

Reducing Total Cost Of Ownership In Media Filtration

White Paper

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Overview

The production of monoclonal antibodies (mAb) and recombinant proteins has undergone significant progress in recent decades. Higher titers and increasing cell densities 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sterilizing-grade filtration technology from filter manufacturers, many biopharmaceutical companies continue to utilize outdated technology, which is costlier and less efficient.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 housings to a single capsule that can be sterilized along with a single-use bag, if desired).

Drawbacks of Existing Filter Membranes

Many companies are operating with 0.2 μm (0.22 μm) or 0.1 μm membrane filtration technology – PVDF, cellulose acetate, and nylon membranes, for example – that is over ten years old. 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 newly developed 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.

Lack of Standardization for Validation of 0.1 μm Filter Membranes

ASTM International established ASTM F 838-83, a standard for 0.2 μm filters in 1983, (it was subsequently reviewed and reissued as F838-05 in 2005 and is in review again in 2015). 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 ($\text{LRV} \geq 7/\text{cm}^2$ for *Brevundimonas diminuta*). Though 0.1 μm filters are usually validated as sterilizing-grade filter membranes in the same way that 0.2 μm filter membranes are validated, a similar standard does not currently exist to ‘prove’ that the filter carries a 0.1 μm rating. It’s important for 0.1 μm filter purchasers to understand that not all 0.1 μm filters are created equally, and that they must work with their specific filter supplier and research how their mycoplasma validation was performed to determine if filters are robust for their application.

Parental Drug Association (PDA) is currently in the process of publishing a Technical Report on a consensus method for rating 0.1 μm rated filters, which will include a standardized method for the preparation of *Acholeplasma laidlawii* as the test organism.

New PES Membrane Technologies Specific to Media Filtration

Application-specific, media-specific PES filter membranes are now 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 no risk of pathogenic contamination because of the lack of animal components.

PES Membranes

PES membranes are composed of a high-strength 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).

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).

Sartorius Stedim Biotech 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.

- 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 $\geq 7/cm^2$ 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).

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.

The Sartoguard® Prefilter Family from Sartorius Stedim Biotech is a range of PES membrane prefilters which can be used for protection of final filters, all available in 0.1 and 0.2 µm nominal retention ratings:

- 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.

- The Sartoguard® NF prefilter, which includes a triple-layer configuration and newly developed nanofleece technology, offers significant cost-saving potential due to its ultrafine retention performance, which ensures removal of even extremely small particulate-based contaminants.

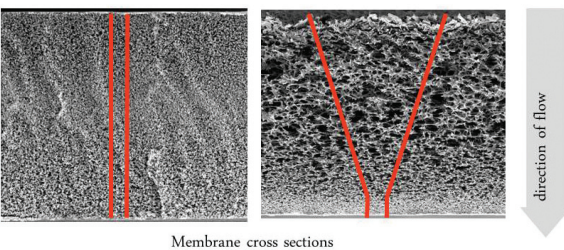


Figure 1. Comparison of symmetrical membrane (Cellulose Acetate, left) with asymmetrical membrane (Polyethersulfone, right).

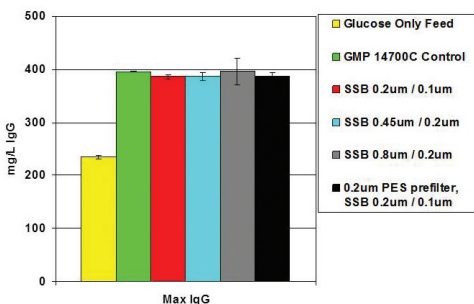
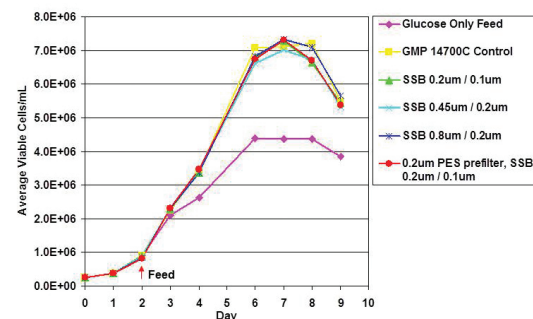


Figure 2. A fed-batch study was performed with CHO-IgG. The maximum cell density and IgG production for all filtration conditions are similar indicating no performance differences based on filtration trains.

All three of the Sartoguard® PES prefilters provide effective bioburden control and have demonstrated superior

throughput when compared to systems using Mixed Cellulose Esters (MCE) or PES/PVDF prefilter membranes (Figure 5).

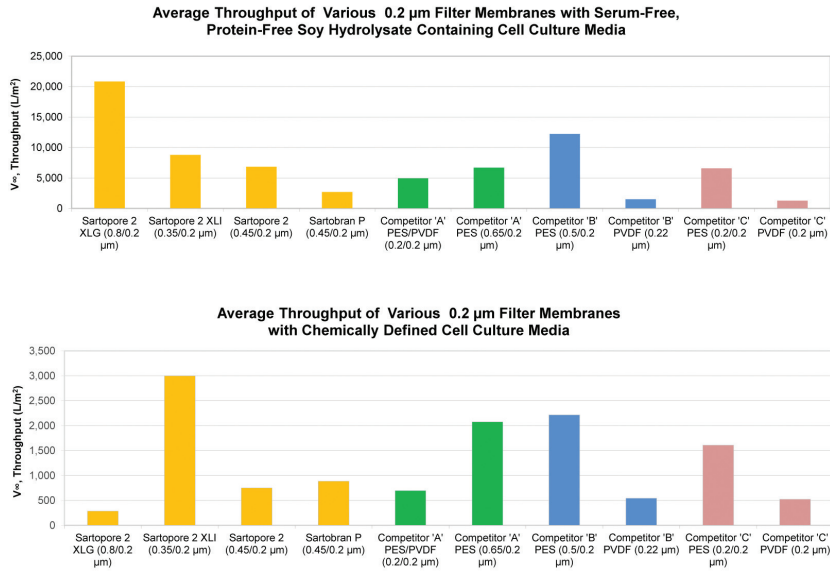


Figure 3. Average throughput (L/m²) using 0.2 µm filter membranes with (1) a serum-free, protein-free soy hydrolysate containing media (top) and (2) a chemically defined cell culture media (bottom).

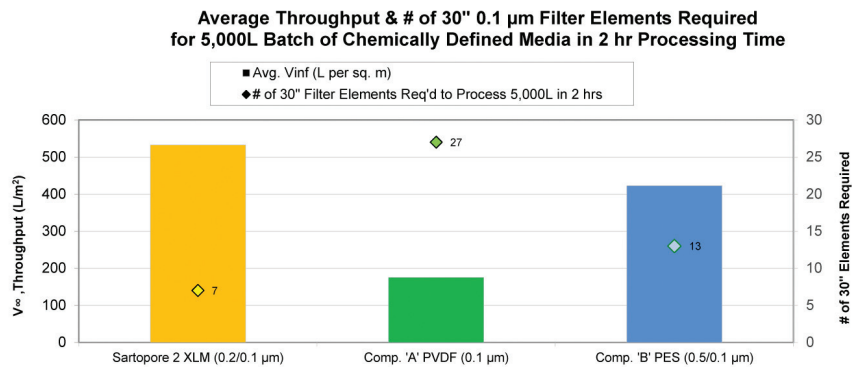


Figure 4. Average throughput (L/m²) of 0.1 µm filter elements and number of 30" elements required for 5,000 L batch of a chemically defined cell culture media (2 hour processing time).

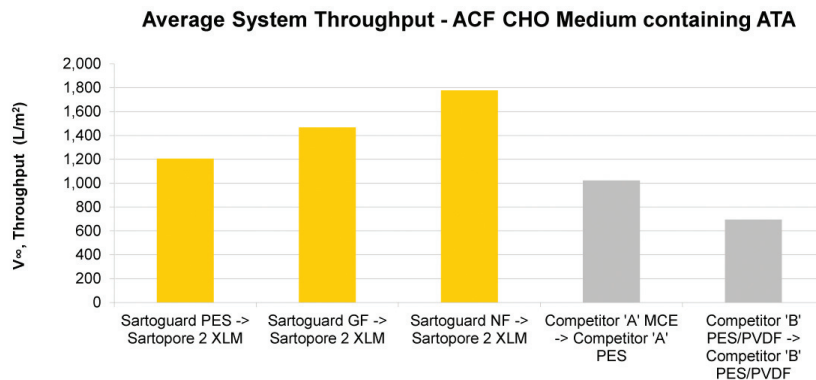


Figure 5. ACF CHO medium (containing ATA) system throughput (L/m²) of Sartoguard® prefilters (PES, GF and NF) each with Sartopore® 2 XLM final filter, compared to systems using MCE prefilter with PES final filter and PES/PVDF prefilter with PES/PVDF final filter.

Benefits of Application-Specific PES Membranes

PES membranes from Sartorius Stedim Biotech 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 Stedim Biotech offers all of its filters in single-use format.

Sartorius Stedim Biotech 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 Stedim Biotech filter capsule can be purchased as part of a ready-to-use, pre-sterilized filter transfer set; gamma-irradiatable filters are provided gamma-irradiated, and if a particular filter is not gamma-irradiatable (Sartoguard® GF, for example) the filter transfer set is provided pre-sterilized via autoclave.

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 Stedim Biotech is currently developing a viral filter specifically for media filtration. Though viral filtration is one way to address this risk, other customers have also implemented HTST (high-temp short time) or UV-inactivation.

Closing Thoughts

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

About The Authors

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A profile of Sartorius Stedim Biotech

Sartorius Stedim Biotech is a leading provider of cutting-edge equipment and services for the development, quality assurance and production processes of the biopharmaceutical industry. Its integrated solutions covering fermentation, cell cultivation, filtration, purification, fluid management and lab technologies are supporting the biopharmaceutical industry around the world to develop and produce drugs safely, economically and in a timely manner. Sartorius Stedim Biotech focuses on single-use technologies and value-added services to meet the rapidly changing technology requirements of the industry it serves. Strongly rooted in the scientific community and closely allied with customers and technology partners, the company is dedicated to its philosophy of "turning science into solutions."

ambr® systems are designed and manufactured by TAP Biosystems (now part of the Sartorius Stedim Biotech Group), a leading global provider of automated cell culture and fermentation systems for life science research, development and production. ambr systems are widely used for cell line development and process optimisation at pharmaceutical, biotechnology and academic laboratories. They are proven to provide a reliable model and consistent scalability to a range of upstream processes.

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