

Processing mAb streams

How a bioburden reduction filter can improve process efficiency

Summary

Millipore Express® SHC membrane filters contain an onboard prefilter and are the preferred filter for sterilizing-grade filtration of process intermediates. However, for downstream processing steps that may require bioburden control, rather than sterilizing-grade filtration, Milligard® PES filters are an alternative to Millipore Express® SHC filters and offer high capacity and excellent microbial retention at lower cost.

This report summarizes capacity advantages of Milligard® PES as compared to Millipore Express® SHC filters following clarification and ultrafiltration and diafiltration (UF/DF) steps.

Background

Biopharmaceuticals such as monoclonal antibodies (mAb) or recombinant proteins are produced by mammalian cells in a bioreactor. Following harvest, material is clarified then processed through a series of sequential steps that purify the molecule of interest

from process impurities. Sterilizing-grade membrane filters are used throughout these downstream purification steps for bioburden control and to protect costly unit operations from particulate impurities, **Figure 1** ⁽¹⁾.

For filtration of process intermediates that contain particulate impurities, we typically recommend Millipore Express® SHC membrane filters; these filters contain an onboard prefilter, which maximizes the throughput capacity of the sterilizing-grade membrane. Milligard® PES filters could be considered as an alternative to Millipore Express® SHC filters offering bioburden reduction rather than sterilizing-grade performance, **Table 1**.

This report summarizes relative throughput capacity performance of these filters at different processing steps with mAb fluid streams. The information provided may guide product selection however it is always recommended to run process development screening studies before selecting a filtration product. Please contact our technical support representatives for additional information.

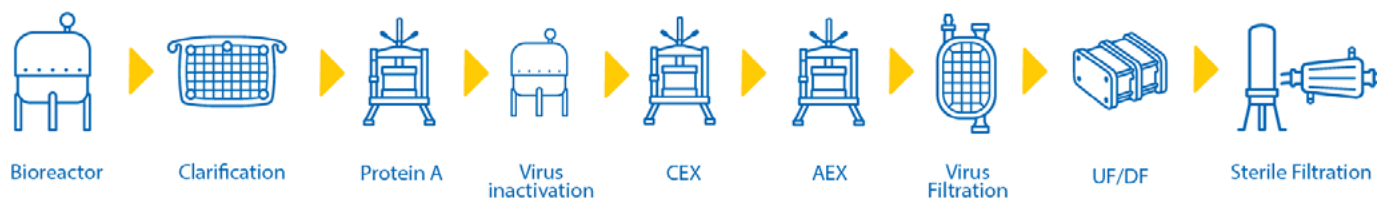


Figure 1. Typical mAb process train. Sterilizing-grade membrane filters may be placed immediately upstream of multiple chromatographic or UF/DF purification steps.

Specification	Milligard® PES 1.2/0.2 µm nominal	Millipore Express® SHC
Membrane Material	Polyethersulfone	Polyethersulfone
Pore Size	1.2/0.2 µm nominal	0.5/0.2 µm
Bacterial Retention Specification	Bioburden reduction Typically $\geq 6 \log_{10}$ reduction of <i>Brevundimonas diminuta</i>	Sterilizing-grade Quantitative retention of <i>Brevundimonas diminuta</i>

Table 1. Comparison between Milligard® PES and Millipore Express® SHC filters.

Filtration Following Clarification

Clarification reduces cellular debris and particulates from the cell culture harvest material before downstream purification. Typically, the approach to clarification, in terms of centrifugation or filtration, is determined by batch volume ⁽²⁾.

Approach to Clarification - depends on volume processed

≤1000 L volume: clarification using multi-stage depth filtration offers cost savings compared to centrifugation.

~2000 L volume: costs are similar between depth filtration and centrifugation. Important factors in selecting clarification approach include: facility utilization, capital, ease of process development, timelines and process performance.

≥5000 L volume: clarification using centrifugation followed by depth filtration offers significant cost savings.

To protect downstream operations from particulate impurities and bioburden contaminants, clarified harvest is usually filtered through a sterilizing-grade membrane filter. As compared to sterilizing-grade filters, Milligard® PES filters offer improved throughput capacity with bioburden control, and the added appeal of cost savings.

Improved filter capacity

Cell culture harvests were clarified using different methods. Material for Tests 1 and 2 was clarified using continuous centrifugation, then processed over depth filters. Test 3 harvest material was processed over two depth filters, while material for Tests 4-6 was processed over a single depth filter.

Harvest material was then filtered over Milligard PES 1.2/0.2 µm nominal or other bioburden reduction or sterilizing-grade filters. Filter capacity at 90% flow decay (V90) is shown in **Figure 2**.

For all clarified harvest streams, Milligard® PES 1.2/0.2 µm filters demonstrated higher capacity than other bioburden reduction or sterilizing-grade filters, with capacity improvements ranging from 1.28x -2.73x.

Relative Throughput (L/m²) at 90% Flow Decay

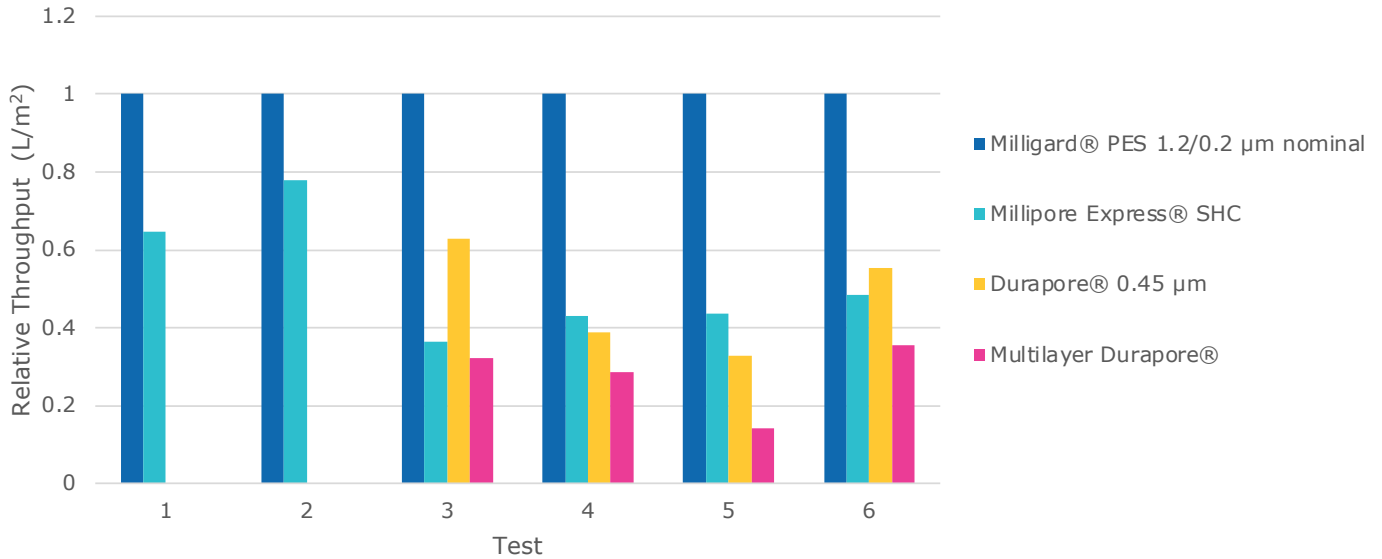


Figure 2. Relative throughput capacity of clarified harvest streams over bioburden reduction and sterilizing-grade membrane filters. Millipore Express® SHC filters contain 0.5/0.2 µm membrane, Multilayer Durapore® filters contain 0.45/0.22 µm membrane.

Filtration post UF-DF

After virus filtration, process intermediates may be concentrated, and buffer exchanged through ultrafiltration and diafiltration (UFDF) before formulation and final filtration and filling steps. However, high concentration process intermediates can be challenging to process over sterilizing-grade filters, resulting in low filter capacity.

Maximizing filter capacity

The relative capacity of Milligard® PES 1.2/0.2 µm nominal and Millipore Express® SHC membrane filters were compared for a high concentration (200 g/L), post UFDF, mAb feed.

For this high concentration process stream, the capacity of Milligard® PES 1.2/0.2µm nominal filters was almost double that of Millipore Express® SHC filters, **Figure 3**.

Relative Throughput (L/m²) at 90% Flow Decay

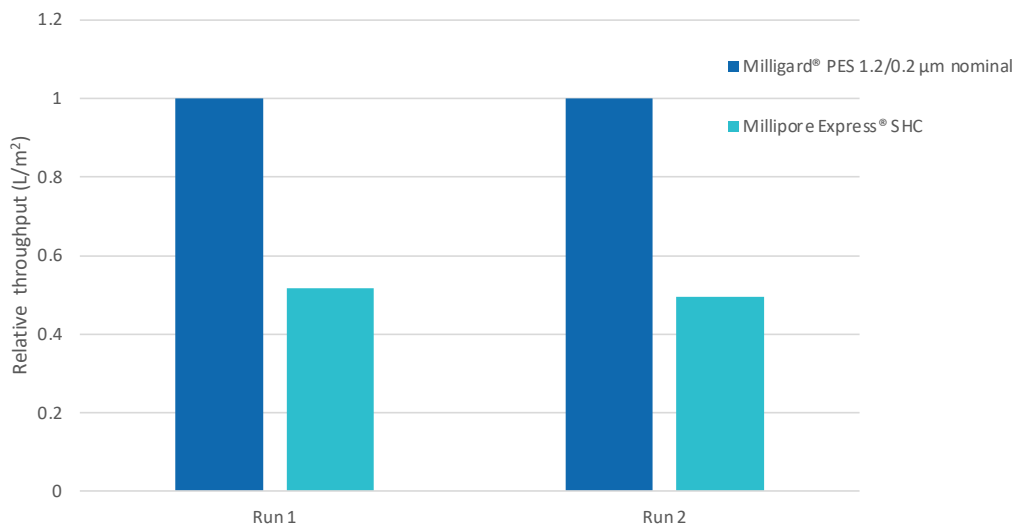


Figure 3. Relative throughput capacity of a high concentration UFDF mAb feed stream over Milligard(R) PES 1.2/0.2 µm nominal and Millipore Express® SHC filters.

Conclusions

Sterilizing-grade membrane filters are used throughout mAb downstream purification to control bioburden and protect unit operations. For many process intermediates, Milligard® PES filters provide higher throughput capacity than sterilizing-grade filters and offer opportunities for significant process efficiency. Higher throughput means less filtration area, fewer filters and reduced resources dedicated to the different steps of filter purchasing, storage, installation and use.

As biopharma manufacturers drive efficiencies across the entire process, Milligard® PES filters are an attractive, cost-effective, alternative to sterilizing-grade membrane filters for non-critical process steps.

References:

1. Bain, D. "Microbial Monitoring For Biological Drug Substance Manufacturing: An Industry Perspective," BioPhorum Operations Group. 2015.
2. Felo M., Christensen B., Higgins J. (2013). Process Cost and Facility Considerations in the Selection of Primary Cell Culture Clarification Technology. *Biotechnol Prog.* 29(5):1239-45. doi: 10.1002/btpr.1776. Epub 2013 Jul 11.

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