Cleaning Validation References

Contents

Pharmaceutical Cleaning Validation Method References for Alconox, Inc. Detergents

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.

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
- 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 714K or 761K have been used, these are available in kits with clean sample containers. For HPLC testing, the Texwipe 716 swab works well. 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.

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.

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:

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

*Acceptable Daily Intake:

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

† *a conversion safety factor*

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

10 ppm Carryover Limit:

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

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

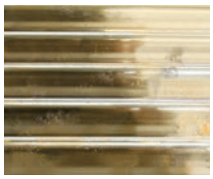
$$ADE = \frac{NOAEL \times BW}{UFc \times MF \times PK}$$

Maximum Allowable Carryover

$$MACO = \frac{ADEprevious \times MBSnext}{TDDnext}$$

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.

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		●		●		●	●	●	●

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

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.

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.

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 analysis methods for the following detergents based on their alkylbenzene sulfonate content: ALCONOX® (14%), LIQUINOX® (19%), TERGAZYME® (14%), ALCOTABS® (7%), and CITRANOX® (8%).

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. Xiaodong Liu, Mark Tracy, and Christopher Pohl, New Developments in Surfactant Analysis by HPLC Dionex Corp Sunnyvale, CA 2009.

B. EDTA by HPLC — Ethylene diamine tetra acetic acid (EDTA) can be detected in ALCONOX®, ALCOJET®, TERGAZYME®, TERGAJET® at roughly 0.7%, ALCOTABS® at 0.4%, and KEYLAJET® at roughly 2.5%.

1. Hamilton Company, The Application Notebook, "EDTA by Anion Exchange," LCGC on dvm360.com, Sept 1, 2009.

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 absorbence 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 absorbence at 196–197 nm with a secondary maxima at 225–226 nm and that TERGAZYME® has a maximum absorbence 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.
3. Dionex, Determination of Polyphosphates using Ion Chromatography with Suppressed Conductivity Detection, Application Note 71, (2002).

E. Protease enzyme detection method for TERGAZYME® detergent:

1. "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® (19% w/w), TERGAZYME® (11% w/w), ALCOJET® (1.5% w/w), ALCOTABS® (10% w/w), DETERGENT 8® (38% w/w), LUMINOX® (20% w/w) CITRANOX® (16% w/w), CITRAJET® (14% w/w), DETOJET® (0.5% w/w), TERGAJET® (9% w/w) and SOLUJET® (6% w/w), KEYLAJET® (3% w/w), DETONOX® (12% 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 found in ALCONOX®, TERGAZYME®, ALCOJET®, ALCOTABS®, and TERGAJET®.

G. When using deionized water, it has been reported that conductivity has been used to detect conductive salts present in ALCONOX®, LIQUINOX®, TERGAZYME®, ALCOJET®, ALCOTABS®, DETOJET®, DETERGENT 8®, CITRANOX®, TERGAJET®, KEYLAJET® 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. Organic Acid analysis can be used for the detection of CITRANOX® and CITRAJET® both contain around 15% Citric Acid and LUMINOX® around 2.5%. LIQUINOX® around 2%. TERGAJET® and ALCOTABS® contain around 20% and SOLUJET® 7%. DETOJET® and KEYLAJET® each contain roughly 1% gluconic acid that can be detected as gluconate.

1. HPLC using Bio-Rad HPX-87H column, Bio-Rad Cation H Refill pre-column, 0.01 M H2S04 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).
4. Organic Acids in Beer, Phenomenex HPLC Application ID 14171, info@phenomenex.com, 2013.
5. Method Validation Report for Assay of Citric Acid (Alconox, Inc. 2013)

I. Ion selective electrode or flame photometry to detect potassium in DETOJET® (approx 13% by wt) SOLUJET® (approx 7% by wt) KEYLAJET® (approx 12% by wt) — Standard Methods For the Examination of Water and Wastewater 20th Ed. Section 3-87.

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.

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 12 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)

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

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.

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 defection methods
- Conducting recovery studies
- 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 degredation 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.

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.

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 714K or 761K have been used, these are available in kits with clean sample containers. For HPLC testing, the Texwipe 716 swab works well. 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.

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

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:

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

The size of the device is then be factored into the calculation. 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 µg of residue was spiked on the surface and only 90 µg 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 µg per swabbed area would have to be interpretted as actually being 100 µg 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.

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

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.

A. Anionic surfactant analysis methods for the following detergents based on their alkylbenzene sulfonate content: ALCONOX® (14%), LIQUINOX® (19%), TERGAZYME® (14%), ALCOTABS® (7%), and CITRANOX® (8%).

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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.
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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		●		●		●	●	●	●

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.

B. EDTA by HPLC — Lethylene diamine tetra acetic acid (EDTA) can be detected in ALCONOX®, ALCOJET®, TERGAZYME®, TERGAJET® at roughly 0.7%, ALCOTABS® at 0.4%, and KEYLAJET® at roughly 2.5%.

1. Hamilton Company, The Application Notebook, "EDTA by Anion Exchange," LCGC on dvm360.com, Sept 1, 2009.

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 absorbence 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 absorbence at 196–197 nm with a secondary maxima at 225–226 nm and that TERGAZYME® has a maximum absorbence 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.
3. Dionex, Determination of Polyphosphates using Ion Chromatography with Suppressed Conductivity Detection, Application Note 71, (2002).

E. Protease enzyme detection method for TERGAZYME® detergent:

1. "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® (19% w/w), TERGAZYME® (11% w/w), ALCOJET® (1.5% w/w), ALCOTABS® (12% w/w), DETERGENT 8® (38% w/w), LUMINOX® (20% w/w), DETOJET® (0.5% w/w), CITRANOX® (16% w/w), CITRAJET® (14% w/w),TERGAJET® (9% w/w) and SOLUJET® (6% w/w), KEYLAJET® (3% w/w), DETONOX® (12% 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 found in ALCONOX®, TERGAZYME®, ALCOJET®, ALCOTABS®, and TERGAJET®.

G. When using deionized water, it has been reported that conductivity has been used to detect

conductive salts present in ALCONOX®, LIQUINOX®, TERGAZYME®, ALCOJET®, ALCOTABS®, DETOJET®, DETERGENT 8®, CITRANOX®, TERGAJET®, KEYLAJET® 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. Organic Acid analysis can be used for the detection of CITRANOX® and CITRAJET® both containing around 15% Citric Acid and LUMINOX® around 2.5%. LIQUINOX® around 2%. TERGAJET® and ALCOTABS® contain around 20% and SOLUJET® 7%. DETOJET® and KEYLAJET® each contain roughly 1% gluconic acid that can be detected as gluconate.

1. HPLC using Bio-Rad HPX-87H column, Bio-Rad Cation H Refill pre-column, 0.01 M H2S04 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).
4. Organic Acids in Beer, Phenomenex HPLC Application ID 14171, info@phenomenex.com, 2013.
5. Method Validation Report for Assay of Citric Acid (Alconox, Inc., 2013)

I. Ion selective electrode or flame photometry to detect potassium in DETOJET® (approx 13% by wt) SOLUJET® (approx 7% by wt) KEYLAJET® (approx 12% by wt) — Standard Methods For the Examination of Water and Wastewater 20th Ed. Section 3-87.

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.

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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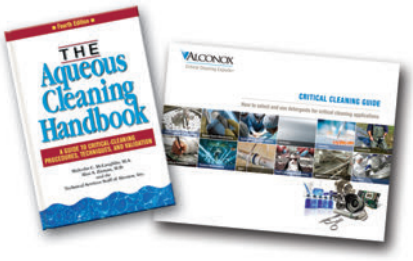

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