Millipore®
Preparation, Separation,
Filtration & Monitoring Products

Tech Note

How Membrane Prefilters Enhance Bioprocessing Efficiency

Milligard® PES filters improve sterilizing-grade filter capacity and process economics

Summary

Membrane filters are used extensively in bioprocessing to protect process fluids from microbial and particulate contaminants. Milligard® PES filters contain polyethersulfone (PES) membranes in different pore sizes. In addition to particulate removal, Milligard® PES 1.2/0.2 µm nominal and Milligard® PES 1.2/0.45 µm filters have been validated to reduce bioburden. These gamma-compatible filters are compatible with both steam-in-place and autoclave sterilization methods and are available in both cartridge and capsule formats for maximum flexibility.

This tech note summarizes studies that highlight the benefits of prefiltration for increasing throughput capacity of sterilizing-grade filters challenged with streams containing a wide range of particle size distributions. Milligard® PES filters performed as well as, or better than, other commercially available prefilters with both polyvinylidene fluoride (PVDF) and PES sterilizing-grade filters. Further analysis confirmed the benefits of prefiltration on process economics.

Introduction

Membrane filters are used throughout bioprocessing to reduce contaminants such as particulates and bioburden from process fluids. Milligard® PES filters contain two layers of asymmetric polyethersulfone (PES) membranes: a 1.2 µm upstream layer and a downstream layer offered in three pore sizes, Table 1. These gamma-compatible, thermo-stable filters can be integrated into single-use assemblies and provide options for biomanufacturers looking to improve filtration efficiency.

Table 1: Milligard® PES Filter Family.

Milligard® PES Membrane	Typical Bioburden Reduction
1.2/0.2 µm nominal	≥6 logs of *Brevundimonas diminuta*
1.2/0.45 µm	≥6 logs of *Serratia marcescens*
1.2/0.8 µm	Not determined

While all three membrane options for Milligard® PES remove particulates, Milligard® PES 1.2/0.2 µm nominal and 1.2/0.45 µm filters also have bioburden reduction claims. These filters offer an alternative to sterilizing-grade filter applications where bioburden control, rather than sterility, is the goal. Examples of such applications include buffer preparation, column protection, or filtration of process intermediates. Throughput, bacterial retention performance, and scalability of these filters with different process streams when used stand-alone without a sterilizing-grade filter downstream have been reported previously[1].

Milligard® PES filters can also be used as prefilters upstream of sterilizing-grade filters. In these applications, the goal is to remove particulates and increase the throughput capacity of costly sterilizing-grade filters to improve process economics. When placed upstream of a sterilizing-grade filter, users should consider whether the Milligard® PES prefilter will be integrity tested as this may impact steam-in-place sterilization of the filtration train. Best practices for different scenarios were outlined previously[2].

The purpose of this tech note is to summarize studies that demonstrate how Milligard® PES filters enhance the throughput capacity of both Millipore Express® PES and Durapore® 0.22 µm polyvinylidene fluoride (PVDF) sterilizing-grade membrane filters in several model streams. Results from the studies show how prefiltration reduces sterilizing-grade filter area requirements and improves overall process economics.

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Materials and Methods

Membranes and Devices

Tests were performed to compare the throughput performance of Milligard® PES filters with commercially available prefilters positioned upstream of both PES and PVDF sterilizing-grade membrane filters, Table 2.

Table 2: Summary of filters evaluated.

Milligard® PES membrane filter	Benchmark prefilters (membrane pore size)	PES sterilizing-grade membrane filter (membrane pore size)	PVDF sterilizing-grade membrane filter (membrane pore size)
Milligard® PES 1.2/0.2 µm nominal	[1]Polysep™ II (1.0/0.2 µm)	Millipore Express® SHF (0.2 µm)	Durapore® 0.22 µm
	[2]Milligard® (0.5/0.2 µm)	Millipore Express® SHF (0.2 µm)	Durapore® 0.22 µm
Milligard® PES 1.2/0.45 µm	Polysep™ II (1.0/0.5 µm)	Millipore Express® SHF (0.2 µm)	Durapore® 0.22 µm
	Milligard® (1.2/0.5 µm)	Millipore Express® SHF (0.2 µm)	Durapore® 0.22 µm
Milligard® PES 1.2/0.8 µm	Polysep™ II (2.0/1.2 µm)	Millipore Express® SHF (0.2 µm) Millipore Express® SHC (0.5/0.2 µm)	Multilayer Durapore® (0.45/0.22 µm)

[1] Polysep™ II filters are offered in different pore sizes and comprise mixed cellulose esters and glass microfibers.
[2] Milligard® filters are offered in different pore sizes and contain cellulose esters on a polyester web.

Challenge Streams

These studies used four model streams representing a range of particle size distributions, **Figure 1**. Details of the stream compositions are described elsewhere[1]. To minimize the volume of challenge solutions required, model streams were formulated in buffer at a concentration high enough to achieve 90% flux decay of the filtration train at 500–1000 L/m^2.

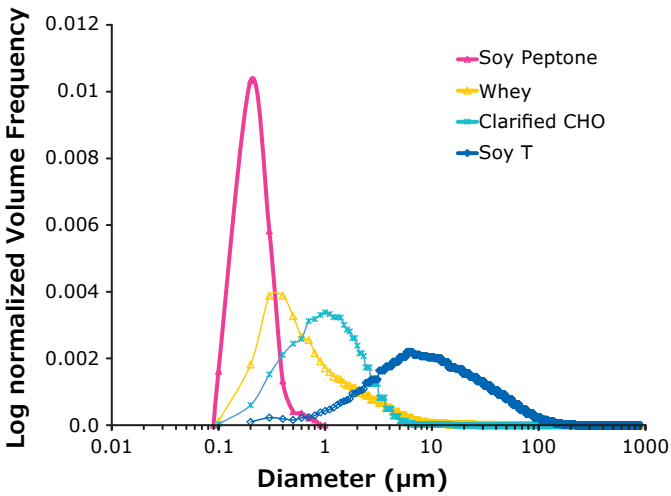

Figure 1. Particle size distributions of the challenge streams. Particle sizing was performed with Malvern MasterSizer and PMS Liquilaz.

Throughput testing

Water permeability of Milligard® PES filters was measured at 10 psi and 21–25 °C, with no sterilizing-grade filter downstream. All values were adjusted to 23 °C by correcting for viscosity.

Throughput testing of all filtration trains was performed using OptiScale® 25 capsules (3.5 cm^2 of effective filtration area) at a prefilter:final filter area ratio of 1:1. All tests were run at constant trans-membrane pressure differential of 10 psi until permeability of the filtration train was reduced by 90% compared to the water permeability (90% flow decay). During testing, temperature, pressure, and filtrate volume data were collected as a function of time, **Figure 2**.

Throughput performance of the various filter trains was normalized to that of the Milligard® PES filter train in each model stream. Throughput within 20% of that of the Milligard® PES filter train benchmark is considered equivalent.

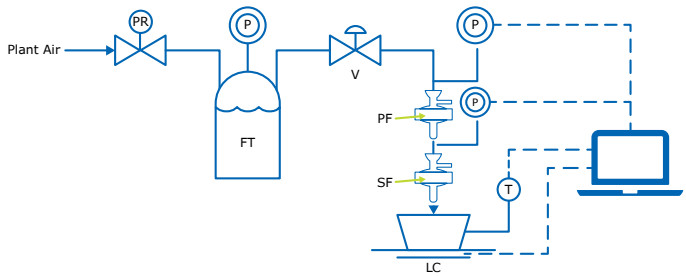

Figure 2. Test setup for filtration train throughput tests. Symbols: FT, feed tank; PF, prefilter; SF, sterilizing-grade filter; LC, load cell; P, pressure measurement; PR, pressure regulator; T, temperature measurement; V, valve. Temperature, pressure and changes in filtrate volumes were captured by a data acquisition system.

Discussion

Filtration train: benefits of prefiltration on throughput capacity of sterilizing-grade filters

To assess the benefit of prefiltration on throughput, tests were performed with Milligard® PES filters upstream of both PES and PVDF sterilizing-grade filters in multiple model streams.

Performance of Milligard® PES 1.2/0.2 µm nominal and 1.2/0.45 µm filters were assessed upstream of Millipore Express® SHF (**Figure 3A**) and Durapore® 0.22 µm filters (**Figure 3B**) that contain a single layer of sterilizing-grade PES or PVDF membrane respectively.

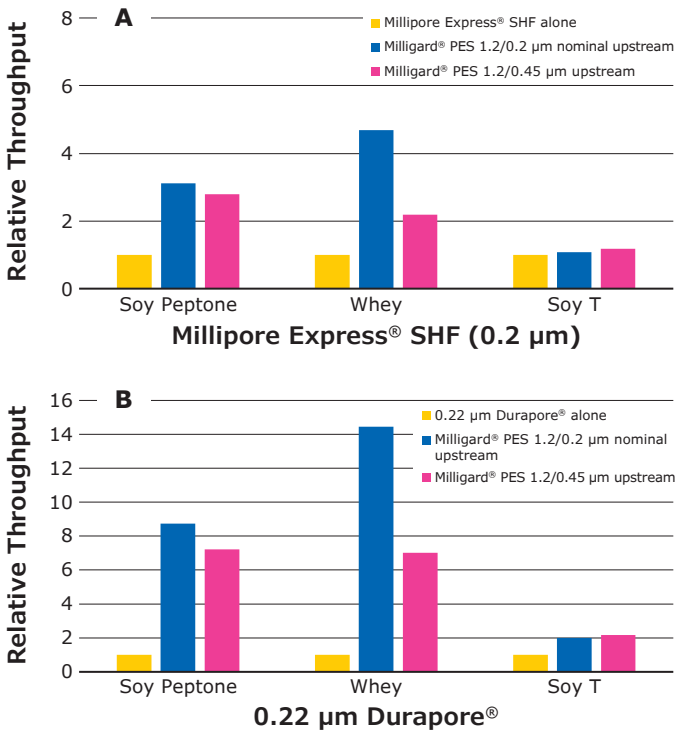

Figure 3. Relative throughput of (A) Millipore Express® SHF and (B) Durapore® 0.22 µm sterilizing-grade filters with Milligard® PES 1.2/0.2 µm nominal and 1.2/0.45 µm filters upstream. Capacity was assessed at 90% flow decay for the filtration train and is relative to sterilizing-grade filter capacity without a prefilter.

The larger pore size Milligard® PES 1.2/0.8 µm filters, were tested upstream of sterilizing-grade filters with onboard prefilters: Millipore Express® SHC (PES), and Multilayer Durapore® (PVDF) filters, **Figure 4**.

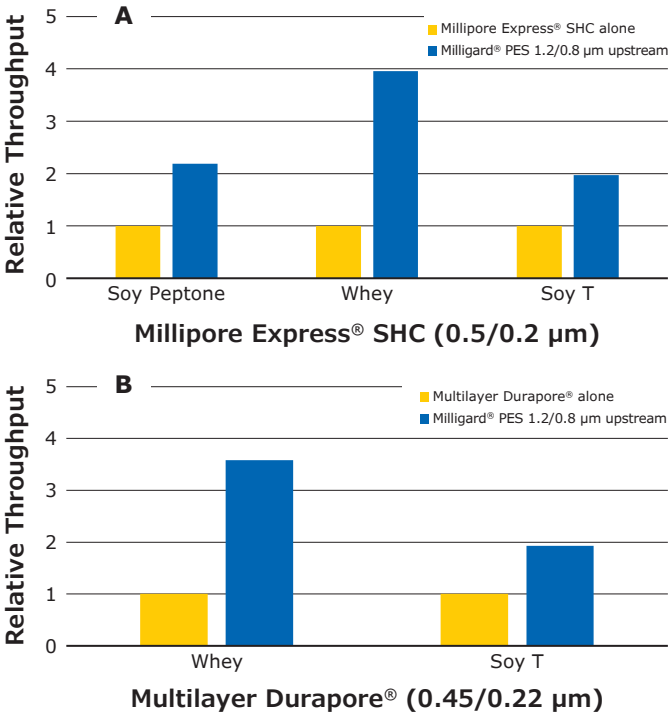

Figure 4. Relative throughput of (A) Millipore Express® SHC (PES) and (B) Multilayer Durapore® (PVDF) sterilizing-grade filters with Milligard® PES 1.2/0.8 µm prefilters upstream. Capacity was assessed at 90% flow decay for the filtration train and is relative to sterilizing-grade filter capacity alone.

In all tests, prefiltration improved the sterilizing-grade filter capacity with the benefits most pronounced in soy peptone and whey feed streams where most particles were below 1 µm in diameter. For these feed streams Milligard® PES 1.2/0.2 µm nominal filters offered the biggest benefits to capacity improvement of both PES and PVDF sterilizing-grade filters. Improvements in filter capacity were particularly noticeable for the symmetric Durapore® 0.22 µm PVDF membrane filter where they ranged from ~200–1300%, dependent on prefilter membrane and particle size distribution of the process stream. In the soy T stream, where most particles are larger than 10 µm, prefiltration offered some, but limited, benefits.

Prefiltration with Milligard® PES filters can markedly improve sterilizing-grade filter capacity but, the improvement is dependent on filter pore size, challenge stream, and the type of sterilizing-grade filter. For streams with particles below 1 µm in diameter, Milligard® PES 1.2/0.2 µm nominal filters outperformed the larger pore size filters. However, for feed streams with larger particle sizes, Milligard® PES 1.2/0.45 or Milligard® PES 1.2/0.8 µm filters may be preferred. To identify the most appropriate filter for their process conditions, it is highly recommended that users evaluate each Milligard® PES filter pore size option.

Filtration Train: how Milligard® PES filters compare to other prefilters

Milligard® PES 1.2/0.2 µm Nominal Filters

Milligard® PES filters, like other prefilters, remove particulates and improve the capacity of sterilizing-grade filters. The relative performance of Milligard® PES 1.2/0.2 µm nominal filters compared with that of Polysep™ II and Milligard® filters is shown in **Figures 5** and **6**. **Figure 5** shows results when these prefilters are upstream of Millipore Express® SHF PES filters, while **Figure 6** shows results with the prefilters upstream of Durapore 0.22 µm PVDF filters. For simplicity, comparisons were made from throughput values established at 90% flow decay for the filtration train and in all examples throughput of the various filtration trains is normalized to that of Milligard® PES filter train in the appropriate model streams. Throughput within 20% of that of the Milligard® PES filter train is considered equivalent.

When protecting both PES and PVDF sterilizing-grade filters, Milligard® PES 1.2/0.2 µm nominal filters performed equivalently to Polysep™ II (1.0/0.2 µm) filters in three of the four streams tested. In all streams, with both PES and PVDF sterilizing-grade filters, they offered better protection than Milligard® (0.5/0.2 µm) prefilters.

These results confirm that Milligard® PES filters offer similar or better protection for both PES and PVDF sterilizing-grade filters as other prefilters. Importantly, these benefits can be expected in feed streams containing a broad range of particle size distributions.

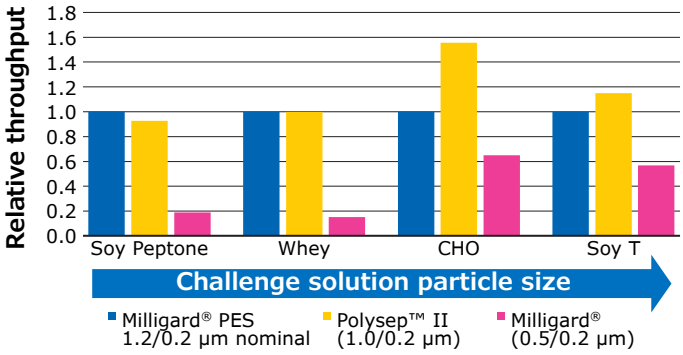

Figure 5. Relative throughput of filtration trains with Millipore Express® SHF filters. Throughput for each filtration train is normalized to that of the Milligard® PES train in each model stream.

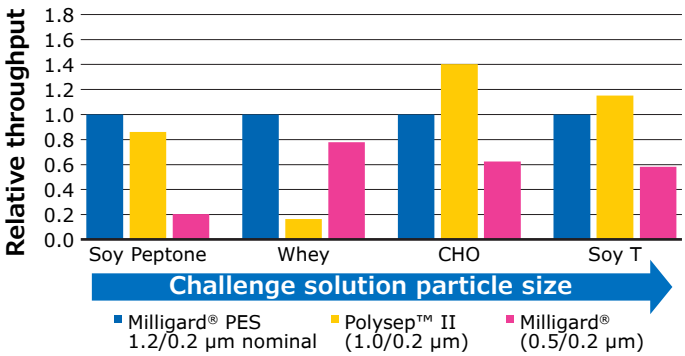

Figure 6. Relative throughput of filtration train trains with Durapore® 0.22 µm filters. Throughput for each filtration train is normalized to that of the Milligard® PES train in each model stream.

Milligard® PES 1.2/0.45 µm filters

Figure 7 shows results with Milligard® PES 1.2/0.45 µm filters upstream of Millipore Express® SHF filters. When positioned upstream, Milligard® PES 1.2/0.45 µm filters performed equivalently or better than Polysep™ II (1.0/0.5 µm) and Milligard® (1.2/0.5 µm) filters in three of the four streams. Similarly, performance of Milligard® PES 1.2/0.45 µm filters upstream of Durapore® 0.22 µm filters was equivalent or better than that of Polysep™ II in all streams and better than Milligard® prefilters in three of the four streams tested, **Figure 8**. As was the case with Milligard® PES 1.2/0.2 µm nominal filters, the relative benefit to capacity improvement was dependent on the characteristics of the feed stream and the downstream sterilizing-grade filter.

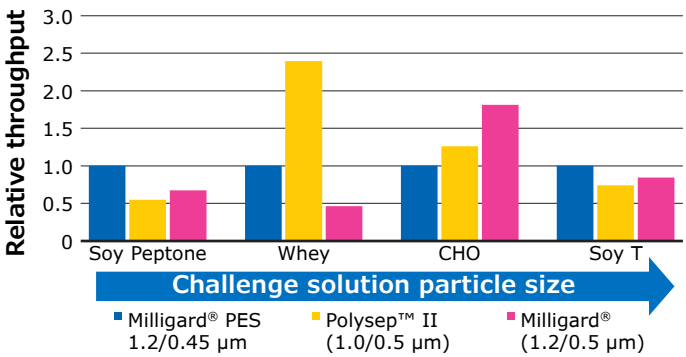

Figure 7. Relative throughput of filtration trains with Millipore Express® SHF filters. Throughput for each filtration train is normalized to that of the Milligard® PES train in each model stream.

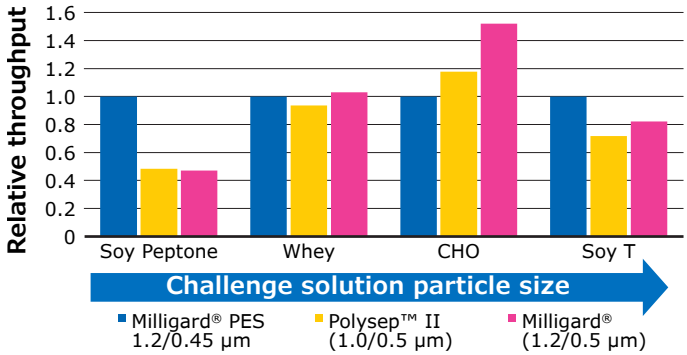

Figure 8. Relative throughput of filtration train trains with Durapore® 0.22 µm filters. Throughput for each filtration train is normalized to that of the Milligard® PES train in each model stream.

Milligard® PES 1.2/0.8 µm filters

Milligard® PES 1.2/0.8 µm membrane has a more open pore structure than the other membrane filters and can be used to protect filters that contain a single layer of sterilizing-grade membrane as well as those that contain onboard prefilters.

Figure 9 shows the relative throughput performance of filtration trains containing Milligard® PES 1.2/0.8 µm and Polysep™ II (2.0/1.2 µm) upstream of Millipore Express® SHC filters (onboard 0.5 µm PES prefilter). In three of the four streams, Milligard® PES 1.2/0.8 µm filters demonstrated equivalent performance to Polysep™ II filters, which was slightly better in the CHO stream. Similar results were obtained with these same prefilters upstream of Millipore Express® SHF filters, which do not contain an onboard prefilter (data not shown).

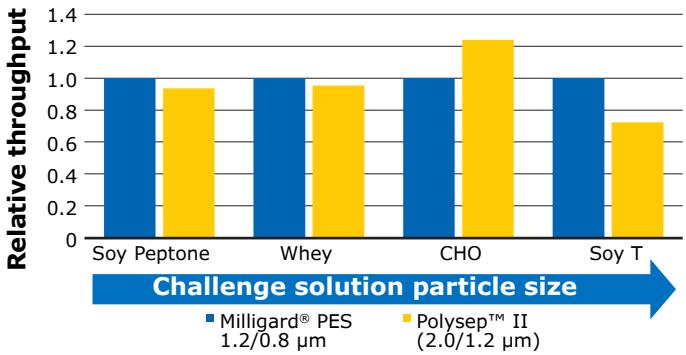

Figure 9. Relative throughput of filtration train trains with Polysep™ II (2.0/1.2 µm) filters upstream of Millipore Express® SHC filters. Throughput for each filtration train is normalized to that of the Milligard® PES train in each model stream.

Performance of Milligard® PES 1.2/0.8 µm filters was also assessed upstream of Multilayer Durapore® filters (0.45 µm onboard prefilter upstream of the 0.22 µm sterilizing-grade PVDF membrane). As with the PES filtration train, Milligard® PES 1.2/0.8 µm filters provided similar protection as Polysep™ II prefilters, **Figure 10**.

With similar particle retention performance as Polysep™ II filters, Milligard® PES 1.2/0.8 µm filters offer an option for efficient particle removal in a gamma-compatible filter format.

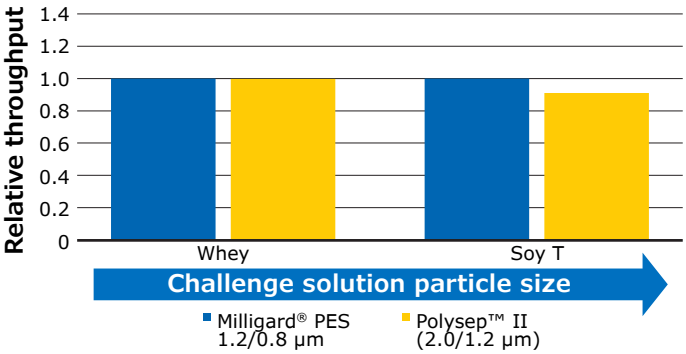

Figure 10. Relative throughput of filtration train trains with Polysep™ II (2.0/1.2 µm) filters upstream of Multilayer Durapore® filters. Throughput is normalized to that of the Milligard® PES train in each model stream.

In summary, these results provide an overview of the relative performance of Milligard® PES filters compared to benchmark prefilters in various model streams. These versatile filters remove particulates and improve capacity of sterilizing-grade filters in a range of process streams. Where filter users lack information on the particle size distribution of their process fluid, identifying the preferred membrane to maximize throughput performance may require process development screening studies.

Economic benefits of prefiltration

Results have demonstrated Milligard® PES filters can improve the throughput capacity of both PES and PVDF sterilizing-grade filters in a broad range of fluid streams. As prefilters are generally offered at lower cost than sterilizing-grade filters, this increased filter capacity will result in lower filter area requirements, which can translate to reduced costs.

The economic benefit of prefiltration with Milligard® PES 1.2/0.2 µm nominal filters was examined with the soy peptone stream, which contains particles less than 1 µm in diameter with a median particle size of about 0.2 µm. Analysis was based on a prefilter/final area ratio of 1:1. Filtration area estimates were calculated from test results and along with filter costs were used to generate the economic analysis shown in **Figure 11**.

Milligard® PES 1.2/0.2 µm prefiltration significantly increased the capacity of the sterilizing-grade filters, reducing the number of filters needed to process a batch and thereby significantly reducing the cost of filtration. In this example, the benefit of prefiltration was greater for the symmetric PVDF filter compared to the asymmetric PES filter.

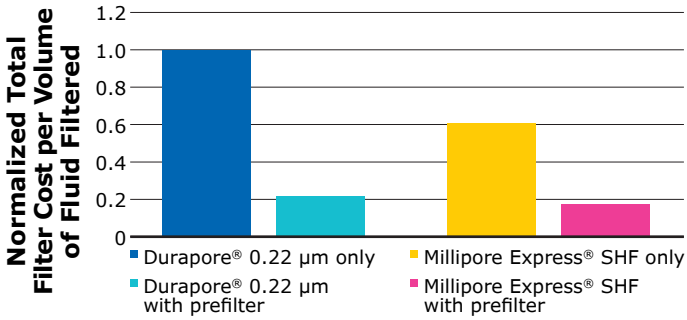

Figure 11. Filtration cost comparisons for filtration trains with Durapore® 0.22 µm and Millipore Express® SHF sterilizing-grade filters when Milligard® PES 1.2/0.2 µm nominal filters are positioned upstream.

Conclusions

Milligard® PES filters contain PES membranes in three pore size combinations. Each membrane removes particulates to varying degrees, and Milligard® PES 1.2/0.2 µm nominal and Milligard® PES 1.2/0.45 µm filters also provide significant bioburden reduction. Our results demonstrate that:

- Milligard® PES filters improve the throughput capacity of sterilizing-grade PES and PVDF filters. Capacity improvement provided by these gamma-compatible and thermo-stable prefilters was equal to or better than that of prefilters that cannot be sterilized. The level of improvement is dependent on prefilter pore size, process feed and the downstream sterilizing-grade filter.
- Implementing Milligard® PES prefilters can significantly improve filtration process economics by reducing the number of sterilizing-grade filters required.
- Selection of the most appropriate Milligard® PES membrane option for a specific process feed will likely require process development screening studies. Please contact our Technical Support representatives for additional information.

References:

1. Bioburden Reduction and Particulate Retention Using Milligard® PES Filters. Tech. Note TN5193EN.
2. Recommendations for Steam-in Place Sterilization of Filtration Trains containing Milligard® PES Prefilters. Tech. Note TN5022EN.

MilliporeSigma
400 Summit Drive
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