TECHNICAL BRIEF

Steaming-in-place and integrity testing of a sterilizing-grade filter assembly

Principles of Steam-In-Place

Steaming-in-place (SIP) is a widely adopted method in the pharmaceutical industry for the in-line sterilization of entire processing equipment such as vessels, valves, process lines, and filter assemblies.

SIP provides a very effective, safe and convenient form of sterilization easy to automate and validate. The main advantage of SIP relies on the reduction of manipulations and aseptic connections that might compromise the integrity of the downstream equipment. SIP involves the use of specific components such as steam traps, pressure regulators and sterilizing vent filters to evacuate air and condensate, and to cool down, dry, and maintain the sterility of the equipment following sterilization.

Engineering Considerations

Adequate configuration of SIP systems is vital and must be considered at the early conception stage of the plant. The critical requirements associated with SIP are the proper steam distribution, the removal of non-condensable gases and the continuous elimination of condensate. Good engineering practices, adequate piping design, steam traps, valves and monitoring instrumentation are essential to ensure that SIP validation is easy to achieve.

Steam Trapping

A steam trap is a self-actuating automatic device which opens in contact of condensate, and shuts in the presence of steam. Steam traps offer the possibility of discharging both air and condensate. There are three types of steam traps available, mechanical, thermostatic, and thermodynamic, which exhibit different characteristics (see Table A). For the steam sterilization of aseptic equipment, good venting properties

Type	Mechanical	Thermodynamic	Thermostatic
Function mode	density	velocity	temperature
Resistance to blockage	good	poor	good
Cleanability	fair	poor	excellent
Resistance to corrosion	poor	good	good
Air venting capability	good	poor	excellent
Failure mode	closed	open	open
Applications	Steam generators Stills, large vessels Heat exchangers	Distribution WFI systems Steam separators	Autoclaves Process vessels Fermentors

Table A: *Current steam trap operating characteristics*

MILLIPORE

are critical to promote quick temperature rises and complete air removal, and hence ensure an effective sterilization.

- Mechanical traps operate on the density difference between steam and condensate by means of a float or bucket actuating the valve. Float traps usually incorporate a thermostatic air vent to allow for air discharge. This type of trap is suitable for generators, stills, heat exchangers and large vessels because they present excellent air venting capabilities and quick continuous type of discharge.
- Thermodynamic traps detect velocity difference between steam and condensate by means of a disc which closes under high velocity of steam, and opens to lower velocity of condensate. Thermodynamic traps should not be used on aseptic equipment because their small passage design induces product retention and eventually complete blockage. High air velocity during air removal could cause the disc to shut. Since air does not condense the traps cannot re-open. In fact, their robust construction makes them more suitable for steam distribution lines, where they are continually exposed to steam, and WFI systems.
- Thermostatic traps detect temperature difference between saturated steam and condensate. The valve is open when the sensor is exposed to temperature below the saturation temperature to discharge air, condensate and air-steam mixture (see figure 1). The most commonly used balanced pressure thermostatic traps are operated by fluid evaporation. The water-alcohol mixture contained in the thermostatic trap capsule evaporates at a temperature below the steam saturation temperature and then closes the valve. They are the best choice for aseptic process applications.

  They are excellent air vents and discharge condensate and are close to steam temperature, preventing condensate back-up. They offer self-draining design, and excellent cleanability.

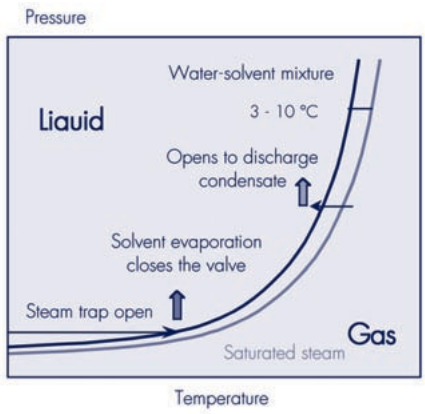

Figure 1: *Response curve of balanced pressure thermostatic steam traps*

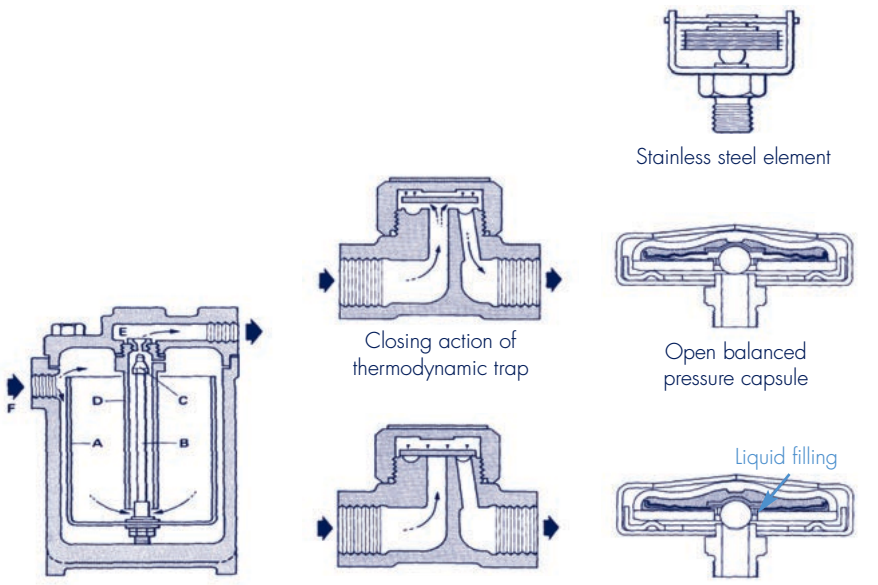

Figure 2: *Steam trap designs.*

Condensate Systems

Condensate drains must be designed to avoid back flow into the sterilized equipment. This condensate back flow may occur when the system is cooled down after steaming. It is necessary to discharge the condensate via individual trapping lines as illustrated in figure 3. Additionally, air breaks should be installed to avoid siphon formation upon cooling. Preferably, condensate may be eliminated outside the clean room. In pharmaceutical processes involving the use of path-ogenic organisms, condensate is collected in a kill vessel for subsequent decontamination.

Distribution System

Air and condensate must be continually drained off by means of thermodynamic steam traps located at intervals of at least every 30 meters of pipework. Appropriate steam traps must also be installed upstream of control and isolation valves, and at the bottom of vertical risers. The horizontal distribution lines must be sloped in the direction of the flow with a gradient of at least 1/100. Condensate is then drained from steam traps using gravity and air breaks as shown in figure 4. The sizing of the distribution lines is also important, and should produce typical pipeline velocity of 20 to 30 m/s. Steam must be supplied at the correct pressure, the proper velocity and through the correct pipework size, as indicated.

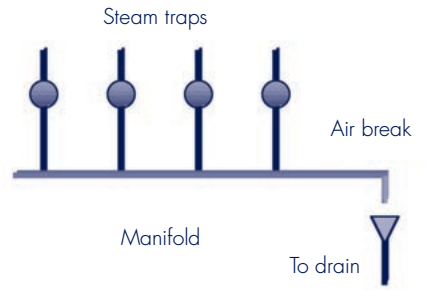

Figure 3: *Condensate system with individual trapping lines and air break.*

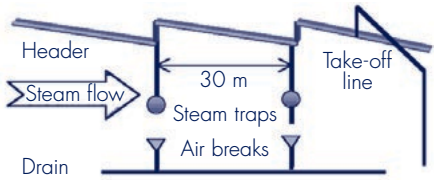

Figure 4: *Condensate discharge in distribution lines.*

Design of distribution systems

1 – Adequate piping fall 1/100 in the direction of steam flow
2 – Individual condensate legs with same diameter as header
3 – Never group steam traps
4 – Air breaks: 2 times pipe diameter
5 – Steam velocity 20 – 30 m/s

Pressure	Velocity	Steam flow rate in kg/h vs piping size in mm								
in barg	in m/s	15	20	25	32	40	50	65	80	100
0.5	20	10	20	32	57	77	126	216	301	513
	30	16	30	47	85	116	189	324	451	770
1	20	14	26	41	74	101	165	282	393	672
	30	20	39	62	111	152	248	424	590	1008
1.5	20	17	32	51	91	125	203	348	485	827
	30	25	48	76	136	187	305	522	727	1241
2	20	20	38	60	108	148	241	413	575	983
	30	30	57	90	162	222	362	619	863	1474
3	20	26	50	79	141	194	316	541	754	1287
	30	40	75	118	212	291	474	812	1131	1931
4	20	32	62	97	174	240	390	667	930	1588
	30	49	93	156	262	359	585	1001	1395	2382
6	20	44	85	138	240	324	536	917	1277	2181
	30	67	127	200	359	493	804	1375	1915	3271

Table B: *Steam flow rate in stainless steel pipeworks in function of pressure and velocity*

It is almost impossible to produce and distribute dry steam because water aerosols are entrained by the steam flow in the steam generator, and in the distribution lines where condensate is always present. The dryness fraction obtained with current industrial generators is normally 95%. That means that 5% of water aerosol is present in steam. Wet steam contains less heat than theoretical dry steam. The actual total heat of steam produced at 4 barg, with a dryness fraction of 95%, must be re-adjusted using the following equation (see table C):

Total Heat=(153 + (0.95 X 504))= 632 kcal/kg < 657 kcal/kg.

Wet steam has therefore less energy than dry steam. Since moisture will reduce steam temperature and its latent heat of condensation, it is recommended to dry steam before its distribution to the points of use. A first way to increase the dryness fraction of steam is to operate the steam generator below its normal capacity, and at elevated operating pressure, in the range of 3 to 5 barg.

Then, steam separators must be installed downstream of the generator, and directly upstream of the points of use to remove droplets of condensate entrained with the steam flow in the distribution lines.

Finally, reducing the pressure of wet steam at the point of use is very effective to increase its dryness fraction (see figure 5). As shown in the saturated steam table, the total heat of steam decreases when its pressure drops, and the difference of energy obtained by steam expansion is used to re-vaporize water aerosols. As an example, if steam is distributed at 4 barg with a dryness fraction of 97% downstream of the separator, its total heat is:

(153 + (0.97 X 504)) kcal/kg = 642 kcal/kg
When the pressure is reduced to 1.5 barg, the total heat still remains at 642 kcal/kg. It's new dryness fraction at 1.5 barg is then: (642 – 128)/521 = 99%.

Reducing steam pressure is an easy way to dry steam but could also produce superheated steam. As a rule of thumb, absolute pressure drops should not exceed a ratio of 2 in order to avoid superheat.

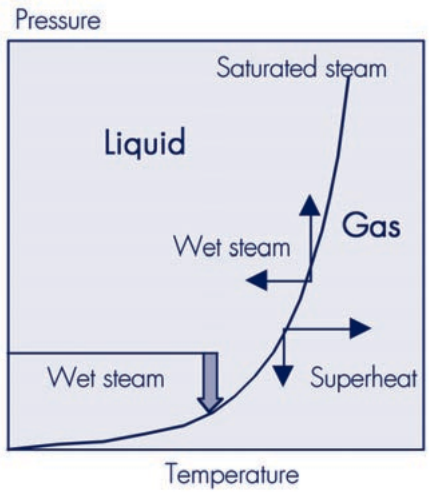

Figure 5: *Drying of wet steam by reducing its pressure of constant temperature.*

Pressure in barg	Pressure in bar A	Sensible heat in kcal/kg	Latent heat in kcal/kg	Total heat in kcal/kg
1.5	2.5	128	521	649
4	5	153	504	657

Table C: *Saturated steam properties at 1.5 and 4 barg*

Producing and distributing steam at higher pressure brings the following advantages:

1 – Steam generator yields a higher dryness fraction for saturated steam
2 – The size of the distribution lines is reduced
3 – Better control of the set pressure at the point of use
4 – Pressure reduction at the point of use will contribute to steam dryness

Point of Use

Steam separators should be installed at the point of use to eliminate residual water droplets. Separators are designed to produce an increase in the diameter of the line, and changes in the direction of the steam flow. The speed of the steam is suddenly reduced and water droplets can be separated from the steam flow by gravity. As shown in figure 6, separators are equipped with a mechanical or thermodynamic steam trap to drain the collected water. Following the separator, the steam pressure is reduced by means of a pressure regulator, which also contributes to drying the steam.

Since air and condensate may be present in the distribution line before steam introduction in the heat transfer equipment, a steam trap must be located upstream of the isolating valve. This valve will be open to the heat transfer equipment only once air and condensate have been removed from the distribution line.

Superheated will be present at the starting of the steaming cycle due to the pressure drop and steam expansion in the volume of the heat transfer equipment. Larger volumes will increase the risk and the time of superheat. Because filters could be damaged in presence of superheated steam, it is not recommended to steam sterilize product filters in line with their associated downstream equipment, especially when large tanks are involved. A safer procedure is to separate the sterilization of the filter from the production tank, in order to minimize the downstream volume and hence reduce the expansion volume of steam on sterilizing filters.

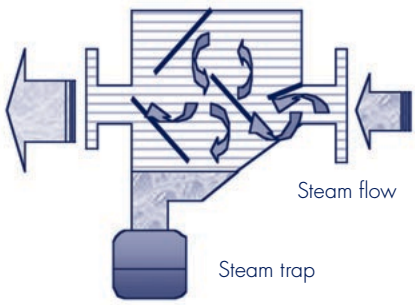

Figure 6: *Steam separator equipped with mechanical or thermodynamic steam trap.*

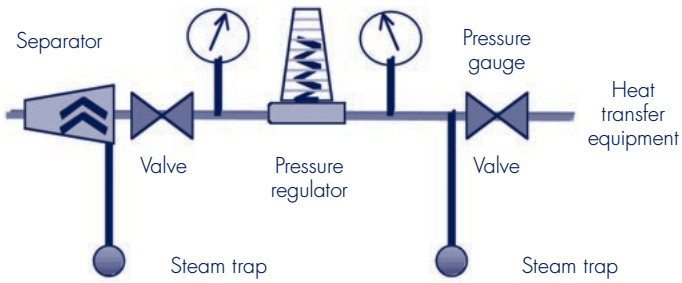

Figure 7: *Design of the points of use. A separator with a steam trap first separates entrained water droplets from the steam flow. Then pressure is reduced to re-vaporize the residual humidity. A steam trap located upstream of the isolation valve allows the complete draining of the line before starting the SIP cycle.*

Piping Design and Orientations

The heat transfer equipment must be designed for proper air elimination, effective steam penetration, and free drainage of condensate. Given that air is denser than water vapor, steam should be introduced at the highest point. Sterile lines must be sloped in the direction of the steam flow with a minimum gradient of 1 cm every meter to allow air elimination and condensate removal in the drains and collection legs located in the lowest point of the installation. The connection of the trapping lines must be identical in diameter to the process line, as shown in figure 8. Thermostatic traps are installed at a distance of at least 1 meter from the isolating valve in order to allow for a certain condensate hold up before the system opens.

Fittings and pipe reductions must be designed so as to properly remove condensate and avoid subsequent product hold up in dead flow areas (see figure 9). The use of sanitary clamp type connections or welded connections, using orbital welding, is preferred for SIP operations. Dead legs must be eliminated to avoid cold spots, and a dynamic steam flow is necessary through all interior surfaces and extremities of the system. Normally, pipe dead legs should be shorter in length than 6 times their diameter. In fact this rule could lead to sterility issues. Length/diameter ratios should be kept at a minimum, especially when small pipe diameter is involved. If a dead leg creates air or condensate entrapment, a bleed valve and a steam trap must be installed to properly sterilize this critical area.

Complex equipment must be sterilized in sections and separately. When sections are steam sterilized simultaneously, there should be a unique direction for steam. Sterile boundaries must be sterilized in two steps, as indicated in figure 10.

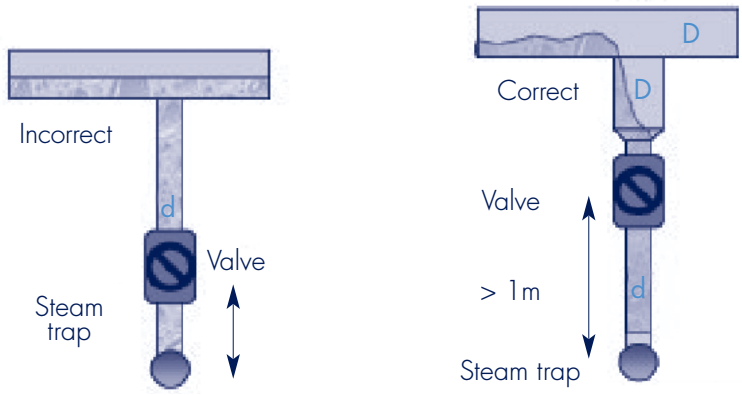

Figure 8: *Design of trapping lines. The connection is of the same diameter (D) than the process line. The rest of the line to the steam trap (d) is generally reduced to 8mm.*

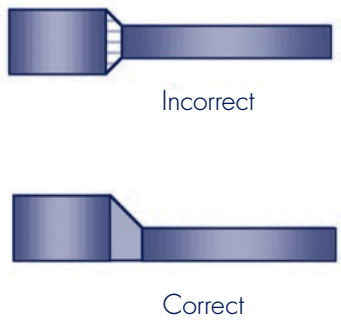

Figure 9: *Correct pipe reductions avoid condensate and/or product hold-up.*

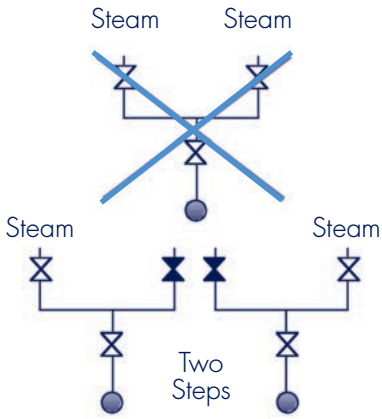

Figure 10: *Steaming in opposite direction at the same time is not correct. Two steps are necessary to allow stem across the sterile boundaries.*

Vessels Characteristics

Vessels submitted to steam sterilization must withstand the set steam pressure with an adequate safety margin and resist to depth vacuum to prevent any risk of collapsing during the post SIP cooling phase. Tanks must be equipped with calibrated pressure relief devices and sanitary type pressure gauge. The material of choice for steam sterilized tanks is 316 L stainless steel with electro-polished inner finish. Prior to SIP the tank must be leak tested by mean of a pressure hold test for safety reasons.

Materials of Construction and Surface Finish

Pure steam condensate is very corrosive due to its high temperature and ion avidity. Therefore, the recommended material for aseptic processing components such as valves, steam traps and monitoring instruments is stainless steel 316 L. Internal surface finish must be defect and crevice free to minimize product and bacteria adhesion. Mechanical polishing followed by electropolishing will provide a surface roughness average (Ra) of 0.6 µm or less, and enhance cleanability and corrosion resistance. The best surface finish is obtained with electropolishing at a minimum of a 150 grit finish, passivation processes and orbital welding.

Control and Monitoring Instrumentation

Pressure Regulators

Pressure regulators are used to control the inlet steam pressure and the compressed gas used for blowing down of the system after SIP. During manual SIP, it is not advisable to attempt to adjust steam pressure by cracking open an ordinary diaphragm valve as this is very difficult to control. Direct acting pressure regulators provide a more accurate downstream pressure control in pure steam service. They are used to set the desired steam pressure irrespectively of upstream pressure changes. Depending on the size of the heat transfer equipment, the inlet

pressure is generally above the required set value in order to compensate for the potential pressure drop in the lines and the filters. For a SIP cycle at 121 °C, the inlet steam is generally supplied in a range of 1.2 to 1.5 barg.

Valves and Pressure Gauges

Valves installed upstream and downstream of filters are used during manual SIP to control the steam flow and adjust the desired pressure differential across the filters. Product contact parts must be crevice free and all area must be accessible to steam in order to achieve efficient sterilization. Ball valves often contain crevices making sterilization difficult. Diaphragm valves are the preferred choice for the heat transfer equipment because the lack of dead flow area, their cleanability, their self draining characteristics and leak tightness make sterilization easy to achieve and to maintain. It is recommended to install them with a certain angle to allow self-drainage.

Conversely, diaphragm valves have limited life in continuous steam service, therefore ball valves will be preferred for the steam distribution systems. The diaphragm material being in direct contact with steam, CIP agents, and products must meet FDA requirements. Typically, aseptic diaphragm valves are constructed of PTFE, EPDM, or Viton components.

The addition of pressure gauges helps controlling the pressure differential across filters throughout the SIP cycle. Diaphragm pressure gauges with clamp fitting are preferred for their sanitary aspect.

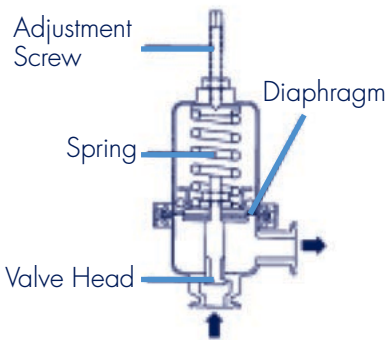

Figure 11: *Direct acting pressure regulators provide accurate set pressure irrespectively of upstream pressure changes.*

1 – Points of use must be equipped with separators, steam traps, pressure gauges and regulators.
2 – Liquid filters must be sterilized with minimum downstream volume to avoid superheat.
3 – Steam should be introduced at the highest points.
4 – Trapping lines must be identical in diameter to the process line.
5 – Thermostatic traps must be installed at a distance of 1 meter from the isolating valve.

Temperature Probe

As required by the EC guide to GMP, the position of the temperature probes used for controlling the sterilization cycle should have been determined during the validation. During validation, coldest spots are identified by means of thorough coverage of the system with thermocouples. Monitoring temperature probes are then installed in the slowest heating points, which are generally the farthest drain points from the steam supply, to record the set temperature for the required sterilization time. Very often, as saturated steam presents a relationship between temperature and pressure, only the pressure is considered for routine SIP monitoring. This type of monitoring requires a thorough validation documentation to ensure that saturated steam is generated in the heat transfer equipment.

Because thermostatic steam traps will discharge condensate at temperature below the steam saturation temperature, it is necessary to have at least 1m of piping between the sterile barrier and the trap. The temperature probe is installed as close as possible to the valve in order to record temperature at the critical point, as shown in figure 12.

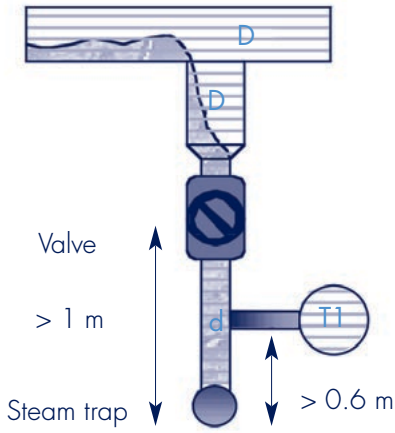

Figure 12: *Installation of temperature probe in the drain for temperature monitoring.*

Regulation Valve

For automatic SIP cycles, the temperature can either be controlled directly, by means of a temperature probe, or indirectly, via a pressure transducer. Indirect control presumes that saturated steam is used since the set pressure is calculated from the pressure/temperature diagram for saturated steam. This type of control is easier to handle because pressure variations are wider than temperature fluctuations (about 50 mbar for 0.7 °C). The temperature probe or pressure transducer is set at the required sterilization temperature or pressure, and will automatically actuate the regulating steam inlet valve (see figure 13). Simple ON/OFF control valves are normally used for SIP control. Those valves must be of a small size to minimize the peaks in temperature obtained each time they will open. Using a continuous control valve results in a more stable temperature profile during the sterilization exposure time.

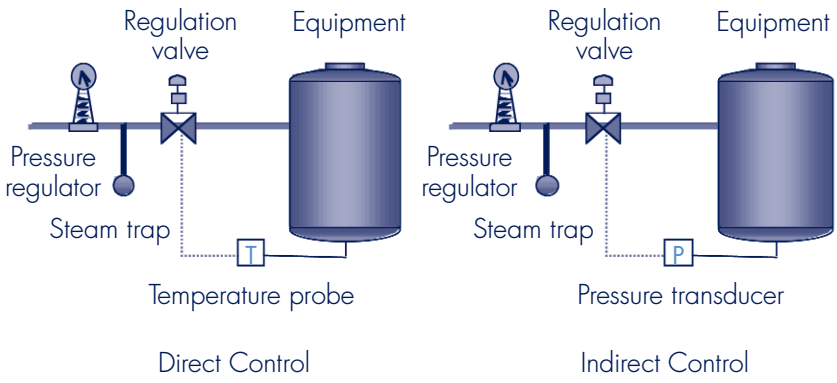

Figure 13: *Direct control: The thermocouple monitors the temperature of the coldest spot, and the regulation valve maintains the steam flow and the set temperature. Indirect control: The regulation valve maintains the set pressure recorded by a pressure transducer.*

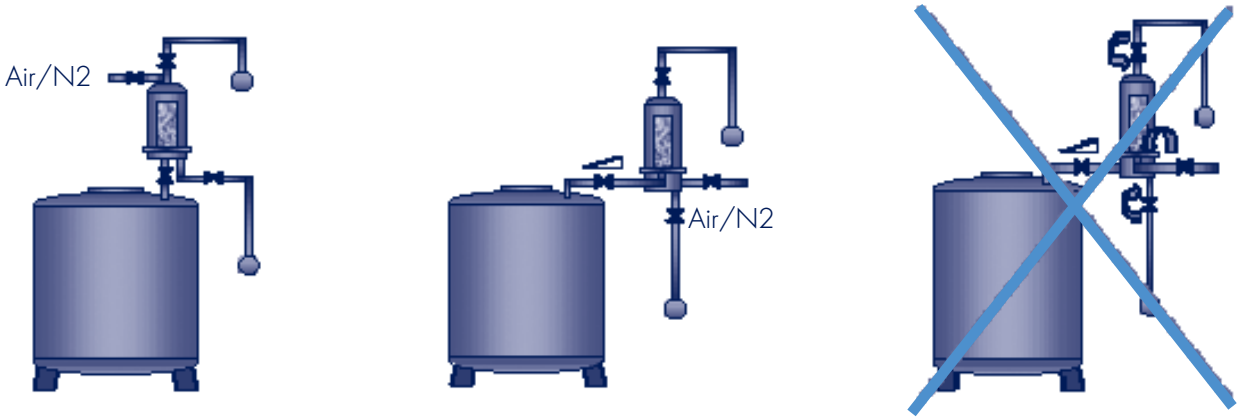

Figure 14: *Left, In-line vent filter housing. Downstream condensate is drained by gravity to the vessel. Middle. T-type gas filter housing (GasLiner). A slope must assist condensate drainage to the tank. Right, wrong set-up.*

Gas Filter Engineering

System Design, Installation and Standard Operating Procedure

Vent filters are required for the sterile introduction of air or nitrogen after sterilization of vessels and during the process. Gas filters are made of hydrophobic materials such as PTFE to prevent blockage by humidity during their 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, thus leading to incorrect sterilization.
The filter housing must therefore be designed and installed for a correct drainage of condensate, with the inlet sterile side of the cartridge fitted on the sterile vessel. This set up is preferred since the housing closure, and the connections to vent and drain valves, that may present risks of leakage, are on the upstream side of the filter. A reverse mounting would result in the by-pass of the filter and would compromise the sterility of the equipment.

Figure 14 shows the correct installation of a vent filter. The in-line design of the Ventliner™ Plus housing allows the drainage of downstream condensate through the vertical connection to the vessel. The T-type Gasliner™ 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 must also be installed on the top of the filter to evacuate non-condensable gases during the sterilization cycle, and to ensure that steam penetrates all extremities of the filter assembly. In most cases, vent filters are steam-sterilized along with their associated vessels.

Because large amounts of steam are required at the starting of the SIP cycle to heat up 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. Such a procedure is preferred to a forward steam injection from the filter to the

tank because it limits the steam flow rate, it avoids high differential pressure over the filter and prevent from contact with superheated steam. The reverse steam flow through the filter is then significantly reduced, since it only serves for the compensation of condensate eliminated by the steam traps opening upstream of the filter assembly. Reverse steaming is safe as long as a code 7 filter with lock in tabs or Optiseal™ device are used. As shown in figure 16, some installations such as WFI tanks or fermentors may require separate sterilization of vent filters, to allow their replacement without resterilizing the vessel.

All configurations require the installation of a pressure relieve safety valve, and pressure gauges upstream and downstream of the filter to control that the reverse differential pressure does not exceed the specification throughout the SIP procedure. Temperature probes are located in the coldest points of the filter assembly and the vessel (i.e. the drain points) and serve to monitor the SIP process. The addition of steam traps downstream of the bleed valves allows condensate removal and reduces both the steam flow rate and the pressure differential across the filter.

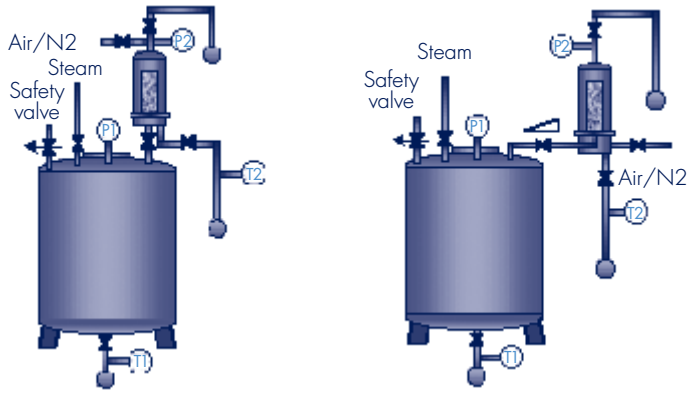

Figure 15: *Reverse steam sterilization of vent filters along with the associated vessels.*

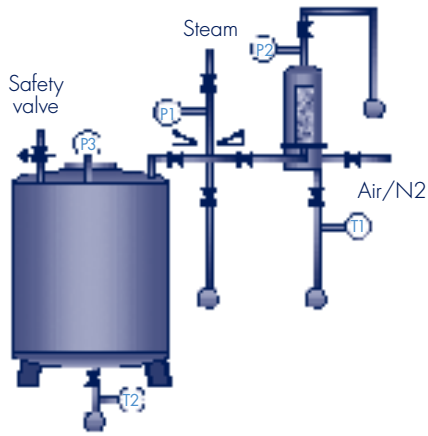

Figure 16: *Separate sterilization of the filter and the vessel. This configuration allows 3 different SIP procedures: separate sterilization of the filter in the case of replacement, sterilization of the vessel only, and simultaneous sterilization of the filter and the vessel.*

Flushing of Non-condensable Gases and Heating up of the System

Before starting the SIP cycle, it is advisable, for obvious safety reasons to check for leak-tightness of the system. A 5 minute pressure hold test is generally carried out at 2 barg pressure.

Superheated steam will be present at the beginning of the sterilization cycle due to high velocity and sudden steam expansion into the tank. It is therefore better to first admit regulated saturated steam into the tank and maintain the filter isolated from the tank at this stage of the process.

All the bleed valves on the vessel must be open to ensure condensate and non-condensable gases removal. The duration of this operation depends on the size of the equipment and is established during the validation of the SIP cycle. When the temperature of the drain reaches 110 °C or when the pressure in the tank is about 0.5 barg, the valve is open to the filter, and the steam quickly fills up and heats up the filter housing.

Eliminating all non-condensable gases normally requires flushing of the system with about 10 volumes of saturated steam, which might take between 5 and 20 minutes.

The maximum amount of condensate is generated at the start up of SIP because the heat transfer is important due to the high difference in temperature between steam and the heat transfer equipment.

Once the steam exits the drain and vent valves, indicating that air and condensate have been removed, steam traps automatically shut to limit the steam flow and to allow the system increase and maintain to the desired sterilization temperature. Steam traps will then intermittently open to evacuate con-densate and allow replacement with fresh saturated steam. For manual SIP systems that may not include steam traps, the bleed valves must progressively open to avoid excessive pressure differential when steam flows through the filter. The bleed valves remain cracked open during the SIP cycle, in order to eliminate conden-sate and to adjust the flow rate across the filter.

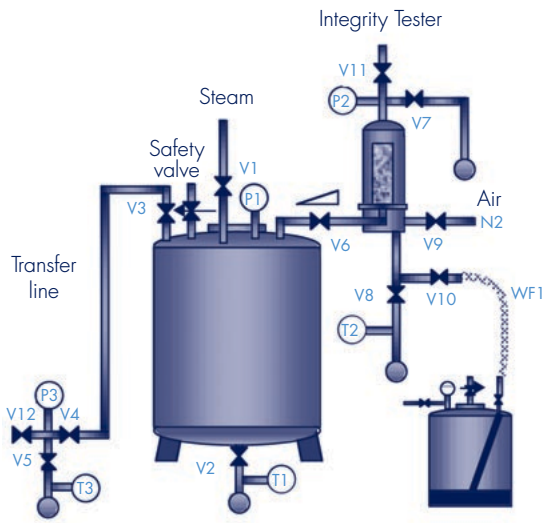

Figure 17: *System designed for SIP and Integrity testing of vent filter.*

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 starts and remains for the required time period as defined by the validation study. The pressure differential over the filter must not exceed 100 mbar during the entire sterilization cycle in order to maintain the integrity of the filter. 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 EN 285. A current industry practice is actually to check for both pressure and temperature during the validation, using tighter acceptance criteria for the deviation (±1 °C). Provided that routine SIP operations are carried out using the same validated standard operating procedure, only the temperature is then monitored.

Automatic SIP can be directly or indirectly regulated via a steam inlet control valve. Another possible regulation simply involves pressure regulator 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 the pressure differential, are regulated via the manual steam supply valve and the bleed valves which remain cracked open. Air and condensate are continuously eliminated through the cracked open bleed valves throughout the SIP cycle.

Venting of Steam, Drying and Cooling

Upon SIP completion, it is necessary to release the steam pressure and to remove residual condensate from the lowest drain points of the system. This step of the process is critical because steam condensation can create vacuum and compromise integrity of the system. A mole of saturated steam at 121 °C occupies a volume of 15 L whereas the same mole of condensate only occupies 18 mL. Condensation needs to be compensated by sterile gas such as air or nitrogen. Sterile compressed gas is required to pressurize the system and to completely purge the condensate through the bleed valves. The maintenance of sterility is ensured as long as pressure gauges indicate a positive pressure in all parts of the system. This operation also allows the cooling of the equipment and the filter, which is critical when post SIP integrity testing has to be performed.

Integrity Testing of the Vent Filter

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

Valves	Heating tank	Heating filter	SIP cycle	Steam purge	Cooling drying	Filling filter	Test filter	Drain filter	Dry filter
V1	■	■	■	x	x	x	x	x	x
V2	■	■	■	■	■	x	x	x	x
V3	■	■	■	■	■	x	x	x	x
V4	■	■	■	■	■	x	x	x	x
V5	■	■	■	■	■	x	x	x	x
V6	x	■	■	■	■	■	■	x	x
V7	x	■	■	■	x	■	x	■	■
V8	x	■	■	■	x	x	x	■	■
V9	x	x	x	■	■	x	x	x	■
V10	x	x	x	x	x	■	x	x	x
V11	x	x	x	x	x	x	■	x	x
V12	x	x	x	x	x	x	x	x	x

Table D: *Standard operating procedure.* ■ = open x = closed

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 the occurrence of blind filters is reduced. Conversely, the hydrophilic nature of product filters makes their pre and post SIP drying difficult since water wet filters do not allow air passage when the pressure is below the bubble point pressure (typically 3.5 to 4.2 barg).

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

The filter system must be equipped with appropriate vent and drain valves and must be designed and positioned in the upright position to properly remove air and condensate. These valves also allow a continuous steam flow during SIP and thus eliminate potential dead flow areas.

Figure 18 shows 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 extremities of the filter assembly. In all cases, the upstream condensate is eliminated via a steam trap fitted on the drain port of the housing.

Liquid filters are preferably sterilized in the forward direction, separately from their associated downstream equipment, in order to reduce the expansion volume of steam at the beginning of the SIP cycle. Such a procedure will limit superheat effects and will 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 downstream of the bleed valves allows condensate removal and reduces both the steam flow rate and the pressure differential across the filter.

Sterilization Cycle

If the filter was integrity tested prior to sterilization, it must then be dried with pressurized air or nitrogen to provide a path for subsequent steam flow-through without exceeding the maximum pressure drop of 0.35 bar across the filter.

Water present in the steam line at the beginning of the sterilization cycle must first be purged upstream of the filter to avoid wetting and subsequent blocking of the filter. 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 starts and remains for the required time as defined during validation. The pressure differential over the filter must not exceed 350 mbar during the sterilization cycle in order to maintain the integrity of the filter. 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 the steam traps. Manual procedures are regulated via the manual steam supply valve and the downstream bleed valves. The bleed valves must be progressively open to avoid excessive pressure differential and remain so during the SIP cycle, in order to eliminate air and condensate.

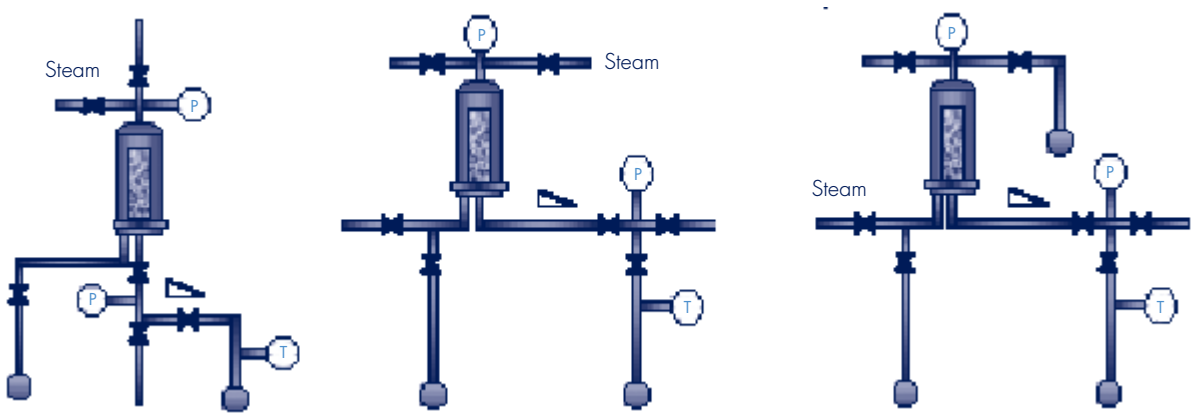

Figure 18: *Left, In-line filter housing. Middle, T-type filter housing. Right, T-type filter housing equipped with a steam trap on top for air evacuation.*

Drying, Cooling and Integrity Testing of the Filter

After SIP, the steam supply valve is closed, and compressed air or nitrogen is admitted to the system to cool down and dry the filter. Quick drying is obtained with both the gas flow and the high temperature of the system. As required by the EC GMP Guide, integrity of the filter must be performed after sterilization, before the process. This operation can be performed without compromising the sterility of the system, using the set-up depicted in figure 20. In most cases water cannot be introduced into the system because of subsequent dilution of the product. Using the product as the wetting medium enables integrity testing of the filter after steaming, and before the process, and avoids loss of time and product reject due to a damaged filter. Post-use testing is also required to ensure that the filter has remained integral throughout the entire manufacturing process.

Validation of Filter SIP

Steaming-in-place (SIP) is the preferred method for the sterilization of entire processing equipment, including vessels, valves, process lines, filter assemblies, manifolds and filling nozzles. Steam-in-place cycles need to be validated, using thermocouples and biological indicators, and must be carried out following documented standard operating procedures. The Millipore Access^{SM} program includes a suite of services that helps our customers to design filtration systems, optimize and validate sterilization procedures, and assure compliance with regulatory authority requirements. Contact the Millipore Access service department for assistance in SOP development and validation of steam-sterilization cycles.

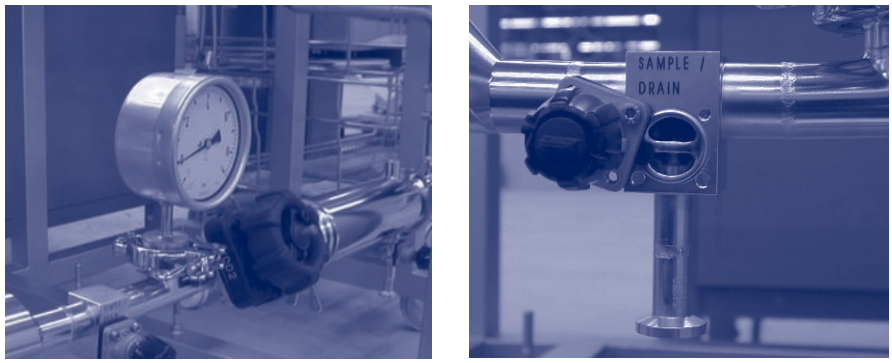

Figure 19: *Design of bleed valves installed upstream of filters.*

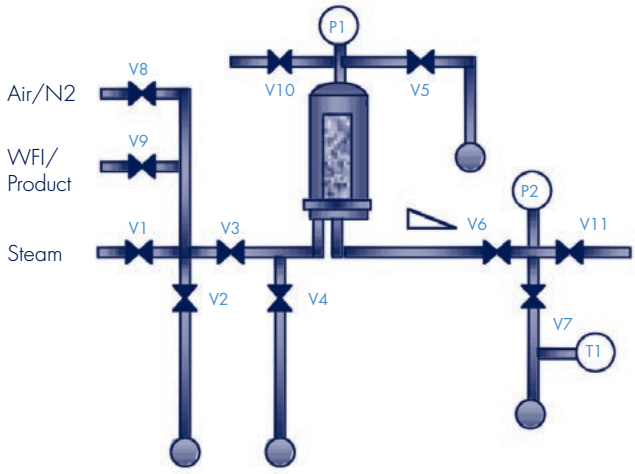

Figure 20: *SIP and post SIP integrity testing of liquid filters.*

Valves	Purge steam	Heating filter	Steam cycles	Purge steam	Drying & Cooling	Filling filter	Filter wetting	Filter drain	Test filter	Dry filter	Vent system	Filtration
V1	■	■	■	x	x	x	x	x	x	x	x	x
V2	■	■	■	■	■	x	x	x	x	x	x	x
V3	x	■	■	■	■	■	■	x	x	■	x	■
V4	x	■	■	■	x	x	x	■	x	x	x	x
V5	x	■	■	■	■	x	x	x	x	x	x	x
V6	x	x	■	■	■	x	■	■	■	■	■	■
V7	x	x	■	■	■	x	x	■	x	x	x	x
V8	x	x	x	■	■	x	x	x	x	■	x	x
V9	x	x	x	x	x	■	■	x	x	x	x	■
V10	x	x	x	x	x	■	x	■	■	x	■	x
V11	x	x	x	x	x	x	■	x	■	■	■	■

Table E: *Standard operating procedure.* ■ = open x = closed

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