked at 50%, 100% and 150% of the acceptable limit and at lower expected actual levels to show linearity with documented % recovery as analyzed and to determine the limit of detection and limit of quantitation. Ideally the expected values and limits should be multiples of the limits of quantitation. The % recovery is used to correlate amount detected with amount assumed to be on the surface as an acceptable residue. This is a good time to consider wipe or rinse sample storage conditions and time limits to get the sample analyzed. Rinseability profiles showing the complete rinsing of the individual detergent ingredients should be undertaken if the solubility of any detergent ingredients or the rinseability after drying is in doubt. In some cases bioburden/endotoxin levels may need to be validated. It is recommended that this process be done separately from the cleaning process so that the cleaning validation can be completed while the lengthier bioburden/endotoxin evaluation is done.

The written procedure and training of operators—involves writing out assigned responsibilities, protective clothing needs, equipment disassembly needs, monitoring procedures, documentation needs, labeling of in process and

cleaned equipment with cleaning expiration date, post cleaning inspection procedures, storage conditions, and inspection required before next use. The operators then need to be trained and certified in the procedures.

Directory of cleaner residue detection methods for each Alconox detergent

	A. Anionic Surfactant HPLC, Titrate, Kit	B. Nonionic Surfactant by HPLC	C. Direct UV/Vis	D. Phosphate by Titration	E. Enzyme by Assay	F. Organic Carbon by TOC	G. Conductivity	H. Citric Acid by HPLC, Assay, UV/Vis	I. Potassium by Flame or IC	J. Glycol Ether by GC
ALCONOX®	•	•	•	•	•	•	•			
LIQUI-NOX®	•	•	•			•	•		•	
TERG-A-ZYME®	•		•	•	•	•	•			
ALCOJET®				•	•	•				
ALCOTABS®	•		•		•	•				
DET-O-JET®				•			•		•	
DETERGENT 8®						•				•
CITRANOX®	•	•	•			•	•	•		
LUMINOX®						•				•
CITRAJET®					•		•			
TERGAJET						•	•	•		
SOLUJET						•	•	•		

A. Anionic surfactant analysis methods for ALCONOX®, LIQUI-NOX®, TERG-A-ZYME®, ALCOTABS®, and CITRANOX®. Note that the anionic surfactant is present at approximately 20% by weight in each of these detergents. SOLUJET contains 1 - 5 % surfactant that can be analyzed by HPLC, but a method needs developing.

1. Chemetrics Inc. water testing kit for anionic detergents, which is sensitive to 1/4 ppm. Contact Chemetrics, Inc. at 1-800-356-3072 or +540-788-9026.
2. LaMotte Chemical water testing kit for anionic detergents, which is sensitive to 1 ppm. Contact LaMotte Chemical at 1-800-344-3100 or +410-778-3100.
3. Hach Company water testing method for anionic detergents, which is sensitive to 1 ppm. Contact Hach Company at 1-800-227-4224 or 303-669-3050.
4. A gradient HPLC method in "Journal of Chromatography," 302, (1984) 65-78 by Bear, Lawley and Riddle, Separation of Sulfonate and Carboxylate mixtures by ion exchange HPLC.
5. A "Synthetic Anionic Ingredient by Cationic Titration" method from ASTM D 3049-75 (reapproved 1962) which has been reported to us as having a detection limit on the order of 10 ppm using normalities of 0.004 N Hyamine. It has been suggested that using lower normality Hyamine would give lower detection limits.

B. Nonionic surfactant analysis—the detectable levels are: LIQUI-NOX contains roughly 3-7% and CITRANOX contains roughly 1-5% detectable nonionic.

1. M J Shifflet, M Shapiro, C Levin and R DeNisco "Validating a Reversed-Phase HPLC Method to Determine Residual Nonoxynol-9 on Pharmaceutical Process Equipment Using a nonporous Silica Column" LCGC Vol 19 Number 3 March 2001 pp 312-317.

C. Direct UV/Visible determination:

1. Direct UV/Visible determination by making a broad-spectrum scan of the detergent to determine a maximum absorbed wavelength. Make standard dilutions of the detergent you wish to analyze for, using 1ppm, 2ppm, 4ppm, 8ppm and 16ppm dilutions. Then measure their absorbance at the maximum wavelength to derive a standard curve against which you analyze the unknown sample from the rinse water or the wipe extract to determine if there is any residue. It has been reported to us that LIQUINOX® has a maximum absorbance at 196-197 nm with a secondary maxima at 225-226 nm and that TERGAZYME® has a maximum absorbance at 192-193 nm. The reported detection limits were 1-2 ppm. The other detergents, ALCONOX®, ALCOTABS®, and CITRANOX® should be detectable at 196-197 nm and 225-226 nm secondary wavelength.

D. Phosphate detection methods for the complex polyphosphates present in ALCONOX®, ALCOJET®, TERGAZYME®, DETOJET® and ALCOTABS®. Note that the content of phosphate expressed as %P is printed on the containers of the detergent. Note that these methods test for ortho-phosphate. The polyphosphates present in the detergents are acid hydrolyzable to ortho-phosphate by adding 10% of the sample volume amount of 5 N sulfuric acid and boiling gently for 30 min.

1. American Waterworks Association vol. 57 p. 917-926, 1965 by Edwards, Molof and Schneeman, Determination of Orthophosphate in Fresh and Saline Waters
2. Hach Company phosphate analysis methods and kits. Call Hach Company at 1-800-227-4224 or 303-669-3050.

E. Protease enzyme detection method for TERGAZYME® detergent:

"Assay in Enzymatic Processing of Food Proteins: II. Method for Detection of Residual Proteolytic Activity" IB number 195a-GB April 1979 from Novozyme, contact them at Tel: 919-494-3000 or www.novozymes.com.

F. Total Organic Carbon (TOC) analysis can detect the organic surfactants present in ALCONOX® (11% w/w), LIQUINOX® (21% w/w), TERGAZYME® (11% w/w), ALCOJET® (1.5% w/w), ALCOTABS® (20% w/w), DETERGENT 8® (38% w/w), LUMINOX® (26% w/w) CITRANOX® (17% w/w), CITRAJET® (14% w/w), TERGAJET (10.5%w/w) and SOLUJET (6%w/w). You must go through the acid neutralization step or use the inorganic carbon channel on the TOC analyzer to account for inorganic carbon. The GE cleaning Validation Support Package for Sievers TOC Analyzers is available for sale by GE (303.444.2009 geai@ge.com).

G. When rinsing with deionized water, it has been reported that conductivity has been used to detect conductive salts present in ALCONOX®, LIQUINOX®, TERGAZYME®, ALCOJET®, ALCOTABS®, DETOJET®, CITRANOX®, TERGAJET and SOLUJET. Standard solutions of known dilution should be made up to determine the detection limits using your equipment. These limits should be reviewed to see if they are suitable for you.

H. Citric Acid analysis can be used for the detection of CITRANOX and CITRAJET both contain around 15% Citric Acid. Tergajet contains around 22% and Solujet 9%.

1. HPLC using Bio-Rad HPX-87H column, Bio-Rad Cation H Refill pre-column, 0.01 M H2SO4 mobile phase, degas, 52 deg C column, 0.6 ml/min flow, 20 microliter sample loop, Waters Model 401 Refractometer detection.
2. Enzymatic detection – Taraborelli and Upton, "Enzymatic Determination of Citrate In Detergent Products" JAOCS Vol. 52, 1975 (248-251).
3. By derivatization and spectroscopy – Hartford, "Rapid spectrophotometric method for the determination of itaconic, citric aconitic and fumaric acids." Analytical Chemistry, Vol 34, No 3 1962 (426-428).

I. Ion selective electrode or flame photometry to detect potassium in Detojet (approx 13% by wt) Solujet (approx 7% by wt)—Standard Methods For the Examination of Water and Wastewater 20th Ed. Section 3-87.

J. Propylene glycol ether detection by GC—DETERGENT 8 and LUMINOX contains roughly 25% by weight dipropylene glycol methyl ether detectable using the the Dow Chemical analytical method DOWM-100765-ME90A June 25, 1990, contact Dow Quality/Methods at 517-636-5602. Due to evaporation, low recoveries are normal.

This information is presented to help communicate our understanding of how cleaning validation has been carried out in pharmaceutical and medical device processing. The information given here is made without any representation or warranty, as it is presented for your own investigation and verification. Request a technical bulletin for a chemical description of the ingredients in each Alconox, Inc. detergent.

To speak to a technical representative about cleaning validation, call 914-948-4040 for Malcolm McLaughlin (x160) mmclaughlin@alconox.com.

References

1. Brewer, Rebecca Designing and Documenting Your Cleaning Validation Program to Meet FDA Requirements, Washington Group International, Philadelphia. presented at Cleaning Validation and Cleaning Processes Feb 1-2 Philadelphia, PA (2001)
2. FDA "Guide to Inspection of Cleaning Validation" (1993)
3. FDA "Guide to Inspection of Bulk Pharmaceuticals Chemicals" (1991)
4. FDA "Biotechnology Inspection Guide" (1991)
5. 21 CFR 211 and Proposed Revisions
6. Fourman and Mullen, "Determining Cleaning Validation Acceptance Limits for Pharmaceutical Manufacturing" Pharm Technol. 17 (4), 54-60 (1993)
7. Leblanc, "Establishing Scientifically Justified Acceptance Criteria for Cleaning Validation of Finished Drug Products," Pharm Technol 22 (10), 136-148 (1998)
8. Cooper, "Using Swabs for Cleaning Validation: A Review" Cleaning Validation, IVT, p 74-89 (1996)

ALCONOX, LIQUINOX, TERGAZYME, ALCOJET, ALCOTABS, DETOJET, DETERGENT 8, LUMINOX, CITRAJET and CITRANOX are registered trademarks of Alconox, Inc.

MEDICAL DEVICE CLEANING VALIDATION REFERENCES



Medical Device Cleaning Validation Method References for Alconox, Inc. Detergents

A cleaning validation involves testing for acceptable residues on pharmaceutical manufacturing or medical device surfaces. The validation involves:

- Identifying residues,
- Selecting a residue detection method,
- Selecting a sampling method,
- Setting residue acceptance criteria,
- Validating residue detection methods
- Conducting recovery studies, and finally
- Writing procedures and training operators.

This procedure is used to document acceptable residues 3 or more times and then a rational monitoring program, to maintain a validated state can be put in place. If you are changing any part of the cleaning procedure including the cleaner, you must revalidate. To do this first clean the new way, collect data and then clean the old way before using any equipment. Follow these steps until the new procedure is fully validated.



Identifying residue—in a medical device environment involves: the process fluids, polishing compounds, mold releases, bioburden, endotoxins, cleaning agents and any degradation or interaction products. This document is intended to help with the cleaner residue identification.

Selecting a residue detection method—for cleaners, may involve choosing a specific method or a non-specific method. Specific methods test for a specific ingredient and include: high-performance liquid chromatography (HPLC), ion selective electrodes, flame photometry, derivative UV spectroscopy, enzymatic detection and titration. Non-specific methods test for, the presence of a blend of ingredients, such as: total organic carbon, pH, and conductivity. The FDA prefers specific methods, but will accept non-specific methods with adequate rationale for their use. For investigating failures or action levels, a specific method is usually preferable. (A later section of this chapter lists references to several methods for each cleaner brand.)

Selecting a sampling method—for cleaners, involves choosing between rinse water sampling, swabbing surfaces, coupon sampling and placebo sampling.

Rinse water sampling involves taking a sample of an equilibrated post-final rinse that has been recirculated over all surfaces. Rinse samples should be correlated to a direct measuring technique such as swabbing.

Swabbing uses a swab, or wipe, moistened with high purity water (WFI), that is drawn over a defined area using a systematic, multi-pass technique always moving from clean to dirty areas to avoid recontamination. A typical swabbing pattern might begin with ten side by side vertical strokes, followed by ten horizontal strokes and then ten strokes with the flip side of the swab in each diagonal direction. You then cut off the head of the swab and place it in the pre-cleaned TOC vial. For TOC analysis very clean low background swabs or wipes and sample vials such should be used. The Texwipe large Alpha Swab 714A and 761 have been used successfully. These are available in kits with clean sample containers. For UV testing, Texwipe TX 762 swabs have been used in conjunction with running a swab blank to set the zero level on the UV-visible analyzer.

Quartz glass fiber filter papers have also been used successfully. Coupon sampling involves the use of a coupon or a removable piece of actual pipe that is dipped into high purity water to extract residues for analysis.

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

Setting residue acceptance criteria—acceptance criteria are set based on potential for the residue to effect biocompatibility, toxicity, or functionality of the finished device. Where historical data, on particulate contamination, from existing successful manufacturing processes exists, it can be used to set acceptance limits for particulate levels. This

will serve as a general control and facilitate cleaning consistency. For existing devices with a history of acceptable performance, the mean level of residue plus three standard deviations can be used for particulates and other types of residues. For a new device, a series of residue spiking biocompatibility studies at different levels can be done to determine the failure point. A lower level, possibly half the failure point, could be used to perform an analysis demonstrating that device performance was not effected and toxicity levels were not exceeded. When testing a new device, you can determine the expected level of residue, spike the device at a suitably higher level of residue and then evaluate for biocompatibility and functionality. If it passes, then that is where to set the limit. With cleaning agents and process fluids, consider systemic toxicity based limits. These can be derived if systemic toxicity is known. If not, estimate the acceptable daily intake (ADI) from LD50 (lethal dose for 50% of the population by compatible route of exposure depending on device) and a conversion factor using the equation below.

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

Conversion factors 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:

1. Kramer, van den Ham, Slob, and Pieters, "Conversion Factors Estimating Indicative Chronic No-Observed-Adverse-Effect Levels from Short Term Toxicity Data," *Regulatory Toxicology and Pharmacology*, 23, 249-255 (1996).
2. Conine, Naumann, and Hecker, "Setting Health-Based Residue Limits for Contaminants in Pharmaceuticals and Medical Devices," *Quality Assurance: Good Practice, Regulation and Law*, 1 (3), 171-180 (1992).
3. Layton, Mallon, Rosenblatt and Small, "Deriving Allowable Daily Intakes for Systemic Toxicants Lacking Chronic Toxicity Data," *Regulatory Toxicology and Pharmacology*, 7, 96-112 (1987).

According to the equation above, acceptable residue per square centimeter will depend on the size and quantity of devices being used. Consider the following example. A cleaner has an LD50 of greater than 500 mg/kg. Acceptance criteria is to be set for a device with less than one week of patient exposure. A safety factor of 10,000 is appropriate and the resulting limit should not exceed acute biocompatibility limits such as irritation. The calculation for a 70 kg adult would be:

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

The size of the device is then be factored into the calcula-

tion. If the device had a surface area of 100 square cm, then the surface residue limit for that detergent would be 35 micrograms per square cm (3.5 mg/device / 100 square cm). Of course, a process requirement of visually clean might very well be more stringent. In this example, we are working with a fairly non-toxic detergent, a fairly short contact time medical device and the resulting safety-based limit is fairly high. When working with more toxic residues on devices with greater exposure risk, such as implantable devices, conversion factors would be higher and acceptance limits lower. In such cases visibly clean levels might not stringent enough.

Validating methods and implementing recovery studies—involves validating your residue detection method by establishing accuracy, precision, linearity, reproducibility, selectivity, specificity (if it is a specific method), limits of detection, limits of quantitation, and ruggedness of the analytical residue detection method. Recovery studies involve the use of the sampling and detection methods on known spiked surfaces at representative levels. Typically, spikes are set at 50%, 100% and 150% of the acceptable limit and at lower than expected actual levels. This helps show linearity with documented % recovery as analyzed. It can also help determine the limits of detection and quantitation. Ideally, the expected values and limits should be multiples of the limits of quantitation. The % recovery is used to correlate amount detected with amount of assumed surface residue found acceptable. For example if 100 ug of residue was spiked on the surface and only 90 ug was detected after swabbing, extracting and analyzing, then there was 90% recovery. When used in a cleaning validation, any results would have to be adjusted by this recovery factor. In this example, a result of 90 ug per swabbed area would have to be interpreted as actually being 100 ug per swabbed area to adjust for the 90% recovery. This is a good time to consider wipe and rinse sample storage conditions as well time frame for sample analysis. A rinseability profile, showing complete rinsing of an individual detergent ingredient, should be done when the solubility of that ingredient or its rinseability after drying is in doubt. If your analytical detection method is only sensitive to one ingredient in the detergent, document that all ingredients rinse at the same rate or that the ingredient that you are testing for is the last to rinse away. If you cannot demonstrate either of these, provide a rationale that explains why you believe one or both to be true. For example, a surface active agent, or surfactant, is a good candidate to represent the entire detergent formulation. A scientific rationale can be made for this. Because a surfactant, is attracted to the solution-surface interface, it is likely to be the last ingredient to rinse away. However, this is only true if the other detergent ingredients are significantly water soluble at the rinse concentrations. In fact, in the cases where all detergent ingredients are at least somewhat water soluble, have solubility greater than 10,000 ppm, they should all rinse at similar rates when tested using detergent spiked coupons in sequential rinses. To test by this method, dip coupons in rinse water, then analyze water for the detergent ingredients. In this crude form of testing, expect no detectable difference in rinse rate for somewhat water soluble ingredients at typical cleaning concentrations within the solubility limit of the detergent ingredients. This can be verified by comparing rinse rate for a specific ingredient analyzed by a specific method with rinse rate for a non-specific

method such as TOC. In some cases, bioburden/endotoxin levels may need to be validated. As this takes longer, it is recommended that this process be done separately from the validation of the cleaning process so.

Writing procedures and training operators—are necessary components of cleaning validation in both medical device and pharmaceutical industries. Written procedures should include the following: assigned responsibilities; protective clothing requirements; equipment disassembly and monitoring procedures; documentation requirements; labeling instructions, for in process and cleaned equipment, that include cleaning expiration date, post cleaning inspection procedures, storage conditions and inspection requirements before next use. The operators must then be trained and certified in the procedures. Appropriate retraining should also take place.

Directory of cleaner residue detection methods for each Alconox detergent

	<i>A. Anionic Surfactant HPLC, Titrate, Kit</i>	<i>B. Nonionic Surfactant by HPLC</i>	<i>C. Direct UV/Vis</i>	<i>D. Phosphate by Titration</i>	<i>E. Enzyme by Assay</i>	<i>F. Organic Carbon by TOC</i>	<i>G. Conductivity</i>	<i>H. Citric Acid by HPLC, Assay, UV/Vis</i>	<i>I. Potassium by Flame or IC</i>	<i>J. Glycol Ether by GC</i>
ALCONOX®	•		•	•		•	•			
LIQUINOX™	•	•	•			•	•	•		
TERGAZYME™	•		•	•	•	•	•			
ALCOJET®				•	•	•				
ALCOTABS®	•		•			•	•			
DETOJET™				•		•		•		
DETERGENT 8®						•			•	
CITRANOX®	•	•	•			•	•	•		
LUMINOX®						•			•	
CITRAJET®						•		•		
TERGAJET®						•	•	•		
SOLUJET®						•	•	•		

A. Anionic surfactant analysis methods for ALCONOX®, LIQUINOX™, TERGAZYME™, ALCOTABS®, and CITRANOX®.

Note that the anionic surfactant is present at approximately 20% by weight in each of these detergents. SOLUJET contains 1-5% surfactant that can be analyzed by HPLC.

1. Chemetrics Inc. water testing kit for anionic detergents, which is sensitive to 1/4 ppm. Contact Chemetrics, Inc. at 1-800-356-3072 or +540-788-9026.
2. LaMotte Chemical water testing kit for anionic detergents, which is sensitive to 1 ppm. Contact LaMotte Chemical at 1-800-344-3100 or +410-778-3100.
3. Hach Company water testing method for anionic detergents, which is sensitive to 1 ppm. Contact Hach Company at 1-800-227-4224 or 303-669-3050.
4. A gradient HPLC method in "Journal of Chromatography," 302, (1984) 65-78 by Bear, Lawley and Riddle, Separation of Sulfonate and Carboxylate mixtures by ion exchange HPLC.
5. A "Synthetic Anionic Ingredient by Cationic Titration" method from ASTM D 3049-75 (reapproved 1962) which has been reported to us as having a detection limit on the order of 10 ppm using normalities of 0.004 N Hyamine. It has been suggested that using lower normality Hyamine would give lower detection limits.

B. Nonionic surfactant analysis—the detectable levels are:

LIQUINOX contains roughly 3-7% and CITRANOX & TERGAJET contains roughly 1-5% detectable nonionic.

1. M J Shifflet, M Shapiro, C Levin and R DeNisco "Validating a Reversed-Phase HPLC Method to Determine Residual Nonoxynol-9 on Pharmaceutical Process Equipment Using a nonporous Silica Column" LCGC Vol 19 Number 3 March 2001 pp 312-317.

C. Direct UV/Visible determination:

1. Direct UV/Visible determination by making a broad-spectrum scan of the detergent to determine a maximum absorbed wavelength. Make standard dilutions of the detergent you wish to analyze for, using 1ppm, 2ppm, 4ppm, 8ppm and 16ppm dilutions. Then measure their absorbance at the maximum wavelength to derive a standard curve against which you analyze the unknown sample from the rinse water or the wipe extract to determine if there is any residue. It has been reported to us that LIQUINOX® has a maximum absorbance at 196-197 nm with a secondary maxima at 225-226 nm and that TERGAZYME® has a maximum absorbance at 192-193 nm. The reported detection limits were 1-2 ppm. The other detergents, ALCONOX®, ALCOTABS®, and CITRANOX® should be detectable at 196-197 nm and 225-226 nm secondary wavelength.

D. Phosphate detection methods for the complex polyphosphates present in ALCONOX®, ALCOJET®, TERGAZYME™, DETOJET™ and ALCOTABS®. Note that the content of phosphate expressed as %P is printed on the containers of the detergent.

Note that these methods test for ortho-phosphate. The polyphosphates present in the detergents are acid hydrolyzable to ortho-phosphate by adding 10% of the sample volume amount of 5 N sulfuric acid and boiling gently for 30 min.

1. American Waterworks Association vol. 57 p. 917-926, 1965 by Edwards, Molof and Schneeman, Determination of Orthophosphate in Fresh and Saline Waters
2. Hach Company phosphate analysis methods and kits. Call Hach Company at 1-800-227-4224 or 303-669-3050.

E. Protease enzyme detection method for TERGAZYME™ detergent:

"Assay in Enzymatic Processing of Food Proteins: II. Method for Detection of Residual Proteolytic Activity" IB number 195a-GB April 1979 from Novozyme, contact them at Tel: 919-494-3000 or www.novozymes.com.

F. Total Organic Carbon (TOC) analysis has been reported to detect the organic surfactants present in ALCONOX® (11% w/w), LIQUINOX™ (21% w/w), TERGAZYME™ (11% w/w), ALCOJET® (1.5% w/w), ALCOTABS® (20% w/w), DETERGENT 8® (38% w/w), LUMINOX® (26% w/w) CITRANOX® (17% w/w),

CITRAJET® (14% w/w), TERGAJET (10.5% w/w) and SOLUJET (6% w/w). You must go through the acid neutralization step or use the inorganic carbon channel on the TOC analyzer to account for inorganic carbon. The GE Cleaning Validation Support Package for Sievers TOC Analyzers is available for sale by GE (303.444.2009 or geai@ge.com)

G. When rinsing with deionized water, it has been reported that conductivity has been used to detect conductive salts present in ALCONOX®, LIQUINOX™, TERGAZYME™, ALCOJET®, ALCOTABS®, DETOJET™, CITRANOX®, TERGAJET and SOLUJET. Standard solutions of known dilution should be made up to determine the detection limits using your equipment. These limits should be reviewed to see if they are suitable for you.

H. Citric Acid analysis can be used for the detection of CITRANOX and CITRAJET both contain around 15% Citric Acid. Tergajet contains around 22% and Solujet 9%.

1. HPLC using Bio-Rad HPX-87H column, Bio-Rad Cation H Refill pre-column, 0.01 M H2SO4 mobile phase, degas, 52 deg C column, 0.6 ml/min flow, 20 microliter sample loop, Waters Model 401 Refractometer detection.
2. Enzymatic detection – Taraborelli and Upton, "Enzymatic Determination of Citrate In Detergent Products" JAACS Vol. 52, 1975 (248-251).
3. By derivatization and spectroscopy – Hartford, "Rapid spectrophotometric method for the determination of itaconic, citric aconitic and fumaric acids." Analytical Chemistry, Vol 34, No 3 1962 (426-428).

I. Ion selective electrode or flame photometry to detect potassium in Detojet (approx 13% by wt) Solujet (approx 7% by wt)—Standard Methods For the Examination of Water and Wastewater 20th Ed. Section 3-87.

J. Propylene glycol ether detection by GC—DETERGENT 8 and LUMINOX contains roughly 25% by weight dipropylene glycol methyl ether detectable using the the Dow Chemical analytical method DOWM-100765-ME90A June 25, 1990, contact Dow Quality/Methods at 517-636-5602. Due to evaporation, low recoveries are normal.

This information is presented to help communicate our understanding of how cleaning validation has been carried out in pharmaceutical and medical device processing. The information given here is made without any representation or warranty, as it is presented for your own investigation and verification. Request a technical bulletin for a chemical description of the ingredients in each Alconox, Inc. detergent.

To speak to a technical representative about cleaning validation, call 914-948-4040 for Malcolm McLaughlin (x160) mmclaughlin@alconox.com

References

1. FDA "Guide to Inspection of Cleaning Validation" (1993).
2. Fourman and Mullen, "Determining Cleaning Validation Acceptance Limits for Pharmaceutical Manufacturing" Pharm Technol. 17 (4), 54-60 (1993)
3. LeBlanc, "Cleaning Validation for Medical Device Manufacture," Cleaning Validation Course 5/04
4. Association for the Advancement of Medical Instrumentation AAMI TIR12:1994, Designing, testing and labeling reusable medical devices for reprocessing in health care facilities: A guide for device manufacturers
5. Association for the Advancement of Medical Instrumentation AAMI TIR30: 2003, A compendium of processes, materials, test methods, and acceptance criteria for cleaning reusable medical devices.
6. Quality System Inspection Technique (US FDA Center for Device and Radiological Health CDRH August 1999)
7. System Regulation; Part 803 Medical Device Reporting; Part 806 Medical Device Corrections and Removals; and Part 821 Medical Device Tracking
8. 21 cfr 210, 211, 820 and revs.



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