

CLEANING AND SANITIZATION

INTRODUCTION

Cleaning and sanitization is essential to ensure microbial quality in the manufacture of cosmetics and personal care products. These procedures should be validated in order to consistently meet hygienic manufacturing requirements. The design of these procedures should take into account the product formulation and all aspects of manufacturing.

SCOPE

This document provides a guideline for a cleaning and sanitization program for a cosmetics manufacturing facility. It includes guidance on training, documentation, manufacturing facilities, manufacturing and filling equipment, cleaners, and sanitizers.

If cosmetics and over-the-counter (OTC) drugs are manufactured with the same equipment, refer to FDA guidelines for the manufacture of OTC drugs.^{1, 2, 3}

Formal cleaning and sanitization procedures are essential in the manufacture of personal products and cosmetics. Specific internal programs for cleaning and sanitization should be established. These programs are essential to ---

- Assure the microbiological quality of the product
- Meet legal regulations where required
- Minimize the microbial load contributed by processing, filling, and storage equipment
- Avoid the cost associated with microbial failure
- Help maintain the company commitment to quality

This document provides guidelines for:

- Cleaning, which is the process of removing product residue and contaminants such as dirt, dust, grease from the surface. Cleaning is the essential first step in any cleaning and sanitization procedure.
- Sanitization, which is the process utilized to reduce viable microbial contaminants to an acceptable level. All surfaces must be clean for the sanitization procedure to be effective.
- Validation, which is the process of substantiating and verifying that the process does what it purports to do.
- Documentation, which is the process of organizing all relevant information in an orderly and easily understood format. This documentation is required to validate a process and to maintain an historical record of the process and equipment usage.

Guidelines for the development of operating procedures will be addressed in each section as appropriate. Written protocols are required prior to attempting to validate

any process. For more information, see the "Microbial Validation and Documentation Guidelines for the Cosmetic Industry."⁴

TRAINING

Personnel should be properly trained and supervised in the cleaning and sanitization of the facility and equipment. A document should be written to outline the training process. Ongoing training should be conducted according to a pre-planned schedule. Performance should be monitored to verify that the training is effective and proper procedures are being followed.

A. Purpose

Training should be used to:

- Bring new employees to the required level of competency.
- Introduce new cleaning and sanitization methods and products to all employees.
- Reinforce existing programs.

Conduct re-training according to a predetermined schedule, with more frequent training if needed.

B. Content

A training program should impart an understanding of the elements listed below and how they affect product quality:^{5, 6}

- Overall microbiological awareness and basic microbiology
- Basic concepts of microbial contamination, common contamination sources, and their avoidance
- The consequences of microbial contamination and the risks associated with not following appropriate sanitary practices
- Sanitary practices
- Good housekeeping
- Personal hygiene
- Equipment operation and design
- The importance of cleaning and sanitization and a clear understanding of each process
- Product type and proper procedure based on product formula ingredients
- Proper and safe use of cleaning and sanitizing agents
- Concentration, dilution, and contact time of cleaners and sanitizers
- Product and chemical residues, including cleaners and sanitizers

Training should also include:

- A review of the procedure for proper cleaning and sanitization of the equipment and areas in their care
- Effects of changes to process, formula or equipment changes on cleaning and sanitization requirements (i.e., change control)
- Recordkeeping of cleaning and sanitization performed

- A mechanism for reporting to appropriate personnel any observations that indicate a potential for contamination

C. Documentation

Training should be documented. This written record should include:

- Name of the qualified trainer
- Attendees
- Date/ time of training
- A tool to measure comprehension and verification of understanding

Additional items such as training materials may also be included in training documentation.

DOCUMENTATION

Documentation is the keeping of all essential records of cleaning and sanitization. All these records should be complete, clear, and concise. In addition to the training documentation discussed above, manufacturing facilities should maintain documentation for cleaning and sanitization validation and for routine or ongoing cleaning and sanitization.⁴

A. Validation

All cleaning and sanitization procedures should be validated. Validation documentation consists of two components, a protocol and a summary document.

1. *Protocol*

The cleaning or sanitization procedure protocol consists of

- A written description of the objective of the validation study and acceptance criteria
- A written explanation of the process

This documentation should include a detailed description of the product, process, and equipment involved, as well as the protocol and test procedures to be used.

2. *Summary*

The summary document consists of

- A report summarizing the raw data supporting conformance to acceptance criteria, with raw data either attached or available
- A conclusion to include at least a statement of acceptance, any recommendations, and revalidation requirements

See reference 4 for further guidance.

B. Routine Documentation

Routine or ongoing documentation includes routine logs which are necessary to maintain a history of the equipment usage and is an essential part of any investigation.

This information can also be part of a validation information package, utilized for trend analysis, and evaluating cycle reduction and cost saving opportunities.

1. *Logs*

The routine log should include the following information for each cleaning, sanitizing or changeover activity

- Date, start and end times of the cleaning
- Date, start and end times of the sanitization; include expiration time
- Product and batch preceding the cleaning and sanitization
- Operating procedure, SOP, or procedure number for the cleaning and sanitization being carried out
(Any variation from the established operating procedure should be recorded.)
- Sign off by operator
- Review, approval and sign off by verifier/reviewer
- Time, date and identity of next batch start up
- Date and description of any repairs or equipment down time

2. *Status*

In addition to permanent logs, current cleaning and sanitization status should be clearly displayed on equipment. Examples of status designation labels are

- Contents and Batch or Lot Number
- Empty Needs Cleaning
- Needs Cleaning
- Clean Needs Sanitizing
- Sanitized

Information on equipment status should also note the date sanitized and the expiration time and date.

MANUFACTURING FACILITY

The environment of the manufacturing facility strongly influences the microbial quality of the finished product. Appropriate building design and maintenance contribute to this goal. Standard procedures for facility cleaning and sanitization should be written and a record of their implementation should be maintained.^{6,7}

A. Design and Maintenance

Buildings should be designed for ease of cleaning and sanitization to allow for the sanitary manufacture of product. This design should minimize cross contamination and contamination from the surrounding environment. Maintenance of the building should maintain the integrity of the sanitary design.

The building layout should be designed to minimize the risk of contamination. The layout should be organized to accommodate a rational flow of materials, clean operations, and adequate supporting activities in the facility. Separate areas should be maintained for material receipt, storage, weighing, compounding, filling, packing etc. to prevent cross contamination.

It is critical that there be access to all surfaces for cleaning and sanitizing . These surfaces include equipment, walls, storage cupboards, piping, under stairs, behind tanks, etc.

The following are important points to be considered in the design of a facility:

- Building openings should be designed to prevent potential contamination. These may include automatic closing doors, screens on windows, screened vents, sealed pipe entries, and loading bays designed to minimize environmental contamination. These should be kept in good repair.
- Exterior walls and entryways should be designed to prevent access to pests, vermin, birds, and insects.
- Building systems, including heat, air conditioning, and compressed air, should be monitored to assure that they do not contribute to contamination. Scheduled preventative maintenance such as filter changes should be performed.
- Leaks should be repaired immediately.
- Adequate drainage should be provided to rid wastewater effectively because stagnant or standing water allows for microbial growth.
- Positive air pressure can be used to reduce the risk of contamination in areas where product is openly exposed to the environment, as in compounding and filling operations.
- Equipment should be raised from the floor or otherwise constructed so that floors can be kept clean.
- To avoid extraneous material from contaminating product, piping, wiring, transport belts, and other potential sources of contamination, should not be positioned above tanks or filling lines.
- Floor, wall and ceiling surfaces should be free from cracks, crevices, and open joints.
- Finishes should be smooth and non-porous to allow for easy cleaning and sanitization. Peeling paint should be removed.
- There should be access to all wall areas to allow cleaning and to eliminate conditions that contribute to build up of debris.
- Adequate storage should be provided for items not in use in order to minimize clutter.
- Areas where equipment is washed should be of sanitary design and properly maintained.
- Adequate lavatories with hand washing facilities should be provided.
- Locker areas and lunchrooms should be separate from the manufacturing area.

B. Manufacturing and production areas

The frequency of cleaning and sanitization is determined by the types of activities conducted in any given area. Qualified personnel should visually monitor each area routinely. Cleaning and sanitizing schedules can be adjusted and remedial action can be taken as needed. Recommendations are given below for some specific areas.

1. *Walls, ceilings, pipes, and fixtures*

Clean and/or sanitize on a scheduled basis (for example, monthly, quarterly or more frequently, if needed). Vacuum to remove loose material.

2. *Floors*

Clean floors on a scheduled basis, to include the following

- Vacuum and/or sweep frequently.
- Minimize airborne dust during cleanup.
- Wet mop or machine scrub on a predetermined schedule.
- Sanitize as appropriate.
- Promptly clean up spills of raw materials, product or packaging components.

3. *Cleaning equipment and supplies*

Store cleaning equipment and supplies properly in a clean area. Maintain the supply area in an orderly manner. Separate supplies and equipment for lavatory cleaning from other cleaning supplies.

C. Warehouse Areas

Raw materials, packaging components, finished products and equipment should be stored in warehouse areas under acceptable environmental conditions. Precautions should be taken to prevent contamination from any source.

General guidance for the warehouse area includes the following:

- Aisles should be kept neat and clean by sweeping, damp mopping or machine scrubbing. An appropriate, freshly prepared cleaner should be used.
- An established, monitored, and documented insect and rodent control program should be in place.
- Stored materials and containers should be kept clean, orderly, protected and correctly identified.
- Container exteriors should be cleaned before transferring material into manufacturing areas.

D. Waste Disposal Area

Provisions should be made for regular and timely removal and disposal of waste out of the proximity of finished products, components, and manufacturing areas to minimize the risk of microbial contamination.

- Place refuse for disposal in designated containers using plastic liners. Construct containers so that they are leakproof and rustproof, and cover whenever possible.
- Empty refuse containers at a minimum of once daily, and clean when necessary prior to reuse.
- Clean spills immediately and remove debris from the manufacturing areas.
- Use disposable towels and discard immediately after single use. Do not use rags.

- Isolate waste disposal areas from manufacturing, and routinely clean and sanitize to minimize odors.
- Dispose of product or process waste in accordance with current government regulations.
- All hazardous waste, including spills, should be handled per the facility hazardous waste management plan.

E. Documentation

In general, the written procedures for the cleaning and sanitization of the floors, walls, ceilings, pipes, and general building environment should include the following:

- Type(s) of cleaner and/or sanitizer
- Instructions for the preparation of the proper concentration of cleaner and/or sanitizer.
- Instructions for the proper use of cleaning and sanitizing equipment
- Written schedule for the routine cleaning/sanitizing of each area including:
 - Areas to be treated
 - Method(s) of treatment
 - Frequency of treatment

The cleaning and sanitizing procedures performed should also be documented. The record should be signed by the individual doing the work as it is completed and should be routinely checked and initialed by a qualified individual.

MANUFACTURING AND FILLING EQUIPMENT

Manufacturing and filling equipment has direct contact with product. The following topics applicable to this equipment are covered below:^{8,9}

- Documentation of cleaning and sanitization of equipment
- Sanitary equipment design
- Frequency and monitoring of cleaning and sanitization
- Procedure for cleaning and sanitization
- Special equipment and procedures
- Criteria for cleaning and sanitization.

A. Documentation of Equipment Cleaning and Sanitization

1. *Operating Procedures*

Operating procedures for each piece of equipment should be in place and include the following:

- Equipment identification
- Equipment disassembly instructions, where necessary
- Product specific instructions where applicable
- Type of cleaners and sanitizers to be used
- Instructions for preparation of the proper concentrations of cleaning and/or sanitizing solutions
- Proper application technique, and rinse procedure, contact times, and temperature for cleaning and sanitizing solutions

- Proper storage, labeling and protection of equipment once it has been cleaned and /or sanitized
- Time limit between sanitization of equipment and use
- Safety considerations

2. *Equipment status log*

For each piece of equipment, a cleaning and sanitizing log should be prepared, maintained, and made readily available. This log should include the product to be made, name of the equipment, and the cleaning and sanitization date. In addition, the log should be signed and dated after each procedure. It should be routinely checked and initialed by the operator and a qualified individual. Equipment status tags are recommended to assure proper identification. See "Routine Documentation" in the **DOCUMENTATION** section.

B. Sanitary Equipment Design

It is essential that process and filling equipment have good drainage and be designed for ease of cleaning and sanitization. In addition, the equipment should be durable enough to withstand sanitizing chemicals and/or physical agents.

1. *General equipment design*

The following guidance on overall equipment design is intended to minimize conditions that may lead to microbial growth in the equipment. It also offers suggestions to reduce the potential degradation of the equipment by the effects of the sanitizers and cleaners used.

- Design process and filling equipment to minimize retention of residual product and/or wash water. Residual water will dilute product and/or sanitizer which can lead to microbial growth and the development of adaptable microorganisms.
- Minimize condensation in equipment that can dilute product and create an environment for good microbial growth.
- Internal and external surfaces of equipment should be accessible and easily cleanable. All surfaces should be as free as possible of crevices that harbor product or microorganisms.
- Equipment and its surface finish should be easily cleanable and durable; 316 or 316L stainless steel with a 140 grit or better finish, a type 2B finish, or equivalent quality, is recommended for susceptible products.
- Materials should not be degraded, etched, or react when in contact with the product or sanitizers.
- Gaskets are readily contaminated and should be routinely inspected and replaced when necessary.
- Sanitary welding techniques should be used to avoid creating crevices or rough surfaces that are difficult to clean. Orbital welding and/or gas tungsten arc welding is recommended.

Common sanitary design practices for specific types of equipment are discussed in the following sections.

2. *Tanks/Vessels*

- Minimize sharp corners because they are difficult to clean.
- Avoid narrow recesses that could trap product and water.
- Design tanks with a domed head to minimize condensation.
- Conical or dish shaped bases, with a center drain, are recommended as they allow for complete draining.
- Design vessel openings and surfaces to be cleanable.
- Covers should be designed and maintained to fit well and close easily.
- Design vents to minimize debris.
- Eliminate unused drop leg pipes.

3. *Transfer Pipes*

- Minimize the length of pipe runs to make cleaning easier and reduce the risk of biofilm formation.
- Slope pipe runs to be self draining and cleanable with no dead legs/ends.
- Design piping systems to have a minimal number of T's.
- Use sanitary welding techniques to avoid the creation of difficult to clean crevices and rough surfaces.
- Use sanitary fittings for all connections.
- Avoid screw threaded piping that comes in contact with the product.

4. *Valves*

Valves should be easily cleanable with no dead spaces to collect product residue or water. An example of a sanitary valve is a diaphragm valve.

5. *Pumps*

Sanitary pumps are recommended. The design and installation should allow for complete drainage. Pumps should be easily accessible for inspection, cleaning, and sanitization.

6. *Filling Equipment*

Fillers should be designed to be easily cleaned and sanitized. Avoid drip pans and water lubricated belts. If positive air is used in filling equipment, microbial air filters and air line dryers should be monitored to prevent air line condensate from contaminating finished product.

7. *Gaskets*

Gaskets are potential sites for contamination. Gasket materials should be compatible with the product as well as the cleaning and sanitizing solutions. Non-porous, chemically inert materials are recommended. Care should be taken to assure that gaskets are properly installed.

8. *Hoses*

Transfer hoses should be of a material that is compatible with product and with cleaners and sanitizers used. They should have sanitary fittings. Cleaned and sanitized hoses should be drained to dry and capped when not in use.

C. Schedule

1. *Frequency*

All equipment should have a regular cleaning and sanitization schedule. The frequency should be determined based on several factors:

- Product vulnerability to contamination
- Type of equipment used
- Difficulty in removing product from the equipment
- Whether continuous process batching is being performed

2. *Validation*

Cleaning and sanitization schedules should be validated. Ideally, cleaning and sanitization between batches of products and /or at the end of the day's production is preferable. Continuous process of the same product may alter this frequency. An additional determination of an effective time interval between equipment sanitization and start-up should also be made. This is achieved by validating the process.

3. *Expiration limit*

A validated time or expiration limit should be set for each equipment sanitizing procedure. This will depend on equipment and method of sanitization. This expiration limit reflects the allowable time a piece of sanitized equipment can stand before requiring resanitization.

D. Monitoring

1. *Personnel*

A microbiologist or suitable trained individual should review the entire processing system to determine potential areas for microbial contamination.

2. *Areas*

Areas may include processing lines, storage and mixing vessels, fillers, pumps, pipe connections, flexible hoses, pressure relief valves, pigging systems, strainers, utensils, and other related equipment. Most probable areas include low point drains, internal seams and gaskets, internal filler nozzles, and the interior pump.

3. *Procedures*

Visually inspect dismantled equipment for residual product or water. Determine the presence of microbial contamination by a method appropriate to the equipment. This monitoring should be documented.

If a chemical sanitizer is used for sanitization, a neutralizing media, specific for that sanitizer must be employed in the equipment monitoring procedure. Methods used to determine the presence of microbial contamination may include swabbing, direct contact, or testing the final rinse water.

4. *Methods*

a. Swabbing: A sterile cotton or calcium alginate swab is wetted in sterile buffer, saline solution, or broth and rubbed over a measured portion of the surface of the sanitized

equipment. The swab is then either streaked across an agar plate or placed into a sterile broth tube. The plate or tube is incubated for the appropriate length of time.

Examination of the plate will give an organism count and the individual colonies can be lifted from the plate and identified. Tubes are examined for turbidity. This is a pass / fail test. Swabbing is very useful for irregular surfaces or curved equipment

b. Direct contact: Contact plates contain agar which has a convex surface. These plates are pressed against the surface of equipment then incubated. Examination of the plate will give an organism count and individual colonies can be lifted from the plate and identified. The surface of the equipment touched by the contact plate must be cleaned of any agar residue. Contact plates cannot be used for irregular surfaces and are practical only for flat surfaces...

c. Final Rinse Test: Water of known microbiological quality and volume is rinsed through the equipment. The water is recovered and filtered via membrane filtration technique. The membrane is placed onto a plate and incubated. Examination of the plate will give an organism count and individual organisms can be identified. Note that rinse water analysis may not detect the presence of biofilm on equipment surfaces.

5. *Validation*

Validation of equipment sanitization efficacy can be done via swabbing onto hardened agar plates. Frequency may be based on the manufacturing history of the product or on the discretion of the microbiologist or hygienist e.g. can be done after each sanitization or on a periodic basis. If a chemical sanitizer is used, analytical testing may be used to detect residues.

E. General Procedures

1. *Water*

Water utilized in the cleaning and sanitizing processes may be described as

a. Make water: The water used to make up cleaners and sanitizers should have a low microbial bioburden to avoid contaminating the cleaner or to avoid consuming the sanitizer.

b. Rinse water for cleaned equipment: Water used to rinse cleansers from cleaned equipment should be fresh, potable water that has a microbiological quality which meets EPA drinking water quality standards.¹⁰

c.. Rinse water for sanitized equipment: Water used to rinse chemical sanitizers from sanitized equipment must have no higher microbial bioburden than the microbial specifications of the product to be made in that equipment.⁴

When water is used to rinse equipment the equipment, it must be drained and used within a validated expiration time.

2. *Equipment cleaning and sanitization*

Clean and sanitize all lines; processing, storage and filling equipment; pumps; pipe connections; flexible hoses; and utensils as well as plant facilities in the immediate processing and filling areas as follows:

- Remove product residue from all contact surfaces by thoroughly rinsing with water or water/detergent solution between 120°F (49°C) and 180°F (82°C). Temperature is dependent on product type and equipment compatibility. NOTE: Non-aqueous-type product residues should be removed by appropriate predetermined methods.
- Pipeline pigs are devices made of non-porous materials used for recovery of product, product separation, and cleaning of manufacturing pipelines. The pig launcher and receiving station must be sanitary in design as this equipment can easily harbor microbial contaminants. Diligence must be taken to assure thorough cleaning and sanitization of pigging equipment and of the pig itself. When not in use, pigs must be handled and stored under sanitary, dry conditions.
- Circulate a cleaning solution for a period of time and at a temperature capable of effectively removing soil residue in the circuit and/or equipment. All surfaces not accessible by this cleaning procedure should be cleaned manually and/or by using special equipment or methods.
- Rinse the cleaning solution thoroughly from the system with microbiologically acceptable water, as determined by in-house standards.
- Before use, equipment should be sanitized according to the written procedure for the piece of equipment involved. See Section F below, "Special Equipment and Methods."
- It is suggested that rinse water for sanitized equipment contain no higher microbial content than the limits established for the formulated products.⁴

Used process equipment should be cleaned as soon after processing as possible in order to facilitate removal. Product dried and hardened on equipment surfaces can be difficult to remove thoroughly.

Cleaned/sanitized equipment should be properly stored before use to prevent recontamination. In general, equipment should be drained dry and open ends covered to prevent recontamination.

F. Special Equipment and Procedures

Special cleaning and sanitizing equipment and methods may be employed for processing and filling apparatus. The equipment and methods are generally designed to fit the individual needs of each manufacturing facility. There are several methods for cleaning and/or sanitizing.

1. *Manual*

This method involves the preparation of cleaning solution and the scrubbing of equipment or parts using a brush, single-use cloth, or pad. It is an effective but highly time consuming method.

2. *Soak*

This method involves the soaking of utensils or equipment parts in containers of detergent solution for extended periods of time. Generally, this method is used in combination with manual cleaning.

3. *Spray*

Low or high-pressure sprays are used to remove soil. In most cases, the cleaning action of the pressure sprays is enhanced by the use of detergents. High-pressure spray nozzles such as spray balls or injectors may be permanently installed in mixing or storage tanks. High-pressure spray wand equipment is also widely used. This type of equipment is mobile and/or portable. It is used for general surface cleaning. Spray pressures developed should range from 200 to 1000 p.s.i.

4. *Fog*

Fogging is a method of generating a mist for the application of sanitizers. Large areas of equipment surfaces can be treated by fogging in a very short time, using small amounts of sanitizers. This method should only be used in closed systems by properly trained personnel.

5. *Clean In Place (CIP)*

CIP is a semi- or fully automated, self-contained system for the cleaning and sanitizing of equipment. Cleaning and sanitizing solutions are circulated for a specific time at a specified temperatures. No disassembly of equipment is necessary. Each system is unique and to work well it should be properly designed, evaluated and controlled. Factors to consider when using CIP are: detergent/sanitizer type; detergent/sanitizer concentration; temperature; and design of equipment. Some equipment design factors include type, number, positioning of spray balls, type of pump, velocity rates, baffles that may shadow areas of a tank, etc.

G. Acceptance Criteria

Prior to validation of the cleaning and sanitization process for each piece of equipment, the acceptance criteria should be selected. Criteria should take into account the types of products processed by the equipment. Typically, criteria include, microbial bioburden that meet specific requirements or limits of the products, the absence of pooled water, limitations on product residue, absence of objectionable organisms.

Alert and action levels for microorganisms should be established by quality assurance based on finished product specifications.

CLEANERS (See *Table I*)

A cleaner can be defined as a chemical or blend of chemicals formulated to remove undesirable soils from a contact surface. These chemicals may be solvents, acids, bases, detergents, and/or water based chemical blends. Industry has focused on aqueous cleaners because of concerns for the environment and employee exposure.

Aqueous cleaners are defined as blends of water soluble chemicals designed to remove soils into a water-based solution with a water continuous phase during cleaning. These consist of surface active ingredients and other cleaning chemicals that use detergency to lift soils from surfaces by displacing the soil with the surface active materials. This occurs because the surface active ingredients have a higher affinity for the surface than they do for the soil.^{8, 11}

A. Characteristics of an Efficient Cleaner

Aqueous cleaners are typically formulated to contain several ingredients to allow for maximum cleaning effectiveness. The ingredient requirements depend on the intended use of the cleaner. Efficient aqueous cleaners utilize surfactants (anionic, nonionic, cationic and/or amphoteric), dispersants, emulsifiers, wetting agents, builders, chelating agents, sequestering agents, corrosion inhibiting agents and stabilizers. The surfactants are used for emulsification, wetting and penetration; builders for neutralizing hard water interferences, chelating inorganic soils and saponification of natural oils; and additives for corrosion inhibition, anti-redisposition and good rinseability. See Table I for information on specific chemical cleaners. For additional information, see the references.^{8, 9, 11}

Characteristics essential to a good cleaner include

- Compatibility with equipment, i.e. non-corrosive
- Quickly soluble
- Good wetting action
- Good penetration properties
- Good emulsification and soil dispersion properties
- Good rinsing properties
- Economical and readily available
- Environmentally friendly and non-hazardous

Table 1 gives examples, descriptions and advantages/disadvantages of several different cleaners.

B. Selection of a Cleaner

Although the characteristics of an efficient cleaner may be more general, the selection of a particular cleaner for a particular cleaning task requires specific information. The most important considerations include knowledge of the type of substrate to be cleaned and the type of soil to be removed. The cleaner type should be matched to the surface to be cleaned (metal, glass, plastic, etc.), the soil type (organic, inorganic, oils, heavy soils, light soils) and the desired cleaning method (manual, soaking, CIP, power spray wand, etc.). The cleaner should also be widely available and economical. Information on the level of cleanliness required (acceptance criteria) should also be known. Several questions can be asked prior to the selection of a cleaning system:

- Does the cleaner have good detergency on the type of soil to be removed?
- Is the cleaner recommended for the cleaning process to be used?
- Is the cleaner free rinsing?
- Is the cleaner hazardous or environmentally unfriendly?

- Is the cleaner economically priced at the use level and widely available?

C. Factors Effecting Cleaner Efficiency

Besides the selection of an efficient cleaner, several other factors are extremely relevant to the success of a cleaning process. Beyond the cleaner itself, cleaning efficiency is influenced by cleaner concentration, agitation, temperature, cleaning /contact time, rinse method and drying method. These process variables must be considered, specified, and controlled to ensure a consistent and optimized cleaning process.

1. *Cleaner Concentration*

The concentration of the cleaner should be selected through consultation with the manufacturer followed by in-house validation. Optimizing cleaning temperature, time or agitation may reduce the concentration of cleaner required.

2. *Temperature*

Generally speaking, the higher the cleaning process temperature, the more efficient the cleaning, however, this is dependent on the soil type (melt point issues). Temperature should be optimized for the soil being cleaned and validated using in-house methods. Safety considerations should be included when personnel exposure is possible.

3. *Time*

Generally speaking, the longer the cleaning process, the more thorough the cleaning. Again, cleaning time is dependent on the other factors of the process to include agitation, temperature and cleaner aggressiveness. Soaking may take hours, whereas high-pressure sprays may require from seconds to minutes. Cleaning time should be considered in the validation of the entire cleaning process/system.

4. *Agitation*

Depending on the product/soil to be cleaned, the range of applied mechanic/fluid energy required for effective cleaning will vary. Equipment can simply be soaked/immersed in a cleaner solution, manually scrubbed, or cleaned with direct impingement using dynamic spray balls or jet-spray devices. In general, increased agitation and turbulence improves cleaning efficiency.

5. *Rinse*

It is important that the rinse procedure completely removes debris detached from the equipment during cleaning. The specified volume of rinse water should be validated for each particular rinse program. A general recommendation is that the rinse water volume be at least three times the volume of the cleaner solution used. Assure there is no cleaner residue.⁸

6. *Drying*

To reduce the potential for corrosion, eliminate the opportunity for microbial regrowth, and prevent dilution of chemical sanitizers, equipment should be properly drained and dried after rinsing. Evaporation is the simplest and least expensive drying method. Other methods include circulated hot air, vacuum drying or forced air, blow drying. For these methods the air source should be filtered to provide high quality air for drying. Use of 70% alcohol, as a finishing step can aid in the evaporation of water. Alcohol can be used as a dryer /sanitizer and is especially useful for anhydrous products where it is essential that no moisture remain on the equipment. Caution should be used when using alcohol on equipment that could present a fire hazard.

D. Testing to Measure Cleaning Process for Efficacy

The development of a testing and measurement system is key to optimizing and validating the effectiveness of a specific cleaning process. The method selected for measuring the effectiveness of the cleaning process should provide information needed to determine that key criteria are met. Testing of the cleaning process initially requires the development of a baseline level of cleanliness and an effective method to measure cleanliness. In many cases, visual assessments of equipment or simple gravimetric analysis will suffice. Alternatively, video scopes, chemical tracer measurements (fluorescent whiteners, total organic carbon (TOC) in residual water, or conductivity) may be used. Various methods involve the extraction of the contaminating soil from the surface followed by quantitative chemical analysis.⁸ The simplest method that provides appropriately sensitive results should be used.

After the cleaning system has been selected, it should be validated against the targeted product and on the equipment where the production will occur. Either a quantitative or qualitative method may be used to judge the cleaning process, and then an acceptance criteria should be established. Experimentation may occur initially on a smaller bench or pilot plant scale, however the cleaning system should be validated on the actual equipment due to concerns with scale-up. Each variable of the cleaning process (cleaner concentration, time, temperature, agitation, etc.) should be considered to determine the optimal conditions.

SANITIZERS

A. Definition

A sanitizer is either a chemical or physical agent that is effective in reducing microbial contamination on product contact surfaces. A sanitizer should achieve a 99.9% [3 log] reduction of pathogenic or unacceptable microorganisms and reduce other organisms to a minimal acceptable level. A sanitizer may be considered effective if it reduces microorganisms to acceptable levels, with no detectable objectionable microorganisms, as determined by the cleaning and sanitization protocol.^{8, 9, 12, 13}

B. Characteristics and Selection of an Efficient Sanitizer

The following are desirable characteristics of a sanitizer

- Effective against a broad range of microorganisms.

- Provides adequate microbial reduction, 99.9%, effective against organisms of concern.
- Effective in a relatively short contact time.
- Stable and efficacious over time, both in concentrate form and at use levels.
- Economical to use.
- Non-toxic at use levels.
- Non-corrosive.
- Compatible with products and equipment.
- Free from objectionable odors and residue.
- Meets regulatory requirements.
- Biodegradable.

C. Chemical Sanitizers

Combined cleaner/sanitizer agents are available. However these agents can have reduced detergent and/or disinfectant activity compared to each agent alone.

Additionally, cleaners have a high optimal pH whereas most chemical sanitizers are most effective at neutral or acidic pH.

Some useful chemical sanitizing agents are chlorine, iodophores, quaternary ammonium compounds, ethyl alcohol, phenolic compounds, formalin, phosphoric acid, hydrogen peroxide, peracetic acid, and ozone. See Table II for information on frequently used chemical sanitizers.

D. Physical Sanitizers

The most common physical sanitizer is thermal energy, either in the form of steam or hot water (180°F or 82°C minimum). A major advantage of heat is its ability to penetrate into small cracks and crevices. Heat is also non corrosive, cost effective, leaves no residue, measurable with recording devices or thermal strips, efficient, and is effective against a broad range of microorganisms.

See Table III for information on frequently used physical sanitization methods.

E. Factors Affecting Efficacy

Cleaning must always precede sanitization. In-house validation of each specific piece of equipment is needed to assure sanitizer efficacy. Roughness of surface, bad welds or other defects can make the equipment difficult to sanitize.

Care should always be taken to follow label directions and manufacturer instructions and recommendations.

Water incorporated into sanitizers should be of acceptable microbial quality.

Operators should be properly trained. Improper use may give ineffective results, emit toxic fumes, or corrode equipment.

The following process variables should be considered, specified, and controlled to ensure consistent sanitizer performance.

- Condition of equipment surfaces
- Materials of construction
- Concentration of sanitizer
- Contact time
- Temperature
- Optimal pH range.
- Mechanical energy (pressure and flow rate)

F. Measurement and Validation of Sanitization Effectiveness

Prior to validation of the sanitization process, the acceptance criteria should be selected for specific equipment and products. Typical or suggested criteria include , microbial bioburden that meet specific requirements or limits and the absence of pooled water or product residue.

A suggested approach for validating the sanitization procedure effectiveness is

- Sanitize the equipment
- Break down the equipment
- Evaluate microbial bioburden and organism type on product flow surfaces including difficult to reach areas such as gaskets, valves, pumps etc.
- Check both microbial levels and organism types

The validation of a sanitization procedure should not be performed immediately after cleaning but at the longest potential time the equipment will stand before use. This gives an expiration time for sanitization after which the equipment must be resanitized.

See above, "Monitoring" in the section on **MANUFACTURING AND FILLING EQUIPMENT**.

SUMMARY

The selection and effective use of a cleaning or sanitizing agent and/or method is dependent on several factors: the manufacturing facility, the type of product processed, and the design and layout of the equipment. All cleaning and sanitizing procedures should be properly designed and their use documented and validated. Personnel should receive adequate instruction and training in these areas.

With attention to these details, a cleaning and sanitizing program will positively contribute to achieving a sanitary manufacturing facility.

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Table 1. Chemical Cleaners

Cleaner Type	pH Range	Soils Removed	Examples	Advantages/Disadvantages
Mineral-Acid and Mild Acid Cleaners	0.2 - 5.5	Heavy scales to Inorganic salts and Soluble metal complexes	<ol style="list-style-type: none"> Strong acids: Hydrochloric acid Sulfuric acid Phosphoric acid Weak acids (dilute solutions of organic acids): Acetic acid Citric acid 	<ol style="list-style-type: none"> Good for acid soluble soils Efficient for metal oxide removal May be harsh on hands May have toxicity, environmental and handling issues
Neutral Cleaners	5.5 - 8.5	Light oils Small particulates	Mild, unbuil surfactant solutions (may include water-miscible solvents such as alcohols or glycol ethers)	<ol style="list-style-type: none"> Rely on dissolution and emulsification, rather than aggressive chemical attack Lowered toxicity and corrosivity concerns
Mild Alkaline and Alkaline	8.5 - 12.5	Oils Fats Grease Particulates Films	Ammonium hydroxide Sodium carbonate Sodium phosphate Borax solutions.	<ol style="list-style-type: none"> Alkalinity promotes <ol style="list-style-type: none"> saponification solubilization of alkaline soluble soils hydrolysis
Corrosive Alkaline	12.5 - 14	Heavy Grease and Oils	Sodium Hydroxide Potassium Hydroxide Sodium Silicates.	<ol style="list-style-type: none"> Work best when soil can be hydrolyzed; i.e. saponification of fatty soils Harsh on hands Some exposure hazards and product toxicity hazards Corrosivity

Table II
Chemical Sanitizers

Below are listed general types and uses, however, refer to manufacturers use direction included on material safety data sheets (MSDS)

<i>Type</i>	<i>Description</i>	<i>Suggested concentrations and contact times</i>	<i>Advantages</i>	<i>Disadvantages</i>
Chlorine	Sodium hypochlorite Calcium hypochlorite Lithium hypochlorite Chlorine gas Chloramines Chlorocyanurates	200 ppm as free chlorine 30 minutes Somewhat temperature dependent (higher temperature increases biocidal effect) Chlorine releasing compounds may require other conditions of use; e.g., pH contact time, concentration.	1. Excellent activity 2. Readily available 3. Can be used alone in cold water on clean equipment 4. Rapid, sensitive test available to determine concentration during sanitization and to verify removal of residual after rinsing.	1. Odor 2. Chlorine is less reactive as pH increases 3. Inactivated by organics 4. Reactive with metal surfaces- corrosive if misused; must carefully regulate exposure time. 5. Sensitive to light and temperature 5. NIOSH recommended employee exposure limit 0.5 ppm ceiling for 15 minutes. ¹⁴
Cationic surfactants	Quaternary ammonium compounds (normally in combination with nonionics)	200 ppm at time recommended by manufacturer	1. Cleans (has excellent detergent properties) 2. Excellent activity 3. Noncorrosive 4. Can be used alone in water 5. Deodorizes 6. Residual activity 7. Odorless 8. Very stable	1. Not sporicidal 2. Most effective against microorganisms at neutral or slightly alkaline pH 3. Hard water tolerance may vary 4. Residue may be incompatible with product 5. Inactivated by anionic cleaners 6. May not be compatible with non-ionics 5. Exit monitoring requires titration

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<i>Type</i>	<i>Description</i>	<i>Suggested concentrations and contact times</i>	<i>Advantages</i>	<i>Disadvantages</i>
Iodophors	Iodine in nonionic surfactants with H ₃ PO ₄	12.5 - 25 ppm 10 minutes	<ol style="list-style-type: none"> 1. Cleans as fomulated 2. Excellent activity 3. Residual activity 4. Non-toxic at use concentrations 5. Stable at use concentrations 	<ol style="list-style-type: none"> 1. Poor sporicidal activity 2..May stain 3. Usually formulated 4. Rinsing required
Alcohol	Isopropyl Ethyl	60- 70% isopropyl alcohol for 15 minutes 60-95% ethyl alcohol for 15 minutes; some applications to 30%	<ol style="list-style-type: none"> 1. No rinsing 2. Readily available 3. Fast drying 4. Used alone 	<ol style="list-style-type: none"> 1. Not effective against bacterial spores
Phenols (Phenolic derivatives)	Phenyl and/or chlorinated phenols	1:200 solution	<ol style="list-style-type: none"> 1. Cleans 2. Excellent activity 3. Deodorizes 	<ol style="list-style-type: none"> 1. Must be formulated 2. Rinsing required 3. Used solution may be unstable (use within 2-3 hours) 4. Worker exposure limits 5. Activity reduced by presence of organic matter
Pine	Pine oils formulated with soap or surfactants	Per manufacturer's use directions	<ol style="list-style-type: none"> 1. Cleans 2. Excellent activity 3. Deodorizes 4. Degreases 	<ol style="list-style-type: none"> 1. Must be formulated 2. Odor may be incom patible with certain products

Table II
Chemical Sanitizers

Below are listed general types and uses, however, refer to manufacturers use direction included on material safety data sheets (MSDS)

<i>Type</i>	<i>Description</i>	<i>Suggested concentrations and contact times</i>	<i>Advantages</i>	<i>Disadvantages</i>
Formalin	37% w/v solution (aqueous, as free formaldehyde)	1% (as formaldehyde) 30 minutes	<ol style="list-style-type: none"> 1. Excellent activity 2. Readily available 3. Can be used alone 	<ol style="list-style-type: none"> 1. Odor 2. Highly reactive 3. Toxicity 4. Should be used cold in a closed system 5. Skin protection required 6. NIOSH/OSHA exposure limit to formaldehyde is airborne concentration ceiling of 0.1 ppm, 15 minute contact time¹⁴
Phosphoric acid	H ₃ PO ₄ solution	Varies, refer to manufacturer's use directions	<ol style="list-style-type: none"> 1. Good activity 2. Stainless steel 3. Used cold 4. Short contact time 	<ol style="list-style-type: none"> 1. Used under acidic conditions to be effective. 2. Most used in combination with iodophors
Hydrogen peroxide	Purchased as a stabilized solution	1.5% of a 35% solution for 30 minutes.	Effective vs. organics	<ol style="list-style-type: none"> 1. Explosive at high levels 2. Reactive 3. Minimal disinfection capacity
Chlorine dioxide	Mixture of oxychloro species: (chlorite/chlorate/ oxychloro species, chlorine dioxide)	1-10 ppm ClO ₂ 100-200 ppm expressed as chlorine dioxide	<ol style="list-style-type: none"> 1. Strong oxidizing chemical 2. More tolerant of organic matter than chlorine 3. Less corrosive to stainless steel 4. Less pH sensitive 	<ol style="list-style-type: none"> 1. Sensitive to light and temperature 2. NIOSH recommended employee exposure limit to chlorine is 0.5 ppm ceiling for 15 minutes¹⁴

Table II
Chemical Sanitizers

Below are listed general types and uses, however, refer to manufacturers use direction included on material safety data sheets (MSDS)

<i>Type</i>	<i>Description</i>	<i>Suggested concentrations and contact times</i>	<i>Advantages</i>	<i>Disadvantages</i>
Peroxy-hydrogen peroxide	Peroxyacetic acid Peracetic acid	Refer to manufacturers instructions	<ol style="list-style-type: none"> 1. Low residue 2. Environmentally responsible 3. Broad spectrum - bacteria 4. Generally non-corrosive to stainless steel and aluminum 5. Relative tolerance to organic soil 6. Active at up to pH 7.5 7. Good activity against biofilms 	<ol style="list-style-type: none"> 1. Metal ion sensitivity 2. Corrosive to soft metals 3. Odor of concentrate 4. Varied activity against fungi 5. Corrosive and toxic only in concentrated solutions (>40%). 6. Potential of fire hazard.
Acid Anionics	Anionic surfactants and acids	Minimum 100 ppm	<ol style="list-style-type: none"> 1. Stable 2. Generally non-corrosive 3 Non-staining 4. Low odor 5. Not affected by hard water minerals 6. Removes and controls mineral films 	<ol style="list-style-type: none"> 1. pH sensitive (opt. pH 2-3) 2. Limited and varied antimicrobial activity (poor vs. mold & yeast) 3. High foaming
Ozone ¹⁵	Oxidizing gas	1-3 ppm; 30 minutes	<ol style="list-style-type: none"> 1. Powerful oxidizing gas 2. Broad spectrum activity 3. Fast acting 4. Deodorizes 5. Minimal handling 	<ol style="list-style-type: none"> 1. Unstable 2. pH sensitive (optimal pH 6-8.5) 3. Temperature sensitive 4. Corrosive 5. No residual 6. Must be generated at site 7. OSHA airborne exposure limit 0.1 ppm ozone

**Table III
Physical Sanitization Methods**

Type*	Description	Suggested concentrations and contact times	Advantages	Disadvantages**
Steam Heat	Water at 100°C	30 minutes Temperature must be reached at furthest point in system	<ol style="list-style-type: none"> 1. High product compatibility 2. Easy availability 3. Efficacious 4. Breaks down biofilm 5. Non-selective 	<ol style="list-style-type: none"> 1. Possible residues (boiler/pipes) 2. Excessive dwell time 3. High energy consumption 4. Condensation 5. High humidity
Hot Water	80° - 100°C (70° - 80°C)	30 minutes (2 hours)	<ol style="list-style-type: none"> 1. High product compatibility 2. Easy availability 3. Effective over long distances of pipes 4. Exit monitoring simple 5. Not corrosive 6. No residue 7. Non-selective to all microbial genera 	<ol style="list-style-type: none"> 1. Volume required 2. High energy consumption 3. High humidity 4. Condensation 5. Excessive dwell time
Direct Heat	Electrical heat tape	In combination with other methods	Effective for hard to reach equipment or piping (specialized or limited use)	Not for general use

* Heat may cause equipment damage by expansion of close-fitting and / or moving parts. Heat must be used with thermal stable materials

**Scalding water poses potential hazard.

reference to cationic surfactants chapter 10 of Phamaceutical Microbiology, page 225

reference to ozone May-June 1999 issue of the PDA Journal of Pharmaceutical Science and Technology, Vol. 53, No. 3, p 125.