Applications in Medical Device Manufacturing

The Benefits of Aqueous Critical Cleaning

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The use of aqueous cleaning in medical device manufacturing can provide numerous benefits in terms of efficacy, minimal surface contact and reduced residue potential, and easier cleaning validation.

About Aqueous Cleaners

Aqueous cleaners are typically formulated to ensure maximal cleaning performance by using key ingredients such as surface active agents (surfactants) — excellent wetting agents that allow the cleaning solution to penetrate into crevices and get under soils to facilitate removal. Often very dilute solutions of aqueous cleaner can be used effectively, resulting in minimal chemical contact with the device surface — which in turn minimizes potential residue and makes cleaning validation easier. Aqueous cleaners are available in low toxicity formulations and often are accompanied by biocompatibility data that can make it easier to set residue acceptance limits, an important part of medical device cleaning validation.

Aqueous cleaners are suitable for all cleaning methods commonly employed in medical device manufacturing:

- Ultrasonic
- Manual
- Soak
- Automated

The range in aqueous cleaner formulations — from acidic to basic, high emulsifying to low foaming, liquid concentrates to powder blends — ensures that a cleaner can be found to handle whatever residues

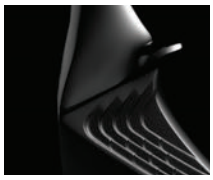
are encountered by any cleaning method.

Aqueous cleaners are usually biodegradable, causing them to have low environmental impact, and are readily disposable after use without further treatment. Moreover, aqueous cleaners have excellent worker safety characteristics and replace semi-aqueous or solvent-containing cleaners that tend to have more worker safety and environmental concerns.

The Aqueous Critical Cleaning Process

The aqueous critical cleaning process involves using aqueous cleaners to remove residues from those surfaces which without successful cleaning would prevent the device from functioning properly. This is distinguished from simple cleaning for appearance. Aqueous critical cleaning processes are often used to clean Class I, II, and III medical devices to ensure they are scrupulously clean and free of all interfering residues.

This can be challenging because many medical devices have structures that are difficult to clean. By design, aqueous cleaners contain key ingredients known as surfactants: excellent wetting agents that can penetrate crevices and lift out soil. This is extremely important because any contamination or interfering residue left on the device renders the medical device unusable. Furthermore, releasing a contaminated device for human or animal use — thereby putting their health at risk — exposes the manufacturer to liability. For these reasons, medical device cleaning is among the most critical of all aqueous critical cleaning processes.



Medical devices such as the prosthetic hip joint shown here must be critically pre-cleaned prior to coating and packaging.

Swab tests validate successful cleaning with ALCONOX-brand detergents.

Selecting the Proper Aqueous Cleaner in Medical Device Manufacturing

Aqueous cleaners are available in a broad range of formulations, so it is possible to find a cleaner that will work on even the most difficult structures and residues by whatever cleaning method is preferred. In this regard, aqueous cleaners are classified according to pH value, and are classified as acidic, neutral, or alkaline. A cleaner's pH value can have a direct effect on cleaning effectiveness and is directly correlated to the residue being removed. Certain soils are removed more easily using an acid cleaner; others, by an alkaline cleaner, as summarized in **Table 1**.

In addition to considering the soil being removed, it is imperative to select a cleaner that will not damage the surface or disturb the integrity of the component material. Though most medical devices are made of fairly robust materials, it is still critical to factor in the device material composition when selecting an aqueous cleaner, since damage to the device renders it useless and is costly to the manufacturer.

Medical devices are usually assembled under clean conditions, so a light-duty cleaner is most often all that is needed to remove small amounts of light oils or surface residues. This, plus the fact that medical devices are frequently manufactured in limited quantities, makes them ideal for batch-cleaning operations using ultrasonic tanks.

The use of heated ultrasonic tanks, followed by rinsing with suitably pure water, is the most common cleaning technique in medical device manufacturing. Since medical devices must be free of interfering

TABLE 1: CLEANER PH VALUE AND SOILS REMOVED

TYPE OF CLEANER	pH RANGE	SOILS REMOVED
Mineral-acid cleaner	0.0–2.0	Heavy scales
Mild acid	2.0–5.5	Inorganic salts, water, and soluble metal complexes
Neutral	5.5–8.5	Light oils, small particulates
Mild alkaline	8.5–11.0	Oils, particulates, films
Alkaline	11.0–12.5	Oils, fats, proteins
Corrosive alkaline	12.5–14.0	Heavy grease or soils

TABLE 2: RELATIONSHIP OF pKa, CONJUGATE BASE AND HYDRONIUM ION CONCENTRATION

$HA + H_2O \rightarrow H_3O^+ + A^-$

HA = acid concentration	H_2O = water	H^3O^+ = hydronium ion concentration	A^- = conjugate base concentration

$pKa = -\log [H_3O^+] [A^-]/[HA]$

residues, it's important to select extremely free-rinsing cleaners proven effective for immersion cleaning.

Depending on the types of residues involved, it is sometimes advantageous to use a two-step process. First, an alkaline cleaner is used to remove all oily residues, followed by a brief rinse to prevent dragout. Second, this is followed by an acid cleaner and thorough rinse to remove alkaline-insoluble inorganic materials.

Time, temperature, and agitation also play important roles in cleaning. But while maximum detergency is achieved at high temperatures with high agitation over long periods of time, the surface substrate must be robust enough since corrosion may also be a factor. As a rule of thumb, it is best to use the mildest cleaner that will get the job done.

Understanding the properties of both the residue and the device hard surface are important and can be used beneficially to improve the aqueous cleaning process.

The Role of pH in Aqueous Critical Cleaning

Understanding the properties of both the residue and the device hard surface are important and can be used beneficially to improve the aqueous cleaning process. Often by using an aqueous cleaning solution above or below the defined isoelectric point of the hard surface and the inverse log of the acid dissociation constant (pKa) of the residue, a like-like charge repulsion can be created that facilitates and increases the efficiency of the cleaning process.

The isoelectric point of a surface is the pH at which the surface's electric charge is neutral with regard to its acid/base and electron donor-acceptor reactions. Moving to a higher or lower pH will shift the effective surface charge or electron density in a negative or positive direction. For example stainless steel has an isoelectric point of 8.5 associated with the reactivity of the oxygen in the oxides Fe_20_3, Fe_30_4, and Cr_20_3 on the surface of the metal. Raising the cleaner solution pH past the isoelectric point causes the surface to become more negatively charged.

Likewise, if the residue is an acid or base, their charge can also be manipulated by pH. The pKa of most acids indicates the pH at which the hydronium ions and conjugate base are present in equal concentrations. Moving higher in pH shifts the equilibrium toward the right, thereby increasing the concentration of the negative conjugate base. See **Table 2** (above).

Thus, when cleaning acids off stainless steel, it is desirable to use a cleaning solution with a pH above the pKa of the acid and the isoelectric point of the stainless steel. A repelling negative charge between the acidic residue and the stainless steel surface will result.

Applying the Concept: Removing Stearic Acid From Stainless Steel

To apply this concept practically, let's examine stearic acid ($C_{17}H_{35}COOH$) residue on a stainless steel medical device or instrument surface. In this case, stearic acid has an isoelectric point of around pH 5 that drives formation to the negatively-charged stearate ion ($C_{17}H_{25}COO^-$). If an aqueous alkaline cleaner is employed that is equal to or above pH 8.5, then the stearic acid will predominantly be in the negatively charged stearate ion ($C_{17}H_{25}COO^-$) form. In addition, stainless steel typically has an isoelectric point of 8.5. Given alkaline conditions of pH 8.5 or greater, the metal oxides in the stainless steel surfaces will become negatively charged, setting up an appropriate repulsion between the stearic acid and the stainless steel surface. This repulsion is desirable as it facilitates cleaning and removal of the stearic acid residue from the surface.

The reverse holds true for base residues. By lowering the pH of the residue below the pKa and the isoelectric point of the surface being cleaned,

positive-positive repulsion may be achieved. At the very least, a neutral residue and a positive surface are created, with no attraction between them. See **Table 3** (below).

Ensuring Endotoxin/Pyrogen Free Medical Devices

Removing all endotoxins or pyrogens from device surfaces is critical to the process of manufacturing medical devices designed for internal implantation. These substances are widely present in the environment and are fever-causing cell debris or cellular waste products. Removing them requires the use of a high-emulsifying cleaner, combined with heat, followed by a rinse with endotoxin/pyrogen free water (often referred to as water for injection, or WFI, an exceedingly pure form of water derived from high-purity filtration systems).

Removing all endotoxins or pyrogens from device surfaces is critical to the process of manufacturing medical devices designed for internal implantation.

Specialized cleaners such as LIQUINOX (Alconox, Inc.), together with heat, are used to depryogenate both heat-sensitive and non-heat-sensitive surfaces. Standard cleaning of injectables with a 1% solution of a suitable cleaner at 120ºF (50ºC) using manual, soak, or ultrasonic agitation followed by a thorough WFI rinse will depryogenate the surface. Post-cleaning handling in a pryogen- or endotoxin-controlled environment for packaging provides adequate control. Ports for injectable products are cleaned using suitable powdered detergent solutions.

Medical Device Cleaning Validation Method Guidelines

Medical device manufacturing must conform to current Good Manufacturing Practice (cGMP) guidelines, or what's also referred to as Quality Systems (QS). Additional regulations established by agencies such as the US FDA, EU (European Union), and the International Conference on Harmonization (ICH) must also be followed. Cleaning validation requires documented compliance with specific criteria for medical device manufacturing, and involves testing for acceptable residues on each device's surface. The protocol includes:

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

Some medical devices are manufactured as single-use units that do not have protocols for cleaning and re-use. There are contract companies that clean and repackage single-use devices for re-use. In effect, they are "re-manufacturing" the device and must validate their cleaning in accordance with cGMP.

Biocompatibility Data Simplifies Medical Device Validation

Setting residue acceptance limits as part of your medical device cleaning validation is much easier when appropriate biocompatibility data is available about the critical cleaner you are using.

Different types of biocompatibility data such as oral toxicity, dermal irritation, dermal sensitization, intracutaneous injection toxicity, and cytotoxicity will assist in setting most scientific and exposure-specific residue acceptance limits. Importantly, the derived limits are more practical to achieve, as they are not based on conservative estimates. See **Table 4**.

Case Study: Aqueous Critical Cleaning Used for Medical Devices Manufacturing

Alconox, Inc. is frequently consulted by manufacturers regarding critical cleaning challenges they face. In this case, the engineering support group at one of

TABLE 3: OPTIMIZING THERMODYNAMIC CLEANING CONDITIONS FOR SURFACE/RESIDUE ELECTROSTATIC REPULSION

Acidic residues	pH > pKa and isoelectric point of surface
Alkaline or basic residues	pH < pKa and isoelectric point of surface

TABLE 4: BIOCOMPATIBILITY TESTS

Biocompatibility Test	Description
Oral Toxicity	Reported as an Oral LD50, it is the lethal dose at which 50 percent of a population of animals will die when exposed orally. Oral toxicity is often used to estimate toxicity from other routes of exposure by using safety factors ranging from 1/1,000 to 1/100,000.
Dermal Irritation	Helpful for determining acceptable residue levels for skin contact devices.
Dermal Sensitization	Assists in determining acceptable residue levels on a device that can have repeated exposure to patients.
Intracutaneous Injection Toxicity	Useful in setting acceptable residue limits for skin penetration and open wound exposure devices.
Cytotoxicity	Utilized as a broad indicator of cellular toxicity. To measure cytotoxicity, the L929 cells are exposed to the test article, and the response is observed. L929 cells are commonly used in cytotoxic studies due to their measurable sensitivity to a broad range of materials.

Even the most demanding class III medical devices have been scrupulously cleaned to implantable standards using Alconox, Inc. brands.

the world's largest producers of clinical medical and general diagnostic devices required specific technical support.

The company had developed a new device using a variety of materials in its construction. Since the device's surface consisted of a combination of materials, the engineering team sought a single cleaner that would not harm the surface nor cause interactions between the various materials during the cleaning and packaging process.

Alconox, Inc. technical staff analyzed the materials used in the device and recommended appropriate compatible aqueous cleaners. Authoritative documentation and references were also provided to support the scientific rational for the selected cleaning solution.

Alconox, Inc. Provides an Aqueous Cleaner for Every Medical Device Application

Alconox, Inc. is dedicated to providing the finest leading-edge aqueous cleaners that preserve the integrity of medical device surfaces during manufacturing and properly prepare them for sterilization or sterile packaging. Alconox, Inc. brands of aqueous cleaners have been proven well-suited for critically cleaning virtually any surface found in medical device manufacturing:

- Silicone rubbers
- Polyurethane
- Stainless steel
- Titanium
- Plastics

Even the most demanding class III medical devices have been scrupulously cleaned to implantable standards using Alconox, Inc. brands. This includes cleaning prior to top coating with aluminum plasma spray (TPS) on implants used in dental applications and medical procedures such as knee, hip, and shoulder replacements. Alconox Inc. cleaners have been proven effective in removing residues on high-fidelity, research-quality medical devices such as Doppler flow catheter transducers, thereby eliminating the need for harsh chemicals and ultrasonic cleaning. And Alconox Inc. cleaners have been used to remove wax residues from rigid gas permeable (RGP) contact lenses during manufacturing.

Alconox, Inc. brand cleaners are free rinsing (leaving no interfering residues), biodegradable and readily disposable after use.

Two-Step Ultrasonic Cleaning

Alconox, Inc. brands such as LIQUINOX mild alkaline cleaner and CITRANOX acidic cleaner are commonly

TABLE 5: CLEANER SELECTION GUIDE FOR MEDICAL DEVICE CLEANING

Application/ Key Concern	Articles Cleaned/ Soil Removed	Cleaning Method	Recommended Cleaner
Medical device passing cleaning validation for FDA good manufacturing practice and quality systems compliance	Oils, emulsions, particles, proteins	Manual, ultrasonic, soak	LIQUINOX (mild alkaline)
		Machine washer, power spray	SOLUJET (alkaline low foam)
	Inorganic residues, salts, metallics	Manual, ultrasonic, soak	CITRANOX (mild acid)
		Machine washer, power spray	CITRAJET (mild acid low foam)

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

used in two-step ultrasonic medical device cleaning to maximize removal of all organic, particulate, and inorganic residues. The first-step alkaline cleaning with LIQUINOX removes hydrophobic organic residues and alkaline labile particulates. The second-step acidic cleaning with CITRANOX removes the now-exposed inorganic residues — both those present on the substrate and any that may have formed as alkaline precipitates during the alkaline cleaning. **Table 5** (above) shows recommended cleaners and methods for medical device cleaning.

LIQUINOX brand detergent is well-suited to removing oils from metal and elastomeric-polymer surfaces during manufacturing and has been used in the cleaning of plastic artificial joint materials prior to testing. Even sensitive aluminum class I and II external medical devices can be cleaned using LIQUINOX manually or in ultrasonic tanks, or with SOLUJET brand detergent in spray parts washers or washer/sterilizers. CITRANOX brand cleaner has been successfully used to ultrasonically clean titanium implants and other medical devices in validated cGMP cleaning in accordance with QS protocols.

To help assess the biological effects of cleaner residues, Alconox, Inc. conducted extensive evaluations of biocompatibility of its LIQUINOX and CITRANOX brand cleaners. Available biocompatibility data for LIQUINOX and CITRANOX include oral toxicity, dermal irritation, dermal sensitization, intracutaneous injection toxicity, and cytotoxicity. Rather than conservative estimates, this data can be used to set the most scientific, exposure-specific and practical residue acceptance limits.

Alconox, Inc. cleaners with consistent cGMP-compliant formulations are available worldwide. Certificates of analysis (COA), technical bulletins, SDS and trace analysis for each are available at www.alconox.com.

Alconox, Inc. Provides Validation Support and Expertise

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

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

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

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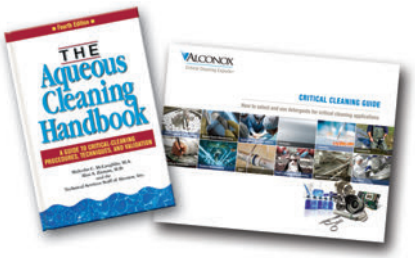
Get Validation Support or Help With Your Critical Cleaning Challenge

Alconox, Inc. has more than 70 years' experience developing aqueous cleaning solutions for pharmaceutical manufacturing. Let us help solve your next critical cleaning challenge.

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

cleaning@alconox.com



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