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CIP in Freeze Drying

During the freeze drying process particulates can be spread onto the freeze dryers internal surfaces. The internal surfaces can be manually cleaned by hand wiping surfaces with water and/or alcohol which also provides some sanitation while cleaning. The validation of manual cleaning can be difficult, so a method of Clean In Place may be requested which is more repeatable and can be more easily validated.

As a concept, Clean In Place is the ability to rinse the inside of the freeze dryer via spray of liquid. CIP systems are designed for the specific application and vary greatly in complexity. The intent of the process can range from simply rinsing surfaces to remove residual material through the spray action to performing a scrub and sanitization using detergents and multiple rinse cycles.

Clean In Place is performed by spray nozzles mounted on manifolds inside the chamber. A typical spray nozzle requires 40 PSI at 1 GPM. To keep the flow requirements to reasonable levels, a zone will typically contain no more than 40 nozzles, for a flow requirement of 40 GPM. Small systems may use 20 nozzles, while large systems may use over 200 nozzles.

CIP cycle designs take the following into consideration:

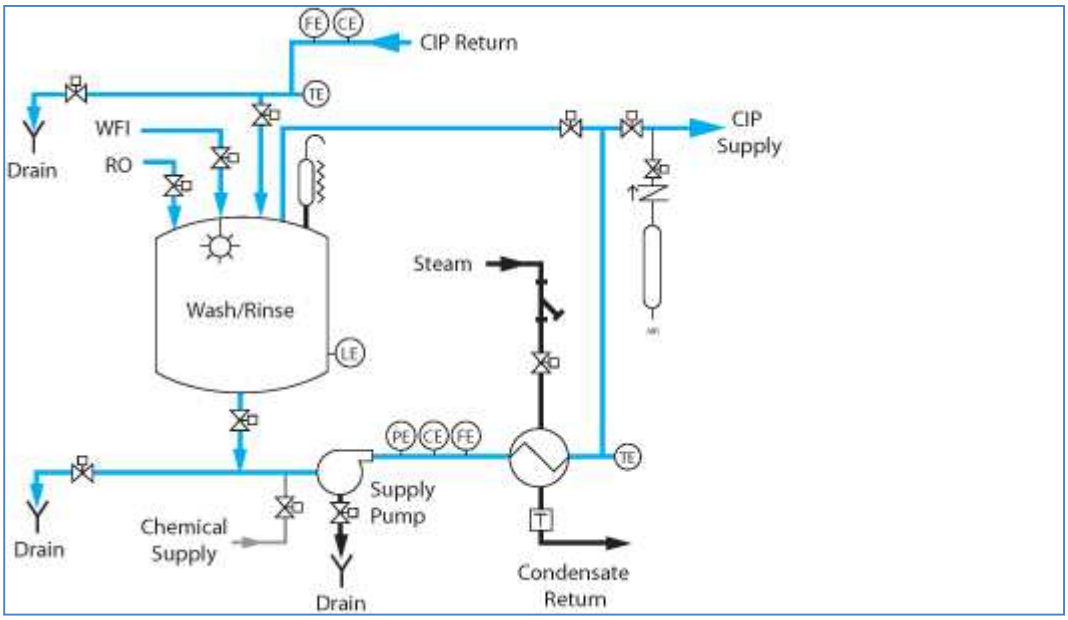
- Type of material for the rinse
    - De-I Water
    - WFI
    - Detergent
    - Caustic and Acid
- Rinse time
- Temperature of rinse
    - Steam or electric heat
- Single pass or recirculation
- Sensing and monitoring
- Manual vs Automation

The simplest CIP system uses potable water to rinse the internal surfaces, washing the materials toward the drain. The amount of water used depends on the number of nozzles required to cover all the surfaces inside the chamber(s). If available, De-I or WFI water can be used.

The system is sized based on the flow rate and time required to cover all the surfaces. For systems with a small required, an external skid may not be required. CIP may simply use the city water supply at 10GPM and 40PSI. If the water supply does not have sufficient flow and pressure, then a storage tank is required. The storage tank can be sized by calculating the amount of water required. If there is a strong supply of make-up water, then the storage tank size may be reduced.

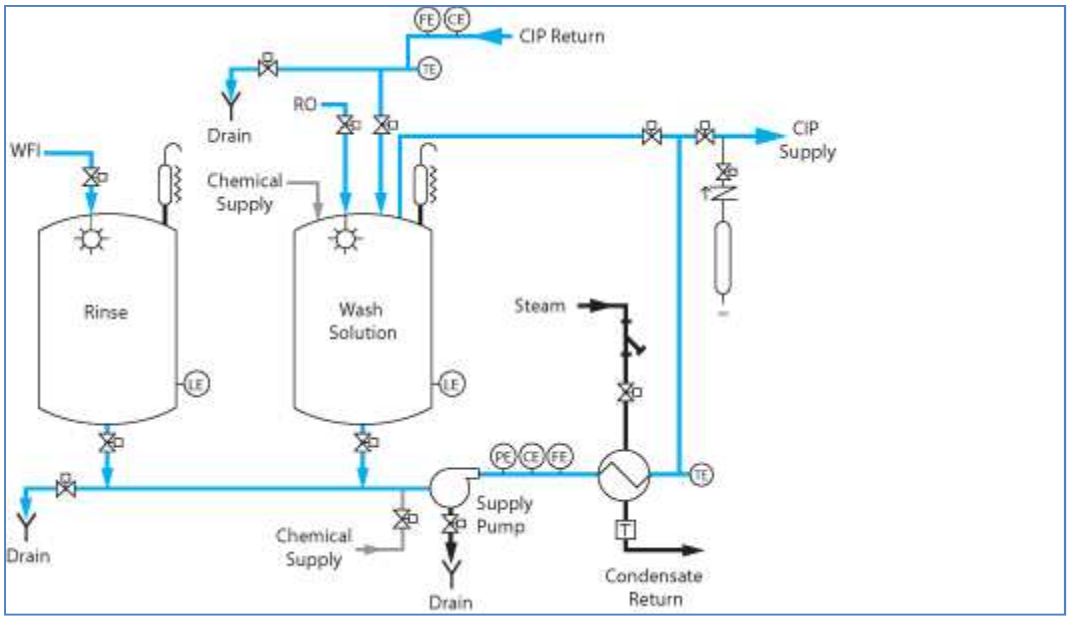
For example, a CIP cycle that requires 20 GPM for 10 minutes would require a 200 gallon tank. If the make-up water is 10 GPM, then the storage tank could be 100 gallons, since the make-up water during the cycle would be 100 gallons.

Using a storage tank offers the opportunity to heat the water. Hot water is more effective than cold water and will dry faster.



Single Tank Example – Courtesy of Sani-Matic

A complex CIP system will provide a potable water pre-rinse (70-145 F), warm detergent wash (70-145F), potable water post rinse, hot De-I or WFI (85 C) post rinse and a system blow-down. The temperature of each step is controlled and the conductivity of the water can be monitored. A complex control system will include full PLC automation with 21 CFR Part 11 compliant operation.



Multi-Tank Example – Courtesy of Sani-Matic

CIP systems are very effective in covering the majority of surfaces, but only reasonably cover 95-98% of the internal surfaces. Larger chambers are more difficult to cover and 95% coverage may be a reasonable expectation. Validation of coverage is performed by spraying the internal surfaces with riboflavin, cycling the CIP system, then inspecting the system using an ultra violet black light to see if there is any residual material visible.

CIP is typically used on steam sterilizable system. The CIP process is executed prior to the steam cycle. The steam cycle raises the temperature of the chamber to a point that allows drying to take place.

In systems that are not steam sterilized, drying after CIP is a lengthy process. The method of drying is selected based on the cost versus the required turn-around time. If a fast turn-around time is required then a liquid ring pump is the best method.

The following methods aid in post-CIP drying:

	Method	Advantage	Disadvantage	Comment
1	**On systems with stoppering, raise the shelves to squeeze off any water on the horizontal surface**	No cost		Performed with doors closed.
2	**Wipe the internal surfaces manually**	Low cost	Requires labor	
3	**Open the chamber doors and allow the system to dry naturally.**	No cost	Long drying time	Acceptable if the time between cycles is long
4	**Raise the shelf temperature and condenser temperature to 60C. The condenser must have hot-gas defrost capability to attain 60C**	No cost	Electrical costs	Combine with 1, 2, and 3.
5	**Air blow-down via the CIP nozzles**	Low cost		Doors closed and drain open. Make sure the chamber can't build up a positive pressure
6	**Raise the temperature of the CIP rinse water to 80C. This will heat the internal surfaces and allow faster evaporation**	Speeds the drying process the most	Requires a CIP skid with electric or steam heat. Generally expensive.	If a storage tank is used, the water may require circulation.
7	**Use a liquid ring pump to pull a vacuum on the system**	Speeds the process	Additional cost. Consumes large amount of water.	The best method and can be combined with 4 and 6.