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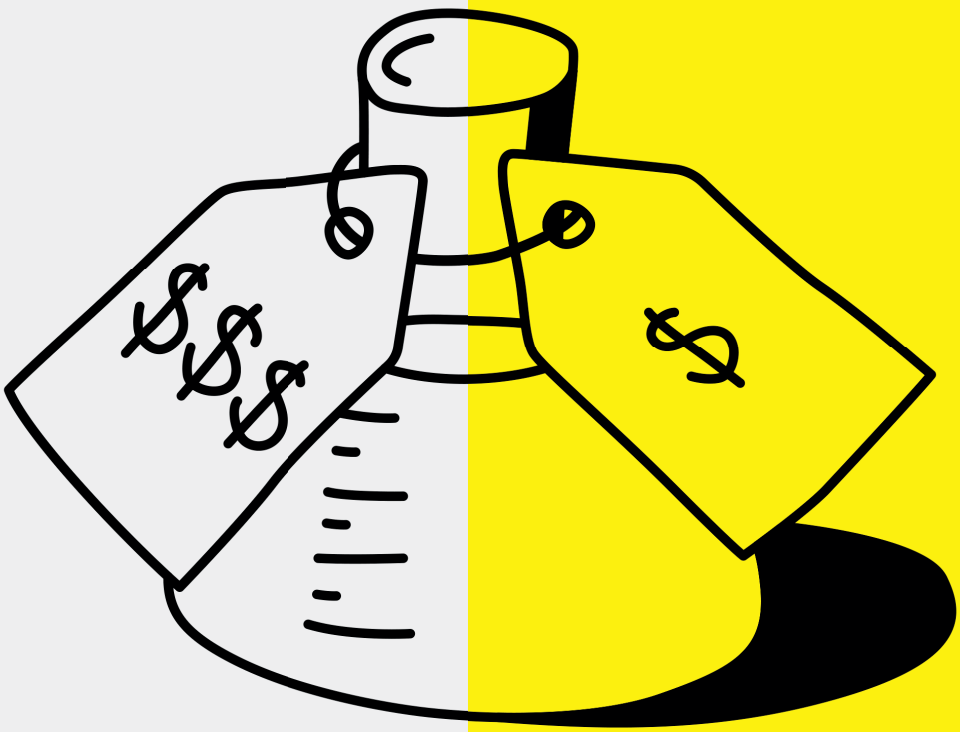
The New Economics of Biologics: Breaking the $50/g Barrier—Now



BioProcess International
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The New Economics of Biologics

Breaking the $50/g Barrier — Now

Jean-Marc Cappia, Jon Kruger, Gerben Zijlstra, Beatrice Claverie, Fabrizio Pelella, Vincent Lam, Sherwin Ting, Behnam Partopour, and Katy McLaughlin

As sustained demand growth, increasing molecular complexity, cost pressure, and sustainability requirements continue to shape biopharmaceutical production, process intensification (PI) enables manufacturers to improve productivity, reduce cost of goods (CoG), shorten timelines, and increase facility flexibility (see the "Intensification" box). Through holistic application across upstream processing (USP), downstream processing (DSP), facility design, and digital operations, PI now makes it possible to consistently reduce monoclonal antibody (mAb) manufacturing costs to below US$50/g — a threshold that once was considered theoretical but now can be achieved by some innovative companies (**1–3**).

Progress among PI adopters has brought manufacturing economics into sharp focus. High-profile initiatives, most notably from the Gates Foundation, have established an aspirational target of $10/g for mAb production to broaden global access, particularly in low- and middle-income countries (**4**). Such targets highlight both the feasibility of further cost reduction and the growing urgency to close the remaining gap.

Importantly, cost structures are not uniform across manufacturers. Companies operating large, established facilities could achieve costs well below $50/g because capital expenditures (CapEx) for such assets largely have been amortized. New market entrants must build new greenfield facilities, whereas companies with existing brownfield infrastructure can reduce CapEx by leveraging and upgrading their current assets. Organizations with legacy operations and overseas facilities also benefit from supplier relationships, discounts, and relatively low labor costs, allowing them to reach CoG in the range of $20/g.

Over the past three decades, mAb manufacturing has shifted from large, stainless-steel batch processes to smaller, more flexible processes based on single-use (SU) systems, intensified steps, and increasingly continuous operations. Costs already have fallen to <$100/g for large-demand production scale, driven by improvements in cell-culture productivity, platform processes, and SU technologies. Further reductions toward the <$50/g goal will be enabled in greenfield facilities by system-level transformation (**1, 5**).

Key cost-reduction approaches include increasing upstream titers through optimized cell lines and bioreactor conditions and adopting SU and continuous DSP technologies — such as membrane chromatography and multicolumn chromatography (MCC) — to enhance throughput while reducing labor, buffer consumption, and equipment footprint. Collectively, those innovations combined with process automation and real-time monitoring and control can lower production costs to well below $50/g without compromising product quality or regulatory compliance, making mAbs more affordable for global therapeutic use.

This report examines how such approaches are implemented in practice, detailing the methods, technologies, decision tools, collaborations, and organizational enablers required to support efficient, scalable manufacturing.

What Is Process Intensification (PI)?

PI has become a foundational strategy for the future of monoclonal antibody (mAb) manufacturing. We define it here as the systematic increase of productivity per unit volume, time, and footprint through enhanced yields and mass transfer, reduced process residence times, parallelization of unit operations, and continuous operation.

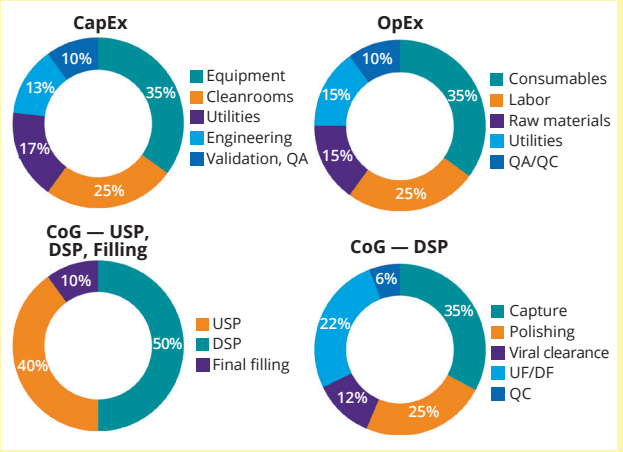
PI is a holistic framework aimed at maximizing productivity at the level of individual unit operations, processes, and facilities. It is implemented incrementally, progressing from conventional batch processes (Level 0) to intensified batch (Level 1), connected operations (Level 2), and fully continuous manufacturing (Level 3), as shown in Figure 3 (**11**).

Current Cost Structures and Drivers

Although CoG represents only a small percentage of a mAb product's sale price, it remains a pivotal factor, especially for large biomanufacturers (**6**). The industrial cost of mAb manufacturing typically ranges $50–500/g, with an average of about $300/g depending on annual production volume, process efficiency, and facility footprint and utilization, with some companies already reaching <$50. In well-optimized, large-scale facilities, costs of $50–100/g are steadily becoming achievable (**1**).

Manufacturing cost distribution is broadly consistent across the industry, with USP representing about 40% of

Figure 1: Cost breakdown for a typical monoclonal antibody (mAb) manufacturing process; CapEx = capital expenditure, CoG = cost of goods, DSP = downstream processing, OpEx = operating expense, QA = quality assurance, QC = quality control, UF/DF = ultrafiltration/diafiltration, USP = upstream processing



total CoG, DSP about 50%, and formulation and fill–finish about 10%. Protein A chromatography is the single largest cost contributor (Figure 1).

Over the past two decades, improvements in cell-culture productivity have reduced costs dramatically. Average titers have increased from 0.5–1 g/L in the early 2000s to 5–10 g/L in 2026, with intensified processes exceeding 10 g/L. That improvement alone has reduced cost per gram of product by a factor of 2–5.

Production scale and annual volume also have a strong influence on unit cost: Production volumes under 500 kg/year typically incur costs of $250–500/g, whereas production exceeding 2 tons/year can achieve costs close to $50/g without intensification and well below that threshold through high levels of PI (Figure 2). However, even at large scales, conventional batch processes involving protein A–based separation have a practical limit of $50/g (**2, 7**).

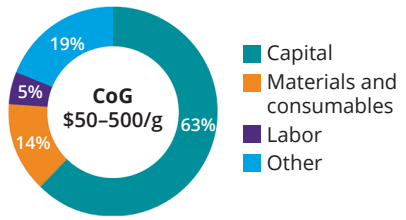
As shown in Figure 2, intensified processes involve much lower capital investments than their batch counterparts. Thus, CoG reduction in intensified facilities is tied less to production volume and more to optimizing technologies and workflows to reduce the costs of consumables, buffers, and labor — enabling intensified processes to break the $50/g barrier of traditional processes.

Trends Driving the <$50/g Target

The mAb market continues to grow at a compound annual growth rate (CAGR) of about 10% (**8**), but average peak sales per molecule have declined while development costs have increased. Pipelines also are shifting toward biosimilars and complex modalities, including multispecifics, antibody–drug conjugates (ADCs), and crystallizable fragment (Fc)–fusion proteins. As molecular diversity increases, demand profiles are changing: More than 80% of

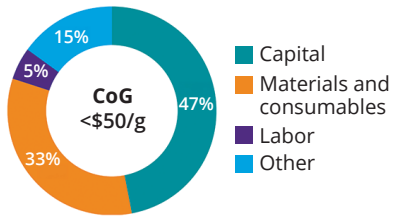
Figure 2: Cost breakdown for traditional and intensified commercial-scale biomanufacturing processes; data were generated using Biosolve Process software. (CapEx = capital expenditure, CoG = cost of goods, OpEx = operating expense)

Traditional Facility



Parameter	Traditional	Intensified
mAb titer	5–10 g/L	3–5 g/L/day
Bioreactor volume	12 kL (fed batch)	2 kL (perfusion)
Output	300–2000 kg/year	

Intensified Facility



Intensified Versus Traditional Shifting from CapEx to OpEx while reducing overall CoG	
Capital	–70%
Labor	–40%
Other	–50%
Material and consumables	+25%

commercial biologics require production volumes of <500 kg/year, and almost 50% require <100 kg/year (**9**).

Those demand trends are reshaping biomanufacturing requirements and driving the need for rapid facility build-out, high asset use, and efficient multiproduct operations. Meanwhile, regionalization and sustainability pressures are pushing manufacturers toward lean production models. Such developments fundamentally challenge the economics of traditional, large-scale batch manufacturing and favor smaller, more agile, and more productive facilities enabled by PI. Likewise, companies are shifting from scaling up to scaling out and scaling by time (**10**).

PI continues to be implemented incrementally across the industry. Efforts have focused primarily on adoption of SU technologies and upstream PI, featuring the development of increasingly productive cell lines and culture media combined with intensified fed-batch or perfusion technologies. As upstream yields improve, DSP efficiencies

become the next challenge. Stepwise downstream PI — ranging from intensified batch operations to fully continuous DSP workflows — can significantly reduce timelines, cut chromatography CoG, and reduce facility footprint while providing a pathway to end-to-end intensification for sustainable and cost-effective facilities (Figure 3).

Methods for Reducing CoG Below $50/g

SU Systems as the Base Manufacturing Platform: SU technologies are a foundational element of cost-efficient intensified manufacturing. Their influences extend beyond reducing CapEx and facility construction timelines to diminishing operating expenditure (OpEx) and operational complexity. SU systems eliminate clean-in-place and steam-in-place (CIP/SIP) operations, reduce qualification requirements, and expedite turnaround between campaigns.

From a process-engineering perspective, SU systems facilitate flexible, modular process layouts and reduce nonproductive time, increasing effective annual operating hours per unit operation. Those characteristics are critical for intensified processes, in which throughput is driven by productivity rather than equipment size.

SU systems reduce both direct costs (e.g., for utilities) and indirect costs (due to downtime, lost capacity, and validation effort). When combined with intensified processes, SU systems enable modular and adaptable facilities that are correctly sized and optimized for actual product demand rather than theoretical capacity. SU technologies likewise support efficient multiproduct operations. That is particularly relevant given that the majority of commercial mAb products are produced at annual volumes below 500 kg. Facilities with large stainless-steel equipment entail large upfront capital investment, chronic underuse in single-product facilities, and changeover inefficiencies in multiproduct operations.

Upstream Levers: USP has benefited from decades of innovation in cell-line engineering, omics-driven process understanding, advanced media and feed strategies, scalable SU solutions, and real-time process analytical technology (PAT). Together, those developments are increasing viable cell densities (VCDs), cellular productivity, metabolic control, and product-quality consistency.

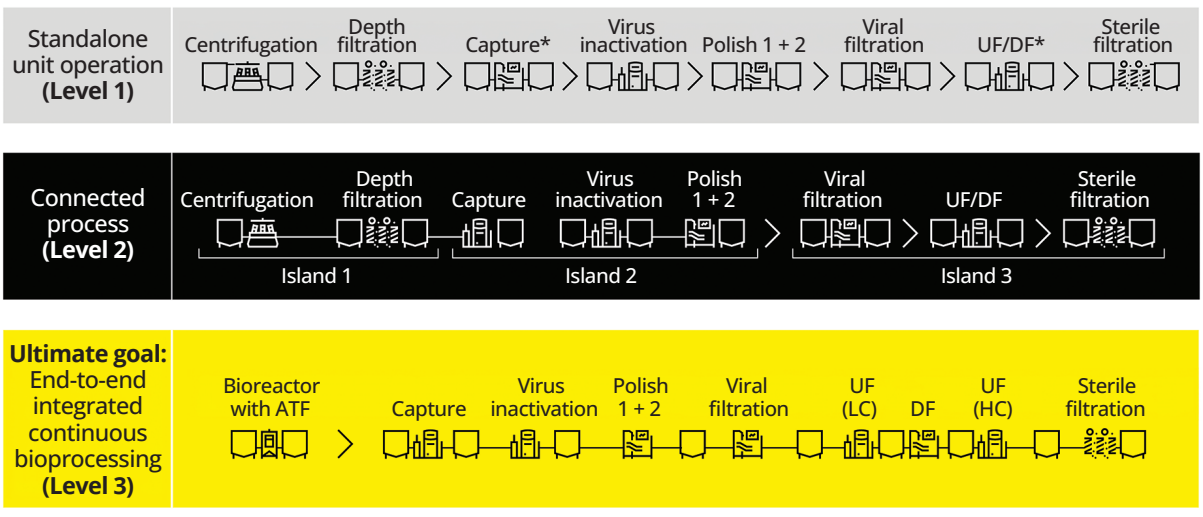
Following such improvements, upstream PI has become a critical driver of cost reduction that can be achieved through high-titer, intensified fed-batch or high-productivity perfusion cell culture. Perfusion cultures sustain high VCDs through continuous nutrient supply and removal of inhibitory metabolites, decoupling productivity from batch duration.

Perfusion bioreactors help to lower CoG by significantly increasing volumetric productivity (g/L/day). That reduces facility footprint per kilogram of product, needed batch number, total campaign duration, and changeover time. Perfusion strategies can be categorized into three operating modes, each aligned with different objectives (Figure 4).

***N* – 1 Perfusion with High-Inoculation Fed-Batch (Level 1):** At this level, the production bioreactor is inoculated at elevated cell densities (5–10 million cells/mL) to reduce the growth phase and increase overall output per bioreactor, enabling rapid productivity gains (≈2×) with minimal facility disruption when integrated into existing fed-batch processes.

Concentrated Fed-Batch (CFB, Level 2): Such processes involve continuous retention of cells and product and simultaneous removal of spent media. CFB provides a 3–5× increase in yield within a batch framework, provided that facility constraints allow for expanded media-preparation capacity and logistics. The method also enables SU setups to

Figure 3: Levels of process intensification for monoclonal antibody (mAb) manufacturing, from intensification of standalone unit operations to fully integrated continuous bioprocessing; an asterisk (*) indicates use of an intensified consumable. (ATF = alternating tangential-flow filtration, DF = diafiltration, HC = high concentration, LC = low concentration, MCC = multicolumn chromatography, UF = ultrafiltration)



match the outputs of large stainless-steel bioreactors, but it requires complex media logistics, suitable clarification solutions, and increased harvesting and DSP capacity. CFB's high media consumption makes culture media a major cost driver that must be managed accordingly.

***N*-Stage Perfusion (Dynamic or Continuous, Level 3):** This highest level of USP intensification involves continuous product harvest, which maximizes volumetric productivity and enables direct integration with continuous DSP systems. *N*-stage perfusion achieves cell densities of >100 million cells/mL and productivities of >3 g/L/day, increasing yields of some molecules by >10-fold. The method is particularly suitable for unstable or low-expressing proteins, but it requires advanced control strategies, flow balancing, and orchestration or integration with DSP automation.

High levels of USP intensification enable 1000–2000-L SU bioreactors to match the production capacities of 10–20 kL stainless-steel systems while reducing facility footprints and CapEx per kilogram of product. When combined with precise integrated control (automation and PAT), perfusion methods also reduce manual interventions, operator workload, deviations, and risk of batch failure. Perfusion also helps to align upstream output with downstream steps, enabling continuous or connected DSP without oversized chromatography columns or process-intermediate hold tanks. However, perfusion significantly increases culture-media consumption.

Downstream Levers: With DSP typically accounting for 50% of total mAb CoG and chromatography alone contributing 25–30% (**7**), the ultimate goal is for companies to achieve a DSP cost below $25/g to pave the road to an overall cost below $50/g.

Traditional DSP involves sequential, batchwise operations over three to six days, creating bottlenecks as upstream titers increase. As with USP, downstream intensification is implemented in three levels (Figure 4).

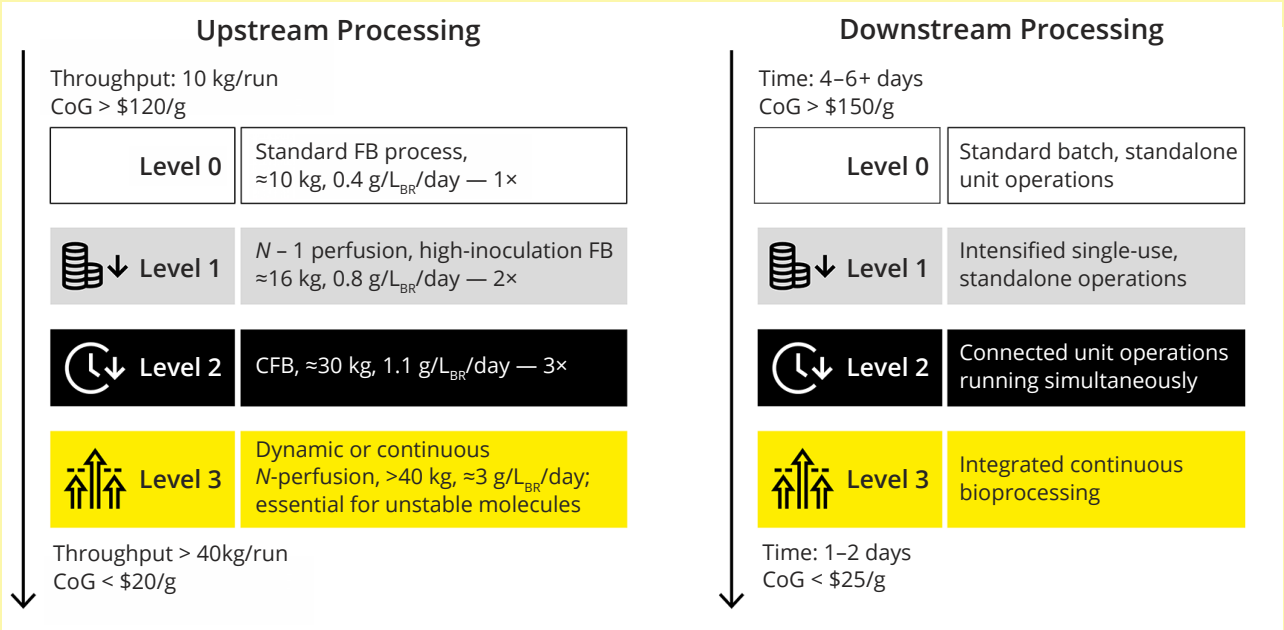
Intensified Batch Operations (Level 1): At this level, standalone unit operations are intensified but remain sequential. For instance, manufacturers might leverage rapid-cycling chromatography (RCC), MCC, or continuous virus inactivation. An intensified batch process can lower costs by up to 30% while shortening DSP time by ≈24 hours.

Connected Batch Operations (Level 2): In connected batch operations, steps for capture, virus inactivation, and polishing operate in parallel using controlled surge volumes and residence times. That approach reduces both operational and preparation time as well as needed resin and buffer volumes. The minimized need for large hold tanks decreases facility footprints by ≈50% while increasing throughput by ≈2×.

Continuous DSP (Level 3): This level of PI involves a fully integrated, digitally orchestrated flow of steps for continuous capture, virus inactivation, polishing, and ultrafiltration/diafiltration (UF/DF). Intermediate hold tanks are minimized or eliminated, buffer preparation is synchronized with demand, and downtime between steps is removed. Continuous DSP can be coupled with either fed-batch or perfusion culture processes, cutting DSP timelines to two days or less when coupled with a fed-batch bioreactor and providing fully integrated and continuous bioprocessing when combined with a perfusion process.

Although end-to-end bioprocessing represents the ultimate goal, continuous biomanufacturing does not

Figure 4: Stepwise approach to process intensification; CoG = cost of goods, DSP = downstream processing, FB = fed batch, L_{BR} = liter of bioreactor material, *N* = production-stage bioreactor, USP = upstream processing



require an all-or-nothing transition. Manufacturers can adopt Level 1 and Level 2 intensification strategies to capture significant cost benefits while building experience and confidence toward fully continuous operation.

Chromatography as the Key Downstream PI Enabler: Chromatography is the primary cost driver in DSP, with protein A capture alone accounting for up to 35% of a mAb product's total DSP expenses. Thus, breaking the $50/g barrier is fundamentally a DSP challenge that requires transformation of the chromatography train through innovations in resin or membrane use, process design, and technology integration.

Strategies include use of high-capacity resins, MCC, or membrane chromatography to increase throughput and reduce costs. Polishing steps leveraging cation-exchange (CEX), anion-exchange (AEX), or hydrophobic-interaction chromatography (HIC) can be optimized with ready-for-use membranes or integrated continuous formats, minimizing buffer consumption and cycle times. In-line conditioning and integrated chromatography sequences further decrease labor and facility footprints.

By focusing on chromatography-centered innovations, manufacturers can achieve significant cost reductions while maintaining regulatory compliance and product quality, ultimately helping to increase biotherapeutic accessibility.

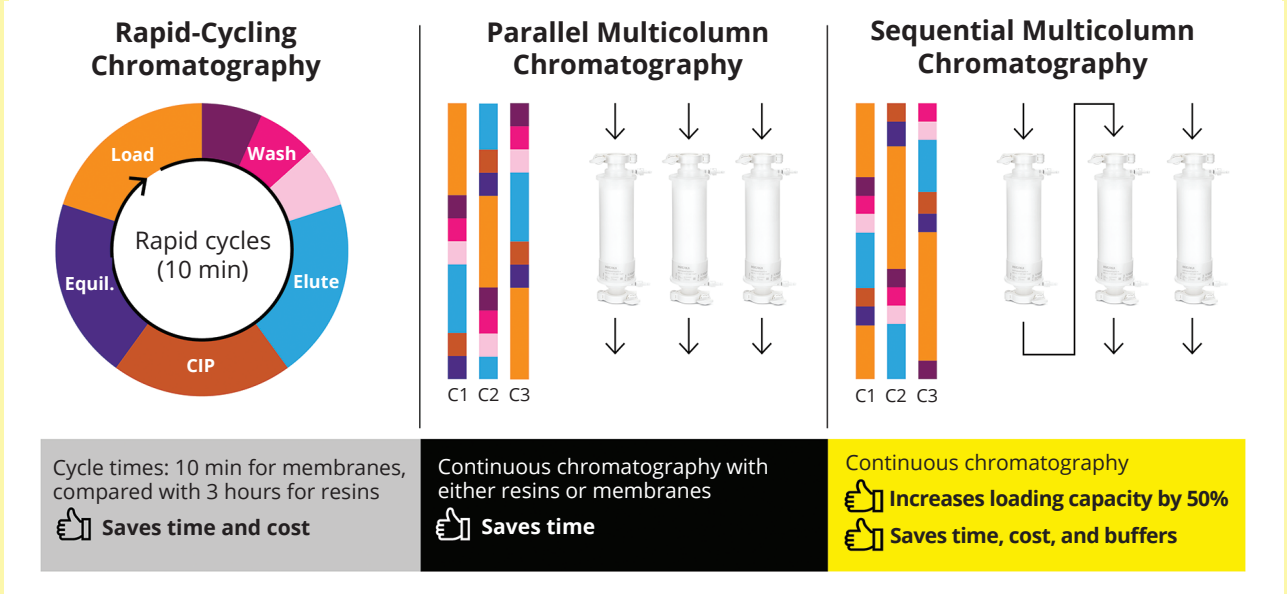
Membrane-Based RCC: Manufacturers can leverage membrane chromatography to address intrinsic limitations of traditional resin-based systems (e.g., long cycle times), operational complexities with column packing and storage, and resin lifetime underutilization. Membrane adsorbers enable residence times in the order of seconds and cycle times in the order of minutes (Figure 5).

Membrane-based protein A RCC, in which multiple short cycles replace a small number of long resin cycles, delivers large increases in productivity (g/L/hour) while maintaining yields and product-quality levels comparable with those achieved by resin-based capture. The approach also enables complete use of membrane capacity in fewer than four production runs, compared with more than 50 runs required to fully use resin capacity. Because PI enables the production of large amounts of mAb with a limited number of batches, resins used in intensified processes will suffer from capacity underutilization, whereas membranes will provide full capacity utilization and economy of scale. Implementing membranes also shortens validation timelines significantly and helps in optimizing consumables use, both of which are particularly beneficial in clinical, low-volume, and multiproduct environments.

Polishing operations can leverage flow-through membrane chromatography, exploiting charge-based and hydrophobic interactions to remove host cell proteins (HCPs), residual DNA, and protein aggregates while maintaining high product recovery. When extended to fully membrane-based workflows, typically involving bind–elute capture followed by double flow-through polishing, chromatography costs can be reduced to below $10/g, creating the margins required to achieve overall CoG below $50/g (**12–15**).

Multicolumn Chromatography: MCC is a key amplifier of downstream intensification and an essential bridge toward continuous manufacturing. It increases a resin's effective binding capacity, reduces resin volumes and buffer consumption, and enables continuous or semicontinuous operation.

Figure 5: Intensification methods for chromatography — rapid-cycling chromatography (RCC) with membranes and multicolumn chromatography (MCC) with membranes or resins; C1, C2, and C3 = columns 1, 2, and 3; CIP = clean in place



Different MCC configurations can be applied depending on process context (Figure 5). In *parallel-batch MCC*, continuous capture is enabled by distributing feed across multiple columns or membrane devices. This method is particularly suited to perfusion-based USP. In *sequential MCC,* breakthrough from a primary column or membrane is captured by a secondary column or membrane, increasing binding capacity and decreasing media cost per gram of product.

MCC can be applied to both membrane- and resin-based systems, depending on scale and reuse requirements. When applied to membrane chromatography, sequential MCC enables ≈25% buffer reduction, supporting cost-effective continuous capture compatible with perfusion upstream processes while maintaining flexibility and scalability from clinical to commercial production.

When applied to resins, sequential MCC increases effective binding capacity by 40–50%, reduces column size requirements, and improves lifetime utilization, all of which are critical for late-stage and high-demand products. In both parallel-batch and sequential configurations, MCC enables use of small columns or devices while helping to increase facility throughput and lower CoG, representing a natural bridge toward continuous DSP.

Connected and Continuous DSP: At high levels of intensification, DSP timelines for material from a batch upstream process can be reduced from 5–6 days to 24–48 hours by automating and parallelizing operations and reducing wait times. Optimizing the DSP workflow and operation cycles helps increase productive unit operation time and cycling efficiency while still reducing overall DSP duration. As a result, connected DSP can reduce the sizes of columns and intermediate tanks, cutting buffer and resin costs while enhancing DSP facility flexibility and throughput.

Intermediate hold steps are minimized, buffer preparation is synchronized with process demand, and idle time between unit operations is reduced significantly. Continuous DSP can be coupled with either fed-batch or perfusion upstream processes, enabling partial or end-to-end continuous manufacturing.

Using the example of a USP suite comprising six 2000-L fed-batch bioreactors operating at titers of 8 g/L, Figures 6 and 7 show how continuous DSP can halve processing time and, as a result, double facility throughput. In a traditional batch DSP configuration, annual production capacity is limited to 40 purification runs and <500 kg of mAb per year due to the five-day DSP cycle. By contrast, running simultaneous, continuous, and automated DSP unit operations eliminates overnight holds, reduces DSP duration to <48 hours, and boosts facility throughput to 90 runs and >1000 kg of mAb per year.

Figure 7 shows how continuous DSP also can decrease needed column sizes for capture and polishing steps. Continuous DSP using MCC can reduce resin volumes by 65% (from 295 L to 141 L) and buffer volumes by 26% (from 29 kL to 21 kL) per batch. Such reductions result in an annual saving of $1.2 million and 300,500 L of buffers.

As processes become intensified and interconnected, manual operation becomes inefficient and unsustainable. A robust digital ecosystem is therefore mandatory for PI (**16**). Core digital capabilities include:

- real-time monitoring of critical process parameters (CPPs) and critical quality attributes (CQAs) with linked PATs and multivariate data analytics
- predictive and model-based control
- synchronization of parallel unit operations
- automated deviation detection and response
- electronic batch records and data integrity.

For example, automated control and flow balancing of perfusion rates, chromatography loading, buffer preparation, and virus inactivation reduces labor requirements, minimizes operator-induced variability, and improves right-first-time performance.

Model-based control enabled by machine learning and/or artificial intelligence (ML/AI) could allow manufacturers to anticipate process deviations, optimize operating conditions dynamically, and maintain steady-state performance, all of which are critical in continuous processes. Such capabilities directly translate into lower CoG through higher effective capacity utilization and reduced product loss from deviations or failures.

Collaborative Partnerships and Data-Driven Codevelopment: Achieving and sustaining CoG below $50/g requires expertise across USP, DSP, automation, analytics, and regulatory strategy. Few organizations possess all of those capabilities internally.

Partnering with experienced technology and solution providers gives access to technoeconomical models, integrated USP and DSP platforms, and the digital infrastructure needed for predictive process control. Such partnerships also streamline development, reduce costs, and provide the technical and validation support required for implementation.

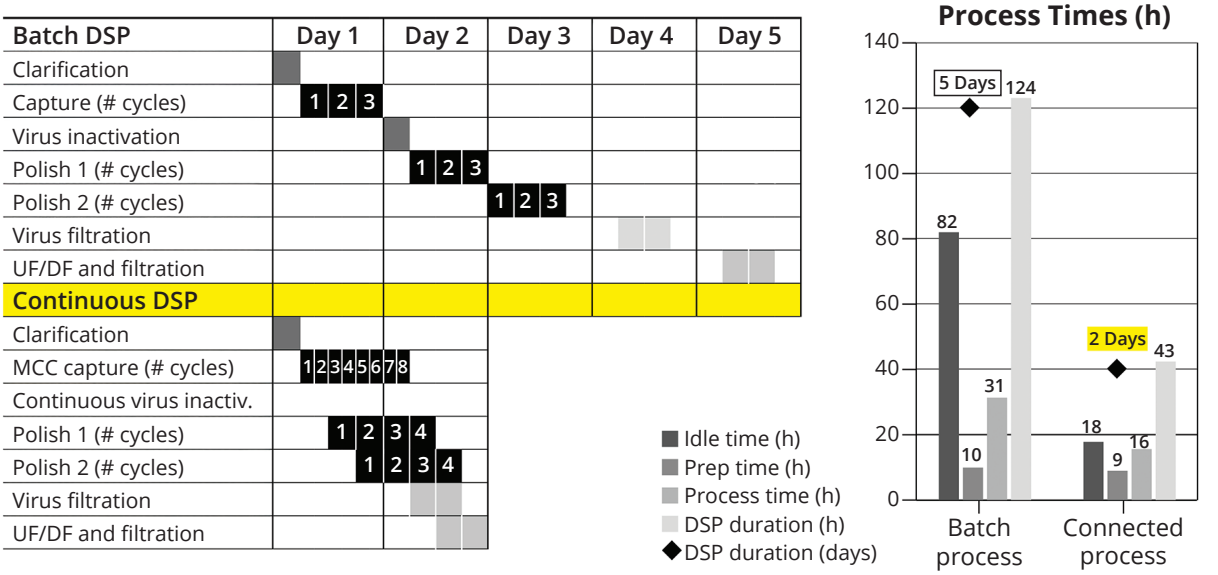
There is no one-size-fits-all PI model for all mAbs. Collaborative use of data analytics to identify bottlenecks, cost-modeling tools to predict PI benefits, and process simulations to demonstrate feasibility enables data-driven decision-making early in development, which is essential for delivering sustainable CoG reductions.

For example, the Expert Chromatography Intensifier Tool (ExCIT) is a Sartorius-developed modeling and decision-support platform that helps biomanufacturers optimize all key parameters across capture, intermediate purification, and final polishing. The tool enables comparison of

- batch, connected, and continuous DSP configurations
- resin and membrane workflows
- bind–elute and flow-through strategies for individual processes.

With such modeling, companies can predict CoG, buffer requirements, throughput, and timelines. Used correctly,

Figure 6: Continuous downstream processing (DSP) reduces processing time from 5 days to <48 hours and doubles facility throughput through parallel unit operations and elimination of overnight holds. (UF/DF = ultrafiltration/diafiltration)

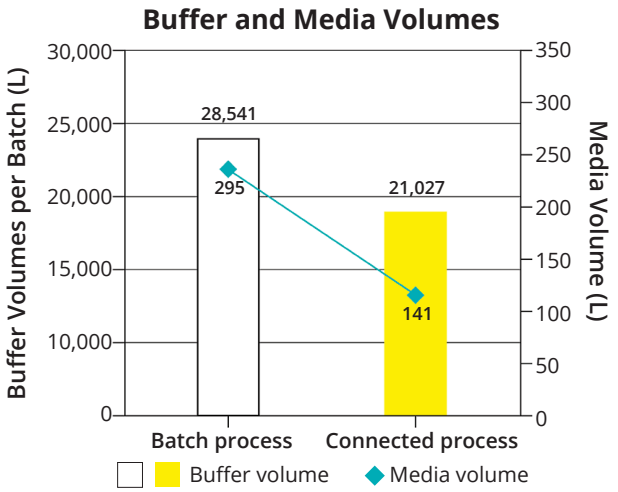


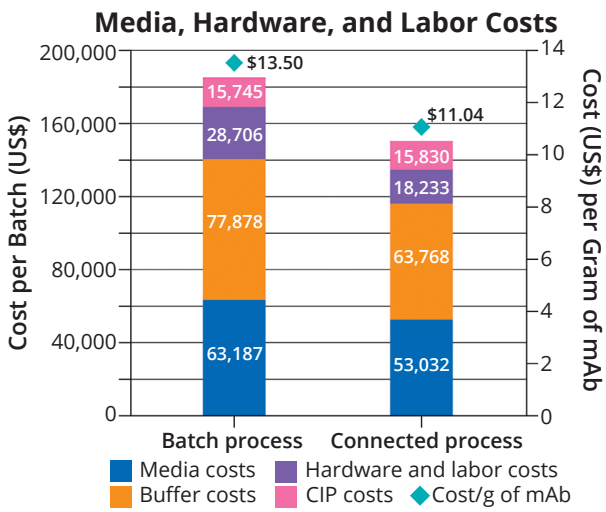
65% time savings per year (3235 hours)

2.5× throughput increase (from <500 to >1000 kg/year)

Figure 7: Continuous downstream processing (DSP) coupled with an upstream process based on 6 × 2000-L fed-batch cell cultures significantly reduces chromatography column size, decreasing annual costs (by 19%), buffer consumption (26%), and footprint (40%). (CIP = clean in place, mAb = monoclonal antibody)

	Column Size, Capture	Column Size, Polish 1	Column Size, Polish 2	Total Columns
Batch DSP	80 × 20 cm	80 × 20 cm	45 × 20 cm	3
Continuous DSP	40 × 8 cm (×3)	60 × 20 cm	40 × 20 cm	5





ExCIT reduces risk, accelerates development, and supports data-driven decision-making from early process development through commercial scale.

Understanding PI Economics: CoG, CapEx, and OpEx

Effective planning for commercial biomanufacturing requires clear alignment between facility strategy, production style, and anticipated market demand. Although traditional stainless-steel capacity continues to serve as a reliable backbone for large-scale supply, industry leaders are accelerating investment in next-generation facilities that can adapt to shifting portfolio needs.

Traditional biomanufacturing involves large upfront capital investments and therefore relies heavily on increasing the number of batches and annual production volumes to achieve economies of scale. PI fundamentally decouples production volumes from equipment size and footprint by increasing productivity per unit volume, footprint, and time. As a result, smaller, single-use facilities with much lower capital investments can achieve annual outputs previously associated with large stainless-steel plants — without the associated capital and operating costs (**10, 17**).

This section provides a comparative assessment of production approaches across different demand levels, examining how PI influences capital deployment, operational flexibility, costs, and the timing of new facility construction for greenfield investment. Our corporate research team used BioSolve Process software for cost modeling based on representative production scenarios. The "Methods" box summarizes the evaluated production schemes and underlying analytical assumptions.

We modeled different process scenarios to evaluate their influence on CoG at different fed-batch titers (5 and 10 g/L), concentrated fed-batch titers (15 and 25 g/L), and perfusion productivities (2, 4, and 5 g/L/d). Table 1 summarizes the annual production volumes and campaign sizes.

Impact of Titers, Cell-Culture Productivity, and Production Volumes: Titer, cell culture productivity, and production volume are the basis for economy of scale. Overhead costs (e.g., labor, utilities, building operation and maintenance) often are maintained or increase at a slower rate as batch output increases with titer or volume. Figures 8–11 all show decreasing costs when fed-batch titers, perfusion cell-culture productivity, production volume, and campaign size increase. Figures 8 and 9 also show the maximum throughput achievable with different process formats, highlighting that doubling bioreactor titer not only reduces cost per gram, but also can double maximum facility output and revenue.

Understanding such effects through solid cost modeling allows manufacturers to make informed decisions on facility build for a given process when demand is well defined. However, commercial demand is uncertain, and facilities designed for large volumes might be underused.

Early in facility planning, often four years before launch, demand uncertainty can be significant (**17**). When demand is overestimated and capacity use declines, stainless-steel facilities become particularly vulnerable due to their high capital intensity and fixed overhead (Figures 8 and 9). Our modeling shows that SU technologies and intensified processing provide alternative strategies to increase output while mitigating high CoG associated with capacity underuse.

Influences of SU and Stainless-Steel Equipment: SU technologies, especially in the context of membrane

Production Methods and Assumptions

Upstream Processing Scenarios

- **3 × 15,000-L Stainless-Steel Fed-Batch Process:** 14-day fed-batch process with centrifugation and one-stage depth filtration harvest
- **6 × 2000-L Single-Use Fed-Batch Process:** 14-day fed batch process with two-stage depth filtration harvest
- **8 × 2000-L Single-Use Concentrated Fed-Batch (CFB) Process:** 14-day, high-seed–density fed-batch production using product retaining filters and perfusion at one vessel volume per day; centrifugation and one-stage depth filtration harvest
- **4 × 2000-L Single-Use Continuous Process:** Perfusion process at two vessel volumes per day after initial four-day growth phase; duration is limited to 28 days.

Downstream Processing Scenarios

- **Batch:** Capture, two-tank virus inactivation, flow-through anion-exchange (AEX) chromatography, bind–elute cation-exchange (CEX) chromatography, viral filtration, and ultrafiltration/diafiltration (UF/DF)
- **Single-Use Continuous:** Three-column capture, Pionic Spin virus inactivation, two-column flow-through AEX chromatography, multicolumn (MCC) bind–elute CEX chromatography, continuous viral filtration, in-line concentration, and continuous diafiltration.
- **Stainless-Steel Continuous:** Continuous capture through polishing chromatography, batch viral filtration and UF/DF

Assumptions

- Final concentration: 120 g/L
- Media cost: $10/L
- Protein A resin cost: $18,000/L
- Stainless-steel batch capture cycles: 4–8
- Single-use batch capture cycles: 3–5
- Flow-through cycles: 1–2
- Continuous DSP time: 48 hours
- Protein A resin capacity: one column = 60 g/L; three columns = 72 g/L
- Base utilization: 80%
- Cost of capital: 8%
- Facility type: Multiproduct

Table 1: Production scenarios used in cost modeling; conditions and model assumptions are detailed further in the "Methods" box. (CFB = concentrated fed-batch process, FB = fed batch, SS = stainless steel, SU = single use)

Scenario	Upstream Strategy	Downstream Strategy
Greenfield Midscale Scenarios		
1	6 × 2000 L, SU, FB	SS, batch
2	6 × 2000 L, SU, FB	SU, batch
3	6 × 2000 L, SU, FB	SS, continuous
Greenfield Large-Scale Scenarios		
4	3 × 15,000 L, SS, FB	SS, batch
5	8 × 2000 L, SU, CFB	SU, continuous
6	4 × 2000 L, SU, perfusion	SU, continuous
7	8 × 2000 L, SU, CFB	SS, continuous

chromatography, already have proven to be more cost effective than stainless-steel equipment and resin-based chromatography for process development, clinical production, and low-demand commercial production, in which low batch numbers and production volumes cannot justify large upfront CapEx investment. That is evident in Figure 8, which compares a stainless-steel DSP (Scenario 1) and a SU DSP (Scenario 2).

Yet it is a common misconception that blockbuster drugs cannot be produced with SU technology. In fact, one 2000-L SU bioreactor operated in perfusion mode can produce the same amount of material as a 15,000-L bioreactor operated in batch mode depending on the productivity of the cell line in batch and perfusion.

Figures 9–11 show that intensified SU processes (Scenario 6) have lower CoG than do stainless-steel processes (Scenario 4) for large annual volumes and large campaigns. Assuming overall capacity utilization of ≈80%, a 15,000-L bioreactor produces 50–100 kg per batch across the range of campaign sizes shown in Figure 10. The stainless-steel process (Scenario 4) becomes cost-competitive against SU processes only at high titers and demands above 500 kg per campaign. Even then, the stainless-steel process remains more expensive than the SU continuous process (Scenario 6).

Build time also can be a challenge with large stainless-steel facilities, influencing lifetime return on investment (RoI) and creating vulnerability to demand uncertainties. Increasing capital costs in recent years have magnified the impact of indirect costs on overall CoG and profitability for new builds. Figure 12 shows that fully continuous facilities consistently offer a lower net present cost than do stainless-steel batch facilities regardless of capacity.

Such dynamics reflect the trade-offs inherent to each facility type. Stainless-steel facilities entail higher capital costs and longer build times, but they benefit from lower direct costs and less logistical complexity with smaller warehousing and material transfers. However, stainless-steel facilities have increased validation requirements and engineering complexity because of needed SIP/CIP operations.

By contrast, SU facilities offer greater operational flexibility, enabling rapid changes in unit operations and facility layout. Such adaptability supports multiproduct and multimodality manufacturing while helping to maximize facility use and throughput under uncertain demand conditions. Those features reinforce the cost advantages of SU technologies in variable production scenarios.

Comparing Continuous and Batch Processes: Our models show that high-productivity perfusion (4 g/L/day and 5 g/L/day) with continuous SU DSP (Scenario 6) are the most cost-effective options for large-demand facilities (Figures 9–11). Alternatively, a concentrated fed-batch with continuous DSP (Scenario 5) can be a good choice when perfusion productivity is limited to below 3 g/L/day.

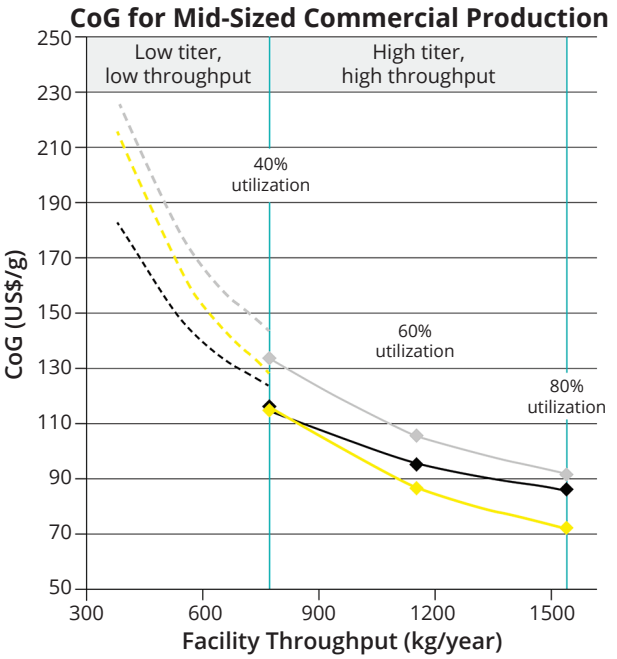
The effects of low titer and reduced facility utilization also are observed in continuous processes. In our mid-sized campaign models, continuous stainless-steel DSP (Figure 8, Scenario 3) delivers the lowest cost at 10 g/L and 80% utilization; however, that cost advantage disappears at 5 g/L and 40% utilization, at which that setup becomes more costly than a fully SU batch process (Figure 8, Scenario 2). Such results highlight the need to apply cost modeling case by case to evaluate PI strategies. At low titers, the resin-efficiency benefits of continuous processing do not offset the additional capital cost of stainless-steel continuous processing equipment required for MCC (Scenario 3, Figure 8). However, our analyses consistently show that the economic benefits of continuous DSP increase substantially as titers and throughput rise (Figures 8–11).

When deciding between batch and continuous DSP, upstream cadence is important to consider. At 80% utilization, a traditional six-pack SU facility (Figure 8) will have a three-day cadence. Thus, any DSP that ties up a suite for more than three days will decrease facility utilization because upstream batches cannot be purified as quickly as they are produced. Facilities taking five days or more to clear previral purification will push their utilization below 50%.

Continuous DSP could remedy that concern with a one- or two-day purification train. To that point, in Figure 8, the facilities considered might not operate at the same utilization and throughput. A continuous DSP could reach full utilization more easily than would the other configurations due to shorter timelines.

The CFB facility is a notable example of the potential differences in utilization due to bottlenecks. The facility modeled in Scenarios 5 and 7 (Figures 9–11) houses eight SU bioreactors. That configuration would have a cadence of two days at full utilization, representing the theoretical limit for a single continuous DSP. Potential bottlenecks going into DSP could be solved by scaling up flowrates and reducing purification time or by scaling out to a second downstream suite. Such measures illustrate the significant capital investment associated with DSP.

Figure 8: Effect of titer, production throughput, facility utilization, and downstream processing (DSP) mode on cost of goods (CoG) for a 6 × 2000-L single-use (SU) batch upstream process producing material for 100-kg monoclonal antibody (mAb) campaigns; changes in titer and throughput represent a drop in facility utilization from 80% to 40%. Scenario 1 involves stainless-steel batch DSP, Scenario 2 calls for SU batch DSP, and Scenario 3 is for stainless-steel continuous DSP.



Cost Reduction Levers

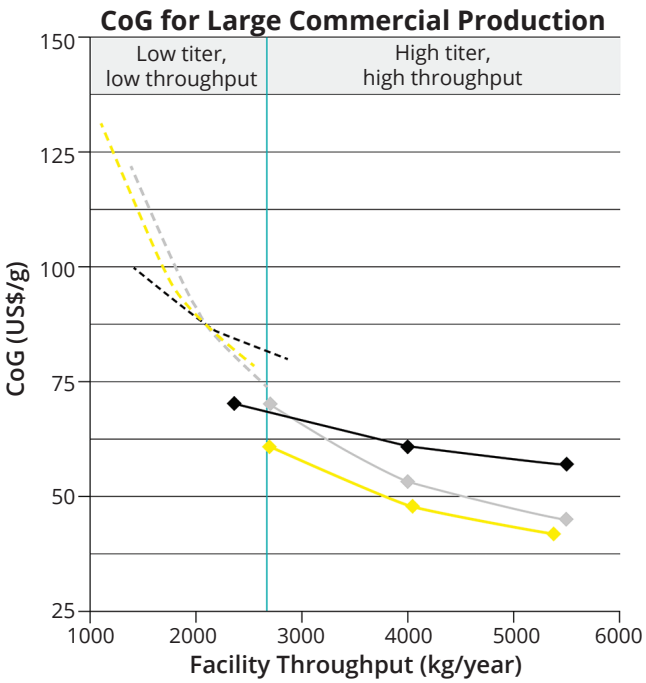
Titer and throughput	Doubling titer can **double outputs** and **cut costs by 38%.**
Single use or stainless steel?	Single-use downstream processing can **reduce cost by 20%.**
Continuous or batch?	• Continuous downstream processing can **reduce costs by 22%.** • Continuous processing is cost-effective at high titers and throughputs by **reducing equipment size and process duration (to <48 hours).**

Scenario 1: Stainless Steel
- 5 g/L
- 10 g/L

Scenario 2: Single Use
- 5 g/L
- 10 g/L

Scenario 3: Continuous
- 5 g/L
- 10 g/L

Figure 9: Effect of titer, throughput, upstream processing (USP) mode, downstream processing (DSP) mode, and facility utilization on cost of goods (CoG) for three processing scenarios in 1000-kg monoclonal antibody (mAb) campaigns; changes in titer and throughput represent a drop in facility utilization from 80% to 40%. Scenario 4 involves fed-batch (FB) processing in three 15-kL stainless-steel bioreactors (outputs of 5 and 10 g/L). Scenario 5 calls for continuous fed-batch (CFB) production in eight 2-kL single-use bioreactors (15 and 25 g/L). Scenario 6 involves continuous processing in four 2-kL single-use bioreactors (2 and 4 g/L/day).



Cost Reduction Levers

Titer and throughput	Doubling titer doubles facility throughput and **reduces cost by 36%.**

Single-use, continuous upstream and downstream processing	• Traditional plants reach <$50/g after 5 tons/year.
	• Single-use, continuous plants break the barrier at <4 tons per year.
	• **Continuous processes** provide the **best CoG** at >2.5 tons/year:
	  • **smaller equipment** (e.g., bioreactors and chromatography columns)
	  • **lower consumables costs** (e.g., for bags, filters, and resins).

Scenario 4: Stainless Steel
- 3 × 15 kL, 5 g/L
- 3 × 15 kL, 10 g/L

Scenario 5: Single Use
- 8 × 2 kL CFB, 15 g/L
- 8 × 2 kL CFB, 25 g/L

Scenario 6: Continuous
- 4 × 2 kL, 2 g/L/day
- 4 × 2 kL, 4 g/L/day

Perfusion-based processing has several operational challenges, including downstream capital utilization. The continuous facility (Scenario 6) in Figure 9 would need four separate lines of purification equipment to process four perfusions simultaneously, bringing down the utilization of an individual continuous DSP line. Although diminished utilization would be a drawback of using perfusion in such cases, the savings on USP, labor, and consumable intensity give fully continuous processing higher viability (Figures 10–11).

Choosing the Right Path to <$50/g

Achieving optimal CoG in clinical and/or low-demand production — and CoG below $50/g in large-demand manufacturing — requires careful evaluation of processes, technologies, and business environments. There is no one-size-fits-all path or single PI format for all mAbs; a structured, stepwise approach enables manufacturers to secure early gains while building toward fully integrated, intensified operations. Data-driven technoeconomic modeling tools, such as ExCIT and BioSolve Process software, help to predict PI benefits and support selection of an appropriate platform in silico. In-depth technology evaluations should validate such decisions and facilitate development of an effective, stepwise PI strategy.

To support true end-to-end continuous manufacturing, Sartorius launched the Pionic platform integrating chromatography, filtration, viral inactivation, and UF/DF processes. The platform's modular design enables manufacturers to transition smoothly from traditional batch methods to continuous manufacturing, either through stepwise intensification or fully continuous processing, reducing footprint, increasing throughput, and ensuring compliance and connectivity from the start (Figures 13 and 14).

The following sections provide a decision framework for selecting and implementing stepwise PI strategies across different manufacturing scales and demand scenarios.

Process Development and Early Clinical Manufacturing: Both contract partners that provide services for process development and early clinical manufacturing and biopharmaceutical companies with large development pipelines require flexible small-scale operations capable of handling multiple projects with diverse molecules and modalities. SU technologies are adapted perfectly to meet those challenges. Leveraging membrane chromatography also significantly reduces the cost of resins, which are largely underused in clinical manufacturing.

Agile capacity adaptation is a second prerequisite. It is required to optimize slot times, maximize available capacity, and increase new project throughputs. Given the low batch numbers (less than three runs) and volumes (less than a few kilograms) needed for clinical manufacturing (**6**), a fed-batch, SU USP suite followed by a semi- or fully

Figure 10: Impact of campaign size and titer on cost of goods (CoG) for different processing strategies; 80% of the maximum theoretical output for each facility is shown. Scenario 4 involves fed-batch (FB) processing in three 15-kL stainless-steel bioreactors (outputs of 5 and 10 g/L). Scenario 5 calls for continuous fed-batch (CFB) production in eight 2-kL single-use bioreactors (15 and 25 g/L). Scenario 6 involves continuous processing in four 2-kL single-use bioreactors (2 and 4 g/L/day).

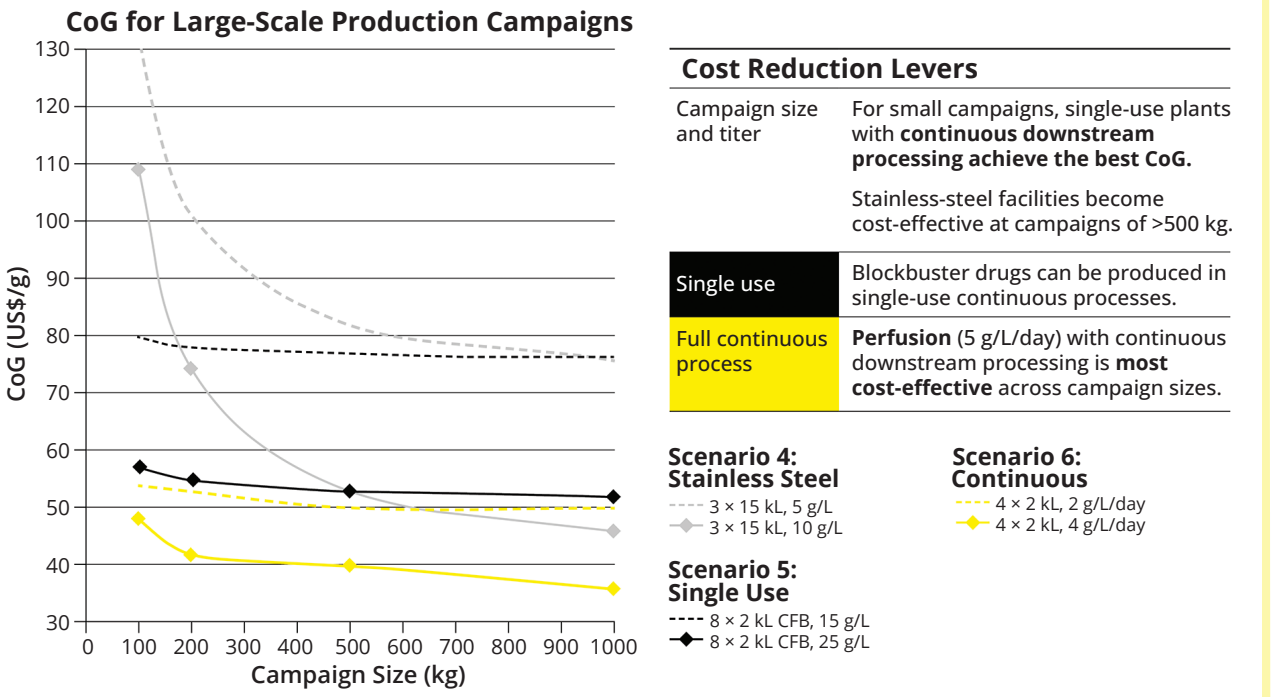
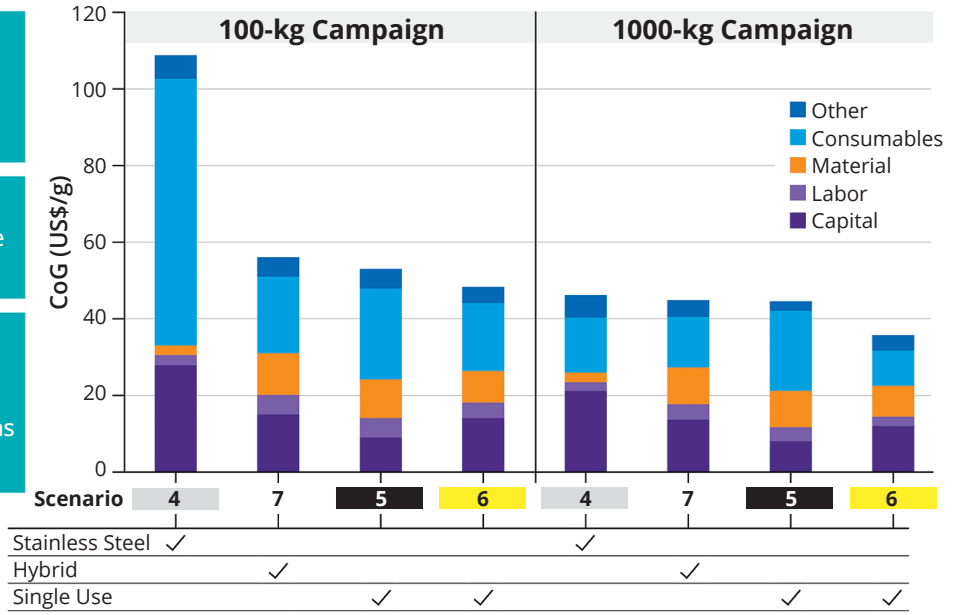


Figure 11: Cost breakdown of 100-kg and 1000-kg campaigns across different production scenarios; 80% of the maximum theoretical output for each facility is shown. (CoG = cost of goods)

For small campaigns, high equipment costs and underused resins drive high CoG (Scenario 4).

Membranes increase productivity and reduce CoG significantly.

Single-use continuous processes provide the best CoG (<$50/g) from small to large campaigns (Scenario 6).



continuous SU DSP would double process-development and clinical capacity by reducing DSP timelines from >5 days to <48 hours.

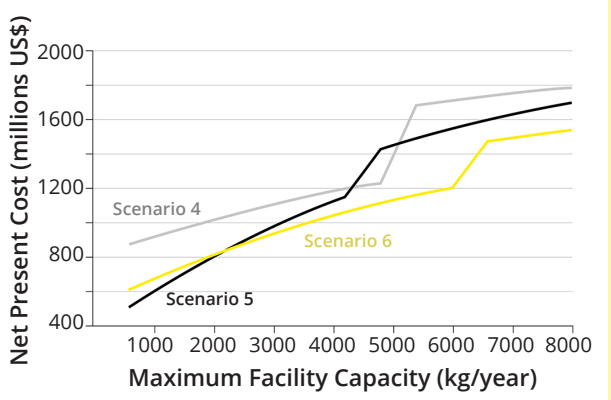
That setup would require multiple SU bioreactors segregated in different areas to cultivate different cell lines and produce different molecules simultaneously. Adopting membrane-based chromatography and/or MCC can reduce CoG significantly during early good manufacturing practice (GMP) production, addressing the high costs associated with resin underuse in clinical and/or low-demand production. Figure 13 depicts an optimized setup for process development and clinical manufacturing.

Large-Demand Commercial Production: Adopting continuous or intensified manufacturing involves significant capital investment and operational risk, both of which contribute to hesitation across many organizations. Skepticism around tangible benefits, coupled with concerns over downtime, training, equipment changeout, and validation, creates a high barrier to change. In regulated environments, such factors frequently result in resistance to transitioning from established batch processes.

At contract development and manufacturing organizations (CDMOs), where manufacturing cadence and batch success rates are critical to business health, the "activation energy" is particularly high. The CDMO industry has been particularly active in PI efforts given its strong alignment with an intensified operating model: Greater process efficiency reduces costs and increases batch numbers per year.

To realize PI benefits while mitigating risks associated with process change, intensification should be implemented

Figure 12: Net present cost of three facilities producing 4000 kg of monoclonal antibody (mAb) per year; 80% of the maximum theoretical output of each facility is shown (**18**). Scenario 4 calls for 3 × 15,000-L stainless-steel batch upstream processing (USP) and stainless-steel batch downstream processing (DSP). Scenario 5 specifies 8 × 2000-L single-use concentrated fed-batch (CFB) USP and single-use continuous DSP. Scenario 6 involves 4 × 2000-L single-use perfusion USP and single-use continuous DSP.



stepwise, prioritizing solutions with minimal impact on development timelines and routine operations. Technologies such as dual column chromatography offer measurable benefits without requiring changes to process development and with limited operational disruption.

From dual column implementations, organizations can advance progressively to systems such as sequential MCC or integrate downstream polishing steps, incrementally introducing connected and semicontinuous processing while

Figure 13: Optimized upstream processing (USP) and downstream processing (DSP) workflow for process-development, clinical, and low-demand commercial production using membranes, multicolumn chromatography (MCC) and continuous processing in the Pionic platform to address the high costs of underused resins and double facility throughput; CoG = cost of goods, DF = diafiltration, UF = ultrafiltration, VI = virus inactivation

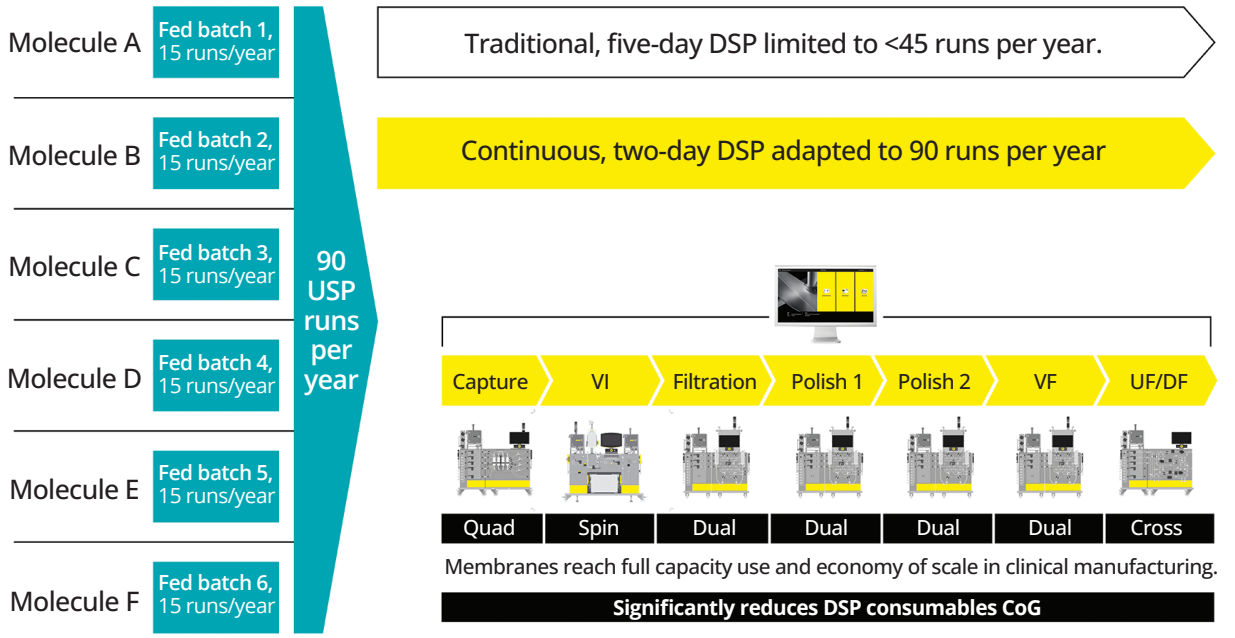


Figure 14: Optimized downstream processing (DSP) workflow from low- to large-demand commercial production, integrating concentrated fed-batch or perfusion upstream processing (USP) with the Pionic modular platform for fully continuous biomanufacturing; CFB = continuous fed-batch process, CoG = cost of goods, DF = diafiltration, UF = ultrafiltration, VI = virus inactivation

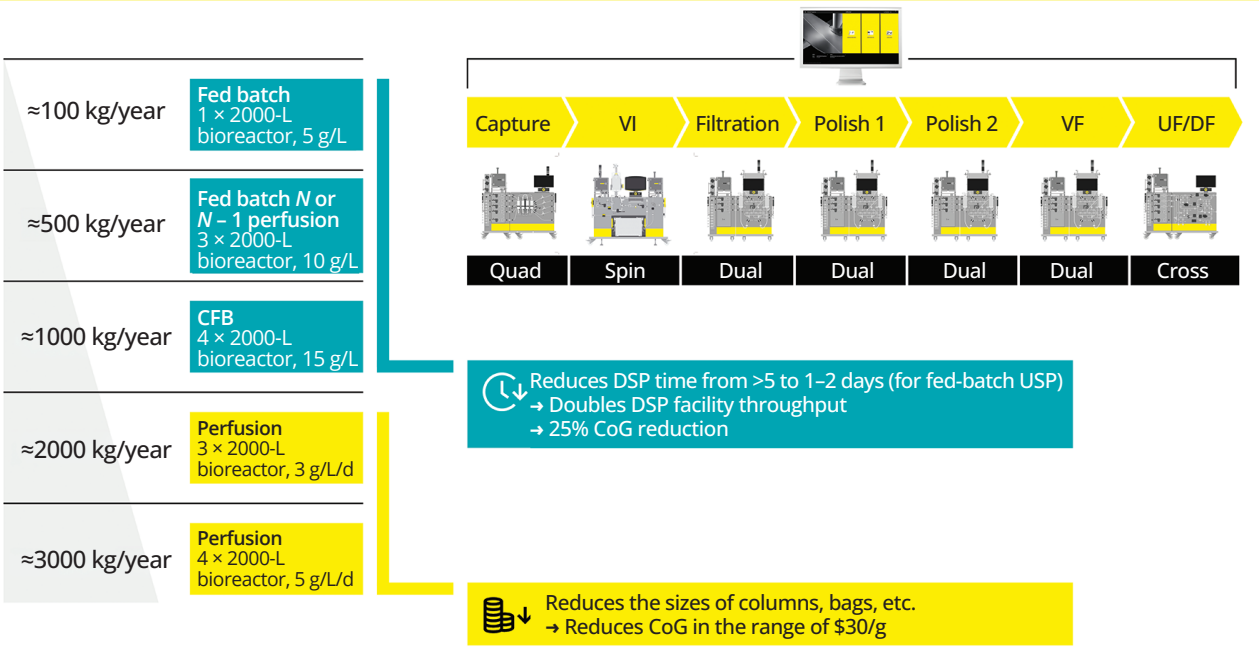
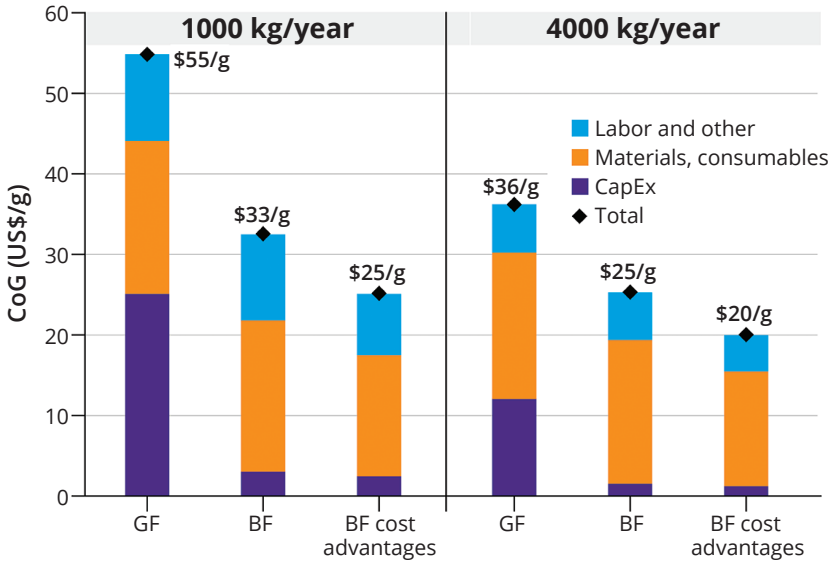


Figure 15: Impact of greenfield (GF) and brownfield (BF) investments on cost of goods (CoG) for process intensification (PI) Scenario 6 (4 × 2000-L single-use perfusion upstream processing with single-use continuous downstream processing); CapEx = capital expenditure

New market entrants (e.g., biosimilar developers) must build manufacturing infrastructure from scratch (*greenfield*).

Companies with existing brownfield infrastructure can reduce CapEx by leveraging and upgrading current assets.

Organizations with legacy operations and overseas facilities benefit from supplier relationships, discounts, and lower labor costs.



building organizational confidence and experience. Capture and polishing steps then can be connected to continuous virus inactivation for a fully continuous primary purification island, reducing purification duration while remaining compatible with both batch and perfusion USP.

Ultimately, production volumes will drive the choice of the appropriate PI strategy and process model. As production volumes increase with drug-product maturity, a stepwise, modular approach enables gradual intensification while building knowledge, developing expertise, and mitigating risk (Figure 14).

Toward Productivity-Driven Scaling

Biologics manufacturers are under increasing pressure from biosimilar competition, margin compression, diversifying portfolios, and global demands for equitable drug access. Cost per gram of mAb production is now a key limiting factor as well as a critical factor in recuperating development costs, particularly for indications with small patient populations. Achieving the <$50/g benchmark will require manufacturers to change fundamentally how their processes are designed and operated at scale rather than effecting incremental improvements to legacy systems and workflows.

PI addresses that need for fundamental change by shifting away from scale-driven manufacturing toward productivity-driven scaling, increasing output per unit volume and time. PI enables relatively smaller, more flexible facilities, and the approach is particularly suited to biosimilars, multiproduct operations (e.g., at CDMOs), and products with uncertain or regional demand.

With PI, sustainable industrial costs below $50/g are realistic for high-volume antibodies, but only through the combination of multiple levers. Implementing upstream PI by combining highly productive engineered cell lines with CFB processes (reaching titers >20 g/L) or continuous perfusion can reduce costs by enabling small, SU setups to achieve outputs comparable with those of large, stainless-steel facilities. But such an approach is insufficient on its own. The largest PI gains come from DSP; approaches such as low-cost or alternative protein A resins, membrane chromatography, and continuous capture and polishing reduce costs by lowering chromatography media and buffer consumption.

Further gains are achieved through integrated continuous biomanufacturing, which reduces CapEx, OpEx, and cycle time while increasing asset utilization. Combined, those measures realistically can bring manufacturing costs down to $30–40/g for large production volumes, as demonstrated in this report for greenfield investments.

During cost modeling, we assumed that new plants would be built for the processes described, and our simulations are based on standard list prices for systems, consumables, and labor costs in Western countries. Some regions could benefit from lower labor costs. Additionally, companies with already amortized large-scale infrastructure, combined with volume-based discounts on consumables and low labor costs, may not require the level of CapEx investment assumed in this study. In such cases, CoG in the range of $20/g realistically could be achieved (Figure 15).

The main limitation remains the traditional “protein A + batch” approach. Moving beyond it requires coordinated

changes in USP and DSP, SU technologies, digital integration, and overall manufacturing strategy. An integrated approach will be essential to delivering sustainable cost reductions without compromising quality or compliance.

It's time to intensify.

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Jean-Marc Cappia *is head of product management for process intensification,* ***Jon Kruger*** *is a bioprocess engineer in corporate research,* ***Gerben Zijlstra*** *is senior bioprocess solutions expert,* ***Beatrice Claverie*** *is head of product excellence for bioreactor technologies,* ***Fabrizio Pelella*** *is market development manager for downstream process intensification,* ***Vincent Lam*** *is a product specialist in process intensification for bioreactor technologies,* ***Sherwin Ting*** *is bioreactor technologies business area manager for the Asia region,* ***Behnam Partopour*** *is a principal scientist in corporate research, and* ***Katy McLaughlin*** *is an expert scientific writer, all at Sartorius; https://sartorius.com.*