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Reducing Total Cost of Ownership in Media Filtration

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Abstract

Cell culture media is an essential component of all biopharmaceutical processes. Due to the high consumption of media, its preparation, handling, and filtration is an excellent target for process optimization under economic aspects. Especially membrane filters made of polyethersulfone (PES) have set a gold standard related to their overall performance. Variations in pore size, membrane structure as well as the addition of different fleeces allow for dedicated filter types that show outstanding performance in their target applications. This paper shows how PES-based membrane filters can be used for optimizing filtration of different media types to reduce the total cost of ownership.

Introduction

The production of monoclonal antibodies (mAb) and recombinant proteins has undergone significant progress in recent decades. Increasing cell densities and higher titers present challenges to upstream and downstream bioprocessing groups alike. In downstream processing, this challenge is quite clear (i.e., purification of larger product masses with currently available equipment | technologies is an on-going industry topic), but these changing conditions bring major challenges in upstream bioprocessing as well. In some cases, mammalian cell culture media volumes are getting larger, but in others, media formulations are becoming more and more process-specific to where higher titers are observed and smaller volumes are needed, which is a situation conducive to single-use processing. Regardless of volume, these changes require improvements to media filtration technology to sterilize cell culture media entering the bioreactor as well as to improve process efficiency.

Despite advances in sterilizing-grade filtration technology from filter manufacturers, many biopharmaceutical companies continue to utilize outdated technology, which is costlier and less efficient. Whether companies are looking into changing their media filtration operations to troubleshoot bottlenecks or to be proactive in reducing costs, this large volume step represents a major opportunity to upgrade technology. Optimizing the media filtration step also facilitates adaptation of the filters themselves into single-use processes because fewer amounts of filters are required (for example, moving from a multi-round housing to a single capsule that can be sterilized along with gamma irradiatable tubing and single-use bags).

Drawbacks of Existing Filter Membranes

Many companies are still operating with 0.2 µm (0.22 µm) or 0.1 µm membrane filtration technology – polyvinylidene fluoride (PVDF), cellulose acetate (CA), and polyamide (PA) membranes, for example. Issues associated with these filter membranes include filter clogging (i.e., large numbers of filter elements used per batch) and longer cycle times. Non-optimized filter membranes provide lower flow rates and throughput compared to polyethersulfone (PES) membranes, and also result in increased utility costs associated with large flush volumes required for larger filter sizes prior to steam-in-place.

Additionally, frequent filter replacement leads to higher costs in terms of both the number of filters needed and the labor and utility costs that result from process interruptions. Frequent filter replacement also means there is a greater chance of operator error (e.g., improper installation of the filter) since more process manipulations are required. Consequences of this could include nonconformances due to contamination (often resulting in a lost batch), incorrect filter usage, and unfiltered media due to bypass.

Even in production environments where media filtration is currently functioning without problems, companies should recognize that media filtration is an ideal place to reduce manufacturing costs because media often requires such a large amount of filtration area.

Out of all steps in a bioprocess, this step is usually the largest "dead-end" filtration area requirement (and largest filter spend), so technology – both advancements in filter membrane technology and the wide availability of filters that are now specifically designed for media filtration – can make a substantial impact in cost reduction.

Legacy membranes may not be able to handle process changes well. If a media formulation parameter changes (e.g., raw material change), it is possible that older membranes may not perform as well in terms of throughput (in L/m^2) because those membranes are not optimized for these situations.

Standardization for Validation of 0.1 µm Filter Membranes

The American Society for Testing and Materials (ASTM) International established ASTM F 838-83, a standard for 0.2 µm filters. This benchmark signifies that there is a foundation on which filter manufacturers can build their 0.2 µm retention rating, and customers have peace of mind that 0.2 µm filters have passed bacterial challenge testing (LRV ≥ $7/cm^2$ for *Brevundimonas diminuta*).

Parental Drug Association (PDA) published a Technical Report (ANSI/PDA Standard 05-2021) on a consensus method for proving 0.1 µm rated filters in 2021, which includes a standardized method for the preparation of *Acholeplasma laidlawii* as the test organism.

It is important for filter purchasers to understand that not all 0.1 µm filters are designed equally and that they must work with their specific filter supplier and clarify how their mycoplasma validation was performed to determine if filters are suitable for their application.

PES Membrane Technologies Specific to Media Filtration

Application-specific, media-specific PES filter membranes are available in several types (prefilters and final filters for both 0.1 µm and 0.2 µm ratings), designed around certain common formulations.

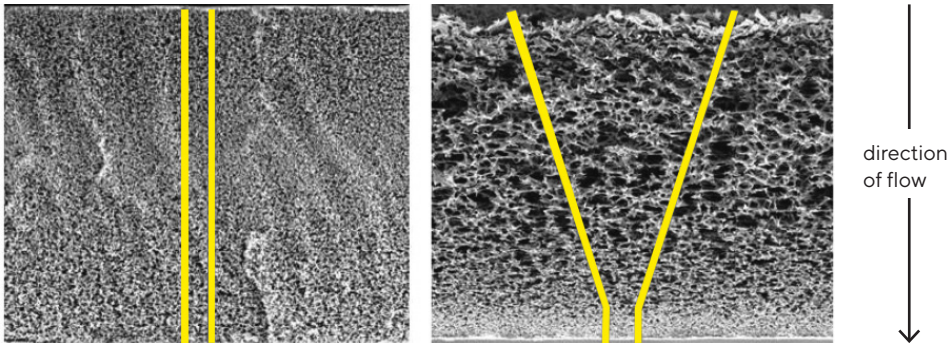
Commonly used cell culture media fall into three categories:
(1) conventional media containing glucose, salts, amino acids, vitamins, and sera, (2) serum-free media, which includes complex media, soy hydrolysate-containing media (plant peptone), and protein-free media, and (3) chemically defined media, which is serum-free and does not contain plant or animal ingredients.

Use of chemically defined media continues to grow due to the greater reproducibility of expression of the protein of interest, and the fact that there is less risk of pathogenic contamination because of the lack of animal components.

PES Membranes

PES membranes are composed of a highstrength polymer, and because of the high degree of membrane asymmetry that can be achieved with PES, they allow for superior filtration and higher throughputs and flow rates compared to other membranes in media filtration applications (Figure 1).

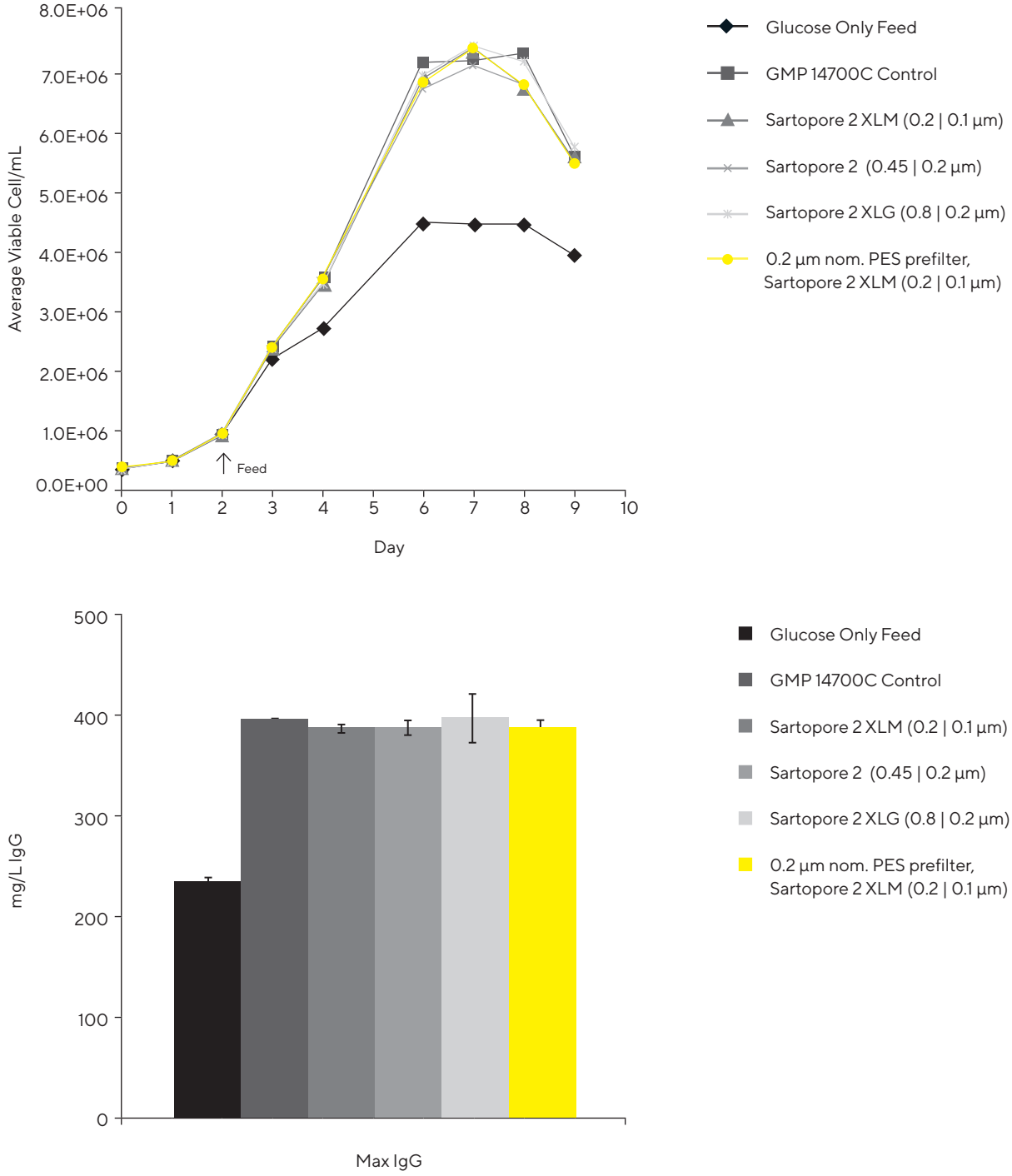
Figure 1: *Membrane Cross Sections*



Note. Comparison of symmetrical membrane (Cellulose Acetate, left) with asymmetrical membrane (Polyethersulfone, right).

Additionally, use of PES membranes does not adversely impact cell growth or productivity. A fed-batch study, performed with CHO-IgG and a chemically defined media from a major media supplier, demonstrated that the maximum cell density for all media filtration conditions were similar, indicating no growth performance differences based on filtration trains (Figure 2).

Figure 2: *Results of a Fed-Batch Study With CHO-IgG to Verify No Intereference of PES Membranes on Cell Growth and Viability*



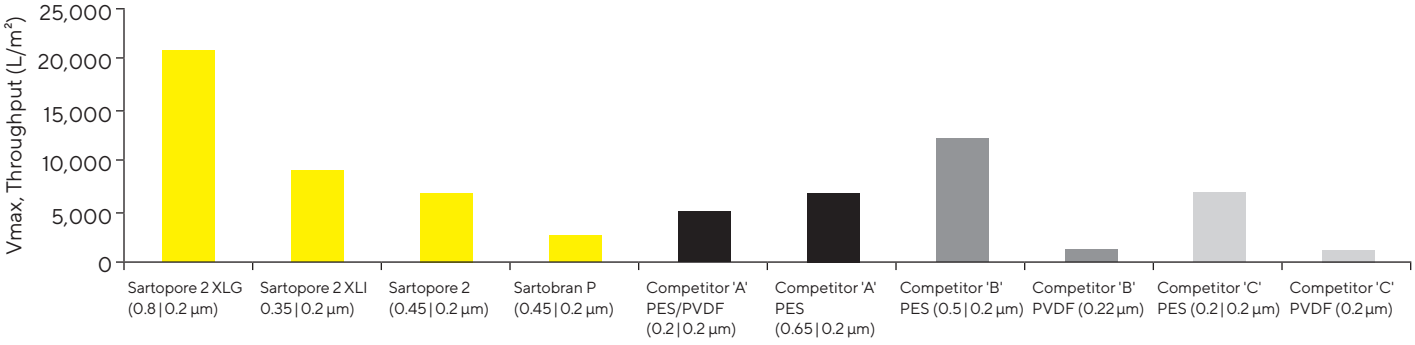
Sartopore® XL Series - Sterilizing-grade and Mycoplasma Retention Filters

Sartorius offers PES membranes in a range of configurations to suit many applications, such as the Sartopore® 2 XL series:

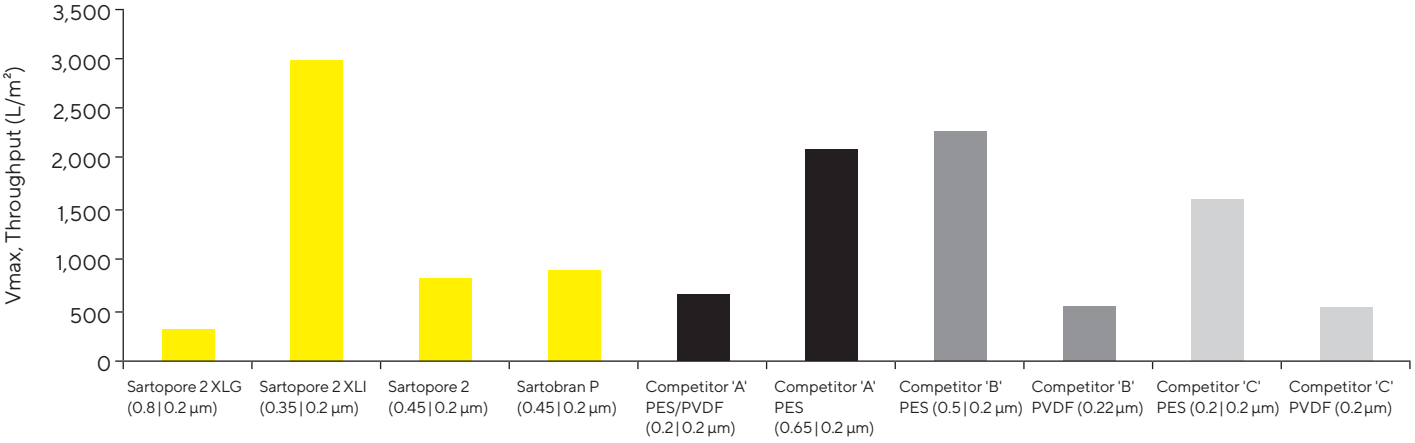
- Sartopore® 2 XLI and XLG: Dual-layer filters with a prefilter layers of 0.35 µm for XLI and 0.8 µm for XLG, in front of a 0.2 µm sterilizing-grade filter membrane layer. These filters offer high effective filtration area and provide outstanding total throughput and flow rate performance for optimized filter sizing and shorter cycle times (Figure 3). The Sartopore® 2 XLI is suited for chemically defined culture media, while the XLG is suited to most other types of serum-free media.

Figure 3: *Average Throughput (L/m²) of Different 0.2 µm Membrane Filters for Specific Cell Culture Media Types*

Serum-Free, Protein-Free Soy Hydrolysate Containing Cell Culture Media



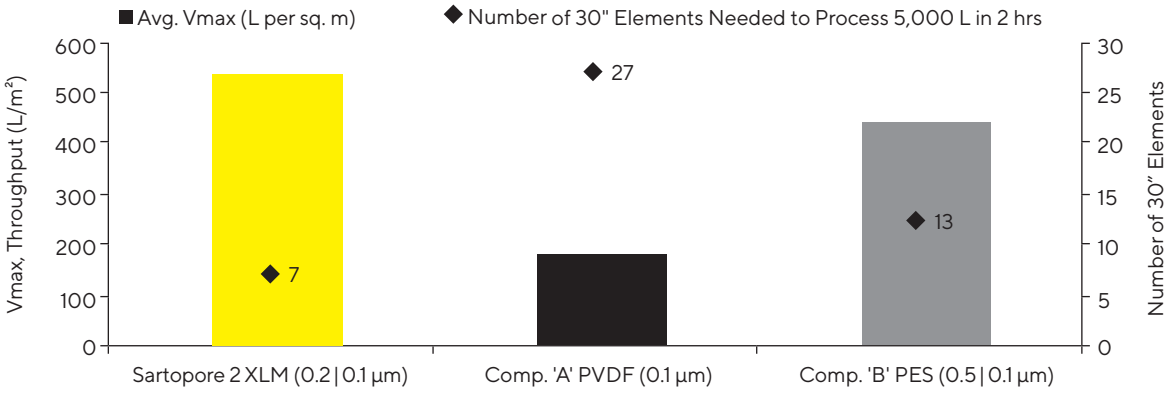
Chemically Defined Cell Culture Media



- Sartopore® 2 XLM: This 0.1 µm rated filter is especially designed for sterilizing-grade filtration for modern cell culture media requiring 0.1 µm filtration and is validated for mycoplasma removal (LRV ≥7/cm² for *Acholeplasma laidlawii*). A recent study showed that Sartopore® 2 XLM had higher throughput and required significantly fewer filter elements compared to competitors' PVDF and PES membranes (Figure 4).

Figure 4: *Impact on Filter Consumption by Average Throughput Performance*

Average Throughput and Number of 30" 0.1 µm Filter Elements Needed for 5,000 L Batch of Chemically Defined Media in 2 hr Processing Time



- The unique, highly asymmetric, heterogeneous double-layer PES membranes offered by the Sartopore® 2 XL series provide throughput and flow rate performance that significantly reduces filter costs and the footprint of filtration systems.

Sartoguard Prefilters

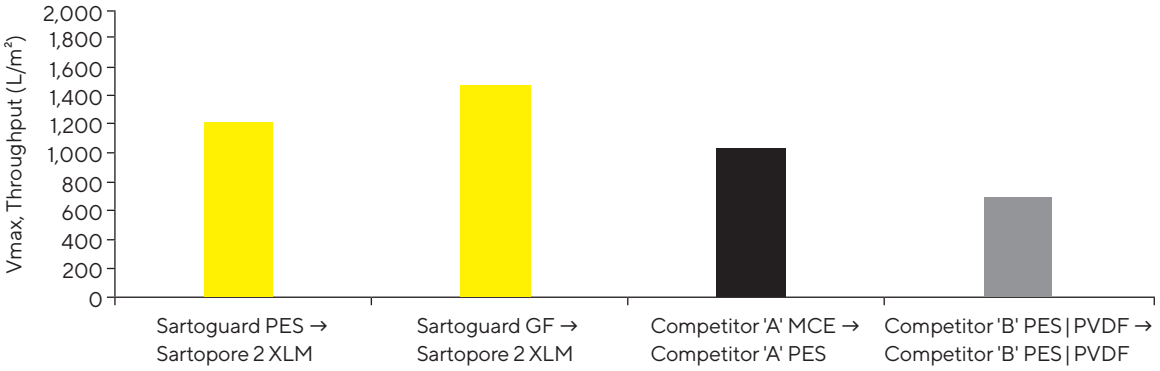
The Sartoguard prefilter family from Sartorius is a range of PES membrane prefilters which can be used for protection of final filters. All types are available in 0.1 and 0.2 µm nominal retention ratings, designed for protection of 0.1 and 0.2 µm absolute, sterilizing-grade filters:

- Sartoguard PES features a unique heterogeneous dual-layer membrane construction, ideal for protection of mycoplasma retentive or sterilizing-grade filters. It also allows for downsizing of filtration systems and cost saving in applications where the use of validated sterilizing-grade filters is not required, but reliable bioburden and turbidity reduction are needed.
- Triple-layer Sartoguard GF, which combines the defined retention performance of membrane filters with the high adsorptive power of glass fiber fleeces, is ideally suited for retention of particles, colloids, and lipids, which block more expensive sterilizing-grade or mycoplasma retentive membrane filters quickly.

Sartoguard prefilters provide effective bioburden control and have demonstrated superior throughput in combination with Sartopore® XL final filter elements when compared to systems using Mixed Cellulose Esters (MCE) or PES/PVDF prefilter membranes (Figure 5).

Figure 5: *ACF CHO Medium (Containing ATA) System Throughput*

Average Throughput of Various Filtration Trains for Mycoplasma Retention of Cell Culture Media



Benefits of Application-Specific PES Membranes

PES membranes from Sartorius show improved performance, allowing for higher throughput and flow rates; a three to five fold difference in throughput performance requires three to five times less membrane area in PES compared to legacy membranes (Figures 3-5). One customer reported savings on the order of ~6-7 figures/year for large-scale commercial manufacturing using the Sartopore® 2 XLM as compared to the incumbent 0.1 µm PVDF membrane.

High performance PES membranes reduce the number of filter installations as well as the overall media filter footprint, in turn reducing the downtime and labor costs for setup and cleaning. Studies have also indicated that growth performance does not differ with use of PES membranes (Figure 2).

Single-use Integration

Single-use filtration solutions continue to become more widely adopted, particularly in clinical manufacturing. Manufacturers looking to add the ease and flexibility of single-use to their operations can take advantage of PES filtration technology, as Sartorius offers all of its filters in single-use format.

Sartorius also offers sterile filter transfer sets that provide a variety of options for sterile connectors, tubing, and, as stated previously, different filter types, providing a high degree of flexibility. Any Sartorius filter capsule can be purchased as part of a ready-to-use, pre-sterilized filter transfer set; gamma-irradiatable filters are provided gamma-irradiatable, and if a particular filter is not gamma-irradiatable (Sartoguard GF, for example) the filter transfer set is provided pre-sterilized via autoclaving.

Risk Mitigation and Future Cases

There is much discussion in the bioprocessing industry centered on reducing adventitious agents. While it is not a regulatory requirement, the elimination of viruses from media streams is an important consideration for risk mitigation. Along these lines, Sartorius is offering the virus filter Virosart® Media specifically for media filtration. Though viral filtration is one way to address this risk, other customers have also implemented HTST (High Temperature Short Time) or UV-inactivation.

Closing Thoughts

Studies have demonstrated that PES membranes can have significant effects on throughput with superior clarification capabilities, without impacting cell culture performance. Opportunities exist to upgrade to media-specific PES filtration technologies that allow for both easier implementation into single-use processes and reduced costs associated with media filtration.

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