Principles of Steam-In-Place

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Steaming-in-place (SIP) is a widely adopted method for the in-line sterilization of processing equipment. The main advantage of SIP relies on manipulation reduction and aseptic connections that might compromise the integrity of the downstream equipment.

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Adequate configuration of steam-in-place (SIP) systems is vital and must be considered at the early conception stage of the plant. The critical requirements associated with SIP include proper steam distribution, noncondensable gases removal, and continuous condensate elimination. Good engineering practices, adequate piping design, steam traps, valves, and monitoring instrumentation are essential to ensuring SIP validation.

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Gas filter engineering

System design, installation, and standard operating procedure. Vent filters are required for the sterile introduction of air or nitrogen during and after the process of vessel sterilization. Gas filters are made of hydrophobic materials such as PTFE to prevent blockage by humidity during use. Therefore, condensate may accumulate on the membrane during SIP and produce blind filters. In such circumstances, the steam no longer passes through the membrane, leading to incorrect sterilization. The filter housing must there-

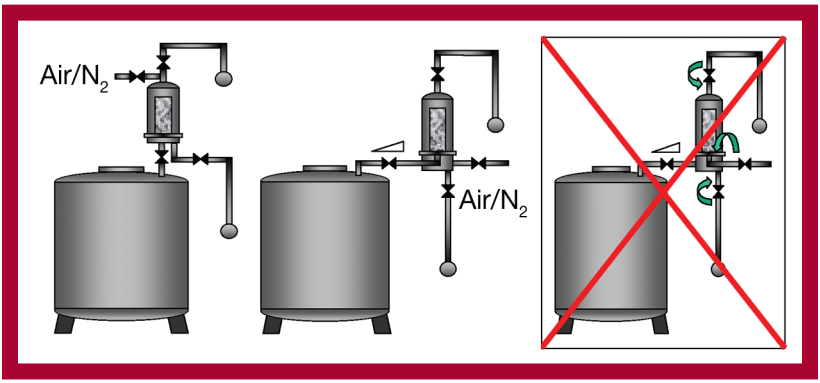

Figure 1: (Left) In-line vent filter housing, where downstream condensate is drained by gravity to the vessel. (Middle) T-type gas filter housing in which a slope must assist condensate drainage to the tank. (Right) Incorrect set-up.

fore be designed and installed for correct drainage of condensate, with the inlet sterile side of the cartridge fitted on the sterile vessel. This setup is preferred, since the housing closure as well as the connections to vent and drain valves may present risks of leakage on the upstream side of the filter. A reverse mounting would result in the filter bypass and would compromise the equipment's sterility.

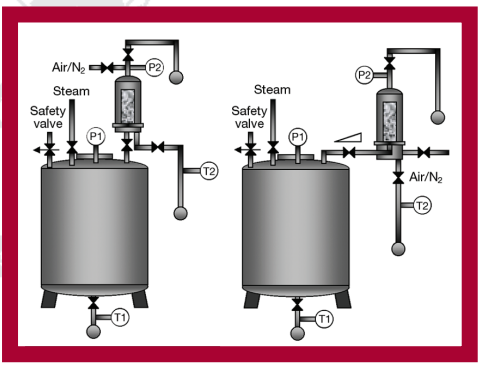

Figure 2: Reverse steam sterilization of vent filters along with the associated vessels.

Figure 1 shows the correct installation of a vent filter. The in-line design of the housing allows the drainage of downstream condensate from the vertical connection to the vessel. The T-type housing needs a fall on pipework to ensure condensate drainage to the vessel. In both cases, the upstream condensate is eliminated through a steam trap fitted on the drain port of the housing. A thermostatic steam trap also must be installed on the top of the filter to evacuate noncondensable gases during the sterilization cycle. This ensures the penetration of steam to all filter assembly extremities.

In most cases, vent filters are steam-sterilized along with their associated vessels (see Figure 2). Because large amounts of steam are required to start the SIP cycle, heat the system and remove non-condensable gases, it is better to introduce

steam into the vessel first, and then sterilize the vent filter with a reverse steam flow. This procedure is preferred to a forward steam injection, from the filter to the tank, because it limits the steam flow rate. It also avoids high differential pressure over the filter and prevents contact with superheated steam. The reverse steam flow through the filter is reduced significantly, because it only compensates for condensate eliminated by the steam traps opening upstream of the filter assembly. Reverse steaming is safe if using a locked filter.

As shown in Figure 3, some installations such as water for injection (WFI) tanks or fermenters may require separate vent filter sterilization to allow their replacement without re-sterilizing the vessel. All configurations require the installation of a pressure-relief safety valve as well as pressure gauges upstream and downstream of the filter. This ensures that the reverse differential pressure does not exceed specifications throughout the SIP procedure. Temperature probes are located in the coldest points of the filter assembly and the vessel (*i.e.,* the drain points) to monitor the SIP process. Adding steam traps downstream of the bleed valves allows condensate removal, reduces the steam flow rate, and minimizes the pressure differential across the filter.

Flushing noncondensable gases and heating the system. Before starting the SIP cycle, it is important to check the leak-tightness of the system. A five-minute pressure hold

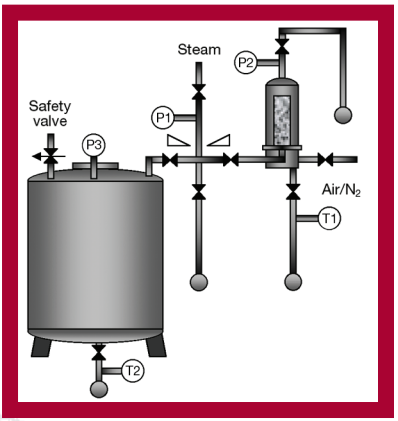

Figure 3: Separate filter and vessel sterilization. This configuration allows three different SIP procedures—separate filter sterilization in the case of replacement, vessel sterilization only, and simultaneous filter and vessel sterilization.

test is conducted at 2 barg pressure.

Superheated steam will be present at the beginning of the sterilization cycle because of high velocity and sudden steam expansion into the tank. Therefore, it is better first to admit regulated saturated steam into the tank and then maintain the isolated filter. All the bleed valves on the vessel must be open to ensure removal of condensate and noncondensable gases. The duration of this operation depends on the size of the equipment and is established during the validation of the SIP cycle. When the drain temperature reaches 110 °C or the tank pressure is approximately 0.5 barg, the valve is open to the filter and the steam quickly rises, and heats the filter housing.

Eliminating all noncondensable gases normally requires flushing the

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system with 10 volumes of saturated steam, which might take between 5 and 20 min. The maximum amount of condensate is generated at the SIP start because of the high temperature difference between steam and the heat transfer equipment. Steam traps shut automatically once the steam exits the drain and vent valves and indicates that air and condensate have been removed. This limits the steam flow and allows the system to be increased and maintained at the desired sterilization temperature. Steam traps will open intermittently to evacuate condensate and allow replacement with fresh saturated steam. For manual SIP systems that may not include steam traps, the bleed valves must open progressively to avoid excessive pressure differential when steam flows through the filter. The bleed valves remain cracked open during the SIP cycle to eliminate condensate and adjust the flow rate across the filter.

Sterilization cycle. Once the monitoring temperature probes located in the slowest heating points of the system (generally the vessel and filter drains) indicate the set sterilization temperature, the SIP plateau begins and continues for the required time period defined by the validation study. The pressure differential over the filter must not exceed 70 mbar during the entire sterilization cycle to maintain the filter integrity. Both pressure and temperature should be monitored to ensure that saturated steam conditions are met. The theoretical saturation temperature calculated from the actual pressure should be in the range of ± 2 °C from the actual temperature, as accepted by the European standard EN 285. A current industry practice checks for both pressure and temperature during the validation and uses tighter acceptance criteria for the deviation (± 1 °C). Provided that routine SIP operations are implemented using the same validated SOP, only the temperature is monitored. This is acceptable because equipment SIP processes generally involve numerous sterilization conditions.

Automatic SIP can be regulated directly or indirectly via a steam inlet control valve. Another possible regulation simply involves accurate pressure regulators for the inlet steam and steam traps at the draining points. During SIP, condensation spontaneously draws fresh saturated steam and energy at the points where it occurs, and the sterilization temperature is maintained at the set value. For manual procedures, the steam flow and pressure differential are regulated via the manual steam supply valve and the bleed valves, which remain cracked open. Air and condensate are eliminated continuously through the open bleed valves during the SIP cycle.

Venting steam, drying and cooling. Upon SIP completion, it is necessary to release the steam pressure and remove residual condensate from the lowest drain points of the system. This step is critical because steam condensation can create vacuum and compromise integrity. A mole of

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saturated steam at 121°C occupies a volume of 15 L, whereas the same mole of condensate only occupies 18 mL. Condensation must be compensated by sterile gas, such as air or nitrogen. Sterile compressed gas pressurizes the system and completely purges the condensate through the bleed valves. The maintenance of sterility is ensured as long as the pressure gauges indicate a positive reading in all parts. This operation also allows the cooling of the equipment and filter, which is critical when post-SIP integrity testing has to be performed.

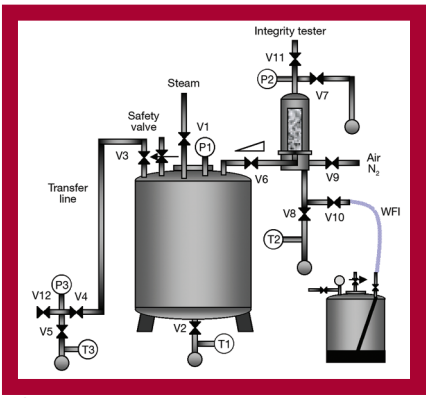

Figure 4: System designed for SIP and integrity testing of vent filter.

Integrity testing the vent filter. Post-SIP integrity testing of the vent filter increases the level of sterility assurance. Integrity testing must be performed without compromising the sterility of the downstream equipment. This is achieved easily by the water-based testing method (see Figure 4). Because water flow through an integral filter is minimal, it can be used in place after SIP. In-line integrity testing of the filter before the process avoids potential time loss and rejected product caused by a damaged filter. The sterilizing vent filter then is used for aseptic compensation of liquid movements in the tank or for product transfer. Post-use testing also is required to ensure that the filter was not damaged during the manufacturing process.

Liquid filter engineering

System design, installation, and standard operating procedure. The ability to wet hydrophilic filters makes their sterilization easier because condensate can pass through the membrane along with the steam and reduce the occurrence of blind filters. Conversely, the hydrophilic nature of product filters makes pre- and post-SIP drying difficult. Water-wet filters do not allow air passage when the pressure is below the bubble point pressure (typically 3.6–4 barg).

Polymer materials used for fabricating hydrophilic filters do not exhibit high thermal conductivity and are good insulators for heat transfer. Furthermore, the air entrapped in the polypropylene support layers, the microporous membrane and the pleated structure of the filter acts as a barrier to the heat transfer process.

The filter system must be equipped with appropriate vent and drain valves as well as designed and placed in the upright position to properly remove air and condensate. These

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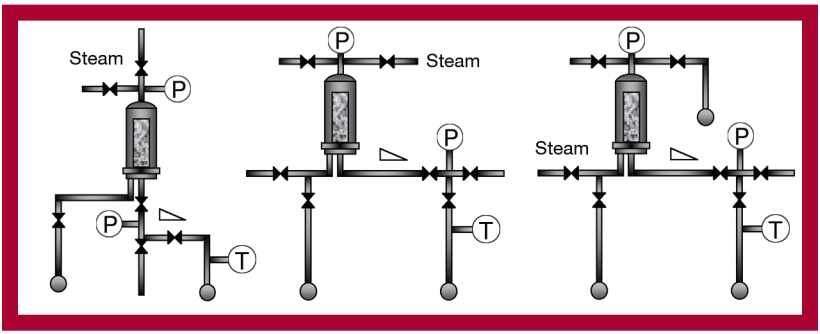

Figure 5: (Left) In-line filter housing. (Middle) T-type filter housing. (Right) T-type filter housing equipped with a steam trap on top for air evacuation.

valves permit a continuous steam flow during SIP and eliminate potential dead flow areas.

Figure 5 depicts possible filter configurations. The in-line housing design allows the downward evacuation of air and condensate through the vertical connection to the downstream thermostatic steam trap. The T-type housing needs a fall on pipework for condensate drainage. If the steam is supplied from the product line, a thermostatic steam trap must be installed on the top of the filter to evacuate air and ensure that steam penetrates all filter assembly extremities. In all cases, the upstream condensate is eliminated via a steam trap fitted on the drain port of the housing.

Liquid filters should be sterilized in the forward direction (separately from their associated downstream equipment) to reduce the steam expansion volume at the beginning of the SIP cycle. Such a procedure will limit superheat effects and reduce the steam flow rate over the filter. Pressure gauges are required upstream and downstream of the filter to control the differential pressure. Temperature probes are located in the drain point downstream of the filter assembly to monitor the set temperature. The addition of steam traps and downstream bleed valves allow condensate removal and reduce both the steam flow rate and the pressure differential across the filter.

Sterilization cycle. If the filter was integrity tested before sterilization, it must be dried with pressurized air or nitrogen to provide a path for subsequent steam flow-through. It cannot exceed the maximum pressure drop of 0.35 barg across the filter.

Water present in the steam line at the beginning of the sterilization cycle first must be purged upstream of the filter to avoid wetting and subsequent blocking. The bleed valves on the filter are open to ensure condensate and air removal. Once the temperature probe indicates the set sterilization temperature, the SIP cycle begins and continues for the required time defined during validation. The pressure differential over the filter must not exceed 350 mbar to maintain the filter

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integrity. Both pressure and temperature are recorded to ensure that saturated steam is present in the system.

Automatic SIP is regulated via the steam inlet pressure reducing valve and steam traps. Manual procedures are regulated via the manual steam supply valve and downstream bleed valves. The bleed valves must be opened progressively to avoid excessive pressure differential as well as eliminate air and condensate.

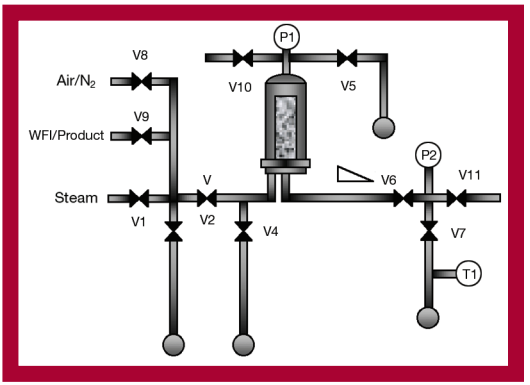

Figure 6: SIP and post-SIP integrity testing of liquid filters.

Drying, cooling, and integrity testing the filter. After SIP, the steam supply valve is closed and compressed air or nitrogen is admitted to the system for cooling and drying the filter. Quick drying is obtained with both the gas flow and the high temperature of the system. As required by the European Commission's Good Manufacturing Practices Guide, filter-integrity testing must be performed after sterilization but before the process (1). This operation can be performed without compromising the sterility of the system by using the set-up depicted in Figure 6. In most cases, water cannot be introduced into the system because of subsequent product dilution. Using the product as the wetting medium enables filter integrity testing after steaming and avoids time loss and rejected product resulting from a damaged filter. Post-use testing also is required to ensure that the filter has remained integral during the entire manufacturing process.

Conclusion

Steaming-in-place (SIP) is the preferred method for sterilizing processing equipment, including vessels, valves, process lines, filter assemblies, manifolds, and filling nozzles. The confirmation of a well-designed and engineered filtration system is the ability to validate the SIP cycles using thermocouples and biological indicators. Following the design and engineering rules detailed in this article will simplify both the validation and ongoing operation of filtration systems in aseptic processing.

Reference

1. European Commission, "Guide to Good Manufacturing Practice. Annex I, Manufacture of Sterile Medicinal Products" (European Commission Enterprise Directorate General, Brussels, Belgium, 1997). **PT**

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