AQUEOUS CRITICAL CLEANING: A WHITE PAPER

PRESCRIBING THE RIGHT METHOD OF AQUEOUS CLEANING IN PHARMACEUTICAL MANUFACTURING

According to FDA rationale, cleaning equipment is meant to be designed to "prevent contamination or adulteration of drug products". Typically pharmaceutical operations require transition from bench scale R&D to pilot studies to full-scale manufacturing. Each transitional stage requires careful consideration of changes to the processing equipment and cleaning techniques. In general, the size of the equipment gets larger as each stage is encountered. In this regard, manual and soak-cleaning procedures tend to be adequate for bench-scale equipment, whereas pilot and large-scale manufacturing process equipment usually requires clean-in-place (CIP) cleaning by automated spray or immersion systems and/or by manual cleaning. All stages of development and production may use manual cleaning or machine washers to clean various parts of equipment or utensils. If feasible, it is desirable to clean the pharmaceutical equipment in place without having to disassemble or move it in order to rapidly get the equipment back into service.

Automated Clean-in-Place (CIP)

Spray and immersion are two kinds of automated clean-in place systems used typically for cleaning pharmaceutical manufacturing equipment. In both these systems there is a primary water source that can be heated, if necessary, that is used to make up the cleaning solutions and as rinse water before and after the cleaning cycles. An external tank can be used for mixing up and storing the cleaning solutions, although sometimes the manufacturing tank is used for this purpose. A separate external tank for holding the rinse water can also be employed as well as a second source of water if the final rinse requires purified water such as water-for-injection (WFI) or deionized (DI) water. There will be pumps and piping connecting these external CIP tanks to the manufacturing equipment that needs to be cleaned. A water conservation system can be installed that pumps the final rinse water into the cleaning solution dilution tank in order to use that water for the first cleaning cycle in the next automated CIP run. There will be automated controllers to run the pumps and control the dosing of cleaning agent and water. These controllers can be full or semi-automated programs that require operator intervention at key steps in the process. There are often monitoring systems that assure that the process is being done according to the program and that all parts of the system are functioning correctly. The automated equipment has sensors and data recorders to assist with the documentation of the cleaning and can often create reports that will become part of the batch log to document that the cleaning was done correctly for regulatory compliance. Automated CIP systems can be permanently integrated into a set of manufacturing tanks, or they can be on mobile skids that are moved from tank system to tank system. Typically, the best results with automated cleaning are achieved when the automated CIP system is integrated into the original design of the manufacturing system. Often an

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existing tank must be retro-fitted with an automated CIP system. This retro fit can involve either spray CIP or immersion CIP systems.

Spray Clean-In-Place (CIP)

Spray CIP involves spraying or re-circulating the initial flush, wash, and rinse solutions under pressure, with proper adjustments of time, temperature, and cleaner concentration through the pipes and spray balls to clean large internal areas of the equipment without having to fill them completely with solution. Efficient cleaning of pilot and large scale mixers, tanks and blenders can be achieved by distributing flush, wash and rinse solutions on the upper surfaces at pumping rates equal to 2.0-2.5 gallons-per-minute (gpm) per foot of circumference for vertical vessels, or 0.2-0.3 gpm per square foot of internal surface for horizontal and rectangular tanks. Piping systems can be effectively cleaned via recirculation at flow rates producing a velocity of 5 feet per second or more in the CIP circuit's largest diameter piping. The advantage of spray CIP is that it can rapidly clean large pieces of equipment using minimal amounts of cleaning solution as well as minimal amounts of energy to heat the solutions and rinse water. The disadvantage of spray CIP is that it requires very careful engineering design to assure successful cleaning. If there are difficult-to-clean places that the automated system fails to clean, manual cleaning may be required. If a new difficult-to-clean product is made in production equipment that has a spray CIP system and it cannot successfully clean the new product, then possibly a new cleaning agent may be required or a change to immersion cleaning or manual cleaning may be necessary.

Immersion Clean-in-Place (CIP)

Pilot scale and smaller manufacturing tanks, blenders and mixers can be cleaned by completely filling all the pipes and equipment with cleaning solution, possibly while gently running any agitators available in the equipment. A successful validation of this cleaning process will define the concentration of the cleaner, the contact time, the level of agitation and temperature of the cleaning solution required to successfully clean the tank. This cleaning method is used in older large manufacturing tanks that do not have integrated spray CIP systems. The advantage of immersion CIP cleaning is that is simple and does not require a carefully engineered spray CIP system. The disadvantage is that it typically takes longer because the equipment, such as a mixer, would have to be filled, heated and drained rather than the faster cycles obtained by using much smaller quantities of cleaning solution as in a spray CIP systems. Additionally, only the areas that are in contact with the cleaning solution get cleaned and usually some manual cleaning of tanks and mixers on the areas above the fill line has to be performed.

Manual Cleaning

Manual cleaning can be done in-place on manufacturing equipment or at a sink or washroom where disassembled pieces of equipment, tools and utensils are brought for cleaning. Often brushes, abrasive pads, scrapers, buckets, spray bottles, or other

appropriate equipment is used for manual cleaning. A good manual cleaning procedure will specify any pre-rinsing, the cleaner concentration, the order which parts of a particular piece of equipment should be cleaned and the rinsing procedures. The advantage of manual cleaning is that it is relatively simple and the operator can give special attention to difficult-to-clean areas or residue until clean criteria is achieved. The disadvantage is that it can take longer, has the cost of human labor, and is very directly subject to human error.

Machine Washers

Machine cleaning is performed on clean manufacturing tools, disassembled equipment and bench-scale production equipment in clean-out-of-place (COP) procedures. A machine that is designed to meet Good Manufacturing Practice (GMP) requirements can provide rapid, reliable, validated cleaning while using minimum amounts of water, resources and space. Historically, "lab style" washers have been modified to conform to GMP requirements. More recently, washers have become available that meet GMP requirements with design features including:

1. A chamber that allows for minimal water retention and provides good drainage from cycle to cycle with a minimum of solution carried over in any inlet or outlet piping.
2. Corners that carry a minimum of a 1" radius and all surfaces are sloped to the drain.
3. Internal chamber structures have rounded edges with no threads or fluid entrapment areas.
4. No mechanical attachment required for the accessory racks with regard to the mating of inventory systems to the hydraulic circuit.
5. Spray headers are positioned on the top and bottom of the racks to provide the most efficient cleaning.
6. A documentation package to complete the validation and qualify the cleaning system.

A well designed machine washer requires GMP compliant procedures for best use. In this regard, a complete inventory of size, weight, and specific cleaning requirements for each part and equipment to be cleaned needs to be taken. Additionally, parts and equipment that need to be cleaned together have to be noted. Cumulatively, with this information, appropriate loading and unloading patterns can be established. The goal of a good loading pattern is to allow good spray and cascading solution contact and good drainage of the parts and equipment. Any opportunity for pockets of solution to fail to drain from parts or equipment in between wash or rinse cycles need to be eliminated. By designing multi-level loading patterns, efficient use of water, detergent and utilities can be achieved. Since loads for GMP cleaning can range from glass to plastic to stainless parts, the design of a loading surface should allow for varying weights. If horizontal drop-down doors are used in the washer, they can serve as both the integrated loading platform when open and can allow for better seals than vertical doors when closed.

Vertical doors typically require the use of separate loading carts. For these reasons, horizontal doors are often preferred.
Once good loading patterns have been established with proper racking, the pre-rinsing, washing, rinsing and drying cycles must be established. This involves selecting the correct cleaning agents, temperatures and time for each cycle. By knowing the substrates and residues that need to be cleaned, the correct cleaning agent can typically be determined. Typically a high alkaline cleaner followed by an acid rinse is used. Other important washer design features that should be taken into consideration at this point include that the delivery systems allows for precise application of additives and that a set-up of drying systems are in place that provide complete coverage of every part of a load. Once the appropriate parameters have been established, cleaning programs using the machine's Programmable Logic Controller (PLC) are set.
The advantages of using machine washers are faster cleaning of parts and equipment using less human labor, less space, less water and less cleaning agent than comparable manual cleaning. A disadvantage of machine washers is that they often require very special racks and correct loading procedures to assure reliable cleaning results on parts or equipment with complex geometry.

For Additional Help with Your Critical Cleaning Challenge

Alconox, Inc has 60 + years in developing aqueous cleaning solutions for pharmaceutical manufacturing and is able to help solve critical cleaning challenges.

Please contact the Critical Cleaning Experts at Alconox Validation Support or Alconox Cleaning Verification Lab for assistance.

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