ALCONOX

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/cm^2), amount in a swab sample (ug or ug/ml), maximum carryover in a train (mg or g), or concentration in equilabrated 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:

$$\textbf{Limit (mg/cm2 or L)} = \frac{\text{ADI carryover – see below (mg)} \times \text{Smallest Next Batch (kg)}}{\text{Size of Shared Equipment (cm2 or L)} \times \text{Biggest Daily Dose or of Next Batch (kg)}}$$

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

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

$$\textbf{Limit (mg/cm2)} = \frac{\text{10 mg residue on just cleaned surface} \times \text{Next Batch Size (kg or L)}}{\text{1 kg of L of next product} \times \text{Size (cm}^2\text{ or L) shared equipment}}$$

Note that for many residues you can validate a visual detection limit on the order of 1-4 ug/cm^2. 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 cm^2 and the daily dose of the next product is 0.005

*conversion safety factor used to convert LD50 to acceptable daily intake, use higher number for low LD50s

kg results in a calculated residual acceptance criteria of 700 mg/cm² (350 mg X1000 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 Deriv. UV-Vis	*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. Spectrophotometric Method for The Determination of Nonionic Surfactants adapted from R. A. Greff, E. A. Sezkorn and W. D. Leslie, "A Colorimetric Method for Determination of Part/Million of Nonionic Surfactants", J. Amer. Oil Chem. Soc., 1965, 42, 180-185

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 TERGAZYME® has a maximum absorbence at 192-193 nm. The reported detection limits were 1-2 ppm. The other detergents, ALCONOX®, LIQUINOX® 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 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).

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 warrantee, 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)

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