THE AQUEOUS CLEANING HANDBOOK

A GUIDE TO CRITICAL CLEANING PROCEDURES, TECHNIQUES, AND VALIDATION

Michael J. Moussourakis
Jeff I. Phillips
Stacy R. Silverstein
Malcolm C. McLaughlin

Technical Communications

The Aqueous Cleaning Handbook

Published in the United States by
AI Technical Communications
White Plains, NY 10603

First edition published 1998. Second edition published 2000. Third edition published 2002. Fourth edition published 2005. Fifth edition published 2023.

ISBN 979-8-9897594-0-8 (Hardcover)
ISBN 979-8-9897594-3-9 (Paperback)
ISBN 979-8-9897594-2-2 (pdf)
ISBN 979-8-9897594-1-5 (epub)

Library of Congress Catalog Card Number 2002110614

Technical Communications

ACHB5.3

Contents

Foreword

As a Professor of Physical Chemistry and the founder and leader of the Cleaning Research Group (CRG) I am focused on deepening the understanding of the science of cleaning.

In my view it does not matter if educational information comes from an academic institution like Sam Houston State University, from standards working groups, or from cleaning equipment / chemical suppliers. The CRG does not sell or recommend specific products or processes. Instead, we educate people in the art and science of critical cleaning. All that matters is if the material is focused on the "why" behind what works.

With this in mind, I was pleased to receive a copy of the 5th Edition of the Cleaning Handbook from Alconox Inc. I found it to be an excellent educational resource, and this handbook will become required reading for newcomers to the CRG. I am pleased to write this foreword introducing you to what can be found inside.

There are several "deep dives" and sections of technical depth. Here is a sampling of gems that will inform your thinking on cleaning process improvement.

Using pH to cause your soil to be repelled by the surface is a clever use of science, and this is possible if you understand the isoelectric point of your surface. Chapter 2 contains a discussion of the isoelectric point of a surface and its relation to pH.

Many have heard of the BATH-O-CARD system during talks at the Parts Cleaning Conference or in the various Alconox PQCWebinars. But it is helpful to have a documented explanation of each of the factors. The extension of the traditional 4-factor TACT scheme (temperature, action, chemistry, and time) for process optimization to a 9-factor BATH-O-CARD scheme is explained in detail in Chapter 3.

If you have a new soil, new substrate, or new geometrical features, you may need to evaluate a new cleaning chemistry. Chapter 5 contains an analysis of common mistakes that people make when evaluating a cleaner for use in a new cleaning process. There are also some tips on setting up overkill, minimal, and optimized process parameters.

I found Chapter 6 to be very informative as it outlines the special considerations and challenges experienced by a near-comprehensive survey of industrial sectors (pharma, biotech, medical, device, laboratory, cosmetics, healthcare, precision manufacturing, cannabis, food and beverage, foodservice, environmental, electronics, optics, and nuclear). And if your process does not neatly fit into any of these listed industrial sectors, there is an outline of special considerations and challenges organized by process (ultrasonic, CIP, GMP washer, passivation, filter cleaning, and biofilm cleaning).

What is done in the test lab needs to be transformed into consistent operational practice through the development of standard operating procedures (SOPs). Chapter 7 discusses this process and gives several relevant cleaning SOP examples.

Consistency is good, but it is not enough. Chapter 8 illustrates how process validation determines if the cleaning meets the minimum requirements. This chapter contains a brief summary of many ISO and US CFR requirements for medical device cleaning validations.

Cleanliness levels are discussed in Chapter 10 with short descriptions of the sensitivities of various cleanliness testing methods.

All processes generate waste, and cleaning operations are no exception. Waste production and disposal considerations are discussed in chapter 9, and the handbook wraps up with a discussion of environmental and safety outcomes in Chapter 11.

It is difficult to name another resource that covers all of these topics in as few as 270 pages. This is why, as I indicated above, I will be adding this handbook to the required reading file for new students who join the Cleaning Research Group. It will be a great way to bring them up to speed on the many aspects involved in industrial cleaning processes.

– Darren L. Williams
Ph.D., Leader of the Cleaning Research Group, and Professor of Physical Chemistry
Sam Houston State University

Introduction

In almost every industry that manufactures a product or provides an important service to people, cleanliness is important. For example, if inadequate cleaning during pharmaceutical manufacturing leads to contamination of a batch of pharmaceutical product, the entire batch must be discarded as waste. Beyond the pharmaceutical industry, similar examples can easily be identified across the commercial spectrum, including electronics, laboratory analysis, medical devices, and the foodservice industry.

When the existence of an unintended residue plays an outsized role in the final finished product or intended goal, we refer to removal of that residue as critical cleaning. Monitoring cleanliness ultimately ensures product potency, purity, and quality. In addition, ensuring clean surfaces also can affect both the health and safety of workers manufacturing the product as well as end-users of the product. Critical cleaning is thus not solely a consideration in a handful of industries, but rather an integral component of the production process in almost every industry to ensure high-quality, valuable finished products are manufactured safely and effectively.

There are virtually an infinite number of specialized critical cleaning challenges, from the R&D laboratory all the way through sophisticated large-scale commercial manufacturing processes. Aqueous detergents have long offered economical, effective, and safe solutions to critical cleaning issues across diverse industries. Use of aqueous detergents and cleaners that are biodegradable, free-rinsing, and free of interfering residues allows for critical cleaning with minimal environmental and hazardous waste. In many cases, aqueous cleaning both is the best available technology and provides a viable long-term solution to environmental issues.

As a leading developer and supplier of aqueous cleaning detergents, we at Alconox Inc. are the critical cleaning experts with over three-quarters of a century of experience. While by no means exhaustive, this handbook is intended to assist laboratory and manufacturing plant scientists and engineers accurately select and maximize the performance of aqueous cleaners and systems. In its pages you will find handy, easy-to-read summaries of what aqueous cleaning is and how it works. To make it easy to find important information, cleaning considerations are presented individually for many different industries. This handbook also contains guidance and direction on how to select an aqueous cleaner and make the most of the cleaning potential of an aqueous cleaning system, including ultrasonic tanks, washers, and clean-in-place systems.

A wealth of additional information can be found on the Alconox Inc. website, where we encourage you to explore the "TechNotes" section to access a compendium of diverse application-driven expert information.

If you have questions that are not addressed in this handbook, contact the Alconox Inc. technical services department at +1-914-948-4040, email: cleaning@alconox.com, or click on "Ask Alconox"

at www.alconox.com. In fact, many ideas for new aqueous cleaning compounds have come from such contact, and our technical service staff is ready and willing to help with your questions or concerns.

Whether you are familiar with aqueous cleaners and systems or are just now considering switching to aqueous cleaning, we hope you find this handbook helpful.

– Michael J. Moussourakis
Jeff I. Phillips
Stacy R. Silverstein
Malcolm C. McLaughlin
and the Technical and Marketing
Support Staff of Alconox Inc.

Chapter One:

What is an Aqueous Cleaner?

An aqueous cleaner is a blend of ingredients designed to enhance the cleaning ability of water. Typically, an aqueous cleaner contains a surface-active agent (surfactant) and builders. The surfactant acts as a wetting agent to allow cleaning solutions to penetrate into crevices as well as around and under soils. Surfactants can act as an emulsifier to help form emulsions with water-insoluble oils. Surfactants also can act as a dispersant to help suspend particulates in solution. Builders typically react with dissolved metal ions to prevent them from interfering with the cleaning process. (Chapter Two provides a thorough discussion of surfactants and builders.)

Types of Cleaning Agents and Their History

Surface cleaning or degreasing can be defined as removal of residues, contaminants, or soils—in other words, unwanted or extraneous material that is deposited on or attached to a substrate surface. The objective of surface cleaning may be aesthetic, medicinal, social, or scientific. The cleaning process typically uses at least one of four types of cleaning compounds: soaps, solvents, synthetic solvents, and aqueous cleaners (Figure 1.1).

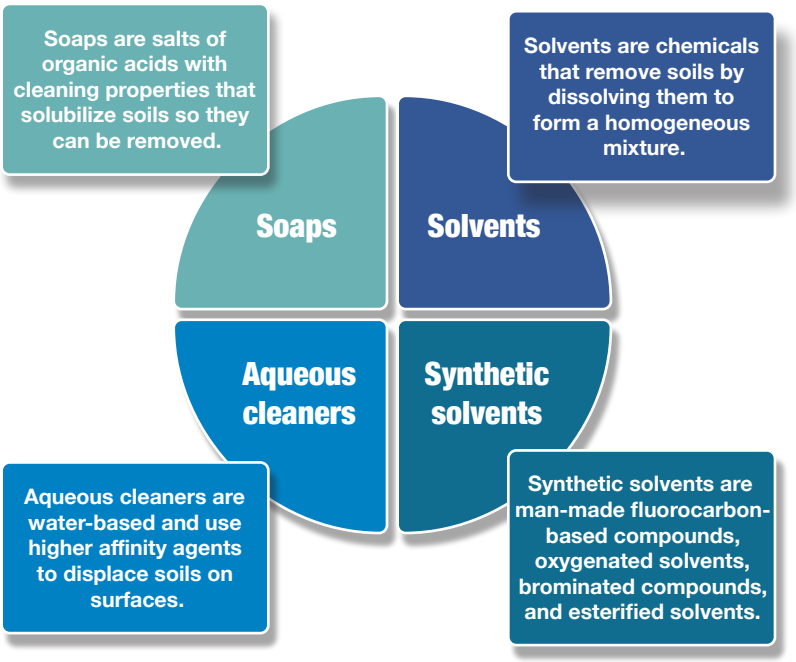

Figure 1.1 Types of cleaning agents.

Soaps

Soaps solubilize soils so that they can be removed. The name stems from the soapberry, a family of deciduous or evergreen trees bearing fruit that contains a soapy substance called saponin. Saponin is a natural cleansing agent produced by the reaction of an alkali, typically sodium hydroxide (NaOH), and animal fat or vegetable oil. Saponin has been used since at least the third millennium BC. Its use dates at least from the third millennium BC. In fact, clay tablets in Mesopotamia contained a recipe for soap that included potash (potassium carbonate) and oil.

The second-century writings of the Greek physician Galen referenced soap as a cleansing, medicinal product that helped cure skin ailments. Later, the ancient Romans shared their knowledge of soap formulations (sapo, the Latin word for soap, is still used to

describe the saponifiers often added to today's synthetic detergents). By the Middle Ages, crude commercial soapmaking manufacturing centers were established in European countries such as France, Spain, and England. Discoveries by Nicholas LeBlanc in the 1800s, and a century later by Michel Chevreul, made it possible to make predictable soap formulations. Today, formulations are reproducible from batch to batch.

Solvents

To understand the strengths and weaknesses of solvents as cleaning agents, it is important to understand "solvency"—the ability to dissolve. A solvent is usually a liquid substance that is capable of dissolving soils. Solvents break down soils into smaller particles, forming a homogeneous solution. Some soils are soluble in certain solvents in all proportions; others are soluble only up to a specific percentage, and any excess precipitates out of the solution.

Another important aspect of a solvent is its volatility, which is highly correlated to boiling point. Solvents that have reasonably low boiling points are more volatile and can be more readily removed by distillation or evaporation. When cleaning substrates, the most common application for industrial solvents is to dissolve soil on machined parts. The dissolved soil is diluted in the solvent; when the solvent evaporates, it leaves behind a proportionally cleaner substrate.

Solvents are also used in vapor degreasers. These degreasers heat low-boiling point solvents in a high-sided tank, causing vapor to hover over the boiling solvent. Parts can be cleaned by dipping in the boiling solvent or by allowing vapor to condense on the colder part and then drip off, carrying residues away. As the part is lifted up through the vapor, distillation-purified vapor condenses on the part and rinses it. When used with hazardous solvents, elaborate solvent containment systems can be used to stop any solvent from escaping to the atmosphere.

Solvent cleaning is based on the principle of "like dissolves like," which was discovered early in human history. In this trial-and-error process, some terpenes—natural organic compounds occurring in the essential oils and oleoresins of plants (lemon, orange) and conifers (balsam, pine)—were found to have solvating powers. It is very important to match the solvent character of your soil or foreign matter to the type of solvent you use for cleaning. A given solvent will be "like" some soils and "unlike" other soils. Therefore, there are no universal organic solvents.

Synthetic Solvents

Synthetic solvents are man-made carbon-based solvents, particularly halocarbons. Halocarbons are compounds in which carbon is bound to one or more halogens (chlorine, fluorine, bromine, and iodine). Synthetic solvents include fluorocarbon-based compounds such as chlorofluorocarbons (CFCs), oxygenated solvents such as glycol ethers, alcohols, brominated compounds such as n-propyl bromide, and esterified solvents such as methyl esters.

Historically, halocarbon chemistry played an important role in the development of solvents and synthetic industrial solvent cleaners. It has also led to development of aqueous cleaners as a replacement for environmental reasons. One important class of halocarbons is chlorocarbons, carbon–chlorine-based solvents. The most common examples of chlorocarbons used in cleaning are carbon tetrachloride, trichlorocarbon (TCA, "trike," or methyl chloroform), and perchloroethylene (PCE, or "Perc"). Carbon tetrachloride ("carbon tet")—a nonflammable solvent for fats, oils, asphalt, rubber, bitumens, and gums and initially used as a degreasing and cleaning agent in the dry-cleaning and textile industries—was first produced in Germany in 1839 and marketed as a grease remover.

The most common example of CFCs used in cleaning is CFC-113. Although CFCs are less toxic than chlorocarbons, they still are significant environmental hazards. Hydrochlorofluorocarbons (HCFCs) were developed as less hazardous replacements for CFCs by modifying CFCs with added hydrogen. HCFCs are still environmentally damaging.

While such carbon-derived synthetic solvents have cleaning advantages, they also have significant environmental liabilities by contributing to global warming. Most of these compounds are volatile organic compounds (VOCs), which means they evaporate at ambient conditions and contribute to ground-level ozone, a primary component of smog.

Because of these environmental concerns, manufacture of ozone-depleting compounds such as CFCs and HCFCs was phased out after a world meeting among industrial and developing nations to restrict their use. This agreement, known as the Montreal Protocol on Substances that Deplete the Ozone Layer, was signed by 24 countries including the United States on September 16, 1987. Today, more than 197 countries have ratified the Protocol. Adoption of the Montreal Protocol fostered development of hydrofluorocarbons (HFCs) to replace CFCs and HCFCs. Nonetheless, HFCs are still considered hazardous. More recently, signatories to the Montreal Protocol also adopted the Kigali Amendment on October 15, 2016. The Kigali Amendment includes a plan to phase down global production and consumption of HFCs, further restricting manufacture and use of synthetic solvents.

In addition to the above-mentioned compounds, brominated hydrocarbons such as dibromomethane (methylene bromine) are also used for cleaning, although on a much smaller scale. In addition to immersion cleaning, vapor degreasers are often used with these types

of compounds in industrial cleaning. However, their mechanical action can be viewed as secondary because of their excellent solvating properties.

Another solvent that was used to replace some CFCs is n-propyl bromide (1-bromopropane). Originally this compound gained use as a good cleaning solvent. However, soon after this gain in popularity as a cleaner, the European Union listed n-propyl bromide as a substance of very high concern as a reproductive toxicant. Later studies by the U.S. National Toxicity Program echoed this finding and classified it as "reasonably anticipated to be a human carcinogen."

Currently, azeotropic blends of solvents are being used for vapor degreasing to replace what previously would have been cleaned using chlorinated or brominated solvents (perchloroethylene, trichloroethylene, methylene chloride, n-propyl bromide). This switch is due to regulation of those chlorinated and brominated solvents by the U.S. Environmental Protection Agency (EPA) under new Toxic Substances Control Act (TSCA) rules. The azeotropic blends are isopropyl alcohol with cyclohexane and mixtures of HFCs, hydroflueroethers (HFEs), or hydrofluoro-olefins (HFOs) with trans-1,2,-dichloroethylene (trans-DCE) to improve detergency. However, trans-DCE also is getting increased scrutiny under TSCA, and currently regulators are asking for more data in their evaluation of how to regulate this solvent. The regulatory uncertainty of these mixtures is one more reason to evaluate the use of aqueous cleaners.

Non-halogenated solvents such as glycol ethers and methyl esters have found some success as cleaning solvents, with no yet identified major environmental or human health concerns. These solvents are used as-is or are mixed with water as semi-aqueous cleaners. Like aqueous cleaners, these solvents can require the use of a rinsing process for critical cleaning applications.

Aqueous Cleaners

The acute and chronic toxicological profiles of the aforementioned organic and first-alternative CFC cleaners, coupled with the negative environmental impact of second-generation HCFC substitutes, stimulated exploration of alternative cleaning techniques. Chief among them was a renewed interest in aqueous and semi-aqueous cleaning, both of which use water as a solvent together with the addition of other compounds. These compounds help displace soils from a surface by using surface-active agents that have greater affinity for the surface than for the soil.

Semi-Aqueous Cleaners

Semi-aqueous cleaning incorporates the principles of both aqueous and organic cleaners. This is accomplished by combining a surfactant with a low-volatility hydrocarbon such as terpene, particularly limonene and pinene (citrus or pine in origin), and glycol ether or oxygenated solvent. Terpenes are homocyclic hydrocarbons and have a characteristic strong odor (e.g., turpentine). Semi-aqueous cleaning involves cleaning with a solvent or solvent/water mixture followed by rinsing with water, consistent with traditional aqueous cleaning.

Unlike traditional vapor degreasing, however, semi-aqueous cleaning does not rely on boiling liquids and is not restricted to a constant boiling composition. In its simplest form, semi-aqueous cleaning involves using organic components to dissolve soils and a water component to remove blend-based residues and other water-soluble soils. Surfactants are used when water solubility of the solvent is limited or to improve emulsifying properties of the cleaner.

Aqueous Cleaners

Detergents, sometimes referred to as synthetic soaps, were introduced in the 1930s and perform better than soaps in hard water (mineral-laden) applications because they contain water softeners to effectively treat dissolved magnesium and calcium ions. Development of complex phosphates used to soften water following World War II increased the cleaning power of detergents.

The first focus for synthetic detergents was how to improve detergency, or the ability of the detergent to effectively clean. Various surfactants were developed as well as optimal mixtures of surfactants. Different builders and mixtures of builders were also optimized, as well as various additives to improve detergency. Roughly, the 1940s–1950s were spent optimizing detergency. Starting in the early 1960s–1970s, environmental concerns began to impact detergent formulation, particularly the need for biodegradable surfactants and builders that do not cause cultural eutrophication of water. Beginning in the 1970s, the emphasis turned to finding formulations with less toxicity or reduced health concerns about carcinogens, teratogens, or mutagens. Today, there is emphasis on finding detergent formulations that are more sustainable. While detergents have generally become safer and less environmentally damaging since the 1950s, they have not necessarily become more effective in terms of detergency. Thus, the current era can be thought of as maintaining safety and increasing sustainability while striving to further detergency.

Aqueous cleaners are synthetic detergent cleaning agents used in a water solution. Water, considered an almost universal solvent, is an important component of aqueous cleaners because it dissolves many types of soils. Water—municipal tap, deionized, or distilled water, depending upon the cleaning application—also functions as a carrying medium for detergent compounds. However, while water is capable of dissolving many inorganic and some organic contaminants,

not all residues dissolve readily in water. For this reason, aqueous detergent cleaners are complex mixtures specifically formulated to create greater chemical and mechanical cleaning action.

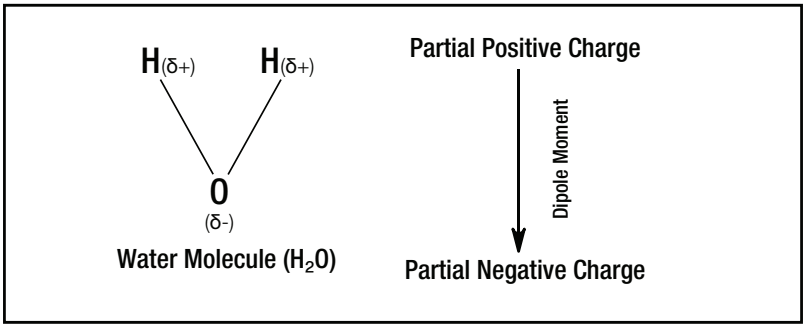

Figure 1.2 The electronegativity that attracts electrons toward oxygen (O) and away from hydrogen (H) gives water an electrical polarity or dipole moment.

Water is a polar solvent. Being polar is the characteristic that makes water good at dissolving a wide range of polar residues, contaminants, and/or soils. Water has a unique "V" shaped structure, with two hydrogen atoms at the top of the "V" and an oxygen at the bottom (Figure 1.2). One can think of the oxygen as being a large, dense electron-rich atom. This gives the water molecule an electron-rich negative end (δ–) at the oxygen base of the "V" as well as an electron-poor positive end (δ+) towards the hydrogen top of the "V." This directional net-negative charge towards the base of the "V" is called a dipole moment. Polar molecules such as water have a dipole moment. This dipole moment is important because it allows stable solutions of other dissolved polar soil molecules to arrange in a more thermodynamically favorable position, with alternating positive and negative ends of molecules (Figure 1.3, next page).

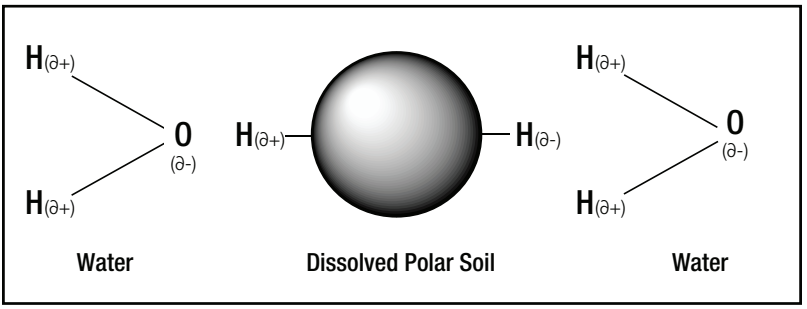

Figure 1.3 Simplified three body model showing possible stabilized arrangement of polar soil molecule with water molecules, with dipole moments arranged negative to positive.

References

A.S. Davidsohn and B. Milwidsky, "Development of the detergent industry," Synthetic Detergents; Wiley (1987).

E. Kikuchi, Y. Kikuchi, M. Hirao, "Analysis of risk trade-off relationships between organic solvents and aqueous agents: case study of metal cleaning processes," Journal of Cleaner Production, Vol. 19, 414–423 (2011).

K.-Y. Lai, Liquid Detergents; Taylor & Francis (2005).

C. LeBlanc, "The evolution of cleaning solvents," Precision Cleaning, 11–16 (May 1997).

L. Manzer, "The CFC-ozone issue: Progress on the development of alternatives to CFCs," Science, Vol. 249 (6 July 1990).

National Center for Manufacturing Sciences, Focus (April 1993).

D. Noether, Encyclopedic Dictionary of Chemical Technology; VCH Publishers (1993).

Shell, "VOC removal catalysts," Shell Global. Available at shell.com/business-customers/catalysts-technologies/catalysts/environmental-catalysts/voc-removal-catalysts.html

P. Somasundaran, Handbook for Cleaning/Decontamination of Surfaces; Elsevier Science (2007).

Toxics Use Reduction Institute, "Handout: Hands-on Cleaning and Degreasing Workshop"; University of Massachusetts, Lowell, MA (1996).

Toxics Use Reduction Institute, "Surface Cleaning Series Fact Sheet No. SC-1: Surface cleaning"; University of Massachusetts, Lowell, MA (1996).

Toxics Use Reduction Institute, "Surface Cleaning Series Fact Sheet No. SC-2: HCFCs and cleaning"; University of Massachusetts, Lowell, MA (1996).

United Nations Environment Programme, "Report of the Technology & Economic Assessment Panel," (1991).

U.S. Federal Register, Vol. 61, No. 173 (5 September 1996).

Resources

alconox.com
turi.org

Chapter Two:

The Chemistry of Aqueous Cleaning

Before reviewing the technologies and processes involved in aqueous cleaning, it is important to understand how aqueous cleaning works—this begins with the cleaner itself. Aqueous cleaners are typically composed of:

- **Surfactants** for emulsifying, wetting, and penetrating;
- **Builders** for neutralizing water hardness, chelating inorganic, and saponifying natural oils; and
- **Additives** for corrosion inhibition, anti-redeposition, and rinsing.

Key Definitions of Aqueous Cleaner Ingredients

Surfactants — Short for "surface-active agent," a surfactant is an organic molecule with a hydrophobic/oleophilic (water-hating/oil-loving) end and a hydrophilic (water-loving) end. Surfactants are often emulsifiers, wetting agents, and dispersants (see definitions below). The most common surfactant is sodium linear alkylbenzene sulfonate (LAS). The positively charged alkylbenzene portion of the molecule is the hydrophobic/oleophilic end of this surfactant, and the negatively charged sulfonate is the hydrophilic end of the

molecule. Surfactants are typically classified as anionic, nonionic, and cationic. Multiple surfactants can be used in a detergent to increase efficacy. Classification of the surfactant is typically used to describe or characterize the cleaner.

- ***Anionic surfactants*** are ionic and are made up of two ions: a positively charged (usually metal) ion, and a negatively charged organic ion. The negatively charged end of the molecule is hydrophilic. These negatively charged parts of the molecule are usually sulfonates, sulfates, or carboxylates and are often neutralized by positively charged metal cations such as sodium or potassium. Examples include sodium alkylbenzene sulfonates, sodium stearate (a soap), and potassium alcohol sulfates.
- ***Nonionic surfactants*** have no ions. They derive their polarity from having an oxygen-rich portion of the molecule at one end and a large organic molecule at the other end. The oxygen component is usually derived from short polymers of ethylene oxide or propylene oxide. Just as in water chemistry, the oxygen is a dense electron-rich atom that gives the entire molecule a partial net-negative charge. This makes the whole molecule polar and able to participate in hydrogen bonding with water (as discussed in Chapter One). Examples of nonionic surfactants are alcohol ethoxylates, nonylphenoxy and polyethylenoxy alcohols, and ethylene oxide/propylene oxide block copolymers.
- ***Cationic surfactants*** are positively charged molecules usually derived from nitrogen compounds. They are not commonly used as cleaning agents in hard-surface cleaners because the cationic positively charged molecule tends to be attracted to hard surfaces (which usually have a net-negative charge).

Many cationic surfactants have bactericidal or other sanitizing properties that are useful to create disinfectants that leave a cationic disinfecting film on the surface. Cationic surfactants are usually incompatible with anionic surfactants because they react with the negatively charged anionic surfactant to form an insoluble or ineffective compound.

- ***Amphoteric surfactants*** change their charge with pH. They can be anionic, nonionic, or cationic depending on pH. Usually, an amphoteric surfactant can be any two of the three charge states.
- ***Dispersants*** help disperse or suspend solid particles in solution. Dispersants include water-soluble surfactants or water-soluble polymers (long-chain organic molecules) that are electrostatically attracted to particulates, creating a bridge between the water and water-insoluble solid particulate (in some cases even repelling the solid surface to help lift particles into suspension).
- ***Emulsifiers*** help pull water-insoluble oils into solution by creating a liquid–liquid mixture. Surfactants that use the hydrophobic (water-hating or repelling) or oleophilic (oil-loving) end of their molecule to mix with water-insoluble oils and their hydrophilic (water-loving) end to mix with water create a bridge to emulsify water-insoluble oils into solution. The specific structure of the bridge is called a micelle—it can be thought of as a hollow, oil-filled round ball with a skin made of surfactants. The hydrophilic ends of the surfactant face out in contact with the water solution, and the hydrophobic ends face in to the oil-filled ball (Figure 2.1). When the micelle has anionic surfactants, certain particulate, clay, and dirt residues can additionally be cleaned by adsorbing

on to the surface of and mixing with the membrane structure of the micelle. With nonionic surfactants, certain oily soils can more easily pass to the middle of the micelle, forming an emulsion. This is why it can be advantageous to have detergents with both anionic and nonionic surfactants.

- ***Wetting agents*** lower the surface tension of water and allow the cleaning solution to wet surfaces and penetrate into, under, and around soils and surface crevices. Wetting agents create a bridge between the water and any hydrophobic (water-hating or repelling) surface. Think of a wetting agent as having one end of the molecule attracted to the surface while pulling the water solution towards the otherwise water-repelling surface, allowing the water solution to contact more of the surface to be cleaned. You might say that wetting agents make water wetter.

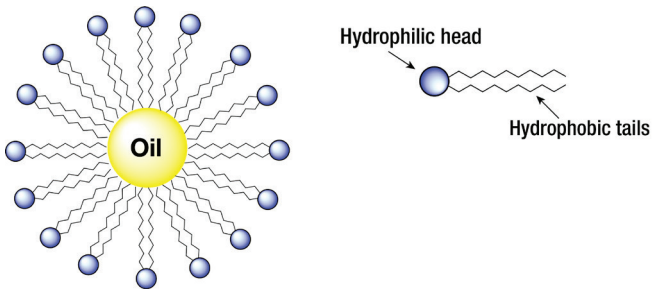

Figure 2.1 To emulsify water-insoluble oils, surfactant molecules form a micelle structure. In a micelle, the hydrophilic ends of surfactant molecules (blue circular heads) face outward and contact water molecules, while the hydrophobic ends (black lines) face inwards and contact oil molecules.

Builders — Builders react with interfering calcium, magnesium, or iron ions that may be present in the water solution. They stop these ions from reacting with soils and other detergent ingredients

to form water-insoluble and difficult-to-clean calcium, magnesium, or iron salts. These metals are present to varying degrees in all water, particularly tap water. Builders are usually alkaline salts, chelating agents, and/or sequestering agents.

- ***Alkaline salt builders*** are inorganic salts such as sodium carbonates or sodium phosphates. They react with calcium, magnesium, or iron to form water-soluble or water-dispersible compounds that bind calcium, magnesium, and iron. Polyphosphates also act as dispersants to help remove particulates. Alkaline salt builders provide alkalinity to help with alkaline hydrolysis and saponification of oily residues, which are discussed later.
- ***Chelating agents*** are negatively charged or oxygen-containing molecules that react with positively charged metal ions to form a stable complex. They have multiple locations in the molecule to react with positive charges that may be present on multivalent metal ions with more than one positive charge. An example of a chelating agent is ethylene diamine tetraacetic acid (EDTA). EDTA has four acetic acid groups, providing the potential for four negatively charged acetates to bond with up to four positively charged sites on metal ions with multiple positive charges, such as calcium with its two associated positive charges.
- ***Sequestering agents*** are chelating agents (see above) that bind particularly tightly with metal ions and sequester or separate them from reacting with other compounds. Classically dissolved calcium, magnesium, and iron, commonly found in tap water, need to be sequestered in solution so they do not react with anionic surfactants and form precipitates. These same ions will react with alkalinity to form metal oxide/hydroxide precipitates if not sequestered.

Additives — The effectiveness of both surfactants and builders is almost always affected by temperature, length of exposure, detergent concentration, nature of the mechanical cleaning method, and other additives not described above. Additives include fragrances, dyes, brighteners, enzymes, flow aids, viscosity modifiers, hydrotropes, foam stabilizers, oxidizing agents, foam control agents, emollients, abrasives, corrosion inhibitors, and antimicrobial preservatives.

- ***Fragrances*** are typically expected in household and janitorial detergents to leave a fresh scent. For most industrial cleaning applications, however, fragrances that leave residues are undesirable.
- ***Dyes*** can improve the appearance of an aqueous detergent. They are sometimes used to mask off-colors from low-grade, low-purity detergent ingredients that can have a dirty brown color. While dyes are common in household and janitorial cleaners, the risk of a colored residue makes dyes undesirable in many industrial applications.
- ***Brighteners*** are a kind of dye that is designed to deposit on a white surface, absorb fluorescent light, and emit white visible light, causing the surface to look whiter. While this is desirable particularly in household laundry applications, brighteners are not desirable in industrial cleaning because they leave residues.
- ***Enzymes*** can be added to a detergent to help remove proteins, starches, and lipids. Other detergent ingredients are generally sufficient to remove starches and lipids, so the necessity of starch and lipid enzymes is debatable. However, proteins tend to cross-link, particularly if heated during cleaning. Thus, addition of protease enzymes can significantly improve the performance of detergents on proteins.

- ***Flow aids*** are sometimes added to powdered detergents to improve flow properties of the powder by helping prevent formation of lumps. Lumps form when powdered detergents hydrate and dehydrate their anhydrous ingredients.
- ***Viscosity modifiers*** or thickeners are often added to inexpensive, low-solids formulations to give them the illusion of being high in solids and therefore appearing to be "strong" detergents. Generally, in high-quality industrial detergents you do not want the additional risk of residues from thickening agents that do not contribute to detergency.
- ***Hydrotropes*** are used to increase the solubility of desirable surfactants and builders in a concentrated detergent formulation. Use of hydrotropes is desirable and necessary to make highly concentrated formulations with high surfactant content.
- ***Foam stabilizers*** are used in manual/immersion cleaning formulations—also referred to as clean-out-of-place (COP) cleaning formulations—to provide a long-lived foam. End users often equate foam with cleaning power, so longer foam stability is perceived as better cleaning. Foam stabilizers are often good surfactants and wetting agents, so they can contribute to detergency in addition to perceived cleaning power.
- ***Oxidizing agents*** add a desirable cleaning mechanism to detergents. A bleach or peroxide compound can help remove a wide range of residues that can be broken down by oxidation. Unfortunately, these compounds also tend to oxidize many other desirable detergent ingredients, so it can be tricky to formulate with oxidizing agent ingredients.

Nonetheless, particularly when trying to remove lingering odors or difficult colored residues, it is often desirable to use a detergent formulated with oxidizing agents.

Foam control agents are used to make a detergent lower foaming. This is desirable in high-agitation, spray-in-air cleaning such as in cabinet washers, dishwashers, or automated clean-in-place with sprayball cleaning. Many foam-controlled detergents need to be used at elevated temperatures because they work by clouding out at higher temperatures to form an "oil slick" at the air–solution interface, where cleaning interferes with the formation of foam. When diluted with rinse water, these same foam control agents drop below the concentration at which they cloud out, rinsing away without leaving residues.

- ***Emollients*** are used to reduce irritation on skin for manual cleaners. They work by depositing a protective layer on skin. While emollients are used in household and janitorial products, emollients are not used in industrial detergents because they leave residues. Industrial cleaners typically are used while wearing skin protection.
- ***Abrasives*** are small, insoluble, abrasive particles used in some abrasive cleaners. These can be effective at removing heavy grime with scrubbing. In many industrial detergents, however, the risk of leaving insoluble particulate deposits makes use of abrasives undesirable.
- ***Corrosion inhibitors*** are additives designed to deposit on metal surfaces, leaving a protective film against corrosion. There are non-depositing corrosion inhibitors that bind metal oxides and stop them from auto-catalytically propagating while the detergent is in contact with the metal; however, these do not survive rinsing, so you must be careful when

using this type of corrosion inhibitor. More common corrosion inhibitors leave a residue that survives a rinse, at least temporarily. In choosing a detergent that contains corrosion inhibitors, decide if the corrosion inhibitor residue is better than the resulting risk of corrosion if they are not used. The highest levels of cleaning are achieved using no corrosion inhibitors and by controlling corrosion during the rinse process.

- ***Antimicrobial preservatives*** are typically used in low-solids detergents that are prone to microbial breakdown. Most detergents are made with biodegradable ingredients, which means the ingredients can feed microbes. In high-solids, concentrated detergents, the osmotic pressure is sufficient to suppress microbial growth, but low-solids formulations may need these preservatives. Often these are cationic surfactants that tend to deposit on hard surfaces, so in residue-free industrial detergents it is better not to use these additives.
- ***Extenders*** are fillers added to detergent that do not improve detergency (and which also tend to increase packaging and handling costs associated with the cleaner itself). For example, water may be added to a concentrated cleaner, or inert powder may be added to dilute a concentrated powder cleaner. It is occasionally necessary to add a small amount of inert powder, as a process aid, to avoid caking of powdered detergent. However, one needs to be careful not to purchase a cleaner that is diluted with excess, cheap inert powder, because it does not improve detergency but does increase packaging and handling costs.

How Aqueous Cleaners Work

A detergent's chemical action saponifies certain oils, producing water-soluble soap material. Surfactants physically reduce surface tension of the solution, in the process emulsifying and lifting soils away from the substrate being cleaned (Figure 2.2). The surfactant lifts oils off hard surfaces to form a suspended oil–water–surfactant emulsion, which is then removed by rinsing.

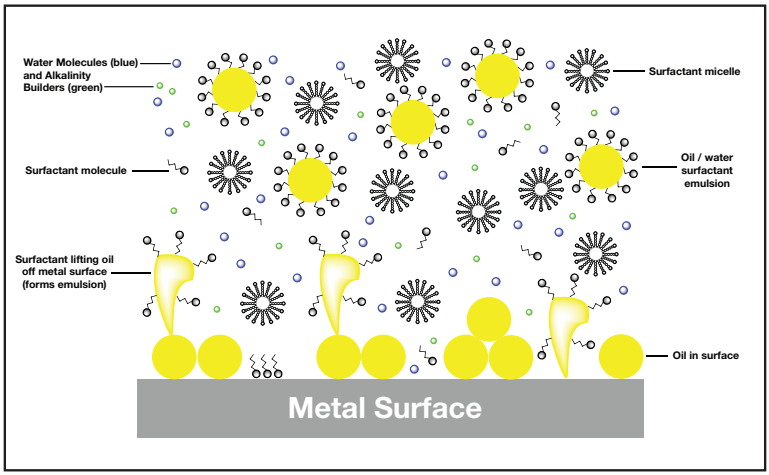

Figure 2.2 Alkaline cleaners lift soils away from a substrate by using surfactants to emulsify oils, allowing the soil to be rinsed away from the surface.

Typically, immersion cleaning involves submerging parts in a bath and providing air agitation, turbulation, and mechanical brushing or ultrasonics to achieve a desired level of cleanliness. In contrast, high-pressure spray cleaning uses the mechanical energy of a pressurized wash stream to create even higher soil removal rates.

Cleaning is then followed by water rinsing. In most aqueous cleaning systems, more water is used in rinsing than in cleaning. Also, rinse water must be purified by a recycling system to a higher

level than the detergent solution. Rinse water also requires different separation equipment, since the rinse water is the last solution to touch the surface being cleaned.

Chemical and mechanical actions involved in aqueous cleaning actually comprise several processes. These can be described as:

- ***Solubilization***—A process that increases the ability of a substance to dissolve in a particular medium.
- ***Wetting***—The process of lowering surface and interfacial tensions so that the cleaner penetrates small spaces while getting under the soil to lift it from the substrate.
- ***Emulsification***—Creation of an oil/water mixture by coating oil droplets with surfactant, preventing them from recombining and migrating to the surface of a cleaning bath (see previous emulsifier discussion).
- ***Deflocculation***—Breaking down the soil into fine particles and dispersing them throughout a cleaning medium to prevent agglomeration.
- ***Sequestration***—Introduction of molecules that react with ions such as calcium, magnesium, or heavy metals in the solution to prevent formation of insoluble byproducts (e.g., soap scum).
- ***Saponification***—Alkaline hydrolysis of fat by the reaction of fatty acids with alkalies to form water-soluble soaps.
- ***Hydrolysis***—Breaking down a larger, more water-insoluble molecule or residue by alkaline or acid hydrolysis to form a smaller, more water-soluble residue.

Unlike organic and chlorinated solvents, which rely on solvating soluble residues, aqueous cleaners may contain several ingredients that help provide maximum cleaning effectiveness for specific and diverse

types of substrates and soils. These ingredients (detailed above, and listed below) reduce surface tension, form emulsions, and/or suspend insoluble particles for removal in the cleaning bath.

- ***Surfactants***—As previously defined, these are polar molecules that emulsify (create stable liquid–liquid mixtures), disperse (create stable particle–liquid mixtures), wet (allow other cleaning chemicals to contact the hard surface), and penetrate (allow other cleaning chemicals to enter small cracks and crevices).
- ***Builders***—These inorganic salts provide alkalinity and buffering capacity common to almost all aqueous cleaners pH may be alkaline (>7), neutral (~7), or acidic (<7)]. Alkalinity may be provided by hydroxides, carbonates, borates, silicates, phosphates, or zeolites (crystalline hydrated aluminosilicates). Builders also soften water or help with saponification or deflocculation.
- ***Additives***—Chemicals that act primarily as contaminant dispersants, anti-redeposition agents, brighteners, viscosity modifiers, antifoaming agents, and corrosion inhibitors, or they may have special detergency on a specific soil type. Examples include enzymes, amine compounds, and various polymers.

Types of Aqueous Cleaners

Aqueous cleaners are classified, in part, according to pH value as being neutral, acidic, or alkaline on a 0–14 scale, with a pH of 7 being neutral. Thus, a pH value of less than 7 is considered acidic and higher than 7 is considered alkaline.

It is important to keep in mind that the pH value of a cleaner can directly affect cleaning effectiveness. Technically speaking, pH is the negative log of the hydrogen ion concentration. This means that the

higher the pH, the greater the increase in hydroxide concentration and the faster that hydrolysis, or breaking down of a natural fat or oil into a soap, occurs.

Certain soils are removed more easily using an acid cleaner, while an alkaline cleaner is best for others. An acidic solution with a pH of 4.5, for example, would be effective in removing metal oxides or scale prior to pretreatment or painting. An alkaline (basic) solution with a pH of 13.5 could be formulated to remove carbonaceous soils, heat scale, rust, oil, and grease. Neutral cleaning solutions include alcohols and other water-soluble formulas and generally contain detergents or other surfactant additives to aid in cleaning. Neutral cleaning agents generally produce less foam. There are also semi-aqueous cleaners that form neutral solutions upon dissolving or emulsifying in water.

The first issue in selecting a cleaner on the basis of pH is how fast it needs to work (although there are other factors, as discussed in later chapters). Most cleaners are alkaline because the cleaning mechanisms of alkaline hydrolysis and alkaline chelation work best at an alkaline pH. Many oily residues are easily broken down by alkaline hydrolysis, so it is generally desirable to use an alkaline detergent. However, a higher pH correlates with a more corrosive cleaner (Table 2.1).

Table 2.1 Types of cleaners that work at different pH ranges to remove specific soils

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, oils

Alkaline cleaners work best when the soil can be hydrolyzed. Typically, this soil category contains natural oils and fats, fingerprints, natural greases, some types of food products, and protein residues. The cleaning process should be enclosed to avoid exposure hazards. Workers should use personal protective equipment with handheld sprays.

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 substrate must be robust because corrosion is also a factor.

As a rule of thumb, it is best to use the mildest cleaner possible that will get the job done.

Application of Isoelectric Points to Cleaning

Stainless steel and glass are common substrates that require cleaning. It is worth taking a closer look at some of their surface properties to determine how they affect cleaning and how to optimize the thermodynamics of cleaning by controlling pH of the cleaning solution.

Much is known about how pH affects aqueous critical cleaning. However, the role pH can play in harnessing electrostatic effects to improve cleaning efficiency is not as well-known. Since like charges repel, choosing a cleaner of appropriate pH relative to the isoelectric point of the surface and the inverse log of the acid dissociation constant (pKa) of the residue makes cleaning more efficient (Table 2.2). This is especially true when cleaning residues such as acids, bases, and amphoteric proteins, all of which can have their electrical charges manipulated by pH.

Table 2.2 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 concentration	[A-] = conjugate base concentration
$pKa = -\log [H_3O+][A-]/[HA$			

The isoelectric point of a surface is the pH at which the surface's electric charge is neutral in relationship 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:

- Steel typically has an isoelectric point of 8.5 associated with reactivity of the oxygen in the oxides Fe_2O_3, Fe_3O_4, and Cr_2O_3 on the surface of the metal and the hydrates and hydroxides formed in aqueous solutions.
- Glass has an isoelectric point of 2.5 associated with SiO_2.

Increasing the cleaner solution pH (past the isoelectric point) causes the surface to become more negatively charged. If the residue to be removed also has a negative charge at that pH, then the negative surface will repel the negatively charged residue.

In addition to material surfaces, many residues also change electrical charge as a result of a simple change in pH. The pKa of most acids indicates the pH at which the hydronium ions and conjugate base are present in equal concentrations. Increasing the pH shifts the equilibrium toward the right, thereby increasing the concentration of the negative conjugate base. Thus, when cleaning acids, it is desirable to use a cleaning solution with a pH higher than the isoelectric point and the pKa of the acid. This results in an increase in the concentration of the negative conjugate base with a pH above its isoelectric point, giving the surface a repelling negative character.

For example, with stearic acid ($C_{17}H_{35}COOH$), the conjugate base is the negatively charged stearate ion ($C_{17}H_{35}COO^-$). The pKa is about 5; this means that at a pH of 5 and higher, the reaction is driven toward the right, thereby converting stearic acid to negatively charged stearate ion.

Suppose the stearate ions form a residue on steel, and the pH is 8.5 or higher—not only are there negatively charged stearate ions but also a negatively charged steel surface with a pH above the isoelectric point. The steel and the stearate ions repel each other, facilitating cleaning.

The reverse holds true for alkaline (basic) residues (Table 2.3). By lowering the pH of the residue below the pKa and the isoelectric point of the surface being cleaned, a positive–positive repulsion may be achieved. At the very least, this creates a neutral residue and a positive surface with no attraction.

Table 2.3 Optimizing thermodynamic cleaning conditions for surface/residue electrostatic repulsion

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

In all cases, it is important to consider the corrosive effect of pH on the surface being cleaned. Typically, it is desirable to choose a cleaner with a pH that will not etch or corrode the surface—for stainless steel, within the limits of passivation, and for glass, within the limits of etching. The addition of corrosion inhibitors can extend the acceptable pH range, like many used in Alconox Inc. detergents during cleaning. In this case, corrosion is inhibited during washing via protection of active sites and/or sequestration of metal oxides, but not during rinsing.

References

A.S. Davidson and B. Milwidsky, Synthetic Detergents, 7th Ed; Longman Scientific and Technical; Co-publisher: John Wiley & Sons, New York (1987).

E.W. Flick, Advanced Cleaner Product Formulations, Vol. 5; Noyes Publication (2013).

T. Hargreaves, Chemical Formulation: An Overview of Surfactant Based Chemical Preparations Used in Everyday Life; RSC Paperbacks (2003).

K.-Y. Lai, Surfactant Science Series Vol. 129: Liquid Detergents; Taylor & Francis (2005).

J. Quitmeyer, "All mixed up: Qualities of aqueous degreasers," Precision Cleaning, Vol. 5, No. 9 (September 1997).

M. Salinas, "Water works," Parts Cleaning, Vol. 1, No. 2 (July/August 1997).

S.S. Seelig, "Making aqueous systems work," CleanTech '97 Proceedings; Witter Publishing (May 1997).

D.G. Urban, How to Formulate & Compound Industrial Detergents; BookSurge Publishing (2003).

Resources

alconox.com
pilotchemical.com
stepan.com
turi.org

Chapter Three:

Aqueous Cleaning Processes

There are nine essential variables to consider in any aqueous cleaning process. It is important to understand and control these interrelated variables in all critical cleaning, but particularly in highly sensitive industrial applications such as medical device manufacturing, metal surface preparation, optics assembly, and electronic component manufacturing. Use these variables—represented in the acronym BATH-O-CARD—to evaluate, diagnose, and optimize your cleaning process (Figure 3.1).

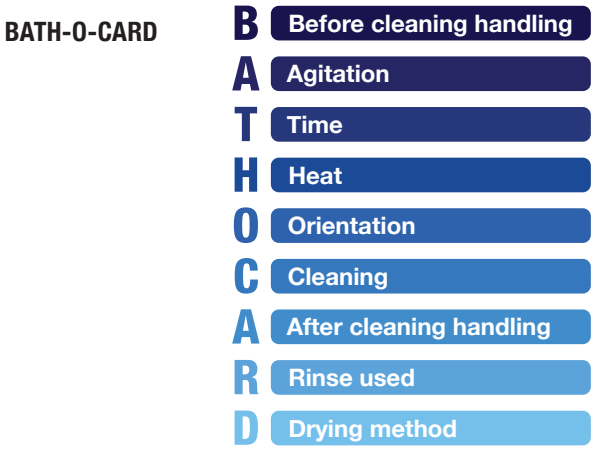

Figure 3.1 Essential cleaning variables can be summarized by BATH-O-CARD.

In the past, the acronym TACT—Time, Agitation, Chemistry, and Temperature—has been used to remember the essential cleaning variables in aqueous cleaning processes. However, we view this more limited set of variables as overly simplistic.

Before Cleaning

How parts and substrates are handled prior to cleaning can significantly impact cleaning results. Soils are more difficult to remove if they are:

- Allowed to dry, set-up, and cross-link
- Stored in a dirty environment
- Stored in a humid or corrosive environment

As a rule, it is important to clean parts as soon as possible after they are soiled. In some instances, it makes sense to take parts directly from a manufacturing process and put them into a soak solution where they may sit for extended periods of time prior to cleaning.

Soiled parts can also be placed in protective packaging, dipped in a protective coating, or immersed in oil or grease to maintain their current state and avoid increasing the cleaning burden. Clean storage conditions and proper packing by an upstream supplier make it easier to clean parts and substrates.

Agitation

Agitation is the process of applying mechanical energy to the cleaning process. This is distinguished from soaking, in which a part or substrate simply lies in a bath. Agitation can be performed through manually applied force (e.g., cloth, sponge, or brush), ultrasonic, flow-through clean-in-place (CIP) (e.g., used in connection with pipes, tanks, and tubes), spray cleaning (e.g., dishwasher), and high-pressure spray cleaning. In general, increasing agitation increases cleaning effectiveness, particularly when removing heavy, bulk soils.

How agitation will be applied in the cleaning process is a significant factor in the choice of a detergent. High-emulsifying, high-foaming cleaners are more effective for cleaning processes with low levels of agitation and longer cleaning times. These clean-out-of-place (COP) methods include manual, soak, and ultrasonic processes. Likewise, low-foaming, high-dispersing cleaners are suitable for high-agitation cleaning with short contact time, as found in spray washing, parts washing, and when using spray CIP systems.

Presoaking generally enhances cleaning, particularly if soils are dried or baked onto the part to be cleaned. As stated above, it is always preferable to clean as soon as possible after soiling to avoid dried or baked-on soils.

Time constraints and volume of parts being cleaned affect choice of an agitation method and thus detergent. When a large number of parts must be cleaned quickly, then a fast, high-agitation method, such as spray washing, with a moderately aggressive detergent is preferable. Likewise, when cleaning fewer parts or batch-continuous quantities of smaller batches rather than large quantities from continuous manufacturing of parts, ultrasonic soak cleaning with a milder detergent is more appropriate for wetting and emulsifying mechanisms that work well in ultrasonics.

The cleaning methods referred to above are discussed below in greater depth.

- ***Manual cleaning***—Typically chosen for small-volume batch cleaning, manual cleaning can achieve high levels of cleanliness. However, much depends on the consistency of operators performing the cleaning. Thus, rigorous operator training and retraining should be arranged. In addition, clearly written cleaning procedures and training procedures are necessary. It may even be appropriate to certify operators in different cleaning methods with periodic recertification.

- ***Soak cleaning***—Usually chosen for cleaning small volumes when time is not critical, soak cleaning is typically a slow process and is not labor intensive. Care should be taken, however, when cleaning delicate parts. Because soaking involves longer cleaning times, there is more opportunity for corrosion to occur. As a result, soaking is best suited for cleaning robust parts.
- ***Ultrasonic cleaning***—Ultrasonic cleaning is essentially soak cleaning enhanced by ultrasonic sound energy. It is particularly effective on small parts with blind holes and crevices that are inaccessible by spray cleaning. It greatly accelerates the speed of cleaning and can improve cleaning in small spaces. Ultrasonic energy helps disperse and replenish fresh cleaning solution to surfaces of parts being cleaned by agitating and moving the solution around as ultrasonic cavitation occurs. While application of ultrasonic energy can be very effective, it can also accelerate corrosion on delicate substrates. Therefore, suitable corrosion inhibitors may be required. Ultrasonic cleaning involves more expensive equipment and is typically suitable for larger volume batches and where a high level of cleaning is required.
- ***Vacuum cycling nucleation***—This cleaning technique involves soaking parts in a solvent or cleaning solution and then pulsing a vacuum over the solution, which results in vapor bubbles forming at nucleation sites on the hard surfaces. This is an emerging technology with application for cleaning deep to blind holes and difficult to reach crevices.
- ***Spray CIP***—Spray cleaning of tanks provides more reliable and more complete coverage of the tank. This approach is used in large tank systems where the increased efficiency

achieved by using less cleaning solution justifies cost of the spray system. An immersion cleaning system frequently does not work well with tanks because the process may not reach the top of a tank, requiring additional manual cleaning.

- ***Spray-in-air***—Spray-in-air is used in cabinet washers, tunnel washers, and dishwasher type cleaning equipment. Parts being cleaned are mounted in racks, and detergent solution is sprayed by appropriately oriented nozzles.
- ***CIP by circulation***—This process is typically used for piping or small tank systems where a spray CIP system cannot be used. It also is an appropriate method for cleaning filtration systems in which filters cannot be accessed by spray nozzles.

When choosing a detergent for tank systems, remember that a detergent that performs well on a substrate in a soak cleaning process may not perform as well in spray cleaning processes. Therefore, if you anticipate scaling up a current system to a spray CIP system, consider using a spray-cleaning detergent that performs adequately in soaking operations.

The choice of a cleaning machine depends both on size of batch and size of parts being cleaned. For example, as batch size increases, an ultrasonic machine may no longer be efficient. It often makes sense to choose some form of cabinet, under-counter, or floor-standing washer.

For washing very high-volume parts, a conveyor cleaning system is a suitable option. Parts placed on a conveyor are cleaned using spray nozzles as they pass through the system.

Spray cleaning systems are suitable for parts and surfaces that are readily accessible. They are not as effective when there are blind holes and small crevices. When cleaning high volumes of parts where it makes sense to use spray cleaning, investigate using spray under immersion.

For cleaning very large parts, such as vehicles or large assemblies (where an operator can physically move around the part), it makes sense to use a power spray wand or handheld pressure spray device to clean the exterior.

Time

In general, the longer the cleaning time, the more thorough the cleaning will be. Many cleaning mechanisms such as emulsifying, dissolving, suspending, and penetrating are time-dependent.

Cleaning time can be accelerated by increased agitation and temperature and by use of a more aggressive detergent. If none of these variables can be changed—perhaps because the substrate is too delicate or the proper equipment is unavailable—be prepared for longer cleaning times. While manual and related COP cleaning may take minutes and spray cleaning take seconds, soaking may take hours, possibly overnight, to achieve comparable results.

There are some instances when long cleaning times may promote substrate corrosion, weakening, or swelling. The optimum cleaning time depends on the specific substrate, temperature, cleaning method, and detergent.

Heat

In general, higher temperature cleaning solutions result in better cleaning. In practice, there is typically an optimum temperature for a given combination of cleaning variables. For example, many soak, manual, and ultrasonic cleaning methods work best at 50°C–55°C (122°F–131°F). Many spray washing techniques work best at 60°C–70°C (140°F–158°F). Waxy or oily soils are more easily cleaned at higher temperatures above the melting point of the wax. Particulate soils tend to be more easily removed at slightly lower temperatures, where dispersions are not broken down. As a general rule, many

cleaning mechanisms follow first-order reaction kinetics whereby the cleaning speed doubles with every increase of 10°C (50°F). Of course, you do not want to use a temperature so high that it damages your substrate.

Certain residues can go through a phase change that can greatly improve the ability to clean them. Many waxes and silicone oils go through a melting point or softening point typically around 77°C (171°F). Often when cleaning silicon oils or waxes, cleaning is dramatically more effective when performed above these temperatures.

Ultrasonic cleaning has a theoretical optimum temperature of around 70°C (158°F) to create cavitation bubbles, depending on detergent type and concentration. Although this temperature may be optimal for cavitation, it may not be the most effective temperature for detergency. Recall that detergency is usually increased at higher temperatures due to the doubling of cleaning speed increase for every 10°C (50°F). The rate of change of cavitation with temperature is not as significant, so this theoretical optimum temperature for cavitation during ultrasonic cleaning is typically not as important as obtaining the optimum temperature for detergent efficacy.

Orientation

Orientation of the part relative to the cleaning and rinsing solution is important for successful cleaning. Be sure to orient parts being cleaned so that all air bubbles are released that might otherwise be trapped in a dead leg of a tubing system or blind hole in a part. The cleaning solution cannot clean what it does not touch, so you must remove all air to avoid interference. In automated spray cleaning, be sure that parts and spray nozzles are oriented such that all surfaces being cleaned can be contacted by the spray coming from the spray nozzle. Make sure there is no shadowing of one surface by another surface that could interfere with cleaning.

When loading parts to be cleaned into an automatic dishwasher, be sure to orient them so that spray nozzles can access all sides of the parts being cleaned. Additionally, when loading parts into an automatic washer, be sure to orient them so that they can drain completely. Avoid loading any parts such that an upturned cup or reservoir can hold dirty wash water. Dirty water that is trapped when a wash cycle ends will be carried over into the rinse cycle, which will spread the dirty water over all parts that have already been cleaned. This residue will then dry on the parts, causing spots. Instead, be sure to tilt parts to ensure they can drain and not trap any dirty wash water.

Cleaner

The cleaner or detergent used should match the desired cleaning method, surface, and types of soils being cleaned. For instance, a low-foaming detergent should be used for spray or machine cleaning, a good anti-redeposition detergent for soak and ultrasonic cleaning, and a high-emulsifying and wetting detergent for manual cleaning. The detergent, temperature, and degree of agitation should be strong enough to remove soils to the desired level of cleanliness without harming the substrate being cleaned.

It is very important to choose a low-foaming or non-foaming detergent when cleaning in or with a machine that relies on spraying for mechanical agitation. Foam is caused by agitation at an air/solution interface when a foaming agent is present. The foam may buildup and spill over from the machine, creating a mess. Foam will also buildup on the substrate and interfere with mechanical cleaning energy of the spray. Foam can float on top of rinse water and remain there, making it difficult to thoroughly rinse surfaces. Finally, foam may get sucked into recirculation pipes, causing problems with pumps in the machine.

Surfactants are often foaming agents. Most aqueous cleaners have surfactants in them. There are three basic types of aqueous cleaners that are suitable for automated spray machine washing: cleaners with no surfactant, cleaners with non-foaming surfactants, and cleaners with low or controlled-foam surfactants. There are important differences among these types of cleaners. Remember that foam forms in the presence of an agitated foaming agent where air is present at the air–solution interface. Many soils are foaming agents. For example, soap formed by saponifiers in electronic solder flux cleaning is a foaming agent. A surfactant-free cleaner will not protect against foam formed by certain soils; therefore, it is advisable to clean only non-foaming soils with surfactant-free cleaners.

A non-foaming cleaner usually has a nonionic polymer surfactant. These surfactants come out of solution at elevated temperatures and form an oil slick on top of the solution. This oil slick is a barrier to air contact, preventing foam from forming or being stable. These non-foaming cleaners will suppress foam from soils. However, they only work properly if the temperature is hot enough, so you must identify the minimum temperature at which to use these cleaners.

Finally, there are controlled foam cleaners that usually have limited foam-suppressing capabilities. The surfactants themselves do not foam excessively, but they cannot control much foam resulting from soils.

It is critical that a detergent is scientifically formulated to clean effectively and to rinse away without leaving interfering residues. A properly formulated detergent will typically have appropriate surfactant ingredients and non-depositing rinse-aids. The surfactant should have sufficient surface tension-lowering properties to assist in proper rinsing. A surface tension below 35 dynes per centimeter

for the cleaning solution is often sufficient for good rinsing. Non-depositing rinse-aids can help complete a formulation to meet the rinsing requirements of critical cleaning.

In addition, used in critical cleaning applications must be manufactured to reasonably tight specifications and proper quality control. In many critical cleaning applications, it is desirable to choose a detergent manufacturer that can provide lot number tracking and certificates of analysis. These certificates document each lot of detergent to assure consistency and quality control to prevent cleaning failure from inconsistent manufacturing or unannounced formulation changes. It is also desirable to choose a detergent from a manufacturer that maintains quality control of raw materials and retains samples of each detergent lot so the manufacturer can respond to concerns about a particular batch.

The detergent should be widely available and economical to use (for optimum economy, a concentrated detergent is typically used at 1:100 to 2:100 dilution). The detergent concentrate should be diluted according to the manufacturer's instructions. Typically, warm (about 50°C) or hot (about 60°C) water is used. Ambient temperature water may be acceptable, especially for presoaking. For difficult soils, very hot water should be used (over 65°C) and the recommended detergent concentration doubled.

Chemistry Bath-Life Extension and Control

To avoid potential cross-contamination, only freshly made cleaning solutions should be used for the highest levels of critical cleaning. For many industrial critical cleaning applications, high levels of cleaning can also be achieved when using techniques to properly extended bath life and by carefully monitoring the solution.

Many residues removed by a cleaning bath tend to neutralize a detergent solution, causing the pH to drift towards neutral as the

detergent is depleted. These types of residues are natural oil, esters, amides, acids (when cleaned by alkaline cleaners), and alkalis (when cleaned by acid cleaners). In general, a pH change of 1 unit towards neutral from the starting fresh bath pH indicates an exhausted cleaning solution. For more critical cleaning applications, a change in pH towards neutral of 0.5 pH units might be a more appropriate time to change out a bath.

Bath life can be extended by physical filtration of particulates, cooling and settling of sludge, and skimming off oils after cooling. Bath life can also be extended by adding one half as much detergent of the initial load after partially depleting the cleaning life of the bath. With frequent daily use, detergent solutions can rarely be used longer than a week or, at most, two weeks, even with these bath life extension techniques. Note that many aqueous detergent solutions start to grow microbes if used for more than a week or two. Conductivity, pH, and percentage of solids, measured by a refractometer, can be used to monitor and control bath detergent concentration and bath life.

Bath life also can be monitored using refractive index measurements. Start by measuring the starting refractive index of a freshly made detergent solution, typically using a refractometer that measures to 0.1 degrees brix. After using the bath for cleaning, replenish the tank with make-up water to replace any lost volume. Then measure the refractive index again. A change of 10% in refractive index is typically when you would dump the cleaning tank and switch to a new fresh solution of detergent.

Free alkalinity titration can be used to control bath life of alkaline cleaners when the soil being cleaned depletes free alkalinity, as is often the case with the same residues that cause pH drift. The process is:

1. Titrate a new solution to determine free alkalinity. Typically, for a 20-mL sample of detergent solution, you can add 50 mL of purified water and titrate the solution dropwise with 1.0 N

acid such as nitric or hydrochloric acid to reach a bromocresol green endpoint of around pH 4.5. Record the number of drops of acid required to reach the endpoint.

2. Titrate the used solution to determine percent drop in free alkalinity. Compare the number of drops of acid required to determine the percent drop in alkalinity. For example, if the initial bath used 25 drops and the used solution used 20 drops, that would be a 20% drop in free alkalinity (25 drops – 20 drops = 5 drops / 25 drops = 20%).
3. Add more detergent to the bath to bring the free alkalinity back to the level of the new solution. For example, if the initial solution is made with 100 mL of cleaner concentrate and a 20% drop in free alkalinity is observed, try adding 20 mL of cleaner concentrate to recharge the solution.

Perform a new free alkalinity titration to confirm the recharge for the first few times this recharging method is used to ensure that the detergent is linear with respect to free alkalinity depletion. This form of bath life extension cannot run indefinitely, however, as sludge will eventually form. Fresh solutions must be made up periodically. It is important to visually inspect the bath for sludge formation to determine when to switch to a fresh bath.

Bath lives can also be extended using conductivity, as most cleaners contain conductive salts that can be detected by conductivity. Once the conductivity response of the detergent is determined, addition of residues typically increases conductivity. By monitoring change in conductivity, you can determine when to discard the cleaning bath and make a fresh bath. Conductivity can also be used to verify and control making up the initial fresh detergent solution concentration.

When using conductivity to monitor bath life, start by measuring the conductivity of a freshly made detergent solution at known temperature and volume. As the bath is used for cleaning, add makeup

water to replace any evaporated water to the same volume, then measure conductivity at the same temperature as your initial reading. An increase of 10% in conductivity is a typical time to replace the bath. For a less critical cleaning process, life of the bath might be able to extend until there is a 20% change in conductivity. Conversely, a very critical cleaning process might require the bath to be replaced upon a 5% change in conductivity.

Many cleaner manufacturers can supply the curves of detergent concentration versus conductivity. By adapting these curves to your conditions and measuring conductivity, initial detergent dilution can be determined. Typically, this kind of measuring the bath and recharging with detergent process can be done 2–3 times before a new bath is needed.

The bath will ultimately reach a point where it forms sludge or some other failure occurs. At that point, the bath must be discarded, and a complete batch of new cleaner must be made. The time to discard the bath and start over can be determined using a cleanliness measurement and is defined in terms of number of parts cleaned or time period of bath use. Table 3.1 gives specific examples of concentration vs. conductivity for several Alconox Inc. cleaners. Use this data to derive the concentration of detergent from measured conductivity. Note that conductivity is temperature-dependent. Detergent solutions do not have the same slope as many default settings on temperature-correcting conductivity meters. For best results, allow hot detergent solutions to cool to a consistent temperature. This table can be used to verify correctly made initial detergent concentrations in a freshly made bath.

Table 3.1 Conductivity (ms) vs. concentration of Alconox Inc. cleaners at 22ºC (72ºF)

Detergent	Concentration					
	0.125%	0.25%	0.500%	1.000%	2.000%	4.000%
Alconox	1.136	2.08	3.83	6.99	12.71	22.6
Alcojet	1.354	2.51	4.6	8.34	15.02	26.6
Tergazyme	1.184	2.21	4.1	7.51	13.65	24.3
Detonox	—	0.3	0.6	1.09	1.96	3.48
Liquinox	0.108	0.213	0.402	0.747	1.38	2.63
Citranox	0.195	0.327	0.475	0.682	0.987	1.47
Detergent 8 (µs)	21.00	29.70	41.60	63.30	87.60	106.40
Detojet	0.614	1.275	2.58	5.05	9.68	18.17
Solujet	0.641	1.259	2.45	4.85	9.20	17.87
Keylajet	—	—	5.5	10.9	21.5	42.1

Chemistry, Cleaning, and Corrosion Inhibition

Corrosion during cleaning is accelerated by the same variables that accelerate cleaning: heat, aggressive chemicals, time, and agitation. To reduce metal corrosion (in approximate order of importance) use less heat, nearer to neutral pH detergent, shorter cleaning time, and less agitation.

In general, use the mildest pH detergent to limit metal corrosion. Higher pH detergents may have metasilicate corrosion inhibitors, making them suitable for cleaning soft metals such as aluminum. In general, to reduce plastic corrosion, use less aggressive cleaners with less solvent or surfactant character, lower concentrations of cleaners, lower cleaning temperatures, less contact time, and less agitation. For cleaning stressed polycarbonates, surfactant-free detergents should be used so that there is no low-surface tension solution in contact with the polycarbonate that can act as a stress cracking agent.

After aqueous cleaning, metal corrosion can also occur during rinsing and drying. Corrosion inhibitors can be added to rinse water provided that inhibitor residue does not interfere with clean surfaces. Using cold rinse water and rapid water removal drying techniques—such as wiping, blowing, dipping in an evaporative azeotrope solvent (e.g., alcohol), centrifuging, or vacuum drying—can minimize metal corrosion. Forced air drying, drying with a hot oxygen-free gas such as nitrogen, and using air knives that physically remove rinse water can also minimize corrosion.

When rinsing mild steel with hot water and drying with hot air, "flash rusting" can occur. The corrosion actually occurs during rinsing as a result of dissolved oxygen in the rinse water. In some instances, lowering the rinse water temperature or drying temperature can help avoid corrosion. For instance, in a case where flash rusting on mild steel had occurred, future rusting was avoided by lowering temperature of the rinse water from 65°C to 50°C, maintaining an ambient air-drying system. Flash rusting can also be avoided by rinsing with a solvent such as isopropyl alcohol promptly after the water rinse. Adding corrosion inhibitors to rinse water can also prevent corrosion, but the corrosion inhibitor may leave residue during rinsing.

After Cleaning

How parts are handled and stored after cleaning determines whether cleanliness is maintained. Depending on the setting, it may be necessary to make special provisions to establish a clean storage place or storage conditions. It may also be helpful, if not necessary, to determine how long a surface or part will stay clean while stored to decide whether it needs to be re-cleaned prior to use. Cleanliness testing can be done to monitor a surface and determine how long it will remain suitably clean. Humid after-cleaning storage conditions can result in corrosion or condensation that promotes microbial

contamination. Obviously, a dirty after-cleaning environment can re-contaminate surfaces. Cleanliness can be maintained by as elaborate a process as sterilizing and using sterile packaging to as simple a process as putting a clean tarp over a piece of equipment that has just been cleaned.

Rinse

With aqueous cleaning, the last thing to come into contact with the cleaned surface is the rinse water. A thorough rinse will remove soils that have been cleaned from the surface as well as detergent residue. Rinsing is when most residues are actually removed from a surface. After the residue/detergent mixture is rinsed away, any contaminants present in the rinse water may be deposited on the surface when rinse water evaporates. For many applications, it is possible to rinse with tap water and then do a final purified water rinse to remove tap water residues. Rinsing is primarily a mass-displacement mechanism involving exchanges of water. This is why a running water rinse is typically the most effective rinse.

With soak or ultrasonically agitated rinsing, it is desirable to have two counterflow cascade rinse tanks dripping "over the tank" to reduce drag-out of dirty wash water from the wash tank into the first rinse tank. In all cases, running water or an otherwise agitated rinse is better than a static soak-tank rinse.

Higher levels of cleaning may require exclusive use of deionized or distilled water and, in some cases, more than three times the volume of rinse water. For the most sensitive analytical chemistry rinsing of glassware, as much as a 12-time rinse may be required.

In most clean-room, electronic-component, and circuit-board cleaning, deionized water is preferred over either tap or distilled water. There is less potential for metallic cation deposition on sensitive electronic components, leaving conductive residues. On metal parts,

use of deionized rinse water reduces the likelihood of depositing calcium, magnesium, or other water-spotting salts. For medical device rinsing, distilled or reverse-osmosis grade water is typically used because it contains fewer organic contaminants.

Drying

Drying can be done by physical removal of rinse water or by evaporation. Physical removal by wiping, blowing, centrifuging, drying fluids, absorption, or other physical techniques eliminates the rinse water before it has a chance to evaporate. Such methods prevent precipitation of any salts or impurities that could form water spots. Water-removing drying methods also minimize the risk of corrosion during drying.

Evaporation methods such as air drying, heat drying, and vacuum drying can deposit nonvolatile impurities present in the rinse water and cause water spots. Although vacuum drying does evaporate water and can lead to deposits, the deposits themselves often evaporate under vacuum drying conditions. Drying can affect residues and corrosion because impurities from rinse water can be deposited during evaporation. Water, particularly high-purity rinse water, can be corrosive to metal substrates during heating and air drying. Physical removal of rinse water, various drying techniques, and the addition of corrosion inhibitors (with tolerance for inhibitor residue) to the rinse water can help minimize such corrosion.

Conclusion

An optimized aqueous cleaning process can be achieved by: handling parts appropriately before cleaning; choosing an appropriate cleaning agitation method; orientating parts correctly during rinsing and drying; using the right rinsing and drying process, with the right cleaner at an appropriate concentration, heat, and time; and handling

parts appropriately after cleaning. If you think about the variables in BATH-O-CARD—before cleaning handling, agitation, time, heat, orientation, cleaner, after cleaning handling, rinse, and drying—while evaluating your cleaning process, you will be more successful at diagnosing problems and optimizing your process.

References

Alconox Inc., "Critical cleaning guide," (2022). Available at https://www.alconox.com/critical-cleaning-guide-download

Alconox Inc., "Improving performance—Controlling the 6 big efficiency variables," Alconox Cleaning Solutions Newsletter, Vol. 1, No. 3 (1997).

Drying Systems, "Appropriate drying technology completes successful cleaning," Precision Cleaning, p. 37 (December 1997).

D. Gray, "Understanding the vacuum cycling nucleation process," Production Machining (November 2016).

B. Kanegsberg and E. Kanegsburg, Handbook for Critical Cleaning, Second Edition; CRC Press, Boca Raton, FL (2011).

M. McLaughlin, "BATHCARD," CleanTech, p. 16 (June/July 2004).

M. McLaughlin, "Variables and vitals of metal and electronics aqueous cleaning," Precision Cleaning (January 1994).

Resources

alconox.com
cleanersolutions.org
corrosionsource.com
productionmachining.com

Chapter Four:

Selecting an Aqueous Cleaning Detergent

Critical cleaning requires careful selection of cleaning chemistry and methods to ensure adequate performance without sacrificing worker or environmental safety. We group aqueous detergent selection criteria into three broad categories: function and efficacy, health and safety, and environmental.

Function and Efficacy

In practice, it is important to choose from a range of detergents to find one that performs well with the cleaning method and is suitable for the soils and surfaces to be cleaned (see Table 4.1). The cleaning method should be noncorrosive to the component, and the detergent chosen should have exceptional free-rinsing qualities.

Key top-level considerations include the following:

Type of substrate—The surface to be cleaned may be composed of various substrates, such as metal (ferrous/nonferrous), glass, plastic, or rubber, which affect the choice of an appropriate detergent. For example, substrates such as magnesium, aluminum, and similar soft metals may be attacked by alkaline detergents. Polycarbonate and acrylic may get stress cracking from low-surface tension detergents. Many other plastics and stainless steel alloys, on the other hand, often have high resistance to both acids and alkalis.

Type of soil—The type of soil you are trying to remove—whether heavy or light, organic or inorganic, oil or particulate matter—is perhaps the single most important consideration when selecting an aqueous detergent. Heavy soils typically require similarly heavy-duty, aggressive detergents or cleaners with high concentrations of cleaning ingredients. Highly dispersing cleaners that can remove bulk quantities of soil without having to react chemically with each individual molecule of soil are best-suited for cleaning heavy soils.

Similarly, lighter soils also require matching detergents. When the cleaning application is removal of small or trace amounts of residue, such as in many life science industries (e.g., medical device manufacturing, biopharmaceutical, analytical laboratories), understanding the soil is particularly vital. In these industries, the expectation is for truly clean, residue-free parts. Therefore, the matching detergent must be effective and completely free-rinsing.

A broad range of organic and inorganic soils are readily removed by mild alkaline cleaners that contain a blend of surfactants and sequestering agents. Metallic and inorganic soils are often readily solubilized by acid cleaners. Proteinaceous soils are effectively digested by protease enzyme cleaners. Organoleptic residues often require oxidation, while tough and adherent organic residues including esters and amides require alkaline hydrolysis mechanisms from alkaline detergents.

One example of detergent matching is that many organic soils do not dissolve easily in water and instead require a highly emulsifying cleaner. An inorganic soil may or may not be water-soluble. If it is not water-soluble, use a detergent that has a strong chelating agent. Another alternative is to enhance solubility by using an acid cleaner (acid solubilization mechanisms are discussed in Chapter Two). Oils are often effectively removed with the same types of cleaners used to remove organic soils. Silicon oils, found in such things as

mold release agents, are a special subset of oils that are difficult to remove and require a highly emulsifying cleaner and usually very high temperatures.

Particulate soils are best removed using dispersant cleaners that lift the soils into solution to form suspensions. Very small particulates such as submicron particulates need very high-wetting, low-surface tension cleaners that can reduce the distance between surface and solution to submicron increments, allowing the cleaning solution to access the submicron particulates when agitated.

Part complexity—If the part being cleaned has complicated/tortuous pathways, blind holes, or numerous cavities, higher-powered wetting detergents with low surface tension may be required to ensure penetration to all part surfaces. Examples of such parts includes speculums, cannulas, guide wires, piping systems, and threaded fittings.

Level of cleanliness required—Properly selected aqueous detergents followed by thorough and appropriate rinsing can achieve essentially all levels of critical cleaning prerequisites across an array of industries. Understanding of the finished part requirements and applicable regulatory standards can dictate what types of cleaners are necessary. In critical cleaning applications, "consumer" grade aqueous detergents with scents or emollients are not acceptable, as they will ultimately leave behind fragrance, brightener, and/or softener residuals.

Free-rinsing and detergent residue—Rinsing is an essential part of high-performance, critical cleaning. A properly formulated detergent contains rinse aids to help the rinse water remove the detergent and soil solution. Use of a non-depositing nonionic rinse aid is vital. Many rinse aids are cationic or positively charged compounds that are attracted to surfaces and then repel water. However, a surface covered with water-repelling rinse aid cannot be considered critically clean.

Manufacturing process—The location of the part or cleaning in the overall manufacturing process also impacts the detergent choice. Use of powdered detergents, while often more cost-efficient because they are free of aqueous concentrate medium, may not be suitable in cleanroom environments. Areas where rinsing to drain is not feasible may require enclosed setups or rinse tanks to help remove the residue–detergent solution combination. Manufacturing cleaning applications that are followed by further soaking or other wetted processes can be ideal for aqueous detergent cleaning.

Altering conditions for cleaning efficiency—As a rule, cleaning efficiency increases with time, temperature, and agitation. However, each of these factors may affect other important considerations, such as foaming, costs, health, or safety. For example, increasing heat when using high alkaline detergents can increase safety concerns. Therefore, you must carefully consider the total impact of adjusting these parameters in comparison to simply performing a second round of cleaning or alternatively choosing a more optimal detergent/concentration.

Appropriate for intended cleaning method—Use low-foam cleaners for high-agitation cleaning, such as high-pressure spray washers, automated clean-in-place (CIP) systems, or dishwashers; use high-foam cleaners for immersion or soaking methods, such as manual or ultrasonic cleaning.

Economics and operating costs—The detergent should be widely available and affordable. For optimal economy, a concentrated detergent is typically used at 1:100 or 2:100 (1%–2%) dilution. However, some applications may require concentrations of 0.5%–5%.

Operating costs for aqueous cleaners are generally low because they are usually concentrated, typically using only 1%–5% of cleaner solution to water. In addition, aqueous cleaning baths last a relatively long time without recycling.

Strong acid cleaners generally require constant system maintenance because their aggressive chemistry can attack tank walls, pump components, and other system parts as well as the materials being cleaned (inhibitors can be used to reduce such attack). Another disadvantage of highly acidic cleaners stems from soil loading — particularly metal loading — which requires frequent decanting and bath dumping, leading to relatively high operating costs compared with alkaline cleaners.

In contrast, alkaline cleaners are often more economical than acid chemistries because they do not cause excessive maintenance problems.

- ***Economic effects of fillers***—There are several ways to tell if a powder or liquid detergent is provided at an optimal concentration or instead contains excess fillers.

– *What are the ingredients?*

  - Powders: When selecting a powdered brand, look at the label, technical bulletins, and safety data sheet (SDS) to see if it contains any sodium chloride or sodium sulfate compounds, which do not perform a useful cleaning function but merely add to volume and weight (and thus shipping costs).
  - Liquids: With liquid detergents, the most common filler is water. While water is an integral component, a detergent should contain no more water than necessary to ensure a good solution, maintain stability, and prolong shelf life.

– *What is the working concentration?*

  - Powders: Most detergents require ≤1%–2% solution of detergent to water for acceptable detergency. For long bath life, in some cases higher concentrations up to 3%–4% are acceptable.

- Liquids: Typically, alkaline cleaners require a dilution of ≤1%. Semi-aqueous or solvent-containing cleaners may require a dilution of ≥2%. For long bath life, higher concentrations may be acceptable.

See the detergent selection guide in Table 4.1 (see table on next page and the full guide in Appendix V) to help you determine what kind of detergent is appropriate for your particular cleaning need in selected industries.

Health and Safety

Human health and safety considerations include detergent toxicity, corrosivity, reactivity, and flammability. These considerations can be evaluated by reviewing the solvent, chemical, or detergent's SDS. The detergent(s) you choose for your application preferably should:

- Be formulated to minimize health safety concerns while still offering outstanding cleaning performance.
- Not have an excessive Global Harmonization System (GHS) hazard classification. Note many detergents are eye irritants, which necessitates being classified as corrosive per GHS guidelines. Further, it is not unusual for a concentrated detergent to be classified as an irritant or corrosive. When diluted for use, detergents often are only irritants. Ideally, avoid systemically hazardous substances (e.g., mutagens, carcinogens, reproductive toxins), acute toxins, and poisons.
- Not have flash points or stability hazards.

Many detergents strong enough to remove fingerprints can also remove oils from skin and thus have the potential to dry out skin. This is especially true of detergents designed for machine spray washing—to perform adequate cleaning in the limited contact time during spray cleaning and to overcome the reduced emulsifying capability of lower-

Table 4.1 Detergent type guide – selected industries

Application	Surface or Soil Cleaned	How Do You Clean?	Recommended Detergent Type
Healthcare/ Veterinary	Surgical, anesthetic, and examining instruments and equipment; catheters and tubes	Manual, ultrasonic, soak	Mild alkaline
		Machine washer, sani-sterilizer	Low-foam alkaline
	Blood, body fluids, tissue on instruments	Manual, ultrasonic, soak	Enzyme active
Pharmaceutical/ Medical device/ Biotechnology	Titanium dioxide, petrolatum, oils, emulsions, ointments, carbopols, lacquers, zinc oxides, proteins, steroids, alcohols, sugars, Eudragit polymers	Manual, ultrasonic, soak	Mild alkaline
		Machine washer, power wash, CIP	Low-foam alkaline
	Inorganic residues, salts, metallics, pigments, Eudragit polymers, amphoterics, coatings, amines, ethers, starches, alkaloids	Manual, ultrasonic, soak	Liquid acid
		Machine washer, power wash, CIP	Low-foaming acid
	Protein/ferment residues, reverse osmosis and ultrafiltration membranes	Manual, untrasonic, soak	Enzyme active
Precision Manufacturing	Glass, ceramic, porcelain, stainless steel, plastic, rubber; oils, chemicals, particulates	Manual, ultrasonic, soak	Mild alkaline
		Machine washer, power wash	Low-foam alkaline
	Aluminum, brass, copper, other soft metal parts; oils, chemicals, particulates (acid for oxides, salts, buffing compounds)	Manual, ultrasonic, soak	Low-foam alkaline
		Parts washer, power	Alkaline or acid
	Inorganics, metallic complexes, trace metals and oxides, scale, salts, metal brightening	Manual, ultrasonic, soak	Mild alkaline or mild acid
		Parts washer, power wash	Alkaline or acid low-foam
	Silicone oils, mold-release agents, buffing compounds	Manual, ultrasonic, soak	Mild alkaline
		Parts washer, power	Low-foam mild acid
	Delicate substrates/ neutral for waste	Manual, ultrasonic, soak, machine wash, pressure spray	Neutral pH

See full detergent selection guide in Appendix V

foaming surfactants, these machine-designed detergents are considered aggressive cleaners. Protective neoprene, butyl, nitrile, rubber, or vinyl gloves are recommended for any extensive manual cleaning operation. In addition, many detergents are potential eye irritants and should not be used without eye protection. See Chapter Eleven, Environmental Health and Safety Considerations, for further discussion.

Environmental

Environmental considerations include concerns about pollution of air, land, and water as well as generation of waste that requires special storage and disposal practices. Ideally, any detergent chosen should be biodegradable, readily disposable, and contain no U.S. Resource Conservation and Recovery Act Hazard Classification or EPA Toxic and Priority Pollutants.

The environmental impact of cleaning operations can often be reduced by selecting the most appropriate aqueous cleaning agent, cleaning device, and/or recycling system. Understanding of local and municipal regulations is therefore a must. For example, where residue is considered hazardous, used detergent solutions must be treated or otherwise contained. If rinse water or rinsing capabilities are limited, recirculation can be considered.

Public awareness and social responsibility make careful consideration of the environmental impact of any choice of cleaner an important moral imperative. Aqueous cleaners have the advantage of being water-based and are often milder cleaning solutions than alternative cleaners, such as solvents and commodity chemicals. Therefore, aqueous cleaning is well-positioned to offer solutions that do not sacrifice cleaning quality for environmental safety. Although aqueous cleaning has long provided such benefits, today even newer industries continue to gravitate to aqueous cleaning because it offers

highly effective yet environmentally sound cleaning. Industries such as the cannabis and cosmetic industries, which have increasingly high-scrutiny requirements for cleanliness, gravitate to aqueous cleaning.

Beyond simply moral imperative, however, a comprehensive consideration of the total cost of environmentally negative practices can lead to a realization that the most environmental choice can also be the best choice from an economic standpoint. The best solutions are often found when sustainable, environmental practices and choices of cleaning agents and cleaning techniques are integrated into normal practices. When this is done, they become simply best practices without having to be specially labeled as environmental practices.

Environmental safety is an important and extremely complex issue and is also discussed further in Chapter Eleven.

References

Alconox Inc., "Aqueous cleaning chemistries," Precision Cleaning, p. 22 (December 1996).

B. Kanegsberg and E. Kanegsburg, Handbook for Critical Cleaning: Cleaning Agents and Systems, Second Edition; CRC Press, Boca Raton, FL (2011).

M. McLaughlin, "Selecting an aqueous cleaner," Precision Cleaning '97 Proceedings (1997).

Resources

alconox.com
epa.gov
technotes.alconox.com

Chapter Five:

Testing and Selecting a Detergent Cleaning System

Testing and selecting an aqueous cleaning system involves a seven-step process:

1. Identify the key goals of the system.
2. Select an evaluation method to determine whether key goals or cleaning criteria are satisfied.
3. Select a test cleaning system that includes a cleaning method, rinse method, and drying method.
4. Select a test substrate for cleaning.
5. Select a test soil and method for applying the test soil to the test substrate.
6. Select an aqueous cleaner for evaluation.
7. Once the test system yields the initial desired results, perform additional testing to optimize the system.

Each step is discussed in detail below.

Identify the Key Goals of the System

Table 5.1 outlines some key reasons for setting up new cleaning systems and key considerations for each.

Table 5.1 Reasons for new cleaning systems and corresponding considerations

Reasons or Goals	Key Considerations
Waste treatment concerns	Estimate quantity and characteristics of discharge, reporting status, hazards, permits needed
Air pollution concerns	Estimate quantity and characteristics of volatile solvents, current and expected regulatory status
Worker safety	Review equipment design and chemical characteristics, flammability, corrosivity, toxicity, need for protective devices, ventilation, thresholds (TLVs), worker training needed
Improved detergency	Review equipment design, rinsing and drying procedures, and cleaner chemical characteristics to see that they fit the type of soil and substrate being cleaned
Improved cleaning speed	Review temperature, agitation, chemistry, and drying conditions
Lower cost	Review recurring costs of chemistry, waste treatment, disposal, safety, regulatory compliance, maintenance, cleaning time labor, utilities, and capital costs
New process	Prioritize and evaluate all of the above and consider retaining use of existing equipment

Organizational considerations—Once you have identified the substrate or surface and contaminants to be cleaned as well as the reasons for a new process, consider organizational implications of the new cleaning system. In short, who and what will be affected by the new system?

When considering a new cleaning process, it is important to present the benefits and concerns to each potentially affected group,

including production personnel, supervisors, engineers, and members of environmental compliance, purchasing, marketing, public relations, and quality control departments. Forming a team of influential representatives from each group will facilitate implementation of the new process and enhance the likelihood of its ultimate success.

Information sources—To help identify options and determine which systems will work best for you, you may wish to consult some of the resources in Table 5.2. These will help narrow the search for optimal cleaning systems and chemistries. Look for information that addresses your particular reasons for cleaning and corresponding key considerations.

Table 5.2 Resources for identifying an appropriate cleaning system

Online	
Alconox detergent selection and use procedures	alconox.com
Toxic Use Reduction Institute	turi.org
U.S. EPA	epa.gov
TURI Cleaner Solutions	cleanersolutions.org
Environment Canada	ec.gc.ca
Publications	
Alconox Guide to Critical Cleaning	Alconox Inc. 30 Glenn Street White Plains, NY 10603 alconox.com
Technical Information Reports *TIR 12, TIR 30*	Association for the Advancement of Medical Instrumentation 1110 North Glebe Road, Suite 220 Arlington, VA 22201 aami.org
NSF White Book *Non-food Compounds*	NSF International 789 North Dixboro Road Ann Arbor, MI 48113 nsf.org

Select an Evaluation Method

Once the key reasons for implementing a new cleaning system are identified, you will need to determine methods for evaluating success of the system. Review available literature on the cleaner for health, safety, and environmental concerns.

Cleaning performance must also be evaluated through test cleaning. First, determine a baseline level of cleanliness and a way of measuring that baseline. (See Chapter Ten for methods to measure cleanliness). Initially, visual inspection is often sufficient. Visual inspection can be enhanced by using a flash camera at a low angle to the surface to enhance visibility of residues. The flash reflects unwanted residues that protrude above the flat surface, such as remaining products, particulates, and films.

A relatively simple gravimetric analysis involves weighing a clean substrate before soiling, after soiling, and after cleaning to determine percent soil removal. It is an effective measure of cleaning performance assuming the substrate is impervious to the cleaner.

Other reflective analytical techniques require special equipment. Examples include optically stimulated electron emission (OSEE) as well as grazing angle Fourier transform infrared spectroscopy (FTIR).

Measurement of contact-angle of deionized water on a flat surface is another method to determine cleanliness. In addition, there are various methods that involve extracting soils from a surface and then analyzing the extracts.

As a rule of thumb, use the simplest method that will provide suitably sensitive results.

Select a Test Cleaning System

In an ideal situation, testing a cleaning system is done full-scale using actual dirty surfaces. In practice, this is often impossible. Accordingly, a small, bench-scale system that mimics the full-scale system must often be created.

In mimicking the actual cleaning conditions for the cleaning process, a rinsing and drying method must be considered. In evaluating a cleaner, it is particularly important to mimic the time, temperature, and agitation that will be available in the scaled-up cleaning process. Table 5.3 outlines some mistakes when evaluating a cleaner using a benchtop cleaning system.

Table 5.3 Mistakes to avoid in evaluating a cleaner when developing a cleaning system

Mistake	Result	Correction
Use immersion in small tanks or beakers to test cleaners that will be used in spray cleaning environment	A high-emulsifying gentler cleaner will work best but will fail in the spray agitation system	Use a Waterpik® device or recirculated pump pouring on coupon, circulated, or spray system-poured cleaning solutions to mimic spray cleaning
Use a higher temperature than will be available in scale-up	A milder cleaner will give adequate cleaning that fails at lower temperature	Match temperatures
Clean for a longer time than will be practical when you scale-up	A milder cleaner will give adequate cleaning that fails in shorter time	Only use available cleaning times
Use flat substrates when small crevices and blind holes will be present in scale-up	A system with inadequate agitation will work on flat scale-up surfaces yet fail on crevices	Use a substrate to mimic the scale-up surface—perhaps take flat plates pressed together
Use a soil that does not represent the real soil	The wrong cleaner may be chosen	Try to use similar soils for testing
Use shorter or longer time between soil application and washing procedure than process scale will use	Inefficient, ineffective, or inaccurate concentrations of detergents, or detergents themselves, may be chosen	Keep the times between soil application and washing on the bench scale as close to intended worst-case full-scale times as feasible

When evaluating a cleaner, it is tempting to put the cleaner in a tank or beaker and add dirty parts to determine whether soaking alone will achieve a modest amount of cleaning (sometimes people also add heat and agitation to enhance cleaning). This is an acceptable bench test only when developing an immersion-cleaning system. Problems often occur with this approach when the ultimate intent is to use a spray washer or mechanical washer in the scaled-up process. The cleaning mechanisms involved in immersion cleaning can be very different from those involved in spray cleaning. A system that cleans by soaking in a beaker may not work in a spray washing machine.

Effective immersion cleaners rely on kinetically slower mechanisms such as emulsifying, enzymatic hydrolyzing, and dissolving. In contrast, cleaners effective in high-agitation spraying systems rely on faster cleaning mechanisms such as acid or alkaline hydrolysis, wetting, penetrating, and dispersing. Spray cleaners must be more aggressive and faster-acting since they have only a fraction of a second to clean before the next droplet of spray sweeps them from the surface. Immersion cleaners may have minutes or hours of contact time.

A cleaner that performs only marginally in an immersion cleaning environment may perform extremely well in a spray-washer. The reverse also may be true.

In particular, high-foaming cleaners that work very well in immersion do not perform well in enclosed spray cabinet washers. There, the foam can create a barrier to the mechanical energy of the spray. In addition, the foam, in an over-foam event, may burst the seals of the cabinet. The foam also may cause problematic cavitation in the circulating pumps.

There is a subtle difference among spray cleaning systems. There are two main types of spray agitation: a high-volume/low-pressure (laminar flow) method, and a low-volume/high-pressure (turbulent

flow) method. The laminar flow method involves spraying a high volume of cleaning solution over the surface of a substrate, resulting in a flood of solution sheeting or running down the surface to be cleaned. This results in near laminar flow at the surface, with a smaller boundary layer that gets some agitation closer to the surface to improve very small particle and thin film cleaning in the 0.1–5.0-micron range of size or thickness. Larger particles and thicker films are better cleaned by turbulent flow.

In low-flow/high-pressure turbulent spray washing, the cleaning solution bounces off surfaces with less cascading and sheeting action. Low-foaming cleaners are required. These systems do better with heavy soil and large particle removal.

In an effort to shorten cleaning cycles, a successful laminar flow cleaning system may improperly be changed to a turbulent flow one, causing problems with small particles or thin film removal. The system will appear to suddenly stop cleaning well. A more effective path to shorter cleaning cycles can be better achieved by raising the temperature. Equally, sometimes a successful turbulent flow system starts to fail when cleaning requirements change towards smaller particles and thinner films. Switching to a laminar flow system by lowering pressure and increasing volume with larger nozzles may help.

Again, when performing bench-scale testing for spray cleaning systems it is important to mimic the characteristics of the actual cleaning system. For instance, drench a surface by pouring or gently pumping cleaning solution over a surface to mimic high-volume/low-pressure cleaning. Use a pump and nozzle or Waterpik® device to imitate pressure and impingement of a surface that occurs in low-volume/high-pressure cleaning.

Although ultrasonic cleaning can result in very high localized agitation from cavitation caused by sound waves, the agitation occurs under immersion. Therefore, immersion cleaning mechanisms are

still effective. Even spray under immersion—achieved where the spray nozzle is submerged—can allow for some kinetically slower immersion cleaning mechanisms to work. As spray velocity and solution movement speed is increased, immersion cleaning mechanisms play a smaller role.

Table 5.4 lists bench-scale cleaning methods and identifies their corresponding full-scale methods.

Table 5.4 Typical bench-scale cleaning systems and the scale-up systems they mimic

Cleaning Methods	
Bench-Scale	***Scale-Up***
Manual cleaning with tool	Manual cleaning with tool
Immersion in a small tank	Immersion in a big tank
Small tank with stirrer	Mechanically cleaned large-scale process or a clean-in-place (CIP), agitated large tank
Small ultrasonic tank (be sure to use same frequencies and power densities)	Larger ultrasonic tank
Gently hosing or pouring	High-volume/low-pressure washer onto a surface
Power spray onto surface	Low-volume/high-pressure washer or CIP

Select rinsing and drying conditions

In any bench-scale cleaning system, it is also critical to understand how the rinsing and drying processes can affect cleaning results. In bench-scale cleaning, it may be practical to use copious quantities of running water for rinsing. Often, simply putting cleaned parts under running water at a sink will be both an acceptable and highly effective rinsing technique. The same level of rinsing, however, must be duplicated in scale-up.

The cleaner loosens soils and prepares them to be rinsed away. A running water rinse is far more effective than a static dip-tank rinse or even a slow counterflow cascade tank rinse. Rinsing relies on essentially two types of mechanisms:

- **Mass displacement**, where the rinse water physically replaces the soil/solution mixture.
- **Concentration gradient dissolving**, where the high-concentration soil/solution mixture at the surface being cleaned dissolves into the rinse water, creating a uniform low-concentration mixture in the rinse water, with a resulting lower concentration of soil present near the rinse solution/surface interface.

In a running water rinse system, mass displacement is the dominant rinse mechanism. In a static soak-tank rinse, concentration gradient dissolving is the dominant mechanism. When testing bench-scale rinsing, mimic the rinsing that will be used in scale-up. For example, a running water rinse may be effective at bench-scale and might allow a less free-rinsing cleaner to perform adequately; however, it may be ineffective or cause failure in scale-up due to detergent residues from the poorly free-rinsing detergents.

It is also desirable to use the same quality of rinse water that will be used in scale-up. If lab-grade deionized water is used for bench-scale rinsing, for example, the same type of water should be available for scale-up. Conversely, it is possible to use tap water rinses in bench-scale testing. Water spots can be avoided by using water removing—as opposed to water evaporating—drying methods. Tap water rinses are often sufficient to show in bench scale that a cleaning system can remove a particular soil from a surface.

For bench-scale testing, first choose a cleaning system, and then test the system with a given cleaner. Table 5.5 identifies typical rinsing and drying methods used in bench-scale and full-scale cleaning systems.

Table 5.5 Bench-scale rinsing and drying methods and corresponding scale-up methods

Rinsing Methods	
Bench-Scale	***Scale-Up***
Static soak	Static soak
Overflowing dip tank	Counterflow cascade tanks
Running water	Running water or efficient counterflow cascade tank series
Drying Methods	
Bench-Scale	***Scale-Up***
Air dry	Air dry
Oven dry	Hot air dry
Hair dryer	Hot directed forced air
Compressed air nozzle	Air knife
Volatile solvent rinse	Volatile solvent rinse

Select a Test Substrate

Once a cleaning method is selected for testing, the next step in developing a cleaning system is to select a substrate and a soil to clean. Ideally, actual parts or surfaces with actual soils that will be cleaned should be used. Sometimes this is not possible, in which case similar materials should be used.

Also, small stainless steel coupons or glass slides are often used for bench-scale cleaning development. For many soils it is not critical what the substrate is, and for many cleaning mechanisms "a surface is a surface," whether that is glass or metal.

When cleaning plastics, however, surface considerations are more critical because some plastics have particular affinity for organic soils. Also, when removing salts or inorganic soils from metals it is often important to use the exact metal that will be cleaned when a process is scaled-up. The same is true for porous surfaces, such as gold and some ceramics, which may require use of the same substrate for bench-scale testing in order to develop a reliable cleaning system.

Similarly, it may be important to use the same surface for testing to ensure that the cleaning system will not corrode or damage the surface. This is especially true for aluminum, other reactive metals, and stressed or otherwise sensitive plastics.

It can be very useful to work with standard clean coupons. There are several suppliers of standard coupons that are more commonly used with corrosion testing but that can be adapted for use in cleaning testing.

Select a Test Soil and Method

It is often more important to consider the soil than the surface when developing a cleaning system, using the same soil in bench-top testing as in scale-up. Pay careful attention to how dried-on the soil will be in the actual process. A freshly applied soil may be very easy to remove in bench-scale processes but may become very difficult to remove if it dries on the surface for several hours. When possible, avoid allowing soils to dry onto a surface in the actual cleaning setting; see Chapter Three: Aqueous Cleaning Processes, for discussion of "Before Cleaning."

If it is not possible to use the same soils that will be present during actual cleaning, try to match characteristics of the soil. Match the particulate sizes, oil viscosities, wax melting points, and/or chemical character (for example, do not use a natural oil to mimic a synthetic or petrochemical oil, and vice versa). Try to apply the soil to the surfaces

in the same manner and quantity that will be present under actual cleaning conditions. (Soiling the substrate on the heavy side can be helpful to design a robust cleaning system.)

In addition, it may be critical to develop a way to uniformly soil a surface to get significant reproducible results that are suitable for comparing cleaning systems. One approach is to create a uniform slurry, paste, or solution of the soil, possibly using a volatile solvent carrier. Then, using a glass rod with spacers, spread a uniform film of soil onto a coupon to achieve uniform reproducible soil levels. If the objective is to find a way to absolutely clean a soil—rather than compare cleaning systems—simply smearing or applying some soil to the surface for visual inspection that the soil is present can suffice.

Select an Aqueous Cleaner

Review the information in Chapter Four: Detergent Selection to ensure you are testing cleaners that have the highest chances of success by matching the cleaner to the desired cleaning method, soil, and surface being cleaned.

Perform Test Cleanings

After establishing all test criteria described above, experiment with different approaches to cleaning, rinsing, drying, temperatures, and detergent concentrations. It is advisable to perform at least three cleanings using each set of conditions to help minimize anomalous results. For critical cleaning system development, it is desirable to perform at least six repetitions of each set of conditions.

Whether selecting an aqueous cleaner and cleaning system for a new manufacturing or processing application or switching to an aqueous cleaner, the process is the same. It is a good idea to start by

using an "overkill" combination of time, temperature, concentration, and agitation than might typically be required in a bench-test scenario to first prove that the system is capable of delivering the cleanliness required.

Finding the minimums—Once you prove that a system can work, the next step is to try an estimated combination of a slightly less than minimum time, temperature, concentration, and agitation, to get an idea of where the system starts to fail. A good less-than-minimum starting point might be 25% of a conservative recommendation from the cleaner's manufacturer. For example, if a cleaner is recommended for use at 2% in water, 60°C (140°F) with a 10-minute soak, you might try the cleaner at 0.5%, 40°C (105°F), and a two-minute soak to see how badly it fails. This provides a sense of the robustness of the cleaning process. You can then choose some combination of time, temperature, and concentration above the minimum based on how poorly the system failed.

Based on these results, try a combination of parameters based on an estimate of what might be slightly above the minimum requirements. You can then optimize the parameters by successive iterations of cleaning performance testing by going halfway between the last combination of variables that worked and the last combination that failed, until you are satisfied that the system is sufficiently optimized for the specific cleaning and cost efficiency needs.

You can also hold one or more variables constant while optimizing the others. For example, if you need to clean a batch of parts in two minutes, then vary the temperature and concentration within the two-minute time constraint.

Once you have determined an "overkill" system that works and a "minimal" system that fails, at least in part, an optimum system can be identified (Table 5.6). Decide when to stop bench-scale optimizing and when to move on to pilot-scale or full-scale use of the cleaning system. Additional optimization can follow during the pilot and larger scale evaluations.

Table 5.6 Common strategies to optimize cleaner testing

Typical Cleaner Test Conditions
Overkill
Double the recommended dilution of detergent
Maximum practical temperature
Maximum practical cleaning time
Minimum
25% of the recommended detergent dilution
Room temperature
Very short cleaning time
Optimized
Recommended dilution
50°C (120°F) for immersion or manual cleaning methods, 60°C (140°F) for spray clean systems

References

D.A. Leblanc, "Design of manual and automated cleaning processes," Cleaning Validation Technologies (21 November 2019).

K. Thomas, J. LaPlante, A. Buckley, Guidebook of Part Cleaning Alternatives; Toxics Use Reduction Institute, University of Massachusetts Lowell, Office of Technical Assistance, Executive Office of Environmental Affairs, Commonwealth of Massachusetts (March 1997).

Resources

alconox.com
cleanersolutions.org
cleaningvalidation.com
ispe.org/tags/clean-in-place-systems
sanimatic.com/cip-system-design
technotes.alconox.com

Chapter Six:

Industrial Cleaning Applications

Pharmaceutical

Pharmaceutical equipment includes everything from bench-scale laboratory apparatus used for trials to full-scale bulk manufacturing equipment. Regardless of scale or complexity, all pharmaceutical equipment must meet government standards for cleanliness. These standards are part of what is commonly referred to as Good Manufacturing Practice (GMP) or current Good Manufacturing Practice (cGMP). One may also be required to conform to Quality Systems (QS). There are additional regulations established by agencies including the U.S. Food and Drug Administration (FDA), European Union, International Conference on Harmonization (ICH), and others that frequently must be followed within the pharmaceutical industry. For a discussion of cleaning validation requirements, see Chapter Eight. For examples of standard operating procedures (SOPs) used in pharmaceutical process equipment cleaning, see Chapter Seven.

Residues found in pharmaceutical cleaning range from easy-to-clean water-soluble excipients to difficult-to-clean petrolatum/metal oxide mixtures. To simplify regulatory compliance and reduce the probability of using the wrong detergent, it is desirable to use as few cleaners as possible to remove the entire range of residues encountered.

It also is desirable for these cleaners to work in a wide range of cleaning procedures, including manual, soak, and ultrasonic cleaning, as well as clean-in-place (CIP) spray systems.

Typically, surfaces to be cleaned are constructed of glass, 316L stainless steel, polytetrafluoroethylene (PTFE), polypropylene, and silicone elastomers used in seals and gaskets. In some cases, pharmaceutical manufacturers will use disposable seals, gaskets, and filters to avoid having to validate their cleaning.

There are few, if any, more demanding or important applications for critical cleaning than pharmaceutical manufacturing—at a minimum, cross-contamination can be costly in terms of lost product; more significantly, cross-contamination can pose a significant risk to human and animal health. Further, the need to reduce manufacturing time to increase throughput only accentuates the need for well-chosen precision detergents for critical cleaning.

Aqueous cleaners provide the kind of critical cleaning required to process pharmaceutical products (Table 6.1). Examples include:

- **Capsules and tablets**—Some pharmaceutical ingredients resist going into solution, making tablet presses and dies difficult to clean. Yet even stubborn, sustained-release product residues come clean quickly with appropriate aqueous cleaners.
- **Creams and ointments**—Properly formulated aqueous cleaners also eliminate intensive scrubbing and human contact when cleaning large stainless steel tanks used to manufacture liquid suspensions.
- **Intermediates**—Aqueous cleaners are ideal for cleaning glass-lined chemical reactors used to process pharmaceutical intermediates such as powders, fillers, binding agents, and other chemicals.

Table 6.1 Detergent selection guide for pharmaceutical cleaning

Application Key	Articles Cleaned/ Soil Removed	Cleaning Method	Recommended Detergent	Alconox Inc. Detergent
Pharmaceutical Passing cleaning validation for FDA good manufacturing practices, European Union regulations, and similar requirements; key substrates include stainless steel, elastomers, glassware, and other pharma substrates	Titanium dioxide, petrolatum, oils, emulsions, ointments, carbopols, lacquers, zinc oxides, steroids, alcohols, sugars, and Eudragit* (L/S/L30/D55/NE30D/ FS30D) polymers	Manual, ultrasonic, soak	Mild alkaline Mild alkaline	Alconox Liquinox
		Machine washer, power washer, clean-in-place (CIP)	Low-foam alkaline Low-foam alkaline Low-foam alkaline	Alcojet Tergajet Solujet
	Inorganic residues, salts, metallics, pigments, Eudragit* (E/RL/RS/E100) polymers, amphoterics, coatings, amines, ethers, starches, alkaloids	Manual, ultrasonic, soak	Mild acid	Citranox
		Machine washer, power washer, CIP	Low-foam mild acid	Citrajet

*Eudragit is a registered trademark of Evonik Röhm GmbH LLC.

In R&D, aqueous cleaners have long been used to clean metal, glass, and polymer components for benchtop labware as well as difficult-to-clean pilot processing equipment such as chemical reactors and fermentation systems for pharmaceutical intermediates and small-molecule vaccines.

Controlling Pyrogens

A key consideration in pharmaceutical process equipment cleaning for parenteral/injectable product manufacture is controlling pyrogens. Pyrogens are endotoxins or cellular debris that can cause fevers after internal exposure. Companies that have intrathecal injectable manufacturing may need to have pyrogen/endotoxin levels of less than 0.25 endotoxin units (EU)/mL. Therefore, eliminating endotoxins from manufacturing is advisable.

Pyrogens are often controlled using heat. Alternatively, mild alkaline powdered and liquid detergent cleaners (e.g., Alconox Inc. products Alconox and Liquinox) can be used to depyrogenate heat-sensitive surfaces as well as non-heat-sensitive surfaces. Many laboratories that do limulus amebocyte lysate (LAL) testing for pyrogens use Liquinox detergent to clean their glassware and testing equipment. Standard cleaning of injectables with a 1% solution of Liquinox at 50°C (122°F) using manual, soak, or ultrasonic agitation should be followed by a thorough rinse with pyrogen-free water, also known as water for injection (WFI). Post-cleaning handling in a pyrogen-controlled environment/cleanroom or packaging will provide adequate pyrogen control. Stoppers for injectables can be cleaned using Alconox powdered or Liquinox detergent solutions.

An article by Hallie Forcinio published in Pharmaceutical Technology ("Pyrogen Control," March 2001, p. 38) references controlling pyrogens with the following:

> Pyrogens on packaging materials can be controlled by heating alone or in combination with alkali or strong oxidizing solutions or by washing with detergent (1)...Pharmaceutical makers can render plastic containers pyrogen-free by washing the containers with an alkaline (i.e., pH 9–10) cleaning agent on a machine integrated with the filling line. When washing is the pyrogen-removal method of choice, any cleaning agent residue must be adequately removed...The favored method of removing pyrogens from stoppers is washing... many stopper makers now offer pre-washed stoppers, which are treated to reduce endotoxin levels by 3 logs.

Biotechnology

Biotechnology is inherently a cross-disciplinary field, including aspects of medical, healthcare, environmental, agricultural, industrial, and biochemical manufacturing. It describes manufacturing and production derived from living organisms. These "large"-molecule drug and other produced substances may consist of amino acids, antibodies, nucleic acids, peptides, proteins, tissues, blood, vaccine conjugates, and other similar compounds. When discussing specific manufacturing of drugs, biotechnology may be used interchangeably with biopharmaceuticals or biopharma. Subfields of biotechnology include gene and cell therapy, using genes (nucleic acids) and whole cells, respectively, for therapeutic purposes.

Cleaning requirements in the biotechnology industry are similar to those in the pharmaceutical industry. Residues resulting from production of biopharmaceuticals and gene/cell therapy products are often complex mixtures produced during fermentation, cell culture, cell lysis, and cell harvesting. The detergents used must be capable of removing interfering residues that inhibit culture and fermentation growth or cause unacceptable batch-to-batch contamination. Biotechnology residues that are organic in nature are traditionally well-handled by aqueous detergents consisting of high-emulsifying surfactants and/or alkaline hydrolysis cleaning mechanisms. For removal of proteinaceous residues, enzymatic, alkaline hydrolysis, and/or oxidative cleaning mechanisms are highly effective.

Substrates and surfaces in biotechnology also are similar to the pharmaceutical industry. Substrates are typically highly compatible across a wide range of aqueous detergents. These substrates include 316L stainless steel, borosilicate glass, elastomers (including ethylene propylene diene monomer, fluoroelastomer, and polytetrafluoroethylene), and polymeric substrates (including polypropylene, nylon, polyvinylidene fluoride, and polyethersulfone).

As in cleaning of pharmaceutical process equipment, disposable single-use items may be used for piping, seals, and filters. When pharmaceuticals are manufactured, even at R&D pilot scale for trials, GMP procedures must be followed. The GMP washers described in the preceding section are often used for biopharmaceutical cleaning. See Chapter Six: Industrial Cleaning Applications ("GMP Washer Cleaning" section), Chapter Eight: Cleaning Validation, and Chapter Seven: Standard Operating Procedures, particularly the example on cleaning fermentation equipment. The Chapter Two section on "Applications of Isoelectric Points to Cleaning" and Chapter Six section on "Clean-In-Place (CIP) Cleaning" also provide insight on the mechanisms of biotechnology critical cleaning.

See Table 6.2 for a brief detergent selection guide for biotechnology cleaning applications.

Table 6.2 Detergent selection guide for biotechnology cleaning

Application Key Concerns	Articles Cleaned/ Soil Removed	Cleaning Method	Recommended Detergent	Alconox Inc. Detergent
Biotech/Biopharma Passing cleaning validation for FDA good manufacturing practices, European Union regulations, and similar requirements; key substrates include stainless steel, elastomers, glassware, polymeric filter membranes, and other biopharma substrates	Protein, organic, cellular, and fermentation residues; reverse osmosis, ultrafiltration membranes	Manual, ultrasonic, soak	Mild alkaline Mild alkaline Enzymatic mild alkaline Low-foam alkaline	Alconox Liquinox Tergazyme Detojet
	Inorganic residues, salts, buffering solutions	Machine washer, power washer, clean-in-place (CIP)	Low-foam alkaline Low-foam alkaline Low-foam alkaline	Alcojet Detojet Solujet
		Manual, ultrasonic, soak	Mild acid	Citranox
		Machine washer, power washer, CIP	Low-foam mild acid Low-foam alkaline	Citrajet Solujet

Medical Device Manufacturing

Cleaning during the manufacturing process prepares medical devices for sterilization and sterile packaging. When selecting a detergent, consider the material composition of the device. Usually medical devices are made of robust materials that can withstand corrosive blood and body fluids. In some instances, a portion of the device is intended to come into contact with skin, blood, or body fluids; other parts of the device may remain exterior to the body and be made of less sturdy plastics or aluminum. If less sturdy materials are present, then a milder detergent may be needed.

Medical devices are usually assembled under clean conditions. As a result, a light-duty yet effective cleaner is usually needed to remove small amounts of light soils. See Table 6.3 for a brief detergent selection guide for medical device cleaning.

Table 6.3 Detergent selection guide for medical device cleaning

Application Key Concerns	Articles Cleaned/ Soil Removed	Cleaning Method	Recommended Detergent	Alconox Inc. Detergent
Medical Devices Passing cleaning validation for FDA good manufacturing practices, European Union regulations, and similar requirements; key substrates include stainless steel, aluminum, and polymers	Cutting and machining oils, lubricants, mold release, environmental residues	Manual, ultrasonic, soak	Mild alkaline Mild alkaline Mild alkaline	Alconox Liquinox Detonox
		Machine washer, power washer, clean-in-place (CIP)	Low-foam alkaline Low-foam alkaline Low-foam alkaline	Alcojet Tergajet Solujet
	Inorganic residues, salts, metallics, oxidation	Manual, ultrasonic, soak	Mild acid	Citranox
		Machine washer, power washer, CIP	Low-foam mild acid Low-foam alkaline	Citranox Solujet
	Reprocessing: protein, organic, biologic films, and related residues	Manual, ultrasonic, soak	Enzymatic mild alkaline Low-foam alkaline	Tergazyme Detojet
		Machine washer, power washer, CIP	Low-foam alkaline	Alcojet

Good designers avoid creating medical devices with small crevices, cracks, or areas that are difficult to clean or reach. Nonetheless, part orientation is important during cleaning, emphasizing the importance of fixtures that properly orient products for optimal cleaning. Due to their relatively small size, most medical device parts usually fit nicely into ultrasonic tanks where part orientation may be controlled. The effectiveness of a good detergent and a thorough cleaning process has made ultrasonic cleaning the gold standard of cleaning in much of the medical device manufacturing industry. Cleaning operations in medical device manufacturing not only need to effectively remove soils or small particulates but also must use extremely free-rinsing detergents that are suitable for use in ultrasonic tanks or other mechanically aided cleaning processes.

For implantable medical devices, especially those that come into contact with cerebral spinal fluid, it is critical to remove endotoxins from the device surface. Endotoxins are fever-causing cell debris or cell waste products widely present in the environment. Cleaning endotoxins requires use of a high-emulsifying cleaner combined with heat, followed by a rinse with endotoxin-limited water (<0.25 EU/mL). This type of water is often called water for injection (WFI). WFI is highly pure and is derived from high-purity water filtration or distillation systems. For water that is certified endotoxin-free, one should use water that goes by names such as cell culture grade pyrogen/endotoxin-free, sterile endotoxin-free, or cell culture grade water.

The most common cleaning process in medical device manufacturing is to use heated ultrasonics with a high-quality detergent, followed by rinsing with suitably pure water. Given the typical types of residues found on most medical devices, a mild alkaline cleaner is often used first to remove oily residues, followed by

a brief rinse to prevent drag-out and then an acid cleaner to remove alkaline insoluble inorganic residues. This two-step cleaning is then followed by a thorough rinse.

Metal medical devices are often passivated using a passivation solution. Because citric acid has less safety issues than nitric acid or other inorganic acids, there has been a shift to using citric acid-based passivation in the medical device industry. The passivation process usually includes mild alkaline detergent cleaning, rinsing, passivation, and at least two final rinsing steps.

Medical device manufacturing must conform to standards set by appropriate governing bodies within the country where the devices are manufactured as well as where they are being sold. A few of these standards are:

- 21 CFR Part 820
- ISO 13485 (current year is 2016 at the time of this printing)
- 21 CFR Part 4 (for combination products)

Depending upon the breadth of manufacturing and upper management decisions, other standards also may be followed, such as ISO 9001. For a discussion of cleaning validation requirements, see Chapter Eight: Cleaning Validation; for examples of standard operating procedures (SOPs) used in cleaning, see Chapter Seven: Standard Operating Procedures.

Some medical devices are manufactured as single-use devices that do not have protocols for cleaning and re-use. However, there are contract companies that clean and repackage single-use devices for re-use. By doing this, these contract companies are effectively "re-manufacturing" the device, so they must validate their cleaning in accordance with good manufacturing practices. These medical device re-processors often adopt healthcare cleaning procedures due to the involved soils and residues. Refer to the Healthcare section

of this chapter for further details. The following provide further insight into critical cleaning in the medical device industry: Chapter Two: Chemistry of Aqueous Cleaning (section on "Applications of Isoelectric Points to Cleaning"); Chapter Six: Industrial Cleaning Applications (sections on "GMP Washer Cleaning" and "Clean-In-Place (CIP) Cleaning"); Chapter Seven: Standard Operating Procedures; and Chapter Eight: Cleaning Validation.

Laboratory Cleaning

Despite increased use of disposable plastics in the laboratory, reusable glassware and other reusable labware are still widely used due to environmental concerns (recycling issues and disposal problems associated with plastics) and because many laboratory procedures require inert surfaces such as glass. In addition, some instruments and equipment must be reused for scientific or economic reasons.

The principal concern for any scientist or technician is that laboratory glassware, instruments, and equipment must be free of interfering residues. These often-unseen residues or contamination can cause invalid analytical results and misleading reactions. For example, residues can erroneously accelerate or decelerate rate-dependent experiments by causing localized high concentrations of reactants inside micelles. Residues can inhibit culture growth, cross-contaminate batches, and cause nonreproducible results.

To address these problems, laboratory equipment must be cleaned thoroughly to remove any interfering residues. This requires both selection of an appropriate laboratory detergent as well as use of an effective cleaning method (Table 6.4, see next page).

Table 6.4 Detergent selection guide for laboratory cleaning

Application Key Concerns	Articles Cleaned/ Soil Removed	Cleaning Method	Recommended Detergent	Alconox Inc. Detergent
Laboratory Reproducible results, no interfering residues, extending equipment life; maintaining laboratory accreditation; laboratory safety	Glass, metal, plastic labware, ceramics, tissue culture, clean rooms, animal cages, bioreactors, tubing, benches, safety equipment	Manual, ultrasonic, soak	Mild alkaline Mild alkaline	Alconox Liquinox
		Machine, power spray, labware washers, washer-sterilizer, cage-washers	Low-foam alkaline Low-foam alkaline Low-foam alkaline Low-foam alkaline	Alcojet Tergajet Detojet Solujet
	Tubes, reusable pipets	Syphon-type washer-rinsers	Mild alkaline tablet	Alcotabs
	Microbiology, water lab, and environmental sampling; phosphate-sensitive labware	Field, manual, ultrasonic, soak	Low-foam alkaline Mild alkaline	Tergajet Liquinox
		Machine washer, labware washer	Low-foam alkaline Low-foam mild acid Low-foam alkaline	Tergajet Citrajet Solujet
	Radioactive equipment/ contaminant; stopcock grease	Manual, ultrasonic, soak	Mild alkalinew	Detonox Alconox
		Machine washer, labware washer	Low-foam alkaline High alkaline	Alcojet Keylajet
	Trace metals, metal oxides, scale, salts, starches, amines	Manual, ultrasonic, soak	Mild acid	Citranox
		Machine washer, labware washer	Low-foam mild acid	Citrajet
	Proteinaceous soils, bio-wastes, tissue, blood and other body fluids, fermentation residues	Manual, ultrasonic, soak	Enzymatic mild alkaline Low-foam alkaline	Tergazyme Detojet
		Glassware washer	Low-foam alkaline Low-foam alkaline Low-foam alkaline Low-foam alkaline	Alcojet Tergajet Detojet Solujet
	Glassware needing surfactant or metal-free cleaning for enzyme kinetics, tissue culture, pipet soaking, and trace inorganics	Soak	Oxidizing sulfuric acid additive	Alnochromix

The following are common laboratory cleaning procedures, along with guidelines for eliminating interfering residues.

1. Soaking is used to clean small items and the insides of larger vessels. Soaking also is recommended as a pretreatment to prevent soils or residues from drying onto labware. A soak tank should be kept at the laboratory bench for immersing used labware until it can be washed. Soaking also is effective for cleaning or pretreating dried-on residues. Select a detergent recommended for soaking and follow the manufacturer's directions to make up the soak solution. Completely submerge the article to prevent any deposits or etching at the air/solution interface. Soak until soils are removed, which may take several hours. There are special cases where you need to eliminate any metal residue for trace metal analysis or use a surfactant-free cleaner for enzymatic kinetics studies or tissue culture; in these cases, a chrome-free acid oxidizing solution for soaking is recommended. Additional agitation or wiping may be needed to remove difficult soils. Follow with a thorough rinse.
2. Manual cleaning, the most common method of laboratory cleaning, is used for small batches of labware, equipment, and benches. To clean manually, wet the article either by immersing it in the detergent solution or by using a soaked cloth or sponge. For nonabrasive scouring, un-diluted detergent should be poured onto a wet cloth or sponge for scrubbing. A cloth, sponge, brush, or pad can be used for cleaning. Follow with a thorough rinse. Protective gloves and eye protection should be worn if recommended or required.
3. Ultrasonic cleaning is used for larger or more frequently cleaned batches of labware. To clean in an ultrasonic tank, make up the solution in a separate container, fill the ultrasonic

tank, and run the machine for several minutes to degas the solution and allow the heater to reach the correct temperature. Small articles should be placed in racks or baskets; irregularly shaped articles should be aligned so that the long axis faces the ultrasonic transducer (usually the bottom). Run the machine for 2–10 minutes until parts are clean (on occasion, up to 20 minutes may be required). Follow with a thorough rinse.

4. Automatic syphon washing is an effective way to clean reusable pipets. Pipets should be completely submerged in a detergent soak solution as soon as possible after use to prevent soils from drying onto the pipets. When ready to clean, the pipets are placed in a holder, and an effervescent tablet cleaner is added to the automatic syphon washer. The holder is positioned over the tablet to prevent effervescent bubbles from floating the tablet to the surface during cleaning. Cold or warm water is added to fill the washer and completely cover all pipets while allowing them to drain thoroughly during the drain cycle. This may take as long as an hour. For analytical use, a final rinse in deionized or distilled water may be required.
5. Machine washing is used in laboratories that clean large quantities of reusable labware. Follow the machine manufacturer's directions for details on correct use. Generally, labware is loaded on racks with open ends facing the spray nozzles. Narrow-necked flasks are placed in the center of the racks, preferably on specially designed spindles with spray nozzles directed into the necks. All labware should be loaded to ensure complete draining of parts, with no configuration that retains dirty wash or rinse water from cycle to cycle. Minimize handling of labware in the racks. Group small articles in baskets to prevent dislodging by spray. Use only low-

foaming detergents specifically designed for these machines. Typically, 10 mL of detergent per liter of hot wash-cycle water [approximately 60°C (140°F)] is used.

6. Rinsing is often overlooked but is a critical part of laboratory cleaning. A thorough running water rinse that contacts all surfaces of an article for at least 10 seconds per surface may be required. Filling and emptying small vessels with rinse water at least three times is a good rinse procedure. For machine cleaning, there should be two to three rinse cycles after cleaning, with a final rinse of purified water for more analytical level cleaning. At minimum final rinses, and perhaps all rinses, in water of suitable purity are necessary to remove tap water residues from analytical labware. For tissue culture and general analytical ware, use a final rinse with deionized or distilled water. Rinse trace organic analytical ware in distilled or organic-free water; rinse trace inorganic analytical ware in deionized water. Pharmaceutical and clinical research labware may require rinsing with sterile, pyrogen-free, or injectable water, depending on the use. Trace analytical rinsing can require up to 12 rinses with purified water. Multiple small rinses are better than fewer large or long rinses. Running water rinses are best, but agitated or flowing rinses also can be quite effective. A single rinse as defined by filling and emptying a beaker or piece of glassware can reduce contaminants by as much as two orders of magnitude on a first rinse, with slightly declining orders of magnitude as more rinses are done.

Following these procedures diligently will help eliminate interfering residues from the surfaces of reusable labware, instruments, and equipment.

Cosmetics

Cosmetic manufacturing involves many oils, pigments, emollients, and "waterproof" ingredients. Because cosmetics are often designed to stick to skin—a surface that resists many substances—often the greatest cleaning challenges are encountered in cosmetics manufacturing. The most difficult-to-clean cosmetic residues are often titanium dioxide and/or zinc oxide cremes, lotions, and silicone oil emollients.

Aqueous cleaning detergents are ideally positioned to clean silicone oils, titanium dioxide, zinc oxide, and other hard-to-clean residues generated in cosmetics processing. Well-designed aqueous detergents use multiple mechanisms of action synergistically to effectively remove residuals from a surface. As with pharmaceutical processing, all residues that could contaminate products and cause skin, eye, or other mucous membrane irritation must be removed. The increasing number of health claims made by cosmetic companies about their products makes the need to remove unwanted residuals critical to the manufacturing process. It is for this reason that Alconox Inc. recommends, and many cosmetic manufacturers are striving towards, adherence to pharmaceutical cleaning validation guidelines and regulations.

Silicone emollients can be removed using very high temperatures in excess of 75°C (170°F) and 2%–5% strength solutions of a high-emulsifying cleaner in a total immersion cleaning system. The addition of mechanical energy often will speed up the critical cleaning process.

Removal through manual cleaning of titanium dioxide and zinc oxide cremes generally requires lower temperatures to avoid formation of titanates and zincates with stainless steel surfaces. Much like silicone and other polymerized oily residues, a high-emulsifying detergent and mechanical energy are effective.

When cleaning with spray balls in large manufacturing tanks and other high-pressure spray in air clean-in-place (CIP) systems, it may seem difficult to clean these residues. However, there are alkaline low-foaming detergents that contain highly effective, low-foam surfactants and either large amounts of chelating agents and/or excellent dispersants. Often higher temperatures must be considered when silicone is together with metal oxides. Higher alkaline chelating/dispersing detergents can overcome and remove metal oxide salt formation. Alternatively, the cleaning process itself may be designed to prevent formation of titanates and zincates by controlling temperature and increasing time.

In summary, cleaning difficult cosmetic compounds starts with understanding the cosmetic ingredients and how they interact with various detergents. With proper analysis, aqueous detergents can safely and effectively remove difficult cosmetic residues, all without the need for harsh, flammable, hazardous solvents.

Table 6.5 provides a brief selection guide for cosmetics cleaning. The following provide further insight into critical cleaning in the cosmetics industry: Chapter Two: Chemistry of Aqueous Cleaning (section on "Applications of Isoelectric Points to Cleaning"); Chapter Six: Industrial Cleaning Applications (sections on "GMP Washer Cleaning" and "Clean-In-Place (CIP) Cleaning"); Chapter Seven: Standard Operating Procedures; and Chapter Eight: Cleaning Validation.

Table 6.5 Detergent selection guide for cosmetics cleaning

Application Key Concerns	Articles Cleaned/ Soil Removed	Cleaning Method	Recommended Detergent	Alconox Inc. Detergent
Cosmetics Manufacturing Avoid cross-contamination; pass cleaning validation for FDA good manufacturing practices	Product contact surfaces (acids for pigments and salts); titanium dioxide, petrolatum, oils, emulsions, ointments, carbopols, lacquers, zinc oxides	Manual, ultrasonic, soak	Mild alkaline Mild alkaline Mild acid	Alconox Detonox Citranox
		Machine washer, power washer, clean-in-place (CIP)	Low-foam alkaline Low-foam alkaline Low-foam mild acid High alkaline	Alcojet Solujet Citrajet Keylajet

Healthcare

Healthcare cleaning procedures are important to maintain clean instruments and equipment, prolong their working life, minimize cross-contamination, and reduce medical waste. The ideal detergent for manual cleaning of reusable instruments has a mildly alkaline pH to prevent corrosion or other surface degradation. A mildly alkaline detergent also generally has a better safety profile than highly alkaline or acidic detergents. Detergents that contain proteolytic enzymes will degrade and remove proteinaceous soils from blood or body fluids on medical device surfaces by soaking and gentle cleaning rather than abrasive scrubbing. This prolongs working life of the instrument, limits the possibility of cross-contamination, and enables critical cleaning.

In a healthcare setting, cleaning often means preparing a surface for sterilization. It is crucial to remove all biological and chemical unwanted residuals from the surface to avoid unsuccessful sterilization of the medical device surface. Thorough cleaning before disinfection or sterilization also reduces the probability of contaminating the surface with endotoxins from killed but incompletely removed microbes.

Although healthcare instruments themselves are usually made of robust plastics or stainless steel, often the trays that hold the instruments or the handles of the devices may have their own unique cleaning or surface crazing issues. Choose a detergent that will not damage lightweight plastic or aluminum instrument handling trays. See Table 6.6 (next page) for a brief detergent selection guide.

Many cleaned healthcare instruments are often examining instruments of one kind or another. Most healthcare instruments that come into contact with blood or body fluids are disposable, substantially reducing risk of cross-contamination from bloodborne pathogens. Reusable examining and probing instruments (e.g., endoscopes) that come in contact with blood or body fluids must be cleaned very carefully.

Table 6.6 Detergent selection guide for healthcare cleaning

Application Key Concerns	Articles Cleaned/ Soil Removed	Cleaning Method	Recommended Detergent	Alconox Inc. Detergent
Healthcare/ Veterinary Effective preparation for sterilization, longer instrument life; reduced waste	Surgical, anaesthetic, and examining instruments and equipment; catheters and tubes	Manual, ultrasonic, soak	Mild alkaline Mild alkaline	Alconox Liquinox
		Machine washer, sani-sterilizer	Low-foam alkaline Low-foam alkaline	Alcojet Detojet
	Blood, body fluids, tissue on instruments	Manual, ultrasonic, soak	Enzymatic mild alkaline Low-foam alkaline	Tergazyme Detojet

The volume of healthcare instruments requiring cleaning can vary widely. For instance, in an individual doctor's office, small groups of instruments are generally cleaned in small soak trays and sometimes ultrasonically. Ultrasonic cleaning takes advantage of the mechanical energy of cavitation, which agitates the solution to enhance cleaning capability. However, hospitals and large medical centers instead use "control cleaning"—soiled instruments from the entire facility are grouped in trays and sent to a central cleaning facility. Such central facilities maximize throughput using washer/disinfectors and sterilizers as well as large automated ultrasonic cleaning systems.

Precision Manufacturing

In many high-tech metalworking applications, surfaces must be prepared by removing debris, oxides, scale, and salts to achieve extraordinary levels of cleanliness. Cosmetic factors also can influence buyer perceptions, with a bright, oxide-free finish serving as a visual indicator of product quality.

Numerous metalworking and metal finishing businesses find that aqueous detergents perform as well as or better than solvent cleaners in removing residues without harmful environmental side effects. For example, high-tech applications for which aqueous cleaners are ideally suited include:

- **Anodized parts**—Anodizers that produce aluminum substrate caps with anodic coatings for mounting personal computer integrated circuit chips use aqueous cleaners to remove conductive tail-end residues and to prevent toxicity and flammability.
- **Computer parts**—Thermocouples and wafers used in computers and medical devices that contain ceramics and copper paste are cleaned with aqueous cleaners in heated [66°C (150°F)] ultrasonic baths prior to nickel plating.
- **Aluminum**—Heat sinks for cooling computer chips in NASA space shuttles use aqueous detergents to remove oil and organic debris to eliminate any chance of non-condensable gas formation.

In general, precision manufacturing with metals involves preparing the surface for bonding, coating, or exposure to an environment that is highly sensitive to residues, such as a vacuum. Therefore, corrosion inhibitors that leave deposits are generally inappropriate for precision cleaning. It also is important to ensure the metal will not be attacked by any materials used in the cleaning, rinsing, or drying process. To clean precision manufacturing equipment, use mild cleaners, short contact times, and rapid rinsing and drying to minimize the chance of corrosion. It also is critical to avoid using extremely high-purity deionized rinse water, which can be so "ion-hungry" that it is corrosive to the metal substrate being rinsed.

Many industrial parts with oily, greasy residues were previously cleaned by vapor and vacuum degreasing. However, this requires use of harsh solvents as opposed to drain-safe aqueous detergents. As of 2020, the EPA lists two common degreasing solvents—1-bromopropane (n-propyl bromide) and trichlorethylene—as unreasonable risks to workers. Efforts are currently underway to replace solvents including these degreasing agents with aqueous detergents. Many metal applications can be safely and critically cleaned with high-emulsifying, mild to moderate alkaline aqueous detergents.

Plastics

To clean plastics, select a mild and non-damaging cleaner strong enough to remove the soils that are present. As indicated in Table 6.7,

Table 6.7 Plastics compatibility with cleaners

Generally Acceptable with Mild Aqueous Cleaners	Clean with Caution, even with Mild Aqueous Cleaners
Polyethylene (LLDPE, LDPE, PE)	Polycarbonate (PC)
Polypropylene (PP)	Alcotabs (POM: acetal)
Polyallomer (PA)	Nylon
Polymethylpentene (PMP, TPX)	Polymethylmethacrylate (PMC)
Fluoroethylenes (FEP, TFE, PFA, ECTFA, ETFE, PFTE)	
Polysulfones (PSF)	
Polyvinylchloride (PVC)	
Polystyrene (PS)	
Polyvinyl fluoride (PVDF)	
Polyeurethane	
Ethylene propylene (EPM)	
Buna-N rubber	
Polyether ether ketone (PEEK)	
Ethylene propylene diene terpolymer (EPDM)	
Fluoropolymer elastomer	
Polyphenylene oxide	
Polyphenylene sulfide	
Polyepoxide	

many plastics are resistant to attack by typical mild alkaline aqueous cleaners. For delicate plastics, consult the manufacturer for cleaner recommendations or use a specially formulated plastic cleaner.

For more delicate plastics, a mild alkaline cleaner can often be used at modest temperatures, low concentrations, and short contact times. The most challenging plastic to clean without damage is stressed polycarbonate, which is prone to stress cracking and crazing when exposed to low-surface tension solutions such as solvents and aqueous cleaners. Very dilute cleaner solutions may be needed to clean stressed polycarbonate, and a surfactant-free cleaner that may be high-alkaline or contain bleach is often preferred.

Most plastics are organic, which makes them attractive to organic film residues. A high-emulsifying cleaner is often required to remove organic films from plastic substrates.

Glass and Ceramics

Glass and ceramics have excellent insulating, transparency, and dimensional characteristics that make them desirable materials for many high-tech manufacturing applications.

Because these are inorganic matrix materials, they often attract and hold inorganic soils such as salts and ions. Aqueous cleaners with good chelating properties or acidic pH are often effective at removing such inorganic soils. For example, in a ceramic crucible cleaning application, mobile ionic residues need to be removed for use in semiconductor manufacturing. To solve this problem, aggressive immersion cleaning using heated ultrasonics with high-wetting, high-chelating, high-emulsifying cleaners provides successful cleaning of the ceramic crucibles.

General Purpose Cleaning

Aqueous cleaners have been widely adopted in solvent-reduction programs for metalworking and parts-washing operations. Often, the level of cleanliness required is for "appearance only" or to prepare surfaces for painting, bonding, or coating. It is critical to choose a detergent that is compatible with the type of parts washer being used.

For example, high-agitation cleaning machines such as bubble/air agitated immersion, spray wand, spray booth, and conveyorized spray machines require use of low-foaming cleaners. In contrast, it is preferable to use high-emulsifying and high-foaming cleaners when performing circulated, static, and ultrasonic immersion cleaning. Less rigorous rinsing is often acceptable. Tap water may be a sufficient rinse, and traces of water spots may be acceptable.

However, for appearance cleaning a "no-rinse" process involving merely wiping the parts or air-blowing them may be better when using highly dilute cleaner solutions.

High-Vacuum Cleaning

Equipment used with a vacuum needs to be cleaned of all vacuum-degrading outgassing residues. Surfaces for vacuum applications are typically cleaned with high-emulsifying mild to alkaline cleaners, followed by extremely thorough rinsing with purified water. Higher levels of vacuum require increased purity and quantity of rinsing.

Delicate Metal Cleaning

Iron, mild steel, aluminum, brass, and copper can be attacked by alkaline or oxidizing cleaners. Iron and steel are typically labile to corrosion from dissolved oxygen in rinse water or from oxidizers in the cleaner. Aluminum, brass, and copper are labile to alkaline attack, darkening, and oxidizing from the cleaners.

To clean iron and steel, use the appropriate alkaline or acid detergent to remove residues—generally alkaline cleaners for organic and oily residues, and acid cleaners for inorganic and scaly residues. Use an acid or alkaline cleaner that has good chelating function, which will tend to control formation of iron oxide rust during the washing process. Rinse quickly with cold/ambient temperature water and then quickly dry with water-removing drying methods, such as blowing, wiping, centrifuging, or dipping in alcohol or drying solvent. Do not dry using heat, air drying, or any slower water-evaporating method. It is best practice to avoid extended contact time with rinse water containing dissolved oxygen when cleaning steel or iron.

For aluminum, brass, and copper, avoid using alkaline cleaners; use mild acid cleaners that do not tend to darken or corrode. Mild acid cleaners will tend to dissolve and remove existing dark oxides and brighten the metals, including brass and copper. To remove dark aluminum oxides, use extremely strong mineral acid cleaners based on hydrofluoric acid, ammonium bifluoride, and/or sulfuric acid. Mild acid cleaners can remove dirt, grit, and grime from aluminum but not dark aluminum oxide.

See Table 6.8 (next page) for a brief detergent selection guide for precision manufacturing.

The following provide further insight into critical cleaning in the precision manufacturing industry: Chapter Two: Chemistry of Aqueous Cleaning (section on "Applications of Isoelectric Points to Cleaning"); Chapter Six: Industrial Cleaning Applications (sections on "GMP Washer Cleaning" and "Clean-In-Place (CIP) Cleaning"); Chapter Seven: Standard Operating Procedures; and Chapter Eight: Cleaning Validation.

Table 6.8 Detergent selection guide for precision manufacturing

Application Key Concerns	Articles Cleaned/ Soil Removed	Cleaning Method	Recommended Detergent	Alconox Inc. Detergent
Precision Manufacturing Clean parts; avoiding volatile solvents, strong acids, and other hazardous chemicals; key substrates include stainless and carbon steels, aluminum, and polymers	Aluminum, brass, copper, other soft metal parts; oils, chemicals, particulates (acid for oxides, salts, buffing compounds)	Manual, ultrasonic, soak	Mild alkaline Mild alkaline Low-foam alkaline Mild acid	Alconox Liquinox Tergajet Citranox
		Parts washer, power washer	Low-foam alkaline Low-foam alkaline Low-foam alkaline Low-foam mild acid	Alcojet Tergajet Solujet Citrajet
	Oxidation, metallic complexes, trace metals, rust, scale, salts, metal brightening	Manual, ultrasonic, soak	Mild acid	Citranox
		Parts washer, power washer	Low-foam mild acid High alkaline	Citrajet Keylajet
	Delicate substrates/ neutral for waste	Manual, ultrasonic, soak, machine washer, pressure spray	Neutral pH	Luminox
	Heavily soiled steel with grease, grime, scale	Soak, ultrasonic, machine washer, spray	High alkaline	Keylajet

Cannabis and Related Botanical Residues

The cannabis, cannabidiol (CBD), and botanical industries present many specialized and potentially difficult cleaning challenges, from the laboratory all the way through sophisticated large-scale commercial manufacturing processes. Sticky resins are encountered at every step along the process. Critical cleaning needs span a wide range of hard surfaces from delicate laboratory glassware, processing tools, and equipment, to large extraction vessels, boiling flasks, and tanks.

Currently, U.S. legalization of cannabis is under discussion, but it remains a controlled substance from a U.S. federal law perspective. Acceptability varies from state to state, with some allowing for

recreational use, others permitting medicinal use only, and yet other states classifying cannabis as totally illegal. Similar variability is seen across the globe. If and when cannabis becomes broadly legalized, questions abound regarding the type of regulatory structure and oversight that will follow. Current regulatory strategies tend to draw from existing frameworks established for alcohol, tobacco, food and beverage, or pharmaceutical, or even a hybridized approach.

It is recommended that, as for cannabis-derived FDA-approved drugs already on the market, medicinal cannabis continue to follow the pharmaceutical regulatory scheme and thus the pharmaceutical cleaning pathway. It also is recommended that in connection with production of cannabis for the commercial market (i.e., recreational use), manufacturers use the same stringent pharmaceutical standards for cleaning. Edible formats of cannabis and cannabis-derived products also may be well-served by following food and beverage regulations.

Critically clean processing equipment in cannabis and related botanical industries is vital, whether labware, glassware, instrumentation, trimmers, or separation and extraction equipment. As indicated by several regulatory bodies including the FDA, potency, purity, and quality—essential characteristics of any product—rely on critically clean surfaces. Cleaning for cannabis industry processing is more challenging than cleaning for traditional drug manufacturing. Waxy, resinous, oily, and sticky residues are highly adherent and difficult to emulsify because these plant residues are complex conjugates of terpenes, cannabinoids, pesticidal agents, phenolic compounds, and more.

Critical cleaning in this industry is further necessitated by the nature of cannabis itself. Unlike traditional pharmaceutical drug products, cannabis can be consumed as a whole product, as opposed to isolating individual chemicals (e.g., tetrahydrocannabinol, cannabidiol) as in traditional pharma. Natural variabilities occur from

plant to plant, much like any other plant life. As in pharmaceutical manufacturing, this requires that product-to-product (plant-to-plant) and batch-to-batch products be completely cleaned away to prevent cross-contamination.

Since most cannabis industry-related soils are acidic or alkaline hydrolyzable, alkaline cleaners are very effective. Alkaline cleaners remove organics including oils, tars, resins, extracts, proteins, and an array of other soils. Most cleaning applications will involve an alkaline cleaner or a combination of an alkaline cleaner and an acidic cleaner.

For specific residues of cannabis, CBD, and other similar botanicals to be cleaned via manual scrubbing, soaking, or ultrasonic cleaning, a mild alkaline, high-emulsifying cleaner with anionic and nonionic surfactants is used. When applications with automated, high-pressure spraying are considered, including washers, spray cabinets, and clean-in-place (CIP) systems, a high alkaline detergent with good emulsifiers is used.

In concert with micelle-forming surfactants for emulsifying, aqueous detergents are the safe, efficient, and effective alternative compared to the hazards of flammable and dangerous solvents including acetone and ethanol.

Table 6.9 Detergent selection guide for cannabis cleaning

Application Key Concerns	Articles Cleaned/Soil Removed	Cleaning Method	Recommended Detergent	Alconox Inc. Detergent
Cannabis Critically clean cannabis, CBD, and related botanical labware, glassware, instrumentation, and processing and extraction equipment; ensuring strain-to-strain and batch-to-batch processing is clean and contaminant-free	Glassware, processing tools, extraction vessels, boiling flasks, and clean-in-place (CIP) manufacturing equipment; sticky oils, waxes, and resins	Manual, ultrasonic, soak	Mild alkaline Mild alkaline Mild alkaline	Alconox Liquinox Detonox
		Parts washers, power spray	Low-foam alkaline High alkaline	Alcojet Keylajet
	Irrigation lines, pesticide and organic water buildup	Manual, ultrasonic, soak	Enzymatic mild alkaline	Tergazyme

See Table 6.9 for a brief detergent selection guide for cannabis cleaning.

Food and Beverage Processing

Food and beverage processing encompasses a wide array of food residues on a wide variety of surfaces. High-emulsifying cleaners are needed where there is a significant amount of organic food residue. Manual cleaning with detergents designed for immersion works well on benches, counters, mixers, extruders, and processing equipment.

In meat or poultry processing plants, an enzymatic mild alkaline cleaner is recommended. This type of detergent addresses a wide range of food residues in addition to blood and raw protein residues. The types of hard surfaces found in processing environments are typically stainless steel or robust plastics such as high-density polyethylene, or ceramics.

Alcoholic beverage manufacturing includes a complex range of residues from wines, distilled spirits, brewing yeasts, grains, hops, and other alcoholic residues as well as oils, sugars, and food residues. A mild alkaline cleaner will resolve all of these residues, leaving laboratory and tasting room glassware clean for optimal sampling and processing equipment surfaces clean for product purity. Breweries using cold filtration also can benefit from an enzymatic mild alkaline detergent.

Large-scale industrial frying represents another challenge within the food processing industry. Oil residues like baked-on carbon buildup will create off flavors and aromas, and deposits of unsaturated fats will denature the frying oils quickly, with costly consequences. A liquid mild alkaline cleaner designed for immersion is a safe choice with less concern about disposal than standard high-alkaline caustic cleaners commonly used to clean industrial frying equipment.

Processing dairy products presents challenges with milkstone

residues. Using a mild acid detergent will safely and effectively remove these residues and also will work well on starch buildup, oxides, salts, water scale, and rust and corrosion.

Filtration membranes are unique surfaces found in food or beverage processing plants to filter various process streams. Filtration membranes are used in juice and decaffeinated coffee processing as well as cheese manufacturing. Such processes often result in highly fouled, difficult-to-clean filter membranes that are often very expensive. Effective cleaning maximizes their useful life and restores their flow rate and performance.

Membranes are frequently fouled by biocontamination growing on the food, causing a condition called bio-fouling or biofilm. Biofilm polysaccharide and proteinaceous residue is often effectively removed by an enzymatic mild alkaline detergent. Enzyme cleaners also are desirable because they can be made with a neutral or near-neutral pH that will not damage filter media that is sensitive. Since some membranes are delicate and will be damaged by harsh alkaline or acid cleaners, it is crucial to select a mild detergent.

See Table 6.10 for a brief detergent selection guide for food and beverage processing cleaning.

Table 6.10 Detergent selection guide for food and beverage processing cleaning

Application Key Concerns	Articles Cleaned/ Soil Removed	Cleaning Method	Recommended Detergent	Alconox Inc. Detergent
Food and Beverage Processing Food and beverage processing equipment must be critically cleaned per FDA and related requirements, ensuring safe, contamination-free products and prolonging equipment life	Stainless steel, food contact equipment, industrial fryers/grease buildup, oils, wine, sugars, distilled spirits, alcoholic beverages, food residues	Manual, ultrasonic, soak	Mild alkaline Mild alkaline Mild alkaline	Alconox Detonox Liquinox
		Machine washer, pressure washer, clean-in-place (CIP)	Low-foam alkaline	Alcojet
	Oxides, scale, salts, milkstone, trace metals, soft metals, corrosion	Manual, ultrasonic, soak	Mild acid	Citranox
		Machine washer, pressure washer, CIP	Low-foam mild acid	Citrajet
	Filter membranes, beer brewing residues, proteins, biofouling	Manual, ultrasonic, soak	Enzymatic mild alkaline	Tergazyme
		Machine washer, pressure washer, CIP	Low-foam alkaline Low-foam alkaline	Detojet Solujet

Foodservice

In the foodservice industry, food preparation surfaces must be cleaned of residues that interfere with equipment performance and consistency of product. In addition, cleaning is important to ensure not only longevity of foodservice equipment but also food safety and customer satisfaction. Worker safety and environmental considerations are also vital to selecting the appropriate cleaning products for a commercial kitchen.

Heavy baked-on carbon buildup and polymeric residues from zero trans fat cooking oils present cleaning challenges. Maintaining commercial fryers to an acceptable level of cleanliness is a common difficulty for restaurants, often requiring hazardous chemicals and

intense effort that can waste time and thus money. A high-foaming, mild alkaline detergent is suitable for these kinds of residues. The same mild detergent often is suitable to clean other food preparation surfaces and facilities as well, such as shelving, hoods and filters, floors, warming ovens, drive-through pavement, and parking lots.

Water scale, dairy milkstone, starch buildup, and rust represent another set of residue challenges in the foodservice industry. These residues all can be addressed with a mild acid cleaner, although strong acids are often used. Varying the temperature and concentration of a mild acid detergent will remove composite resides from equipment such as combi ovens. Combi ovens often contain water scale, grease, and rust within the same cavity. Continually used combi ovens can be rendered inoperable without proper daily cleaning and preventative maintenance.

Raw protein residues can present profound food safety issues if not cleaned properly from food preparation surfaces. Using a mild alkaline enzymatic detergent is a safe and effective preparation step prior to sanitizing—the detergent will remove the residue, and the sanitizer (for example, bleach) will sterilize the cleaned surface. Recommendations from the U.S. Centers for Disease Control and Prevention (CDC) and Environmental Protection Agency (EPA) indicate that cleaning is a vital initial step in any disinfection process.

Facilities cleaning is another critical area in foodservice. Points of concern include customers' experience, staff and customer safety, costly repairs, and inspection results. A mild alkaline detergent—which can be the same detergent used on food preparation equipment—will work to remove grease stains on drive-throughs and to clean windows, walls, and floors. While the industry standard is harsh alkaline detergents that are hazardous to both employees and surfaces, a mild alkaline detergent will provide the same cleaning results with improved safety as well as more efficient procurement.

Mild alkaline manual detergents that are free of fragrance, dyes, and rinse aids also are appropriate to clean glassware, tableware, and smallware. In particular, wine glass cleaning with a mild, free rinsing, alkaline liquid detergent will allow for a complete customer experience of the wine menu in both taste and bouquet; residual aromatic components from a detergent that does not rinse away freely would interfere with this experience.

See Table 6.11 for a brief detergent selection guide for foodservice cleaning.

Table 6.11 Detergent selection guide for foodservice cleaning

Application Key Concerns	Articles Cleaned/ Soil Removed	Cleaning Method	Recommended Detergent	Alconox Inc. Detergent
Foodservice Avoid interfering residues on food-contact equipment and effectively remove soils commonly found in food operations	Stainless steel, food contact equipment, industrial fryers/grease buildup, oils, food residues	Manual, ultrasonic, soak	Mild alkaline Mild alkaline Mild alkaline	Alconox Liquinox Detonox
		Machine washer, pressure washer, clean-in-place (CIP)	Low-foam alkaline	Alcojet
	Oxides, scale, trace metals, salts, milkstone, corrosion	Manual, ultrasonic, soak	Mild acid	Citranox
		Machine washer, pressure washer, CIP	Low-foam mild acid	Citrajet
	Filter membranes, proteins, biofouling	Manual, ultrasonic, soak	Enzymatic mild alkaline	Tergazyme

Environmental and Water Testing

Trace analyses—usually seeking to detect trace organics—are typically conducted for pesticides, known carcinogens, and known toxic organic compounds. The U.S. EPA provides a list of organic compounds that can be tested for in trace analyses. Other trace analyses focus on toxic inorganic compounds, typically trace metals (e.g., mercury, cadmium, zinc).

Table 6.12 provides a brief detergent selection guide for environmental cleaning.

Table 6.12 Detergent selection guide for environmental cleaning

Application Key Concerns	Articles Cleaned/ Soil Removed	Cleaning Method	Recommended Detergent	Alconox Inc. Detergent
Environmental Reproducible results, no interfering residues, extend equipment life; maintain laboratory accreditation; laboratory safety	Tubes, reusable pipets	Siphon-type washer-rinsers	Mild alkaline tablet	Alcotabs
	Microbiology, water lab, and environmental sampling; phosphate-sensitive labware	Field, manual, ultrasonic, soak	Low-foam alkaline Mild alkaline	Tergajet Liquinox
		Machine washer, labware washer	Low-foam alkaline Low-foam mild acid Low-foam alkaline	Tergajet Citrajet Solujet
	Glass, metal, plastic labware, ceramics, tissue culture, porcelain, clean rooms, animal cages, bioreactors, tubing, benches, safety equipment	Manual, ultrasonic, soak	Mild alkaline	Liquinox
		Machine, power spray, labware washer, washer-sterilizer, cage-washers	Low-foam alkaline Low-foam alkaline	Tergajet Solujet
	Trace metals, metal oxides, scale, salts, starches, amines	Manual, ultrasonic, soak	Mild acid	Citranox
		Machine washer, warewasher	Low-foam mild acid	Citrajet

The purpose of water and environmental laboratory tests is to determine general water or soil quality. In such cases, trace analysis is often performed for toxins. Quantitative analysis is used to test drinking water as well as to determine soil quality for farming or gardening.

Cross-contamination from previous soil or water testing is a key concern when cleaning sampling and handling equipment and glassware. The following two procedures can help prevent cross-contamination.

1. Use a laboratory-grade cleaner with no analyzable ingredients to eliminate the possibility of cross-contamination with detergent residues. For example, use a phosphate-free detergent when analyzing for phosphates.
2. Perform equipment "blanks" by cleaning glassware or handling/sampling equipment and then testing the clean glassware or equipment for contaminants. For example, U.S. EPA protocols for laboratory-grade detergents for cleaning sampling equipment specifically call for the use of Liquinox, which is phosphate-free, and Alconox. Phosphate-free cleaners are specified because of the potential risk of cross-contamination from phosphates. While Alconox detergent, when rinsed thoroughly, does not leave interfering phosphate residues, phosphate-free Liquinox detergent is often considered for an added layer of protection.

General Electronics Cleaning

Electronic components are usually made of metal that is conductive and can be easily bonded by soldering. Soldering involves use of flux, an undesirable contaminant because it is often acidic and can cause corrosion of electronic components. Flux also is conductive, so flux residue can cause short circuits of electronic components.

The conductive metals in electronic components are frequently embedded in insulating substrates, often glass or ceramic. It is important to clean the surfaces of insulators completely to preserve their insulating properties. Oils or other conductive residues or particulates must be removed.

Special consideration and care must be used when cleaning electronic components that use a vacuum for insulation. These include light bulbs and vacuum tubes where residue can "outgas" into the

vacuum, degrading insulator performance. This type of cleaning requires a thorough understanding of the soils present on the part to select an effective detergent.

Additional soils encountered in electronics cleaning are mold release agents, and metal oxides may be found on frame holders. Removal of organic residues usually requires an emulsifier or co-solvent, whereas removal of metal oxides is generally achieved using an acid cleaner with high chelating or sequestering capacities.

Table 6.13 provides a brief detergent selection guide for electronics cleaning.

Table 6.13 Detergent selection guide for electronics cleaning

Application Key Concerns	Articles Cleaned/Soil Removed	Cleaning Method	Recommended Detergent	Alconox Inc. Detergent
Electronics Avoid conductive residues, avoid CFCs, pass cleaning criteria	Circuit boards, assemblies, screens, parts, conductive residues, resins, rosins, fluxes, particulates, salts	Manual, ultrasonic, soak, machine washer, power spray board, and screen washers	Ion-free alkaline Low-foam neutral pH	Detergent 8 Luminox
	Ceramic/glass insulators and components	Manual, ultrasonic, soak	Mild alkaline Mild alkaline Low-foam neutral pH	Alconox Liquinox Luminox
		Parts washers	Low-foam alkaline Low-foam alkaline Low-foam neutral pH	Alcojet Solujet Luminox

Precision Electronics

Aqueous cleaning technology meets the stringent cleaning requirements for precision electronics manufacturing, such as disk drives, semiconductors, and electro-optics. These industries use high-purity aqueous cleaners in controlled environment manufacturing settings. The cleaners are made from high-purity ingredients and integrate filtration and purification steps during their manufacture. Delivery of finished cleaner that is filtered to sub-micron levels requires

manufacturing, filtering, and packaging in a cleanroom environment using special clean containers and clean plastic bags to package the bottles and maintain their particulate-free purity. Alternatively, a customer may perform sub-micron or lower-level filtration at the point of use.

PC Boards

A wide variety of contaminants can remain on the completed assembly surface of printed circuit (PC) boards if they are not properly cleaned. These contaminants can be:

- **Ionic**—Contaminants with an ionic charge are typically salts containing sodium, potassium, and/or chloride. Ionic contaminants are of particular concern because they are potentially conductive, mobile residues.
- **Polar**—Contaminants with a dipole moment (a molecule with partially charged positive and negative ends or poles). Consistent with the principle that "like dissolves like," these contaminants tend to solvate ionic residues.
- **Nonpolar**—Contaminants with no dipole moment that are generally organic films with insulating and adhesion interfering properties for bonding or marking.
- **Nonionic**—Organic compounds that have no ionic charge and are not salts. They may be either polar or nonpolar.

Salts such as plating salts, etching salts, and activators are typically ionic. Many organic species are nonionic; however, organic acids such as rosin acids and organic acids used as activators are ionic. A good circuit board cleaner should be able to remove both ionic and nonionic residues.

The most detrimental type of contaminant is ionic. If not removed, ionic contaminants can cause serious problems including leakage currents between traces on boards as well as severe corrosion.

The presence of moisture greatly accelerates the activity of ionic species because water solvates the ions and enables them to become mobile. In the presence of moisture and an applied voltage across circuit traces, dendritic growth can occur. This is when atoms of the circuit trace migrate outward across the bare laminate until they bridge the circuit width, causing an electrical short.

Mobile ionic species accelerate dendritic growth. Mobile ionic species also are responsible for corrosion products formed on assembly surfaces. Military and other contractors are often required to apply a conformal coating to protect assembly surfaces from moisture. A conformal coating is a polymeric material such as an epoxy, polyurethane, or acrylic designed to protect the assembly surface from moisture. In addition, conformal coatings isolate contaminants and prevent them from migrating or being dislodged during conditions such as temperature-moisture cycling, high vibration, and shock environments.

Nonionic contaminants remaining on the assembly surface also can lead to performance problems. These contaminants can interfere with electrical bed-of-nails testing (a surface conductivity test) by creating electrical "opens." They also can lead to adhesion problems if a conformal coating is applied.

Ionic materials and some hygroscopic nonionic materials under conformal coatings can cause blistering during temperature/humidity cycling. This phenomenon is also called mealing or vesication, and it takes place because no conformal coating is completely effective against moisture penetration. In fact, the presence of ionic or hygroscopic material on the surface under the conformal coating promotes water penetration since such contamination attracts water. Once the contaminant becomes hydrated, it builds up osmotic pressure that lifts the conformal coating, forming a blister or vesicle. This phenomenon is considered detrimental to the finished assembly.

Finally, there is the phenomenon of white residue, which is not always white and can be gray, tan, beige, or amber. There are several possible causes of white residue. In some instances, the assembly butter coat is removed, revealing glass weave intersections. This is known as measling and can result if the solvent used for cleaning is too harsh. White residue also can occur when activator materials are left behind on the assembly surface. This happens when the solvent used for defluxing has become depleted of alcohol.

Another cause of white residue is solder paste. Solder paste contains materials known as thickening agents (thixotropic agents or rheological modifiers). These materials are difficult to remove during defluxing, especially without using mechanical energy (e.g., sprays). Thickening agent residues are prone to form white residues, especially if exposed to alcohol. Exposure to alcohol can be from alcohol in the defluxing solvent or alcohol in an ionic contamination tester.

However, the principal cause of white residue is thermal degradation of rosin. Rosin readily undergoes degradation and polymerization (molecules bond together to form a much larger molecule). This is especially true when rosin is heated to ≥260°C (500°F). The rosin also interacts with tin and lead salts in solder formed during fluxing by activator action on the solder oxides. The rosin typically contains abiatic acid, which can react to form white tin and lead abietates. The polymerized rosin and/or tin and lead abietates are much more difficult to remove by defluxing solvents because they are less soluble. Other acids used in fluxes can form tin or lead salts that are typically white.

White residue usually appears at the end of the defluxing operation, after the defluxing solvent has flashed off. Both rosin fluxes and rosin pastes are prone to form white residue. If white residue appears, make sure that it is caused by the flux (or paste) and does

not have another cause. To mitigate this problem, you must remove the rosin, abiatic acid, or other flux acids using a high emulsifying or solvating cleaning procedure so white residues do not have a chance to form. Once they form, they are difficult to remove with a solvent-based cleaner. An acidic, chelating cleaner can remove white residues. After an ionic acidic cleaner is used, rinsing with deionized water is required to ensure the ionic acidic cleaner does not leave behind conductive residues.

Optics

Aqueous detergents are frequently used in the manufacturing process to clean optics, particularly in the final stages of production. Such optical surfaces range from scientific applications to consumer products such as contact lenses.

An example of a scientific application is aluminum-coated mirrors used in telescope-based space exploration, and these mirrors require particularly precise specifications and surfaces devoid of unwanted residues. Manufacturers of scientific optics often use machining oils and heavy waxes to grind and polish optics to exacting tolerances. An alkaline detergent is ideal for removing these oils and waxes from the surfaces of finished products.

In terms of consumer products, contact lens manufacturers often use a wax to secure silicon/acrylic copolymer lenses to collets for machine formation of the base curve layer, which ensures proper contact lens fit and wearer comfort. The wax must be removed when the process is complete. pH-neutral aqueous detergents in ultrasonic cleaning systems are effective at removing the compounds used to grind rigid gas-permeable contact lenses. As described elsewhere in this handbook, when cleaning in ultrasonic tanks or lab washers, special racks are used to separate the lenses so they do not nest and trap water between them and so that rinse water can sheet off the lenses easily

and completely. A mild alkaline detergent used in ultrasonic tank cleaning is highly effective. When cleaning in an automated washer, a higher alkaline low-foaming detergent is used.

See Table 6.14 for a brief detergent selection guide for optics cleaning.

Table 6.14 Detergent selection guide for optics cleaning

Application Key Concerns	Articles Cleaned/ Soil Removed	Cleaning Method	Recommended Detergent	Alconox Inc. Detergent
Optics Clean parts; avoid volatile solvents, strong acids, and other hazardous chemicals	Glass, ceramic, stainless steel, plastic, rubber; oils, chemicals, particulates	Manual, ultrasonic, soak	Mild alkaline Mild alkaline	Alconox Liquinox
		Machine washer, power washer	Low-foam alkaline Low-foam alkaline Low-foam alkaline Low-foam alkaline	Alcojet Tergajet Detojet Solujet
	Delicate substrates/neutral for waste	Manual, ultrasonic, soak, machine washer, pressure spray	Neutral pH	Luminox

Nuclear

Nuclear power plants require effective cleaners that can decontaminate walls, floors, tools, and equipment inside nuclear power reactor containment cavities without having to use expensive strippable coatings. Ideally these cleaners should be effective at removing radioactive isotopes while not interfering with ion exchange waste treatment techniques.

If the cleaners contain interfering chelates, then the cleaners should not be volatile so they can be treated by evaporative waste treatment techniques. These cleaners need to be very high-purity with no contaminants or ingredients such as halides, low-melting metals, and sulfur, which can potentially embrittle/corrode and thereby shorten the service life of stainless-steel components that must have robust performance in nuclear power generation piping and equipment as well as waste storage.

Laboratories that handle nuclear materials similarly require radioactive decontamination of stainless steel, glassware, and laboratory equipment. A mild alkaline detergent with strong wetting agents and chelators will effectively decontaminate these surfaces. The detergent binds radioisotopes and allows for waste treatment by evaporation.

See Table 6.15 for a brief detergent selection guide for nuclear cleaning.

Table 6.15 Detergent selection guide for nuclear cleaning

Application Key Concerns	Articles Cleaned/ Soil Removed	Cleaning Method	Recommended Detergent	Alconox Inc. Detergent
Nuclear Avoid waste interference	Laboratory decontamination, pipes, tools, protective equipment	Ultrasonic, soak, scrubbing, spray	Mild alkaline Ion-free alkaline	Alconox Detergent 8
	Reactor cavity decontamination	Manual, soak, high-pressure spray	Ion-free alkaline	Detergent 8

Ultrasonic Cleaning Systems

Ultrasonic cleaning uses transducers to pulse high-frequency sound waves through a solution. These sounds waves form small pockets of vacuum that subsequently collapse, creating energetic cavitation in the solution. This process provides efficient mechanical energy to clean surfaces of parts and instruments when used with appropriate cleaning solutions.

Ultrasonic tanks, which also may be referred to as ultrasonic systems, units, or cleaners, are ubiquitous in laboratories and manufacturing floors in all critical cleaning industries. (For the purposes of this book, the term "ultrasonic cleaners" refers to detergents that may be used in an ultrasonic tank.) Common uses of ultrasonic tanks include cleaning labware and glassware from reagent residues, removing cutting oils and lubricants from manufactured

medical devices, reprocessing reusable healthcare instruments, clearing mold-release residues from molded polymer parts, and removing thin-film and oxidative residues from fabricated precision pieces.

Ultrasonic tanks can range in size from benchtop units of less than 1 gallon (3 liters) to industrial tanks greater than 500 gallons (2000 liters), accommodating various sized parts and devices. Ultrasonic critical cleaning applications traditionally use frequencies of 25–60 kHz but can extend below this range and far higher, even into the megasonic (1,000 kHz) range. Lower frequencies provide more energy and are useful for larger parts, while higher frequencies deliver less energy and are useful for cleaning delicate or small parts.

Efficacy of the transducer and ultrasonic tank can be verified with automated monitors. Alternatively, a simple test is often referred to as the "aluminum foil test." A small piece of foil is held submerged in the ultrasonic tank under the intended settings. After 30 seconds, the aluminum foil should be uniformly filled with pinprick holes or dents (no clear dead zones without holes or dents) as the pulsing cavitation waves breach the foil surface (see Chapter Seven, section on "Ultrasonic Cleaner Test Procedure"). Such a result is considered a successful test, and holding the foil to a light source can help clarify this result.

As discussed in previous chapters, application of heat via the heating element of an ultrasonic tank often benefits cleaning by softening hardened residues and thereby expediting cleaning. However, while increased heat frequently expedites the cleaning process, it decreases efficacy of the ultrasonic pulse. As temperature of the ultrasonic bath cleaning solution increases, the vacuum bubbles created become filled with vapor. This softens collapse of the cavitation void and reduces the amount of energy delivered to the surface of the contaminated substrate surface. Therefore, one must optimize the balance of heat versus transducer efficacy. Typically, trial work can

determine the proper time and temperature for thorough critical cleaning applications involving ultrasonic tanks. Chemical action of detergent in the ultrasonic tank generally follows first-order reaction kinetics, such that every 10°C (50°F) increase in temperature doubles the rate of chemical cleaning. The mechanical energy of cavitation from ultrasonic transducers increases to a typical maximum around 70°C (158°F) for most water-based detergent solutions. Above 70°C (158°F), the rate of cleaning from combined chemical and mechanical means improves more slowly than below 70°C (158°F).

While ultrasonic cleaning is not classified as manual cleaning due to automation of the unit, ultrasonic cleaning may be grouped into manual methods because it works well with the same types of detergents used in manual cleaning processes. Ultrasonic cleaning allows use of foaming aqueous detergents that would otherwise only be used in manual scrubbing or soaking cleaning applications. Unlike manual cleaning methods, specific and repeatable automated settings can be established, allowing for cleaning cycles of exact time, temperature, and agitation. Multi-tank ultrasonic systems come into use when similar settings can perform the necessary rinses following cleaning. Two or three subsequent rinse ultrasonic tanks can be similarly controlled with precision and repeatability as the original wash ultrasonic tank. Ultrasonic rinsing, while not as effective as mass displacement in flowing water rinses, can be a very effective rinsing technique.

More contemporary methods to improve ultrasonic cleaning include vacuum cycle nucleation (VCN). Where an ultrasonic tank provides pulses working from the outside in, VCN works from the inside out. Parts submerged in a cleaning solution are subjected to a vacuum that rapidly lowers the boiling point of the solution, forming bubbles starting from the inside of a part. This method is most useful for cleaning tortuous 3D-printed parts, intricate

medical devices, and complex labware like rotovaps, among other such applications. Similarly, a VCN device can provide controlled, effective, and repeatable rinsing.

Ultrasonic cleaning works best with mild alkaline and mild acidic foaming detergents for organic and inorganic residues, respectively. For reactive metals including brass and copper, acidic detergents are preferred. Avoid cleaning mixed metals in an ultrasonic bath, as galvanic plating may occur via the electrolytic solution. For VCN applications, both low-foaming detergents can be used because vacuum pulse and frequency can be modulated, although low-foaming detergents are often preferred.

See Table 6.16 for a brief detergent selection guide for ultrasonic cleaning.

Table 6.16 Detergent selection guide for ultrasonic cleaning

Application	Articles Cleaned/ Soil Removed	Cleaning Method	Recommended Detergent	Alconox Inc. Detergent
Ultrasonics Ultrasound transducers pulse sound waves through a solution; allows for efficient mechanical energy to clean surfaces reliably and reproducibly	Aluminum, brass, copper, tool steel, and other soft metal parts	Manual, ultrasonic, soak	Mild acid	Citranox
	Oils, chemicals, particulates (acid for oxides, salts, buffing compounds)	Manual, ultrasonic, soak	Mild alkaline Mild alkaline	Alconox Liquinox
	Stainless steel, plastics, glass with challenging, adherent residues	Manual, ultrasonic, soak	Mild alkaline Mild alkaline	Alconox Detonox
	Blood, body fluids, tissue on instruments, glass, labware	Manual, ultrasonic, soak	Enzymatic mild alkaline Low-foam alkaline	Tergazyme Detojet

Clean-in-Place (CIP) System Cleaning

Pharmaceutical, biotech, cosmetic, and precision manufacturing operations typically include tabletop R&D processes and pilot studies, in addition to their full-scale manufacturing processes.

Generally, cleaning techniques and equipment change with the scale of production. Manual and soak cleaning procedures may be adequate when cleaning bench-scale equipment, whereas CIP systems are generally more efficient for cleaning large-scale manufacturing process equipment. Part of the following discussion on CIP cleaning is paraphrased from Dale Seiberling's publications.

CIP cleaning involves spray to drain or recirculation of the initial flush, wash, and rinse solutions under pressure. Effective cleaning is achieved by adjusting time, temperature, pressure, and cleaner concentration.

- Piping systems can be effectively cleaned via recirculation of flush, wash, and rinse solutions at flow rates that produce a velocity of 5 feet per second or more in the largest diameter piping in the CIP circuit.
- Mixers, tanks, and blenders can be effectively cleaned by distributing flush, wash, and rinse solutions on the upper surfaces at pumping rates equivalent to 2.0–2.5 gallons per minute per foot of circumference for vertical vessels, or 0.2–0.3 gallons per minute per square foot of internal surface for horizontal and rectangular tanks.
- Integrated CIP design is a process of cleaning vessels and piping in one operation. Flush, wash, and rinse solutions are combined and circulated through the spray systems. Solutions are returned to the CIP system. This form of CIP cleaning is cost-effective and minimizes the risk of post-CIP recontamination that can occur when lines and vessels are cleaned separately.

A CIP monitoring and control system can be installed to ensure that the CIP system works reliably, rendering the process vessels and piping clean after every product run or a loud alarm will sound. The CIP monitoring and control system can document the

system's operation and history and can archive this information for regulatory compliance. To set up a monitoring system, first circulate and then flush water through the CIP system with the control system monitoring the valves and pressure to ensure and record proper operation. Next, proceed to the wash cycle, possibly using conductivity control to measure and record proper addition of cleaner solution. Then, flush out the cleaner solutions and proceed to neutralization and rinsing steps. Final rinses can be circulated to equilibration for rinse water sampling if desired.

See Table 6.17 for a brief detergent selection guide for CIP system cleaning.

Table 6.17 Detergent selection guide for CIP system cleaning

Application Key Concerns	Articles Cleaned/ Soil Removed	Cleaning Method	Recommended Detergent	Alconox Inc. Detergent
CIP System Cleaning CIP cleaning involves spray to drain or recirculation of the initial flush, wash, and rinse solutions under pressure; effective cleaning is achieved by adjusting time, temperature, pressure, and cleaner concentration	Titanium dioxide, petrolatum, oils, emulsions, ointments, carbopols, lacquers, zinc oxides	CIP	Low-foam alkaline	Solujet Keylajet
	Inorganic residues, salts, buffering solutions, acidic rinses	CIP	Low-foam mild acid	Citrajet
	Protein, organic, cellular and fermentation residues; reverse osmosis, ultrafiltration membranes, oxidation	CIP	Low-foam alkaline	Detojet

GMP Washers/Dryers

GMP washing machines are especially useful for equipment parts that are disassembled for cleaning—manufacturing tools and bench-scale production equipment that can be loaded into racks are often best cleaned in a dishwasher capable of validated cleaning.

Design — Within the pharmaceutical, biotech, cosmetic, and medical device industries, there are no definitive standard specifications for mechanical washer/dryers that meet all GMP requirements. GMP regulations include several guidelines (Part 133.4, 1963; Part 211.67, 1978) for GMP washer/dryer design and construction. Unfortunately, these regulations leave many areas open to interpretation. With no clear standard, many approaches to laboratory-style washers have been developed, yet their limitations do not become evident until long after purchase and installation.

There are certain inherent criteria required for washers/dryers used to clean parts, glassware, plasticware, and tooling to achieve GMP compliance in regulated industries. Following FDA rationale, the goal is to design cleaning equipment that will "prevent contamination or adulteration of drug products."

Structural flexibility—Design of the GMP washer has continuously evolved. Initially, modified laboratory washers were manufactured in common production lines. More recently, the most up-to-date manufacturing companies have established specific product divisions to manufacture GMP washers. Complete separation of tooling and superior welder qualifications are now requirements for this group of products. The washer/dryer must be able to perform without taking up too much space, and effective placement in the process plant will allow for easy service and technician access. In addition, documentation of quality control monitoring for the entire construction process is provided by the washer/dryer manufacturer.

The outer shell of the washer should be constructed of at least 316L stainless steel to withstand cleaning chemicals used in the clean suite area, allowing for easy integration of the equipment into this area. Service panels should allow access to the critical components through mechanical chassis or locations allowed by the facility's design. Many times, the washer must be adapted to operate in a

particular space or room so that the internal components can be easily accessed by service people, technicians, or validation engineers during and after the installation and calibration process. Temperature and monitoring instruments should be easily removed from their ports via tri-clamped connections and should have enough coil to be placed on a metrology cart outside the washer. This will facilitate calibration and verification during validation. Freestanding or recessed models must be available to give the facility the product flow characteristics required for its process.

Chamber flexibility—Effective use of the chamber will allow for faster and/or fewer cycles and higher throughput of the washer/dryer during production.

Chamber design should allow for minimal water retention. Chamber corners should carry a minimum 1-inch radius, and all surfaces should be sloped to the drain. Internal structures of the chamber should feature rounded edges with no threads or entrapment areas. 316L stainless steel finished to a uniform 25 Ra for all surfaces is an appropriate baseline for all surfaces and structures within the chamber.

Care should be taken with respect to mating of the inventory systems to the hydraulic circuit. There should be no mechanical attachment required for the accessory racks. Spray headers should be positioned at the top and bottom of the basin to help clean parts. In keeping with the goals of minimizing utility costs and GMP design and construction, the chamber volume should be sized to match the load configuration required for a specific facility.

Care also should be taken to match the items to be cleaned so that an effective load and unload pattern can be established to minimize operator errors. Multiple-level loading configurations will allow for maximum utilization of the chamber space while minimizing the consumption of injected water.

Effective use of Teflon and stainless steel will allow racks and baskets to mate to the chamber of the washer. (Avoid threaded connections, as they are entrapment areas for water and particulates that could lead to cross-contamination of the products being cleaned.)

Because loads for GMP cleaning can range from glass to plastic to stainless parts, the design of a loading surface should allow for the weight associated with these components. Two types of doors are typically available:

- *Vertical doors*—These allow easy access to the items being cleaned but make it difficult to provide a strong seal. In addition, they require use of loading trolleys, which add to the number of accessories in the clean suite. Vertical doors typically have a built-in window that is popular but has no GMP function. (Internal lights required for their use need gaskets that require maintenance. The doors also are prone to leakage and may need service maintenance, which is not always possible during a production run.)

- *Horizontal drop-down doors*—Also easy to access and to load, these doors serve as containment structures. Gaskets that can be matched to GMP requirements allow complete sealing of the chamber, preventing particulate migration into or out of the chamber. In the down position, the door becomes a loading table for operators, allowing them to easily access three sides of the rack where components are placed for cleaning. Heavy parts can be placed on the door so that operators do not have to reach into the chamber of the washer. Teflon wheels on the rack provide a smooth transition into the chamber.

Component selection—Internal components must be compliant with GMP requirements. Sanitary diaphragm valves should be available for all areas that come into contact with process fluid. Plumbing should use orbital welds wherever possible and should be finished to a minimum of 25 Ra. Dead legs should be kept to a minimum of 6 pipe diameters. 316L stainless steel should be the material of choice for all metallic areas. Cold rolled steel, copper, and other forms of stainless (except 304L for the frame) should be avoided at all times.

Special attention should be given to the chemical delivery system. This has been an overlooked area in GMP washer design because of the difficulty and expense of finding an effective solution. Delivery systems must allow for precise amounts of additives (caustic detergents and acid-based products) and must withstand delivery of harsh ingredients. Often, a commercial laundry delivery system is installed only to fail a few months after qualification, resulting in costly downtime at the production facility.

Drying systems should provide complete coverage of all aspects of the load. Additionally, the washer itself should be dried entirely and prepared for the next validated cycle. Non-shedding materials should be used throughout the drying circuit. High temperature-rated HEPA filters should be the final point for the air entering the basin or accessories to provide a clean, particulate-free drying process. Dispersed oil particulate (DOP) challenge ports should be provided so that HEPA integrity can be tested regularly. Separate circuits for the basin and the hydraulic unit (including internal parts for loading accessories) will provide the fastest and most effective cycles. This design is inherently more expensive but can be justified quickly based upon process requirements.

Inventory systems—While construction of the chamber, chassis, and internal components is important to overall washer performance, inventory is an equally important yet frequently overlooked consideration. Most often, manufacturers are criticized for not considering the inventory compared to the chamber and the parts to be cleaned. A complete inventory involves documenting size, weight, and specific cleaning requirements for all components to be cleaned. Once this information is assembled, parts can be grouped together in loads, and necessary chamber volume can be calculated. Ergonomic principles should be applied to prevent operator overload, maximize the parts per run, and minimize utility consumption.

Documentation requirements—A documentation package is needed to complete the validation and qualify the GMP cleaning system. The package should contain the following minimum components:

- User manual
- Maintenance manual
- Instrument list
- Electrical diagram
- Piping and instrumentation diagram
- Spare parts list
- Exploded view
- Welding report and welder certificate
- Source codes (written or electronic)
- Passivation report
- As-built drawings
- IQ/OQ documentation

In summation, cleaning components used in a pharmaceutical, biotech, cosmetic, or medical device manufacturing environment present obstacles not found when cleaning glassware or parts used in laboratory research or many other industries. Materials of construction, soiling of active compounds and other relevant

residues, load configurations, and regulatory constraints must each be considered when cleaning at production level. However, when properly managed, obstacles can be overcome and an effective cleaning system can be implemented. Developing a wash protocol typically involves the following steps:

A. Clear understanding of the items to be cleaned is paramount to success of a validated system. The operator must load and unload the washer in specific steps to maintain cycle validation. Ergonomic principles regarding the load and the rack must be addressed at this point to make additional design and steelwork feasible.

B. An understanding of the residues to be removed is the next step. Determine whether the residues can be removed within the constraints of available time, temperature, cleaning chemistry, and agitation.

C. Load patterns must then be addressed. To meet validation requirements, specific components must be cleaned together. This is a challenge requiring designers of inventory systems for GMP washers to have complete knowledge of the material make-up and dimensions of the parts being cleaned. Parts can then be arranged on a CAD drawing to determine whether there are any load/unload problems to overcome. At this point, a clear picture of the cleaning cycle protocol comes into focus.

D. The programmable logic controller (PLC) or microprocessor can then be programmed, taking into account the established cleaning protocol. System monitoring and data transfer to other monitoring locations are additional elements of the system design.

By following the steps outlined above, a successful protocol for cleaning pharmaceutical, biotech, medical device, and related equipment using a GMP washer can be put in place.

See Table 6.18 for a brief detergent selection guide for GMP washers/dryers.

Table 6.18 Detergent selection guide for GMP washers/dryers

Application	Articles Cleaned/ Soil Removed	Cleaning Method	Recommended Detergent	Alconox Inc. Detergent
GMP Washers/ Dryers Especially useful for equipment parts that are disassembled for cleaning—manufacturing tools and bench-scale production equipment that can be loaded onto racks are often best cleaned in a dishwasher capable of validated cleaning	Titanium dioxide, petrolatum, oils, emulsions, ointments, carbopols, lacquers, zinc oxides	Cup-in-door washer Washer requires phosphate-free Liquid dispensing washer	Low-foam alkaline Low-foam alkaline Low-foam alkaline Low-foam high alkaline	Alcojet Tergajet Solujet Keylajet
	Inorganic residues, salts, buffering solutions	Washer rinse cycles	Low-foam mild acid	Citrajet
	Protein, organic, cellular and fermentation residues; reverse osmosis, ultrafiltration membranes, oxidation	Liquid dispensing washer	Low-foam alkaline	Detojet

Passivation Cleaning

Passivation is the process of making a surface less electrically or chemically active, resulting in a surface that is less prone to corrosion. In reference to steel, especially stainless steel, passivation refers to the removal of surface free iron. This process causes a relative increase in chromium (Cr) and hence chromium oxide on the surface relative to iron (Fe) or iron oxide. This is important because reducing surface potential or conductivity facilitates a decreased rate of corrosion

of steel and stainless steel. Corrosion in industries such as medical device, pharmaceutical, and precision manufacturing can cause serious structural and performance problems and thus should be avoided.

Before chemical passivation, steel or stainless steel substrates should be effectively cleaned with an appropriate cleaner to remove dirt, oil, and dust contamination that could be a barrier to passivation solution reactions. This is usually a mild alkaline manual/ultrasonic detergent with high emulsifying capabilities, or a higher alkaline detergent if using a spray/CIP type of system. Further, using a well-formulated passivation solution will synergistically enhance chelation, sequestration, lifting, wetting, and rinsability.

Chemical passivation is primarily done with acidic solutions. These solutions include phosphoric acid, nitric acid, and citric acid. Maximizing the Cr/Fe surface ratio is advantageous to prevent corrosion on steel and stainless steel. Although less common, phosphoric acid solution can give a passive surface with a Cr/Fe ratio of up to 1.2. Phosphoric acid is more commonly used in electropolishing, although phosphoric acid has safety concerns.

Nitric acid passivation as referenced in documents such as ASTM A967, ASTM A380, and AMS 2700 has been extensively used to passivate steel or stainless steel surfaces. Nitric acid passivation can achieve a Cr/Fe ratio from 1.0 to as high as 1.5. Although nitric acid can effectively passivate a steel or stainless steel surface, it has significant safety and disposal concerns.

Formulated citric acid passivation such as stated in ASTM A967 has the advantage of being safer than other means of acidic passivation of steel and stainless steel while being able to achieve a Cr/Fe ratio of up to approximately 2.0. This often requires longer time (up to 3 hours) and higher temperatures [up to 80°C (176°F)]

but leads to better surface passivation. In addition to superior safety and efficacy, citric acid has the ability to chelate and thus can better deactivate metal ions and allow them to be removed from the surface, preventing subsequent corrosion. A well-built passivation solution can synergistically assist this removal of free iron.

A well-passivated surface with a chromium-rich layer can be scratched or damaged within the chromium-rich layer and still reform a passive chromium oxide layer, as the freshly exposed chromium-rich layer will form chromium oxide upon exposure to oxygen in the air (Figure 6.1).

See Table 6.19 for a brief detergent selection guide for passivation cleaning.

Table 6.19 Detergent selection guide for passivation cleaning

Application Key Concerns	Articles Cleaned/ Soil Removed	Cleaning Method	Recommended Detergent	Alconox Inc. Detergent
Passivation Forming a passive layer of chromium oxide on the surface of stainless steel to protect against corrosion	Removal of free iron, creating a passive layer of chromium oxide	Manual, ultrasonic, soak	Mild acid	Citranox
		Machine washer, pressure washer, clean-in-place (CIP)	Low-foam mild acid	Citrajet

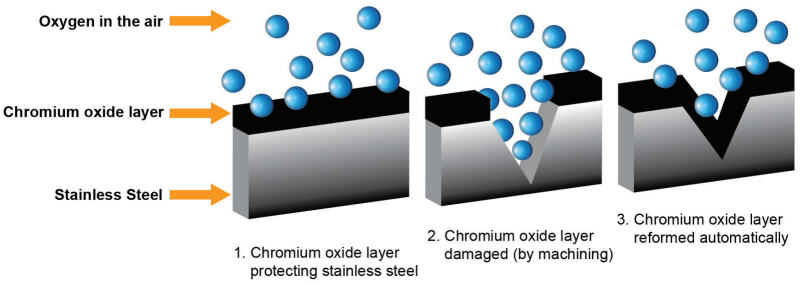

Figure 6.1 Stainless steel passivation.

Filter Cleaning

Filtration—and thus filtration cleaning and reuse—spreads across essentially all industries. Types of filtration media that are traditionally cleaned include tangential flow filtration (TFF) modules and cassettes. TFF modules are frequently characterized as either microfiltration or ultrafiltration. The range for microfiltration is often described as 0.1–1.0 μm (10 μm in some fields), and ultrafiltration as 0.01–0.1 μm. Other filters can be considered for cleaning and reuse as well, including traditional direct flow or dead-end filtration.

TFF membrane materials are polymeric in nature (e.g., polyvinylidene fluoride, polyethersulfone, cellulose acetate) or ceramic. These substrates are compatible with most aqueous detergents intended for manual cleaning.

Biotechnology, pharmaceutical, healthcare, and associated fields often encounter protein-based residues in connection with drug production, blood filtration, and other biologic-derived matter. Cleaning these membranes requires mild alkaline, high-emulsifying detergents and/or high-emulsifying detergents enhanced with protein enzymes. High-emulsifying protein enzyme detergents play a vital role in reducing and controlling biofilm buildup in filters by removing residues and organic buildup associated with biofilms, allowing subsequent use of sanitizers and disinfectants per CDC/EPA requirements.

Water filtration may encounter residues that are both organic and inorganic. Biologic-derived residues are removed as described above, while inorganic water scale, minerals, salts, and similar residues are cleaned with an acidic detergent. Reverse osmosis (RO) filters for water desalinization are cleaned with acidic detergents to remove the inorganic buildup that reduces filtration performance. Organic

buildup in RO filtration applications with brackish water can also reduce filter life and performance, requiring a mild alkaline detergent for removal.

Other industries where filter reuse is a critical process step include food and beverage, foodservice, and oil filtration industries, where organic and inorganic residues are cleaned by mild alkaline and acidic detergents, respectively.

In all applications of filter cleaning, setups where air is introduced in the fluid path or where foaming detergents are otherwise undesirable should use low-foaming detergents. Low-foaming detergents compensate for reduced emulsification capacity (due to lower use of foaming surfactants) and can include oxidative and/or alkaline hydrolysis cleaning processes to remove organic residues. Likewise, low-foaming acidic detergents are used to remove inorganic residues when foaming must be avoided.

See Table 6.20 for a brief detergent selection guide for filter cleaning.

Table 6.20 Detergent selection guide for filter cleaning

Application Key Concerns	Articles Cleaned/ Soil Removed	Cleaning Method	Recommended Detergent	Alconox Inc. Detergent
Filter Cleaning Returning reusable reverse osmosis and ultrafiltration filters to specified flux requires thorough residue-free cleaning	General cleaning of fouled ultrafiltration membrane and reverse osmosis modules	Soaking, recirculation clean-in-place (CIP)	Mild alkaline Mild alkaline Mild acid	Alconox Liquinox Citranox
		High-pressure CIP or other low-foaming requirement	Low-foam alkaline Low-foam alkaline Low-foam alkaline Low-foam mild acid	Alcojet Solujet Detojet Citrajet
	Removal of proteinaceous and similar residues	Soaking, recirculation CIP	Enzymatic mild alkaline	Tergazyme

Biofilm Cleaning

Biofilm typically consists of bacteria adhered to a surface, forming a complex architecture of microbial communities. An established biofilm has a matrix composed of microbial cells and cell-secreted extracellular polymeric substance (EPS) typically involving hydrophobic polysaccharides. This matrix forms a defined architecture and provides an optimal environment for microbes to communally evolve to adapt to their environment. Biofilms can thus be tenacious and difficult to eliminate.

When removing biofilm, both low-foaming clean-in-place (CIP) as well as higher-foaming enzymatic detergents are effective.

- ***Low-foaming CIP detergents:*** A reliable way to remove biofilms from stainless steel process piping and tank surfaces is to use a two-step, high-temperature process with an aqueous alkaline cleaner (low-foaming alkaline) followed by an aqueous acidic cleaner (low-foaming mild acid).

  For heavy biofilm applications or for biofilms that have persisted over a long period of time, a typical effective process consists of a 3% alkaline cleaner at 75°C (167°F) applied for 30 minutes, followed by a cursory rinse to mitigate neutralizing the next acid step. The second step uses a 3% acidic cleaner at 75°C (167°F) applied for 30 minutes, followed by a final thorough rinse with water. This two-step process, at the specified temperatures, produces a very clean result on stainless steel. It can be desirable to use a disinfectant after cleaning to slow down the return of the biofilm.

  These methods may be used to clean and prepare tanks, process lines, centrifuges, and similar equipment. In addition to removing well-established biofilms, biofilm cleaning processes are typically incorporated into preventive maintenance programs to prevent biofilm formation.

- ***High-foaming manual/clean-out-of-place (COP) detergents:*** When using scrubbing, soaking, sonication, or recirculation applications that avoid high pressure/air entrainment (e.g., filter cleaning), use an enzymatic cleaner that contains protease, surfactants, and builders. Such formulations remove biofilm at lower temperatures than typically used in CIP systems. Low temperatures are typically required to avoid denaturing the enzymes used for cleaning. The protease addresses both cells and proteins bound in the lipopolysaccharide portion of the biofilm, whereas the surfactants improve wetting and penetration through the hydrophobic lipopolysaccharide portion of the biofilm. When used appropriately, this solution completely removes the inanimate portions of biofilm.

  To manually clean or remove biofilm, use powdered enzymatic detergent mixed at 1%–3% in warm water (35°C–55°C to ensure optimal enzyme activity). These detergents are high-foaming cleaners and are not suitable for spray-in-air CIP systems. Solutions can be pumped and gently agitated; however, using high agitation at an air/solution interface will result in excessive foam. For an old biofilm, consider a 30-minute 1%–3% detergent solution (soak/recirculation) at 35°C (95°F) before the acid/alkaline cleaning protocol above.

  This approach with enzymatic detergent also can be used reliably in manual surface cleaning and cleaning preparation for subsequent disinfectant-based biofilm removal, such as in cleanrooms. Removing proteinaceous, organic, and inanimate residues of biofilm will lengthen the amount of time before the biofilm returns. Use enzymatic cleaning

processes in intermittent preventive maintenance between alkaline/acidic cleaning to remove dead cells and traces of lipopolysaccharide portions of biofilm.

Bleach alone is sometimes used to treat biofilms, but often the hydrophobic nature of the biofilm interferes with the efficacy of oxidization; therefore, bleach alone may not provide sufficient cleaning. Incorporating an alkaline cleaner or detergent improves the effectiveness of biofilm removal compared to cleaning with bleach alone. Bleach used at concentrations suitable for food contact surfaces does have some efficacy on thermophilic bacilli and similar biofilms, although efficacy may be intermittent. The bleaching mechanism breaks down membranes at sulfhydryl groups and unsaturated side chains; as potential exposed sites are used up, efficacy of the cleaning may fail, allowing the biofilm to persist. Further, minimizing use of bleach may be preferable in light of the potential for bleach to cause chloride stress cracking on stainless steel.

Table 6.21 provides a brief detergent selection guide for biofilm cleaning.

Table 6.21 Detergent selection guide for biofilm cleaning

Application Key Concerns	Articles Cleaned/ Soil Removed	Cleaning Method	Recommended Detergent	Alconox Inc. Detergent
Biofilm Pass cleaning validation for FDA good manufacturing practices, European Union regulations, and similar requirements	Protein, bacteria, organic, cellular, and fermentation residues; reverse osmosis, ultrafiltration membranes	Manual, ultrasonic, soak	Enzymatic mild alkaline	Tergazyme
		Machine washer, power washer, clean-in-place (CIP)	Low-foam alkaline Low-foam mild acid	Solujet Citrajet

References

Alconox Inc., "How to clean an aluminum coated mirror," Alconox Inc. TechNotes (3 March 2020). Available at technotes.alconox.com/industry/optical/how-to-clean-an-aluminum-coated-mirror

K. Hildebrandt, "Identifying, inspecting and addressing shallow injection wells," U.S. Environmental Protection Agency (2019). Available at epa.gov/sites/default/files/2019-08/documents/hildebrandt_-_class_v_shallow_wells_2019.pdf

B. Kanegsberg and E. Kanegsburg, Handbook for Critical Cleaning, Second Edition; CRC Press, Boca Raton, FL (2011).

B. Kanegsberg and E. Kanegsberg, "Making the most of your ultrasonic cleaning system: Understanding critical variables can help maximize the return on your cleaning system investment," Metal Finishing, Vol. 106, Nos. 7–8, 39–44 (July–August 2008).

New York State Pollution Prevention Institute (NYSP2I), "Vacuum cycle nucleation overview," Rochester Institute of Technology. Available at rit.edu/affiliate/nysp2i/sites/rit.edu.affiliate.nysp2i/files/docs/resources/Vacuum_Cycle_Nucleation_Technology_Overview_2019.pdf

D.A. Seiberling and B.B. Daneker. One Man's Quest to Keep You Safe: Dale Seiberling and Clean-In-Place Innovation (2020).

U.S. Environmental Protection Agency, "EPA releases final chemical risk evaluation for TCE," (23 November 2020). Available at epa.gov/chemicals-under-tsca/epa-releases-final-chemical-risk-evaluation-tce

U.S. Environmental Protection Agency, "Risk evaluation for 1-bromopropane (1-BP)," (11 August 2020). Available at epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-1-bromopropane-1-bp

U.S. Environmental Protection Agency, "Method 1637: Determination of trace elements in ambient waters by off-line chelation preconcentration and stabilized temperature graphite furnace atomic absorption," (January 1996).

U.S. Environmental Protection Agency, "Environmental Compliance Branch Standard Operating Procedures and Quality Assurance Manual," (1991).

U.S. Food and Drug Administration, "Inspection Technical Guides: Bacterial endotoxins/pyrogens," (original publication 1985). Available at fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-technical-guides/bacterial-endotoxinspyrogens

U.S. Food and Drug Administration, Code of Federal Regulations (CFR) Part 210: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs (original publication 1978). Available at ecfr.gov/current/title-21/chapter-I/subchapter-C

U.S. Food and Drug Administration, Code of Federal Regulations (CFR) Part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals (original publication 1978). Available at ecfr.gov/current/title-21/chapter-I/subchapter-C

Resources

alconox.com
cdc.gov
epa.gov
fda.gov
ich.org
ispe.org
pda.org
technotes.alconox.com
thecannabisindustry.org

Chapter Seven:

Standard Operating Procedures

A large part of successful cleaning depends on having standardized, reproducible procedures, also known as standard operating procedures (SOPs). A system of SOPs helps ensure consistent cleaning and can be useful to train operators properly. In general, a good SOP includes a list of the materials and people involved in the cleaning procedure. It identifies the surface or part to be cleaned and addresses the nine cleaning variables—BATH-O-CARD—that impact cleaning effectiveness (Figure 7.1; see Chapter Three).

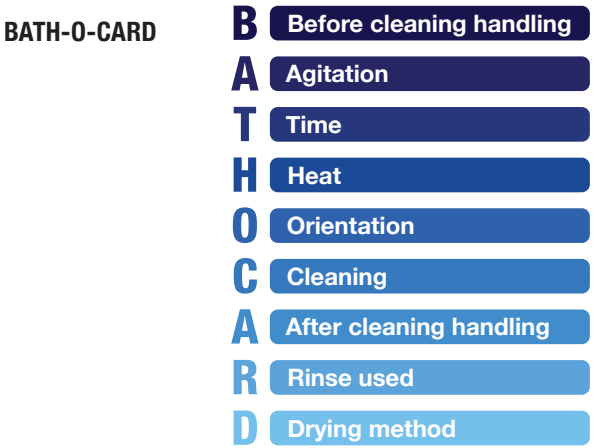

Figure 7.1 Cleaning variables of BATH-O-CARD.

Below are examples of SOPs for manual cleaning, ultrasonic cleaning, machine washer cleaning, and large-tank cleaning. In some cases, these SOPs were written for specific combinations of detergent concentrations and cleaning temperatures for certain soils. As a result, you may need to adapt these SOPs for your applications. However, they provide an idea of what to include in a typical SOP.

Wherever cleaning solutions are re-used in baths or sumps, determine the following: control parameters (e.g., pH, conductivity, refractive index/dissolved solids, or titration amounts), equipment to be used (e.g., conductivity meters, pH meters or refractometers, or titration equipment), person or persons responsible for monitoring the baths, type of report or logbook entry to be made, trigger points and alert levels, when and what actions should be taken in response to these levels, and the conditions under which the bath should be replaced.

Manual Parts or Manual Surface Cleaning SOP

1. List parts or surfaces to be cleaned. State the maximum number of parts or surface area that the process is designed to clean. Describe any training or certification requirements for those who will perform the cleaning operation.
2. List the materials to use for cleaning, including the following.
    a. Detergent—provide full name, manufacturer, manufacturer part number, distributor/supplier, and internal part number as appropriate.
    b. Water of suitable purity—determine whether tap water, deionized water, distilled water, or water-for-injection is appropriate.
    c. Whether a brush, absorbent cloth, or sponge is used.
    d. Define size of the container for the detergent solution.

e. Specify any baskets for handling small parts, if used.
f. Specify any rinsing containers, if used.
g. Specify any drying equipment, if used.
h. Identify required personal protective equipment (PPE), such as gloves, eye protection, or clothing.

3. List requirements for handling prior to cleaning. Example requirements and validated procedures might include the following.
    a. Identify parts to be cleaned quickly after use (e.g., within 1–4 hours) to remove residue, especially residues that become more difficult to remove as they dry.
    b. Tank to be cleaned within a "dirty hold" time (e.g., 1–2 days of last use), if you validated that the tank could sit dirty for a specified amount of time and still be cleaned successfully by this manual procedure.
    c. Do not remove parts from shipping containers until they are about to be cleaned, if you know that unpacking parts increases the risk of new contaminants and residues.
    d. Handle all parts with finger cots or gloves to avoid adding fingerprints to surfaces, especially when using a cleaning process that is only designed to remove particulates.
    e. Presoak parts in a specific detergent solution for a specified time and at a specified temperature prior to cleaning, if you know the parts have dried-on protein soils that are difficult to clean without presoaking. For example: Presoak parts completely immersed in

1%–2% Tergazyme detergent (1.25–2.5 oz. Tergazyme in 1 gal. of water) at 50°C (120°F) for 20 minutes prior to cleaning.

4. Provide directions for making up detergent solution following the manufacturer's instructions. Address required temperature, water purity, and container size. The following is one such example.
    a. Mix 1.25 oz. of Alconox powdered detergent in 1 gal. of 50°C (120°F) hot tap water in a 2.5-gal. bucket. Use cleaning solution within 15 minutes before the temperature drops below 50°C (120°F).
5. Provide manual cleaning instructions, such as the following.
    a. Wet part or surface with solution by (1) dunking the part in the solution, or (2) wiping the part with a solution-soaked brush, absorbent cloth, or sponge.
    b. Clean by scrubbing with a brush, absorbent cloth, or sponge. Define any particular cleaning or scrubbing actions required, such as: Brush all surfaces vigorously, but particularly be sure to use brush vigorously on the inside of the port for at least 30 seconds.
6. Itemize rinse procedures. Examples include the following.
    a. Place parts in basket and position under running tap water for 20 seconds while moving basket to ensure all parts are exposed to running water.
    b. Hose down all surfaces with running water, ensuring that all parts of surface are rinsed for at least 10 seconds.
    c. Dip part in bucket of rinse water for initial rinse, dip in second bucket of rinse water for second rinse, and then place under running water for 10 seconds as a final rinse.

7. Describe drying procedure. Examples include the following.
    a. Place parts on rack and allow to air dry when evaporative drying is appropriate.
    b. Place parts on tray and place in a drying oven for a set temperature and time (will vary based on part substrate composition).
    c. Air blow parts/tanks with dry, filtered air.
    d. Use alcohol or other cosolvent to facilitate removal of water.
8. List any post-cleaning handling procedures. Examples include the following.
    a. Visual inspection methods and other validated means to confirm inspection actions. For example: Take 10 parts from the batch and inspect for particulates and visible smudges with a 10X magnifying glass. Record results in batch record. Reject entire lot if there are any failures.
    b. Mark tank and vessels with "clean tags" recording time, date, and operator who performed cleaning.
    c. Dispose of used detergent solution down the drain or, as appropriate, based on local disposal regulations.

Ultrasonic Cleaning SOP

1. List parts to be cleaned. Indicate the maximum number of parts per batch. Define any training or certification requirements needed to perform this cleaning operation.
2. List the materials to use for cleaning, including the following.
    a. Detergent—provide full name, manufacturer, manufacturer part number, distributor/supplier, and internal part number as appropriate.

b. Water of suitable purity—indicate whether tap water, deionized water, distilled water, or water-for-injection is appropriate.
c. Ultrasonic cleaning tank—define size, frequency, configuration, manufacturer, and identifying specifications.
d. Specify any baskets for handling small parts, if used.
e. Specify any rinsing containers or equipment, if used.
f. Specify any drying equipment, if used.
g. Identify any required personal protective equipment (PPE), such as gloves, eye protection, or clothing.

3. List any requirements for handling prior to cleaning. Typical requirements may include the following.
   a. Degas solution for 10 minutes to remove dissolved gasses that will dissipate cavitation energy and decrease cleaning performance.
   b. Turn on heaters and preheat the tank to 50°C (122°F).
   c. Identify parts to be cleaned quickly after use (e.g., within 1–4 hours) to remove residues, especially residues that become more difficult to remove as they dry.
   d. Do not remove parts from shipping containers until they are about to be cleaned, if you know that unpacking parts increases the risk of new contaminants and residues.
   e. Handle all parts with finger cots or gloves to avoid adding fingerprints to surfaces, especially when using a cleaning process that is only designed to remove particulates.

f. Presoak parts in a specific detergent solution for a specified time and at a specified temperature prior to cleaning, if you know the parts have dried on protein soils that are difficult to clean without presoaking. For example: Presoak parts completely immersed in 1%–2% Tergazyme detergent (1.25–2.5 oz. Tergazyme in 1 gal. of water) at 50°C (120°F) for 20 minutes prior to cleaning.

4. Provide instructions for making up the detergent solution following manufacturer's directions. Address degree of water purity required, container size, and suitable temperature. Examples include the following.
    a. Mix 1.25 oz. of Alconox powdered detergent in 1 gal. of 50°C (122°F) hot tap water, which will fill tank to within 1 inch of the top.
    b. Fill tank within 1 inch of top and turn on heaters. Make up 1% Alconox solution in a beaker (20 g Alconox in 200 mL water in a 250 mL beaker). Place the beaker of Alconox solution in a beaker tray, immersing it in the heated water. Fill three other beakers with deionized water for rinsing and place them in the beaker tray.
5. Provide step-by-step cleaning instructions. Examples include the following.
    a. Include directions for part placement in the cleaning device. Never place parts or receptacles directly on the bottom of the unit. It can cause the unit to fail because the parts will reflect ultrasonic energy back into the transducer. Always allow at least one inch between the

tank bottom and the beaker or receptacle for adequate cavitation. Keep solution within one inch of the top of the unit when a beaker or tray is in place.

b. Describe the use of a holder. If using a tray or basket to lower parts into solution, it is better to use an open-construction holder, either an open mesh basket or an insert tray, that is adequately perforated for drainage. This also permits free access of sound waves to the parts.

c. Clean the parts in solution by:

i. Placing them in a basket and immersing them in the ultrasonic tank for 10–20 minutes.

ii. After this time, lift the basket and allow it to drip off for 1 minute to reduce dragout.

iii. Cover ultrasonic tank after removing and draining basket.

6. Itemize rinse procedures. Examples include the following.

a. Place basket containing parts under running tap water for 20 seconds while moving basket to ensure all parts are exposed to the water.

b. Do a final rinse by immersing in a second ultrasonic tank filled with deionized water for a final rinse. Change rinse water when it reaches 50 kOhms resistance.

7. Describe drying procedure. Examples include the following.

a. Place parts on rack and allow to air dry when evaporative drying is appropriate.

b. Place parts on tray and place in a drying oven for a set temperature and time (will vary based on part substrate composition).

c. Air blow parts/tanks with dry, filtered air.

d. Use alcohol or other cosolvent to facilitate removal of water.

8. List any post-cleaning handling procedures Examples include the following.
    a. Visual inspection methods and other validated means to confirm inspection actions. For example: Take 10 parts from the batch and inspect for particulates and visible smudges with a 10X magnifying glass. Record results in batch record. Reject entire lot if there are any failures.
    b. Mark tank and vessels with "clean tags" recording time, date, and operator who performed cleaning.
    c. Dispose of used detergent solution down the drain or, as appropriate, based on local disposal regulations.

Ultrasonic Cleaner Test SOP

When cleaning using ultrasonics, you should test the performance of your ultrasonic washer. Refer to your manufacturer's recommended method.

Once such procedure is the aluminum foil test. Other procedures include hydrophone, standardized soil, and chlorine release tests. Note that no ultrasonic performance test substitutes for appropriate validation/verification of the cleaning procedure itself. The following is an example of an aluminum foil test SOP.

1. Prepare an aluminum foil sample using standard lightweight household aluminum foil. Unroll a rectangular piece of foil measuring approximately the length (long dimension) of the tank by one inch greater than the depth. For example: A tank with dimensions of 9 inches long by 5 inches wide by 4 inches deep would require a foil sample measuring 9 inches by 5 inches. Use scissors to cut the foil; do not tear.

2. Prepare a fresh cleaning solution according to the manufacturer's instructions and fill the ultrasonic tank to one inch of the brim.
3. Heaters should be turned off for the test. Any variable ultrasonic power setting should be set to maximum.
4. Before placing the foil in the tank, turn the ultrasonic cleaner on for 5 minutes to degas the tank.
5. Place the foil sample, prepared in Step 1, into the tank in a vertical position. The long dimension of the sample should be positioned parallel to the long side of the tank. The foil should extend downward but should not touch the tank bottom.
6. Hold the foil, approximately centered front to back, as steady as possible. Turn the ultrasonic cleaner on for 20 seconds.
7. Turn the cleaner off and remove the foil sample. Shake the foil sample to remove any water droplets and allow it to air dry. Be careful not to wrinkle the foil.
8. If the unit is functioning properly, the entire foil surface will be uniformly "peppered" (covered with a tiny pebbling effect). If areas greater than one-inch square show no pebbling, there may be a problem with the unit. Retest with new foil to substantiate the failure. If both samples fail, return the unit, along with the latest foil record, to your service center or to the manufacturer for repair. Retain foil samples for reference. If future tests show marked changes over time, you may need to service your unit. Always include foil samples when you send the unit in for service.

Machine Washer SOP

Clean-out-of-place in rack-loaded spray-in-air washer

An SOP for the wash cycle in a machine washer, which does not include the scope and list of materials, is as follows.

1. Precleaning, required only to remove bulk ingredients, can be accomplished by thorough rinsing. Handle the items you are cleaning according to manufacturer's recommendations. Follow your company's safety regulations when handling and transporting items.
2. Chemical composition and concentration of cleaners is specific to the soils and residues to be removed. A GMP washer uses precise dosing pumps to deliver chemicals to the wash chamber, which contains a fixed volume of water. The dosing time will determine the amount of chemical delivered to the chamber.
3. cGMP wash temperatures are programmed by the user up to 95°C (200°F).
4. Adequate exposure time of cleaning chemistry at setpoint temperature will ensure proper cleaning. cGMP washers validate exposure time through continual monitoring.
5. Purified water rinsing ensures removal of all cleaning chemicals at the end of the wash cycle. Measure conductivity of final rinse water to validate rinsing efficiency.
6. On drying models, a drying step with temperatures up to 110°C (230°F) can be performed. All drying air is HEPA-filtered.
7. Post-cleaning handling of washed items must follow internal company procedures that assure cGMP compliance.

During inspection and qualification of the cGMP washer, verification of the effectiveness of the inventory system as described above must be demonstrated. Testing protocols must be established.

One test protocol for establishing cGMP washer operation as part of installation qualification (IQ) or performance qualification (PQ) is the riboflavin UV test:

- Soil the parts with a riboflavin solution.
- Let dry for 2 hours, and then soil them again.
- Let dry overnight.
- Perform a wash cycle that does not include drying.
- After cycle, check wet parts with a UV lamp.
- Does riboflavin remain?
    - Test 1: Yes / No
    - Test 2: Yes / No
    - Test 3: Yes / No

After the system has been inspected and verified, operators must be trained to load/unload the racks efficiently.

Clean-in-Place (CIP) Ultrafiltration SOP

CIP brine water filter system cleaning

1. Scope:
    a. To clean a large ultrafiltration brine water filter system.
    b. Operators must be trained and qualified.
2. Materials:
    a. Good-quality chlorine-free tap water (total dissolved solids <5,000 mg/L).
    b. 316 stainless steel mix tank sized appropriately to the

system (minimum of 3-minute retention time during circulation) with an exhaust fan, mixer, cooling coil, and temperature indicator.

   c. 316 stainless steel centrifuge pump sized for appropriate flow rates.
   d. 10-μm cartridge prefilter.
   e. Flow meters.
   f. Suitable flexible piping, sampling ports, and port connectors.
   g. Tergazyme (Alconox Inc. catalog number 1350) enzyme cleaner.

3. Pre-cleaning conditions:
   a. Filter system suffering from biofouling and/or inorganic particulate buildup.
4. Cleaning, rinsing, and drying description:
   a. In large systems, isolate the one block of filter elements to be cleaned, allowing the rest of the blocks to operate normally.
   b. Flush filter element block with water once through (10 gal. for a typical 4-inch diameter filter element unit; different sized units would take proportionally more or less water).
   c. In the mix tank, dissolve enough Tergazyme to make a 0.5%–1% solution, taking into account the volume of the tanks and filter element blocks (2.5 gal. for a 4-inch system).
   d. Turn on mixer to dissolve detergent.
   e. Circulate cleaning solution through the filter block. Send the first 20% of solution to drain via the brine

return valve. Circulate the rest of the cleaning solution at 4.5 gal./minute at 50–150 psig (345–1035 Kpa) pressure for a 4-inch system. Use the chiller to maintain the temperature below 35°C (95°F).

f. The cleaning progress can be monitored by observing the color of the effluent. Circulate continuously or alternate circulate and soak cycles for 15 minutes each. Circulate for at least 2 hours for a 4-inch system. Continue until the return effluent is no longer badly discolored.

g. When cleaning is complete, stop recirculation and drain mix tank to waste. Flush residual cleaner with feed water at 4.5 gal./minute (17 L/minute) at 50–75 psig (345–518 Kpa) pressure (for 4-inch systems), sending both brine and product side to drain. Collect sample of effluent in a small jar; cover, shake, and observe foam to indicate the presence of detergent. Rinse jar between uses. Continue flushing until no foam is observed in the shaken sample jar.

5. Post-cleaning handling:

   a. Perform post-treatment procedures and return block to normal operations. Check pressure and performance to determine whether further treatment with a citric cleaner such as Citranox (Alconox Inc. catalog number 1815) is needed to reduce particulate and inorganic scale buildup.

CIP large tank fill, soak, and agitate cleaning

1. Scope:

   a. To clean a large stainless steel tank to remove a blended material that contains a thick high-melting wax.

    b. Operators must be trained and qualified.
2. Materials:
    a. Detergent.
    b. Brush.
    c. Bucket.
    d. Recirculation pump.
    e. Hot water hose.
3. Precleaning conditions:
    a. Tank to be cleaned within maximum dirty hold time (e.g., 24 hours).
    b. Tank ports should be kept closed while in holding.
4. Cleaning, rinsing, and drying:
    a. Fill tank full with hot plant water.
    b. Add detergent recommended for the type of residue in the tank.
    c. Turn on mixer wipers to agitate.
    d. Turn on tank heaters to raise temperature above 95°C (200°F) (see note below).
    e. Turn on pumps and connect pipes to recirculate through any lines that need to be cleaned. Note: Pumps should be operated with sufficient head pressure or at a slow enough speed to avoid cavitation from foam.
    f. Run for 4 hours. Depending on how well-sealed the tank is, you may need to add make-up solution to compensate for evaporation during the 4 hours.
    g. Open top and, using a brush dipped in hot solution, manually scrub the unexposed top sections of the tank that were not immersed by the cleaner.

h. Drain the tank.
i. Fill the tank with hot plant water heated to 95°C (200°F). Keep the agitation and any recirculation pump turned on for 10 minutes.
j. Use a hose with hot water to rinse the top part of the tank above the immersion line.
k. Drain the tank.
l. Visually inspect the interior of the tank and clean any known problem areas with a hot bucket of detergent solution and brush.
m. Rinse the tank thoroughly with hose of hot plant water or a spray ball apparatus with hot plant water.
n. Drain the tank.
o. Air dry the tank with open ports using appropriate positive pressure, air filters, or other measures appropriate to the level of cleanliness required in the tank.

5. Post-cleaning conditions:
    a. Tag the tank as clean with a date to allow control for clean hold times.
    b. Record cleaning in equipment log, including date, time, and operator.

Note: As experience is gained with specific soils and tanks, you may need to adjust cleaning time. The cleaning regimen described above was designed to remove a wax that melts at ~90°C (194°F). You will not need this much heat to remove most soils and residues. For example, many waxes melt at 75°C (167°F)—adapt this procedure by lowering temperatures as appropriate.

The SOPs above are examples that can be adapted for other cleaning situations. There are many varieties of cleaning machines, including vibratory washers, oscillating washers, reel-to-reel washers, spray cabinet washers, and a range of other industrial washers. Each requires a different SOP. The machine manufacturer can help you understand how to operate a washer correctly. Use the above examples as guides and your own experience to formulate an effective SOP.

References

Cleaning Technologies Group, "Aluminum foil test" (2020). Available at techblog.ctgclean.com/2020/03/aluminum-foil-test

J. Durkee, Management of Industrial Cleaning Technology and Processes; Elsevier: Amsterdam (2006).

D. LeBlanc, Pharmaceutical Cleaning Validation Training Program: Cleaning Validation Design of Automated Manual Cleaning Processes (2019).

U.S. Food and Drug Administration, "Validation of cleaning processes (7/93)." Available at fda.gov/validation-cleaning-processes-793

Resources

alconox.com
ctgclean.com
fda.gov
ispe.org
lancer.com

Chapter Eight:

Cleaning Validation

A cleaning validation study is a set of procedures to certify that a cleaning process can be performed reliably and repeatedly to meet predetermined levels of cleanliness. The study involves testing manufacturing surfaces to ensure that they are being cleaned to an acceptable level of residue, documenting that testing data, and establishing procedures to maintain that level of cleanliness. The cleaning process must combat potential contaminants including previously manufactured products, residues of cleaning agents, lubricants, dust or particulate matter from the air, and microbes.

The validation study is performed on those critical cleaning steps that affect quality or safety of the final product, which typically means focusing on surfaces that come into contact with the product. Alternatively, in some low-volume, high-value medical device manufacturing, it is more practical to verify cleaning on each individual device manufactured. However, in most pharmaceutical or large-volume medical device manufacturing, verification of acceptable levels of contamination is not practical on every manufactured product—therefore, the cleaning validation study focuses on relevant manufacturing surfaces, and a sample of manufactured products are tested for contamination.

Cleaning validation is a critical component of the pharmaceutical industry, medical device industry, and other industries that adhere to Current Good Manufacturing Practice (cGMP) and Quality Systems Regulations (QSR). Other industries that use cleaning validations include bio-pharmaceutical, bulk pharmaceutical [active pharmaceutical ingredients (APIs)], cosmetic, and clinical diagnostic manufacturing. Cleaning validation also is important in other applications and settings where high precision and purity are critical and where potential contamination must be closely controlled, such as analytical laboratories, nuclear applications, food manufacturing, semiconductor manufacturing, and the electronics industry.

Each industry and application has unique concerns, considerations, and goals regarding cleaning validation. For instance, a primary concern in pharmaceutical cleaning is cross-contamination, as pharmaceutical products must contain precise and specified amounts of substances to ensure their efficacy and safety. Inadequate cleaning of equipment that produces chemicals used for both pesticides and pharmaceutical drugs could lead to trace amounts of pesticides contaminating finished drug products, a serious potential health threat. Past missteps in pharmaceutical manufacturing have led to the development and implementation of regulations for cleaning validation to prevent such contamination.

Each cleaning validation study specifies a particular detergent and method used for cleaning, as well as the product being manufactured, potential contaminating residue, and equipment used for manufacturing. There is no one-size-fits-all solution to cleaning validation studies—any individual validation will depend on the industry, manufacturer, manufacturing product, equipment, cleaning concern, and contamination potential, among other factors.

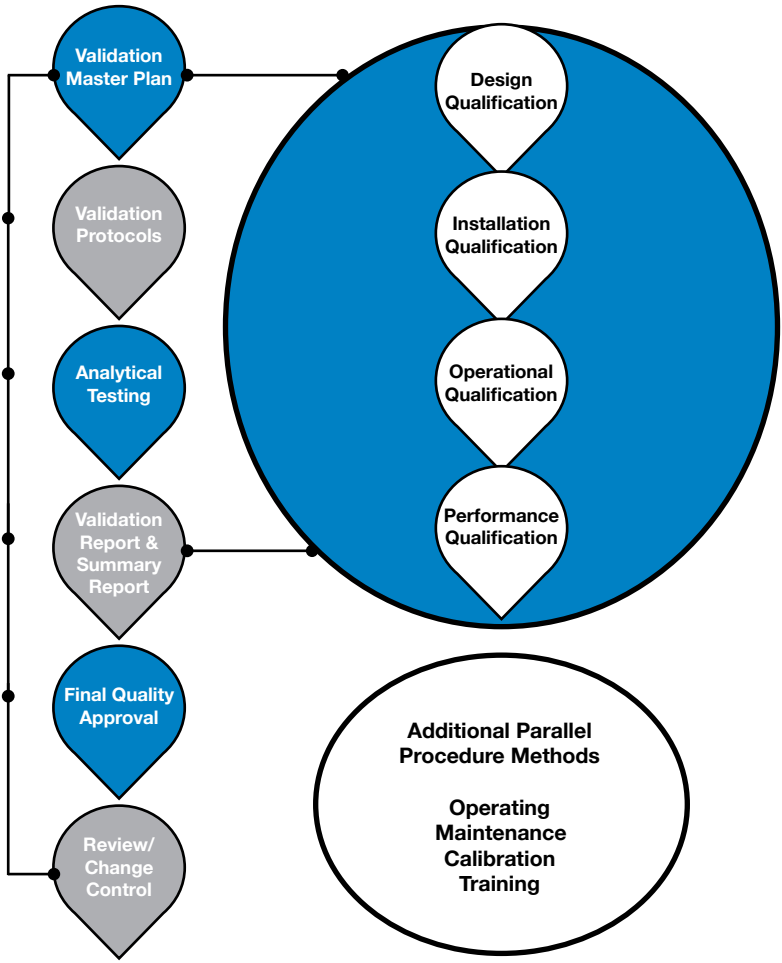

Figure 8.1 Schematic of cleaning validation process and involved qualifications.

Generally, the first step to establishing an appropriate cleaning validation study is to form a "validation team". Together, this team of individuals or departments with clearly defined duties is responsible for carrying out the cleaning validation. A typical committee might include the following:

- **Validation Specialist/Engineer**—writes and coordinates validation
- **Manufacturing**—writes standard operating procedures (SOPs) and provides training
- **Quality Assurance/Quality Control**—approves and carries out analytical methods
- **Engineering**—informs of changes and provides equipment data
- **R&D**—performs recovery studies, validates methods, transfers methods, and selects new cleaners

The validation team defines the important cleaning parameters and establishes a governing document called a Validation Master Plan (VMP), which serves as the roadmap for how to validate the cleaning and why it is necessary (Figure 8.1). This critical master plan uses a risk-based approach to assess how manufacturing may affect the quality of the product, and it outlines a strategy to mitigate those risks and ensure adequate product quality and consistency. The VMP should include the background and rationale for the cleaning validation study, a value statement, resources, and compliance requirements, such as relevant regulations and guidelines pertinent for the particular industry, application, and/or product. The plan should also include details about how to set limits, definitions of key terms, and company/facility policies regarding cleaning validation.

Critically, the VMP should define the objective of the cleaning validation. The objective might be to ensure safety of the product, worker, or environment while controlling the risk of cross-contamination. It is important to consider what specific concerns the cleaning process will address—is it to prevent microbial growth, chemical cross-contamination, or inactivation of sensitive ingredients?

The plan should address how "clean" will be defined, such as when a surface is visually clean or when analytical methods confirm residues are below predetermined acceptance limits.

The VMP serves as a guide to develop written protocols for a cleaning validation. The protocols will state the use of appropriate separately validated analytical methods to quantify specific residue levels. Those validated analytical methods are used to perform recovery studies that provide important information, such as loss factors, needed to calculate accurate residue levels.

Apart from cleaning validation, another important factor to consider is equipment qualification. Equipment qualification ensures that the cleaning validation is performed on properly functioning equipment. Equipment qualification generally consists of four parts: design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ).

Once a cleaning validation study has been concluded, a report is written, summarized, and reviewed. This cleaning validation report then goes into a document control system so that changes can be tracked and maintained.

Once a cleaning process has been validated, it should be periodically verified (often called the lifecycle approach) to ensure that the process continues to work as intended. The process also should be verified any time changes are implemented in any elements of the manufacturing system—this re-evaluation ensures that the process still achieves the predetermined level of cleanliness.

Although cleaning validations have considerable variability depending on the industry, product, manufacturer, equipment to be cleaned, and cleaners to be used, most cleaning validations consist of the following components:

- Objective of the cleaning validation
- Documentation of equipment, products, and cleaning procedures
- Validated testing and inspection protocols
- Definition of acceptance limits (and rationale)
- Sampling procedures and sampling plan
- Validated analytical methods for testing
- Cleaning and testing schedules
- Relevant data and analyses
- Assumptions and constraints
- Responsibilities for aspects of validation
- Change control
- Preventative maintenance programs
- Completed testing data and documentation of any corrective actions taken
- References and required signatures

Because there is no one-size-fits-all process to develop a suitable cleaning validation, the following sections provide examples of typical processes for developing a cleaning validation study with respect to two industries in which such studies are common: pharmaceutical manufacturing, and medical device manufacturing.

Pharmaceutical Cleaning Validation

Cleaning validation is a necessary part of manufacturing pharmaceuticals. After careful consideration, high-volume pharmaceutical manufacturers rely on validated critical cleaning only at certain specified steps in the manufacturing process that have the potential to affect the quality or safety of the final product. In

such manufacturing environments, it is impractical or impossible to verify cleaning with regard to every individual piece of production equipment.

The information below describes various developments and guidelines related to risk management, cleaning validation, and manufacturing facilities in the pharmaceutical industry. Here is a summary of the key points:

1. **FDA 1996 Proposed Revisions to the GMPs:** The FDA proposed changes to the Good Manufacturing Practices (GMPs) in response to industry complaints. The proposed changes included validation activities and the expectation for dedicated facilities for certain classes of compounds.
2. **ICH Q9 Guidance:** The ICH Q9 guidance introduced principles of quality risk management (QRM) and provided a framework for implementing risk management processes in the pharmaceutical industry.
3. **Risk-MaPP:** Risk-MaPP is a guide published by the International Society for Pharmaceutical Engineering (ISPE) in 2010. It helps companies perform risk assessments of cross-contamination on a case-by-case basis to ensure patient safety and product quality, aiming to avoid the need for dedicated facilities based solely on classes of products.
4. **ADE Approach:** Risk-MaPP introduced the concept of an acceptable daily exposure (ADE) as a starting point for evaluating the risks of cross-contamination. ADE is a health-based value used for setting appropriate limits for cleaning and worker exposure.
5. **EMEA Concept Paper on Dedicated Facilities:** The European Medicines Agency (EMEA) proposed dedicated

facilities for certain products, particularly cytotoxics. However, this conflicted with the principles of the quality risk management proposal outlined in ICH Q9.

6. **FDA 2011 Process Validation:** The FDA released updated process validation guidance to the pharmaceutical industry. This guidance utilizes the product life cycle concept and ICH Q8-Q10.
7. **EMA Guidance on Using Health-Based Exposure Limits:** The EMA issued a guideline requiring companies to review pharmacological and toxicological data to determine health-based exposure limits (HBELs) in conjuction with risk identification and cleaning validation justification.
8. **ASTM Standards:** ASTM International developed standards related to cleaning validation, including ASTM E3106 and ASTM E3219. These standards focus on science-based risk analysis and the derivation of HBELs.
9. **Ongoing ASTM Standards in Development:** There are additional ASTM standards in development, such as the calculation of cleaning validation limits and the qualification of visual inspection for residues on manufacturing equipment and medical devices.

These developments and guidelines aim to improve risk management, cleaning validation practices, and the determination of appropriate exposure limits in the pharmaceutical industry.

Cleaning validation studies are undertaken to prove that the documented manufacturing and cleaning processes are sufficient and reliable. FDA guidance indicates that there is no single correct answer for cleaning validation, as there are often multiple approaches to validate a cleaning process. FDA documentation states: "In the end, the test of any validation process is whether scientific data shows

that the system consistently does as expected and produces a result that consistently meets predetermined specifications."

As such, it is impossible to outline an adequate one-size-fits-all process for establishing cleaning validation. Instead, the following general steps outline some factors to consider to develop an effective and qualified cleaning validation for pharmaceutical manufacturing.

Simplify Validation Using a Worst-Case Matrix

To simplify, validation studies create a matrix of worst-case equipment to clean and worst-case residues to remove, which is typically accomplished in two steps:

Step 1: Develop an equipment matrix and residue matrix that defines all shared and dedicated equipment by exposed residues. Specifically, tests are conducted to identify and document a worst case for the most difficult-to-clean equipment and residues. Groups or families of worst-case situations are identified, with one piece of equipment representing a group of similar or easier-to-clean equipment. Residues can also be grouped with one residue representing a group of similar or easier-to-clean residues.

Step 2: Perform complete validation studies on the worst-case equipment and residues. These studies will serve to validate the process for easier-to-clean equipment and residues.

It is important to validate a worst-case scenario and justify its choice. The rationale for why a piece of equipment or residue was determined to be worst-case needs to be documented, and it is usually based on various factors including:

- Product solubility in cleaner
- Toxicity of the products or respective degraded products being cleaned
- Dose size and normal therapeutic dose size (smaller may be more critical to validate)

- Hardest-to-clean equipment
- Worst interactions with the upcoming batch to be cleaned

Whenever a new residue or piece of equipment is used, the manufacturer must evaluate whether it represents a new worst-case that will require a new validation study.

Identify Residues and Select Detection Methods

Before you start identifying residues, first assemble a list of all possible residues that could be left on critical manufacturing surfaces as a result of the cleaning process, including cleaners, primary ingredients, excipients, decomposition products, and preservatives. What residues are critical to monitor and test will be determined by the product being manufactured and its end application as well as the cleaning process.

Once you have a list of residues, you need a detection method for those residues. For detergent residues, selecting the proper detection method involves choosing a specific or non-specific methodology. Specific methods test for a specific ingredient; non-specific methods test for the presence of a blend of ingredients (Table 8.1, next page). Non-specific methods such as total organic carbon (TOC) are commonly used when limits of detection and quantitation are well below residue acceptance limits. TOC also detects virtually all organic residues, so it can be a superior method for showing overall cleanliness. The appropriate detection method will be determined by the specificity and sensitivity required to detect the potential residue, as different methods have differing limits of detection.

If testing with specific methods, consideration must be given to the potential for active ingredients to be affected by the cleaning process itself—if an active ingredient is degraded by cleaning, and the detection method only detects the active ingredient, a residue test may not detect degradants and thus could provide false negative

results. To comply with regulations, generally specific methods are preferred, although non-specific methods can be acceptable with adequate rationale for their use. For investigating failures or action levels, a specific method is usually preferable. Regardless of the kind of cleaning validation, you will need a validated analytical method for detecting detergent residue. Table 8.2 lists residue detection methods that can be used for cleaners made by Alconox Inc.

Table 8.1 Specific and non-specific residue detection methods

	Specific Methods	Non-Specific Methods
Tests for:	*Individual ingredient*	*Blend of ingredients*
Methods:	Derivative UV spectroscopy	Conductivity
	Direct analysis	pH
	Enzymatic detection	Total organic carbon (TOC)
	Gas chromatography/flame ionization detection (GC/FID) or gas chromatography/mass spectrometry (GC/MS)	Visual inspection
	High-performance liquid chromatography (HPLC) and ultra-performance liquid chromatography (UPLC)	
	Inductively coupled plasma spectroscopy	
	Ion chromatography	
	Ion-selective electrodes	
	Titration	
Preferred for:	Initial validation	Broad detection of any residue
	Investigating failure or action levels	Retesting to maintain validated state
		Monitoring

Select Sampling Methods

Several methods are available to sample for critical cleaners used in pharmaceutical manufacturing, including:

- Rinse water sampling
- Swab or wipe sampling
- Coupon sampling
- Placebo sampling
- Direct analysis

Table 8.2 Cleaner residue detection methods for Alconox Inc. cleaners

Alconox Inc. Cleaner	Anionic Surfactant by HPLC	EDTA by HPLC	Direct UV/Vis	Phosphate by Titration and IC	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		●		●	●	●	●	●

HPLC, high-performance liquid chromatography; UV/Vis, UV-visible spectroscopy/spectrophotometry; TOC, total organic carbon; IC, ion chromatography

Rinse water sampling is done when sampling large pieces of equipment or runs of piping. Rinse water samples can be used in areas that are difficult to access. A sample is taken of an equilibrated post-final rinse that is the smallest volume that was re-circulated over all surfaces. Such samples should be correlated to direct measuring techniques, such as swabbing, to ensure that residues are adequately detected and not simply sitting on the surface without dissolving into the equilibrated rinse water. In addition, equipment qualification should verify that rinsing reaches all appropriate areas of the equipment to ensure that samples are reliable.

Swab or wipe sampling is done to directly measure and remove residues from surfaces for analysis. Swabbing is often used in difficult-to-clean areas as well as areas that are easy to access. Swabs are advantageous because they have the benefit of using mechanical force to remove residues. A swab or wipe moistened with high-purity water

is drawn over a defined area using a systematic multi-pass technique—always moving from clean to dirty areas to avoid recontamination. At this point, the swab head is cut off and placed in a sufficiently clean vial. TOC analysis requires use of very clean low-background swabs/wipes and sample vials. It is best to buy certified low-TOC equipment for TOC analysis.

In general, a swabbing area of 5 x 5 cm is suggested. With extreme low-level acceptance criteria on a low-recovery residue, a 10 x 10 cm area may be more appropriate. For detergent residues, you should not need a 10 x 10 cm area to achieve acceptable swabbing results. Swabbing can be done with two or more wet or dry swab samples. For difficult recoveries, sampling steps can be repeated using a second or even third wet swab before a final dry swab. Note that the use of more swabs improves recovery but also increases swab background interference. Specific analytical detection methods such as HPLC will be less affected by swab background than non-specific analytical methods. For HPLC, using two or three wet swabs and a final dry swab often gives the best recovery.

For TOC and most other uses, use Texwipe Alpha® swab 714K or 761K. For HPLC the 716 swab can be used. For specific methods, most pre-cleaned laboratory swabs that show no interference with equipment blanks and demonstrate good recoveries are acceptable.

Training tip: Operators can practice using colored Kool-Aid® powder for visual confirmation of the technique.

Coupon sampling uses a high-purity, water-dipped coupon placed inside a piece of equipment or removable piece of actual pipe to extract residues for analysis.

Placebo testing is performed by manufacturing placebo products and analyzing for residues from the previous batch to demonstrate that there is no carry-over of product. Because potential contaminants may not be evenly found throughout a system and might not evenly

wear off into the placebo product, the FDA requires additional validation as well as combination with rinse and/or swab samples for acceptable placebo testing.

Direct analysis may be performed by an instrument that takes residual readings directly from the surface of manufacturing equipment. A handheld Fourier transform infrared spectrometer (FTIR) is an example of this type of equipment. Direct analysis eliminates the need to measure residuals away from the surface, where you have to consider a recovery factor. A sufficiently sensitive method that can quantify the analyte accurately and with precision is required. Small, occluded, or difficult-to-access locations can be problematic.

For all sampling methods, ensure that procedures for collecting samples are specific, with details such as volume, rinse cycle time, timing of sample collection, sampling material, sampling protocol, and temperature.

Set 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

Acceptable residue limits must account for 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. Determining these limits is important to measure the potential risk of a residue's presence—with

appropriate established residue limits, a cleaning validation can be used to demonstrate that a cleaning process minimizes risk.

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 for a particular residue. Acceptable residue levels are based on all available data that establish safety levels of exposure to that residue. These safety limits consider the potential hazard of a substance and the dose-response relationship of exposure to that substance. A lower internal action level, plus a lower process control level based on actual manufacturing and measuring experience, may also be desirable.

Just as there is no one-size-fits all approach to establishing a cleaning validation, there also is no one-size-fits-all approach to setting acceptable residue limits. What is acceptable is highly dependent on the particular residue in question, the next product being manufactured on the equipment, and the potential risk of contamination with that residue. Calculating a limit does not simply mean establishing a number for process requirements to meet—instead, the limit represents a level that measures the safety of exposure. Thus, considerable thought, data, and scientific rationale should be devoted to establishing acceptable residue limits. The basis of an established limit should be scientifically justifiable.

Because size and surface area affect residue concentrations, 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.

Cleaning agent safety-based limits are most often calculated from an acceptable daily exposure (ADE), or permissible daily exposure (PDE), which are used interchangeably. Historically, the safety-based limits were calculated from acceptable daily intakes (ADI). The use of ADE and PDE based limits are increasingly the standard, but ADI based limits are still in use. If the safety-based limit is greater than the 10 ppm carryover limit, then you can set your final limit to the lower 10 ppm carryover limit if that conforms to your validation master plan (VMP). Your VMP should specify these calculations and how to use them. Note that carryover is the amount of residual that may be present from a previous manufacturing batch.

The following equation can be used to calculate the safety-based limit of cleaner residue on just-cleaned equipment.

Safety-Based Limit
Limit (mg/cm² or mg/mL) =

ADI carry-over (mg) x Smallest next batch (kg)/(Size of shared equipment (cm² or L) x Biggest daily dose of next batch (kg))*

***Acceptable Daily Intake**
ADI carryover (mg) =

LD50 by administration route (mg/kg) x Body weight (kg) x (1/10,000 or 1/1,000)†

† Conversion safety factor

For a comparison calculation of limit based on ≤10 ppm carryover:
10 ppm Carryover Limit
Limit (mg/cm²) =

10 mg residue on just-cleaned surface x Next batch size (kg or L)/(1 (kg or L) of next product x Size shared equipment (cm² or L))

If the safety-based limit is set at 100 mg/cm², 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]. Thus, the same safety limit can be expressed several different ways.

Establishing acceptable daily exposure (ADE) for a compound is a newer method for setting cleaning validation and cross-contamination limits in pharmaceutical manufacturing facilities using health-based data. Defined by the International Society for Pharmacoepidemiology as a dose that is unlikely to cause an adverse effect, even if exposure occurs every day for a lifetime, ADE is protective of all populations by all routes of administration.

A similar measure to ADE is permitted daily exposure (PDE) values. Although ADE and PDE are similar, different agencies preferentially use one or the other—for instance, the FDA uses ADE values, while the European Medicines Agency (EMA) uses PDE values.

Calculations of ADE and PDE incorporate different adjustment factors, which can vary based on the measure and entity calculating the factors. ADE uses a composite uncertainty factor (which reflects, for example, interindividual variability, interspecies differences, and database completeness), a modifying factor to address other uncertainty, and pharmacokinetic adjustment; PDE uses a series of adjustment factors that consider uncertainty. However, either case derives a result that can be used to calculate acceptance criteria. Further, according to the Pharmaceutical Inspection Convention (PIC/S) "Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities", ADE and PDE values are effectively synonymous.

ADE and PDE values are determined by qualified industrial hygienists and toxicologists using all available toxicology and safety data. Once established, ADE and PDE provide the basis for the maximum allowable carryover (MACO), as shown by the following equations.

Acceptable Daily Exposure

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

Permitted Daily Exposure

$$PDE_{previous} = \frac{NOAEL \times BW}{F1 \times F2 \times F3 \times F4 \times F5}$$

Maximum Allowable Carryover

$$MACO = \frac{ADE/PDE_{previous} \times MBS_{next}}{TDD_{next}}$$

Definitions

ADE ..... Acceptable daily exposure (mg/day)
BW ..... Body weight of an average adult (e.g., 70 kg)
F1–F5..... Additional adjustment factors for uncertainties
MACO ..... Maximum allowable carryover; the acceptable transferred amount from the previous product into the next product (mg)
MBS_{next} ..... Minimum batch size for the next product(s) (mg)
MF ..... Modifying factor; a factor to address uncertainties not covered by other factors
NOAEL ..... No observed adverse effect level (mg/kg/day)
$PDE_{previous}$ ..... Permitted daily exposure for the previous product
PK ..... Pharmacokinetic adjustments

TDD_{next} ..... Standard therapeutic daily dose for the next product (mg/day)

UFc ..... Composite uncertainty factor; the combination of factors that reflects inter-individual variability, interspecies differences, subchronic-to-chronic extrapolation, LOEL-to-NOEL extrapolation, database completeness

Table 8.3 Allowable Daily Exposure (ADE) Calculations for select Alconox Inc. Detergents

Alconox	25 mg/day
Liquinox	10 mg/day
Citranox	356 mg/day
Citrajet	17 mg/day
Keylajet	0.95 mg/day
Solujet	145 mg/day

Using known ADEs for detergents, maximum allowable carryover acceptance criteria can be calculated.

It is routine to visually inspect equipment after cleaning and/or before production to verify that surfaces appear visibly clean. Visual inspection should consider both solid residues as well as worn or discolored parts and surfaces.

In addition to good standard practice, visual inspection may be a sufficient measure of cleanliness. For many residues, a visual detection limit can be validated on the order of 1–4 $\mu g/cm^2$, so it is possible that visually clean criteria may be the most stringent criteria. For example, consider a cleaner with a rat oral LD50 of 5,000 mg/kg. The ADI calculation using a 70-kg person and a safety factor of 1,000 produces a result of 350 mg [(5,000 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 $\mu g/cm^2$ [(10 mg x 1,000 kg) / (1 kg x 100,000 cm^2) x 1,000 $\mu g/mg$]. In this case, if the ability to detect visually to 4 $\mu g/cm^2$ is demonstrated, then a visually clean surface will be the most stringent acceptance criteria for residues.

Similarly, an ADE calculation can be used to justify visual inspection. Assuming the same visual inspection of 1-4 $\mu g/cm^2$, and a detergent with an ADE of 145 mg/day the visual inspection is orders of magnitude lower than an ADE calculation. This may be shown by the calculation of [145mg x 1,000 kg/ (100,000 cm^2 x 0.005 kg)] or 290 mg/cm^2. Again in this case, if the ability to detect visually is 1 $\mu g/cm^2$ – 4 $\mu g/cm^2$, then a visually clean surface is the most stringent acceptance criteria for residues.

Validated visual inspection can eliminate the need for analytical instrument residue detection (e.g., HPLC) if your VMP permits. However, because visual inspection is relatively sensitive and accurate, but not precise, visual inspection should first be validated before it is considered an acceptable replacement for analytical instrument residue detection. Even then, having a specific validated analytical method available for investigations is required if an out-of-specification result occurs.

Validate Residue Detection Methods

A residue detection method is validated 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. This ensures

that the analytical method being used to assess cleaning can provide accurate and precise results within the necessary range. Validating a particular detection method can be straightforward or rather complex depending on the method and the residue in question. However, this step is critical to ensure that results—which provide the basis to validate cleaning—are reliable and accurate. The residue detection method often includes use of internal standards or reference samples to provide baseline measurements.

Different analytical methods require different validation procedures. The FDA, the International Conference on Harmonization (ICH), and the European Union all have defined validation requirements for analytical methods used in manufacturing pharmaceuticals. The U.S. Pharmacopoeia (USP) provides method validation guidelines in Chapter 1225. Selective residue detection methods must be shown to be specific, at a 95% confidence level, under the specified conditions of use without significant bias or interference from impurities, degradants, excipients, or other ingredients.

TOC and other non-specific methods are commonly used where the limits of detection and quantitation are well below residue acceptance levels. USP Chapter 1225, Validation of Compendial Procedures, provides information about validating compendial analytical procedures ranging from exacting analytical determinations to limit tests.

Recovery Studies

Recovery studies consist of using the sampling and detection methods on a known spiked surface at representative levels of residue. Generally, spikes are set at 50%, 100%, and 150% of the acceptable limit. This helps illustrate linearity with documented percent recovery as analyzed and helps determine limits of detection and quantitation. Ideally, the expected values and limits should be multiples of the limits

of quantitation. Percent recovery is used to correlate the amount detected with the amount of assumed surface residue found acceptable.

For example, if 100 µg of residue was spiked on a surface, and after swabbing, extracting, and analyzing only 90 µg was detected, recovery is 90%. For cleaning validation, any results would have to be adjusted by this recovery factor. In this example, the resulting 90 µg per swabbed area should be interpreted as actually being 100 µg per swabbed area to adjust for 90% recovery, per the following equation:

$$\frac{\textit{Residue detected / Per sampled area (or device)}}{\textit{\% Recovery}} = \textbf{\textit{Adjusted detected residue}}$$

Solving for the example above, the equation would be:

$$\frac{\textit{90 µg detected / Device}}{\textit{90\% Recovery}} = \textbf{\textit{100 µg / Device detected residue}}$$

Recovery studies should include all detergent contact materials with different surface charges to account for recovery differences. When calculating residuals from different materials that have been swabbed, use the appropriate percentage recovery for each surface.

When the post-drying solubility or rinse-ability of a particular critical cleaning detergent ingredient is in question, a rinse-ability profile detailing complete rinsing should be done. For relatively low-toxicity mixtures like detergents, it is acceptable to use one ingredient of the detergent as a marker to detect detergent residuals.

In some cases, bioburden/endotoxin levels may need to be validated. However, validation of biologics exceeds the scope of cleaning validations.

Write Procedures and Train Operators

Once you have established a cleaning validation process, testing should document that it can achieve acceptable residue levels three or more consecutive times to ensure that the process is consistent and

adequate. If this is achieved, written procedures and training are necessary to ensure consistency and reliability of cleaning. Written procedures should be specific and should contain enough detail to minimize operator variability. Written procedures should include:

- Assignment of responsibilities
- Cleaning conditions
- Documentation requirements
- Equipment disassembly and monitoring procedures
- Frequency of cleaning
- List of consumables and equipment
- Protective clothing requirements
- Schedule for validation
- Scope of procedure
- Labeling instructions for in-process and cleaned equipment that state cleaning expiration date, post-cleaning inspection, storage conditions, and inspection requirements prior to next use

A defined procedure for changing a validated process is necessary and should describe approval and review processes required when making specific changes. Provisions for emergency changes should also be made. Typically, revalidation is required when the cleaner is changed. The level of revalidation may be covered in the VMP. It may be appropriate to continue an old cleaning operation while phasing in a new one. Once implemented, monitor the new process to prove that it produces the same validated results as the old one.

In addition to designing and qualifying a cleaning process initially, the process must be continually verified to show that it is performing as expected and as intended. Include a review of validated processes during an annual product review—this can be an opportunity to determine whether all minor changes made since the previous review

amount to significant changes that exceed assumptions made and thus require revalidation.

Further, operators must be trained and certified in the procedures. Appropriate retraining should also take place as needed.

Final Validation Report

The final validation report should include a section about the cleaning process design. It references the SOPs or work instructions and their evaluation. Also, a section of data analysis should provide statistical justification for conclusions reached. A defined procedure for revalidating an altered validated process is included and should describe approval and review processes required when making specific types of alterations. Whenever any aspect is changed—for example, hardest-to-clean or most-toxic worst cases—a list of constraints and assumptions should be developed for review. All changes need to be recorded and made according to change control policy and procedures.

The final section of the validation report should provide references to any standard methods, journal articles, or government documents that are used or referenced in the VMP.

Medical Device Cleaning Validation

Cleaning validation is a necessary regulatory compliance step in medical device manufacturing and reprocessing. In the medical device manufacturing industry, cleaning validation is generally performed by examining the finished device itself rather than the equipment used to manufacture it.

Validation concerns vary across the industry and depend on the class of medical device. Residues on medical devices might include process fluids, polishing compounds, mold releases, dye penetrants, bioburden, endotoxins, cleaning agents, and any degradation or interaction products. Acceptance criteria are set based on potential for the residue to affect biocompatibility, toxicity, or functionality of the

finished medical device. Devices are classified according to the nature and duration of patient contact. Re-usable examining devices with incidental patient contact might be tested for function and, possibly, bioburden. Implantable medical devices with years of internal patient contact might also be tested for endotoxins, cytotoxicity, sterility, and proper device function.

As mentioned above in pages 163 to 167, cleaning agent safety-based limits are most often calculated from an acceptable daily exposure (ADE), or permissible daily exposure (PDE), which are used interchangeably. Historically, the safety-based limits were calculated from acceptable daily intakes (ADI). The use of ADE and PDE based limits are increasingly the standard, but ADI based limits are still in use. If the safety-based limit is greater than the 10 ppm carryover limit, then you can set your final limit to the lower 10 ppm carryover limit if that conforms to your validation master plan (VMP).

In addition to cleaning validation, sterility validation is required for products sold sterile. Although sterility validation is beyond the scope of this chapter, cleaning validation is important for any device sold sterile. For example, see ISO 11135 (Ethylene Oxide Sterilization) and ISO 11137 (Gamma Radiation).

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

- Corrective and preventive actions
- Management controls
- Production and process controls
- Facility and equipment controls
- Records, documents, and change controls

- Material controls
- Design controls

These subsystems must conform to cGMP in accordance with the QSR (21 CFR Part 820). The International Organization for Standardization (ISO) medical device quality equivalent is ISO 13485. The most relevant sections to critical cleaning and cleaning validation are listed below.

820.3 Definitions

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

§820.70 Production and Process Controls (ISO 13485:2016 6.3 + 6.4 + 7.1 + 7.5.1 + 7.5.2 + 8.2.3)

(e) *Contamination control*. Each manufacturer shall establish and maintain procedures to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality.

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

§820.72 Inspection, Measuring, and Test Equipment (ISO 13485:2016 7.6)

(a) *Control of inspection, measuring, and test equipment*. Each manufacturer shall ensure that all inspection, measuring, and test

equipment, including mechanical, automated, or electronic inspection and test equipment, is suitable for its intended purposes and is capable of producing valid results. Each manufacturer shall establish and maintain procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained. The procedures shall include provisions for handling, preservation, and storage of equipment, so that its accuracy and fitness for use are maintained. These activities shall be documented.

§820.75 Process Validation
(ISO 13485:2016 6.3 + 6.4 + 7.1 + 7.5.1 + 7.5.2 + 8.2.3)

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

Further, the FDA supports a risk-based approach for medical device process validations. These risk-based approaches include factors such as process failure mode engineering analysis. This is a quantitative way of evaluating risk that can be used as part of a design history file.

Cleaning Verification of Finished Devices

The need for cleaning validation or cleaning verification comes from cGMP required production and process controls, as well as design inputs and outputs. Cleaning verification is documented evidence that an individual cleaning event (rather than an entire cleaning process) has produced a device that is acceptably clean. If a medical device manufacturer opts to accomplish cleaning verification by inspecting the finished product, then verification must be done every time cleaning is performed. Accordingly, the approach is much more common only when small batches of devices are manufactured

or re-use devices are being cleaned.

Verification tests may be performed as deemed appropriate by hazard analysis and may include demonstrating:

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

Further testing should be done to show non-viable residuals may be removed. This could be done by applying soils such as those found in Association for the Advancement of Medical Instrumentation (AAMI) Technical Information Reports (TIRs): TIR12 or TIR30, Section 6, Table 6. Examples of soils are Hucker's or ATS-B soils. Another example of a test to demonstrate removal of soil contamination is the ProFormance TOSI® (test object surgical instrument) cleaning challenge (Healthmark Industries, 18600 Maylin Blvd. Fraser MI 48026; hmark.com).

The process for developing a cleaning validation for medical device manufacturing has overlap with that for pharmaceutical manufacturing, although there are important differences. The following steps can serve as an overall guide.

Identify Cleaner Residues

To identify residues left behind by a detergent, you need to know the formulation. The cleaner or detergent supplier should be willing to disclose the cleaner ingredients under a non-disclosure agreement. Sometimes sufficient information about cleaner ingredients can be obtained from safety data sheets (SDS) and cleaning validation technical information supplied by the cleaner supplier. Ask your cleaner supplier which ingredients are likely to be the last to rinse

away and which ingredients are best to analyze as a marker for the cleaner residue.

Select and Validate a Residue Detection Method

Selecting the appropriate detection method for detergent residues begins with choosing a specific or non-specific methodology, according to the criteria shown in Table 8.1.

The FDA often prefers use of specific methods, especially when investigating failures or action levels. Under specified usage conditions, these methods are proven specific at a 95% confidence level, without significant bias or interference from impurities, degradants, excipients, or other ingredients. However, non-specific methods may be accepted, provided there is a scientific rationale for their use. Non-specific methods are commonly used where the limit of quantitation is <50% of residue acceptance levels and where broad detection of any residue is desired.

When performing medical device cleaning validation, analytical methods for detecting detergent residues also must be validated. Table 8.2 lists appropriate residue detection methods for Alconox Inc. detergents and cleaners. Validation of the residue detection method may involve establishing accuracy, precision, linearity, reproducibility, selectivity, specificity (for specific methods), detection and/or quantitation limits, as well as robustness of the residue detection method.

Select a Sampling Method

Residues left behind by a detergent can remain on device surfaces after cleaning and must be tested by sampling. Available sampling methods include:

- Rinse water sampling or solvent extraction
- Surface swabbing
- Direct detection

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

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

Direct detection is use of an analytical device directly on the surface being measured, such as using a handheld Fourier transform infrared (FTIR) or surface enhanced Raman spectrophotometer (SERS).

Set Residue Acceptance Criteria

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

Any applicable historical data on residues from successful manufacturing processes can be used to set acceptable levels.

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

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

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

Acceptable Daily Intake (ADI)

$$\frac{LD50\ (mg/kg) \times Body\ weight\ (kg)}{Conversion\ factor}$$

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

ADI per Device =

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

Considering the surface area of the device, acceptable residue per square centimeter (cm^2) of device will depend on device size and/or the number of devices (e.g., multiple bone screws) that you are setting a limit for. If the device(s) has/have a surface of 100 cm^2, the surface residue limit for that detergent would be 35 mg/cm^2 [(3.5 mg/device / 100 cm^2]. Assumptions about surface area need to be made for parts with complex geometry, such as titanium foams. While a process requirement of visually clean might be more stringent, in this example the detergent used is fairly non-toxic, the medical device has a relatively short contact time, and the resulting safety-based limit is fairly high.

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

- Kramer, H. J., W.A. van den Ham, W. Slob, and M. N. Pieters. "Conversion Factors Estimating Indicative Chronic No-Observed-Adverse-Effect Levels from Short Term Toxicity Data." Regulatory Toxicology and Pharmacology 23 (1996): 249–255.
- Conine, D.L., B. D. Naumann, and L. H. Hecker. "Setting Health-Based Residue Limits for Contaminants in Pharmaceuticals and Medical Devices." Quality Assurance: Good Practice, Regulation, and Law 1 no. 3 (1992): 171–180.
- Layton, D. B., B. J. Mallon, D. H. Rosenblatt, and M. J. Small.

"Deriving Allowable Daily Intakes for Systemic Toxicants Lacking Chronic Toxicity Data." Regulatory Toxicology and Pharmacology 7 (1987): 96–112.

Table 8.4 Acceptable toxicity and biocompatibility exposure concentrations for select Alconox Inc. detergents

Detergent Acceptable Exposure Concentration	Biocompatibility Factor	Results
Liquinox	**Oral toxicity**	**LD50 appears >5000 mg/kg**
10.0 g/L Liquinox	Dermal irritation	Not a dermal irritant
0.1 mg/mL LIQUINOXok	Dermal sensitization	Not a sensitizer
0.1 mg/mL Liquinox	Intracutaneous injection	No differences in response
0.1 mg/mL Liquinox	Systemic injection	Treated sites similar to control
0.1 mg/mL Liquinox	Cytotoxicity	Meets requirements
Citrajet	**Oral toxicity**	**LD50 appears >5000 mg/kg**
0.1 mg/mL Citrajet	Intracutaneous injection	Treated sites more irritated than control
0.1 mg/mL Citrajet	Cytotoxicity	Meets requirements
Citranox	**Oral toxicity**	**LD50 appears >5000 mg/kg**
10.0 g/L Citranox	Dermal irritation	Not a dermal irritant
0.1 mg/mL Citranox	Dermal sensitization	Not a sensitizer
0.1 mg/mL Citranox	Intracutaneous injection	Treated sites more irritated than control
0.1 mg/mL Citranox	Systemic injection	Treated sites similar to control
0.1 mg/mL Citranox	Cytotoxicity	Meets requirements
Solujet	**Oral toxicity**	**LD50 appears >500 mg/kg**
0.1 mg/mL Solujet	Intracutaneous	Treated sites similar to control
0.1 mg/mL Solujet	Cytotoxicity	Meets requirements

Of course, using conversion factors necessarily involves making conservative assumptions to minimize risk. Use of a conservative safety conversion factor will result in a very conservative low acceptance limit for residues. Acceptance limits can be more directly justified by using more direct biocompatibility systemic toxicity data rather than estimating toxicity with conversion factors. Table 8.4 shows biocompatibility and systemic toxicity data for select Alconox Inc. cleaners.

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

Biocompatibility-Based Acceptance Criteria (µg/device) =
Acceptable exposure concentration (µg /mL) x Lowest reasonable volume of extraction body fluid (mL / cm^2) x Surface area of device (cm^2)

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

For example, to determine a worst-case residue for a detergent, assume 1 drop/cm^2 as the lowest reasonable amount of body fluid or (since 1 drop = 0.05 mL) 0.05 mL/cm^2 of liquid that cannot exceed 0.1 mg/mL detergent without exceeding measured acceptable levels for the biocompatibility factors of dermal sensitization, intracutaneous injection, systemic injection, or cytotoxicity. This means the 100-cm^2 device could have 5 mL of liquid (100 cm^2 x 0.05 mL/cm^2), in which case you would not want more than 0.5 mg of detergent (0.1 mg/mL x 5 mL) on the device. This translates to a biocompatibility-based limit of 0.5 mg detergent/100 cm^2 = 5 µg detergent/cm^2, or 500 µg detergent/device.

Note that for an open wound or implantable device, the amount of fluid contacting the device would reasonably be higher and the resulting biocompatibility acceptance limit for detergent would be higher. For example, if you conservatively estimated the amount of body fluid available to extract detergent into a patient was 0.1 mL/

cm^2, then the biocompatibility acceptance limit for detergent residue would be 100 cm^2/device x 0.1 mL fluid/cm^2 x 0.1 mg detergent/mL fluid = 1 mg detergent/device; or 10 μg detergent/cm^2 of device (1 mg/device / 100 cm^2/device).

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

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

Table 8.5 Total organic carbon (TOC) content of Alconox Inc. cleaners

Alcojet	1.5% w/w
Alconox	11% w/w
Alcotabs	10% w/w
Citrajet	14% w/w
Citranox	16% w/w
Detergent 8	38% w/w
Detojet	0.5% w/w
Detonox	12% w/w
Keylajet	3% w/w
Liquinox	19% w/w
Luminox	20% w/w
Solujet	6% w/w
Tergajet	9% w/w
Tergazyme	11% w/w

Further, TOC is commonly used to determine if residue levels meet acceptance limits. You can calculate the theoretical surface concentration of cleaning agent residue if you know the TOC content

of the cleaner. Assume a worst case, where all detected TOC derives from cleaner residue, and then calculate the amount of cleaner residue that would yield that TOC reading.

First, take a TOC measurement by extracting residues from a device in high-purity, organic-free water. Next, use the resulting measurement to calculate cleanliness and simultaneously detect process and cleaning agent residues. Table 8.5 shows TOC contents for Alconox Inc. cleaners.

Use the following equation to calculate how much detergent residue could be on a device surface:

Cleaner Residue (µg/device) =

$$\frac{\textit{TOC reading (µg TOC/mL) x Device extraction volume (mL)}}{\textit{Cleaner TOC content (\% TOC w/w)}}$$

For example, when performing cleaning with Liquinox detergent, which has 19% TOC (w/w), a TOC reading of 1 µg/mL determined for a device exhaustively extracted in 20 mL of high-purity water would indicate a residue of 105 µg detergent/device [(1 µg/mL x 20 mL) / 0.19]. Using both the above examples of biocompatibility acceptance limits, this TOC reading would be acceptable because, even in the worst case, the acceptance limit for detergent was 500 µg/device. Of course, because some of the TOC likely comes from other sources, the actual amount of detergent is probably well below 105 µg/device—but because a non-specific analytical method for detection was used, for the purpose of determining if the acceptance criteria was met or not, it is assumed that all detected TOC is from the detergent.

Typically, TOC is used to detect other carbon-containing residues such as oils. If any of the other residues have lower TOC acceptance limits than the detergent, then you must meet the lowest of these other limits. Once you meet the lowest limit, assuming all

the carbon was from the other residue, then you also will have met the detergent acceptance limit.

Recovery Studies

Recovery studies use selected sampling and detection methods on residues that have been "spiked" on the device surfaces at known levels. Generally, spikes are set at 50%, 100%, and 150% of the acceptance criteria limit. This demonstrates and establishes linearity with documented percent recovery, as analyzed, and helps determine limits of detection and quantitation. Ideally, the expected values and limits should be multiples of the limit of quantitation. The percent recovery is used to correlate amount detected with the amount of assumed surface residue found acceptable.

For example, if 100 µg of residue were spiked on the surface, and after swabbing or extracting the detection analysis yielded 90 µg, the calculated percent recovery would be 90%. For cleaning validation, any analytical results would have to be adjusted by this recovery factor. In this example, the resulting 90 µg per swabbed or sampled area should be interpreted as being actually 100 µg per swabbed or sampled area to adjust for the 90% recovery. If the area is the entire device, then a detection of 90 µg in the extraction fluid can be interpreted as 100 µg per device by the following equation:

$$\frac{\text{Residue detected / Per sampled area (or device)}}{\text{\% Recovery}} = \textbf{Adjusted detected residue}$$

Solving for the example above, the equation would be:

$$\frac{\text{90 µg detected / Device}}{\text{90\% Recovery}} = \textbf{100 µg / Device detected residue}$$

Write Procedures and Train Operators

In addition to the cleaning validation, written procedures should include:

- Assignment of responsibilities
- Cleaning conditions
- Documentation requirements
- Equipment disassembly and monitoring procedures
- List of consumables and equipment
- Scope of procedure
- Labeling instructions for in-process and cleaned equipment that state cleaning expiration date, post-cleaning inspection, storage conditions, and inspection requirements prior to next use

Operators must then be trained and certified in the procedures, and they should also receive regular appropriate retraining.

Final Validation Report

The final validation report also includes a section dealing with cleaning process design. It references the SOPs or work instructions and their evaluation. Also, there is a section of data analysis providing statistical justification for the conclusions reached. A defined procedure for revalidating an altered validated process is included and should describe approval and review processes required when making specific types of alterations. Whenever any aspect is changed—for example, part complexity, material of construction, manufacturing agents, or general process—a list of constraints and assumptions should be developed for review. All changes need to be properly documented and consistent with change control processes and risk management. This may be a part of the validation itself or may be a part of a design history file.

The final section of the validation report should provide references to any standard methods, journal articles, or government documents that are used.

Revalidation is required whenever a major change is made. The

level of revalidation may be covered in a VMP. This is typically required when the cleaner is changed. The validated processes are often reviewed during annual product review, providing an opportunity to determine whether all minor changes made since the previous review amount to significant changes that exceed assumptions and thus require revalidation. It may be appropriate to continue an old cleaning operation while phasing in a new one, and it is important to monitor the new process to prove it produces the same validated results.

Cleaning Supplier Validation Support

When selecting an aqueous cleaner for cGMP manufacturing where a cleaning validation is required, consider both the efficacy of the cleaner and the ability of its manufacturer to support validation efforts. The chosen critical cleaner manufacturer should provide:

- Lot traceability of cleaners
- Certificates of analysis
- Consistent manufacturing
- Cleaner selection consulting
- Ingredient disclosures under confidentiality
- Cooperation on being audited and responding to quality questionnaires
- Ingredient toxicity data
- Ingredient reactivity information to help determine degradations and interactions
- Cleaner shelf life data
- Residue sampling
- Acceptance limits and recovery data
- Residue detection method information
- Assistance with reviewing cleaning procedures

References

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" (1994).

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" (2003).

D.L. Conine, B.D. Naumann, L.H. Hecker, "Setting health-based residue limits for contaminants in pharmaceuticals and medical devices," Quality Assurance, Vol. 1, No. 3, 171–180 (1992).

D.W. Cooper, "Using swabs for cleaning validation: A review," IVT Network Cleaning Validation, p. 74–89 (1996).

European Commission, "Directive 91/356/EEC: EC guidance to GMP for medicinal products" (1991).

European Commission, "Good manufacturing practice (GMP) guidelines – Volume 4, Annex 15: Qualification and validation" (2003).

G.L. Fourman and M.V. Mullen, "Determining cleaning validation acceptance limits for pharmaceutical manufacturing," Pharmaceutical Technology, Vol. 17, No. 4, 54–60 (1993).

Global Harmonization Task Force, "GHTF/SG3/N99-10:2004 (Edition 2): Quality management systems – Process validation guidance" (2004).

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "ICH Harmonised Tripartite Guideline – Pharmaceutical development: Q8(R2)" (August 2009).

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "ICH Harmonised Tripartite Guideline – Quality risk management: Q9, Step 4,9" (November 2005).

International Society for Pharmaceutical Engineering, "Baseline Guide Vol. 7: Risk-based manufacture of pharmaceutical products, Second Edition" (July 2017).

H.J. Kramer, W.A. van den Ham, W. Slob, M.N. Pieters, "Conversion factors estimating indicative chronic no-observed-adverse-effect levels from short term toxicity data," Regulatory Toxicology and Pharmacology, Vol. 23, 249–255 (1996).

D.W. Layton, B.J. Mallon, D.H. Rosenblatt, M.J. Small, "Deriving allowable daily intakes for systemic toxicants lacking chronic toxicity data," Regulatory Toxicology and Pharmacology, Vol. 7, 96–112 (1987).

D. Leblanc, "Establishing scientifically justified acceptance criteria for cleaning validation of finished drug products," Pharmaceutical Technology, Vol. 22, No. 10, 136–148 (1998).

D. LeBlanc, "Cleaning validation for medical device manufacture," Cleaning Validation Technologies Course (May 2004).

Pharmaceutical Inspection Co-operation Scheme, "Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities" (July 2018).

U.K. Medicines Control Agency, "Rules and guidance for pharmaceutical manufacturers and distributors" (2002).

U.S. Food and Drug Administration, "Biotechnology inspection guide" (1991). Available at fda.gov/biotechnology-inspection-guide-1191

U.S. Food and Drug Administration, "Center for Device and Radiological Health (CDRH) Quality system inspection technique" (August 1999).

U.S. Food and Drug Administration, "Center for Drug Evaluation and Research (CDER) 7356.002: Drug Manufacturing Inspection Program" (2017).

U.S. Food and Drug Administration, "Code of Federal Regulations (CFR) Part 210: Current good manufacturing practice in manufacturing, processing, packing, or holding of drugs" (original publication 1978). Available at ecfr.gov/current/title-21/chapter-I/subchapter-C/part-210

U.S. Food and Drug Administration, "Code of Federal Regulations (CFR) Part 211: Current good manufacturing practice for finished pharmaceuticals" (original publication 1978). Available at ecfr.gov/current/title-21/chapter-I/subchapter-C/part-211

U.S. Food and Drug Administration, "Code of Federal Regulations (CFR) Part 803: Medical device reporting" (original publication 2014). Available at ecfr.gov/current/title-21/chapter-I/subchapter-H/part-803

U.S. Food and Drug Administration, "Code of Federal Regulations (CFR) Part 806: Medical device corrections and removals" (original publication 1997). Available at ecfr.gov/current/title-21/chapter-I/subchapter-H/part-806

U.S. Food and Drug Administration, "Code of Federal Regulations (CFR) Part 820: Quality system regulation" (original publication 1996). Available at ecfr.gov/current/title-21/chapter-I/subchapter-H/part-820

U.S. Food and Drug Administration, "Code of Federal Regulations (CFR) Part 821: Medical device tracking" (original publication 1993). Available at ecfr.gov/current/title-21/chapter-I/subchapter-H/part-821

U.S. Food and Drug Administration, "Guide to inspections of bulk pharmaceutical chemicals" (1991).

U.S. Food and Drug Administration, "Guide to inspections of quality systems" (1999). Available at fda.gov/files/Guide-to-Inspections-of-Quality-Systems.pdf

U.S. Food and Drug Administration, "Validation of cleaning processes" (1993). Available at fda.gov/validation-cleaning-processes-793

A. Walsh, M. Ovais, T. Altmann, E.V. Sargent, "Cleaning validation for the 21st century: Acceptance limits for cleaning agents," Pharmaceutical Engineering, Vol. 33, No. 6, 12–24 (2013).

ISPE Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP), International Society for Pharmaceutical Engineering (ISPE), First Edition, September 2010.

Current Good Manufacturing Practice: Proposed Amendment of Certain Requirements for Finished Pharmaceuticals. Federal Register / Vol. 61 No. 87 / Friday, May 3, 1996 / Proposed Rules

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Quality Risk Management – Q9, Step 4, 9 November 2005, www.ich.org.

ISPE Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP), International Society for Pharmaceutical Engineering (ISPE), First Edition, September 2010.

Walsh, A., "Cleaning Validation for the 21st Century: Acceptance Limits for Active Pharmaceutical Ingredients (APIs): Part I," Pharmaceutical Engineering, July/August 2011, Vol. 31, No. 4, pp. 74- 83.

EMA Concept paper dealing with the need for updated GMP guidance concerning dedicated manufacturing facilities in the manufacture of certain medicinal products. Doc. Ref. EMEA/152688/04. Feb 2, 2005

FDA Guidance for Industry: Process Validation - General Principles and Practices January 2011, U.S. Food and Drug Administration (FDA), www.fda.gov

EMA Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities,

EMA/CHMP/CVMP/ SWP/169430/2012, 20 November 2014

American Society for Testing and Materials E3106 "Standard Guide for Science-Based and Risk-Based Cleaning Process Development and Validation" www.astm.org

American Society for Testing and Materials E3219 "Standard Guide for Derivation of Health Based Exposure Limits (HBELs)" www.astm.org

Walsh, A., "Introduction To Science- And Risk-Based Cleaning Validation Using ASTM E3106 & E3219" Pharmaceutical Online, 6 May 2020

Resources

alconox.com
cleaningvalidation.com
fda.gov
fdainfo.comich.org
ivtnetwork.com
picscheme.org

Chapter Nine:

Wastewater Treatment and Waste Minimization

Cleaning with aqueous detergents creates wash solutions mixed with residue and contaminated rinse water that must be disposed of or recycled. Most of these solutions can be discharged to drain, although occasionally a cleaner may be too alkaline or too acidic to discharge without treatment. Contaminants in used wash solutions may include: insoluble oils, emulsified oils, other dissolved organics, suspended solids, and dissolved inorganic solids such as chlorides, nitrates, phosphates, and metals. To minimize waste, you can recycle rinse water, recycle detergent solutions, or control and optimize the bath life of cleaning solutions.

The criteria for discharge of a waste detergent solution varies by country, state, and municipality and is frequently set forth in a discharge permit. Most local governing authorities specify acceptable criteria for pH, biological oxygen demand (BOD), and chemical oxygen demand (COD). If wastewater must be treated prior to discharge, a typical treatment system involves several steps including pretreatment to reduce the volume of solids and wastewater.

Treatment of Contaminants

- ***Solids***—Acidic conditions are used to separate oil–water emulsions. The oil layer is separated as described below. The water layer containing solids is pumped into a chamber, where a polymer flocculent is added. The wastewater is pumped into a clarifier, where most of the solids condense into a floc and settle to the bottom of the chamber. Flocculated solids are then transferred to a filter press, where they are dried for disposal. The remaining supernatant liquid is pumped into a process tank where the pH is increased to help metals precipitate out of solution. A polymer is then added to flocculate the metals.
- ***Oils***—Removal of trace quantities of floating oil in a cleaning bath improves cleaner performance and extends bath life. Further, by filtering out any particulates or fines, oils collected may be evaluated for reuse rather than disposal. Traditional mechanical separation of oil from wastewater uses skimmers, tank overflow, and decanting methods.

Equipment Options for In-House Treatment

- ***Evaporators***—Evaporation is commonly used to reduce the volume of water for further treatment. Contaminants concentrate at the bottom as sludge, and the water is transferred to a holding tank to cool to room temperature. The water is either discharged to drain (with the necessary permits and approvals in place) or treated further.
- ***pH adjustment***—Sometimes the only reason a waste stream is too hazardous to discharge to drain is that its pH is too alkaline or acidic. Tanks with mixers, pH monitoring,

temperature monitoring, and dosing systems to adjust pH can be used to treat a spent cleaning solution and adjust it to a pH that can go to drain.

- ***Separators***—Gravity separation of non-emulsified oil in wastewater can occur in the clarification tank. The influent and effluent flow rates are optimized to allow efficient separation of the lighter oil layer from the water. An inclined plate can be used to direct flow of the oil layer away from the wastewater. Another more current method of oil–water separation applies Bernoulli's principle, whereby the wastewater is split into two laminar flows. Oil is continuously collected and concentrated in a second chamber, which is separated by a baffle from the primary chamber and a reduced-pressure area below. The reduced pressure directs the flow of water down, away from the second chamber. Oil is recovered from the top of the concentrated layer when it reaches a designated thickness. High-quality, reusable oil can be recovered this way.
- ***Activated carbon***—Suspended organic materials can be removed from the waste stream using an activated carbon filter. The filter's extensive pore network can absorb material many times its own weight. However, activated carbon is used for organic materials only. Metal contaminants and other inorganic materials will remain dissolved or suspended in the wastewater and thus are not separated by a carbon filter. Accordingly, an activated carbon filter is frequently used as one of the last stages before discharge or recycling to assure cleanliness. Filters can be arranged in series or in parallel. A parallel arrangement allows for replacement of one filter while the others remain operational. Serial filters can be used to

enhance removal. Clarifying depth filters may be used as an additional component of a filtration system for waste streams with a high concentration of particulate matter.

- ***UV systems***—Ultraviolet (UV) light is effective to destroy biological organisms, so a UV-oxidation system can be used to reduce the bioburden of wastewater.

System Selection Considerations

Basic guidelines for selection of a wastewater treatment system include the following:

- Treatment options should be studied by an engineer to assess process alternatives. The system should be optimized for proper flow rates, filter capacities, throughputs, etc.
- Design, maintenance, and operations should allow for downtime.
- Capital and operating costs may justify recycling wastewater in a closed-loop system.

Cleaner and Rinse Water Recycling

Recycling can help reduce or eliminate liquid waste by trading dilute liquid waste for more easily disposable solid waste in the form of spent filters or concentrated sludge. Recycling can also help reduce detergent consumption. It may also save manufacturing time by increasing throughput and reducing system set-up procedures.

The original cleaner recycling systems were solvent-based vapor degreasers. These systems evaporated dirty solvent and then condensed it to purify for re-use. However, many of the solvents used in these systems are hazardous.

The shift from solvent-based cleaners to aqueous cleaners was initially driven by the desire to replace ozone-depleting fluorocarbon solvents, although aqueous-based cleaners were quickly identified

to be very effective. Early research on the effectiveness of aqueous cleaning was first undertaken by the Toxics Use Reduction Institute at the University of Massachusetts at Lowell, a public laboratory that studies solvent replacement, which demonstrated the efficacy of aqueous cleaning in industrial settings. In fact, the Institute's review of industrial applications on a laboratory scale found that aqueous cleaning provides a sound alternative to vapor degreasing in approximately four out of five applications. Functionally, anything that can be cleaned by a solvent can typically be cleaned successfully by an appropriate aqueous cleaner. The waste streams from an aqueous cleaning system are different from solvent cleaners and generally are more environmentally friendly and much easier to dispose.

Modern closed-loop aqueous cleaning systems remove contaminants from both the cleaning bath and rinse water. In such systems, it is best to keep the wash water separate from the rinse water, which is easier to purify. Some systems actually only recycle rinse water.

The first place to install recycling equipment is the rinse water portion of a cleaning system. One example is sequential tank cleaning, which uses a series of countercurrent cascading rinse tanks. Water from each tank is reused successively. Because water use is limited, this system is easy to use and inexpensive, yet it ensures that the final rinse stages contain the cleanest water.

It is easier to recycle a detergent solution separately from rinse water because the equipment only needs to separate soils rather than generate high-purity water. Creating such high-purity water requires the use of activated carbon, deionizing resins, ultra-filtration, or reverse osmosis. To extend bath life and recycle cleaning solution baths, use one or more of the following procedures.

- ***Physical filtration***—Gravity or low-pressure pump cartridges at 1–100-mm levels of filtration are used to remove suspended particulates.
- ***Microfiltration***—Low-pressure pumps, dead-end (direct flow), or cross-flow filter membranes are used to achieve 0.1–1.0-mm levels of particulate filtration (to disperse and remove very fine suspensions of particulates and microbes). Microfiltration is sometimes abbreviated MF.
- ***Ultrafiltration***—In this process, membrane filters (0.0005–0.1 mm) are packaged into a variety of element, module, or cassette configurations and integrated into the cleaning process. A feed solution to be recycled is pumped through the filter tangentially to the surface, and the feed is separated into a permeate or filtrate (recyclable fluid free of residues) and a retentate (fluid and material retained by the membrane that is not recycled). The soil-free permeate stream is then recycled back into the parts washer. Ultrafiltration membrane pore sizes are also specified by molecular weight cutoffs (MWCOs). Contaminants with a diameter greater than the membrane's MWCO are thus filtered out. Keep in mind that both microfiltration and ultrafiltration are flow- or pressure-driven processes. Neither will reject salts (which require reverse osmosis filtration), which can adversely affect performance and require disposal. Therefore, it is important to monitor salt content of both the recycled bath and rinse water. Ultrafiltration is sometimes abbreviated UF.
- ***Physical separation***—This includes cooling and skimming, settling, and emulsion breakup. Cooling solutions allows emulsions and suspensions to break. Settling allows water-insoluble materials to separate by density; heavy sludge

generally settles to the bottom when a suspension breaks. In emulsion breakup, light oils generally rise to the surface, and the overflow can be physically skimmed off with oleophilic wicks or cycling bands of oleophilic material, leaving reusable cleaning solution.

- ***Solution recharge***—Adding fresh detergent can extend the life of an exhausted detergent solution. For example, adding 50% of the original dose of detergent to a used solution will sufficiently raise the concentration of useable detergent to achieve effective cleaning.
- ***Reverse osmosis***—This process uses a partially permeable membrane and applied pressure to purify rinse water and return it to a very high-purity state.

It is very difficult to completely remove all contaminants from a wash solution while leaving behind only the detergent. As such, most detergent recycling systems generally leave some contaminants in the treated wash solution but retain sufficient detergent to clean surfaces or parts before the next recycling filtration restores the solution to usable cleaning capacity. These recycling systems are best for non-critical cleaning applications in which it is sufficient to clean with partially dirty wash solutions, such as floor cleaning and less critical industrial parts washing. The detergents used are often fairly alkaline to mitigate the risk of growth of foul-smelling microbes. The detergents used in recycling systems should not have alkaline salts such as phosphates and silicates that can break down and form sludges. Equally, anionic surfactants should typically be avoided because they can precipitate out of solution if sufficient calcium, magnesium, or iron build up in the recycled wash solution.

Filter Selection

Advances in membrane technology and evolution of systems with greater temperature and chemical stability have enabled development of many types of filters for ultrafiltration. For example, extremely hydrophilic (water-absorbing and oil-repellent) polymeric membranes resist fouling by free oils, emulsions, and other hydrophobic solutes to maintain efficient filtration rates over extended periods.

Filters can be either symmetric, with a fairly uniform pore size distribution throughout the membrane, or asymmetric, where a pore size gradient, typically coarse to fine, is constructed through the membrane. Dual layer filters, or filters with a built-in prefiltration layer, are also available. These membranes are constructed with a layer of one or more coarser pore sizes directly upstream of a finer filter.

Membrane selection is critical to the effectiveness of any recycling system. Before deciding on a system, users should ask the following questions.

- ***Surface chemistry***—Has the membrane been engineered for easy cleaning or to resist fouling by free-floating and emulsified oils? Are there adsorptive chemistries to remove expected contaminants?
- ***Stability***—Is the membrane physically and chemically stable when exposed to a broad pH range and aggressive chemicals?
- ***Pore size rating***—Has the membrane been designed to ensure complete passage of all cleaner components while sufficiently retaining oils?
- ***Processing parameters***—Has the membrane been designed with sufficient void volume, size, and porosity for the required process flow rates and pressures?
- ***Temperature tolerance***—What is the membrane's temperature tolerance?

While not required for all aqueous cleaning, membrane-based filtration can be particularly helpful to achieve a steady-state condition, which is desirable for maintaining quality control in high-production applications. Detergents must be selected for their compatibility with specific membranes and vice versa. Membrane resins, charges, binders, and structure material are among the attributes to consider for filters, while pH, use temperature, and active chemistries are among the attributes to consider for aqueous detergents.

Monitoring and Controlling Cleaning Baths

Another technique to optimize a cleaning system is to monitor and control the cleaning bath. Even high-precision critical cleaning systems can be optimized. Free alkalinity and total alkalinity are common tests for monitoring cleaning baths. Free alkalinity is a measure of the hydroxides, silicates, and some of the carbonate alkalinity as determined by titrating to a pH of 8.3, typically using phenolphthalein as a titration indicator. Total alkalinity is measured by titrating to a pH of 4.5 using bromocresol green–methyl red indicators, which measure all free alkalinity plus the buffering alkalinity of any carbonates present. These tests can work well for monitoring simple heavy-duty alkaline cleaners that rely on brute alkalinity rather than synergistic blends with surfactants, dispersants, and chelating agents. However, neither free alkalinity nor total alkalinity tests measure the level of surfactants, which makes them less appropriate for procedures that rely on surfactant emulsifying as a main cleaning mechanism. Some simple yet effective techniques can be used to monitor bath life, including the following.

- ***Conductivity***—Most detergents have sufficient dissolved solids to provide an easily detected conductivity reading, which can be used to confirm that the target detergent concentration has been reached when a cleaning bath is

being prepared. Monitoring conductivity while the bath is being used can detect significant changes that can indicate when to change the bath. To most reliably track changes in a bath, you should always return the bath to the original volume by adding water to make up for any evaporation. Evaporation will increase the concentration of detergent, which typically does not evaporate; thus, without make-up water, evaporation alone will result in a higher conductivity reading. Once make-up water is added to restore the original volume, then any increased conductivity is due to only the dissolved residues that are depleting the detergent.

Parts can be monitored for cleanliness and to determine how much conductivity increase the bath can tolerate before reaching cleaning failure. You can use an arbitrary number such as a 10% increase, or even 5% for very critical cleaning applications. Note conductivity may not be an ideal bath control method if you are cleaning parts with complex geometry and blind holes that have high dragout of cleaning solution into the rinse water—especially if you add makeup water to restore tank volume, conductivity will be decreased due to the depleted detergent being dragged out into the rinse water. Thus, conductivity is best used to control baths for cleaning parts with low dragout. In a bath used at lower temperatures with little evaporation, such as 50°C–55°C (122°F–131°F), and parts with high dragout, you can compensate by adding back correctly diluted detergent solution to restore tank volume rather than water. Alternatively, you can simply not add back any makeup solution, so that any increase in conductivity is due to dissolved residues that are depleting detergent capacity.

- ***Refractometry***—This is an indirect measure of the concentration of dissolved components, which influence the refractive index of a sample of solution. The measurement may be taken using a simple handheld refractometer. Refractometry can also be used to monitor buildup of soils and concentration of a solution as a result of water evaporation. Refractometry works much like conductivity. In high-evaporation baths, water must be added to maintain volume and thus produce meaningful refractive index results. In high-dragout baths, it is best to add dilute detergent to make-up the volume or nothing at all to get the most meaningful results. Again, you can observe parts to determine when cleaning failure occurs to identify the refractive index that indicates it is time to change the bath. Alternatively, you can set an arbitrary 10% increase in refractive index as the point to change out the bath. In general, conductivity is more sensitive than refractometry. Refractometer instruments often read to 0.1 degree brix, which is sufficient to control a cleaning bath within the method's limits.
- ***Foam height***—Measuring foam height and foam stability is a fairly crude bath control method that only works with high-foaming detergents. Nonetheless, it is a very simple method to estimate the depletion of surfactants and buildup of oils in a solution, which inhibit foam. Foam height and foam stability in a sample of cleaning solution in a vigorously-agitated, stoppered test tube will decrease as oils accumulate. When foam height decreases, recharge or discard cleaning solutions. Observations must be made at consistent temperatures. Unfortunately, foam is increasingly inhibited near the point of emulsifying failure and when free-floating oils begin to

form on the surface of the solution, further inhibiting foam. If a bath is so depleted that it has free-floating oils, it may not have sufficient detergency for critical cleaning. However, lower-level cleaning can use foam height as a general guide for when to change a cleaning bath.

- ***pH***—pH measures the acidity or alkalinity of a solution on a scale of 0–14. It represents negative log of the hydrogen ion concentration, which is measured using electrodes dipped in the solution and connected to a pH meter. Detergents with pH below 7 are acidic, and those with pH above 7 are alkaline. Note that pH paper should not be used with surfactant-containing cleaners, because they commonly hamper accurate reading. A given brand of detergent will have a typical pH. For alkaline cleaners, if soils are acidic, inorganic, or saponifiable natural oils, pH will decrease as the cleaning solution is used up. Typically, when pH changes 0.5 unit towards neutral, the detergent should be recharged. Then the solution can be used to exhaustion as it drops one full pH unit. For critical cleaning, changing the bath at a 0.5 pH unit change might be appropriate. By the same token, for acid cleaners, if the soils are alkaline, saponifiable esters, or oils, then the pH will increase as the cleaner becomes spent. Again, a change of 0.5 pH unit towards neutral would be a sufficient change to recharge the detergent solution in less critical cleaning applications and possibly to change out the bath for critical cleaning applications.

The technique chosen to monitor bath life will depend on both the type of detergent you are using and the soil or residue you are removing (Table 9.1). For example, when cleaning with an ionic detergent, use conductivity to monitor dilution, dragout, and loss of

detergent. When using a high-emulsifying or dispersing detergent to remove oils or particulate soils, refractometry is an effective means of measurement and control. Foam height is most effective when cleaners contain foaming surfactants that rely on emulsification to remove oily soils. When using an alkaline cleaner to remove a soil that is either acidic or neutralizing in character (as most soils are), pH can be used as a control measure.

Table 9.1 Basic bath monitoring and control techniques

Selection Based on Type of Detergent Used	
Conductivity	Ionic cleaner removing nonionic soil, such as a high-alkaline cleaner used for degreasing
Refractometry	High-emulsifying and dispersing cleaner used on mixed particulate and oily soil
Foam height	High-foaming cleaner used to clean oily soils
pH decrease	Alkaline cleaner used to clean acidic or hydrolyzable soils that react with the cleaner (most soils are acidic or hydrolyzable)
pH increase	Acidic cleaner used to clean an alkaline or neutral soil (most inorganic soils)

Economic Factors

Where detergent recycling is concerned, it is important to carefully consider economic factors across the entire system. It may not be worth risking inadequate or even uncontrolled cleaning in a misguided attempt to get every last penny of performance from a detergent solution. Further, the cost of installing recycling and reuse equipment and procedures must be weighed against the cost of disposal and solution use. The value of the parts being cleaned, the increased risk of cleaning failure with each new part cleaned, and the chance of cleaner exhaustion or soil redeposition must all be considered. Answer the question: Is it cheaper and/or more efficient to send partially used cleaner to drain and make up a fresh batch?

When working with nonhazardous or easily treated detergents

and wastes, it is generally cheaper and more efficient to send the bath to drain and make fresh solution; with difficult-to-treat hazardous wastes, recycling may be a more economic option. Where regulatory compliance costs are prohibitive or no drain is available, recycling may be the best option.

Another factor to consider is the volume of the cleaning system. In high-volume, high-performance cleaning applications with quality control inspection or low-fault-tolerance parts such as electronic components and optical parts, recycling may be worth it. But in low-volume, extreme-cleaning performance applications such as pharmaceutical process equipment, medical devices, and expensive soil-sensitive equipment, recycling the detergent may not be cost-effective.

Before considering recycling as an option, determine whether the EPA needs to be involved. Complete a Superfund Authorization and Reauthorization Act (SARA) report stating the quantity of any chemical found either in the soil or detergent discharge.

Fully review the following parameters:

- ***Toxicity***—by toxicity characteristic leaching procedure
- ***Corrosivity***—pH less than 2 or greater than 12.5
- ***Ignitability***—flash point below 60°C (140°F) ignitable

Also look at compressed gases and oxidizers as well as reactivity of the waste stream to determine whether Resource Conservation and Recovery Act (RCRA) regulations apply. Refer to 40 CFR 261.21–.24 as well as any applicable state and local discharge regulations.

Proven Technologies

There are suppliers of closed-loop aqueous cleaning systems designed to increase process efficiency by decreasing waste generation. Implementing such systems should not be based solely on short-term economic concerns but must include a careful review of environmental and regulatory considerations. The benefits of sophisticated closed-loop systems must be weighed against the costs of maintaining those systems. For example, membrane systems need periodic cleaning or may need to be replaced. In the long run, recycling may be more economical than playing catch-up with evolving regulations surrounding industrial parts cleaning.

Note that manufacturers already using aqueous cleaning solutions do not need a closed-loop system to begin recycling—recycling can be as simple as making up a large soak tank for continuous use throughout the manufacturing process. Time and money are saved merely by recycling wash-tank water through a skimmer and recharging it with detergent at midweek intervals. This prevents downtime during draining, refilling, recharging, and reheating the tank.

References

B. Kanegsburg and E. Kanegsburg, Handbook for Critical Cleaning: Cleaning Agents and Systems, Second Edition, p. 441–469; CRC Press, Boca Raton, FL (2011).

E. Linclau, J. Ceulemans, K. De Sitter, P. Cauwenberg, "Water and detergent recovery from rinsing water in an industrial environment," Water Resources and Industry, Vol. 14, 3–10 (2016).

M. McLaughlin, "Closed-loop cleaner recycling," Precision Cleaning, p. 17–24 (June 1997).

Membrex Inc., Alkaline Cleaner Recycle Handbook, Membrex Inc.; Fairfield, NJ, p. 3–5 (1994).

J. Quitmeyer, "Sifting through filtration options," Precision Cleaning, p. 16–23 (December 1997).

L. Suárez, M.A. Díez, R. García, F.A. Riera, "Membrane technology for the recovery of detergent compounds: a review," Journal of Industrial and Engineering Chemistry, Vol. 18, No. 6, 1859–1873 (2012).

Toxics Use Reduction Institute, "Closed-loop aqueous cleaning," University of Massachusetts; Lowell, MA, p. 6, 10 (1995).

Warsaw University of Technology, "Effective water and detergent recycling solution for industrial laundries" (7 August 2019). Available at pw.edu.pl/engpw/Research/Business-Innovations-Technology-BIT-of-WUT/Effective-water-and-detergent-recycling-solution-for-industrial-laundries

Resources

alconox.com
epa.gov
separationdynamics.com
turi.org

Chapter Ten:

Measuring Cleanliness

Depending upon the method selected, cleanliness can be detected to varying degrees or levels (Figure 10.1). While it is common to refer to measuring cleanliness, cleanliness is more accurately described as a measurement of remaining soil or other unwanted residues.

The first level can detect cleanliness to soil quantities as low as 0.01 grams per square centimeter (g/cm^2); the next level detects soils of 0.01–0.001 g/cm^2, a level suitable for aerospace, electrical, automotive, and many surface preparation applications; and the most precise level detects soils less abundant that 1 mg/cm^2, which is suitable for use in semiconductor, disk drive, and medical device applications. Measuring techniques appropriate to each level of cleanliness are summarized below.

Cleanliness Detection to 0.01 g/cm^2

- ***Atomizer test***—The atomizer test involves gently spraying water mist over the test area. Any areas that display water repulsion indicate the presence of a hydrophobic soil. The atomizer test is slightly more sensitive to hydrophobic soils than the water-break test (described below) because the

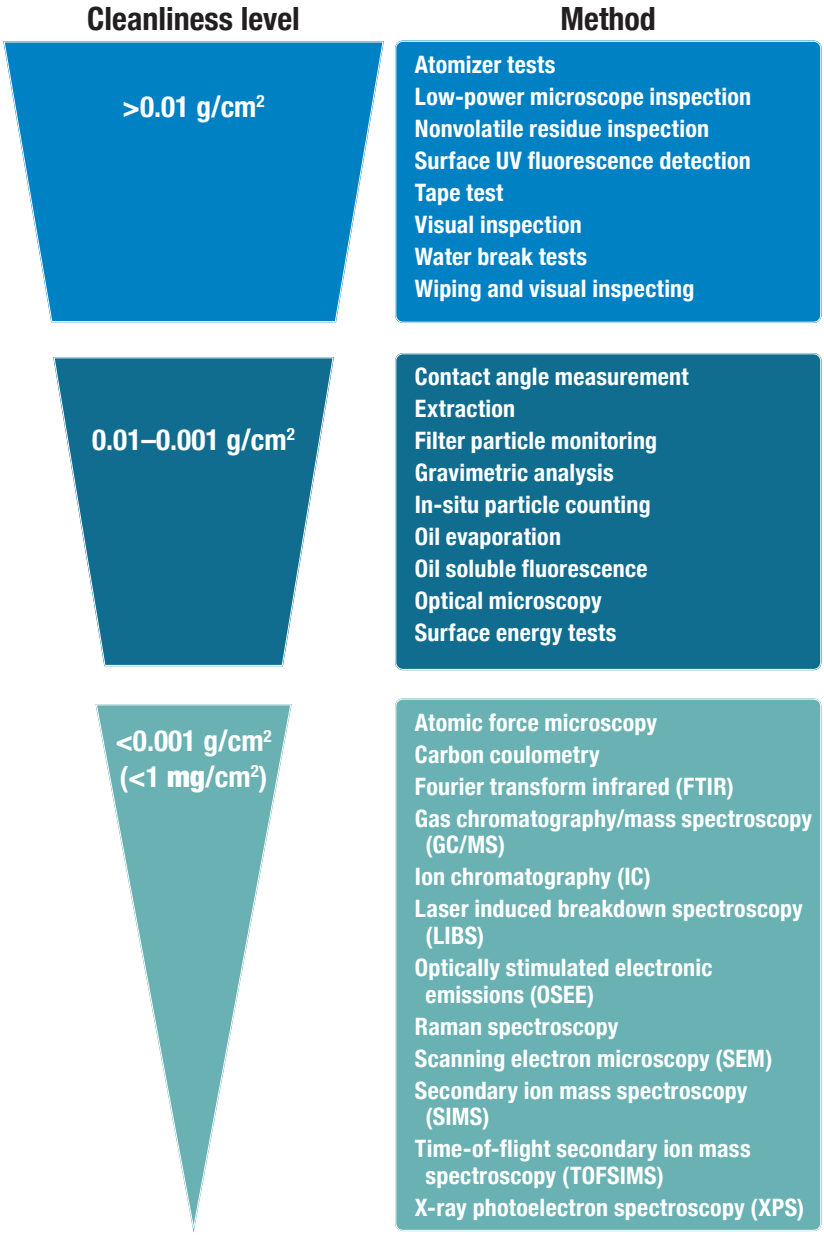

Figure 10.1 Methods for measuring cleanliness at varying levels of sensitivity.

kinetic energy of flowing water may overcome a hydrophobic residue. In contrast, the atomizer test allows you to see a small droplet of water being repelled by a hydrophobic contaminant.

- ***Low-power microscope inspection***—This is a quick and efficient visual method to verify cleanliness of residual oils and greases, flux residues, particles, and surfaces.
- ***Nonvolatile residue inspection (NVR)***—NVR involves extraction of soil from a dirty surface into a solvent. The solvent is then evaporated onto a coupon of known weight, depositing any residue on the coupon. The coupon is then re-weighed, and any weight increase is attributed to the nonvolatile residue. Many solvents can be used (e.g., isopropyl alcohol, methylene chloride, acetone), but it is important to use a solvent that can dissolve the soil being detected.
- ***Surface ultraviolet (UV) fluorescence***—Many organic and some inorganic contaminants will fluoresce under UV light. The surface UV fluorescence test is performed by shining UV light on a surface to observe fluorescent color—typically yellow, orange, or green, although sometimes red—that glows under the light. Shining a UV light on the surface makes residues more visible, particularly in a slightly darkened or dark room. A higher intensity of light will detect a lower level of contaminants. Note, however, that the typical black light found in novelty or specialty gift stores may not be strong enough to fluoresce residues. More powerful UV lights available from scientific supply houses or industrial suppliers will provide better results.
- ***Tape test***—The tape test is a simple method to aid visual inspection and is well-suited for testing the cleanliness of smooth metal and plastic parts. The test involves attaching

transparent adhesive tape to the surface being measured, firmly pressing the tape down, carefully removing the tape, and then placing the tape on a sheet of clean white paper. Visually comparing the sample with an adjacent piece of white paper is a fast and easy way to monitor particulates and sometimes even film residues.

- ***Visual inspection***—This method is best used to detect residues of contrasting color or texture. Good lighting can enhance visual inspection. Magnification and fiber optic lighting, which throws light across a surface, can improve detection. This low angle viewing, often with flash, is discussed in Chapter Five as well. Under ideal lighting conditions, the limits of visual detection can reach 0.001 g/cm^2.
- ***Water-break test***—This test uses running water across a surface to form a sheet. Breaks in the water sheet indicate the presence of hydrophobic (water-repelling) residues. The water-break test is a fairly crude test that is suitable for detecting films of process oils and heavy fingerprints. It does not readily detect hydrophilic (non-hydrophobic) residues. This test is often used for parts washing and may not be suitable for precision cleaning applications.
- ***Wiping***—Wiping with a white wipe provides a contrasting surface to detect dark residues (often referred to as the white glove test).

Cleanliness Detection at 0.01–0.001 g/cm^2

- ***Contact angle measurement***—A liquid droplet stabilized on a surface will have a characteristic contact angle between the edge of the droplet and the surface. Contact angle measurement is a variation of surface energy testing and

quantifies the relationship of surface energy of the surface and interfacial tension of the liquid on the surface. This method can be used to determine cleanliness because different contact angles reflect the properties of contaminated surfaces. Contact angle measurement is especially suited to manufacturing operations such as wire bonding on printed circuit boards or the application of thin films on quartz glass, as these operations require nondestructive cleanliness testing. Vapors resulting from the manufacturing operation itself (e.g., vacuum or diffusion pump oils), various process chemicals, and even human perspiration are all contaminants that can be detected by changes in the contact angle. (For a full description of this measurement technique, see below: "More on Contact Angle Measurement Methods.")

- ***Extraction***—Extraction is a particularly useful method for detecting detergent residues. Solvent-soaked glass filter paper or a high-purity swab is used to wipe the surface. Residue is then extracted or digested from the filter paper or swab, and trace analysis is performed on that extract. The procedure can be quantitative if a known area is wiped. Extraction methods can be highly sensitive to a wide range of possible soils and residues. However, it is important to use an appropriate solvent to extract any soils. When performing trace analysis for detergent residues, it is advisable to use water as the solvent. (Sensitivity of an extraction test depends on the method of trace analysis.) The most frequently used types of trace analysis are UV visible spectrophotometry, total organic carbon (TOC) analysis, high-performance liquid chromatography (HPLC), atomic absorption (AA) of inorganic residues, and liquid chromatography (LC) (see below: "Detection below 1 mg/cm^2").

- ***Filter particle monitoring***—Filter particle monitoring involves collecting a cleaning bath, rinse bath, or sample rinse of a finished part, and then passing that through a filter of known size exclusion. The resulting filtrate is examined under a microscope for any particle-per-micron contaminants. (The membrane can also be weighed to determine total contaminants in milligrams.) Filter particle monitoring is used to monitor particle load in a wash bath to determine if the wash bath is overloaded, to monitor particle load in a rinse bath to determine if the rinse bath is overloaded, and to sample finished parts to determine remaining particle loads.
- ***Gravimetric analysis***—Small parts of known weight can be weighed after cleaning; any excess weight detected represents the amount of soil present. If the part returns to its original weight after cleaning, the part can be considered clean. Gravimetric analysis also is useful as a screening tool in lab cleaning. When a coupon is weighed before soiling, after soiling with an artificial soil, and then weighed again after cleaning, the percent of soil removed can be derived.
- ***In-situ particle monitoring (ISPM)***—Part cleanliness becomes critically important with decreasing size of mechanical, optical, and electronic parts—formerly inconsequential particles become more significant due to the relative size proportions. ISPM provides a tool to observe particle removal in ultrasonic bath cleaning in real time. This helps to adjust and optimize the cleaning process quickly and easily. Once cleaning is optimized, ISPM can be used to monitor bath performance as well as filtration recycle performance. ISPM measures particle counts directly during both ultrasonic wash and rinse baths. (See below, "An Example of In-Situ Particle Monitoring.")

- ***Oil evaporation***—When working with filmy residues, a few drops of organic solvent can be deposited on the surface and then removed via pipette and placed on a watch glass. If any filmy residues are present, a characteristic ring of organic material will be deposited.
- ***Oil-soluble fluorescence***—This process involves immersing a part in a fluorescent oil-soluble penetrant dye and then observing the part under fluorescent light. If any dye penetrates or adheres to the part, oil is present. This method is outlined in ASTM F601-98 "Standard Practice for Fluorescent Penetrant Inspection of Metallic Surgical Implants." Of course, cleaning procedures need to be established to remove the dye after testing.
- ***Optical microscopy***—High-power compound microscopes also can be used (typically on circuit boards), although these are more delicate and more expensive than low-power microscopes and generally require greater operator skill and training.
- ***Surface energy tests***—Any hard, flat material has a characteristic surface energy. As a result, a deposit of a known volume of pure liquid (typically deionized water) will form a droplet of predictable size. Measuring droplet size will determine surface cleanliness. Generally, hydrophobic soils create smaller droplets, while hydrophilic soils create larger ones. The surface energy test is far more sensitive than the atomizer or water-break tests and has the advantage of detecting both hydrophilic and hydrophobic soils. However, the surface energy test only tests the surface directly underneath the droplet that you are measuring. If measuring

a small surface area that is characteristic of a larger one, this can be an excellent and highly sensitive method. If a part is full of cracks, crevices, and holes, however, the surfaces that are accessible for measurement may not contain the same soils that are hidden in the cracks, crevices, or blind holes. (For a complete description of this technique, see below: "More on Water Drop Surface Energy Test.")

More on Contact-Angle Measuring Methods

Accepted methods of measuring contact angles to determine surface characteristics include the inverted bubble, Wilhelmy plate, and sessile drop techniques. The latter is the most widely practiced quality control technique, as it is relatively quick and requires minimal investment of time and money.

In the sessile drop technique, the sample to be measured is loaded onto a sample holder. A liquid droplet 3–4 mm in diameter is carefully deposited onto the substrate surface. A tangent line is drawn at the three-phase interface point to determine the contact angle. Alternately, a line is drawn from the three-phase interface point through the apex. This angle is equal to half of the tangent angle and is reproducible by different operators. Videos available online can help visualize this process (search for "sessile drop techniques").

A real-world example helps illustrate use of the contact angle measuring technique to determine the existence of impurities on a surface. Liquid crystal display (LCD) panel surfaces contaminated with organic matter are less accepting of a variety of films, including metals and protective layers, resulting in poor manufacturing yields. Sources of such contaminants include the vapor of process materials, chemicals, and human perspiration. Very thin organic contaminants several monolayers in thickness (>10 angstroms) can be evaluated using the contact angle technique. It is generally agreed that the wetting behavior involves only the last layer or two of atoms on either side

of a solid's interface. The water contact angle correlates "cleanliness" of the surface to the adhesion of copper deposited onto the surface of the LCD.

Water contact angles can be used in many situations to determine contamination levels, predict cleanliness and adhesive bond strengths, and monitor cleaning operations. Whether you are checking the moisture effects on silicon wafers or LCD quartz panel glass metal adhesion, all that is needed is an understanding of the basic theory involved and proper measurement techniques.

Recent advances in contact angle measurements offer portability of the devices as well as an increased number of angle measurements made on the droplet. This technology can enhance the utility of using contact angle measurements in critical cleaning industries and can provide further quantification in pilot scale screening studies of parts and surfaces.

An Example of In-Situ Particle Monitoring

John Hunt's work for Pacific Scientific Instruments, located in Grants Pass, OR, demonstrates the use of in-situ particle monitoring. To select the best cleaning agent and determine the correct concentration, Hunt began by depositing known types and amounts of particle contamination on glass slide test coupons. Several cleaning agents were tested for effectiveness by monitoring the rate of particle removal from soiled plates in a bath. To do this, bath water was recycled through a filtration loop, and particles were detected just before filtration and removal from the recycle loop. Hunt studied the effectiveness of several detergents at various concentrations on varying particle sizes. Particle removal was observed in the bath for each detergent concentration when the soiled glass plate was added to the bath. The number of particles per milliliter per minute was determined by integrating the area under the particle size counting

curves for a given length of time for each particle size monitored at each concentration of each detergent. By evaluating this comprehensive information, the best detergent, concentration, and cleaning time can be determined for a given particle size.

When determining optimal detergent concentration, be sure to allow bubble activity to subside after adding more detergent but before placing the soiled plate in the bath. Typically, you will see an initial spike of particles coming off the plate when it is added to the bath. Particles continue to come off over time, but the rate slows. Generally, after 10 or 15 minutes, no more particles are observed. This information can also be used to optimize cleaning time. During actual cleaning, parts should be removed from the bath when particle counts have dropped back to baseline.

More on Water Drop Surface Energy Test

Surface energy can be indirectly detected by measuring the size of a droplet of known volume sitting on a surface. Using a volumetric pipette, a drop of typically 0.2 mL of water is placed carefully onto a surface being investigated. The droplet size is measured with a micrometer. If the droplet is circular, determine area by calculating πr^2. Note that any machining or scoring will distort droplets. Multiplying length times width, and assuming a more rectangular area, may be a more robust way to calculate area. Whichever method you choose, do not vary area calculations within a set of tests. Typically, a surface with a hydrophobic oily residue film will repel the water and cause the droplets to be smaller than those observed on a clean surface.

This method works well when testing glass and metal surfaces. It is better for detecting films than particulates on smooth surfaces. If the surface is scratched during cleaning, the droplet size will become smaller, causing a false "after" reading in a before and after test. If a volumetric pipette is not available, use an eyedropper to deposit drops

and a scale sensitive to 0.001 grams to measure droplet weight. The ratio of droplet weight to area can be used to detect changes in surface energy. Again, an increase in this ratio occurs when comparing a dirty surface to a clean one. It is useful to work with a known clean surface to observe droplet size behavior and known soiled surfaces to confirm that the residue will give the expected decrease in droplet size caused by the presence of an oily film. Note that if the film is hydrophilic, unlike most oily films that are hydrophobic, then the droplet size will increase, not decrease. By working with known clean and dirty substrates, you can empirically observe the expected change.

As with other cleanliness verification techniques, special tips for contact angle measurement can increase the repeatability and validity of results. The following tips will help you achieve accurate results:

- Use gloves when handling the samples to be measured. Organics, such as finger oils, cosmetics, and other contaminants, will skew the contact angle results.
- Note the nature of the droplet after applying it to the surface. Wait until the droplet has ceased its advancement and no more change in lateral movement has occurred. Measure this time interval, making sure that you wait this period of time after every measurement. Retain consistent time intervals between the placement of the droplet and its measurement.
- Use medical-grade, ultra-purified deionized water from a laboratory supply house for a consistent measuring liquid. This will limit the number of measurement variables.
- Use test liquids of larger surface tension than the solid's surface energy to obtain easy-to-read results.
- Neutralize the effects of static charges on substrates. Substrates that are electrostatically charged can skew contact angle readings up to 5°.

- Accurately control liquid droplets so that they are repeatedly deposited onto the sample. Gently move the sample to the liquid droplet formed at the end of the syringe/dispenser to minimize gravitational effects.
- In the case of very high contact angles, it is difficult to attach the droplet from the needle to the solid sample. Use a Teflon-coated needle of a higher gauge (smaller inner diameter).
- In case of very low contact angles, use the highest possible needle gauge (smallest inner diameter) for controlling very small droplet volumes onto the sample.

Cleanliness Detection Below 1 mg/cm^2

- ***Atomic force microscopy***—A surface scanning technique whereby a sensitive "needle" or probe measures surface topography down to atomic dimensions, thus measuring angstroms worth of contaminating particles.
- ***Carbon coulometry***—This technique uses in-situ direct oxidation of surface carbon to carbon dioxide (CO_2), followed by automatic CO_2 coulometric detection. (For a more complete description of in-situ monitoring, see above: "In-situ particle monitoring.")
- ***Fourier transform infrared spectroscopy (FTIR)***—FTIR spectroscopy is used for structural characterization of organic and inorganic molecules on surfaces and in solids, liquids, and gases. Spectrometers record the interaction of light energy in the form of infrared radiation with an experimental sample, measuring the frequencies at which the sample absorbs the radiation and the intensities of the absorption. To determine the chemical composition of a sample, use an extraction method or a surface scanning machine and then compare the unknown spectra from your sample to the standard frequency

at which specific molecules absorb infrared light. Most FTIR machines have standard libraries of known molecules for comparison purposes. Even if you do not get an exact match, information about the type of chemical present can be derived by looking for telltale frequencies of absorbance for typical functional groups.

- ***Gas chromatography/mass spectrophotometry (GC/MS)***—GC/MS is used to identify surface contamination by ***extracting*** contaminants into a solvent and analyzing them. Organic compounds are then separated via GC and identified by molecular weight using MS.
- ***Ion chromatography (IC)***—IC is a form of liquid chromatography of aqueous samples used to determine ionic contamination on critical components. Columns containing ion-exchange resins are used to separate the atomic or molecular sample ions based on their partition ratios of how attracted to the column vs. how attracted to the carrier those ions are as they pass through the columns. It is one of the techniques that can provide quantitative analysis of anions at the part-per-billion (ppb) level of an extract that has been swabbed or wiped from a surface and extracted into solution for analysis.
- ***Laser induced breakdown spectroscopy (LIBS)***—This rapid detection technology can detect down to the part-per-million (ppm) range. LIBS sends a laser pulse towards a surface, ablating the surface and creating a microplasma. As this plasma cools, spectra are emitted than can be analyzed to determine elemental composition.
- ***Optically stimulated electronic emissions (OSEE)***—This technique directs high-energy UV light onto a surface,

causing emission of electrons and subsequently measuring the reflected current. A clean surface will give the highest return current, so any decrease in current represents contamination. This method can determine low levels of contamination (both ionic and nonionic). However, while OSEE can detect contamination, it cannot identify the contaminants.

- ***Raman spectroscopy (RS)***—A technique similar to FTIR, RS is useful for smaller samples and can provide "fingerprints" of the sample's molecular structure. Thus, it also can be used for surface mapping.
- ***Scanning electron microscopy (SEM)***—By scanning high-energy electrons across a specimen, SEM enables study of the composition and morphology of biological and physical materials. When high-energy primary electrons impact the specimen, they are deflected or scattered, or pass through the specimen to become secondary electrons. Detectors are used to derive topography and composition information about the sample.
- ***Secondary ion mass spectroscopy (SIMS)***—SIMS is an extremely sensitive surface analytical technique. It is used for chemical determination of surface constituents, both elemental and molecular, as well as ppb concentrations of impurities in semiconductors and metals. The material under investigation is bombarded with primary ions that, upon impact, cause release of secondary ions from the sample's surface. Secondary ions can be identified by their mass, which is determined by measuring their travel time from surface to analyzer.
- ***Time-of-flight secondary ion mass spectroscopy (TOFSIMS)***—This analytical technique uses a pulsed ion beam to remove

molecules from the surface being analyzed. Analysis of the ions released in this "splattering" provides information about surface-contaminating species.

- ***X-ray photoelectron spectroscopy (XPS)*** or photoelectron spectroscopy—Also known as electron spectroscopy for chemical analysis (ESCA), XPS is an extremely surface-sensitive technique that uses the photoelectric effect to detect elements and determine elemental composition. Electrons are ejected from a solid surface by irradiating the surface with an X-ray monobeam. The emitted photoelectrons have a kinetic energy equal to the X-ray less the binding energy of the electron. The measured kinetic energy of the electrons can therefore be converted to binding energies, enabling element identification.

References

ASTM International, "ASTM F22-13: Standard test method for hydrophobic surface films by the water-break test," ASTM International, West Conshohocken, PA (2013).

ASTM International, "ASTM F601-18: Standard practice for fluorescent penetrant inspection of metallic surgical implants," ASTM International, West Conshohocken, PA (2018).

A. Carrasco, "Moisture induced stress sensitivity reduction of FSRAM 52 lead PLCCs," 1996 Surface Mount International Conference, p. 607–611 (1996).

Cleantech, "Cleanliness verification," CleanTech, Vol. 3, No. 3, p. S1–S12 (March 2001).

F. Djennas, E. Prack, Y. Matsuda, "Investigation of plasma effects on plastic packages delamination and cracking," IEEE Transactions on Components, Hybrids, and Manufacturing Technology, Vol. 16, No. 8, p. 91–924 (1993).

C. Geosling, J. Koran, "Chapter 3.2: Contamination control and analytical techniques," p. 431–448, Handbook for Critical Cleaning, B. Kanegsberg (Ed.); CRC Press, Boca Raton, FL (2001).

A.D. Gilpin, B.R. Oakley, R.G. Dillingham, "Water contact angle as a quantitative measure of total polyethylene surface energy," Journal of Adhesion Science and Technology, Vol. 29, No. 9, p. 890–895 (2015).

R.J. Good and R.R. Stromberg (Ed.), Colloid and Surface Science, Vol. 11; Plenum, New York (1979).

G. Gould, E.A. Irene, "An inside study of aqueous HF treatment of silicon by contact angle measurement and ellipsometry," Journal of The Electrochemical Society, Vol. 135, p. 1535–1539 (1988).

G. Hawkins, G. Ganesan, G. Lewis, H. Berg, "The PBGA: A systematic study of moisture resistance," ISHM Journal of Microcircuits & Electronic Packaging, Vol. 18, No. 2, p. 122–132 (1995).

L. Herard, "Surface treatment for plastic ball grid array assembly and its effect on package reliability," p. 1, ISHM Workshop on Flip Chip and Ball Grid Arrays, Berlin, Germany, November 13–15 (1995).

J.D. Hunt, "In-situ particle monitoring," Parts Cleaning Magazine, p. S–4 (March 2001).

L. Hymes (Ed.), "Testing for cleanliness," p. 94, and "Cleanliness verification, p. 197, Cleaning Printed Wiring Assemblies in Today's Environment (1991).

K.-G. Japan, "Comparative studies of the contact angle as a measure of adherence for photoresist," Thin Solid Films, Vol. 75, p. 319–329 (1981).

B. Kanegsburg and E. Kanegsburg, Handbook for Critical Cleaning: Cleaning Agents and Systems, Second Edition; CRC Press, Boca Raton, FL (2011).

R. Kohli and K. Mittal, Developments in Surface Contamination and Cleaning, First Edition (2011).

C. LeBlanc, "Toxics Use Reduction Program for The 22nd Mr. Clean Conference," Turi, MA (October 1996).

K.L. Mittal (Ed.), Contact Angle, Wettability and Adhesion, Volume 1; CRC Press (1993).

R. Powitz, "Measuring cleanliness," Journal of Cleaning Restoration and Inspection (August 2014).

T. Thompson, "Moisture absorption and autoclave performance optimization of glob top ball grid array," Surface Mount International Conference, p. 587–592 (1996).

M. J. Toshiaki, "Relationship between surface energy and surface contamination," Physical Chemistry, Vol. 71, p. 4176 (1967).

R. Williams and A.M. Goodman, "Wetting of thin layers of SiO_2 by water," Applied Physics Letters, Vol. 25, p. 531–532 (November 1974).

Resources

alconox.com
astm.org
astp.com
photoemission.com
pmeasuring.com
technotes.alconox.com

Chapter Eleven:

Environmental Health and Safety Considerations

Aqueous cleaners, by definition, use water for cleaning and rinsing—this has both advantages and disadvantages. Water is an inherently environmentally sound and substantially safe chemical, and it is a recyclable natural resource. Yet, as populations grow, clean surface water becomes increasingly scarce. Further, water, after it has been mixed with detergents and used to remove unwanted residues from the surfaces being cleaned, also can be a transport medium for various polluting or hazardous chemicals.

One way to look at the environmental health and safety of a cleaning process is to consider:

- *How hazardous is the cleaning process?*
- *How hazardous is the effluent resulting from the cleaning process?*
- *How sustainable—in terms of energy and resources—is the process?*

All critical cleaning processes can be defined by where they fall on the safety continuum. At one end are polluting, hazardous processes; at the other end are clean and safe processes that are sustainable and

produce little waste. Aqueous cleaning may fall anywhere along this continuum as a function of both the residue being removed as well as the choice of detergent.

Of course, some aqueous cleaners contain hazardous ingredients that may be used to clean hazardous soils, which may, in turn, produce hazardous and polluting waste. But, by the same token, industrial cleaning may use an aqueous cleaner that contains no hazardous ingredients to clean the same hazardous soil, resulting in a clean and relatively safe process.

Safety can be improved by eliminating the source of the hazardous soil in the process. Going a step further, waste can be reduced by integrating recycling of the soil, cleaning solution, and/or rinse water into the cleaning process. It is possible to design a so-called "zero-discharge" system with no fluid effluent, limited volatile effluent, and reduced solid waste by recycling cleaning and rinsing solutions using filters. Moving toward a clean, safe, and sustainable process, however, requires eliminating the hazardous soil and replacing it with a nonhazardous, biodegradable soil. Then, after water used in the cleaning and rinsing process has been recycled sufficiently for energy efficiency, the now nonhazardous soil in the effluent does not pose an environmental threat. Any water released could safely be incorporated into the natural water cycle (surface water evaporates to form clouds, which later precipitate as rain, and return as surface water).

It is generally much more difficult to clean safely and sustainably using nonaqueous cleaning methods. Many nonaqueous cleaners are themselves health hazards, water pollutants, or air pollutants. Certainly not all nonaqueous cleaners are hazards and/or pollutants, but most lack a basic natural means, such as the water cycle, of purifying and/or recycling key ingredients. Of course, this is an oversimplification—

given enough time, almost anything can complete a natural cycle of synthesis and decay. However, "enough time" in this context may be the period of a human lifetime.

One could argue that the carbon cycle, nitrogen cycle, oxygen cycle, and other elemental cycles are involved in decomposition and purification of ingredients used in nonaqueous cleaners. In fact, some of these cycles are also involved in purification of ingredients in aqueous cleaners, but to a lesser degree. All of these cycles involve multiple chemical transformations. They are slow processes in which chemicals may remain in one state for many years before degrading to a purer form. For example, nitrogen in the nitrogen cycle typically remains in the air for years. Likewise, carbon in the carbon cycle takes the form of geological carbonates for extensive periods of time, in some cases millennia. Oxygen also remains tied up in the form of geological carbonates. These elements simply do not cycle rapidly to a pure state, the way water does.

Environmental Issues in Aqueous Cleaning

Generally, the environmental issues involved in aqueous cleaning are with the ingredients used and their ultimate discharge into the environment. Taking a broader view, it is also important to consider the energy and resources consumed in making and using the cleaner.

There are several important factors concerning discharge of spent cleaning solutions into the environment: biodegradability, aquatic toxicity, and acceleration of eutrophication. Early detergent formulations contained poorly biodegradable surfactants that often caused foaming of lake and river surfaces after spent solutions were discharged to drain. Today, all modern detergent formulations instead use biodegradable surfactants that do not buildup or persist in the environment and cause foaming problems.

Aquatic toxicity can come from very high or very low pH or from toxic ingredients. When extreme pH cleaning is required, it is advisable to neutralize or discharge spent solutions in small enough quantities to avoid problems. The surfactants in aqueous cleaners also may be a source of aquatic toxicity. Use of biodegradable surfactants and discharge of limited quantities of cleaning solutions generally result in safe concentrations of surfactants on water surfaces.

Eutrophication involves cleaners that contain phosphates. Phosphorus is an essential nutrient for algae. When significant amounts of phosphorus are discharged into surface water that is phosphorus-limited, vigorous algae blooms may result. The algae die and settle, rapidly filling lakes and ponds with silt and organic matter. Although eutrophication is a natural process, acceleration of this process by phosphates is undesirable. The main source of phosphorous in surface waters is agricultural run-off from farming. There are no national regulations restricting use of phosphates in cleaners, although many states and municipalities have enacted legislation that restricts use of phosphates in household cleaners. Further, there are no current restrictions on use of phosphate-containing cleaners in industrial cleaning applications in the US. Globally, many countries and their governing subdivisions do limit use of phosphates in household detergents, yet there also are no global restrictions on use of phosphates in industrial detergents.

Safety Issues in Aqueous Cleaning

Worker safety issues for aqueous cleaners involve skin exposure, eye exposure, ingestion, inhalation, and chronic systemic exposure. Consult the label and safety data sheet (SDS) on the cleaner for warnings and safety precautions.

When cleaning by hand, it is good practice to wear protective gloves. Even the mildest cleaners can sometimes cause "dishpan hands".

Gloves also provide protection and comfort when working by hand with hot solutions. In fact, many highly acidic or alkaline cleaners require use of chemical-resistant gloves for worker safety.

Eye exposure also is a concern with many aqueous cleaners. Eye tissue is sensitive and particularly vulnerable to damage by chemically active aqueous solutions. Accordingly, it is also considered good industrial practice to wear safety glasses or other eye protection when working with aqueous cleaning solutions. Particularly hazardous aqueous cleaners should have warnings and recommended eye protection on the label.

In addition, there may be inhalation hazards with some aqueous cleaners. Because aqueous cleaners generally do not have volatile solvent ingredients, it is somewhat unusual to find the need for respiratory protection with aqueous cleaners. However, it is considered good industrial practice to have some respiratory protection when working with sprays and mists in open-spray cleaning. Any special ventilation required should be noted on the SDS. Some semi-aqueous cleaners may contain volatile solvents that require special ventilation and possibly even flammability controls.

While it is relatively unusual for an aqueous cleaner to contain carcinogenic ingredients, the cleaner's SDS—or, if sold in the state of California, the label—should disclose any suspected long-term chronic exposure concerns related to carcinogenicity. Note that in some instances there is a zero-threshold for reporting carcinogens and chemicals that cause birth defects or other reproductive harm. Therefore, it is worth doing a risk assessment about how much of the hazardous chemical is in the detergent you are evaluating to decide if the amounts present are sufficient to not use the detergent.

Physical safety issues with aqueous cleaners generally concern storage and handling to avoid hazardous reactions with other industrial chemicals. Good industrial practice usually involves storing acid and

alkaline chemicals separately to avoid any reactions between them in the event of accidental spills. Some aqueous cleaners contain bleaches or other oxidizing agents that should be stored away from reactive chemicals that might undergo hazardous oxidation reactions. As previously mentioned, most completely aqueous cleaners are not flammable. However, some aqueous cleaners contain ingredients that form hazardous chemicals when burned. (It is considered good practice to wear respiratory protection when fighting any fire involving industrial chemicals.)

Practical Regulatory Review

In today's manufacturing environment, it is possible to use safe, clean, reduced-waste cleaning processes that are ultimately sustainable. At the very least, use processes that comply with current environmental and health safety regulations.

The first step in evaluating the environmental health and safety of an aqueous cleaning process is to secure the SDS and technical bulletins for the cleaners you plan to test or use, and to assemble as much information as you can about the soils you will be removing. Review of this information should disclose important environmental and health hazards as well as regulations. In most parts of the world, SDS are written in accordance with Global Harmonization Standards (GHS). In the US, the Occupational Health and Safety Administration (OSHA) requires conforming to GHS in hazard communication standards.

Note that in the process of trying to simplify and standardize hazard communication by using GHS, some of the subtlety in hazard warnings has been lost. Historically, mild skin and eye irritants would have been listed on an SDS as "mild." Today, under GHS guidelines, a substance is classified as either an irritant or not. Thus, if a certain percentage of the formulation is an irritant, then the formulation is

labeled "corrosive." As a consequence, many concentrated aqueous detergents are now commonly marked "corrosive"—yet this label includes both dangerous caustic solutions and those that might give you dishpan hands, with no distinction in between. However, some aqueous detergent SDS also provide the hazard communication standard for the diluted product as used, which may have a sufficiently low concentration of irritants such that it does not require the "corrosive" label.

When performing an initial review of regulations for an aqueous cleaner, it is important to consider several regulatory sources of guidance. Among them are: OSHA regulations, National Pollutant Discharge Elimination System (NPDES) discharge permits, Department of Environmental Protection (DEP) sewer connection/extension permits, and any Resource Conservation and Reclamation Act (RCRA) hazardous waste class or Clean Water Act regulations. State and local environmental regulations should also be considered.

It is wise to conduct a full-scale environmental audit no matter what type of cleaning system you are using. Ensuring you have the most up-to-date SDS for the detergent(s) used is the clear recommended starting point. Such an audit may result in changes in the way you currently manufacture and clean. In fact, after conducting a full-scale environmental audit, many companies turn to aqueous cleaning to achieve regulatory compliance easily and safely. A program of regular re-auditing can ensure continued regulatory compliance.

Compared to hazardous nonaqueous and semi-aqueous cleaners—particularly those containing ozone-depleting fluorocarbon solvents, carcinogenic organic solvents, and/or flammable components—aqueous cleaners are good choices for safe, environmentally sound cleaning. By choosing high-quality aqueous cleaners, most cleaning problems can be solved without endangering workers or the environment.

References

L.N. Britton, "Surfactants and the environment," Journal of Surfactants and Detergents, Vol. 1, No. 1 (January 1998).

B. Kanegsberg and E. Kanegsberg, Handbook for Critical Cleaning: Applications, Processes, and Protocols, Second Edition, p. 455–519; CRC Press, Boca Raton, FL (2011).

Occupational Safety and Health Administration, "Hazard communication" (2016). Available at osha.gov/hazcom

U. Zoller (Ed.), Handbook of Detergents, Part B: Environmental Impact; Marcel Decker, New York (2004).

Resources

alconox.com
epa.gov
osha.gov
technotes.alconox.com

Appendix I

List of Abbreviations

Abbreviations	*Description*
AA	Atomic absorption
AAMI	Association for the Advancement of Medical Instrumentation
ADE	Acceptable daily exposure
ADI	Acceptable daily intake
API	Active pharmaceutical ingredient
BOD	Biological oxygen demand
BW	Body weight
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFC	Chlorofluorocarbon
CFR	Code of Federal Regulations
CFU	Colony forming unit
cGMP	Current Good Manufacturing Practice
CIP	Clean-in-place
COD	Chemical oxygen demand
COP	Clean-out-of-place
DEP	Department of Environmental Protection
DOP	Dispersed oil particulate
DQ	Design qualification
EDTA	Ethylene diamine tetraacetic acid
EMA	European Medicines Agency
EPA	Environmental Protection Agency
EPDM	Ethylene propylene diene terpolymer
EPM	Ethylene propylene
EPS	Extracellular polymeric substance
PPE	Personal protective equipment
ESCA	Electron spectroscopy for chemical analysis
EU	Endotoxin units

Appendix I – List of Abbreviations

Abbreviations	*Description*
FTIR	Fourier transform infrared spectroscopy
GC/FID	Gas chromatography/flame ionization detection
GC/MS	Gas chromatography/mass spectrometry
GHS	Global Harmonization System
GMP	Good Manufacturing Practice
HCFC	Hydrochlorofluorocarbon
HFC	Hydrofluorocarbon
HFE	Hydroflueroether
HFO	Hydrofluoro-olefin
HPLC	High-performance liquid chromatography
ICH	International Conference on Harmonization
IQ	Installation qualification
ISO	International Organization for Standardization
ISPE	International Society for Pharmaceutical Engineering
ISPM	In-situ particle monitoring
LAL	Limulus amebocyte lysate
LAS	Linear alkylbenzene sulfonate
LC	Liquid chromatography
LCD	Liquid crystal display
LD50	Lethal dose for 50% of population
LIBS	Laser induced breakdown spectroscopy
LOD	Limit of detection
LOQ	Limit of quantitation
MACO	Maximum allowable carryover
MBSnext	Minimum batch size for next product
MF	Modifying factor
MWCO	Molecular weight cutoff
NOAEL	No observed adverse effect level
NPDES	National Pollutant Discharge Elimination System
NVR	Nonvolatile residue inspection
OPQ	Office of Pharmaceutical Quality
OQ	Operational qualification
OS	Office of Surveillance
OSEE	Optically stimulated electron emission

Abbreviations	*Description*
OSHA	Occupational Health and Safety Administration
PA	Polyallomer
PC	Polycarbonate
PCE	Perchloroethylene
PDE	Permissible daily exposure
PDEprevious	Permitted daily exposure for previous product
PE (LLDPE, LDPE)	Polyethylene (linear low-density polyethylene, low-density polyethylene)
PEEK	Polyether ether ketone
PIC/S	Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme
PMC	Polymethylmethacrylate
PMP	Polymethylpentene
PP	Polypropylene
PPB	Part-per-billion [microgram/liter (ug/L)]
PPM	Part-per-million [milligram/liter (mg/L)]
POM; acetal	Alcotabs
PQ	Performance qualification
PS	Polystyrene
PSF	Polysulfone
PTFE	Polytetrafluoroethylene
PVC	Polyvinyl chloride
PVDF	Polyvinyl fluoride
QS	Quality Systems
QSIT	Quality System Inspection Technique
QSR	Quality Systems Regulations
RCRA	Resource Conservation and Recovery Act
Risk-MaPP	Risk-Based Manufacture of Pharmaceutical Products
RO	Reverse osmosis
RS	Raman spectroscopy
SARA	Superfund Authorization and Reauthorization Act
SDS	Safety data sheet
SEM	Scanning electron microscopy
SERS	Surface enhanced Raman spectrophotometer
SIMS	Secondary ion mass spectroscopy

Appendix I – List of Abbreviations

Abbreviations	*Description*
SOP	Standard operating procedure
TCA	Trichlorocarbon
TDDnext	Standard therapeutic daily dose for next product
TFF	Tangential flow filtration
TIR	Technical Information Report
TLV	Threshold limit value
TOC	Total organic carbon
TOFSIMS	Time-of-flight secondary ion mass spectroscopy
TOSI	Test object surgical instrument
trans-DCE	Trans-1,2,-dichloroethylene
TSCA	Toxic Substances Control Act
UFc	Composite uncertainty factor
UPLC	Ultra-performance liquid chromatography
USP	United States Pharmacopoeia
UV	Ultraviolet
VCN	Vacuum cycle nucleation
VMP	Validation Master Plan
VOC	Volatile organic compound
WFI	Water for injection
XPS	X-ray photoelectron spectroscopy

Appendix II

Alconox Inc. Cleaners by pH Category

Cleaner pH Category	pH	Typical Soil	Powder	Liquid
Oxidizing sulfuric acid	0–2	Organics, tissue culture	Alnochromix	None
Mineral acid	0–2	Heavy scales	None	None
Mild acid	2–5.5	Scales, oxides, salts	None	Citranox, Citrajet
Neutral	5.5–8.5	Light oils, particles	Alcotabs	Liquinox, Luminox
Mild alkaline	8.5–11	Oils, fats particles, films	Alconox, Tergazyme	Detonox
Alkaline	11–12.5	Oils, fats, grease, resins	Alcojet, Tergajet	Solujet, Detergent 8, Detojet
High alkaline	≥12.5	Difficult oils, fats, resins, scales, oxides	None	Keylajet

Appendix III

Alconox Inc. Cleaners by Detergent Characteristics

Detergent Characteristics	Cleaning Method	Alconox Inc. Brand
High-emulsifying alkaline powder	Manual, soak, ultrasonic, recirculate clean-in-place (CIP)	Alconox
High-emulsifying, enzymatic alkaline powder	Manual, soak, ultrasonic, recirculate CIP	Tergazyme
High-emulsifying alkaline liquid	Manual, soak, ultrasonic, recirculate CIP	Detonox
High-emulsifying, phosphate-free neutral liquid	Manual, soak, ultrasonic, recirculate CIP	Liquinox
High-emulsifying, phosphate-free mild acid liquid	Manual, soak, ultrasonic, recirculate CIP	Citranox
Low-foaming, phosphate-free mild acid liquid	Manual, soak, ultrasonic, recirculate CIP, pressure/spray CIP, machine washer	Citrajet
Low-foaming, surfactant-free alkaline liquid	Manual, soak, ultrasonic, recirculate CIP, pressure/spray CIP, machine washer	Detojet
Low-foaming, phosphate-free alkaline liquid	Manual, soak, ultrasonic, recirculate CIP, pressure/spray CIP, machine washer	Solujet
Low-foaming alkaline powder	Manual, soak, ultrasonic, recirculate CIP, pressure/spray CIP, machine washer	Alcojet
Low-foaming, phosphate-free alkaline powder	Manual, soak, ultrasonic, recirculate CIP, pressure/spray CIP, machine washer	Tergajet
Low-foaming, neutral phosphate-free liquid	Manual, soak, ultrasonic, recirculate CIP, pressure/spray CIP, machine washer	Luminox
Low-foaming, phosphate-free, ion-free liquid	Manual, soak, ultrasonic, recirculate CIP, pressure/spray CIP, machine washer	Detergent 8
Low-foaming, high-alkaline liquid	Manual, soak, ultrasonic, recirculate CIP, pressure/spray CIP, machine washer	Keylajet
Effervescing neutral tablet	Soak, siphon tube, and pipet washer	Alcotabs
Oxidizing sulfuric acid additive	Soak	Alnochromix

Appendix IV

Resources

Alconox Inc. Resources
Alconox Inc.: alconox.com
Alconox, Inc. TechNotes: technotes.alconox.com
Alconox, Inc. Foodservice Division: alconoxfoodservice.com
Cleaning Resources
Product Quality Cleaning Workshop: shsu.edu/academics/chemistry/cleanresearch/cleaningworkshop.html
BFK Solutions LLC Critical Cleaning Consulting: bfksolutions.com
Manufacturer's Cleaning Association: manufacturingcleaning.org
Cleaning Technologies Group: techblog.ctgclean.com
Toxics User Reduction Institute (TURI), University of Massachusetts Lowell: turi.org
TURI CleanerSolutions Database: cleanersolutions.org
Related Industry Association Resources
ASTM International: astm.org
Association for the Advancement of Medical Instrumentation: aami.org
Center for Pharmaceutical Cleaning Innovation: centerforpharmaceuticalcleaninginnovation.org
Outsourced Pharma articles by Andrew Walsh: outsourcedpharma.com/author/andrew-walsh
Cleaning Validation Support
Food and Drug Administration Validation Cleaning Processes: fda.gov/validation-cleaning-processes-793
Cleaning Validation Simplified: cleaningvalidation.com
Institute of Validation Technology: ivtnetwork.com
Regulatory Resources
Chemical Watch: home.chemicalwatch.com
Food and Drug Administration: fda.gov
International Society for Pharmaceutical Engineering: ispe.org
European Medicines Agency: ema.europa.eu/en

Appendix V – Detergent Selection Guide (1 of 4)

Application Key Concerns	Articles Cleaned/Soil Removed
Laboratory Reproducible results, no interfering residues, extending equipment life. Maintaining laboratory accreditation. Laboratory safety.	Glass, metal, plastic labware, ceramics, tissue culture, clean rooms, animal cages, bioreactors, tubing, benches, safety equipment
	Tubes, reusable ujpipets
	Microbiology, water lab, and environmental sampling; phosphate-sensitive labware
	Radioactive equipment/contaminant; stopcock grease
	Trace metals, metal oxides, scale, salts, starches, amines
	Proteinaceous soils, bio-wastes, tissue, blood and other body fluids, fermentation residues
	Glassware needing surfactant or metal-free cleaning for enzyme kinetics, tissue culture, pipet soaking, trace inorganics
Medical Device Manufacturing Passing cleaning validation for FDA good manufacturing practices, EU regulations, and similar requirements. Stainless steel, titanium, plastics, and other device substrates.	Cutting and machining oils, lubricants, mold release, environmental residue
	Inorganic residues, salts, metallics, oxidation
	Reprocesing: protein, organic, biologic films, and related residues
Pharmaceutical Passing cleaning validation for FDA good manufacturing practices, EU regulations, and similar requirements. Stainless steel, substrates.	Titanium dioxide, petrolatum, oils, emulsions, ointments, carbopols, lacquers, zinc oxides, steroids, alcohols, sugars, Eudragit* (L/S/L30/D55/NE30D) polymers
	Inorganic residues, salts, metallics, pigments. Eudragit* (E/RL/RS/E100) polymers, amphoterics, coatings, amines, ethers, starches, alkaloids
Biotech/Biopharma Passing cleaning validation for FDA good manufacturing practices, EU regulations, and similar requirements. Stainless steel, elastomers, glassware, polymeric filter membranes, and other biopharma substrates.	Inorganic residues, salts, buffering solutions
	Protein, organic, cellular and fermentation residues; R/O, U/F membranes

Cleaning Method	Cleaner: Powder	Liquid
Manual, ultrasonic, soak	Alconox	Liquinox (p-free)
Machine, power spray, labware washer, washer-sterilizer, cage-washer	Alcojet Tergajet (p-free)	Detergent 8 Solujet (p-free)
Syphon-type washer-rinser	Alcotabs (tablet)	
Field, manual, ultrasonic, soak	Tergajet (p-free)	Liquinox (p-free)
Machine washer, labware washer	Tergajet (p-free)	Solujet-base Citrajet-acid
Manual, ultrasonic, soak	Alconox	Detonox
Machine washer, labware washer	Alcojet	Keylajet
Manual, ultrasonic, soak		Citranox (p-free)
Machine washer, labware washer		Citranox (p-free)
Manual, ultrasonic, soak	Tergazyme	Detergent 8
Glassware washer	Alcojet Tergajet (p-free)	Detergent 8 Solujet (p-free)
Soak	Alnochromix	
Manual, ultrasonic, soak	Alconox	Liquinox (p-free) Detonox
Machine washer, power wash, clean-in-place (CIP)	Alcojet Tergajet (p-free)	Solujet (p-free)
Manual, ultrasonic, soak		Citranox (p-free)
Machine washer, power wash, CIP		Citrajet (p-free) Solujet (p-free)
Manual, ultrasonic, soak	Tergazyme	Detergent 8
Machine washer, power wash, CIP	Alcojet	
Manual, ultrasonic, soak	Alconox	Liquinox (p-free)
Machine washer, power wash, CIP	Alcojet Tergajet (p-free)	Solujet (p-free)
Manual, ultrasonic, soak		
Machine washer, power wash, CIP		Citranox (p-free) Citrajet (p-free)
Manual, ultrasonic, soak		Citranox (p-free)
Machine washer, power wash, CIP		Citrajet (p-free) Solujet (p-free)
Manual, ultrasonic, soak	Alconox Tergazyme	Liquinox (p-free) Detergent 8
Machine washer, power wash, CIP	Alcojet	Detergent 8 Solujet (p-free)

Appendix V – Detergent Selection Guide (2 of 4)

Application Key Concerns	Articles Cleaned/Soil Removed
Healthcare/Veterinary Effective preparation for sterilization, longer instrument life. Reduced waste.	Surgical, anaesthetic, and examining instruments and equipment; catheters and tubes
	Blood, body fluids, tissue on instruments
Electronics Passing cleaning validation for FDA good manufacturing practices, EU regulations, and similar requirements. Stainless steel, titanium, plastics, and other device substrates.	Circuit boards, assemblies, screens, parts, conductive residues, resins, rosins, fluxes, particulates, salts
	Ceramic insulators and components
Cosmetics Avoid cross-contamination. Passing cleaning validation for FDA good manufacturing practices. Stainless steel, glass, plastic, elastomer cleaning.	Product contact surfaces (acids for pigments and salts); titanium dioxide, petrolatum, oils, emulsions, ointments, carbopols, lacquers, zinc oxides
Optics Clean parts. Avoiding volatile solvents, strong acids, and other hazardous chemicals.	Glass, ceramic, porcelain, stainless steel, plastic, rubber; oils, chemicals, particulates
	Delicate substrates/neutral for waste
Cannabis Critically clean cannabis, CBD and related botanical labware, glassware, instrumentation, and processing and extraction equipment is vital. Ensures strain to strain and batch to batch processing is kept clean and contaminant free.	Glassware, processing tools, extraction vessels, boiling flasks, and clean-in-place (CIP) manufacturing equipment; sticky oils, waxes, resins
	Irrigation lines, pesticide and organic water build up
Photovoltaic Thin film solar module manufacturing requires clean glass and metal substrates for optimum yield.	Glass and metal substrates
	Removal of salt and inorganic buildup
Food & Beverage Manufacturing Food and beverage processing equipment must be critically cleaned per FDA requirements and to ensure prolonged equipment life.	Stainless steel, food contact equipment, industrial fryers/grease buildup, oils, food residues
	Oxides, scale, trace metals, salts, milkstone, corrosion
	Filter membranes, proteins, biofouling

Cleaning Method	Cleaner:	Powder	Liquid
Manual, ultrasonic, soak		Alconox	Liquinox (p-free)
Machine washer, sani-sterilizer		Alcojet	Detergent 8
Manual, ultrasonic, soak		Tergazyme	Detergent 8
Manual, ultrasonic, soak			Detergent 8
Machine washer, power spray board and screen washers			Luminox (neutral pH)
Manual, ultrasonic, soak		Alconox	Liquinox (p-free) Luminox (neutral pH)
Parts washer		Alcojet	Solujet (p-free) Luminox (neutral pH)
Manual, ultrasonic, soak		Alconox	Detonox-base Citranox-acid
Parts washer, power spray		Alcojet	Solujet base-free CTRAJET acid Keylajet base
Manual, ultrasonic, soak		Alconox	Liquinox (p-free)
Manual, ultrasonic, soak		Alcojet	Detergent 8
Machine washer, pressure spray		Tergajet (p-free)	Solujet (p-free)
Manual, ultrasonic, soak		Alconox Tergazyme	Liquinox (p-free) Detergent 8
Parts washer, power spray		Alconox	Liquinox Detonox
Manual, ultrasonic, soak		Alcojet Tergazyme	Keylajet
Manual, ultrasonic, soak			Liquinox (p-free)
Manual, ultrasonic, soak			Detergent 8
Machine wash, pressure wash, clean-in-place (CIP)			Citranox (p-free) Citrajet
Manual, ultrasonic, soak		Alconox	Liquinox (p-free) Detonox
Machine wash, pressure wash, CIP		Alcojet	Solujet (p-free)
Manual, ultrasonic, soak			Citranox (p-free)
Machine wash, pressure wash, CIP			Citrajet (p-free)
Manual, ultrasonic, soak		Tergazyme	Detergent 8
Machine wash, pressure wash, CIP			Detergent 8 Solujet (p-free)

Appendix V – Detergent Selection Guide (3 of 4)

Application Key Concerns	Articles Cleaned/Soil Removed
Foodservice Avoid interfering residues on food-contact equipment and effectively remove soils commonly found in food operations (For complete foodservice detergent selection guide, visit AlconoxFoodservice.com).	Stainless steel, food contact equipment, industrial fryers/grease
	Oxides, scale, trace metals, salts, milkstone, corrosion
	Filter membranes, proteins, biofouling
Filter Cleaning Returning reusable RO and UF filters to specified flux requires thorough, residue-free cleaning.	General cleaning of fouled UF membrane and RO modules
	Removal of proteinaceous and similar residues
Environmental Reproducible results, no interfering residues, extending equipment life. Maintaining laboratory accreditation. Laboratory safety.	Glass, metal, plastic labware, ceramics, tissue culture, porcelain, clean rooms, animal cages, bioreactors, tubing, benches, safety equipment
	Tubes, reusable pipets
	Microbiology, water lab, environmental sampling; phosphate-sensitive labware; EPA procedures (acid for water rinse cycle)
	Trace metals, metal oxides, scale, salts, starches, amines
Nuclear Avoid waste interference.	Laboratory decontamination, pipes, tools, protective equipment
	Reactor cavity decontamination
Tattoo Equipment Equipment used for tattooing and piercing must be cleaned thoroughly prior to disinfection.	Blood, body fluids, tissue on instruments
Precision Manufacturing Clean parts. Avoiding volatile solvents, strong acids, and other hazardous chemicals.	Aluminum, brass, copper, and other soft metal parts; oils, chemicals, particulates (acid for oxides, salts, buffing compounds)
	Oxidation, metallic complexes, trace metals, rust, scale, salts, metal brightening
	Delicate substrates/neutral for waste
	Heavily soiled steel with grease, grime, scale

Cleaning Method	Cleaner: Powder	Liquid
Manual, ultrasonic, soak	Alconox PFS	Liquinox (p-free) Detonox
Machine wash, pressure wash, clean-in-place (CIP)	Alcojet	
Manual, ultrasonic, soak		Citranox (p-free)
Machine wash, pressure wash, CIP		Citrajet (p-free)
Manual, ultrasonic, soak	Tergazyme	
Soaking, recirculation CIP	Alconox	Liquinox (p-free) Citranox (p-free)
High-pressure CIP or other low-foaming requirement	Alcojet	Solujet (p-free) Detergent 8
Soaking, recirculation CIP	Tergazyme	Liquinox (p-free) Luminox (neutral pH)
Manual, ultrasonic, soak		Liquinox (p-free)
Machine, power spray, labware washer, washer-sterilizer, cage-washer	Tergajet (p-free)	Solujet (p-free)
Field, manual, ultrasonic, soak		
Machine washer, labware washer		Solujet-base Citrajet-acid
Manual, ultrasonic, soak		Citranox (p-free)
Machine washer, warewasher		Citrajet (p-free)
Ultrasonic, soak, scrubbing, spray	Alconox	Detergent 8
Reactor cavity decontamination	Alcojet	Detergent 8
Manual, soak, high-pressure spray		Detergent 8
Manual, ultrasonic, soak	Alconox Tergazyme	Detergent 8
Manual, ultrasonic, soak	Alconox Tergajet (p-free)	Liquinox-base Citranox-acid
Manual, ultrasonic, soak	Tergajet (p-free)	Citranox-acid
Manual, ultrasonic, soak		Citranox (p-free)
Parts washer, power wash		Citrajet (p-free) Keylajet
Manual, ultrasonic, soak		Luminox (neutral pH)
Machine wash, pressure spray		Luminox (neutral pH)
Soak, ultrasonic, machine wash, spray		Keylajet

Appendix V – Detergent Selection Guide (4 of 4)

Application Key Concerns	Articles Cleaned/Soil Removed
Passivation The process of forming a passive layer of chromium oxide on the surface of stainless steel to protect it from corrosion.	Removal of free iron, creating a passive layer of chromium oxide
Ultrasonics Ultrasound transducers pulse sound waves through a solution. Allows for efficient mechanical energy to clean surfaces reliably and reproducibly.	Aluminum, brass, copper, tool steel, other soft metal parts
	Oils, chemicals, particulates (acid for oxides, salts, buffing compounds)
	Stainless steel, plastics, glass with challenging, adherent residues
	Blood, body fluids, tissue on instruments, glass and labware

Cleaning Method	Cleaner:	Powder	Liquid
Manual, ultrasonic, soak			Citranox (p-free)
Machine wash, pressure wash, clean-in-place (CIP)		Alcojet	**Citrajet (p-free)**
Manual, ultrasonic, soak			Citranox (p-free)
Manual, ultrasonic, soak		Alconox	
Manual, ultrasonic, soak		Alconox	Detonox
Manual, ultrasonic, soak		Tergazyme	Detergent 8

Appendix VI – Glossary of Essential Terms

483—A Form 483 is a document from the US FDA used to list/record deficiencies found during an inspection of a facility.

Acid cleaner—An aqueous cleaner that has a pH significantly below 7, typically below 5.5. Acid cleaners contain acids and often other cleaning ingredients such as surfactants. Acid cleaners use a mechanism called "acid solubilization" (see other definitions), in which an acid reacts with a soil molecule to create a water-soluble molecule, and "acid hydrolysis" (see other definitions), in which an acid reacts with a soil molecule and breaks it into smaller water-soluble soil.

Alkaline cleaner—A water-based cleaner that contains alkaline ingredients that significantly increase pH. A cleaner with a pH of 8.5–11 can be considered a mild alkaline cleaner. A cleaner with a pH of 11–12.5 is at least an unqualified alkaline cleaner. A cleaner with a pH above 12.5 would be a high alkaline and corrosive or caustic cleaner. Alkalinity fosters saponification (see other definitions), solubilization (see other definitions) of alkaline soluble soils, and hydrolysis (see other definitions).

Anionic surfactant—A cleaner ingredient that is a surface-active agent (see other definitions) with a negative charge on the organic portion of the molecule. The charge on the surfactant determines the charge of the cleaner or detergent. An anionic detergent contains an anionic surfactant or surfactants. Anionic surfactants can be and usually are emulsifiers (see other definitions) and dispersants (see other definitions). Typical anionic surfactants include organic sulfates, sulfonates, and carboxylates. The most common anionic surfactant is sodium alkylbenzene sulfonate.

Aqueous cleaner—A blend of water-soluble chemicals designed to remove soils into the cleaner solution.

APR—Annual product review: Part of quality systems review of a product.

Bed-of-nails testing—A test for conductive residues on a surface by touching a surface (e.g., circuit board) to a bed of nails that are connected to conductivity detectors.

Bioburden—Microbes on the surface.

Builder—A cleaner ingredient that enhances the cleaning ability of surfactants in at least one and usually a combination of the following

ways: using chelation, sequestration, or binding to soften water to prevent hard water or metal ions from reacting with surfactants and soils; enhance the surface tension-lowering property of surfactants; add alkalinity; buffer cleaners to maintain alkalinity; emulsify oils; disperse particulates; inhibit redeposition of soils; break up clumps of particles by deflocculation; saponify soils; provide corrosion inhibition; and improve handling, flowing, and storage characteristics of the cleaner. A typical builder is sodium polyphosphate.

Cavitation—Creation of a tiny "bubble" of a vacuum in the bath of an ultrasonic tank caused by the "trough" in the sound waves going thru the solutions. These tiny bubbles constantly form and collapse as sound is pumped through the tank. The act of collapsing is the source of mechanical cleaning energy in an ultrasonic cleaning tank.

Chelating—Binding that occurs with metal ions by a chelating agent (see definition below).

Chelating agent—A cleaner ingredient that is a chemical with at least two sites on each molecule available to bind with metal ions in a water-based solution and form a ring compound. Typical examples of chelating agents include sodium polyphosphates and ethylenediamine tetraacetic acid (EDTA). Many chelating agents also are sequestering agents (see other definitions).

Chromatography—A method of separating ingredients in a mixture and identifying them by the length of time they take to pass through a chromatography column along with a carrier solution, using a detector at the base of the column.

Clean-in-place (CIP)—A process used to clean manufacturing equipment in-place without disassembling the equipment. Often this is done by circulating cleaning solutions through pipes and spraying using spray-balls or nozzles to clean the insides of tanks.

Cleaner—A chemical or blend of chemicals designed to clean. These may be solvents, acids, bases, detergents, and/or water-based blends.

Corrosion—The damage caused on a substrate (typically a metal) by reacting with the environment around the substrate. A common form of corrosion is the reaction of ferrous metals with dissolved oxygen in water to form reddish-brown iron oxide, or rusting.

Conductivity—A measure of electric conduction. This analytic technique determines the amount of conductive contaminants in an aqueous solution.

Coupling agents—Cleaner ingredients that are added to improve the solubility of other desirable cleaner ingredients. They allow more concentrated cleaners than would otherwise be possible based on the inherent solubility of the other ingredients.

Degreaser—A cleaner that is designed to remove oils and greases. These are typically heavy-duty cleaners. Unlike light-duty fine cleaners that are designed to remove low levels or trace amounts of oil and leave surfaces measurably or analytically clean, degreasers are designed to remove gross amounts of oil and grease and leave surfaces measurably clean. Most degreasers are either high-alkaline aqueous cleaners or solvent-based cleaners.

Design qualification (DQ)— Documentation that shows a device or process is designed properly according to its quality specifications and appropriate regulations.

Detergent—A blend of ingredients intended for cleaning that include at minimum a surfactant (see other definitions) to provide emulsifying or dispersing properties and a builder (see other definitions) to inhibit water hardness from the precipitation of calcium and magnesium salts. In the industry, the word detergent if often used to mean surfactant.

Dispersant—A cleaner ingredient that reacts with water-insoluble particulates. A dispersant overcomes the electrostatic attraction of a particulate to a hard surface and creates a liquid–solid mixture in the form of a suspension. A typical dispersant is sodium polyphosphate.

Dissolve—To clean using a cleaning fluid to form a stable mixture containing individual soil molecules. In aqueous cleaning, the use of water to dissolve water-soluble soils is an example of this mechanism.

Emulsifier—A cleaner ingredient that lowers interfacial tension between immiscible liquids such as oil and water, allowing them to mix. Typically, an emulsifier forms a micelle, a small droplet of oil surrounded by the emulsifier. The emulsifier is in contact with the water, and the surrounded droplet, or micelle, is dissolved in the water. Emulsifiers are surfactants (see other definitions).

Ester—A molecule made up of an organic acid joined to an alcohol. These types of molecules are natural oils that are found in fingerprints or natural lubricants. Some synthetic lubricants also are esters.

Eutrophication—Enrichment of a water body with nutrients (e.g., nitrogen or phosphorus, either from natural or manmade sources), resulting in excessive growth of phytoplankton, algae, or vascular plants, leading to depletion of oxygen and silting up of the body of water.

Excipients—Fillers or non-active pharmaceutical ingredients.

Flocculation—The combination, agglomeration, aggregation, or coagulation of suspended particles so that they form small clumps or tufts (called floc).

Free-rinsing—The ability to easily be rinsed away from a surface using rinse water. Cleaners and detergents that are completely water-soluble have low surface tension, do not tend to react to form insoluble molecules with typical residues or ions commonly found in water, and are typically free-rinsing.

Gas chromatography (GC)—An analytical technique to separate vaporized components in a gas mixture.

High-performance liquid chromatography (HPLC)—An analytical technique to separate and identify components in a liquid mixture. In HPLC, a liquid sample is pumped through a column of adsorbent material—different components in the sample flow through the adsorbent material at different rates, allowing separation of the individual components.

Hydrolyze—To break a molecule apart using acid (H^+) and hydroxyl ions (OH^-) from water (H_2O). This occurs when a fat or oil is hydrolyzed to make soap, as in saponification (see other definitions), or when an enzyme breaks down a protein.

Hydrotrope—A cleaner ingredient that improves the solubility and stabilizes other detergent ingredients in water. Use of a hydrotrope allows for more concentrated aqueous cleaners.

Hydrophilic—Means "water loving"; a molecule or part of a molecule that is more thermodynamically stable in contact with a polar environment such as water.

Installation qualification (IQ)—Documentation that shows a device is installed properly according to its specification.

Ion chromatography (IC)—An analytical technique for separating ions based on their differing interactions and affinity with a column.

Ion-free cleaner—A cleaner that has no metal ion ingredients. Typically, an ion-free cleaner will contain nonionic surfactants and other ingredients that are not metallic salts. An ion-free cleaner does not contain sodium or other metal salts. Note that a nonionic cleaner is not necessarily ion-free. A nonionic cleaner merely has no ionic charge on the surfactant in the cleaner. A nonionic cleaner can and usually does have builders or other inorganic salt ingredients that contain ions.

Laminar flow—In fluid flow, a smooth flow with no crossflow of fluid particles between adjacent streamlines. This flow is conceived as composed of layers and is commonly distinguished from turbulent flow.

Limit of detection (LOD)—The limit at which an analytical detection method can detect a residue being analyzed [approximately signal to noise (S/N) = 3].

Limit of quantitation (LOQ)—The limit at which an analytical detection method can detect and quantify the amount of a residue being analyzed [approximately signal to noise (S/N) = 10].

Micelle—A sub-microscopic aggregate of molecules. In the context of cleaners, these molecules are surfactants usually arranged in sphere or rod shapes, with their hydrophilic ends facing outward into the water solution and hydrophobic ends facing the inside of the aggregate. Micelles can hold hydrophobic oil molecules at their centers to create stable emulsions.

Neutral cleaner—A cleaner that has a pH near 7, typically ranging 5.5–8.5. These cleaners tend to use mechanisms such as emulsifying and dissolving rather than the more aggressive chemical attacks on soils possible with acid or alkaline cleaners.

Nonionic cleaner—A cleaner that contains nonionic surfactants. The term does not mean an ion-free cleaner. A nonionic cleaner may easily contain nonionic surfactants blended with many ionic builders that are sodium salts or other metal ion salts (see ion-free cleaner).

Nonionic surfactant—A cleaner ingredient that is a surface-active agent (see other definitions) that has no charge on the organic portion of the molecule. The charge on the surfactant determines the charge of the cleaner or detergent. A nonionic detergent contains nonionic surfactants but is not necessarily ion-free (see other definitions). A nonionic detergent

may contain many ionic salts. It is the surfactant alone that has no electrical charge (is nonionic). Nonionic surfactants can be and usually are emulsifiers (see other definitions) and dispersants (see other definitions). Typical nonionic surfactants include organic ethoxylates. The most common nonionic surfactants are alcohol ethoxylates and alkylphenol ethoxylates.

Oleophilic—Means "oil loving"; a molecule or part of a molecule that is more thermodynamically stable when in contact with less polar surfaces such as oils, as distinguished from hydrophilic (see definition).

Operational qualification (OQ)—Documentation that shows a device is operating correctly according to its specification.

pH—A measure of how acidic or basic a solution is. It is the inverse log of the hydrogen ion concentration in water. In practical terms, pH 7 is neutral, higher than 7 is acidic, and lower than 7 is basic or alkaline.

Outgas—The act of a residue evaporating into a vacuum from a contaminated surface that is exposed to a vacuum.

Parenteral—Outside the digestive tract. This term refers to intravenous, subcutaneous, and other nonoral modes of administering medications, devices, and therapies.

Polar—The property of a molecule that has a significant electrical dipole moment, which is a direction of charge resulting from a concentration of negatively charged electrons at one end of the molecule.

Performance qualification (PQ)—Documentation that shows a device is performing properly according to its specification.

Residue acceptance limit—An acceptable level of residue that can remain on a surface or product based on relevant and appropriate quality, regulatory, validation, toxicological, and related specifications.

Saponifier—A cleaner ingredient that reacts with a poorly soluble natural oil ester or resin ester such as rosin to split the ester or resin into a more soluble salt of an acid (soap). In the case of many compounds this converts a water-insoluble oil or resin into a water-soluble soap that, in turn, acts as an emulsifier to emulsify any unreacted oil or resin and assist with cleaning. Typical saponifiers are potassium hydroxide and sodium hydroxide.

Semi-aqueous cleaner—A chemical or blend of chemicals/solvents used for cleaning that relies on a water rinse. Usually a solvent or blend of water-soluble solvents, these cleaners are used without water and then followed by a water rinse, or they may be blended with water during use.

Sequestering agent—A cleaner ingredient that is a chelating agent (see other definitions) that reacts with metal ions in a water-based cleaner. The sequestering agent binds the metal ions tightly, preventing them from reacting with other chemicals or soils. Sodium polyphosphate is a typical sequestering agent.

Soap—The salt of an acid. A typical example is the sodium salt of stearic acid (sodium stearate) formed from sodium hydroxide (a saponifier; see other definitions) and glycerol tristearate (natural animal fat). Soap is a surfactant (see other definitions) with generally good emulsifying properties for the oils or fats from which it was derived by the process of saponification. For example, sodium stearate (a soap) would be good at emulsifying glycerol tristearate (a natural animal fat). However, soap can react with calcium or magnesium ions in "hard" water to form calcium or magnesium salts that are insoluble in water and precipitate out as soap scum or film. For this reason, soaps are not very free-rinsing cleaners.

Solubilizing—A cleaning mechanism that involves dissolving a soil into a single aqueous phase that relies on a principle of "like dissolves like". In an aqueous cleaner, the water acts as a polar solvent to help solubilize polar soils. The main cleaning mechanism of solvent-based cleaners is solubilizing or dissolving.

Solvent cleaner—A cleaner containing one or more organic chemicals that can dissolve soils. Typically, solvent cleaners contain volatile organic compounds. Fluorocarbon-based freon cleaners are solvent cleaners. The cleaning process using solvent cleaners lacks a water continuous phase, and there is generally no water present in the formulations of solvent cleaners. This is distinguished from semi-aqueous cleaners that are blends of water and solvents or solvents that can be rinsed and dissolved with water.

Solvate—The action of solubilizing (see definition above).

Surface tension—A force running parallel to a surface and resulting from the attraction of surface molecules toward those below the surface. This tension minimizes surface area of a solution.

Substrate—A surface or part that is being acted on, for example being cleaned.

Surface-active agent—Also known as a surfactant, an ingredient found in most aqueous cleaners that is a chemical active at the solution–surface interface. In the cleaning context, the surface-acting agent lowers the surface (interfacial) tension at liquid–gas, liquid–liquid, and liquid–solid interfaces. The structure of surface-active agents used in aqueous cleaners is usually oblong—one end of the molecule is hydrophobic, while the other is hydrophilic. The hydrophilic end of the molecule is attracted to and remains stable in water; the hydrophobic end is attracted to air, particulate, oil, or surface and away from water, where it is less stable. This means that a surface-active agent can act as a wetting agent, helping a cleaner wet a surface or penetrate into small cracks and crevices where it can perform. A surface-active agent reacts with a particle as a dispersant and also can act as an emulsifier for oil. Surface-active agents are either anionic, nonionic, cationic, or amphoteric (see other definitions).

Surfactant—See surface-active agent.

Titrate—Wet chemistry test used to detect an unknown amount by measuring how much of the unknown reacts with a known reagent.

Total organic carbon (TOC)—An analytical technique for measuring the total amount of carbon in organic compounds found within a sample. TOC can quantify the presence of contaminating organic compounds within a sample and thus often is used as a measure of cleanliness.

UV-vis—Ultraviolet-visible spectroscopy, a method of absorption or reflectance spectroscopy that uses light in the ultraviolet and visible ranges of the electromagnetic spectrum.

Water continuous phase—A water-based solution that has water continuously in contact throughout the solution. The water may be surrounding oil or micelles, but it is continuously connected around those pockets, rather than the water being separated into pockets of water within an oily solution (oil continuous phase).

Wetting agent—A surfactant (see definition) that lowers the surface tension of water to allow it to more broadly contact a surface and penetrate into cracks. Without the presence of a wetting agent in the water, water will bead up on a given surface; with a wetting agent, the solution will spread out and form a broader bead.

Index

C

D

E

F

G

H

I

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Z

About Alconox Inc.

Alconox Inc., with over 75 years of experience, is a proud 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.

Cleaning validation guidance includes whitepaper and reference documents, 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 the critical cleaning experts, Alconox Inc. can provide valuable consulting, training, and information to vendors, suppliers, and clients in many industries who wish to establish critical cleaning methods and procedures.

If you have specific questions regarding validating Alconox Inc. detergents, please contact cleaning@alconox.com or ask us a question at alconox.com.

Since their first use decades ago in healthcare and laboratory settings, aqueous cleaning detergents, specially formulated to leave no interfering residues, have found increasing application in a wide range of industries. The cleaning process, including the choice of detergent, deserves significant attention where cleanliness has a direct impact on value or result. These situations demand what we refer to as "critical cleaning." The substantial growth in the use of aqueous detergents in critical cleaning is driven by their efficacy, biodegradability and operator safety, and represent a particularly attractive alternative to flammable, hazardous, and/or volatile solvents.

This 5th edition of the Aqueous Cleaning Handbook distills and presents practical information covering the history of such cleaners—what they are, how they work, and how to make best use of them. Manufacturing processes, instruments and parts in many industries require critical cleaning including biotech, medical device, cosmetics, pharmaceuticals, foodservice and food processing, optics, electronics, solar, and precision manufacturing.

This handbook is written by the cleaning experts at Alconox Inc., a New York-based firm which has continued to be a leading supplier of aqueous cleaners for laboratory, healthcare, industrial and related applications for over 75 years. Alconox Inc. specialists each provided their expertise and insight into the latest edition of the Aqueous Cleaning Handbook.

About the Authors

Michael J. Moussourakis is a Vice President, Technical Marketing and Strategy at Alconox Inc. headquartered in White Plains, NY, responsible for Technical Support and Corporate Strategy. He has over 20 years of experience in the biotech, pharmaceutical, medical device, and laboratory industries. Michael holds a BS and MS in Biomedical Engineering from the Columbia University School of Engineering and Applied Science.

Jeff I. Phillips is a Senior Director, Business and Product Development for Alconox Inc. with 20+ years' experience solving complex cleaning issues in the pharmaceutical and medical device industries. His expertise in analytical chemistry and pharmacology assists in connection with cleaning validation matters. Jeff has a BS in Biology and Chemistry from the University of Delaware, pharmacology (ABD) at the University of Pittsburgh and an MBA from NJIT.

Stacy R. Silverstein is a Senior Director, Strategic Programs and Director, Foodservice for Alconox Inc. managing long-term projects and serving the foodservice industry with safer, more effective cleaning solutions. With over 20 years' experience in public health and health education, Stacy earned a BA in biopsychology from Vassar College and an MHS from Johns Hopkins Bloomberg School of Public Health.

Malcolm C. McLaughlin is Senior Vice President for Alconox Inc. with over 40 years' experience in detergent formulation, organic chemistry and critical cleaning applications. Malcolm has overseen the creation and commercial growth of several key Alconox Inc. products. He earned his MS in Chemistry from Columbia University.

ISBN 979-8-9897594-2-2
9 798989 759422 50995

Technical Communications