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Practical CIP System Design

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Introduction

"Rules of thumb" are often used to determine the flow required for cleaning equipment and pipelines in the biopharmaceutical industry. These "rules" may conflict when the desire to maintain supply and return line velocities results in accumulating liquid in the equipment being cleaned. This article provides an overview of CIP as well as a basis for establishing the flow rate for equipment cleaning.

Purpose of CIP

Clean-In-Place (CIP) is the term used in the biopharmaceutical industry to refer to the process of cleaning process systems and equipment without major disassembly of components. In addition to cleaning, CIP also assists in Steam-In-Place (SIP) operations by removing chlorides and proteins. Leaving chlorides could cause stress corrosion when heated and residual proteins would be "baked" on to surfaces when denatured by steam.

CIP involves a specific combination of predetermined manual and automated operations to perform the cleaning, monitor the operations, and document the results. The state-of-the-art involves a series of dedicated CIP skids, each assigned to a particular process area or function, with its own piping system. Figure 1 shows a typical, but simplified, CIP system with the appropriate instrumentation and valves.

A properly designed CIP system will use the minimum amount of water, chemicals, and utilities, and produce the minimum amount of effluent. It will improve safety and reduce maintenance by removing human error and provide documentation for validation by ensuring reproducibility with minimal operator intervention. It will maintain product quality and reduce turn-around time between batches.

Time

Typical biopharmaceutical production operations are based on operating 24 hours per day seven days a week, commonly referred to as 24/7. CIP is only part of a typical 8-hour turnaround (from dirty to clean) cycle, which also includes SIP and the associated heatup, cool down, and integrity testing. The majority of the time is for heating and cooling before and after SIP, but the time for CIP is important in determining the number of CIP systems required.

Factory Acceptance Tests (FATs) typically test the effectiveness of spray balls through the use of a Riboflavin coverage test. This test ensures that the vessel internals are thoroughly wetted by the spray balls, but it does not ensure that the tank will be cleaned by the plant CIP system.

Fixed sprayballs can normally achieve successful coverage test results in 30-90 seconds based on a 15-20 GPM (3-5 m^3/hr) flow and a ΔP of 25 psi (1.7 bar) per spray ball (the number of spray balls is determined by total flow requirements and discussed later). The test is done by spraying a dilute (0.2-0.3 g /L) Riboflavin solution onto vessel internals, allowing the Riboflavin to dry, and then using the spray balls to remove the residue. After the desired time interval, the tank is inspected with a UV light to determine that the Riboflavin has been removed.

Ideally, the test would be successfully done at 15 GPM (3 m^3/hr) per spray ball and 30 seconds to allow for a safety factor and provide for the possibility of increasing the number of holes in the spray balls if the original drillings did not achieve the required coverage.

Because the basis of cleaning is the coverage test results, it's common to use a safety factor of 2-3 on the test time and use the same time for all steps in the CIP cycle. Based on six cleaning steps of 5 minutes each and an allowance for set-up, air blows, heating, and chemical additions, the time to clean a circuit containing a major flow path (tank) and a few minor flowpaths (dip pipe or transfer line) is about 90 minutes.

A thorough analysis of diversity is required to analyze all utility systems including CIP. A

process simulation is performed to determine simultaneous usages of utility systems to ensure that adequate water supplies are provided. The simulation is also used to determine the number of CIP units required to operate simultaneously which will affect both the diversity of operation and the instantaneous need for Deionized Water (DIW) and Water For Injection (WFI).

Temperature

If proteins are present, the pre-rinse should be done at ambient temperature to remove as much protein as possible without denaturation. Subsequent rinses and washes should be done at higher temperatures, typically 140-180°F to improve solubility of other types of contaminants. The temperature is typically raised with a sanitary steam-heated shell and tube heat exchanger.

Solution Concentration and Type

Except for the final WFI rinse, the rinses and washes will consist of ambient DIW. After the pre-rinse, the other solutions will be heated to 140-180°F. A detergent should be selected based on its ability to solubilize residue and the ease with which it can, in turn, be removed. The alkaline wash is usually made up to a 1-2% caustic concentration while the acid wash may have a slightly lower concentration of acid, typically phosphoric, to neutralize residual caustic and remove calcium and magnesium carbonate deposits.

Satisfactory cleaning results can be obtained using a fairly wide range of chemical concentrations. However, to use cleaning solutions of different concentrations, it will be necessary to validate their efficacy over the range of concentration expected.

Solutions can be made from commercially available (typically food grade) bases and acids or proprietary solutions can be purchased from firms specialized in cleaning biopharmaceutical equipment.

Surface Characteristics of Equipment

Historically, there has been disagreement as to the advantage of polishing compared to mill finish. The advocates of using mill finish maintained that microscopic scratches provide surfaces for protein and other contaminant adherence. Although this may have been true for mechanical polishing, this is not the case for electropolishing, where the sub-microscopic "scratches" are too narrow for contaminants to hide.

Internal Finish

Cleaning is a chemical rather than mechanical action. Since it's important to minimize surface degradation caused by mechanical forces and/or chemical action, sufficient, but not excessive chemical concentrations, temperature, and force are applied to the surfaces being cleaned.

The typical biopharmaceutical finish is approximately 15 Ra (Roughness Average) µ-in (0.38 µm) electropolished 316L SS. This is produced by mechanically polishing the mill finish to 25 Ra µ-in (0.6 µm) (max) surface roughness and then electropolishing. Electropolishing will both smooth the surface and reduce the differential between the microscopic peaks and valleys. After electropolishing, the surface roughness is typically reduced by 50% to 15 Ra µ-in, but smoothing of the peaks is more important than the actual Ra value.

In addition to finish, careful attention must be given to details such as dip pipes, agitator couplings, baffle attachments, and nozzle connections to eliminate pockets and dead ends, provide smooth, crevice-free joints, and make equipment self-draining.

Flow Rate/Turbulence

Tanks

Spray balls are quite effective for cleaning equipment such as tanks when properly designed for the particular application. Low-pressure spray is generally adequate since cleaning is performed by a deluge/cascade/soak (chemical) action and not by mechanical (impingement) force. The function of the spray balls is to distribute the washes and rinses to the top of the tank, wet all surfaces by a combination of spray and falling film, and allow the chemical action to take place. It may be necessary to add a removable spray ball at a low elevation to clean agitators, spargers, or side mounted nozzles located in the lower portion of a tank, but generally, top mounted spray balls are sufficient. The top spray balls should be located a minimum of 6" above the highest liquid level to avoid the possibility of process fluids entering the spray ball when not in use and plugging the holes. Although some manufacturers say they simulate a tank head and drill spray balls with holes directed at specific nozzles, off-the-shelf spray balls generally provide adequate coverage with approximately 1 spray ball for every 10-15 ft^2 (1-1.5 m^2) of cross sectional area.

Spray balls are typically sized for 15-20 GPM (3-5 m^3/hr) each and a 25 psi (1.7 bar) ΔP. Performance is generally based on a coverage test. The plan for coverage testing should be based on the lower flow rate to allow flexibility. If full coverage is not obtained during the test, additional holes can be drilled without affecting the allowed pressure drop. Increased pressure is not desirable because it may cause atomization, which would be detrimental as small liquid particles would need additional time to coalesce and produce a cleaning film on the tank walls.

It is best to operate multiple spray balls at the same time. Because of the flow-pressure characteristics of the centrifugal supply pumps, it is important to design all paths within a circuit for the same flow rate. This may require splitting the flow to spray balls. If this is the case, cycling between multiple paths should be performed at frequent intervals, say 30 seconds, to provide a reasonably consistent coverage of internals.

An estimate of the CIP flow rate for cleaning tanks is obtained by requiring a Reynolds Number > 2100 for the film of fluid running down the tank walls. *In Principles of Chemical Engineering*, studies show that with a given film viscosity, mass flow rate and wetted perimeter, Re_f is the same whether or not a cylinder is full.[1]

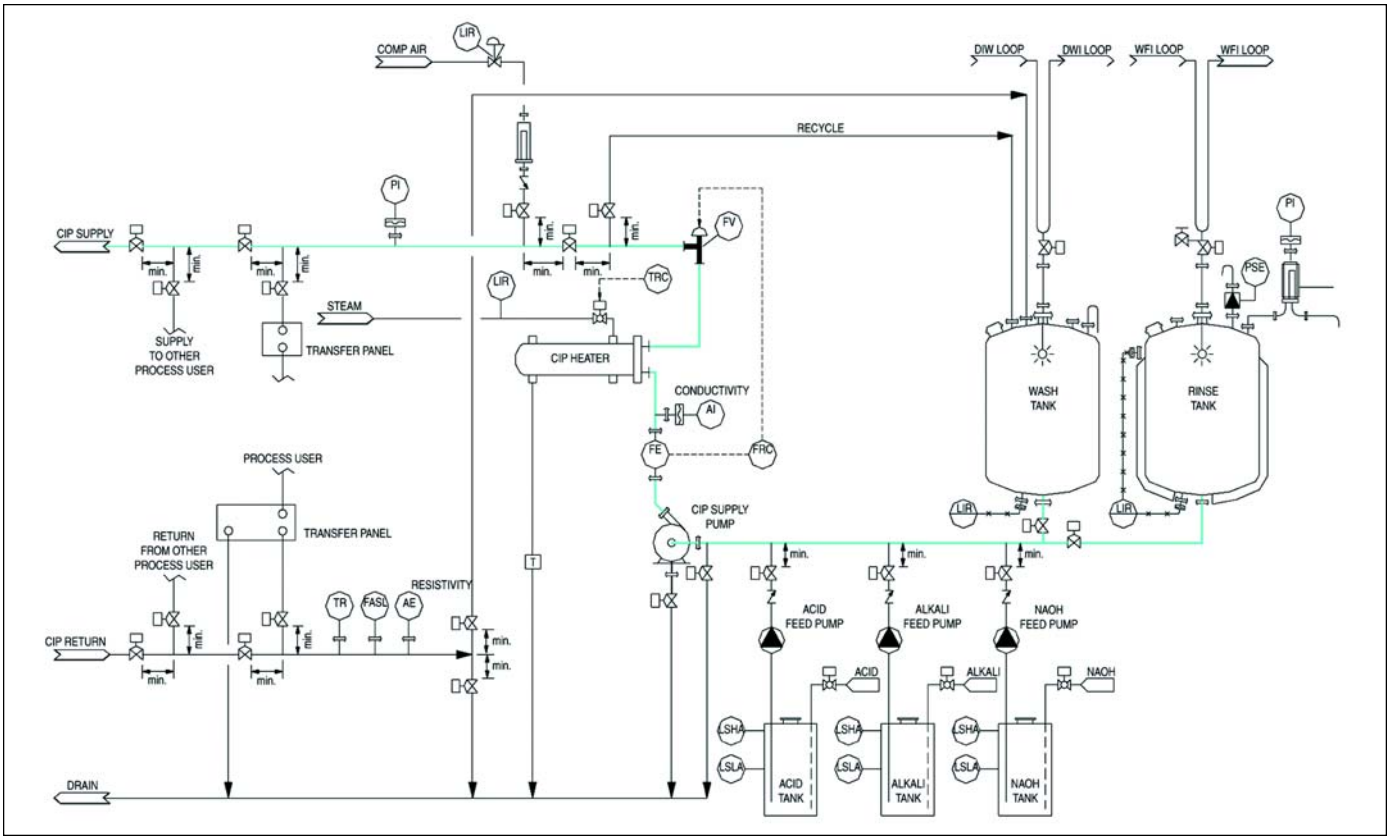

Figure 1. Typical CIP system.

$$V = \frac{m/\rho}{\pi D t} = \frac{m}{\rho \pi D t}$$

$$D_H = 4R_H = 4 \times \frac{\pi D t}{\pi D} = 4t$$

$$\mathrm{Re}_f = \frac{D_H V \rho}{v} = \frac{4tm\rho}{\rho \pi D t \times 0.000672\mu}$$

$$\mathrm{Re}_f = \frac{4m}{\pi D \times 0.000672\mu}$$

$$\mathrm{Re}_f = 5952 \frac{m}{W\mu}$$

where:

	D	Tank Diameter, ft
	D_H	Film Hydraulic Diameter, ft
	m	lb mass per second
	Re_f	Film Reynolds Number
	R_H	Film Hydraulic Radius, ft
	T	film thickness, ft
	V	velocity, ft/hr
	W	vessel circumference, ft
	μ	viscosity, cP
	v	viscosity, lb/ft-sec
	ρ	density, lb/ft^3

This equation can be rearranged and rounded to produce:

GPM / ft = 2.5μ or m^3/hr/m = 2μ

This relationship indicates that considerably less hot fluid is required, when compared to cold fluid, to achieve the same coverage. For example, water viscosity is 0.35 cP at 180°F (80°C) and 1.0 cP at ambient conditions. In terms of absolute values, a 7'-6" diameter vessel would require 25 GPM (5.5 m^3/hr) for a hot rinse and 75 GPM (17 m^3/hr) for a cold rinse.

Lines

Diffusion and convection are the controlling elements of cleaning kinetics and indicate that flow need not be turbulent to clean the straight portion of a pipe. However, turbulence will increase fluid movement to the surface where the solvent can mix and react with protein or other contaminants and also assist in moving the resultant mixture away from the surface.

For tube diameters > 1", a velocity of 0.5 ft/sec (0.2 m/s) is sufficient to achieve turbulent flow. However, other considerations may govern the selection of a suitable velocity. For example, the velocity must be greater than the saltation velocity to remove larger and heavier particles and high enough to entrain gas bubbles in case a portion of the line is not self-venting. The higher velocity in the main run of the pipe also provides better flow into dead ended branches for cleaning when maximum distance criteria are followed. Therefore, the traditional recommendation (not a requirement) of the 3A–Dairy[2] standard for a velocity of 5 ft/s (1.5 m/s) seems

"Historically, there has been disagreement as to the advantage of polishing compared to mill finish."

valid. This velocity should be based on the largest diameter when flowing through different diameter pipes or tubes in series, but if there is more than a one line size change, the circuit should be split to accommodate the different flowrates needed to achieve similar velocities.

Design for Cleaning

Piping

Threaded and flanged connections should not be used as contaminants can accumulate in the threads or the pace between flanges and gaskets. Ideally, the system should be completely welded.

Return lines should have as much slope as possible (preferably 2% but a minimum of 1%) to both encourage gravity draining and discourage air pockets from forming which would prevent cleaning fluids from reaching the surfaces to be cleaned. Pockets must be eliminated in design and fabrication by firmly supporting the lines to maintain the desired slopes.

Branches should join the return header with minimum dead legs.[3] Dead legs and pockets can retain dirt or even cleaning chemicals which will prolong the cleaning cycle or require additional rinse or wash fluids which increase both the plant effluent and the DIW and WFI usage.

Lines should be cleaned individually or in series. Do not attempt to clean lines in parallel since it is difficult to ensure that minimum velocities are achieved in each path and it might be possible for one path to backup into another and actually impede cleaning.

No permanent connections should be provided between CIP and the process: transfer panels, hoses, or mix-proof valves should be used to make and break connections. Use sanitary clamped connections at transfer panels and hoses: bolted for rarely opened and thumb screw for often opened.

Proximity switches or sanitary pressure gauges are used to confirm paths and prevent mis-operation and/or unsafe operation of the CIP circuit.

CIP Skid

The CIP skid normally contains a tank for rinse and chemical solutions. It also may contain a tank dedicated to WFI for the final rinse or WFI may be provided by a common tank to support several CIP skids. A circulating pump, heat exchanger, and chemical day tanks, along with piping and controls, complete the skid. Tanks should contain a means to disengage any air returned to the skid. Provide cleaning (spray) for CIP tanks since the tanks can be the dirtiest part of the system.

Return pumps can be mounted on the CIP skid if the skid is close to the process user(s), but this function is normally provided by pumps located close to the process equipment. The pump pressure and flow rate should be monitored to confirm circulation rate.

Tank Diameter	No. of Spray Balls	GPM	CIP Line Sizes	Tank Outlet Size
3′- 4′	2	40	11/2″	2″
4′-6′	3	60	2″	21/2″
6′ - 10′	4	80	21/2″	3″

Table A. CIP system design.

Filters

Since filters are hard to drain, it may be necessary to remove, and possibly discard, the cartridge for cleaning and then reinstall a new one before sterilization.

Accumulation

Equipment and lines should be free draining to avoid a "bathtub ring" effect. Even over-sized bottom nozzles and valves require a driving force of differential pressure to overcome dynamic losses. Return lines are typically undersized to satisfy the minimum velocity requirements. The result will be accumulation in the tank, and there is a possibility that dirt will accumulate at the air-liquid interface. Outlet nozzles and lines should be sized to minimize accumulation using valve data and appropriate engineering equations.

Accumulation or backup in a tank can be estimated by hydraulic calculations.[4]

$$h = \left(\frac{GPM}{19.636kd^2} \right)^2$$

Valve Characteristic

$$\Delta P = \left(\frac{GPM}{Cv} \right)^2$$

Combining these two equations and substituting k=0.61, the following backup is required to flow through a given valve and nozzle.

$$h = \left(\frac{GPM}{3.5d^2} \right)^2 + 28\left(\frac{GPM}{Cv} \right)^2$$

where

h = backup, in

d = nozzle diameter, in

If there is accumulation in the target tank, the supply tank may empty and stop the cleaning cycle until the accumulated

volume drains back to the supply tank. When this happens, the cycle time will be extended, adversely affecting the reproducibility of the cleaning cycle. Rather than increase the quantity of cleaning chemicals, which may require additional rinse volume and increase effluent quantity, the preferred approach is to remove the restriction at the tank exit.

The combination of sprayball and line size criteria results are shown in Table A.

The process tank can be pressurized to provide the head required to overcome resistance in the outlet nozzle and valve, but it is difficult to control the pressure to maintain the liquid level just at the outlet nozzle entrance. If the pressure is too low, accumulation will still occur, and if too high, there will be additional air entrainment, which will reduce the capacity of the return line and may interfere with cleaning.

There are some who suggest that starting and stopping the CIP feed pump can be used to remove accumulation, but this merely makes the accumulation move up and down the tank wall. It does not eliminate the problem. It also requires a sophisticated control system to keep track of the cleaning time if the system is continuously stopped and started. The solution is to use a return pump to overcome the resistance of the tank outlet.

CIP Systems

It is preferable to use a common philosophy for all CIP systems in a plant. This will avoid operational errors, provide consistent control system configuration, and maintain documentation format between CIP systems and users.

A once-through system is the least costly system from a capital cost viewpoint, but the most costly to operate because chemical solutions are made up, heated, then thrown away.

Systems use either a self-priming pump or an eductor to assist in returning and recycling washes and possibly some rinses to minimize chemical consumption, utilities, and effluent. Drainage also will be improved with return pumps located close to the process equipment. The final rinse may or may not be recovered to provide the pre-rinse for the next cycle. Figure 2 shows a typical CIP skid system which includes wash and rinse tanks, supply and return pumps, a heater, and all necessary, piping, instrumentation, and controls.

Eductor systems use eductors either alone or in combination with pumps to assist with recirculation and to make up the chemical solutions. They can pull vacuum and remove trapped air pockets and may be preferable to pumped returns since they can't lose prime. They also can provide more motive force than a pumped system as they do not have to contend with Net Positive Suction Head (NPSH) requirements. Still an eductor can vapor bind with flashing fluids or entrained air.

Pump systems using low-speed, self-priming pumps have higher flow rates and smaller diameter piping than eductor systems. They have an advantage over eductor systems in that they can be located at the target tanks to eliminate accumulation. Both pump and eductor systems will operate better at colder fluid temperatures because of the lower vapor pressure.

Multiple circuits fed from the same CIP system should be designed for the same operational flowrate. If both large and small equipment is cleaned using the same system with different flow rates, there is the likelihood that both minimum and maximum velocity criteria will be violated in the piping systems. Systems can be balanced by splitting spray balls so that they are utilized either individually, in pairs, or even two of three open at any one time to make all paths within a circuit use the same flow rate.

CIP Cycles

During each stage of a CIP cycle, each moving component should be operated in the same sequence as during normal operation. This includes valves, agitators, and pumps to ensure each fluid successively contacts all surfaces. Typically, each moving component would operate 5-6 times for 3-5 seconds during each step of the CIP cycle.

In order to minimize effluent and reduce chemical utilization, it may be possible to recirculate some portion of the rinses. Perhaps the rinse can be drained for 1/3 - 1/2 of the allocated time and then recirculated for the remaining time. In addition, the remaining rinse can be used as the starting point for caustic and acid makeups.

CIP systems both remove contaminants and prepare equipment for steaming. A discussion of the nature of "dirt" and the chemicals used to remove it is beyond the scope of this article, but a brief synopsis of the solutions for a typical mammalian cell culture process is shown in Table B.

Typical steps in a CIP cycle are:

Pre-Rinse

The pre-rinse uses either a fresh, clean, cool water (typically DIW) source, or reuses the previous final rinse. The pre-rinse is used to remove residual process fluid and debris. The fluid and temperature should be selected to avoid denaturation and precipitation of proteins. As noted earlier, this step might be once through followed by recirculation.

Recirculated Alkaline Wash

Residual rinse water could be heated and fed with caustic or

Figure 2. CIP skid.

Solution	Purpose
Water - 1st rinse	gross removal of contaminants
Base with Hypochlorite	Solubilize and denature proteins
Water - 2nd rinse	Remove base and debris
Acid	Neutralize base Dissolve mineral salts Passivate
Water - 3rd rinse	Remove acid and debris
WFI Rinse	Remove all remaining contaminants
Steam	Destroy pathogens

Table B. Chemical solutions form CIP/SIP.

other detergent to make up the alkaline (typically 1-3% caustic) wash. The step uses the alkaline wash to denature and solubilize the remaining proteins. Although denaturation increases the dirt load and makes proteins more difficult to remove, the bulk of the easy-to-remove proteins should have been removed in the pre-rinse step. If desired cleaning results are not obtained, this is the step which normally provides the most benefit from an increase in time.

Proprietary chemical cleaners are available for both alkali and acid washes. These mixes may contain a mixture of chemicals, detergents, chlorine, or other additives to improve the cleaning action.

Air blows are used after chemical washes to maximize chemical removal and make the succeeding rinse easier.

Hot Rinse

This rinse is used to remove the alkalinity and additional dirt. This step will not remove (solubilize) additional protein and may be recirculated or once through.

Recirculate Acidified Wash

If necessary, an acid wash is used to neutralize residual base, solubilize remaining dirt (inorganic), remove mineral deposits, and passivate the surface. It is sometimes omitted and it may be made up from the residual rinse fluid from the previous step.

Hot Rinse

Residual acid and any additional dirt loosened in the acid wash is removed with a hot DIW rinse. This rinse also may be recirculated.

Final Rinse

A final rinse with WFI removes traces of previous wash. It is monitored with pH, conductivity, or resistivity (compared to inlet) to ensure cleaning by measuring removal of chemical solutions. These variables will not detect protein residues.

Control

Some companies believe that it is easier to validate a manual CIP procedure because the control system is not involved in the validation procedure. However, current control systems, when properly implemented, have many advantages over a manual system and perhaps the ideal situation is a combination of manual and automatic control. It is important that the control system be easy to monitor, control, and validate.

Automated CIP is the most consistent method to achieve reproducible cleaning. The use of a control system will ensure that cycles, duration, and sequence objectives are achieved each time a CIP is performed.

The main control elements are time, temperature, and flow rate. Cleaning is usually verified by monitoring rinse conductivity. Measurements are made and recorded to verify that achievable tolerances consistent with the cleaning objectives are achieved. Typical operating tolerances of chemical solutions concentration is 1-3%, temperature accuracy should be within ±5°F (3°C), and a flow rate variation should not exceed ±10%.

The main function of the control system is to pulse valves and operate rotating equipment within a circuit with each rotating or moving component cycled 5-6 times during each step of the cleaning cycle. Communication with the process control system is essential to coordinate the cycling of pathways in the process circuit with the change in CIP steps to verify that the various operations occur for the desired time at the proper temperature and composition. Other control functions include chemical addition rate and concentration and temperature control.

Once a control system is employed, it is necessary to consider what action(s) to take in the event of a deviation. One potential deviation is an external requirement to stop the system because of a failure such as a hose leak. Another common problem occurs when low level occurs in one of the tanks on the CIP skid and the circuit must be put in recycle to avoid damaging the pump. The CIP system status can be considered as one of three or four states.

(a) Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality or purity of the drug product beyond the official or other established requirements.

(b) Written procedures shall be established and followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include, but are not necessarily limited to, the following:

(1) Assignment of responsibility for cleaning and maintaining equipment;

(2) Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;

(3) A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance;

(4) Removal or obliteration of previous batch identification;

(5) Protection of clean equipment from contamination prior to use;

(6) Inspection of equipment for cleanliness immediately before use;

(c) Records shall be kept of maintenance, cleaning, sanitizing, and inspection as specified in §§211.180 and 211.182.

Figure 3. 21 CFR Parts 210 and 211.

1. Normal - target circuit cycles valves to clean associated paths.

2. Makeup - main path in targeted circuit is open for heatup and chemical addition.

3. Hold - drain valves are closed to prevent loss of chemicals, valves are not cycled, and timer is paused in the CIP PLC until state is returned to normal. This state may be the same as makeup.

4. Abort - systems fail to pre-established safe position.

A control system should be used to validate cleaning. In addition to the controls already discussed, the system should provide for documenting the results of each cleaning operation.

Validation

CIP systems provide for reproducible uniform cleaning and minimize the possibility of human error. The cost of maintenance is reduced, down time is minimized, and operator safety is improved.

With proper documentation, the system can be easily and quickly validated to prove that the cleaning was effective and cleaning agents have not been introduced into the product.

In order to validate a CIP system, written documentation is required to define the procedures for cleaning each piece of equipment, circuit, and flow path. Additional procedures are required to quantify the cleanliness required by the process, a means to measure the cleanliness or residue, and an analytical method to confirm the measurement results. The protocol which describes the validation procedure for CIP must be reviewed, approved, and executed by technically competent personnel.

Figure 3 is an excerpt from 21 CFR-Parts 210 and 211.[3]

Conclusion

Proper implementation of CIP seems to be a mixture of art and science. There is nothing wrong with using empirical relationships provided they don't conflict with good engineering practices. A well-designed CIP system can achieve minimum flow velocities in both supply and return lines without accumulating fluid in the tanks being cleaned. A combination of properly designed outlet connections and return pumps can be used to achieve the desired results.

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About the Author

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