solventum

Advancing process efficiency of biotherapeutic production with a chromatographic clarification platform

Joris Van de Velde, Catherine Bineau, Masa Nakamura, Elliott Zell
Solventum Purification and Filtration – Bioprocessing Filtration, St. Paul, MN

Introduction

Advanced therapies, including monoclonal antibodies, offer promising opportunities for effectively treating various medical conditions, particularly life-threatening diseases and chronic illnesses. These innovative treatments have the potential to improve or save patients' lives, while also enabling biopharma companies to reinvest proceeds into research and development, fueling the discovery of future therapies. As such, it is necessary for biopharmaceutical companies to rapidly advance their candidate pipeline through discovery, clinical, and eventually commercial manufacturing in an efficient manner. Speed to market becomes imperative for manufacturers to deliver these life-changing and life-saving therapies to patient populations and to maintain patent exclusivity in the market.

Monoclonal antibodies have become some of the best-selling biopharmaceutical therapies worldwide, making up half of the top 10 selling drugs in 2023.[1,2] With the large patient populations served and the extensive costs associated with bringing these therapies to market, manufacturing efficiency becomes a critical driver of the path to commercialization.

In this application note, we revisit harvest and clarification as a critical step in the monoclonal antibody (mAb) manufacturing process, and examine how adopting a chromatographic clarification strategy can enhance process efficiency from the perspectives of economics, platformability, and sustainability.

The accompanying case study demonstrates that implementing a chromatographic clarification platform can significantly improve manufacturing economics by increasing productivity through higher product recovery and process simplification across scales and workflows. Furthermore, this approach enhances sustainability by lowering Process Mass Intensity (PMI) compared to traditional clarification methods that rely on wet-laid depth filtration media (Figures 1a and 1b).

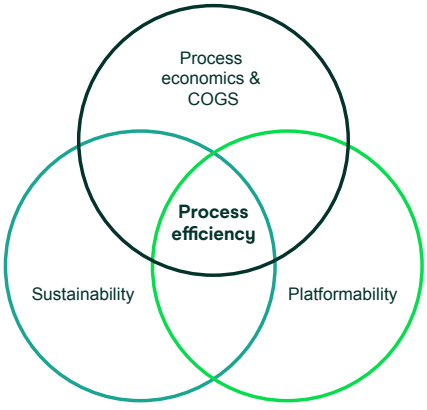


Figure 1a: Components of process efficiency.

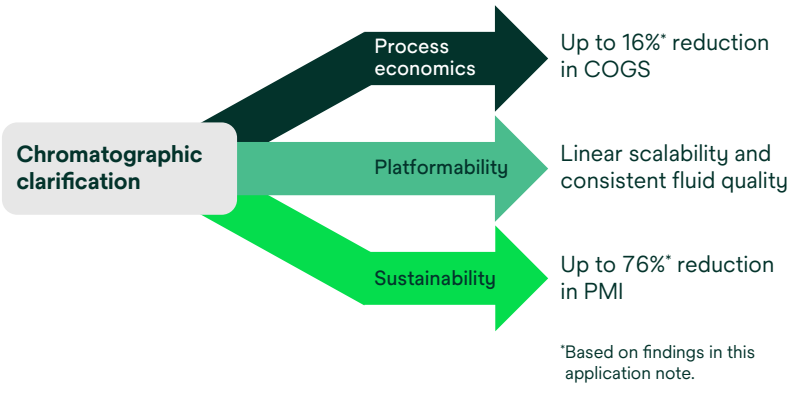


Figure 1b: Process efficiency improvements with chromatographic clarification.

Current state of clarification

Monoclonal antibody manufacturing has relied on a version of the process depicted in Figure 2 to produce monoclonal antibodies since the emergence of these therapies in the late 1990s and early 2000s. Since then, biopharmaceutical organizations have been continually developing and implementing strategies aimed at improving overall process efficiency.

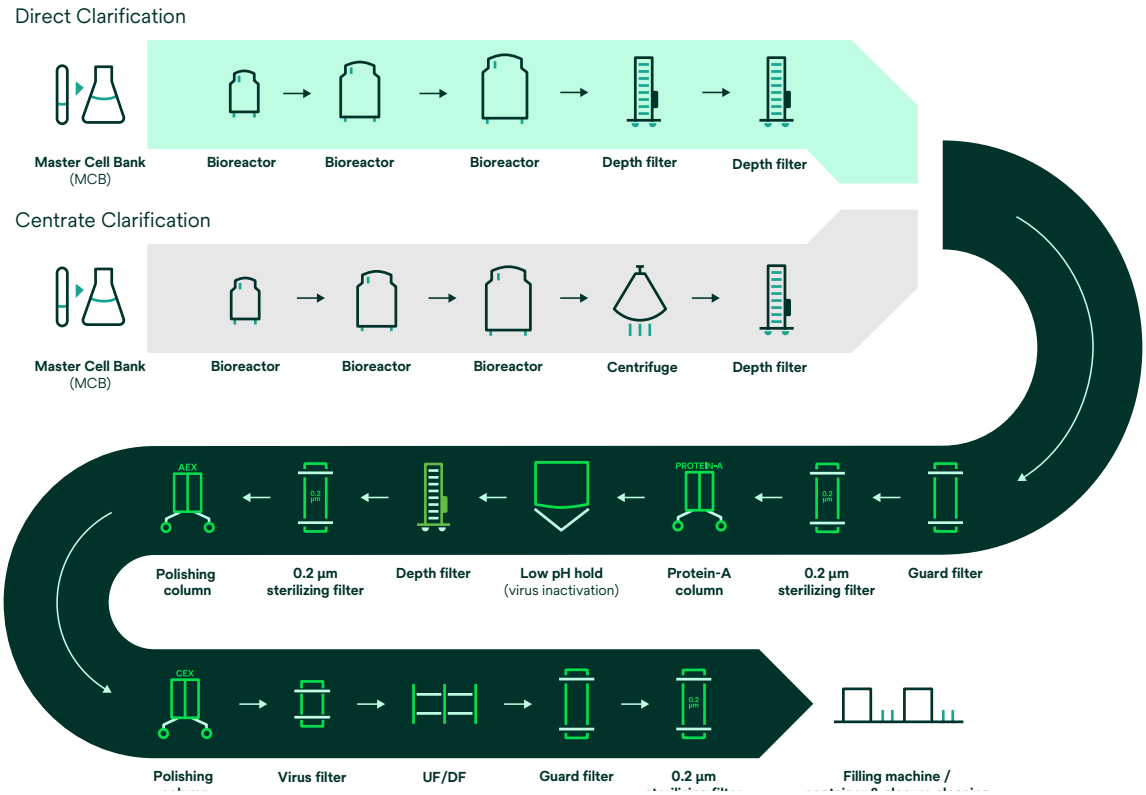


Figure 2: Typical monoclonal antibody process showing both direct harvest and centrate clarification.

Process technology innovation, process strategy innovation, and material science innovation are three integrated and often overlapping approaches designed to enable more efficient bioprocessing (i.e., process intensification).[3] Strategies such as media and feed optimization, perfusion systems, flexible manufacturing facilities, and single-use technologies have collectively advanced continuous improvements across modern bioprocessing unit operations. These intensification approaches have resulted in harvested cell cultures with greater cell mass, more cell debris, and elevated levels of soluble impurities. As a result, purification of monoclonal antibodies from such cell cultures demands larger filtration areas, expanded facility footprints, more efficient resin utilization, and greater reliance of single-use technologies.[4] The adoption of single-use systems also contributes to sustainability by eliminating the need for Clean-in-Place (CIP) and Steam-in-Place (SIP) cycles.[5]

These advances have created new clarification challenges for legacy depth filtration platforms. Higher cell densities often necessitate larger filtration areas and multiple stages, thereby increasing the overall footprint and complexity of the clarification operation. This increased filtration area also results in higher flush volumes and lower product recoveries, negatively impacting process efficiency. Additionally, increased process-related impurities from high cell density cultures can lead to guard and 0.2 µm membrane plugging post-clarification, Protein A capture fouling, and addition of extra polishing chromatography steps. This application note will explore some of the above challenges and their impact on process efficiency.

The true impact of process intensification approaches cannot be completely realized until the clarification unit operation undergoes a similar step change to address the challenges posed by the modern intensified cell cultures. The following sections in this application note will highlight how chromatographic clarification blends equipment, process, and materials innovation to advance monoclonal antibody process efficiency.

Process modeling

To evaluate process efficiency, two process configurations were modeled using BioSolve Process® (version 9.0) from Biopharm Services Limited and will serve as the baseline models for comparison in this application note. The first model represented a typical single-use facility operating at a 2,000 L scale with direct clarification utilizing depth filtration. Such configuration is widely used for clinical and commercial manufacturing of therapies that require up to 500 kg of protein.

The second model simulated a large-scale stainless-steel facility operating at 10,000 L employing disc stack centrifugation followed by depth filtration, reflecting common commercial manufacturing practices. This configuration is typically utilized for blockbuster-type therapies where more than 1,000 kg of Bulk Drug Substance (BDS) is manufactured per year.

The depth filters considered in this assessment are 3M™ Zeta Plus™ Encapsulated System and the modeled processes are summarized in Figure 3 and Table 1.

Direct clarification baseline model:

Step	Bioreactor	Depth filter	Depth filter	Guard filter	Sterile filter	Capture	VIN*	Depth filter	Membrane	AEX	CEX	Virus filter	UF/DF	Sterile filter
Size	2,000 L	2 × 7 22 m²	1 × 7 11 m²	4 × 30" 9 m²	2 × 20" 3 m²	157 L	N/A	2 × 3 m²	2 × 10" 2 m²	62 L	196 L	2 × 2 m²	6 × 7 m²	1 × 10" 1 m²
Load	-	100 L/m²	200 L/m²	300 L/m²	1,500 L/m²	35 g/L 2 cycles	N/A	400 L/m²	1000 L/m²	150 g/L 1 cycle	60 g/L 1 cycle	5,000 g/m²	N/A	250 L/m²
Yield %	-	92	95	98	98	95	98	95	98	95	95	98	98	98

Centrate clarification baseline model:

Step	Bioreactor	Centrifuge	Depth filter	Guard filter	Sterile filter	Capture	VIN*	Depth filter	Membrane	AEX	CEX	Virus filter	UF/DF	Sterile filter
Size	10,000 L	1,800 L/h	5 x 7 56 m²	14 × 30" 33 m²	3 × 30" 7 m²	190 L	N/A	4 × 6 m²	2 × 30" 5 m²	157 L	283 L	7 × 7 m²	23 × 26 m²	2 × 30" 5 m²
Load	-	10,000 L	165 L/m²	300 L/m²	1,500 L/m²	35 g/L 6 cycles	N/A	400 L/m²	1,000 L/m²	150 g/L 2 cycles	60 g/L 2 cycles	5,000 g/m²	N/A	250 L/m²
Yield %	-	90	92	98	98	95	98	95	98	95	95	98	98	98

Figure 3: Baseline models for a 2,000 L single-use facility utilizing depth filtration for direct clarification and a 10,000 L stainless-steel facility with centrifugation followed by depth filtration. *Viral inactivation

Table 1: Attributes selected for baseline models.

	Direct clarification	Centrate clarification
Facility type	Single-use (SU)	Stainless-steel (SS)
Bioreactor setup	Two single-use reactors with 2,000 L working volume	Two stainless-steel reactors with 10,000 L working volume
mAb titer	5 g/L	
Facility output	25 batches/year	
Production scheme	One reactor is harvested and purified at a time	
Facility reference	Greenfield (new)	
Equipment formats	Single-use reactors Single-use bags for product and buffer prep/hold Single-use clarification capsules Single-use membrane capsules Reusable acrylic columns	Stainless-steel reactors Stainless-steel vessels for product and buffer prep/hold Single-use clarification capsules Stainless-steel housings for membranes Reusable acrylic columns

Direct clarification using a two-stage depth filtration train is a common approach at scales up to 5,000 L across single-use, hybrid, and stainless-steel manufacturing facilities. To reflect a typical clinical-scale operation, a model was developed representing a fully single-use facility equipped with two 2,000 L bioreactors processing 25 batches annually.[6]

In large stainless-steel facilities housing bioreactors with volumes of 10,000 L or larger, a primary centrifugal separator is used to remove the bulk of the cell mass before further clarification.[7] Without centrifugation, the necessary depth filtration system footprint would be very large, making the process impractical. For the centrate clarification baseline model, a stainless-steel facility with two 10,000 L bioreactors was simulated. Unlike the single-use model, this facility requires Clean-in-Place and Steam-in-Place procedures for reusable equipment between batches.

Both models include a guard membrane filter stage that serves to protect the 0.2 µm sterilizing grade filter stage by removing fine particles. In some 2,000 L processes, that guard membrane may be left out by utilizing a larger surface area of the final 0.2 µm membrane stage. For consistency, both models include a guard membrane prior to sterilizing grade filtration.

For the downstream purification steps, assumptions were maintained as consistently as possible across both baseline models. Identical loading and recovery values were applied, while equipment size and consumables were scaled based on process volumes. Additionally, the number of chromatography column cycles per batch was adjusted accordingly, as illustrated in Figure 3.

Cost analysis of baseline models

The Cost of Goods Sold per gram of monoclonal antibody (COGS) for both baseline models was evaluated using BioSolve Process® (Figure 4). When comparing the two models, the 10,000 L model simulation resulted in lower COGS compared to that of the 2,000 L model, primarily due to its higher annual productivity.

In both baseline models, overall manufacturing costs are heavily influenced by Downstream Processing (DSP) unit operations. While clarification accounts for 8% of total process costs in the 2,000 L single-use model and 11% in the 10,000 L stainless-steel model, its impact on overall process efficiency is disproportionately significant. Effective clarification can drive improvements across multiple downstream steps, ultimately affecting COGS to a greater extent than the percentage cost contribution alone might suggest.

This application note investigates relative differences in process efficiency between the baseline models depicted in Figure 3 and models that exchange the legacy clarification unit operation for a novel chromatographic clarification solution platform. As such, a comparison between single-use and stainless-steel facilities is out of scope.

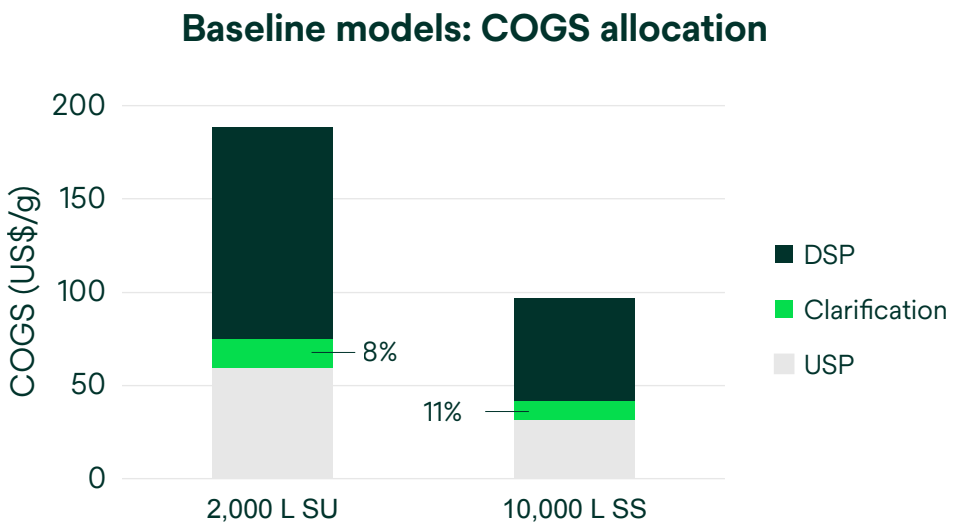


Figure 4: Allocation of Cost of Goods Sold (COGS) for baseline models.

Potential processing challenges linked to clarification with depth filtration

Traditional clarification methods, such as centrifugation using a disc stack separator and/or depth filtration, can introduce several processing challenges due to the inefficient removal of soluble and insoluble impurities. This section examines the following key processing challenges arising from the process inefficiencies related to clarification with traditional depth filtration:

1. Post-clarification membrane fouling: Membrane change out.
2. Post-clarification membrane fouling: Centrate clarification with two-stages of depth filtration.
3. Difficult impurity load: Additional chromatography unit operation.
4. Difficult impurity load: Affinity capture resin lifetime reduction.

To address these challenges, potential process modifications are presented and their subsequent impact on COGS is explored (Figure 5). While the data presented and discussed below focus on the centrate clarification baseline model (Figure 3), the underlying principles are applicable to other scales and facility types.

1. Post-clarification membrane fouling: Membrane change out.

Cell shear and lysis occur during disc stack centrifugation.[7, 8] This lysis can generate significant quantities of submicron particles that are difficult to remove using depth filtration and that may cause fouling of the subsequent membrane stage. If fouling occurs mid-process, filtration must be halted to replace the membrane filters, leading to operational disruptions, regulatory process deviations, and product loss.

To model this challenge in BioSolve Process®, an additional set of guard and sterilizing-grade membrane filters were incorporated, along with an extra CIP and SIP cycle for the corresponding housings. Due to potential fluid loss during filter replacement, the recovery rate for both stages was adjusted from 98% to 97%. When comparing this modified process to the baseline model, COGS increased by over US$3/g, or 3.4% (Figure 5).

2. Post-clarification membrane fouling: Centrate clarification with two-stages of depth filtration.

Since submicron particles that contribute to membrane fouling are not effectively removed by centrifugation followed by a single-stage depth filtration, incorporating a secondary depth filtration stage can help reduce the risk of plugging the guard or sterilizing-grade membranes.[7] This approach offers an alternative to membrane replacement, as discussed in the preceding section.

To evaluate this approach, a two-stage depth filtration train was modeled in BioSolve Process® for the centrate clarification baseline model shown in Figure 3. It was assumed that adding a second depth filter would result in a 5% product loss. While the additional consumable costs are comparable to the previous example, the second depth filtration stage adds over US$7/g, or a 6.7% increase in COGS, compared to the baseline. This example highlights the substantial cost impact of adding process steps, as even a minor increase in product loss can significantly increase COGS (Figure 5).

3. Difficult impurity load: Additional chromatography unit operation.

Centrifugation and depth filtration are often limited in their ability to effectively remove submicron impurities, such as small cell debris and residual DNA.[9,10] Elevated levels of DNA have been correlated with increased host cell protein (HCP) levels downstream. Certain HCP species can compromise product stability or pose significant challenges during purification, particularly if they co-elute or “hitchhike” with the target molecule.[10,11] In such cases, an additional clarification or purification step may be necessary to facilitate impurity removal and maintain product quality.

To model this processing issue, a third polishing column was added to the centrate clarification baseline model (Figure 3) in BioSolve Process®. The additional polishing column is the same size as the earlier AEX column and operates at two cycles per batch with a recovery of 95%. This addition of an extra polishing column adds over US$9/g to total COGS, or 9%, when compared to the baseline scenario (Figure 5).

4. Difficult impurity load: Affinity capture resin lifetime reduction.

Cell shear related submicron particles can contain genomic chromatin complexes that have the potential to cause fouling of the Protein A resin.[12] These chromatin complexes can block access to the resin's pores and ligands, which can lower the effective binding capacity or increase column pressure. Optimized cleaning procedures can help to attenuate most issues, but in some cases, the effects of resin fouling can still be observed.

To model this processing challenge in BioSolve Process® for the centrate clarification baseline model (Figure 3), the maximum number of cycles for the Protein A resin was reduced from 150 cycles to 50 cycles. Due to the high cost of the Protein A resin, this processing challenge adds over US$13/g to COGS, a 14% increase when compared to the baseline scenario (Figure 5).

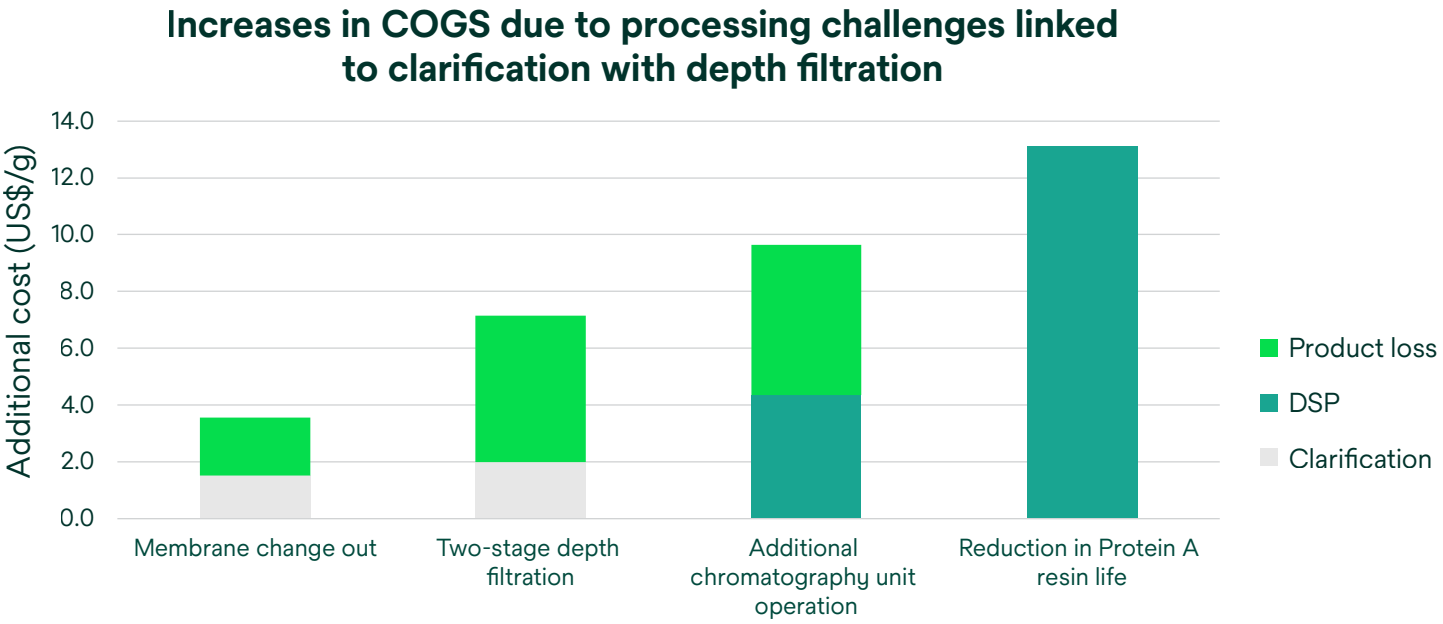


Figure 5: Increases in COGS due to potential processing challenges linked to clarification with depth filtration.

The above analysis highlights how the efficiency of the clarification unit operation, specifically, the removal of soluble and insoluble impurities, can significantly impact the DSP and the overall manufacturing cost of monoclonal antibodies.

The identified process challenges and associated increases in COGS are representative examples and may vary depending on specific process conditions. While this assessment provides an initial estimate of potential COGS increases, actual costs could be higher, as the following factors were not considered:

- Reduced loadings on DSP steps caused by high impurity levels, requiring increased column sizing or additional consumables.
- Product quality and BDS loss because of degradation caused by enzymatic activity from impurities.
- Costs associated with a process deviation. The industry average for a process deviation is US$25,000-50,000 but can reach US$1,000,000 if product loss is included.[13]
- Costs associated with a failed batch, including productivity loss and reduced annual facility output.
- Cost of delays in process development. A single day of delay is associated with US$500,000 in missed sales revenue of a prescription drug.[14]

In the following sections, we will introduce a chromatographic clarification approach with a focus on improving process efficiency from the lens of process economics, platformability, and sustainability.

Chromatographic clarification

Aiming to improve overall bioprocess efficiency, Solventum, formerly 3M Health Care, commercialized 3M™ Harvest RC Chromatographic Clarifier in 2021. This novel direct harvest and clarification solution integrates process and material innovation, forming a single-stage, single-use chromatographic clarification device, which is designed to replace two-stage depth filtration or centrifugation plus depth filtration trains in high-density CHO processes. It produces high product recovery (>95%), removes DNA to <500 ppb, and predictably scales from discovery to commercial manufacturing. Almeida et. al. and O'Mara et. al. have reported significant improvements in both process economics and cumulative product yield when deploying this clarification solution.[15,16]

As bioprocesses scale, efficiently removing large volumes of cell mass within a compact system footprint becomes increasingly challenging for any clarification technology. While 3M™ Harvest RC Chromatographic Clarifier offers linear scalability and is engineered to replace traditional centrifugation and/or depth filtration trains, facility fit and existing infrastructure remain critical factors in platform selection. Additionally, as modern cell cultures trend toward higher densities and titers, centrifugation remains a vital component of many clarification strategies.[7,8,9]

Recognizing the need for a chromatographic clarification technology capable of handling centrate feed streams in large-scale processes, where facility fit and utilization are key considerations, Solventum has recently introduced 3M™ Harvest RC Centrate Chromatographic Clarifier (Figure 6). This solution delivers effluent quality comparable to 3M™ Harvest RC Chromatographic Clarifier, but is specifically designed for centrate feed streams.

By combining 3M™ Harvest RC Chromatographic Clarifier with 3M™ Harvest RC Centrate Chromatographic Clarifier, manufacturers can establish a modern, scalable clarification platform adaptable to CHO-based processes and workflows.

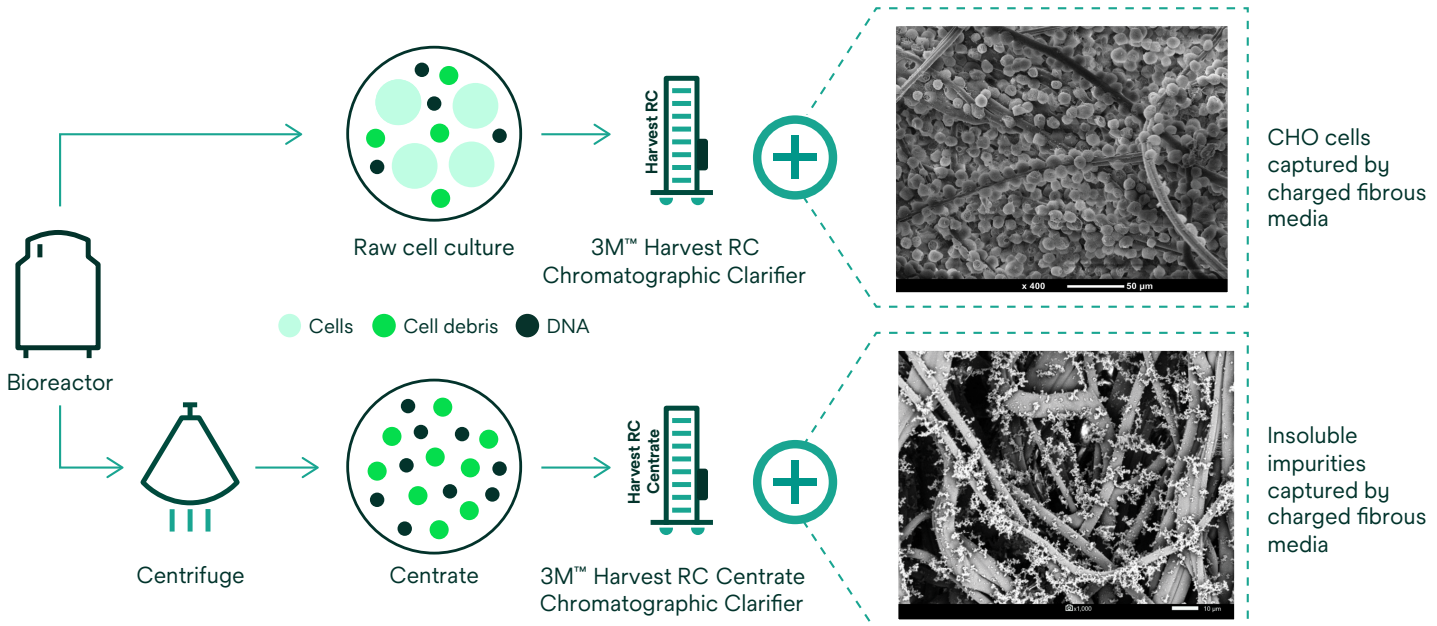


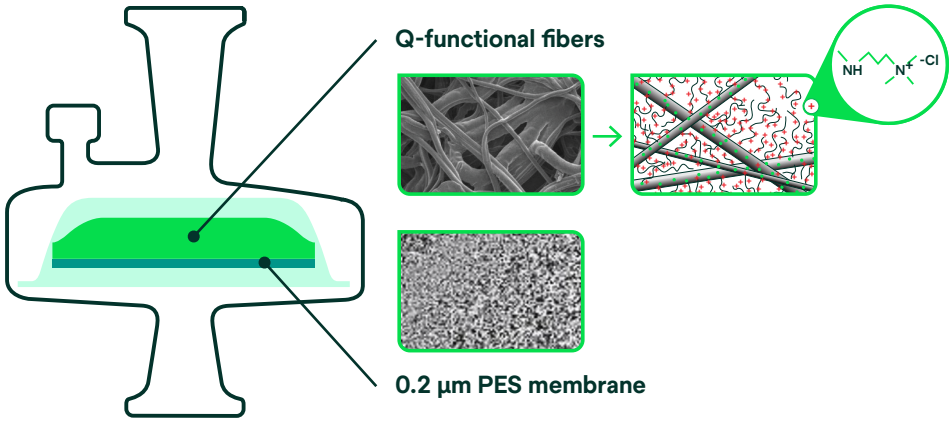
Figure 6: Applications in CHO-based processes for 3M™ Harvest RC Chromatographic Clarifier and 3M™ Harvest RC Centrate Chromatographic Clarifier.

Both products utilize anion exchange (AEX) functionalized fibrous media to capture cells, cell debris, and soluble impurities such as DNA and chromatin. Since direct clarification and centrate clarification present distinct challenges related to particle load and size distribution, each product is specifically designed for its respective application.

For direct clarification applications, 3M™ Harvest RC Chromatographic Clarifier features a more open fiber chromatography media, effectively capturing bulk cell mass and soluble impurities. In contrast, 3M™ Harvest RC Centrate Chromatographic Clarifier is designed with a tighter fiber chromatography media, along with a 0.2 µm quaternary ammonium (Q) functionalized polyamide membrane. This design enables the effective capture of submicron impurities that are found in disc stack separator centrate feed streams (Figure 7). One key advantage of this technology is its ability to deliver consistent, high quality clarified fluid, ensuring predictable performance across different workflows and process configurations.

3M Harvest RC Chromatographic Clarifier

- Quaternary ammonium (Q) functionalized fibrous media
- 0.2 µm polyether sulfone (PES) membrane
- Direct harvest and clarification



3M™ Harvest RC Centrate Chromatographic Clarifier

- Quaternary ammonium (Q) functionalized fibrous media
- 0.2 µm quaternary ammonium (Q) functionalized highly asymmetric polyamide membrane
- Centrate clarification

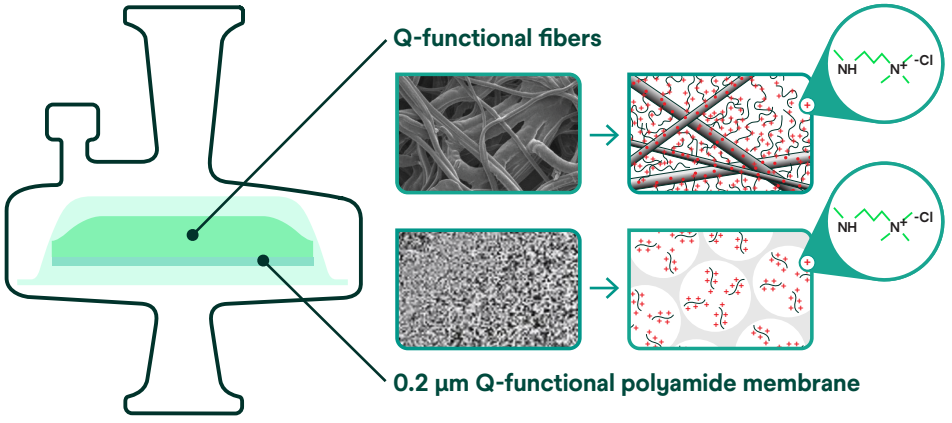


Figure 7: Material differences of 3M™ Harvest RC Chromatographic Clarifier and 3M™ Harvest RC Centrate Chromatographic Clarifier.

Process models with chromatographic clarification

To explore improvements in process economics, platformability, and sustainability, the clarification trains in the baseline models shown in Figure 3 were modified to incorporate chromatographic clarification. Figure 8 illustrates these updated process scenarios, which integrate the appropriate chromatographic clarification solution.

In the 2,000 L direct clarification model, both stages of depth filtration were replaced with a single-stage 3M™ Harvest RC Chromatographic Clarifier. Similarly, in the 10,000 L model with centrifugation, the depth filter positioned after the centrifuge was replaced with 3M™ Harvest RC Centrate Chromatographic Clarifier.

Direct clarification model with chromatographic clarification:

Step	Bioreactor	3M™ Harvest RC	Sterile filter	Capture	VIN*	Membrane	AEX	CEX	Virus filter	UF/DF	Sterile filter
Size	2,000 L	2 ×7 22 m²	1 × 20" 2 m²	157 L	N/A	2 × 10" 2 m²	62 L	196 L	2 × 2 m²	7 × 8 m²	1 × 10" 1 m²
Load	-	100 L/m²	1,500 L/m²	35 g/L 2 cycles	N/A	1,000 L/m²	150 g/L 1 cycle	60 g/L 1 cycle	5,000 g/m²	N/A	250 L/m²
Yield %	-	97	98	95	98	98	95	95	98	98	98

Centrate clarification model with chromatographic clarification:

Step	Bioreactor	Centrifuge	3M™ Harvest RC Centrate	Sterile filter	Capture	VIN*	Membrane	AEX	CEX	Virus filter	UF/DF	Sterile filter
Size	10,000 L	1,800 L/h	4 x 6 44 m²	3 x 30" 7 m²	190 L	N/A	2 x 30" 5 m²	157 L	238 L	8 x 8 m²	27 x 31 m²	2 x 30" 5 m²
Load	-	10,000 L	205 L/m²	1,500 L/m²	35 g/L 7 cycles	N/A	1,000 L/m²	150 g/L 2 cycles	60 g/L 3 cycles	5,000 g/m²	N/A	250 L/m²
Yield %	-	90	97	98	95	98	98	95	95	98	98	98

Figure 8: Process models with chromatographic clarification implemented for direct and centrate clarification. *Viral inactivation

The innovative anion exchange (AEX) fiber chromatography mechanism utilized in 3M™ Harvest RC Chromatographic Clarifier and 3M™ Harvest RC Centrate Chromatographic Clarifier enables enhanced separation efficiency compared to traditional depth filtration. These advanced clarification solutions offer superior removal of submicron particles, particularly those that are smaller than 0.5 µm, ensuring improved process performance and clarified fluid quality.[17]

This clarification approach delivers a higher-quality clarified fluid, enabling the elimination of the guard membrane used upstream of the sterilizing-grade membrane in baseline models. Furthermore, it effectively reduces host cell DNA levels to below 500 ppb, helping to prevent turbidity formation following viral inactivation (VIN). By avoiding post-VIN turbidity, a subsequent depth filtration step prior to polishing can also be eliminated when compared to traditional clarification models. While the high efficiency of impurity removal may increase mAb loading capacity on downstream purification steps, potentially requiring further optimization, these impacts are highly process-dependent and were not accounted for in the chromatographic clarification models presented in Figure 8. They represent a valuable area for future investigation and process refinement.

Process efficiency, in terms of process simplification and intensification, can be achieved when chromatographic clarification is deployed. The number of process steps was reduced from 13 in both baseline models to 10 and 11 steps for the direct and centrate chromatographic clarification models, respectively. Additionally, due to the increased throughput provided by the novel approach, the number of capsules required for clarification was reduced by 30% for both direct and centrate clarification models. Subsequently, 3M™ Encapsulated System Holder requirement was reduced from three to two holders for direct harvest, and from five to four holders for centrate, thereby decreasing the overall clarification footprint.

Table 2: Influence of process compression and intensification by chromatographic clarification on product recovery and COGS.

Facility type	2,000 L – Single-use model		10,000 L – Stainless-steel model	
Model	**Baseline**	**Chromatographic clarification (direct)**	**Baseline**	**Chromatographic clarification (centrate)**
# process steps	13	10	13	11
# SU clarification capsules	21	14	35	24
# production scale 3M™ Encapsulated System Holders	3	2	5	4
DSP recovery	62%	74%	59%	66%
COGS (US$/g)	188.27	158.76	96.88	90.14

The chromatographic separation and optimized blow-down procedure of the synthetic media resulted in a high post-clarification product recovery of >95%.[17] This high product recovery is reflected in the chromatographic clarification models, where product recovery was increased from 92 - 95%, provided by depth filtration in the baseline models, to 97%. The process compression provided by chromatographic clarification allowed the elimination of downstream protective filtration steps and further increased the total DSP recovery when compared to the baseline models. The total batch output was raised by 19% and 13%, for the 2,000 L and 10,000 L chromatographic clarification models, respectively (Figures 3 and 8).

Higher product recovery leads to greater product load on downstream chromatography columns. In the chromatographic clarification models, column sizes remained consistent with the baseline model by increasing the number of cycles where feasible, necessary for the centrate model but not for the direct clarification model. The manufacturing costs presented reflect the full process, including potential increases due to additional column cycles or larger DSP steps required. The increased productivity and other cost benefits outweigh any downstream cost increases.

Implementing chromatographic clarification resulted in a 16% reduction in COGS for direct clarification when compared to the baseline model with depth filtration. In the centrate clarification model, COGS is reduced by 7% with the implementation of chromatographic clarification. These cost savings stem from higher product recovery enabled by chromatographic clarification, the removal of guard membrane filtration and post-VIN depth filtration steps in downstream processing, and the elimination of product loss associated with these steps (Figure 9). Intangible benefits of chromatographic clarification, such as accelerated speed to market enabled by platformability and streamlined process development, were not included in this analysis. However, these advantages likely provide some amount of economic or financial benefit.

Chromatographic clarification offers superior fluid quality and particle size control compared to depth filtration.[17] To maximize its benefits, DSP unit operations have been modified and optimized relative to baseline scenarios as discussed in the previous sections and reflected in Figure 3 and 8. However, chromatographic clarification can also serve as a turnkey solution, implemented via a simple substitution of traditional depth filtration without requiring DSP modifications. Even without additional process adjustments, such as removing the guard membrane in clarification or post-VIN depth filters, the simple substitution of depth filtration with the appropriate chromatographic clarification solution enhances process efficiency by reducing COGS (Figure 9), improving platformability, and increasing process sustainability. The latter two benefits will be discussed in the following sections.

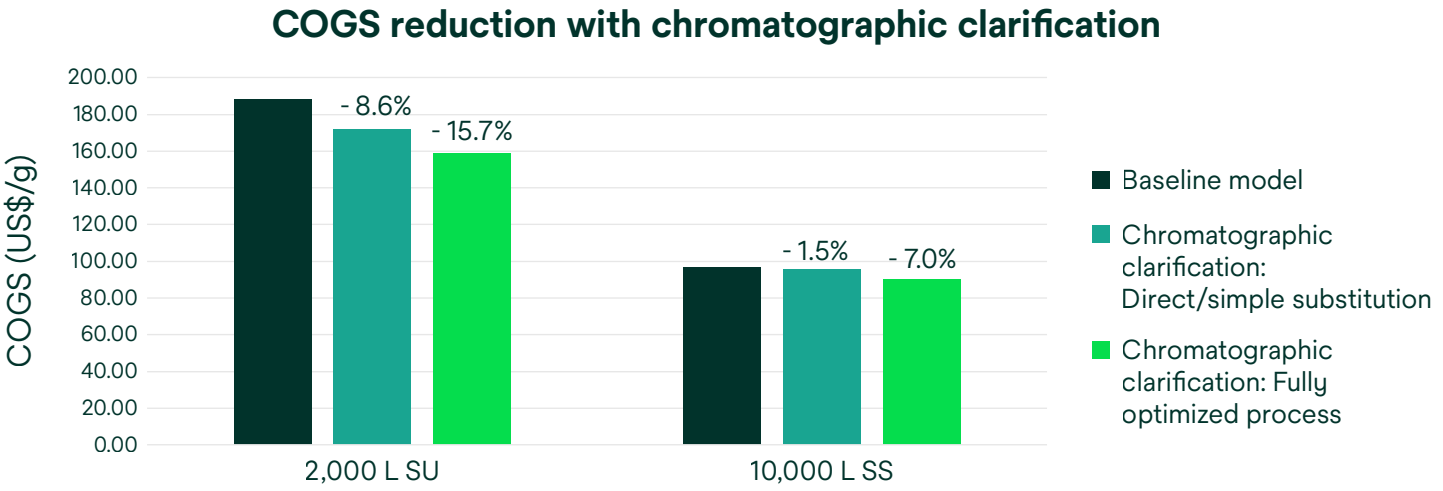


Figure 9: COGS reduction for direct and centrate clarification with chromatographic clarification.

Platformability across scales and facility fit

The industry has traditionally relied on centrifugation and/or depth filtration for large-scale clarification in monoclonal antibody processes. However, representative scale-down models, particularly for continuous disc stack centrifugation, are lacking at lab and bench scales. In commercial manufacturing, increasing cell densities further elevate the likelihood of relying on centrifugation as the primary cell mass separation stage. As molecules transition between development phases and production sites, clarification technologies must be adapted to align with the receiving facility's fit. Consequently, the selection of clarification technology evolves based on process scale and manufacturing needs.

No single legacy clarification technology seamlessly scales from discovery to commercial manufacturing, making platforming a single solution unfeasible (Figure 10). The need to switch between clarification technologies at different scales requires additional process development, as variations in clarification performance can alter impurity profiles. These challenges can create bottlenecks that slow down speed to market. Given that a single day of delay can result in revenue losses of up to $500,000, the financial impact of lacking a scalable clarification platform can be substantial.[14]

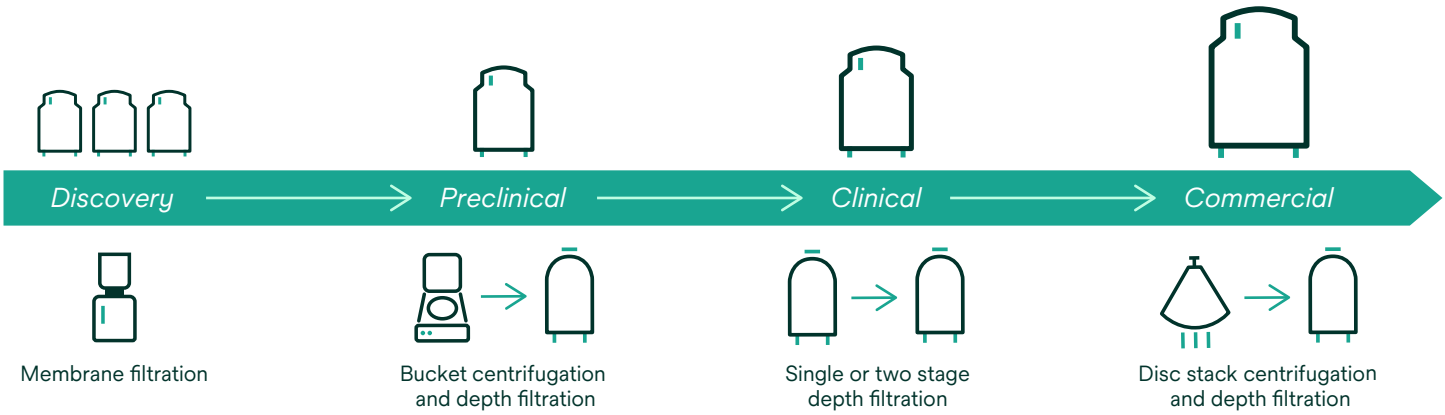


Figure 10: Typical CHO clarification technologies used from discovery to commercial processes for mAb production.

The 3M™ Harvest RC Chromatographic Clarifier platform provides a robust and scalable clarification solution, delivering predictable performance and consistent clarified fluid quality from discovery to commercial scale.[17] Whether used in direct clarification or centrate clarification, the chromatographic clarification technology ensures uniform fluid quality across scales. Its ability to be rapidly deployed at any process scale with comparable results enables seamless scale up and scale down (Figure 11). By facilitating process transfers, standardizing downstream operations, and accelerating speed-to-market, this platform offers a transformative clarification platform for bioprocessing.

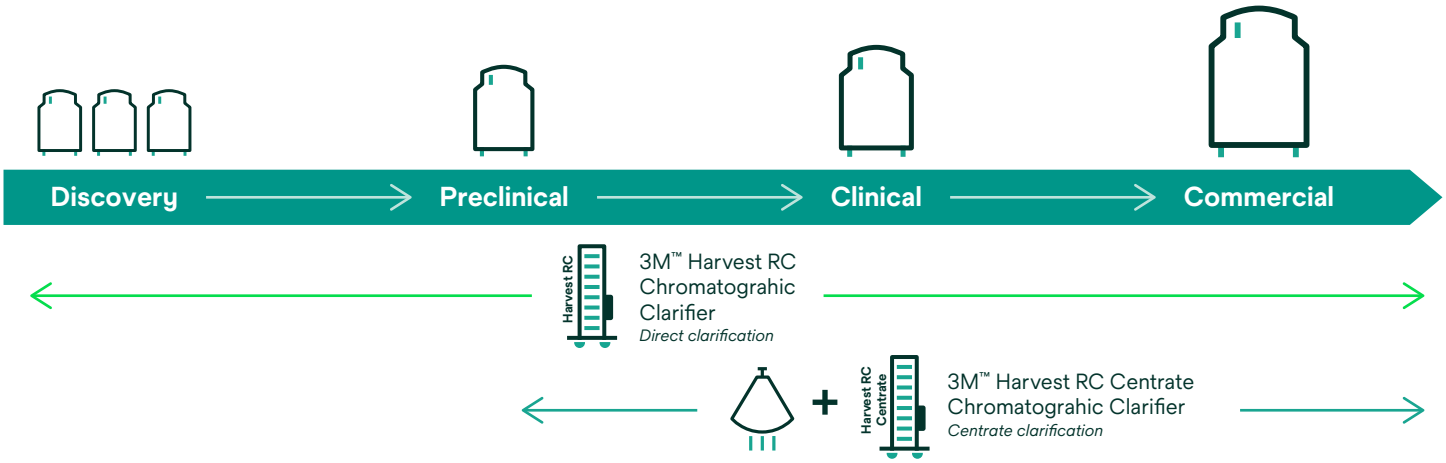


Figure 11: Deployment of 3M™ Harvest RC Chromatographic Clarifier platform across process scales.

Scalability of chromatographic clarification across process volumes and resulting impact on COGS were assessed to align process efficiency with economic and platform considerations. Chromatographic clarification models were compared to baseline models across process scales ranging from 200 L to 20,000 L (Figures 3 and 8). A single-use facility model with a direct clarification approach was applied from 200 L to 2,000 L, while a stainless-steel variant of the same model was used from 200 L to 5,000 L, maintaining identical process steps and assumptions, but adapting to a different facility type. Additionally, a stainless-steel model incorporating a disc stack centrifuge was implemented from 2,000 L to 20,000 L. Figure 12 illustrates the normalized COGS for each chromatographic clarification solution compared to depth filtration within the same facility type and scale. Chromatographic clarification consistently reduces COGS by 7–16%, reaffirming its economic advantages across various scales and facility types.

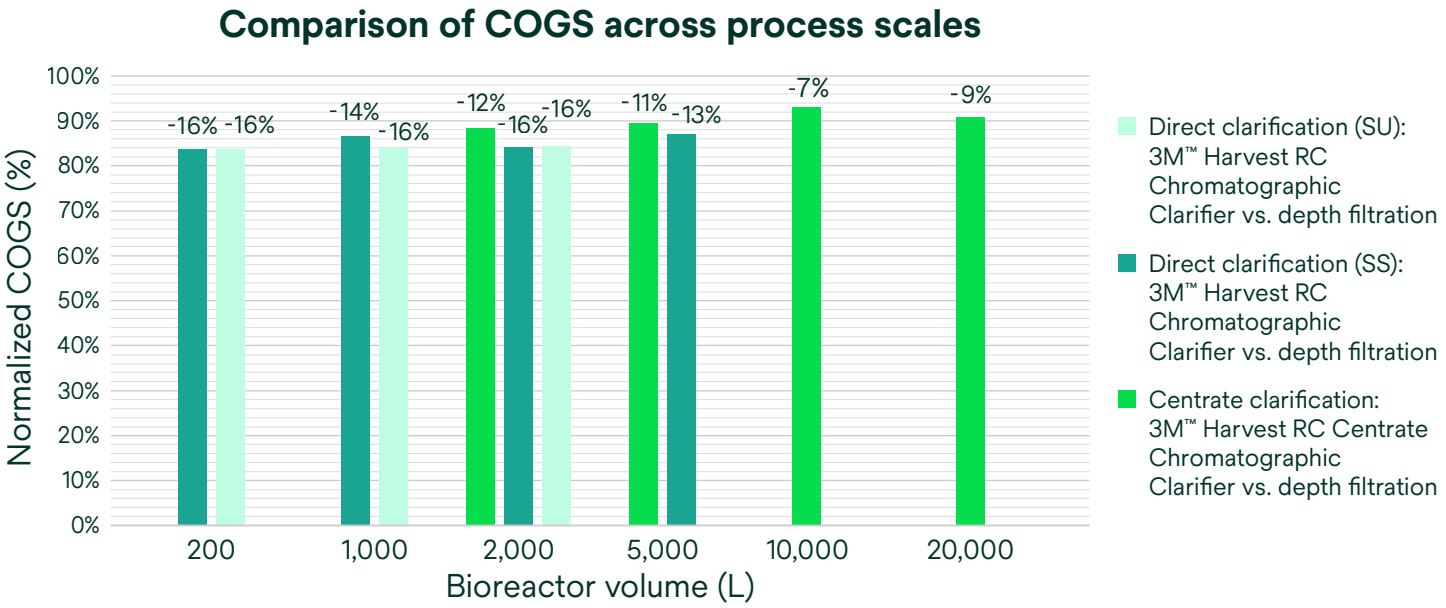


Figure 12: Normalized COGS comparison across process scales of chromatographic clarification and depth filtration.

Process robustness

The ability of a clarification process to consistently deliver reliable, high-performance clarification despite variations in characteristics of the input feed stream and operating conditions is critical for overall process efficiency and speed to market. Chromatographic clarification is specifically designed to enhance process efficiency, ensuring robust performance across various CHO-based processes.

Appendix A presents data from a sensitivity analysis, demonstrating the consistent COGS reduction achieved with chromatographic clarification across a range of process-related parameters.

Resource utilization and sustainability

Implementing chromatographic clarification enhances process efficiency and sustainability by enabling process simplification and increasing overall product recovery. This advanced technology boosts batch output while reducing process inputs and steps, key indicators of overall process efficiency.

Chromatographic clarification reduces the number of required capsules and eliminates the consumables associated with the guard filtration and post-viral inactivation depth filtration steps, significantly decreasing consumable waste. Table 3 summarizes the total weight of clarification consumables and shows a 38% reduction for the 2,000 L SU model and a 28% reduction for the 10,000 L SS model when comparing chromatographic clarification against the baseline model utilizing depth filtration. Additionally, the media used in the chromatographic clarification technology is synthetic, enabling a significantly reduced pre-conditioning rinse volume of 25 L/m², compared to 54 L/m² for the depth filters included in these models.[18,19,20] It should be noted that depth filter offerings from other vendors have preconditioning flush requirements of up to 100 L/m².[21] Incorporating depth filters from alternative vendors in the baseline models would further increase the PMI delta between these models and the models utilizing chromatographic clarification.

Table 3: Impact on Process Mass Intensity (PMI) for two typical GMP configurations.

Facility type	2,000 L - Single-use model			10,000 L - Stainless-steel model		
Model	**Baseline**	**Chromatographic clarification (direct)**	**Difference**	**Baseline**	**Chromatographic clarification (centrate)**	**Difference**
Consumables (kg)	260	160	- 38 %	381	276	- 28 %
Process WFI (L)	2276	576	- 75 %	3984	1175	- 71 %
PMI total process	4741	3602	- 24 %	8898	7870	- 12 %
PMI clarification	613	150	- 76 %	1044	594	- 43 %

PMI is calculated by dividing the total mass of all inputs, including water, raw materials, and consumables, by the mass of the process output (i.e., monoclonal antibody). While PMI is not a comprehensive measure of process sustainability, it serves as a straightforward and valuable metric for evaluating and comparing material efficiency across processes or process modifications.[22]

Due to reduced inputs and increased output, chromatographic clarification lowers PMI by 24% for the modeled 2,000 L SU process and by 12% for the modeled 10,000 L SS process. The PMI reduction is even more pronounced in the clarification operation itself, with decreases of 76% and 43%, respectively.

Figure 13 presents a breakdown of the PMI for clarification in both the baseline and chromatographic clarification models. In the SU model, PMI is primarily influenced by process water usage, whereas cleaning water has the greatest impact in the SS facility. The implementation of chromatographic clarification reduces both process and cleaning water PMI values, enhancing process sustainability and overall efficiency.

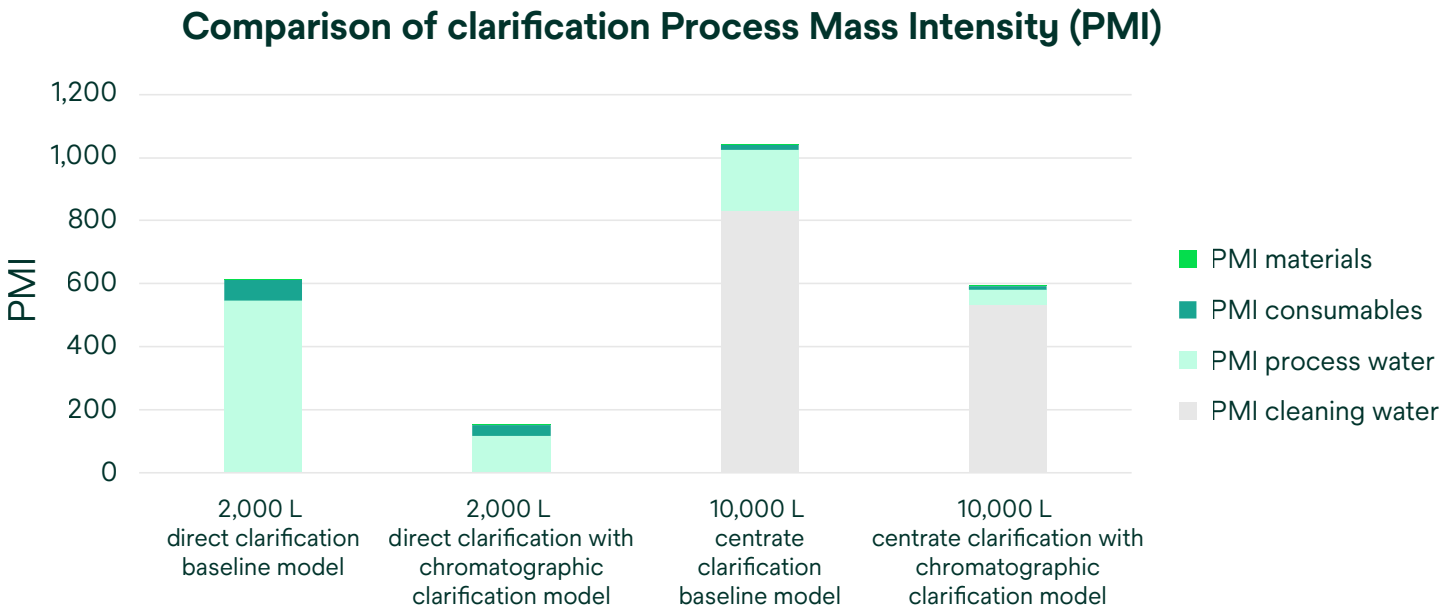


Figure 13: Comparison of Process Mass Intensity (PMI) of clarification trains in the baseline and chromatographic clarification models.

Conclusion

This study has clearly demonstrated the disruptive potential of 3M™ Harvest RC Chromatographic Clarifier platform in evolving CHO-based biopharmaceutical manufacturing. By bringing the fidelity of chromatography to the harvest and clarification unit operation, this innovative technology captures whole cells, cell debris, and soluble impurities in a single, efficient step, delivering a level of process performance that addresses the challenges of modern bioprocessing.

The data confirm that this step-change solution delivers compelling improvements in process economics, driving down Cost of Goods Sold (COGS) and advancing sustainability by lowering Process Mass Intensity. Economic modeling further underscores the platform's value, revealing measurable reductions in both monoclonal antibody manufacturing costs and environmental impact. These benefits stem from superior product yield and early-stage impurity removal, which eliminate the need for extra downstream unit operations or larger chromatography columns, thereby preserving facility footprint and enhancing process robustness.

Aligned with broader trends in process intensification, where technology, strategy, and materials science converge, 3M™ Harvest RC Chromatographic Clarifier platform emerges as a forward-looking, more sustainable alternative to legacy clarification methods, streamlining the path from discovery through commercial manufacturing.

References

1. Philippidis, Alex. "Top 10 Best Selling Drugs." Genetic Engineering & Biotechnology News, June 13, 2024. https://www.genengnews.com/topics/drug-discovery/top-10-best-selling-drugs/.
2. Buntz, Brian. "Best-selling pharmaceuticals of 2023 reveal a shift in pharma landscape." Drug Discovery & Development, May 21, 2024. https://www.drugdiscoverytrends.com/best-selling-pharmaceuticals-2023/.
3. Boodhoo, K.V.K., Flickinger, M.C., Woodley, J.M., Emanuelsson, E.A.C. "Bioprocess intensification: A route to efficient and sustainable biocatalytic transformations for the future." Chemical Engineering and Processing - Process Intensification Volume 172 (2022): 108793. https://doi.org/10.1016/j.cep.2022.108793.
4. Mothes, Benoit, Pezzini, Jerome, Schroeder-Tittmann, Kathrin, Villain, Louis. "Accelerated, Seamless Antibody Purification: Process Intensification with Continuous Disposable Technology." BioProcess International, May 11, 2016. https://www.bioprocessintl.com/single-use/accelerated-seamless-antibody-purification-process-intensification-with-continuous-disposable-technology.
5. Pietrzykowski, Matthew, Flanagan, William, Pizzi, Vincent, Brown, Andrew, Sinclair, Andrew, Monge, Miriam. "An environmental life cycle assessment comparison of single-use and conventional process technology for the production of monoclonal antibodies." Journal of Cleaner Production Volume 41 (2013): 150-162. https://doi.org/10.1016/j.jclepro.2012.09.048.
6. Kelly, Brian. "Industrialization of mAb production technology: The bioprocessing industry at a crossroads." mAbs 1(5) (2009): 443-452. https://doi.org/10.4161/mabs.1.5.9448.
7. Lui, Hui F., Ma, Junfen, Winter, Charles, Bayer, Robert. "Recovery and purification process development for monoclonal antibody production." mAbs 2(5) (2010): 480-499. https://doi.org/10.4161/mabs.2.5.12645.
8. Agarwal, Harshit, Thwin, Capicine, Kumaar, Bala Thangaraj. "Single-use centrifugal separator enables intensification of the clarification process in biomanufacturing of recombinant proteins." Journal of Chemical Technology & Biotechnology 98(5) (2023): 1321-1332. https://doi.org/10.1002/jctb.7351.
9. Dryden, W. Aaron, Laresn, Levi Morin, Britt, David W., Smith, Mark Thomas. "Technical and economic considerations of cell culture harvest and clarification technologies." Biochemical Engineering Journal 167 (2021): 107892. https://doi.org/10.1016/j.bej.2020.107892.
10. Koehler, Kenneth C., Jokondo, Zona, Narayan, Janani, Voloshin, Alexei, Castro-Forero, Angelines. "Enhancing Protein A performance in mAb processing: A method to reduce and rapidly evaluate host cell DNA levels during primary clarification." Biotechnology Progress 35 (2019). https://doi.org/10.1002/btpr.2882.
11. Van de Velde, Joris, Saller, Manfred J., Eyer, Kurt, Voloshin, Alexei. "Chromatographic clarification overcomes chromatin-mediated hitch-hiking interactions on Protein A capture column." Biotechnology and Bioengineering 117, no. 11 (2020): 3413-3421. https://doi.org/10.1002/bit.27513.
12. El-Sabbahy, H., Ward D., Ogonah, O., Deakin, L., Jellum, G., Bracewell, D. "The Effect of Feed Quality Due to Clarification Strategy on the Design and Performance of Protein A Periodic Counter-Current Chromatography." Biotechnology Progress 34(6) (2018): 1380-1392. https://doi.org/10.1002/btpr.2709.
13. Benson, Harry. "Reducing Human Error In Gmp Pharma/Biopharma Operations." Cell & Gene, April 15, 2021. https://www.cellandgene.com/doc/reducing-human-error-in-gmp-pharma-biopharma-operations-0001#:~:text=Industry%20average%20deviation%20costs%20generally,a%20company%20thousands%20of%20dollars.
14. Smith, Zachary, DiMasi, Joseph, Getz, Kenneth. "New Estimates on the Cost of a Delay Day in Drug Development." Therapeutic Innovation & Regulatory Science 58 (2024): 885-862. https://doi.org/10.1007/s43441-024-00667-w.
15. Almeida, Aaron, Chau, David, Coolidge, Thomas, et. al. "Chromatographic capture of cells to achieve single stage clarification in recombinant protein purification." Biotechnology Progress 38(2) (2022) https://doi.org/10.1002/btpr.3227.
16. O'Mara, Brian, Singh, Naveen, Menendez, Alicia, et. al. "Single-stage chromatographic clarification of Chinese Hamster Ovary cell harvest reduces cost of protein production." Biotechnology Progress 39(2) (2023). https://doi.org/10.1002/btpr.3323.
17. Solventum. "3M™ Harvest RC Chromatographic Clarifier platform." Solventum, 2024. https://www.solventum.com/content/dam/public/language-masters/en/pfb/document/2024/harvest-rc-platform-sell-sheet-pf-bf-en.pdf.coredownload.inline.pdf.
18. Solventum. "3M™ Zeta Plus™ Filters with ZB Series Media." Solventum, 2023. https://multimedia.3m.com/mws/media/1238785O/3m-tm-zeta-plus-tm-filters-with-zb-series-media-regulatory-support-file.pdf.
19. Solventum. "3M™ Harvest RC Chromatographic Clarifier Product Information Sheet." Solventum, 2024. https://www.solventum.com/content/dam/public/language-masters/en/pfb/document/2024/harvest-rc-product-info-sheet-pf-bf-en.pdf.coredownload.inline.pdf.
20. Solventum. "3M™ Harvest RC Centrate Chromatographic Clarifier Product Information Sheet." Solventum, 2024. https://www.solventum.com/content/dam/public/language-masters/en/pfb/document/2024/harvest-rc-centrate-product-info-sheet-pf-bf-en.pdf.coredownload.inline.pdf.
21. Millipore. "Tailoring flushing procedure to modern Pods systems." Application note. (2019). https://www.sigmaaldrich.com/deepweb/assets/sigmaaldrich/product/documents/288/704/tailoring-flushing-procedure-modern-pods-system-an3281en-ms.pdf.
22. Budzinski, Kristi, Blewis, Megan, Dahlin, Philip, et. al. "Introduction of a process mass intensity metric for biologics." New Biotechnology 49 (2019): 37-42. https://doi.org/10.1016/j.nbt.2018.07.005.

Appendix A – Process robustness

This appendix presents a comprehensive set of data from sensitivity analyses conducted across a range of process-related parameters. The findings consistently demonstrate that implementing chromatographic clarification results in a meaningful and sustained reduction in Cost of Goods Sold (COGS), underscoring its value as a robust and scalable strategy for process optimization.

Throughput

Figures A1a and A1b depict COGS reduction, in US$/g of product, of the direct clarification and centrate clarification models with chromatographic clarification compared to the baseline models over increasing throughputs. For Figure A1a, only the first stage of depth filtration in the baseline model is considered.

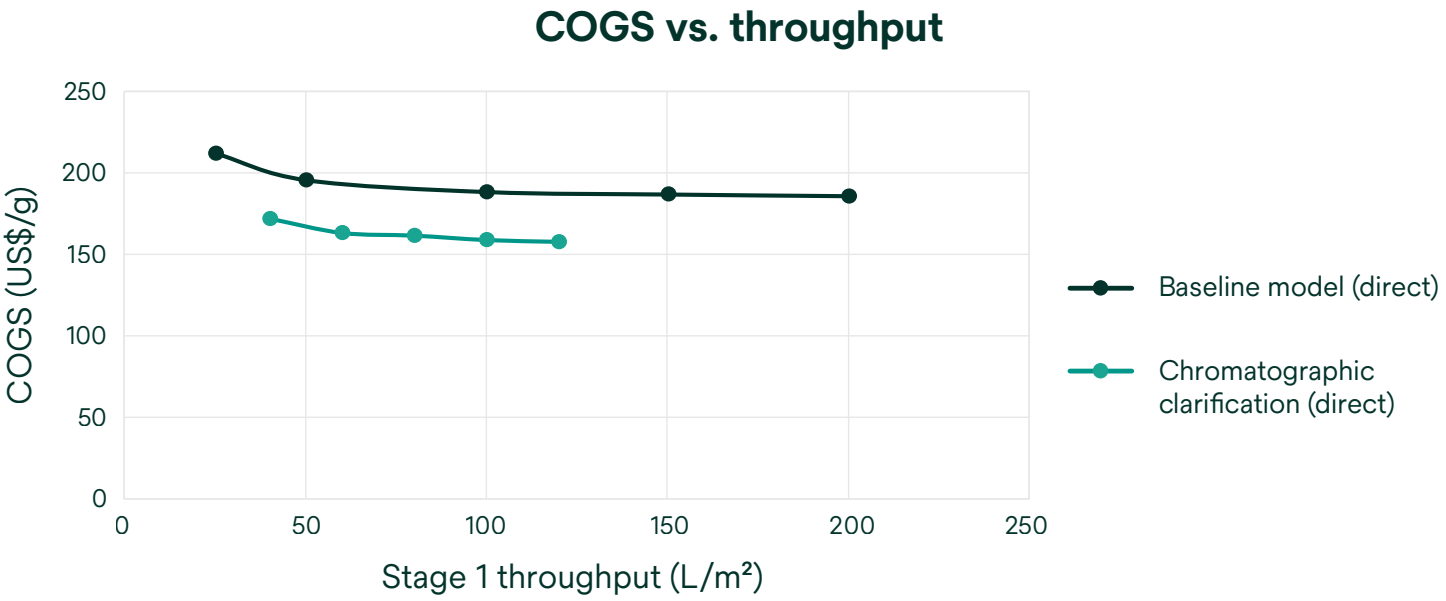


Figure A1a: COGS comparison of the direct clarification baseline model and direct clarification with chromatographic clarification over increasing throughputs.

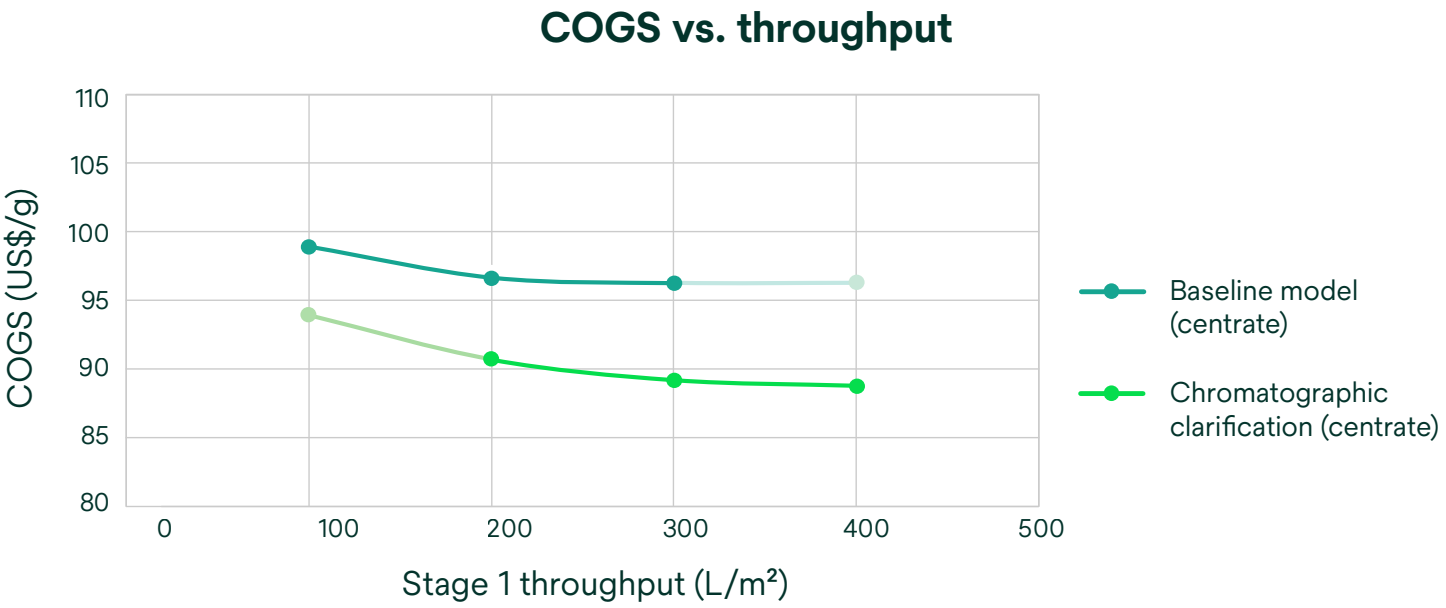


Figure A1b: COGS comparison of the centrate clarification baseline model and centrate clarification with chromatographic clarification over increasing throughputs.

Recovery

Figures A2a and A2b depict COGS reduction, in US$/g of product, of the direct clarification and centrate clarification models with chromatographic clarification compared to the baseline models over increasing product recoveries. For Figure A2a, the total recovery of the first and second stage depth filters in the baseline model is presented.

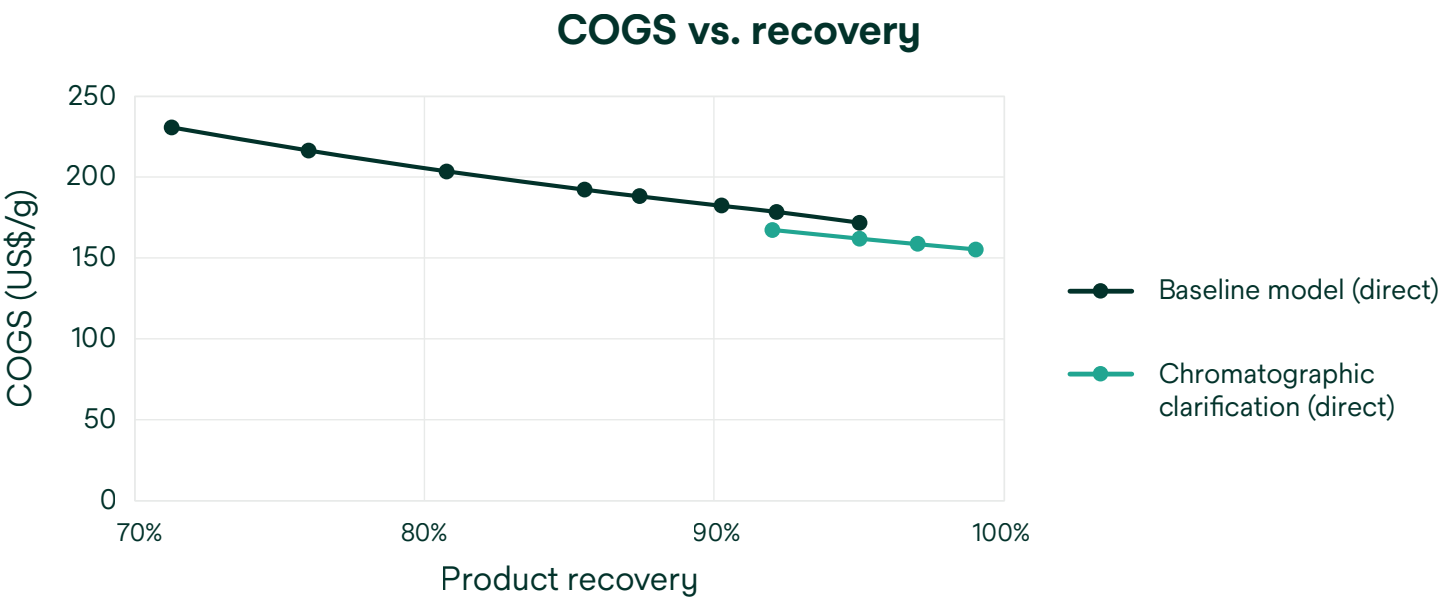


Figure A2a: COGS comparison of the direct clarification baseline model and direct clarification with chromatographic clarification over increasing product recoveries.

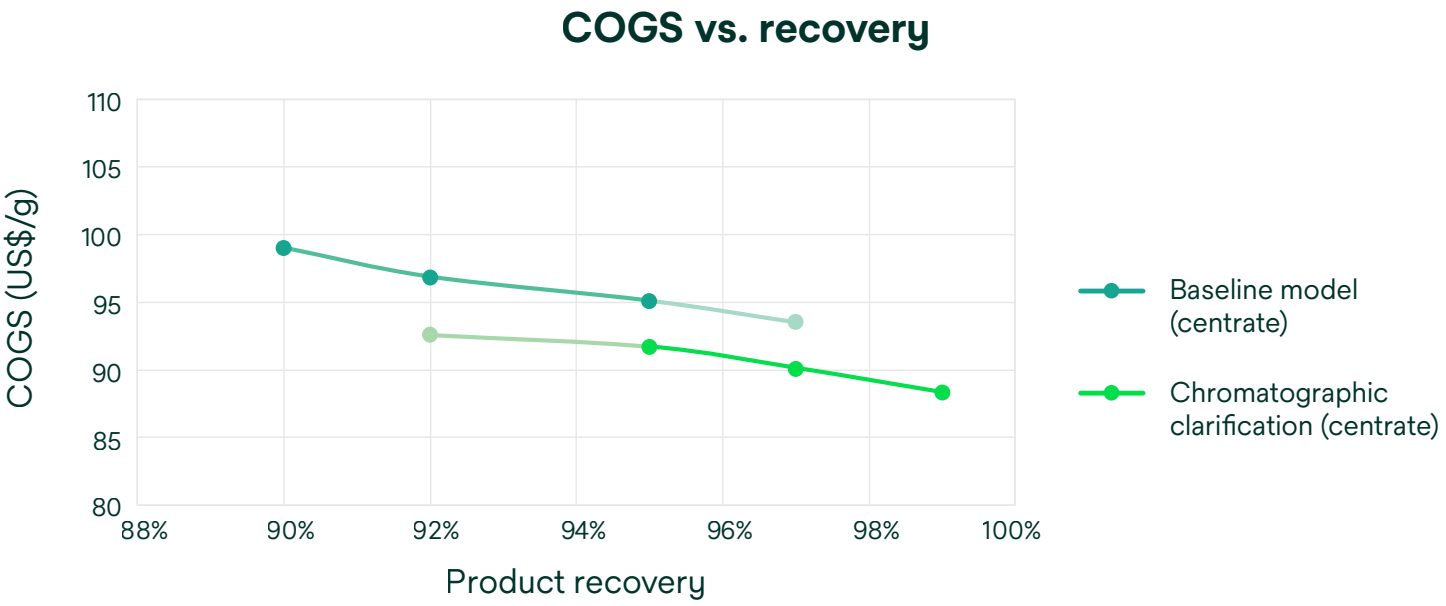


Figure A2b: COGS comparison of the centrate clarification baseline model and centrate clarification with chromatographic clarification over increasing product recoveries.

Cell culture titer

Figures A3a and A3b depict COGS reduction, in US$/g of product, of the direct clarification and centrate clarification models with chromatographic clarification compared to the baseline models over increasing cell culture titers.

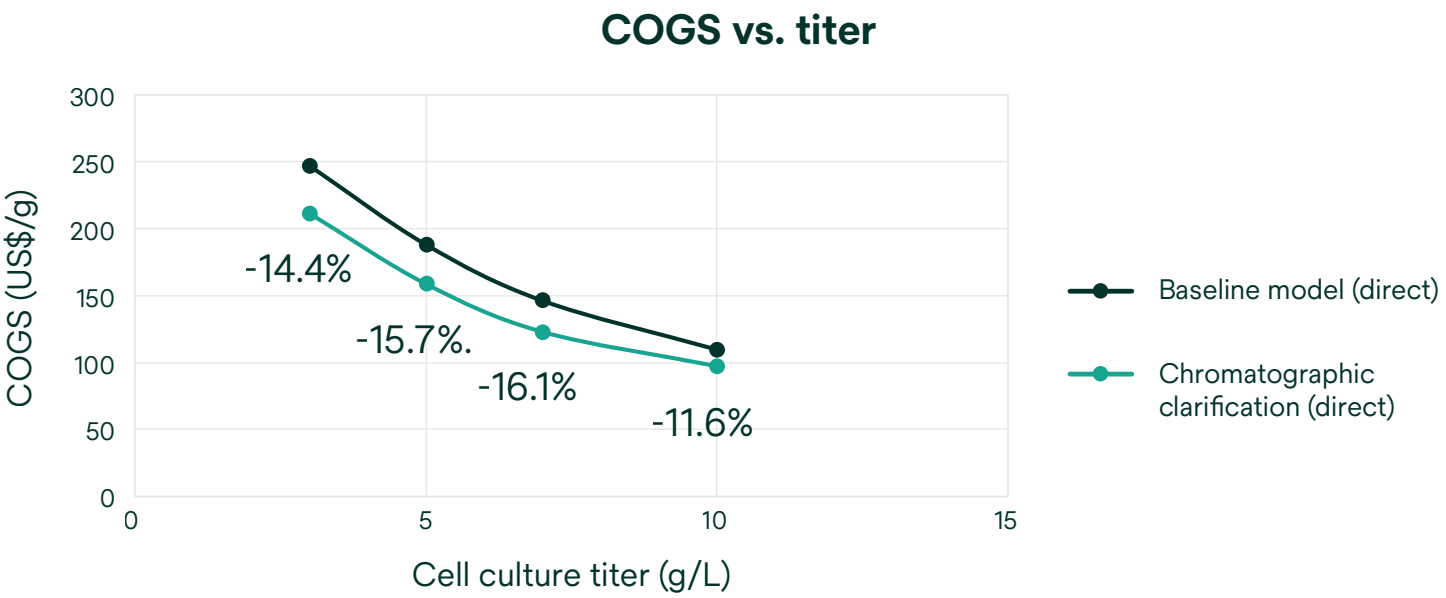


Figure A3a: COGS comparison of the direct clarification baseline model and direct clarification with chromatographic clarification over increasing cell culture titers.

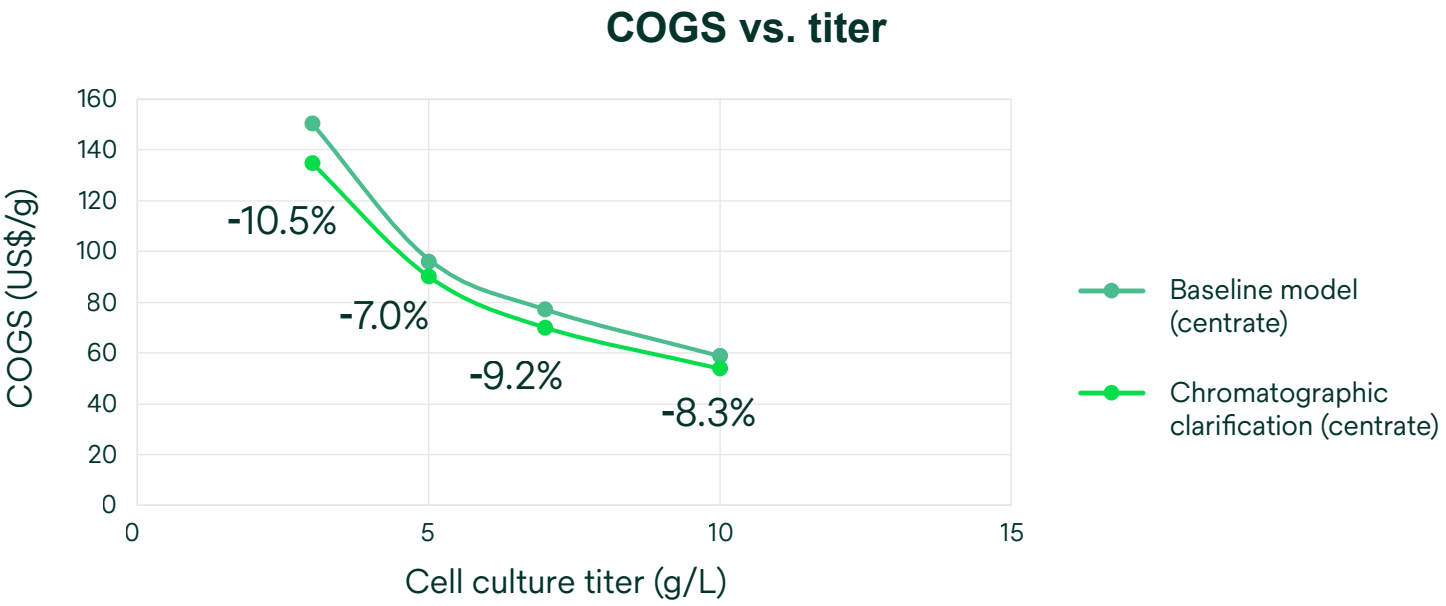


Figure A3b: COGS comparison of the centrate clarification baseline model and centrate clarification with chromatographic clarification over increasing cell culture titers.

Protein A resin life

Figures A4a and A4b depict COGS reduction, in US$/g of product, of the direct clarification and centrate clarification models with chromatographic clarification compared to the baseline models over increases in the maximum number of Proten A cycles achieved.

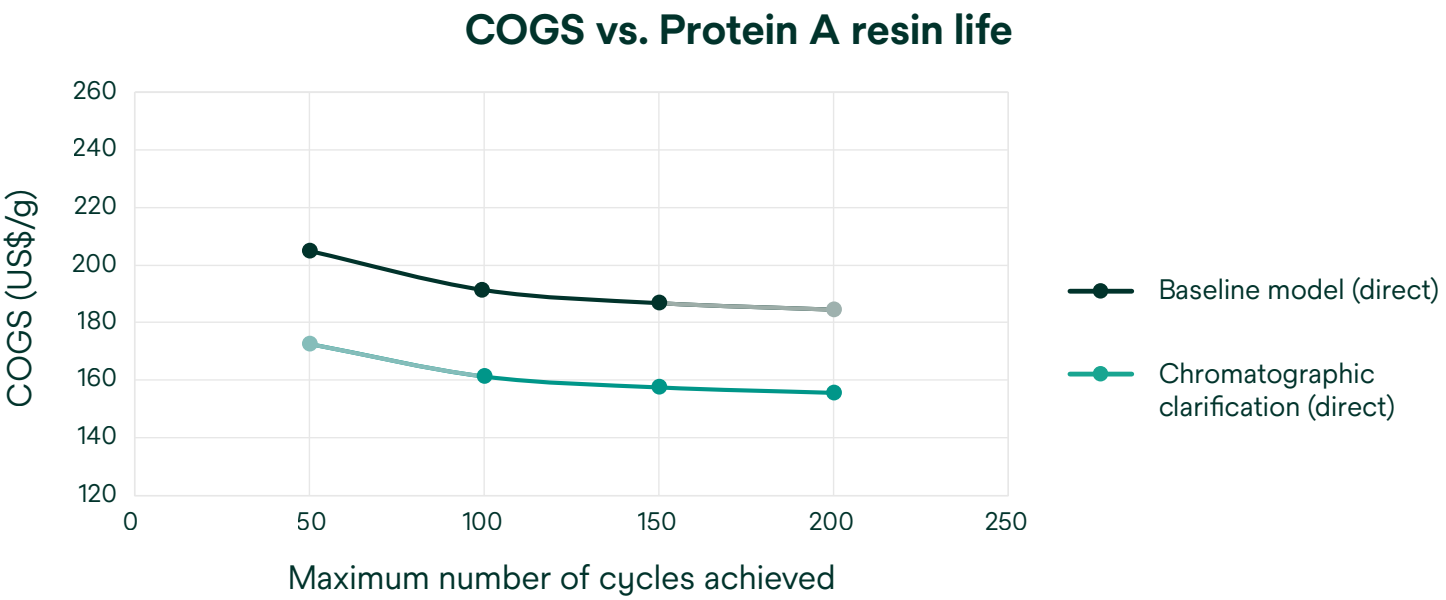


Figure A4a: COGS comparison of the centrate clarification baseline model and centrate clarification with chromatographic clarification over increases in the maximum number of Protein A cycles achieved.

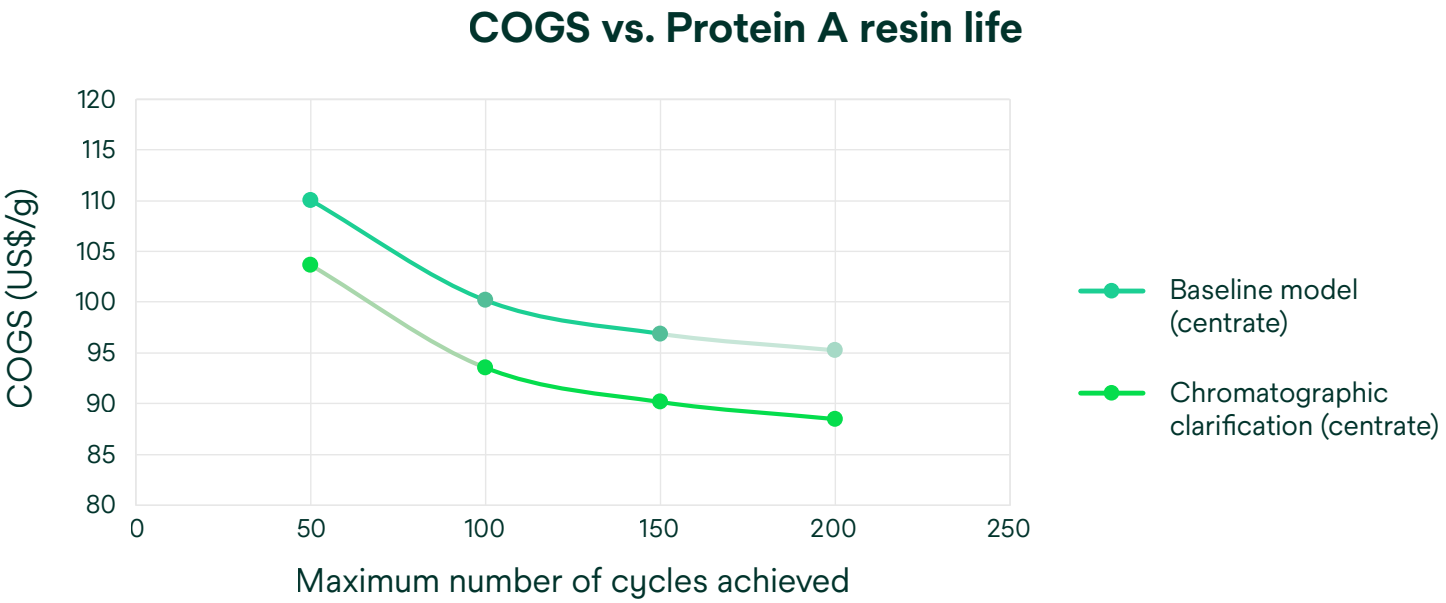


Figure A4b: COGS comparison of the centrate clarification baseline model and centrate clarification with chromatographic clarification over increases in the maximum number of Protein A cycles achieved.

Intended Use Statement: Single-use filter products are intended for use in biopharmaceutical processing applications of aqueous based pharmaceuticals (drugs) and vaccines in accordance with the product instructions and specifications, and cGMP requirements, where applicable. Since there are many factors that can affect a product's use, the customer and user remain responsible for determining whether the Solventum product is suitable and appropriate for the user's specific application, including user conducting an appropriate risk assessment and evaluating the Solventum product in user's application.

Restrictions on Use: Solventum advises against the use of these Solventum products in any application other than the stated intended use(s), since other applications have not been evaluated by Solventum and may result in an unsafe or unintended condition. Do not use in any manner whereby the Solventum product, or any leachable from the Solventum product, may become part of or remains in a medical device that is regulated by any agency, and/or globally exemplary agencies, including but not limited to: a) FDA, b) European Medical Device Regulation (MDR), c) Japan Pharmaceuticals and Medical Devices Agency (PMDA) or in applications involving permanent implantation into the body; Life-sustaining medical applications; Applications requiring food contact compliance.

Technical Information: The technical information, guidance, and other statements contained in this document or otherwise provided by Solventum are based upon records, tests, or experience that Solventum believes to be reliable, but the accuracy, completeness, and representative nature of such information is not guaranteed. Such information is intended for people with knowledge and technical skills sufficient to assess and apply their own informed judgment to the information. No license under any Solventum or third-party intellectual property rights is granted or implied with this information.

Product Selection and Use: Many factors beyond Solventum's control and uniquely within user's knowledge and control can affect the use and performance of a Solventum product in a particular application. As a result, end-user is solely responsible for evaluating the product and determining whether it is appropriate and suitable for end-user's application, including completing a risk assessment that considers the product leachable characteristics and its impact on drug safety, conducting a workplace hazard assessment and reviewing all applicable regulations and standards. Failure to properly evaluate, select, and use a Solventum product and appropriate safety products, or to meet all applicable safety regulations, may result in injury, sickness, death, and/or harm to property.

Warranty, Limited Remedy, and Disclaimer: Unless a different warranty is expressly identified on the applicable Solventum product literature or packaging (in which case such express warranty governs), Solventum warrants that each Solventum product meets the applicable Solventum product specification at the time Solventum ships the product. SOLVENTUM MAKES NO OTHER WARRANTIES OR CONDITIONS, EXPRESS OR IMPLIED, INCLUDING, BUT NOT LIMITED TO, ANY IMPLIED WARRANTY OR CONDITION OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, OR ARISING OUT OF A COURSE OF DEALING, CUSTOM, OR USAGE OF TRADE. If a Solventum product does not conform to this warranty, then the sole and exclusive remedy is, at Solventum's option, replacement of the Solventum product or refund of the purchase price.

Limitation of Liability: Except for the limited remedy stated above, and except to the extent prohibited by law, Solventum will not be liable for any loss or damage arising from or related to the Solventum product, whether direct, indirect, special, incidental, or consequential (including, but not limited to, lost profits or business opportunity), regardless of the legal or equitable theory asserted, including, but not limited to, warranty, contract, negligence, or strict liability.

solventum

Solventum Corporation
2510 Conway Avenue East
St. Paul, MN 55144-1000

Phone 1-800-243-6894
1-203-237-5541
Web Solventum.com

Solventum bioprocessing filtration is now part of Thermo Fisher Scientific