Millipore®

Preparation, Separation,
Filtration & Monitoring Products

Tech Note

Recommendations for Steam-in-Place Sterilization of Filtration Trains containing Milligard® PES Prefilters

Introduction

Steam-in-place (SIP) sterilization is commonly used for process equipment such as piping, housings, bioreactors, and filtration trains used in the manufacture of biotechnology products.

Milligard® PES cartridge and capsule filters are designed to be used as stand-alone filters for reducing levels of bioburden and particulates or as prefilters, protecting downstream sterilizing filters from premature plugging. These filters can be sterilized by SIP, autoclave, and gamma irradiation. However, if prefilter integrity will be assessed, it is recommended that Milligard® PES filters are wet before use. By contrast, our sterilizing-grade Durapore® and Millipore Express® filters are recommended to be dry before SIP sterilization. The different recommended wetting requirements for these filters prompted additional studies to clarify best practices for SIP sterilization of a filtration train containing a Milligard® PES cartridge prefilter upstream of Millipore Express® or Durapore® sterilizing-grade cartridge filters.

Materials and Methods

Filter conditions for SIP Tests

All SIP testing was performed using 10 in. cartridge filters containing Milligard® PES 1.2/0.2 µm nominal membrane upstream of a 10 in. cartridge filter containing either Millipore Express® SHR with prefilter (Millipore Express® SHRp) or Durapore® 0.22 µm membranes.

Table 1 summarizes four filter conditions and methods that were evaluated based on whether Milligard® PES prefilter and sterilizing-grade filter were wet or dry before SIP, whether the filters were SIP treated in series (Milligard® PES prefilter followed by sterilizing-grade filter), or whether a plumbing bypass was set up around the Milligard® PES prefilter. After SIP sterilization, the integrity of all prefilters and sterilizing filters was confirmed using an automated Integritest® instrument.

Table 1: Summary of filter conditions and SIP treatments

Method	Milligard® PES 1.2/0.2 µm nominal filter condition	Millipore Express® SHRp filter condition	System setup for SIP
1*	Dry	Dry	Series
2	Wet	Dry	Series
3	Wet	Dry	Steam bypass from inlet around Milligard® PES filter to downstream filter
4	Wet	Wet	Series

*This test was also performed with a cartridge filter containing Durapore® 0.22 µm membrane in place of the Millipore Express® SHRp membrane.

Figure 1 shows the generalized setup of the prefilter and downstream filter in the filtration train. For all four SIP tests, steam at 135 °C was continuously introduced into the system through valve V1 at 'heat up' and during the 30-minute 'temperature hold' steps; steam exited through valve V7. At the end of the 'temperature hold', steam was stopped and sterile-filtered compressed air at ambient temperature was introduced into the system through valve V2. The compressed air was designed to cool the system and maintain sterility simulating potential customer applications.

Compressed air pressures are listed within the discussion of each method. A drain and valve (V3) positioned upstream of the Milligard® PES prefilter removed system condensation. The downstream sterilizing-grade filter had a similar drain (mid-point drain) and valve configuration (V5) between prefilter and downstream filter. The drains upstream of each filter were critical elements of system setup to reduce the risk of filter damage due to water condensation. V4 and V6 are vent valves that relieved any differential pressure that built up during the sterilization operation, also protecting the filters from damage.

Temperature and pressure were measured throughout the system with multiple thermocouples (TC) and pressure transmitters (PT). During these studies, all valves were operated manually and were adjusted to minimize temperature and pressure differentials across the system.

Confirmation of Flow Performance

Flow rates of cartridge filters containing the three pore sizes of Milligard® PES membrane or sterilizing-grade Millipore Express® SHRp membrane were measured at a constant pressure of 10 psi; all membranes were dry before water flow rate measurement. Following testing, filters were dried, SIP sterilized (dry prefilter, dry sterilizing-grade filter) and then water flow rates were re-measured at 10 psi.

After SIP sterilization, the integrity of all filters was confirmed using an automated Integritest® instrument.

Results and Discussion

Filter Condition and Considerations for SIP Treatments

It is recommended that Milligard® PES prefilters are wet before SIP treatment, and we recognize this presents a challenge when performing SIP sterilization with a dry sterilizing-grade filter. To clarify best practices for SIP sterilization of a filtration train containing Milligard® PES filters, four methods were compared for performing SIP treatment with filtration trains containing Milligard® PES prefilters and Millipore Express® SHRp filters. These methods comprised different wet or dry conditions for the prefilters and sterilizing-grade filters, both serial SIP of the filters in the filtration train, as well as SIP where a bypass was connected around the Milligard® PES prefilter. The bypass enabled bi-directional steaming of the Milligard® PES filter and forward steaming of the sterilizing-grade filter at the same time, reducing the pressure differential across the wet Milligard® PES membrane.

SIP sterilization includes three phases: 'heat up', 'temperature hold', and 'cool down'. The minimum temperature for sterilization is 121 °C (250 °F) with a hold of at least 30 minutes. The impact of the SIP test method on both temperature and pressure across the filtration train are summarized below. After SIP treatment and flow rate tests, both the Milligard® PES prefilters and sterilizing-grade filters passed filter integrity tests.

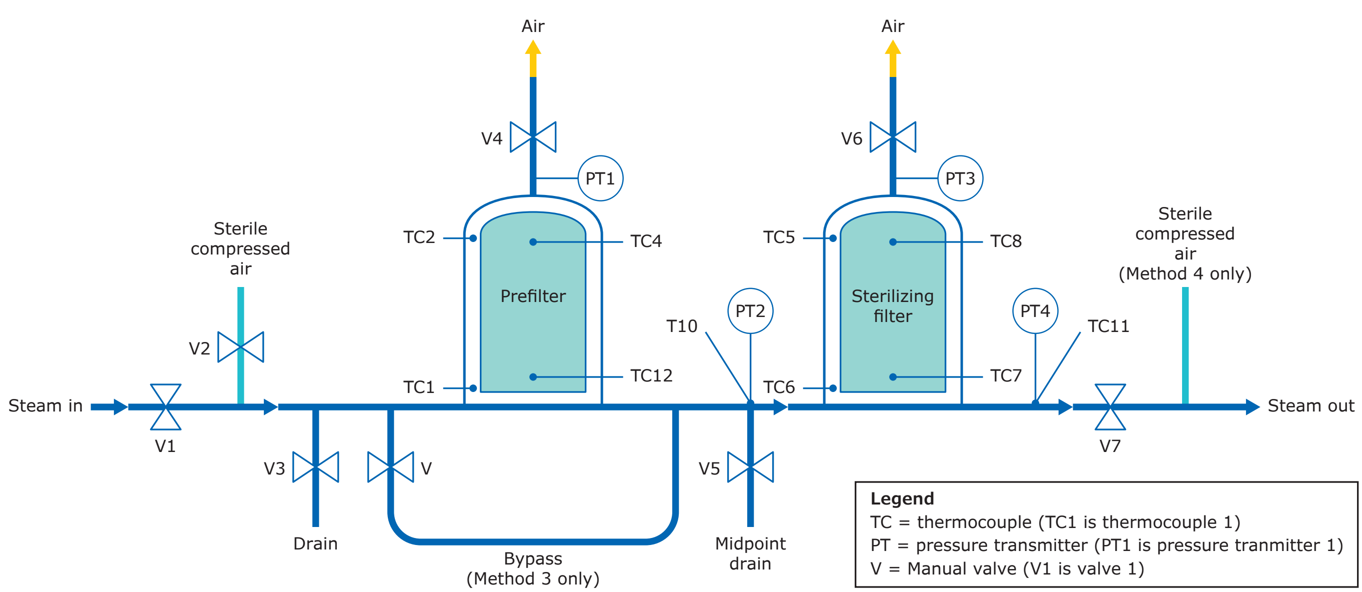


Figure 1: SIP Sterilization Test System Schematic. The prefilter in this schematic was Milligard® PES 1.2/0.2 µm nominal and the sterilizing-grade filter was either a Millipore Express® SHRp or a Durapore® 0.22 µm filter.

Method 1: Dry prefilter, dry sterilizing-grade filter, SIP in series.

Figure 2A and B show the temperature and pressure profiles, where the Milligard® PES 1.2/0.2 µm nominal prefilter and Millipore Express® SHRp sterilizing filter were both dry before SIP treatment. This method was also performed with a Durapore® 0.22 µm sterilizing-grade filter downstream of the Milligard® PES prefilter. Test results with the two different sterilizing-grade filters were similar and, as Millipore Express® SHRp membrane's bubble point is higher than that of Durapore® 0.22 µm membrane, it represents 'worst-case' for the SIP study, so results with this membrane are shown in this report.

Temperature Profiles & Differential Pressure Across System:

- System heated up quickly (<20 minutes), and the temperature was consistent throughout the system. The temperature stabilized at 135 ºC, above the 121 ºC threshold. The cooling compressed air pressure was 10-15 psi, although it could be set to any pressure, and the whole system cooled down to ambient temperature in ~45 minutes.
- Differential pressure was less than 1 psi across both filters during the whole SIP method, minimizing risk of filter damage.

Implementation:

- The drain valve (V5) between the filters was open to minimize the push of condensation to the downstream filter. Minimal valve adjustments needed.

Recommendation:

- We recommend wetting Milligard® PES filters before SIP or integrity testing. However, if the Milligard® PES filter does not need to be integrity tested, the filters in the filtration train do not need to be wet before SIP sterilization.

Figure 2A: Method 1 SIP Temperature Profile

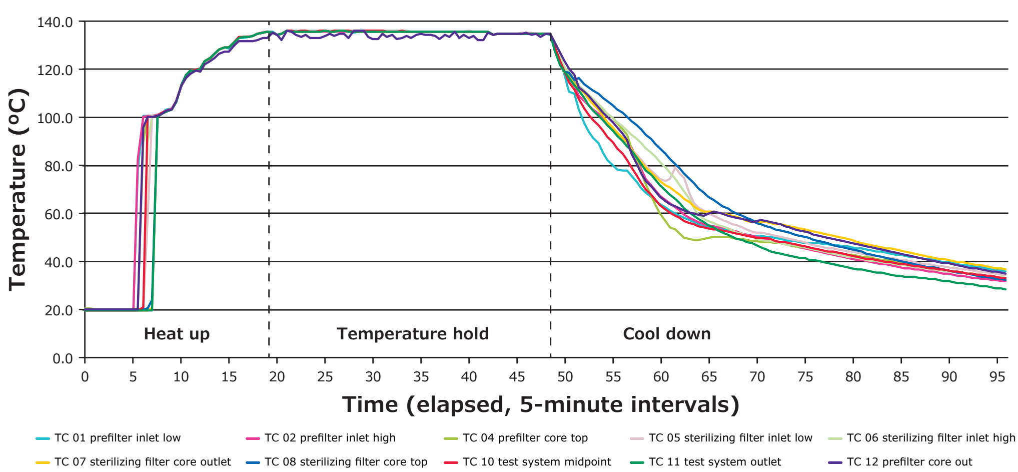
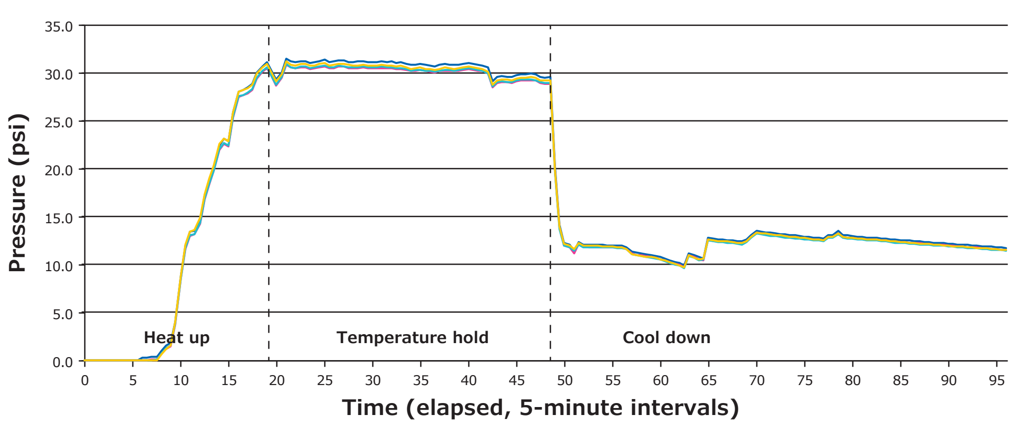


Figure 2B: Method 1 SIP Pressure Profile



Method 2: Wet prefilter, dry sterilizing-grade filter, SIP in series.

Figure 3A and B show the temperature and pressure profiles measured when the Milligard® PES 1.2/0.2 µm nominal prefilter was wet and Millipore Express® SHRp sterilizing filter was dry before SIP sterilization in series.

Temperature Profiles & Differential Pressure Across System:

- During heat up, there were temperature delays in the system and although the temperature stabilized at 133-135 ºC above the 121 ºC threshold, there was ~1 ºC temperature difference across the prefilter during the temperature hold. There was no temperature difference across the Millipore Express® SHRp filter.
- Differential pressure across the Milligard® PES prefilter reached ~7 psi during heat up and reduced to ~2-3 psi during the temperature hold. There was no pressure difference across the Millipore Express® SHRp filter.
- Cool down air pressure was initially set at ~15 psi, however, as the Milligard® PES filter was wet, air could not blow through the prefilter to the downstream filter. To cool the system, air pressure was increased to 50 psi, above the Milligard® PES filter's air water bubble point, to cool down the system and maintain system sterility.

Implementation:

- To cool down the system, inlet air pressure should be set above the prefilter membrane bubble point: recommended cool down air pressure for Milligard® PES 1.2/0.2 µm nominal filters is 50-60 psi; for Milligard® PES 1.2/0.45 µm filters is 40-50 psi, and for Milligard® PES 1.2/0.8 µm filters is 25-35 psi.
- Valve adjustments, especially at the heat up step, were necessary to minimize differential pressure across the filters.
- The drain valve (V5) between the filters must be open to minimize the push of condensation to the downstream filter.

Recommendation:

- This method is feasible but not recommended for SIP sterilization of filtration trains containing Milligard® PES prefilters.

Figure 3A: Method 2 SIP Temperature Profile

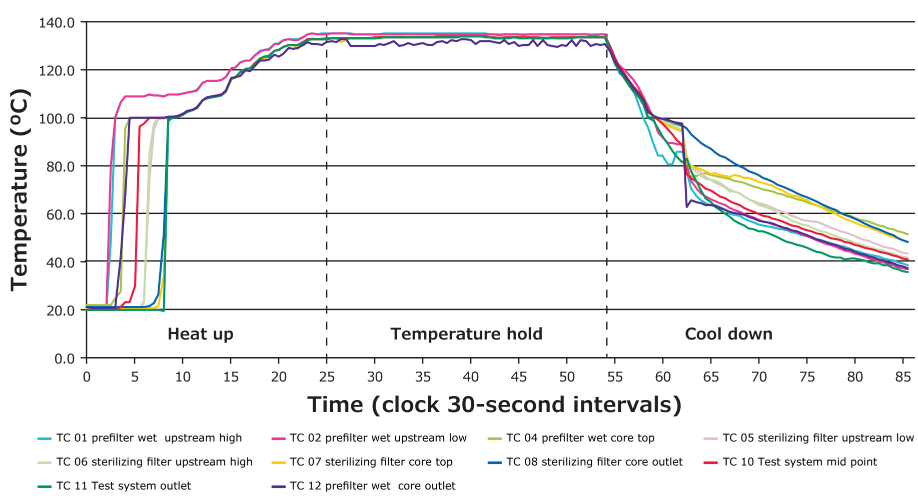
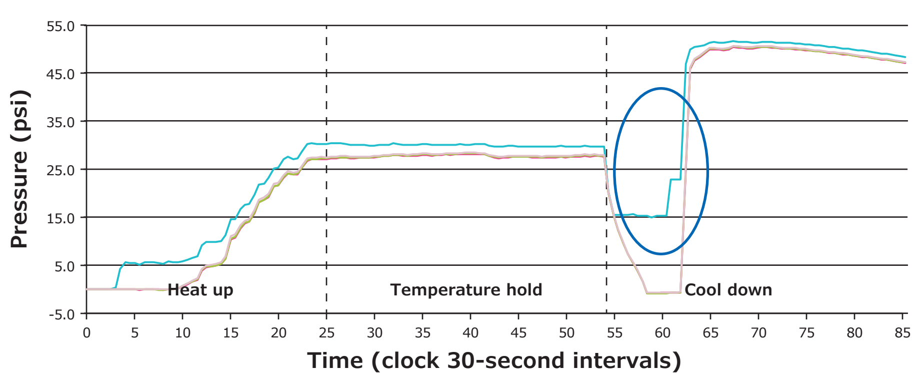


Figure 3B: Method 2 SIP Pressure Profile. Some traces are not visible as the trend lines are superimposed. The circled area indicates no air flow through the wet Milligard® PES filter.



Method 3: Wet prefilter, dry sterilizing-grade filter, steam bypass.

The Milligard® PES prefilter was prewet and the Millipore Express® SHRp filter was dry as with Method 2. However, rather than the filters being SIP treated in series, a bypass was connected from the steam inlet, around the wet Milligard® PES prefilter, and reconnected to the system before the mid-point drain. This configuration enabled both the prefilter and sterilizing filter to be steamed simultaneously and minimized pressure buildup across the wet prefilter. Figure 4A and B show the measured profiles.

Temperature Profiles & Differential Pressure Across System:

- Heat up was rapid and temperature was consistent in the whole system during the temperature hold. The cooling compressed air pressure does not need to be above the prefilter's membrane bubble point. One disadvantage was the slow cool down of the Milligard® PES prefilter, a result of bi-directional air flow without convection.
- No pressure differences were measured, resulting in minimal risk to both the prefilter and sterilizing filter.

Implementation:

- Steam went through the filters simultaneously resulting in rapid heat up and consistent system temperature. Milligard® PES prefilter received bi-directional steam and air.
- The drain valve (V5) before the mid-point drain was partially open to minimize the likelihood that condensation reached the downstream sterilizing-grade filter.
- Minimum valve adjustments were needed.

Recommendation:

- If Milligard® PES prefilter is to be integrity tested after use, it is recommended that this method is used for SIP sterilization of filtration trains containing Milliard® PES prefilters.

Figure 4A: Method 3 SIP Temperature Profile

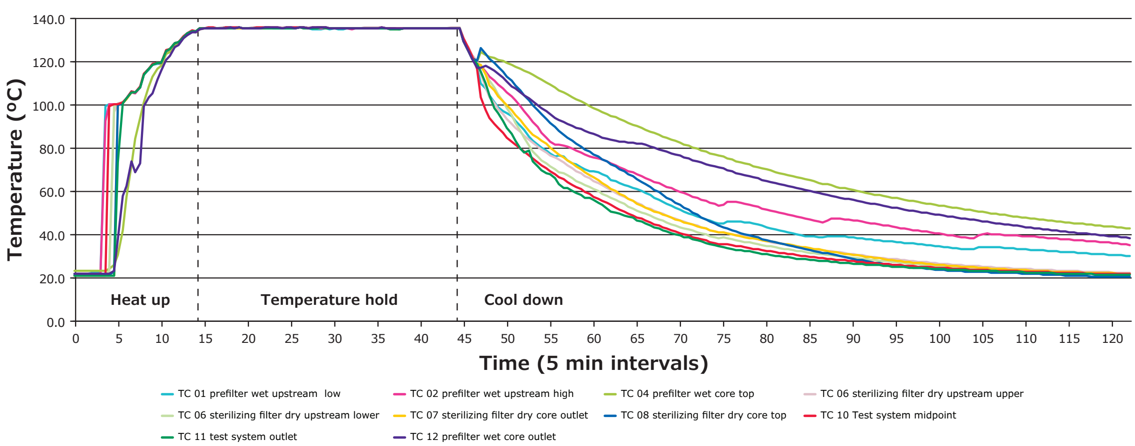
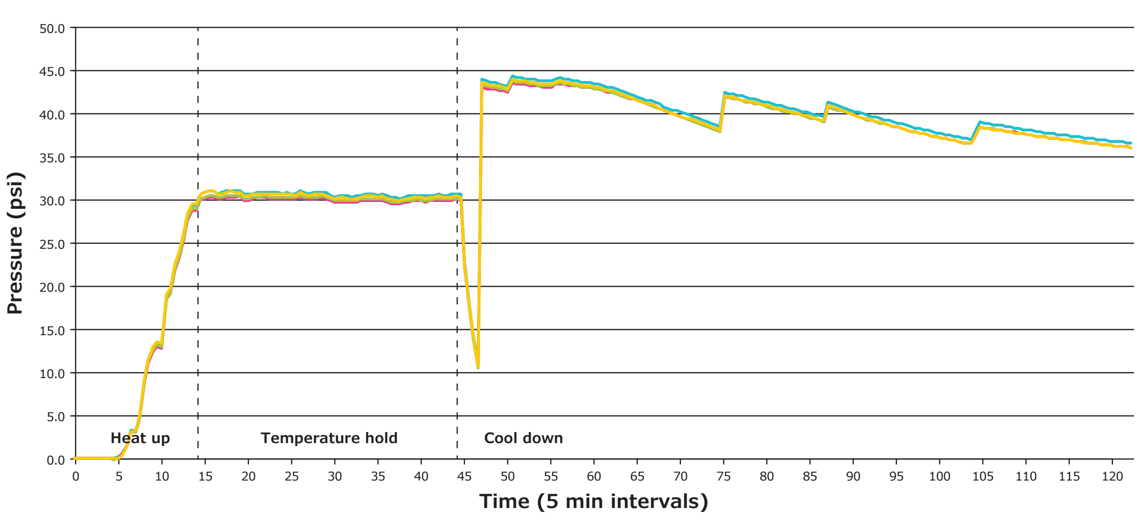


Figure 4B: Method 3 SIP Pressure Profile. Some traces are not visible as the trend lines are superimposed.



Method 4: Wet prefilter, wet sterilizing-grade filter, SIP in series.

Both the Milligard® PES prefilter and Millipore Express® SHRp filters were wet before SIP treatment. This method is only possible when two sterile compressed air inlets are available. Figure 5A and B show the measured profiles.

Temperature Profiles & Differential Pressure Across System:

- Temperature differences were measured throughout the system during heat up and temperature hold steps. Although the entire system exceeded the requirement for sterilization (121 ºC for 30 minutes), temperature stabilization was slow (~45 minutes).
- Pressure differences were measured across the filters, increasing the risk of filter damage: during heat up the pressure differential across the prefilter reached 10 psi, which reduced to 5 psi during the temperature hold.

Implementation:

- Multiple manual adjustments of vent valves were necessary to minimize differential pressure across the filters and possible filter damage.
- During cool down, the cooling inlet air pressure was set to >50 psi, above the Milligard® PES prefilter's bubble point. Because the Millipore Express® SHRp filter membrane's air water bubble point (>90 psi) is higher than the normal housing air pressure, a second sterile compressed air supply was required downstream of the sterilizing filter to maintain system sterility.
- The mid-drain valves (V5) must be open to minimize the likelihood that condensation reaches the downstream sterilizing-grade filter.

Recommendation:

- This method requires more manual control, an additional sterile compressed air source for cool down, and risks filter damage due to high differential pressures. Based on these considerations, we do not recommend this method for SIP sterilization of filtration trains containing Milliard® PES prefilters.

Figure 5A: Method 4 SIP Temperature Profile

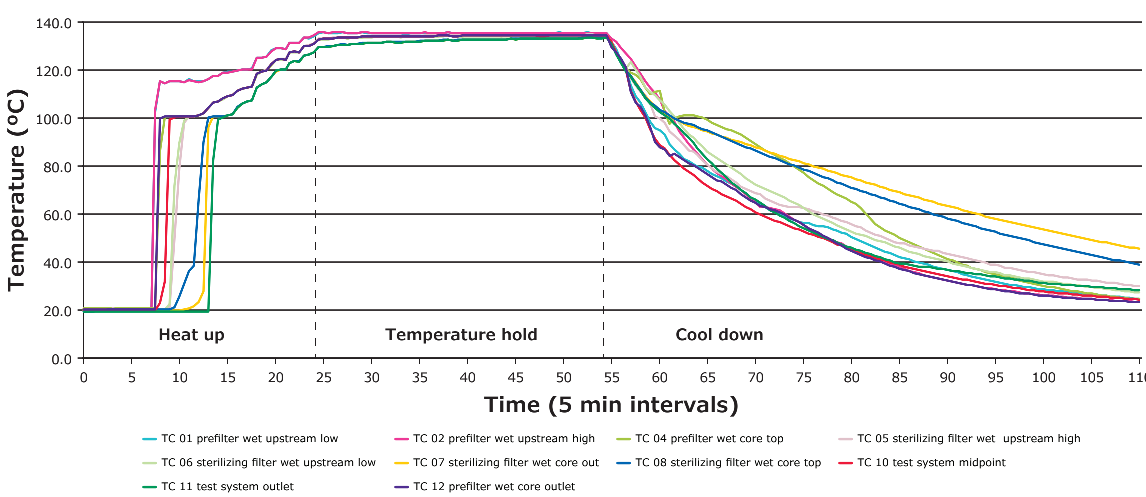
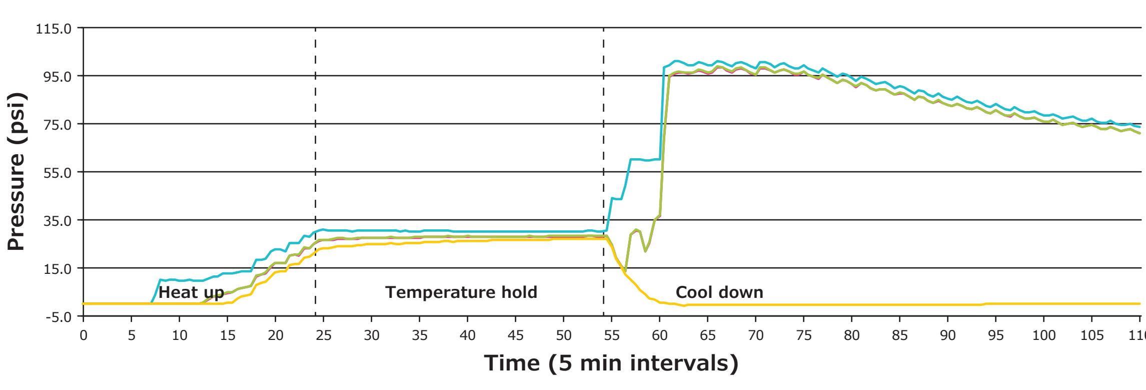


Figure 5B: Method 4 SIP Pressure Profile



Confirmation of Post SIP Flow Rate Performance

Water flow rates of cartridge filters containing Milligard® PES membranes of different pore sizes were tested before and after SIP treatment, to confirm the sterilization procedure did not impact filtration performance, Figure 6.

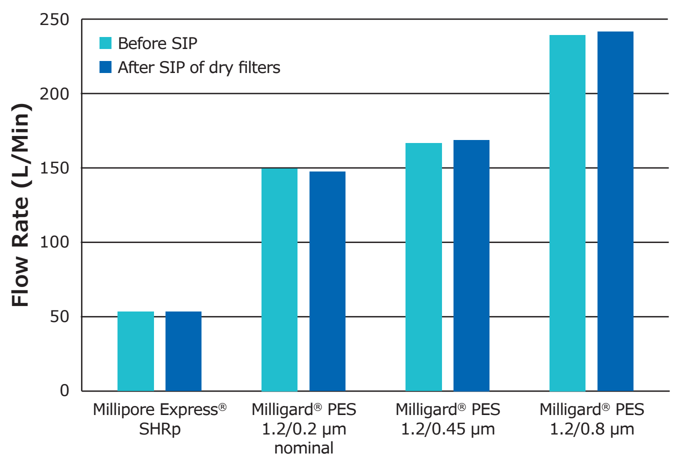


Figure 6: Flow rates of filters before and after SIP. In all cases, dry filters were subjected to SIP.

Flow rates for all filters containing Milligard® PES membranes were the same before and after SIP operation, confirming the sterilization operation, even with dry membranes, did not impact flow rate.

Measurements of filter integrity following SIP treatment indicated that all filters met the bubble point specifications for integral filters, even though they were sterilized dry.

However, in general, when integrity testing is to be performed on Milligard® PES filters, it is highly recommended to thoroughly wet the filters to minimize potential risks to filter integrity measurements that could result from incomplete filter wetting. In the tests described here, integrity measurements were not impacted, but that may not always be the case.

Summary

Milligard® PES cartridge filters can be sterilized by SIP as part of a filtration train with Durapore® or Millipore Express® sterilizing-grade cartridge filters. Four different approaches to SIP were tested and the conclusions are outlined below.

- If the Milligard® PES prefilter is to be integrity tested after SIP or use, it is highly recommended that the prefilter is wet before SIP or autoclave sterilization treatments[1]. SIP treatment should ideally be performed using a bypass connection around the prefilter, and the system setup should include drainage between the wet Milligard® PES prefilter and dry sterilizing filter, as outlined in Method 3.
- If the Milligard® PES prefilter does not need to be integrity tested after use, the prefilter can be dry and the sterilizing filter must be dry before SIP. In these instances, the dry prefilter and sterilizing filter can be SIP sterilized in series using the procedures outlined in Method 1.

Whichever approach is adopted, each customer should perform studies under their own process conditions to confirm their sterilization operations are compatible with measurements of filter integrity.

References

1. Wetting Instructions, Integrity Testing, Sterilizing and Drying Guidelines. Filters with Milligard® PES Membrane. MS_UG1375EN, Rev 2, 7/2019.

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