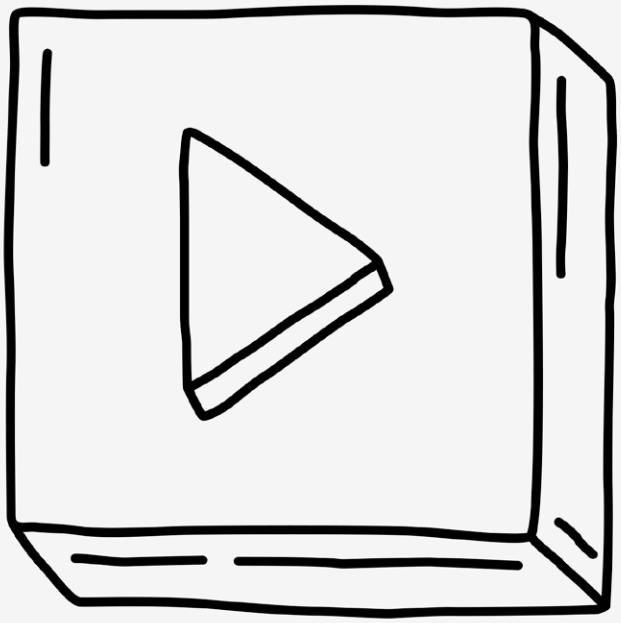

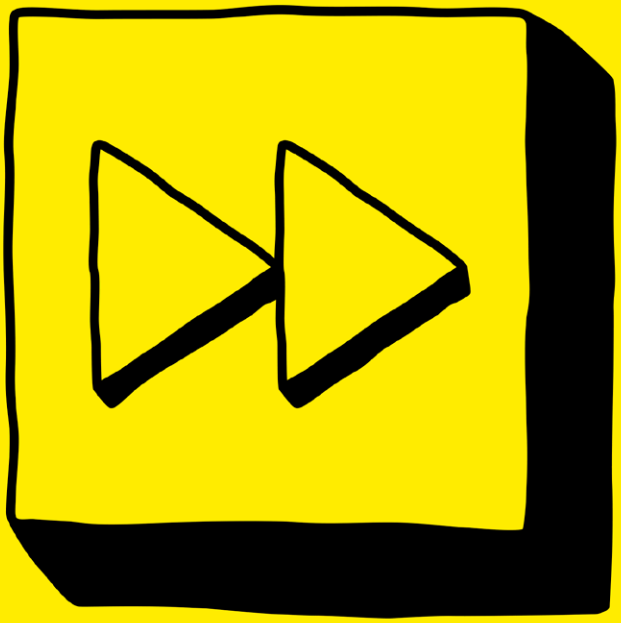

Simplifying Progress

Time to Intensify: Taking mAb Manufacturing to the Next Level

July, 2025 | Gerben Zijlstra, Jean-Marc Cappia

Keywords or Phrases:
Process Intensification, Intensified Bioprocessing, Continuous Biomanufacturing, Connected Bioprocessing, Upstream Intensification, Downstream Intensification, Automated Bioprocess Solution, PI Consultation

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Introduction

The mAb Industry is Evolving Towards Intensified Processing

The monoclonal antibody (mAb) industry is evolving towards intensified processing to meet global healthcare needs and address a broad range of indications, including cancers, infectious diseases, cardiovascular conditions, and autoimmune disorders. With mAb demand growing at over 10% CAGR,[1] there is a pressing need to accelerate drug development, reduce costs, improve capacity utilization, and prioritize sustainability.

Process intensification (PI) offers a holistic approach to maximize productivity in biomanufacturing, improving unit operations, manufacturing processes, and facility output.[2,3] Recent advancements, including single-use technologies, perfusion bioreactors, membrane chromatography, data analytics, automation, and continuous processing, have significantly reduced the cost of goods (COGs) for mAbs from over €1,000/g to under €200/g,[2,4,5,6] with aims to further reduce COGs to below €50/g (Figure 1).

Figure 1: *mAb Process Evolution Towards Intensification and the Impact on Cost of Goods*

1990 – 2000 COGs: ~€1,000/g mAb

Large-Scale Stainless-Steel Process
Batch mode
Driven by low titers

- High costs and energy
- Long lead times
- Very limited flexibility

2000 – 2020 COGs: ~€200/g mAb

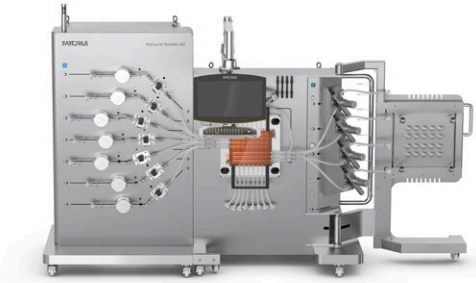
Small-Scale Single-Use Process
Batch mode
Supported by high titers

- Lower investment
- Low risk of cross-contamination
- Higher flexibility

2020 – 2030 COGs: <€50/g mAb

Intensified Process
Continuous mode
Supported by technology innovation, digital solutions, and automation

- Higher productivity
- Lower footprint, COGs, and CO_2
- Higher product quality



PI is particularly relevant in the protein-based therapies market, which is transitioning from conventional mAbs to more complex modalities, such as multi-specifics, antibody drug conjugates (ADCs), Fc-fusion proteins, and personalized molecules with lower demand. PI is also highly applicable to the biosimilars space, where increased competition—driven by more candidates targeting the same indications—is reshaping pipelines and encouraging a shift toward smaller, more regionalized production facilities.[4,7] As shown in Figure 2, most commercial drugs today are produced at annual volumes under 500 kg/year.

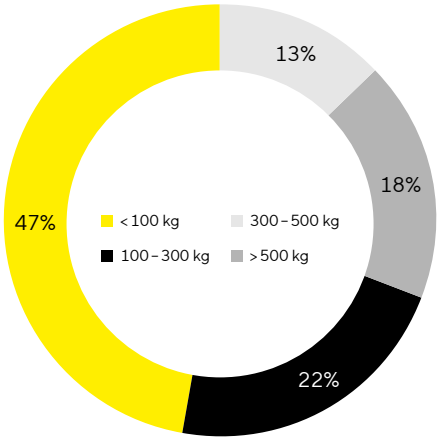
Fed-batch upstream processing (USP) improvements have increased mAb titers up to 10 g/L,[8–18] highlighting downstream bottlenecks and increasing the need for downstream PI. As well as increasing titers, PI also enables efficient manufacturing with lower COGs, wider drug accessibility, and reduced environmental impact (Figure 3). Biopharmaceutical companies typically start exploring PI during the early process development stage as a means to develop and deliver more cost-effective therapeutics faster, supporting more affordable medicine and better health for more people.

In an industry driven by quality and safety, PI progresses incrementally and continually. Over the past decades, efforts have primarily focused on the adoption of single-use technologies and upstream PI, with the development of more efficient cell lines and cell culture media systems, combined with intensified fed-batch and perfusion technologies. mAb titers exceeding 10 g/L in fed-batch mode and productivities beyond 3 g/L/day in perfusion mode, demonstrated at small scale, are expected to be achieved more broadly in future commercial manufacturing.[12,14,15]

As upstream yields improve, downstream efficiencies are the next challenge, paving the way for end-to-end intensification and sustainable, cost-effective, compact facilities in the coming years. Downstream PI is also critical for companies producing more complex recombinant proteins, such as Fc-fusion proteins or multi-specifics, where titers of 6 g/L in fed-batch and up to 11 g/L with N-1 perfusion and high-inoculation seeding, have been reported.[19]

Several front-runners in the biopharma industry have implemented flexible, single-use PI facilities as part of their commercial manufacturing networks. By leveraging standardized single-use unit operations, they have achieved significantly faster build-out times and reduced capital expenditure.

Figure 2: *2027 Commercial Drug Demand in kg/year*

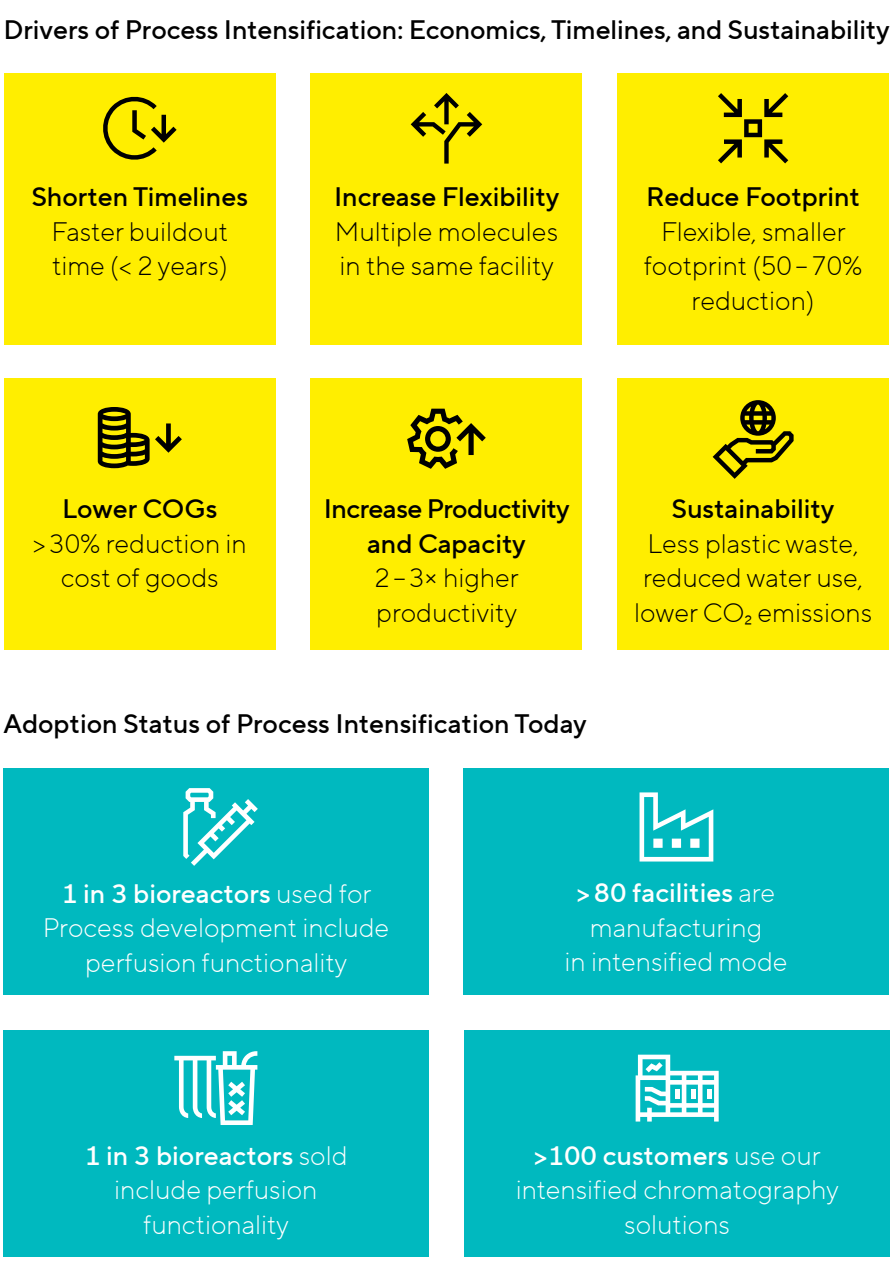


(% of number of commercial drugs in each demand scale)

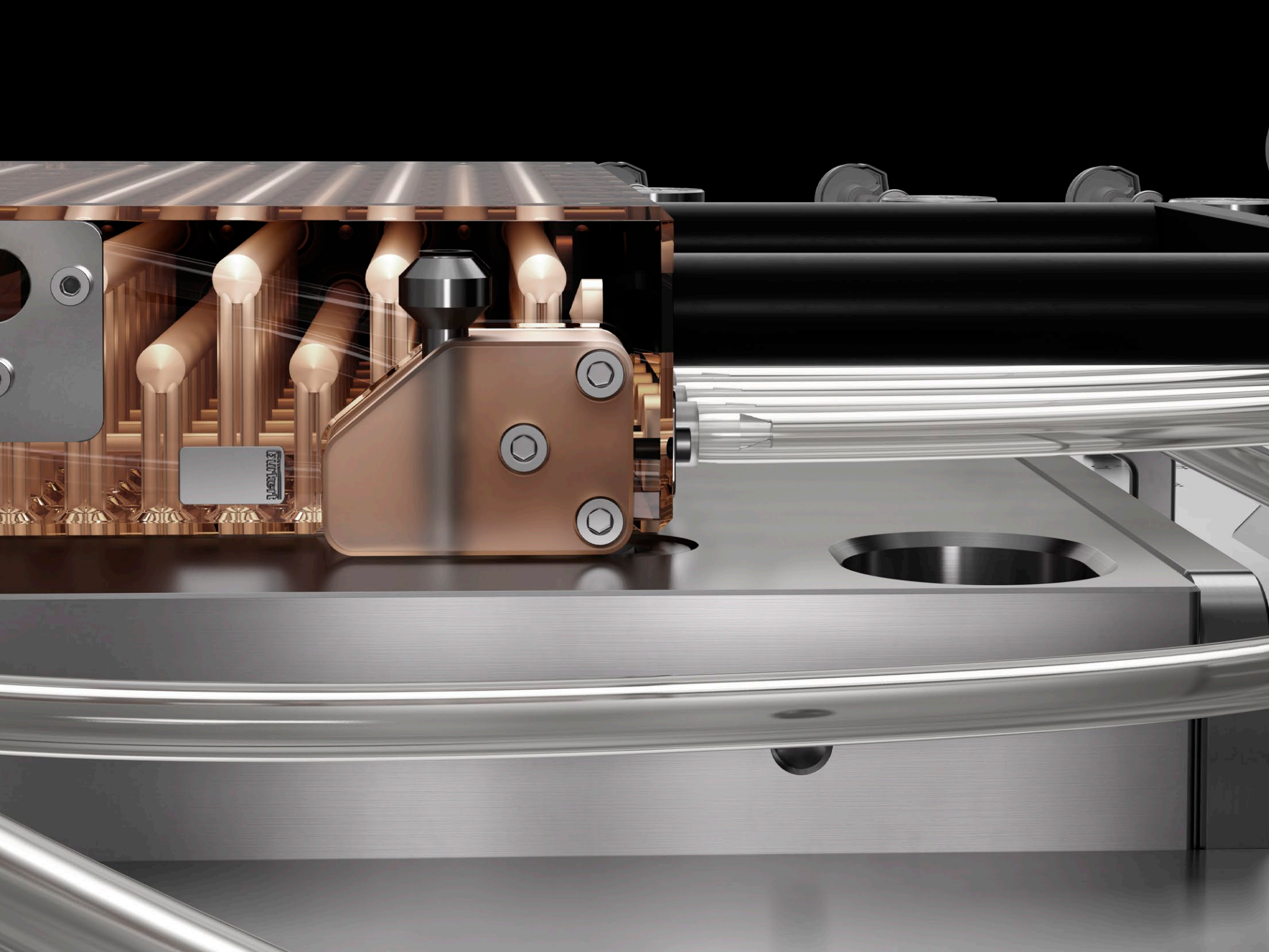
Note. Source: Mammalian Demand Forecast, BioTrak, BDO 2023. Note that the calculation only include mAb products approved prior to 2020 to eliminate bias of newly launched products

"Process intensification can be a stepwise, guided transformation across the full mAb workflow."

Figure 3: *Process Intensification Drivers and Adoption Status*



In this white paper, we outline a practical, stepwise PI approach across the full mAb manufacturing workflow. We explore upstream and downstream PI strategies, innovative enabling technologies, digital solutions, and supporting tools that help simplify the transition to intensified and continuous processing. The goal is to provide actionable insights that help manufacturers accelerate the adoption of PI and maximize its benefits in terms of cost, productivity, and sustainability.

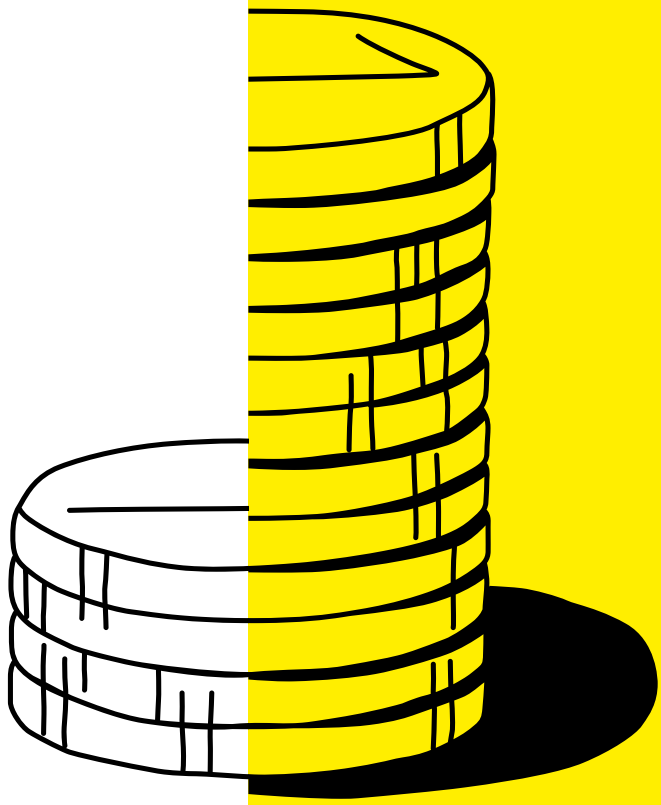


A Stepwise Strategy for USP Intensification

Fed-batch remains the dominant mode of cell culture in conventional mAb manufacturing. PI in fed-batch mode has been driven by continuous improvements in cell line engineering, cell culture media, feeds, and feeding strategies. With the growing understanding of cellular metabolism through omics technologies and the rapid advancement of genetic tools such as CRISPR | Cas technologies, targeted cell line modifications are becoming a viable strategy for large biopharmaceutical companies to optimize their platforms.[20, 21]

These approaches have not only improved cellular protein expression but have also led to increased cell densities and improved cell growth profiles by, for example, the targeted modification of pathways responsible for inhibitor production.

In parallel, omics technologies have enhanced process understanding to the extent that cellular nutrient requirements are characterized across the distinct phases of the fed-batch process. This enables the fine-tuning of basal media and feeds, as well as the development of phase-specific feeding regimes to meet the cellular nutrient needs across different cell culture stages.[22]



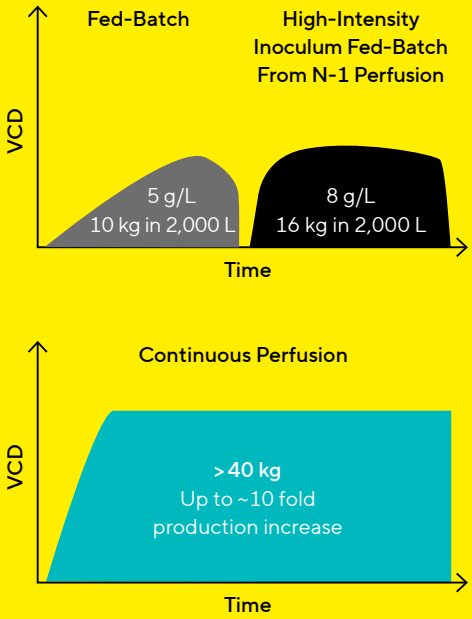
Finally, the increasing implementation of real-time process analytical tools (PATs) like capacitance and Raman probes, even at commercial scale, enables the precise monitoring of cell culture phases and nutrient levels. As a result, suitable infrastructure for these advanced process phase-based control strategies is now in place.[23] Together, these innovations have substantially increased mAb titers, with 5 g/L routinely achieved and 10 g/L no longer an exception—particularly among large biopharmaceutical companies.

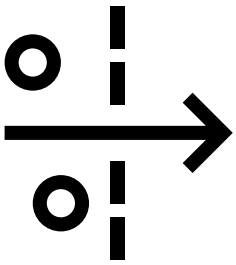
In cases where the titer or product quality in fed-batch mode is insufficient to support progression into manufacturing, PI using different perfusion strategies can be very effective to boost titer or salvage product quality. Such cases are common and can include, for example, biosimilars developed under time pressure, where strategies like N-1 perfusion and high-intensity fed-batch cultures can be used to boost titers. Other cases include new molecular formats that exhibit low expression levels or structural instability, degrading under standard bioreactor conditions, e.g., bispecific antibodies, and requiring the short residence times provided by perfusion.[24]

While perfusion approaches also benefit from ongoing advances in cell line engineering and media development, they offer the added advantage of actively removing inhibitory and toxic cellular byproducts.[25] This allows cultures to reach much higher densities than in traditional batch processes, enabling 1,000–2,000 L single-use bioreactors to match the output of large stainless-steel bioreactors, paving the way for highly productive, flexible single-use facilities. Perfusion processes rely on a cell retention device (CRD) of which various forms exist. For single-use biomanufacturing, hollow-fiber membrane-based CRDs—such as alternating tangential flow (ATF) or tangential flow filtration (TFF) devices—are widely used.[24]

Figure 4: *Different Process Intensification Strategies Using Perfusion Approaches*

Level 0	Level 1	Level 2	Level 3
Standard fed-batch	N-1 perfusion or high-intensity fed-batch	Concentrated fed-batch	Dynamic or continuous perfusion
~10 kg	~16 kg	~30 kg	>40 kg
Batch harvest	Batch harvest	Batch harvest	Continuous harvest
0.4 g/L_{BR}/day	0.8 g/L_{BR}/day	1.1 g/L_{BR}/day	>1.1–3 g/L_{BR}/day
Baseline productivity (1×)	2× productivity	3× productivity	Required for unstable or low-yielding molecules





Upstream PI Approaches

N-1 Perfusion Culture

The first perfusion strategy that can be employed to increase the titer is N-1 perfusion followed by high-inoculation fed-batch (Figure 4). By inoculating the production bioreactor at a much higher cell density (typically between 5 and 10 million cells/mL rather than the traditional ~0.5 million cells/mL), the length of the unproductive growth phase in the main bioreactor is significantly shortened, reducing the overall run time. With further process optimization, this approach can yield up to a twofold increase in productivity.

N-1 perfusion is widely used in industry and can be performed in existing fed-batch facilities with minimal disruption; it maintains batchwise harvesting, simplifying integration with downstream processing (DSP), and requires only a modest increase in media consumption. Still, factors such as additional media preparation and the effects of higher cell densities on downstream operations must be taken into account.[7, 10, 11, 13-18, 24]

Concentrated Fed-Batch Culture

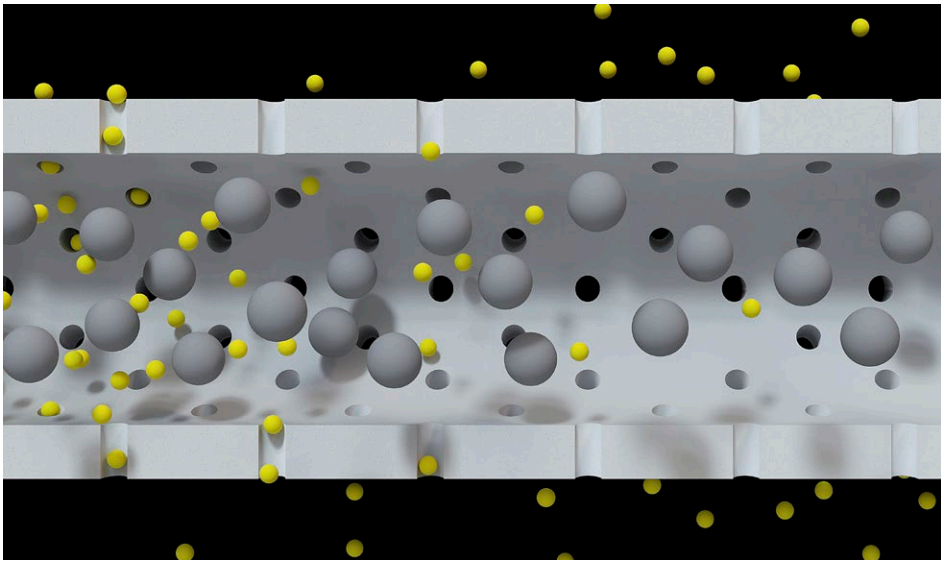
If further titer increases are needed, and media preparation capacity is not a limiting factor, concentrated fed-batch could be a viable option (Figure 4). This approach mimics a fed-batch strategy, but much higher cell densities and productivities can be achieved by continuous removal of inhibitory metabolites using ultrafiltration hollow fiber membranes (typically with a molecular weight cut-off < 200 kDa, depending on the product). These membranes retain both the cells and the product, allowing 3- to 5-fold increases in yield.

Concentrated fed-batch strategies have been implemented in commercial-scale single-use manufacturing facilities, combining the flexibility of single-use solutions with outputs similar to large-scale stainless-steel sites. Because the harvest is still carried out in batch mode, multiple bioreactors can be aligned to feed into a single downstream process, supporting efficient asset utilization. However, the substantially increased media logistics and adapted harvesting strategy should be considered.[18, 26]

Perfusion Culture

Finally, the only technology suitable for unstable molecular formats and capable of delivering the highest volumetric productivity (i.e., grams of product per liter of bioreactor per day) is dynamic or continuous perfusion (Figure 4). In perfusion mode, CRDs are used to retain the cells while allowing the passage of metabolites and the product. One variant is dynamic perfusion, which can run for up to three weeks without cell bleed and may employ cell arrest, e.g., using a temperature shift, to boost productivity. The other variant is continuous perfusion, where a controlled cell bleed removes a certain fraction from the cell culture to keep it in a growing state at a constant cell concentration. While continuous perfusion can theoretically run indefinitely, production batches typically last 30 to 40 days.

Perfusion cultures enable very high cell densities of beyond 100 million cells/mL, significantly increasing bioreactor volumetric output. Continuous product harvest, typically with direct capture and (partial) purification, allows unstable molecules to be continuously extracted and transferred to stabilizing conditions. More than 10-fold increases in yield are possible, and perfusion technology has been implemented in commercial-scale flexible single-use facilities. This combines the high output of large stainless-steel facilities with the agility of single-use solutions, while also providing the flexibility to handle a wide range of protein-based modalities. Since the product from perfusion processes resides in the outgoing perfusion flow—and the concentration can vary between products as well as over the course of a perfusion run, particularly in dynamic perfusion—this presents challenges for connected DSP. Appropriate control strategies are therefore required to manage these variations effectively.[5-9, 12, 24, 25, 27-30]



Choosing an Upstream PI Strategy

Several factors must be considered when selecting the appropriate upstream PI strategy. These include the existing product portfolio and pipeline, properties of the molecule at hand, market demand (and its associated uncertainties), existing facility infrastructure or contract development manufacturing organization (CDMO) partner capabilities, and the marketing strategy, i.e., regional or global.

The key challenges when implementing a PI approach include the extensive, costly, and labor-intensive cell line and process development efforts, as well as the need to scale and implement the advanced control strategies that ensure robust and reliable manufacturing in both clinical and commercial manufacturing sites.

Developing an intensified process requires the high-throughput generation and selection of suitable clones under the appropriate process conditions. It also requires cell culture media and feeds that maximize product output, while minimizing media consumption — particularly in perfusion mode — to achieve acceptable COGs. In addition, the process must be optimized using high-throughput, scale-down models. For perfusion processes, careful characterization and optimization of the CRD is critical, as these components can be very costly and prone to sieving and blocking.

When scaling intensified upstream bioprocesses in single-use facilities, it is critical that the bioreactors, as well as the associated CRDs, can handle the increased cell densities. Platforms should also be compatible with the required PATs and automation systems to enable advanced control strategies, such as cell density-based feeding, temperature shifts, and accurate nutrient concentration control.

Process Development Solutions for Intensified Upstream Processes

For any protein-based therapeutic manufacturing process, including intensified processes, highly productive cell lines are the primary requirement. These cell lines must be supported by the optimal cell culture media and feeds that supply all the necessary nutrients, enabling growth to high cell densities and production of the target therapeutic at the right quality.

Finally, process conditions play a critical role in determining cell density, productivity, and product quality attributes. These include physical parameters such as mixing, temperature, pH, dissolved oxygen, and carbon dioxide, as well as process conditions including inoculation cell density, nutrient and metabolite concentrations, feed formulations, and feeding profiles. For further intensification, perfusion strategies to remove inhibitory metabolites and cell bleeds to improve long-term stability should also be optimized. Together, these variables define a large and complex design space for mAb process development.[18, 25, 27, 28]

To streamline and accelerate mAb process development, large biopharma companies and CDMOs have developed internal platform processes. These combine optimized CHO host cell lines with cell culture media and feeds that achieve robust, scalable performance in their fed-batch process. These platforms enable predictable development and scale-up of new mAb molecules into classical large-scale fed-batch facilities, commonly achieving titers above 5 g/L and even up to 10 g/L.[7, 14]

Cell Line Development and Clone Selection Services for PI Compatibility

For small and mid-size enterprises (SMEs) and CDMOs, developing an in-house platform that matches the performance of large pharma companies can be highly challenging and may not yield a return on investment. However, if these SMEs do not achieve industry-standard performance after in-house development and successful first-in-human studies, the value of their product may be significantly diminished in the eyes of large biopharma partners. Similarly, mid-scale CDMOs that cannot offer competitive cell line performance are less attractive to potential clients.

In these cases, outsourcing to or in-licensing an established cell line development platform could be an attractive alternative. For example, Sartorius' CHO Cell Line Development Service, which uses the 4Cell® CHO Platform, delivers cell lines from DNA to a research cell bank (RCB) in 14 weeks, and a fully characterized master cell bank (MCB) in 10 months, and includes full cell line biosafety testing and characterization services to release the cell banks.

The resulting high-titer cell line, combined with high-performing, 100% chemically defined 4Cell® SmartCHO media, is fully compatible with PI strategies, including N-1 perfusion with high-inoculation fed-batch and N-stage perfusion. The development of a perfusion process tailored to the newly developed cell line is also available as an additional service.[24, 27]

These cell lines, delivering industry-standard performance, provide a strong foundation for either in-house process development, initial scale-up, and early-phase GMP manufacturing, or seamless transfer to any CDMO. This enables full flexibility to accelerate time to clinic and first-in-human studies, while ensuring transferability to large biopharma.

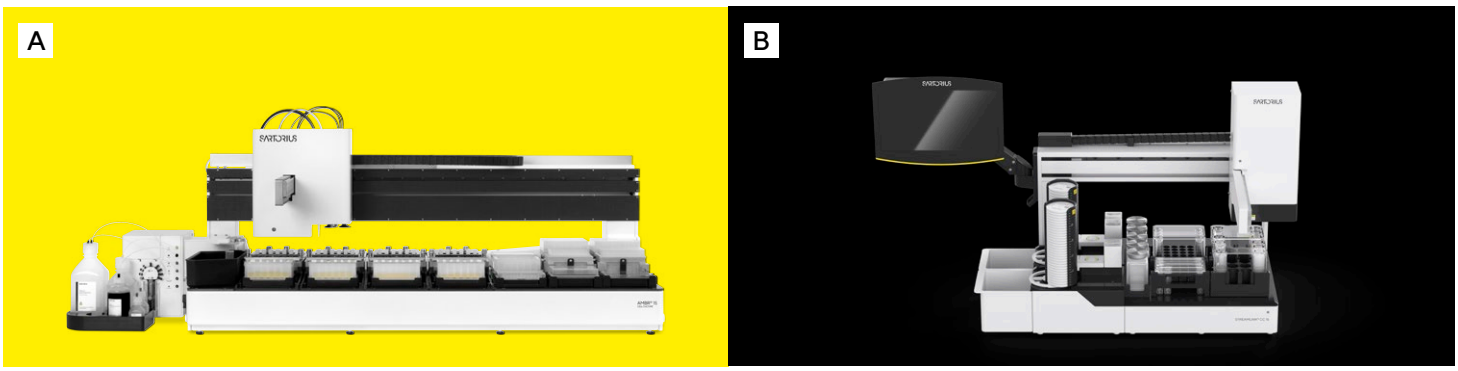
Perfusion-Based Clone and Media Screening, and Initial Process Optimization

For companies performing in-house cell line development, including clone and media screening, as well as initial process optimization, access to high-throughput mini bioreactors is essential. These systems should have sufficient predictability and scalability, and enable high-throughput analytical screening of both product quality attributes and spent media composition.

The Ambr® 15 Generation 2 is the industry standard for screening up to 24 – 48 different conditions — including multiple clones, media, and feeding regimes — at the smallest true microbioreactor scale (10 mL) with full pH and pO_2 control (Figure 5A). The integrated data analysis unit and BioProfile® FLEX2 support accurate and automated daily at-line pH calibration measurements, as well as cell count, viability, and basic metabolite readings. Perfusion conditions can be mimicked through daily bioreactor centrifugation, after which the supernatant is automatically removed via the system's rapid vessel drain option and cells are resuspended in fresh medium.[24] For subsequent analysis of end-of-batch samples — or, in the case of perfusion, daily supernatant — the Streamlink® CC enables rapid and automated sample preparation (Figure 5B). This includes clarification and purification using a Protein A membrane adsorber, generating samples for further product quality assessment.

Efficient process development, experimental execution, data handling, and data analysis can be facilitated with the Ambr®-integrated MODDE® design of experiments software, and the industry-leading SIMCA® multi-variate data analysis software. Finally, with Umetrics® Studio Cell Insights, hybrid modeling is now available. Based on limited (fed-batch) data sets, the software can predict clone behavior under perfusion conditions, supporting informed clone selection for PI.[25]

Figure 5: ***(A)*** *Ambr® 15 Cell Culture: Advanced Microbioreactor System For Cell Line And Early Process Development,* ***(B)*** *Streamlink® CC 15: Automated and High-Throughput System for Sample Preparation in Cell Line Development*



Process Development and Characterization for Establishing Perfusion-Based Processes

For high-throughput process development, and increasingly for process characterization, the Ambr® 250 High Throughput system is the industry standard platform, widely used by large and mid-sized biopharma as well as CDMOs.[28] With its reduced bioreactor set-up time and highly automated, reproducible cell cultures and data generation, the Ambr® 250 High Throughput significantly increases output per operator. When combined with MODDE® software, which supports extensive design space mapping, the system substantially improves process insights, reduces risks, and enables reliable scale-up timelines—particularly when the system has been qualified as a scale-down model for the target large-scale bioreactors.

Ambr® 250 High Throughput bioreactors have become a leading tool for developing intensification approaches, supporting the optimization of perfusion processes within timelines comparable to those of fed-batch processes. These capabilities are further enhanced with the newly launched Ambr® 250 High Throughput Generation 2 (Figure 6), which supports cell densities over 100 million cells/mL and enhanced control through advanced continuous gassing and additional PAT functionality integrated into the vessel—including BioPAT® Viamass for continuous capacitance measurement and a pCO_2 probe. Naturally, the analysis module-based BioPAT® Spectro for scalable Raman spectroscopy, and integration of the BioProfile® FLEX2 allow for at-line analytics and control of multiple process parameters.

Figure 6: *Ambr® 250 High Throughput Generation 2: The Industry-Standard High-Throughput Bioreactor to Accelerate Bioprocess Development*

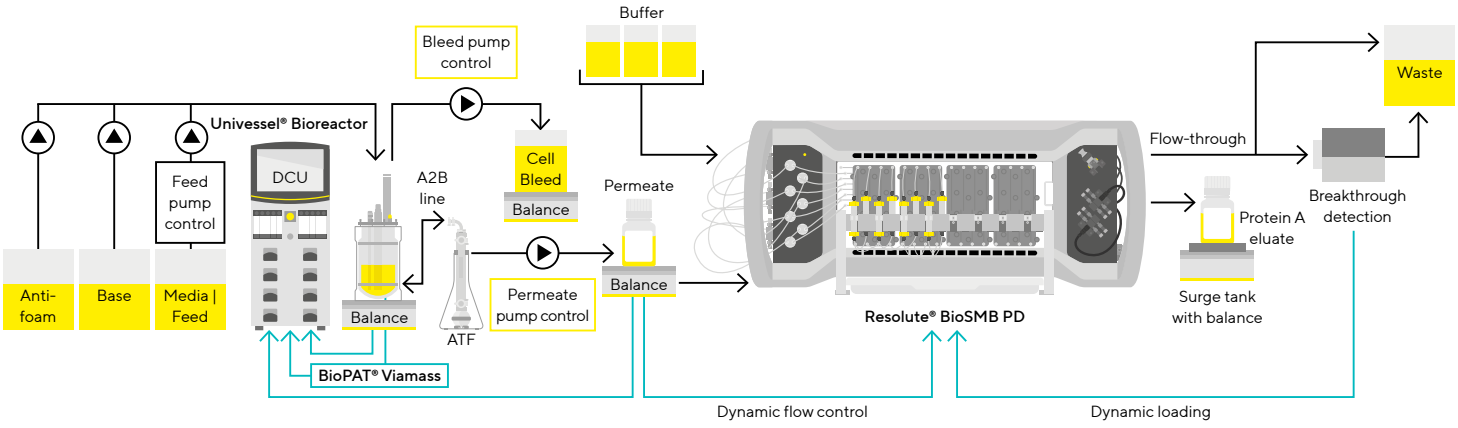
Additionally, Umetrics® Studio Cell Insights can be used to generate bioreactor simulations that support in silico optimization of perfusion conditions. When followed by a limited set of verification experiments, this tool can substantially reduce experimental effort and accelerate timelines for the development and characterization of PI strategies.[25]

For a deeper investigation of nutrient depletion or accumulation of problematic components, spent media analysis is recommended. Sartorius offers comprehensive cell culture media services to help resolve media- or feed-related issues. This may involve evaluating the performance of other standard media and feeds from the Sartorius portfolio, or the development and delivery of customized (perfusion) media compositions up to commercial scale.

Finally, to enable truly downscaled process control with industrial SCADA automation, generate sufficient harvest material for downstream development, or perform connected DSP (e.g., with direct connection to Resolute® BioSMB systems), Biostat® B-DCU benchtop bioreactors are highly useful (Figure 7).

Their advanced PAT options—including highly accurate continuous gravimetric feeding, mass flow controller-based gassing, BioPAT® Viamass for cell density control, and BioPAT® Trace or BioPAT® Spectro for basic metabolite control—can be combined to develop and test advanced, automated, and scalable control strategies using SCADA systems such as Biobrain® Supervise. Depending on the process, Univessel® Glass or Univessel® SU can be applied together with, for example, XCell® ATF (Repligen), to achieve linear scale-down of cell retention functionality and contribute to the development of scalable perfusion processes.

Figure 7: *Schematic Representation of an Integrated Upstream and Downstream Approach at Process Development Scale, Including ATF Perfusion Connected to the Multi-Column Chromatography System*[32]



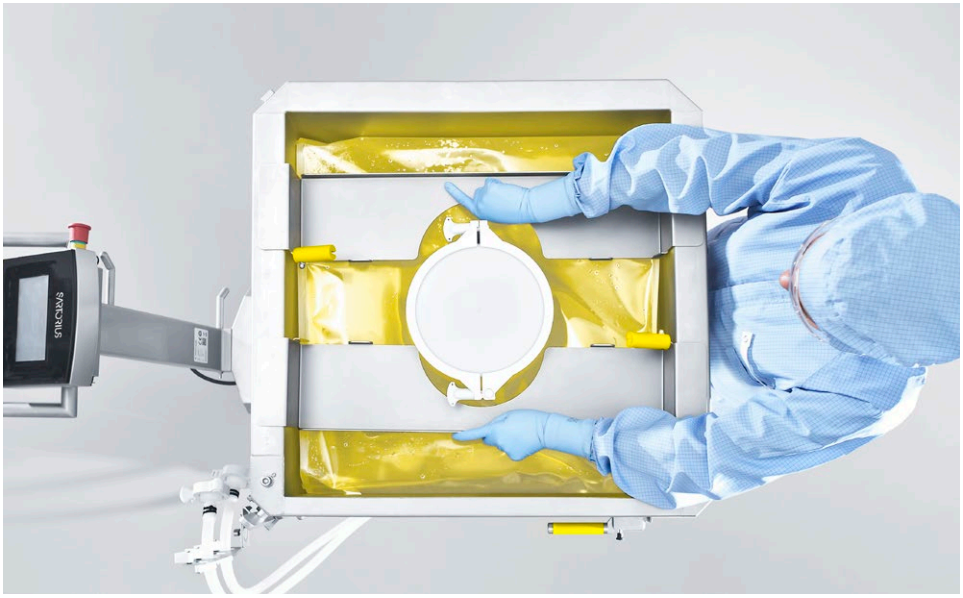
Note. Source: Figure adapted from Kruse et al (2024).[31]

Upstream PI Solutions for Early-Stage Clinical Production

Since large CDMOs often prioritize late-stage projects and depending on market conditions, available manufacturing slots for early-stage programs may be limited or subject to their discretion. It can therefore be beneficial to small- and mid-size biopharma companies to perform scale-up and early phase GMP manufacturing in-house, or to outsource to small- and mid-size CDMOs. This will allow them to maintain flexibility and reduce time to first-in-human trials. However, it remains critical to ensure that processes are scalable for later tech transfer to large-scale biopharma or CDMOs. Equally important is securing the necessary expertise, either internally or through collaboration with a smaller CDMO.

This is where the expertise of biopharma suppliers can be leveraged—especially those with integrated platform capabilities that span GMP-ready cell line development, media and media management, advanced USP bioreactors, process control, data analytics, and comprehensive support services.

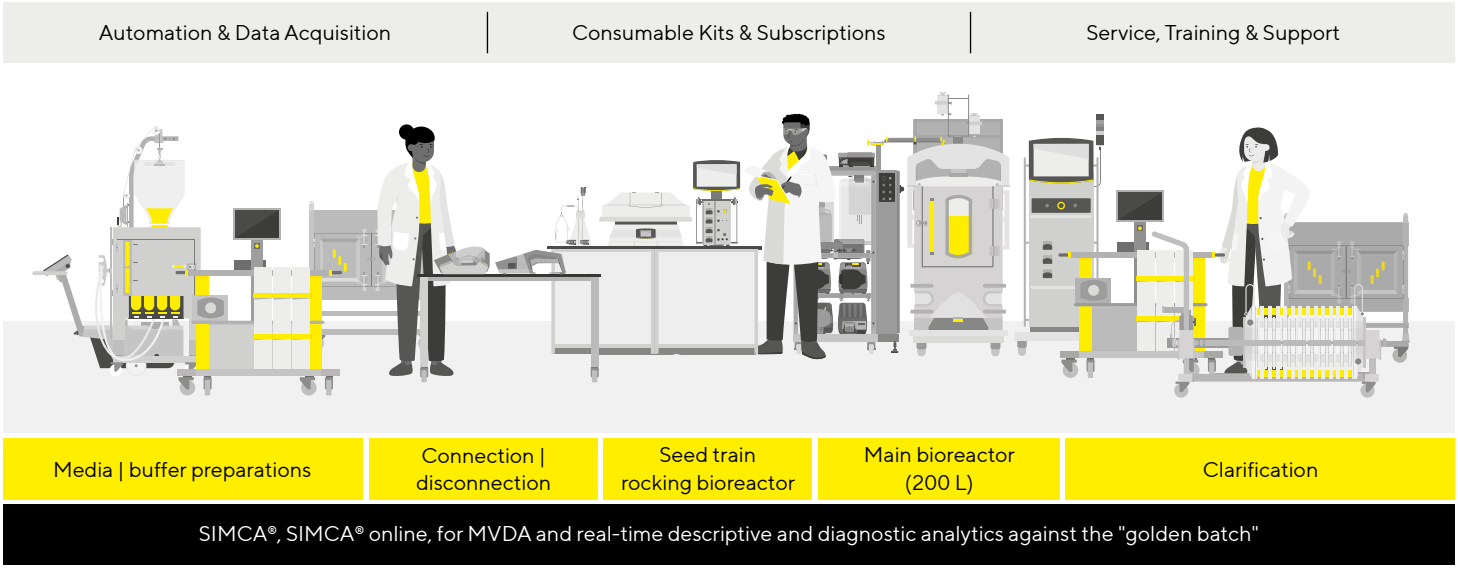
Sartorius ProcessGo® is a turnkey solution that provides a complete, cutting-edge process workflow solution for upstream scale-up, tox material generation, and early-phase GMP manufacturing (Figure 8). Built on decades of experience in designing single-use manufacturing facilities and their automation, Sartorius ProcessGo® consists of pre-engineered upstream platforms suitable for more than 90% of typical early-phase mAb processes. The solution uses only pre-configured hardware and consumables, minimizing engineering and delivery times and costs while maximizing flexibility and efficiency.



The modular package includes solutions for media and buffer preparation, seed train, production bioreactor, and clarification—all qualified using the 4Cell® CHO Platform. PI options are included in the seed train, and the solution includes full automation, data acquisition, and supervisory control as well as data analysis capabilities. To ensure first-time-right installation and operation, full service, training, and support are also included.

Depending on specific project requirements, the Sartorius ProcessGo® solution can be deployed as a ready-to-use solution or modified to meet specific user requirements. Downstream modules can also be added to support end-to-end process alignment.

Figure 8: *Sartorius ProcessGo® Consists of Pre-Engineered Process Solutions to Simplify Setup*

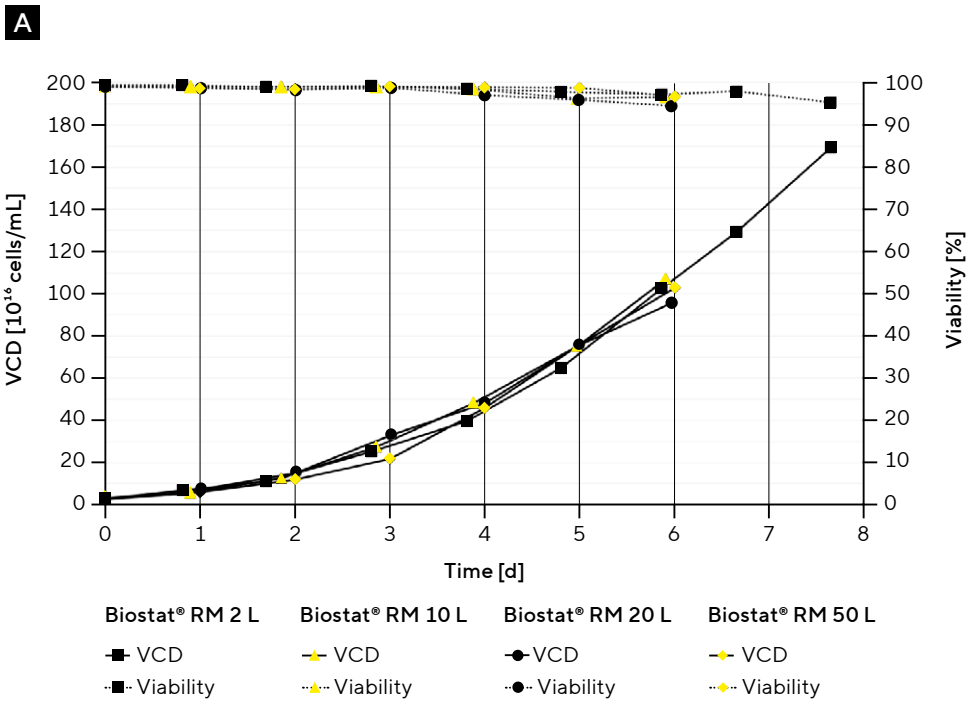


PI Solutions for Late-Stage Clinical and Commercial Production

For late-stage clinical and commercial mAb manufacturing, upstream PI can take many forms. Key enabling technologies include bioreactors capable of meeting the demands of intensified processing, particularly the challenges created by high cell densities, such as higher O_2 and CO_2 mass transfer, adequate mixing, connectivity to robust cell retention systems, and the availability of PAT sensors such as capacitance and Raman probes to accurately control the growth dynamics of perfusion processes.

For seed train intensification, Biostat® RM perfusion bioreactors with cost-efficient 2D bags featuring an integrated perfusion membrane—available in working volumes of 1 L, 5 L, 10 L, 25 L, and even 100 L—have demonstrated excellent performance (Figure 9). They can achieve viable cell densities of 100 million cells/mL (up to 25 L working volume), without the need for relatively expensive external CRDs. As a result, fewer seed train steps are required, and users can inoculate the production bioreactor at a higher starting density. Uniquely, the Biostat® RM also contains a single-use BioPAT® Viamass probe, enabling highly accurate control of media flow based on the cell growth rate, reducing the media usage by up to 30%.

Figure 9: ***(A)*** *Scalable Performance in N-1 Perfusion,* ***(B)*** *Biostat® RM 50 L: Capable of Simplifying Seed Train Intensification*[24]



Note. VCD = Viable cell density

B

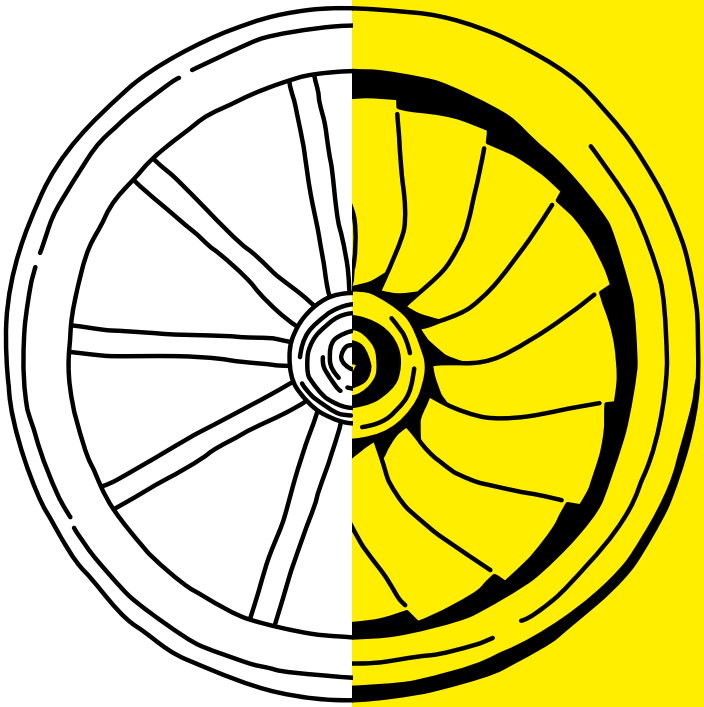
In addition, for N-1 perfusion at 200–2,000 L scale, the Biostat STR® with integrated XCell® ATF (Repligen) represents a highly powerful, fit-for-purpose solution capable of handling the demands of perfusion processes (Figure 10). With its integrated cell retention functionality, the operation of both the bioreactor and CRD from a single user interface becomes highly intuitive, and advanced control and recipe options are available through Biobrain® Supervise.

Figure 10: *Biostat STR® 500 L With Integrated XCell® ATF Control and Connected XCell® ATF 10 (Repligen)*

A Stepwise Strategy for Downstream Process Intensification

A traditional downstream process for mAb production involves a sequence of operations, including capture, viral inactivation, polishing, virus filtration, ultrafiltration | diafiltration (UF | DF), and final filtration—which can be time-consuming and inefficient. DSP typically accounts for over 50% of mAb production costs,[2,6] with unit operations scheduled consecutively over 3–5 days, depending on the mass of the product to be purified.

Downstream PI can be achieved through a stepwise approach, transitioning from staggered batch processes to a concurrent three-level intensification model as described in Figure 11 and Figure 12.



Level 1 focuses on intensifying standalone unit operations using technologies like rapid cycling chromatography (RCC) with membranes, multi-column chromatography (MCC) with membranes or resins, and continuous viral inactivation. These innovations can reduce costs by up to 30% and shorten processing times by up to 24 hours. Level 1 intensification is the simplest and fastest strategy to implement, offering immediate time and cost savings during clinical production.

Level 2 connects standard or intensified DSP unit operations to run simultaneously, including buffer preparation, while still operating each step in batch mode. Initiating the next step in parallel with the preceding operation can save an additional day, reduce the footprint by half, and double the throughput of the facility. Level 2 strategies are typically paired with a traditional fed-batch bioreactor and are often implemented during larger-scale phase 3 clinical and commercial production.

Level 3 integrates all DSP steps into a continuous flow, using small intermediate tanks orchestrated by software to enable a fully continuous process. Each unit operation is carried out in continuous mode, e.g., through MCC. This setup can be linked to a fed-batch bioreactor, reducing DSP timelines from five days to one to two days, or coupled with a continuous perfusion bioreactor for end-to-end continuous manufacturing.

Both approaches enhance throughput and flexibility while reducing footprint, capital, and resource utilization.

Ideal targets for chromatography are COGs of less than €15/g and a downstream workflow timeline of one to two days. Achieving these goals involves implementing a stepwise intensification strategy, as illustrated in Figure 12.

Figure 11: *Stepwise Approach From Batch Production to Three Levels of Intensified Processing*

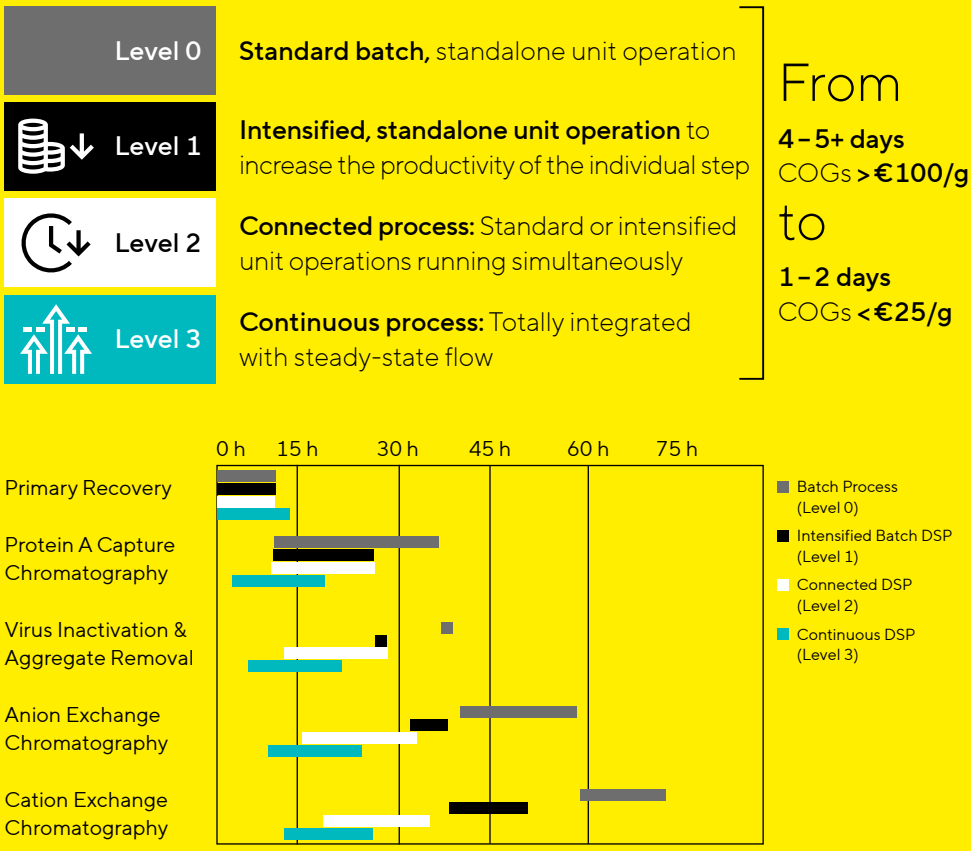
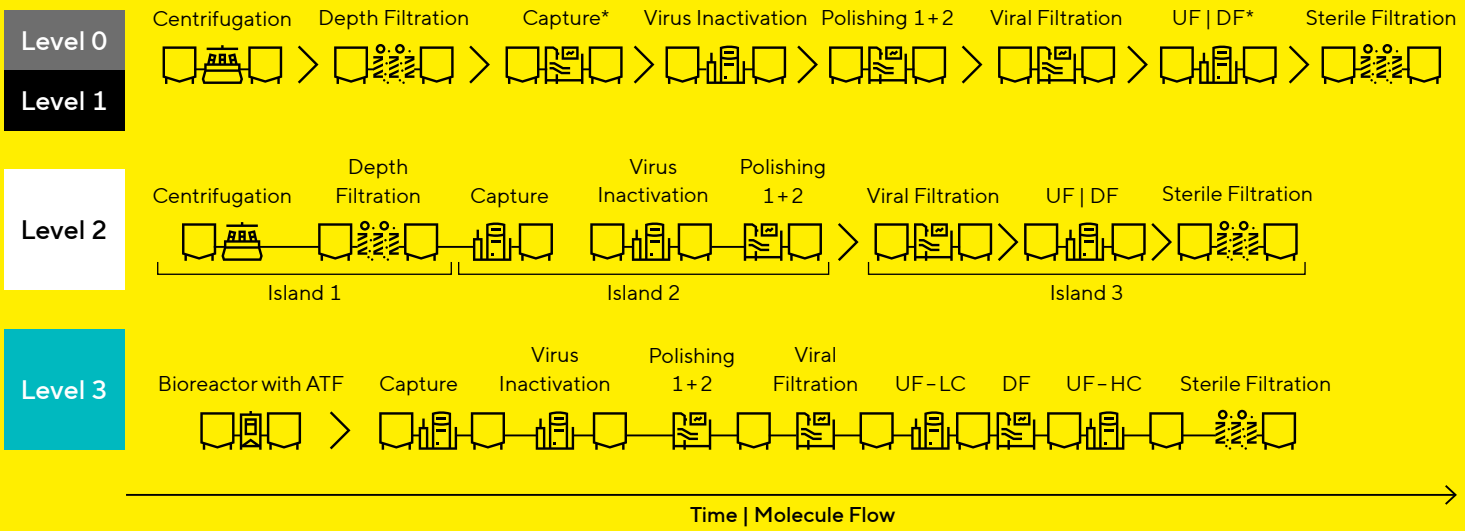


Figure 12: *Three Levels of DSP Intensification to Minimize Costs, Shorten Timelines, Reduce Footprint, and Maximize Throughput*



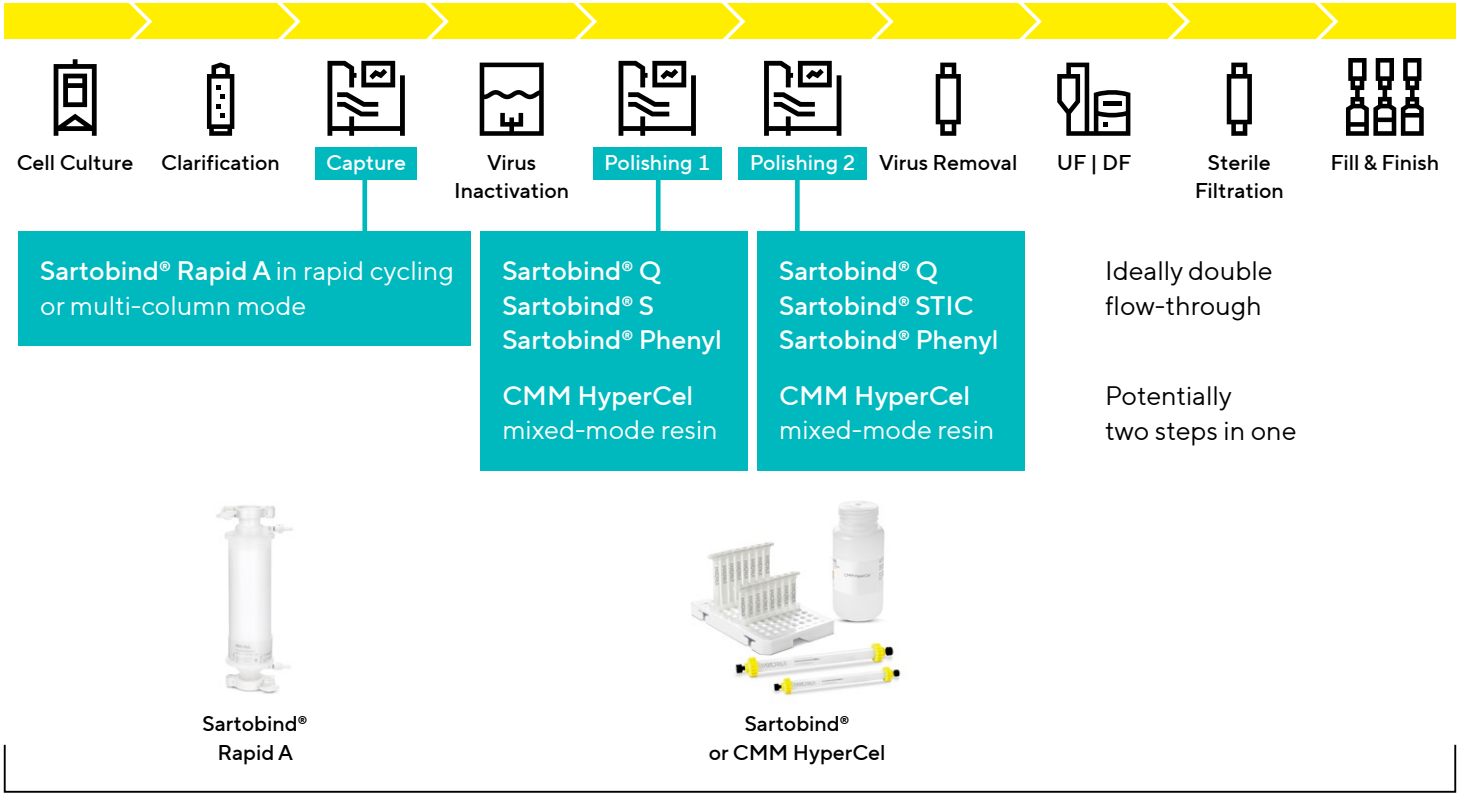
Note. HC = High concentration, LC = Low concentration

* Intensified consumable
** Islands are flexible in terms of which and how many unit operations are involved

Technologies and Methods for Chromatography Intensification

The chromatography steps required for capturing antibodies and removing fragments, aggregates, host cell protein (HCP), and host cell DNA (hcDNA) are among the most costly and time-consuming operations in DSP, accounting for 25% to 30% of the total COGs in mAb production. Key cost drivers are the high cost of resins—which are often underutilized in clinical or low-demand production—long setup times for column installation, resin packing, height equivalent to a theoretical plate (HETP) testing, and validation studies, as well as the need for dedicated storage. These factors present critical bottlenecks for DSP intensification efforts that can be addressed by chromatography technologies such as membranes and mixed-mode resins (Figure 13) and methods such as RCC and MCC (Figure 14).

Figure 13: *Chromatography Solutions for DSP Intensification*



Cost reduction to less than €15/g in commercial production

80% less handling*

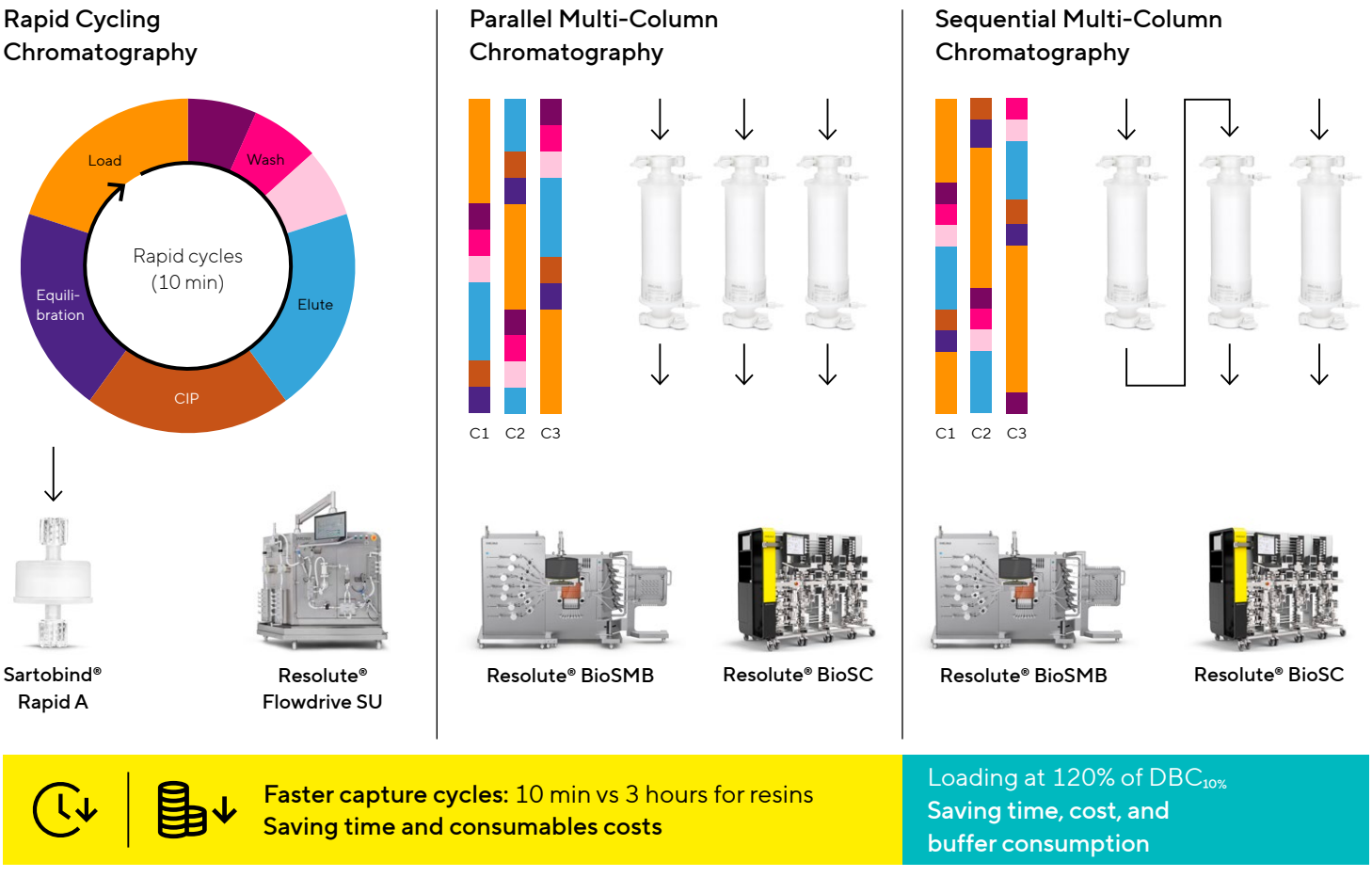
Up to **30x higher productivity**

* Compared to classical resins

There are various strategies for intensifying chromatography, including RCC, MCC, mixed-mode chromatography, and continuous chromatography, either in bind-elute or flow-through modes. While RCC using a single Protein A membrane device is the simplest way to intensify the capture step, applying MCC to membrane adsorbers offers additional benefits. Parallel MCC is a straightforward intensification method in which chromatography devices are installed in parallel to enable continuous capture, particularly beneficial in processes using perfusion bioreactors. For resins, MCC reduces column size and enables the use of smaller, prepacked columns.

Sequential MCC (S-MCC) is the most effective intensification method, reducing costs, time, and buffer consumption while enabling continuous capture. S-MCC maximizes binding capacity by overloading the first membrane or resin and capturing the breakthrough in the second, resulting in a 50% increase in binding capacity and equivalent decreases in costs and buffer consumption.[3]

Figure 14: *Multi-Column Chromatography With Membranes Reduces Costs and Buffer Consumption*



Note. Methods can be developed stepwise from clinical to commercial production, using Resolute® modular systems. CIP = Clean-in-place

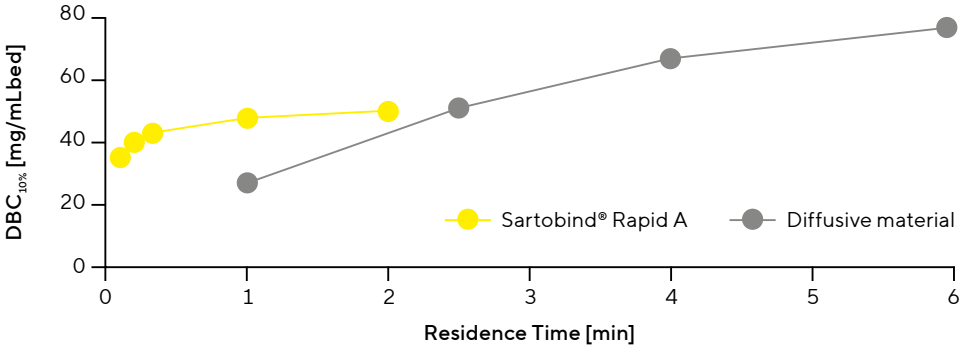
mAb Capture With Rapid Cycling Membrane Chromatography

Protein A chromatography is central to the purification of mAbs, but it is a costly and time-consuming purification step, often targeted first in DSP intensification efforts. Conventional Protein A resins have a narrow pore size distribution of 50 – 200 nm combined with a diffusive region depth of 25 µm, which limits mass transfer speed, requiring residence times of 4 – 6 minutes to reach optimal binding capacity. Consequently, operational cycle times range from 2 – 4 hours, limiting the number of cycles to just 2 – 5 per day. To compensate, oversized resin volumes are often used to accelerate the process, leading to underutilization to achieve acceptable processing times. Large columns and resins are expensive, especially in clinical and low-demand production, where resins are significantly underutilized.

Protein A membrane chromatography, which delivers high flow rates and competitive binding capacities, is being evaluated by numerous biotechnology companies as an alternative to traditional resins for process development and clinical production.[32-41] Sartobind® Rapid A membranes use both convection and diffusion mass transfer mechanisms to achieve an average binding capacity of 45 g/L, with a residence time under 12 seconds and cycle time under 12 minutes. This performance is enabled by the wide 5 µm pore size of the convective matrix combined with the short 3 µm diffusive porous layer. Figure 15 shows that membrane chromatography can achieve binding capacities comparable to resins at significantly shorter residence times (12 seconds compared to 4 minutes for diffusive resins).

The key advantage of membranes and RCC lies in their smaller device size and the potential for full capacity utilization after minimal production batches, which makes them very cost-effective for clinical trials and low-demand production.

Figure 15: *$DBC_{10\%}$ Comparison Between Membrane-Based (Sartobind® Rapid A) and Resin-Based (Diffusive Material) Protein A Chromatography*

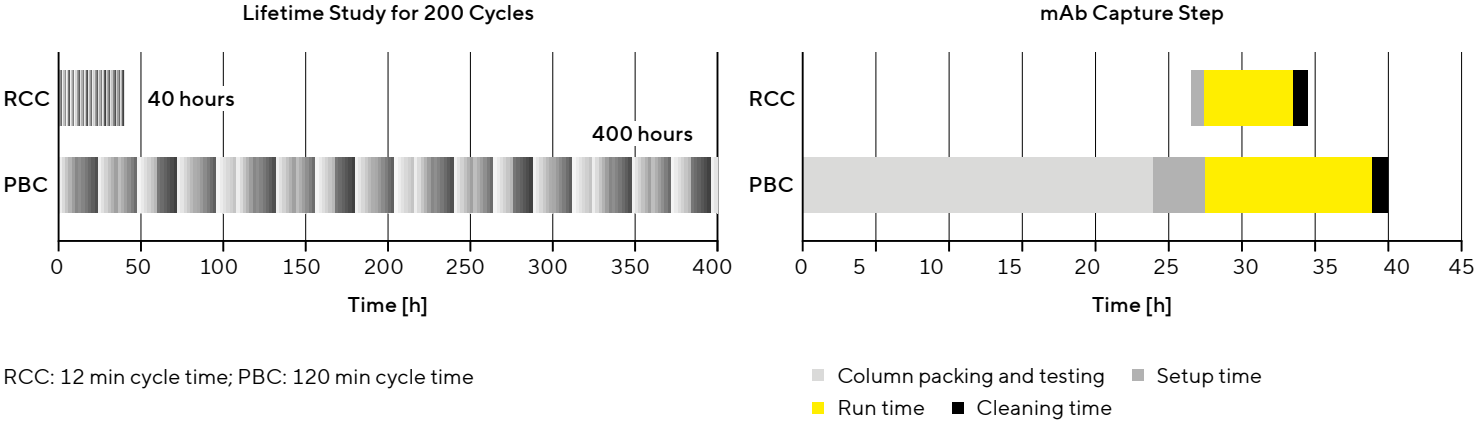


Chromatographic membranes operate at significantly faster cycle times than resins, enabling 10 – 30 times more purification cycles within the same process time. They typically reach their full lifetime of up to 200 cycles after just 2 – 4 production batches, making them highly cost-effective. In contrast, resins require 40 – 60 production batches to achieve full capacity utilization. The number of reuses significantly impacts chromatography consumable costs, making membranes the preferred technology for clinical and low-demand commercial production, where resins are often underutilized, with fewer than 20 cycles used out of a potential 200-cycle lifetime.

Process Development and Clinical Production with Membrane-Based Capture Chromatography

Membrane chromatography, even in single-use mode, offers over 50% cost savings for early clinical phases, multi-product facilities, and CDMOs handling multiple projects with limited production runs. Utilizing Protein A membranes eliminates the need for substantial investments in resin media and column hardware, while also providing faster validation times and greater flexibility. The short cycle time significantly accelerates process development and characterization timelines. As illustrated in Figure 16, a 200-cycle membrane lifetime study can be completed in under 40 hours, compared to 400 hours required for a packed bed column.

Figure 16: *Comparison of Validation and Preparation Timelines Between Protein A Membrane and Packed-Bed Chromatography*



RCC: 12 min cycle time; PBC: 120 min cycle time

PBC = Packed bed chromatography | RCC = Rapid cycling chromatography

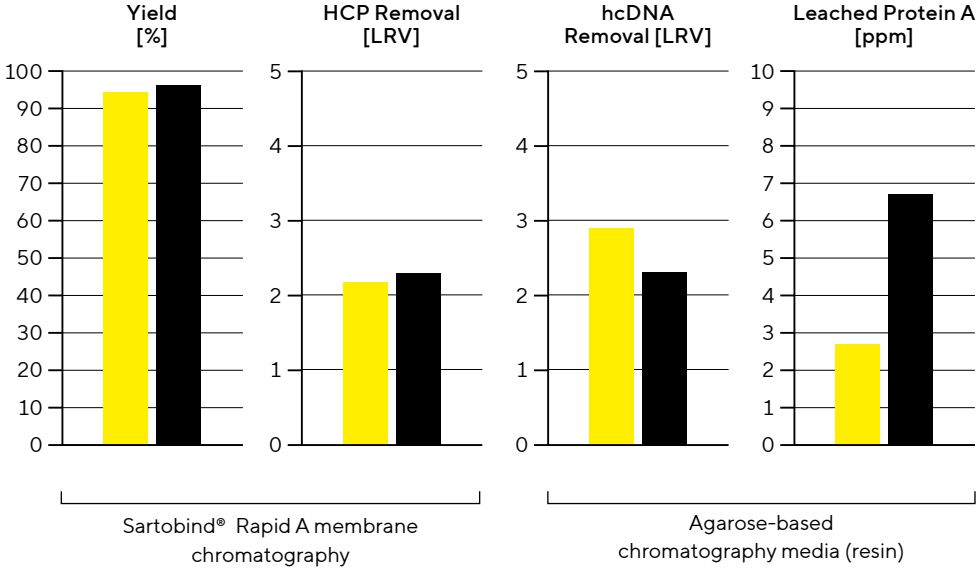
Large-Demand Commercial Production With Membrane-Based Capture Chromatography

For large-scale commercial production, Sartobind® Rapid A enables shorter cycles, reducing the required chromatography media for antibody purification by 10 – 15 times. The ready-to-use format of membrane adsorbers minimizes upfront investment costs associated with columns, packing equipment, and resins. It also reduces time and footprint by eliminating column packing and preparation operations.

Membrane chromatography consumables can also be reused with proper sanitization and storage, making them a viable alternative to resins for large-scale manufacturers. This unlocks the full potential of PI, offering higher productivity, smaller preparation times, elimination of column handling risks, lower clean room footprints, and efficient production processes at comparable costs.

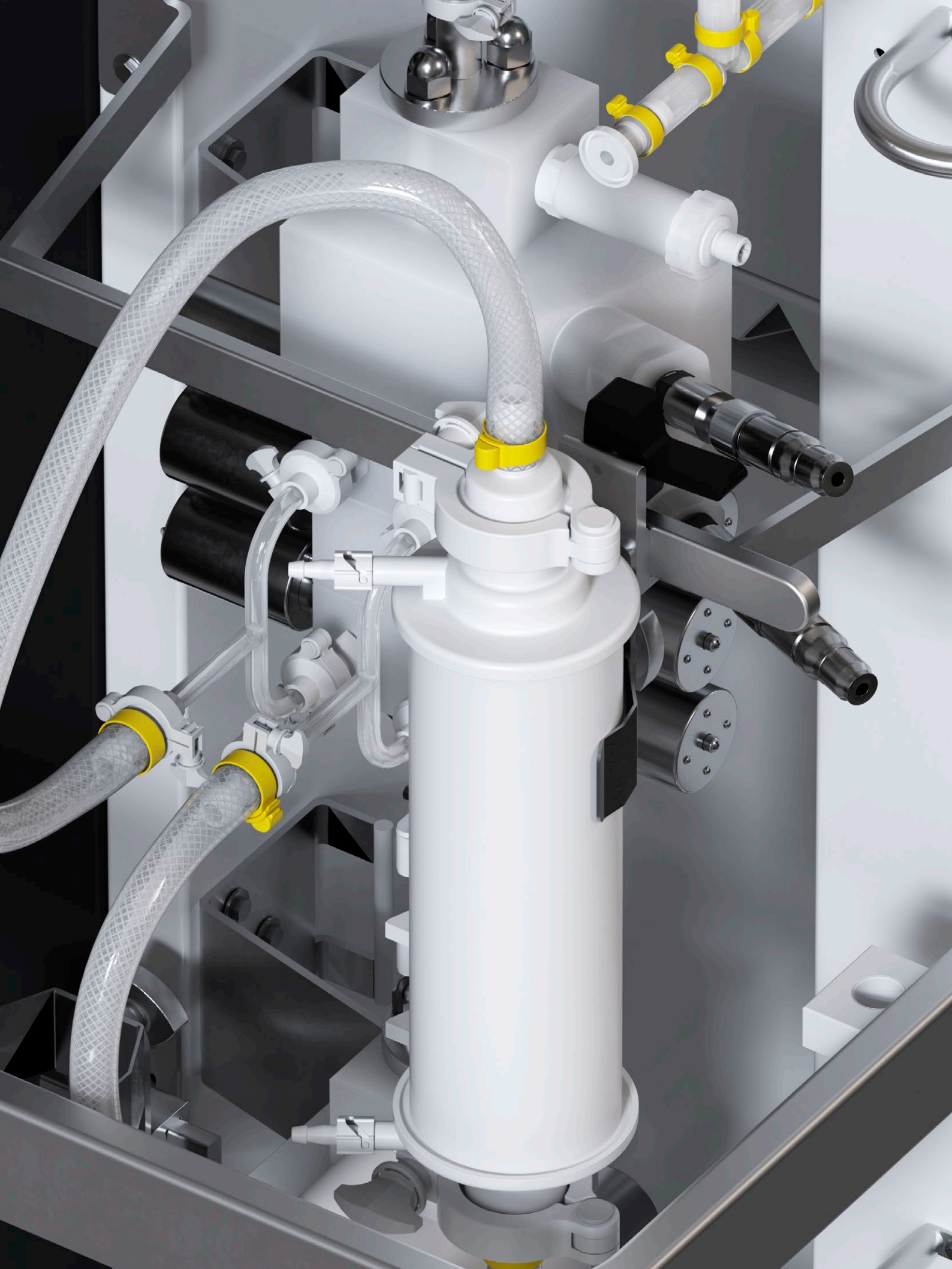
Several studies have shown that membrane adsorbers consistently achieve dynamic binding capacity (DBC), product yield, and product quality attributes similar to resins,[33,34] while cutting validation and preparation timelines by up to 80%, and increasing productivity by 10 to 15-fold.[35]

Figure 17: *Sartobind® Rapid A Chromatography Performance Compared to Legacy Protein A Resins*



Attribute	Sartobind® Rapid A	Protein A Resin
$DBC_{10\%}$ [g/L]	42.9 ± 0.8	30.4 ± 0.5
Residence time [min]	0.2	4.0
Yield [%]	94.7 ± 0.2	96.4 ± 0.4
HCP reduction [LRV]	2.2 ± 0.2	2.3 ± 0.1
hcDNA reduction [LRV]	2.9 ± 0.2	2.3 ± 0.1
Leached Protein A [ppm]	2.7 ± 0.7	6.7 ± 0.3
Av. productivity [g/L/h]	203.6	14.1

Note. LRV = log reduction value

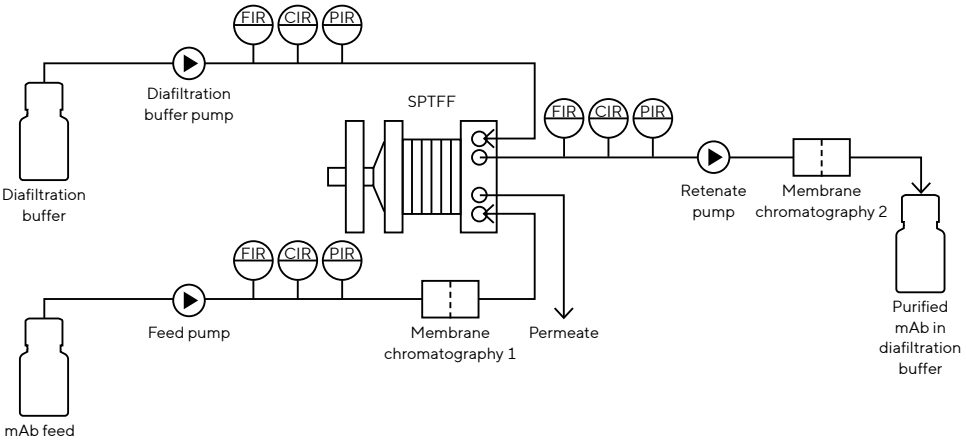


mAb Polishing With Membrane Chromatography or Mixed-Mode Chromatography Resins

Membrane chromatography, introduced decades ago, is widely used in commercial manufacturing to remove fragments, aggregates, leached Protein A, HCPs, and hcDNA following antibody capture. Extending membrane chromatography to both capture and polishing steps can enhance productivity by 15-fold and reduce costs by up to 50%, especially during clinical phases, where traditional resins are underutilized.

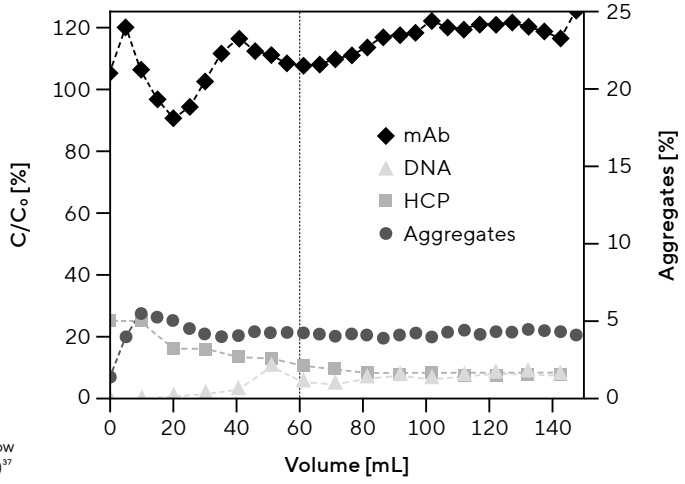
Full membrane chromatography processes—comprising a bind-elute capture step and two flow-through polishing steps—offer optimal cost efficiency and lower buffer consumption, while maintaining product purity levels associated with resin-based processes (Figure 18).[34-40]

Figure 18: *Example of a Process Using Double Flow-Through Polishing With Sartobind® Ion Exchange Membranes*



- Yield > 98% (per step)
- Productivity: 240 g/L/h
- DNA: 2 ppm
- HCP: 29 ppm

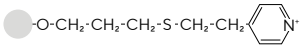
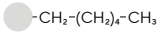
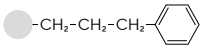
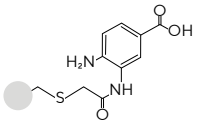
- Purity comparable with classical process
- No column packing
- RCC enables strong footprint reduction
- Full single-batch use



Note. SPTFF = single-pass tangential flow filtration. Data from Schmitz et al (2023)[37]

Another interesting mechanism for intensifying polishing steps is the implementation of mixed-mode resins, which combine ion exchange (IEX) and hydrophobic interaction chromatography (HIC) mechanisms. In some instances, mixed-mode chromatography resins can replace the two conventional polishing steps with one single, more economical step (Figure 19). Challenges to overcome would be a more complex process development, which can be addressed with a proper design of experiments (DoE) software setup.

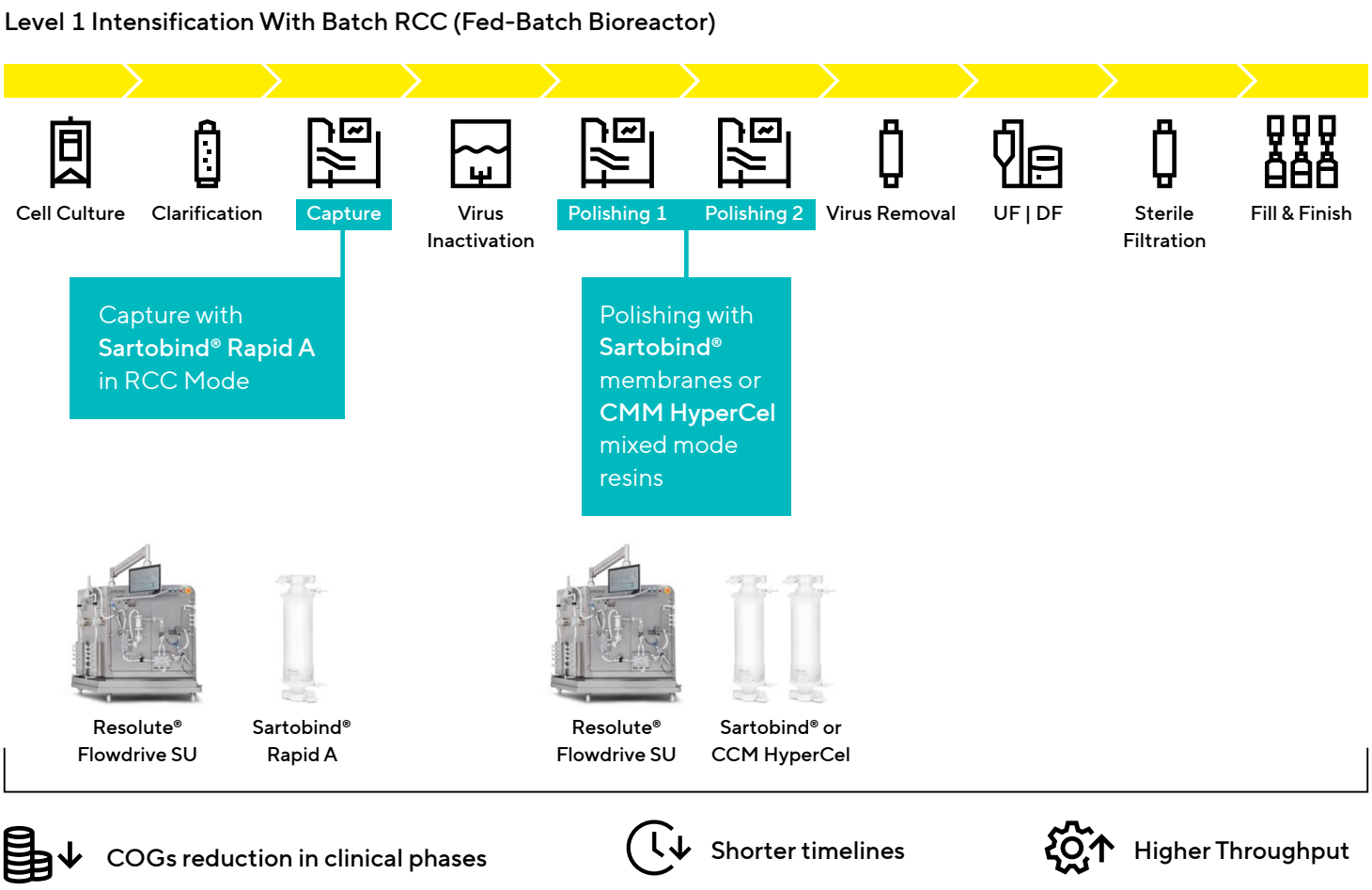
Figure 19: *Mixed-Mode Ion Exchange | Hydrophobic Interaction Chromatography Resins*

Membrane	Description	Mode	pKa	Ligand
MEP HyperCel	Mercaptoethyl pyridine	Weak anion exchange and hydrophobic interaction-based mixed-mode resin — hydrophobic charge induction chromatography (HCIC)	5.8	
HEA HyperCel	Hexylamine	Weak anion exchange and hydrophobic interaction-based mixed-mode resin	10.6	
PPA HyperCel	Phenylpropylamine	Weak anion exchange and hydrophobic interaction-based mixed-mode resin	10.4	
CMM HyperCel	Aminobenzoic acid	Weak cation exchange and hydrophobic interaction-based mixed-mode resin	5.0	

Level 1 DSP
Intensification With Rapid Cycling and Mixed-Mode Chromatography

Figure 20 illustrates a Level 1 downstream PI strategy applicable to an upstream process using a fed-batch bioreactor. This approach uses Sartobind® membrane chromatography or HyperCel mixed-mode resins and a Resolute® Flowdrive single-use chromatography system for both capture and polishing steps. This process is particularly suitable for clinical manufacturing where a small number of batches are produced.

Figure 20: *Example of Level 1 Intensified DSP Using Sartobind® Membranes or Mixed-Mode Chromatography Resins*



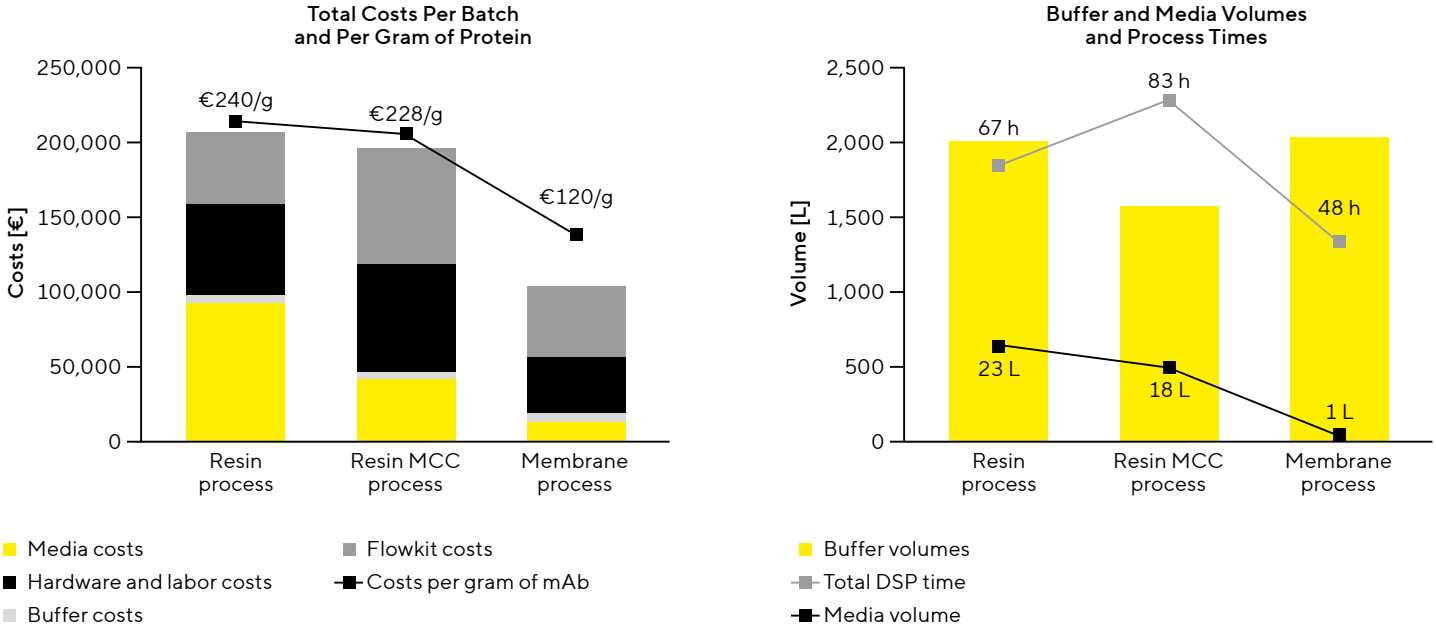
Note. The Resolute® platform can also be used to intensify a resin process. Selection and sizing of the systems can be done automatically with ExCIT.

Figure 21 is an example of how our Expert Chromatography Intensifier Tool (ExCIT) can be used to compare traditional resin processes with full membrane processes for purifying a 200 L scale upstream process at 5 g/L, running four batches annually. The membrane process includes a bind-elute capture step with Sartobind® Rapid A, followed by a bind-elute and flow-through sequence with Sartobind® Q (anion exchange; AEX) and Sartobind® S (cation exchange; CEX) for polishing. This workflow reduces overall purification costs by 50%, from €240 to €120 per gram of antibody, and decreases total processing time from 67 to 48 hours.

To request an ExCIT modelling consultation today, visit: www.sartorius.com/process-intensification

Figure 21: *Example of Data Generated by Our Expert Chromatography Intensifier Tool (ExCIT) to Compare Traditional and Intensified DSP in Clinical Production*

Level 1 Intensification With MCC and RCC

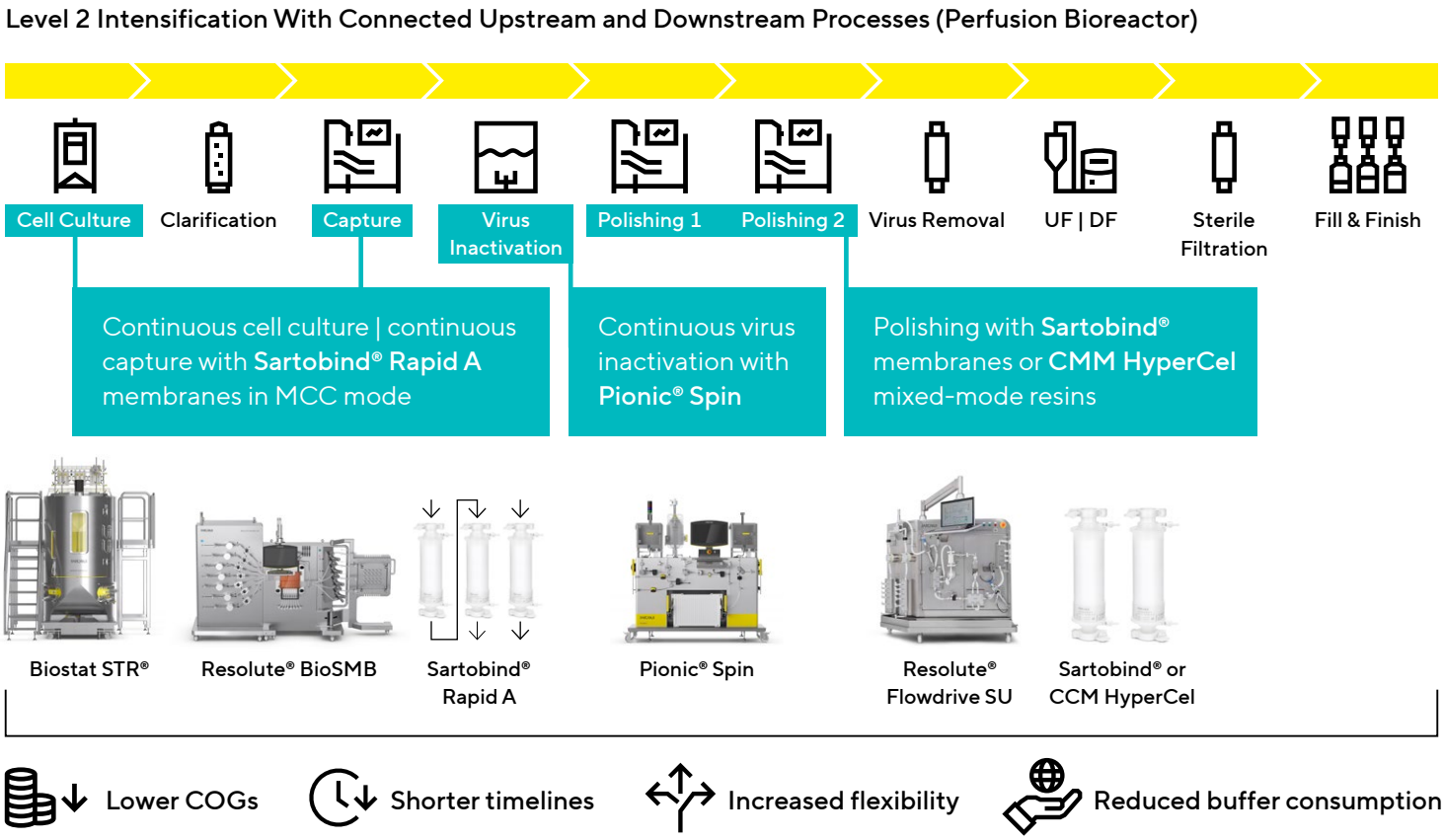


Membranes reduce **chromatography costs by 50% and timelines by 28%**

Level 2 DSP Intensification With MCC and Continuous Virus Inactivation

MCC enables continuous chromatography while reducing the volumes and cost of chromatography media.[32, 41-46] Figure 22 illustrates Level 2 intensified DSP applicable to a perfusion bioreactor. This approach uses Sartobind® Rapid A in MCC mode for the capture, and Sartobind® membranes or HyperCel mixed-mode resins for polishing. The process[32, 41-46] is run with a perfusion bioreactor directly connected to a Resolute® BioSMB for the capture, Pionic® Spin for the flow-through low pH VI, and Resolute® Flowdrive for the polishing steps. All DSP steps are run with single-use flow kits installed on systems to operate in a closed, sterile environment.

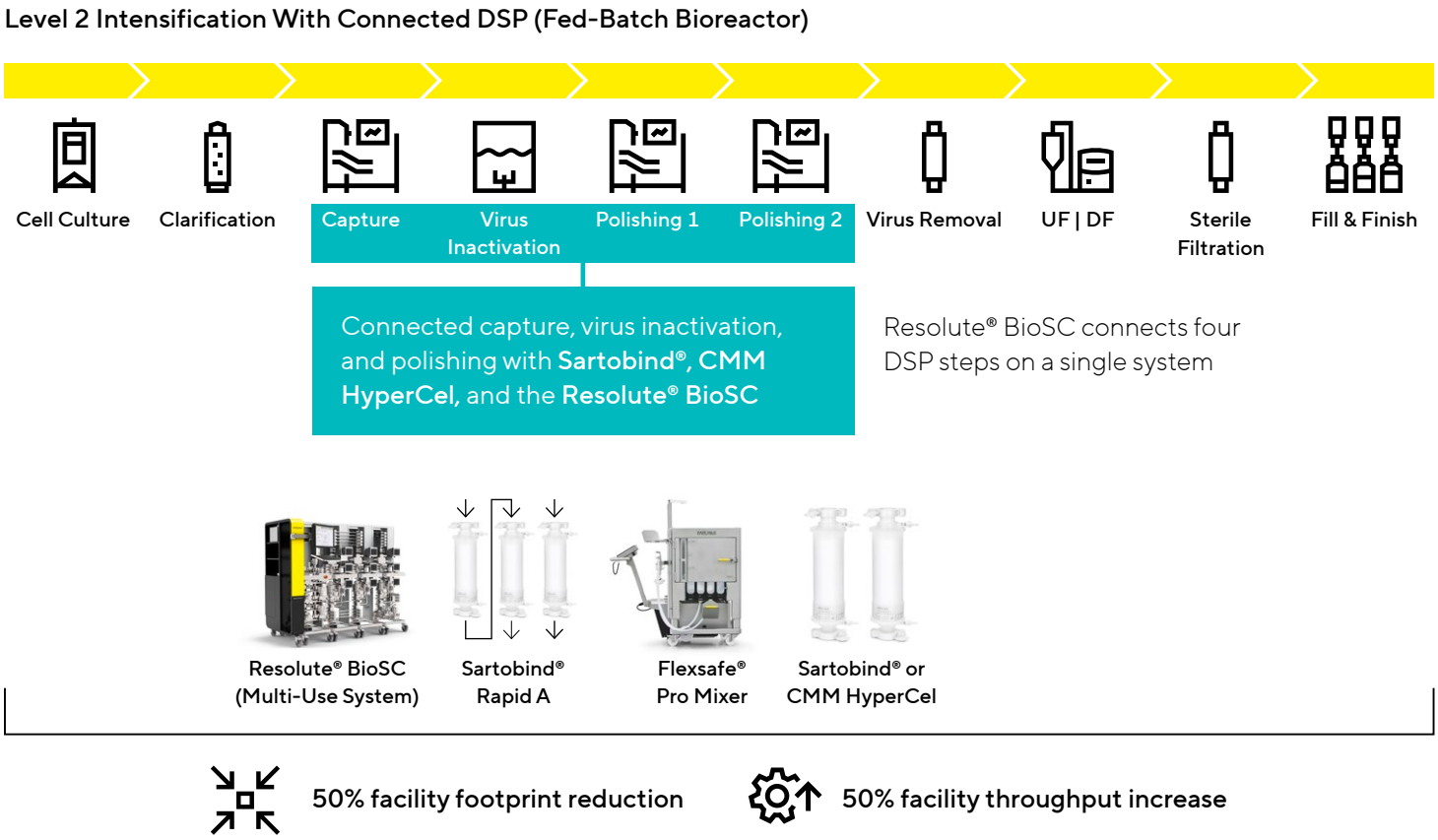
Figure 22: *Example of Level 2 Intensified DSP Using Sartobind® Rapid A in Membranes in MCC Mode for Capture*



Note. The Resolute® platform can also be used to intensify a resin process. Selection and sizing of the systems can be done automatically with ExCIT.

A second Level 2 intensified downstream process applicable to a fed-batch bioreactor is shown in Figure 23. This approach uses Sartobind® Rapid A in MCC mode for capture, and Sartobind® membranes or HyperCel mixed-mode resins for polishing. Using a single Resolute® BioSC system enables the connection of capture, virus inactivation, and polishing steps, saving cleanroom space. Initiating the next step while the previous one is still in operation can reduce the downstream timeline by up to 50%. This Level 2 downstream PI approach is typically implemented when scaling to clinical phase 3 and commercial production.

Figure 23: *An Example of Level 2 Intensified DSP Using a Connected Sartobind® Membrane Workflow on the Resolute® BioSC Multi-Use System*

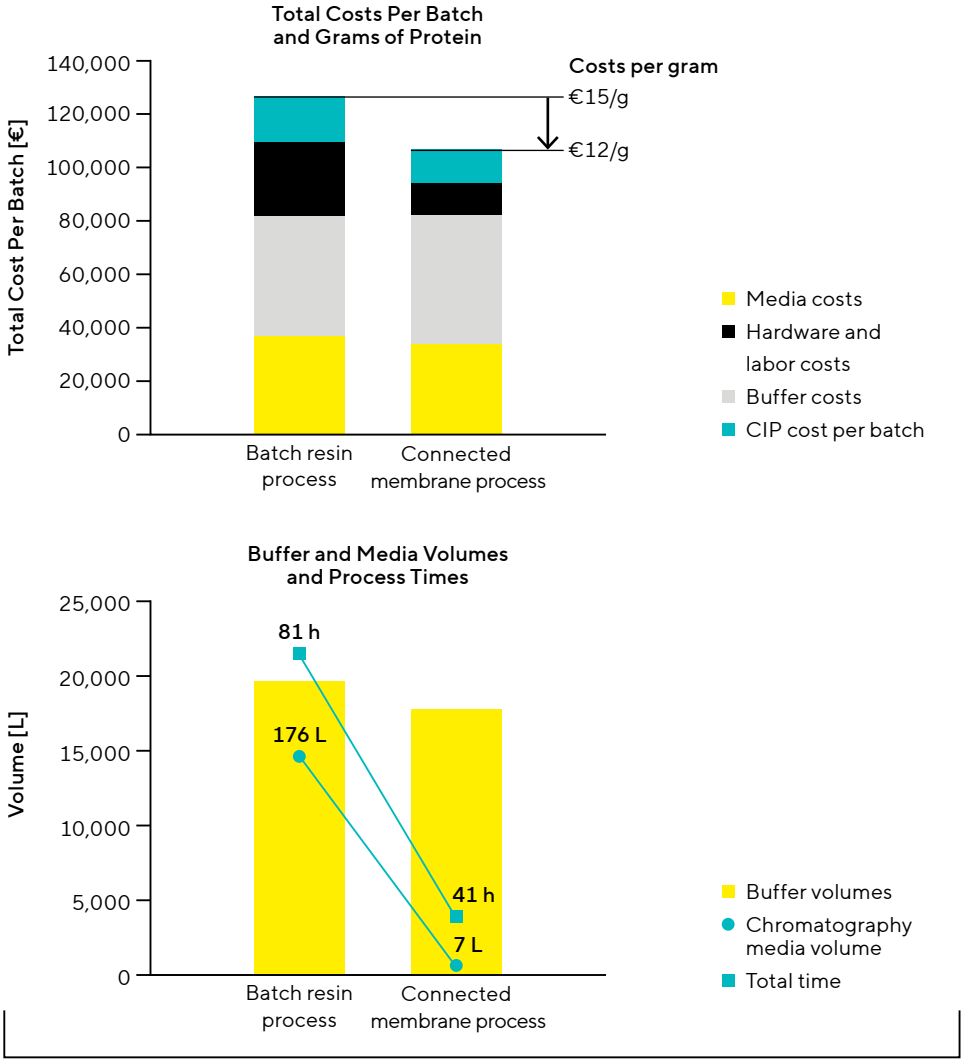


Note. The Resolute® platform can also be used to intensify a resin process. Selection and sizing of the systems can be done automatically with ExCIT.

Figure 24 compares batch and multi-column resin workflows to a full membrane approach for purifying a 2,000 L bioreactor at 5 g/L, running 40 batches annually. The membrane process includes a bind-elute capture step with Sartobind® Rapid A, followed by a bind-elute and flow-through sequence with Sartobind® Q (AEX) and Sartobind S (CEX) for polishing. This workflow reduces overall purification costs by 18%, from €15 to €12 per gram of antibody, and decreases total processing time from 81 to 41 hours.

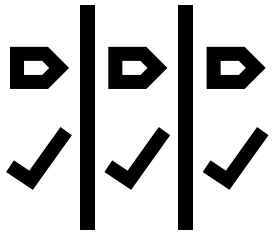
Figure 24: *Example of Data Generated by Our Expert Chromatography Intensifier Tool (ExCIT) to Compare Traditional and Intensified DSP in Commercial Production*

Level 2 Intensification in Commercial Production



Membranes reduce **chromatography costs by 18% and timelines by 48%**

Level 3 DSP
Intensification With Integrated Continuous Processing



Ultimately, the goal is to integrate all downstream steps into a continuous flow using modular systems under software orchestration, creating a fully continuous process. Our newly developed Pionic® solution, created in collaboration with end users, is designed to support this goal by achieving up to Level 3 PI. It significantly reduces the number of systems and modules required in a facility, thereby reducing capital investments, complexity, facility footprint, and energy consumption. Individual units from our Pionic® portfolio can be integrated into an existing DSP, enabling a transition from batch processing to the specific desired level of PI (Figure 25).

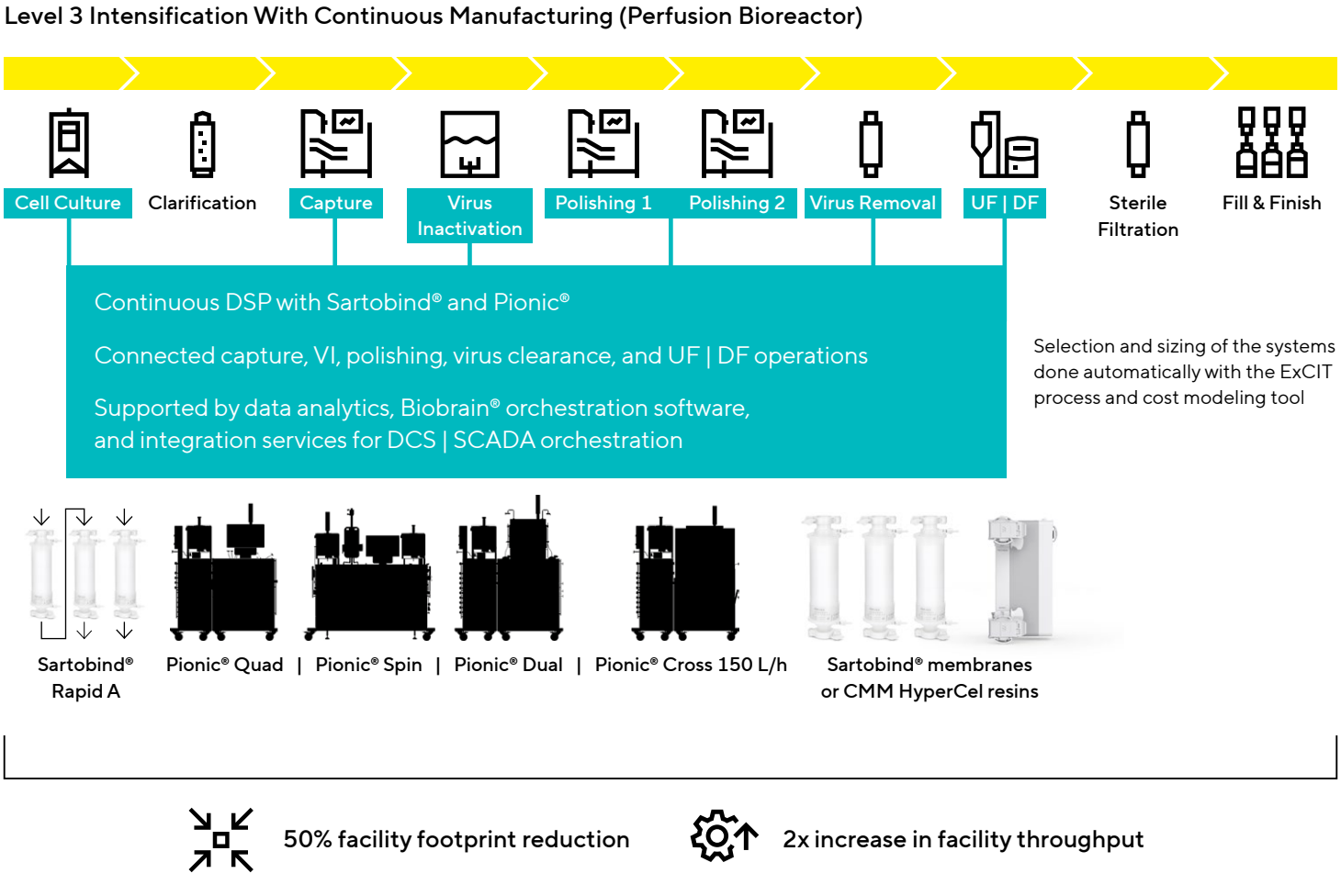
Integrated solutions like Pionic® facilitate advancements in biomanufacturing with ready-to-use, modular systems that seamlessly adapt to new and existing facilities, supporting any intensification strategy. Continuous DSP with the Pionic® platform can be connected to either a fed-batch or continuous perfusion bioreactor, maximizing throughput in both new and existing facilities.

Each component of the Pionic® solution is designed for each unit operation to integrate the capture, virus inactivation, intermediate purification, polishing, virus removal, and UF | DF steps in a continuous flow orchestrated by the Biobrain® Supervise software. When continuous chromatography, virus filtration, and UF | DF solutions already exist, one major innovation within Pionic® is the Pionic Spin® for continuous virus inactivation.

Virus Inactivation Using Pionic Spin®

Pionic® Spin is an innovative operational unit designed for continuous virus inactivation via a fully closed, irradiated, ready-to-use flow path. Virus inactivation represents an essential step in the DSP of active pharmaceutical ingredients, typically located between the capture and polishing steps. It plays a key role in reducing the risk of viral contamination, thereby enhancing the safety of the final product, as required by regulatory authorities such as the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA).

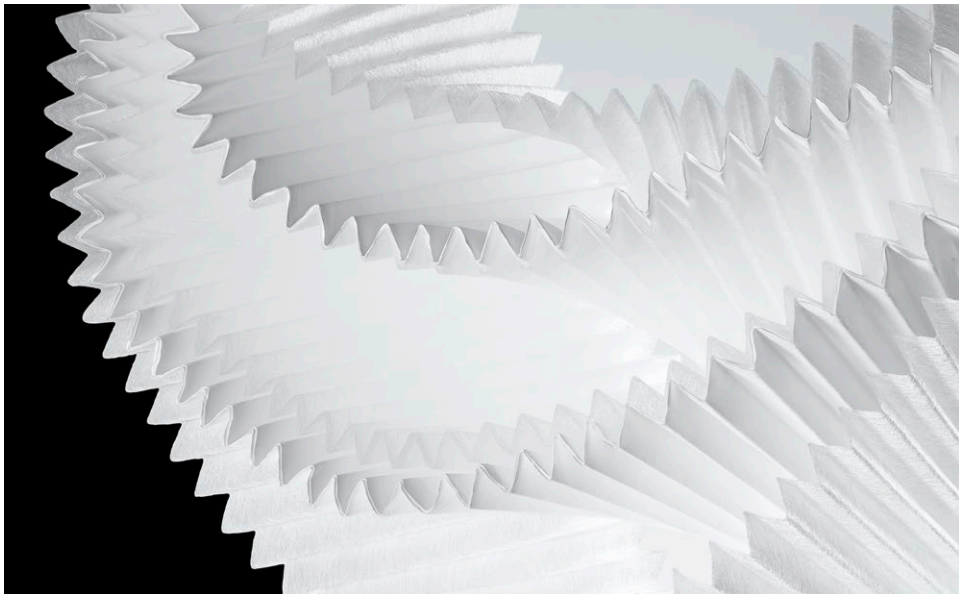
Figure 25: *Pionic® Portfolio Facilitates up to Level 3 PI by Performing All DSP Steps, From Clarification to Fill and Finish*

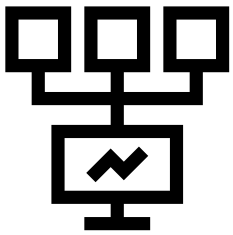


Note. DCS = distributed control system

Pionic® Spin supports PI by enabling autonomous operation of continuous, robust virus inactivation at low pH. It is specifically designed for long-term perfusion-based processing, allowing continuous operation for up to 28 days without the need to exchange ready-to-use PAT components. Automated inline pH titration of the incoming feed is carried out in a single step, allowing a control accuracy of ± pH 0.1. The modular Pionic® Spin Incubator features a serpentine plug flow reactor design that ensures a uniform narrow residence time for low pH incubation. It reduces active enveloped viruses by ≥ 5 log reduction values (LRV; 99.999%), effectively meeting regulatory and end-user requirements. Integrated surge vessels at both the inlet and outlet balance the flow, further supporting consistent processing conditions for an effective continuous virus inactivation.

Figure 25 depicts Pionic® portfolio components. An orchestrated operation of Pionic® Spin with the integrated upstream and downstream units for capture and intermediate purification necessitates close communication between the individual operational units. This is achieved by open communication protocols, allowing seamless integration of Pionic® Spin into SCADA and distributed control system (DCS) platforms. Additionally, the system is compatible with both cyclic and continuous capture outputs from the preceding chromatographic capture step.





Digital Solutions: The Backbone of PI and Continuous Manufacturing

As demonstrated throughout this white paper, PI and continuous manufacturing fundamentally transform bioproduction. However, they also introduce greater complexity. Tighter process windows, simultaneous upstream and downstream operations, and real-time quality requirements mean that traditional automation strategies are insufficient.

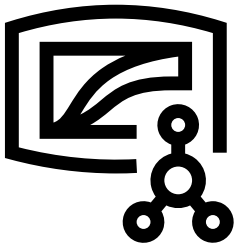
Predictive control will no longer be optional in continuous and intensified manufacturing. Anticipating process trends, detecting deviations before they occur, and dynamically optimizing operations are essential to maintaining product quality, improving yields, and ensuring uninterrupted production flows.

Without advanced control, monitoring, and analytics, intensified and continuous manufacturing processes face higher operational costs, longer time to market, and greater regulatory challenges.

In this new environment, digital solutions are essential.
They enable manufacturers to:

- Synchronize multiple unit operations dynamically and reliably
- Monitor critical process and product parameters continuously (e.g., titers, flow rates, pH, and conductivity)
- Detect deviations early and apply immediate corrective actions, including predictive control and advanced process orchestration
- Shorten batch release timelines through integrated data management
- Reduce failure rates and increase overall process robustness
- Scale processes flexibly from laboratory to commercial production while maintaining full control

A Comprehensive Digital Ecosystem to Simplify Intensified Manufacturing

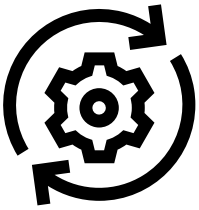


As biomanufacturers move toward PI, a robust digital ecosystem becomes essential to manage the resulting complexity. Integrated digital platforms like Biobrain® enable seamless data flow, real-time control, and cross-system coordination—capabilities that are critical for scaling intensified processes efficiently, maintaining GMP compliance, and accelerating time to market.

Our platform is built around three integrated layers:

1. Biobrain® Control Layer: Local equipment control, operating independently or integrated within broader systems.
2. Biobrain® Supervise Layer: Centralized supervision of multiple units, historical data capture, and advanced operational analytics.
3. Biobrain® Operate Layer: Orchestration of full manufacturing workflows, including digital work instructions, electronic batch records, and batch management.

These layers are enhanced by Umetrics® advanced data analytics software, which brings predictive control, machine learning capabilities, and advanced process modeling into the manufacturing environment allowing a shift from reactive management to proactive optimization. Through data-driven models and machine learning, manufacturers can unlock faster decision-making, better process understanding, and higher operational resilience.



Integration: A Critical Success Factor for PI

Integration across systems and equipment is often one of the most significant barriers to successful PI. In intensified and continuous processes, poor integration can result in:

- Loss of synchronization between process steps
- Delays and extended downtime
- Increased risk of batch failures
- Missing information | gaps in data integrity
- Higher validation, operational, and lifecycle costs

Modern biomanufacturing environments require digital systems that can integrate reliably and flexibly across multiple layers of operation. Key features of a well-integrated setup include:

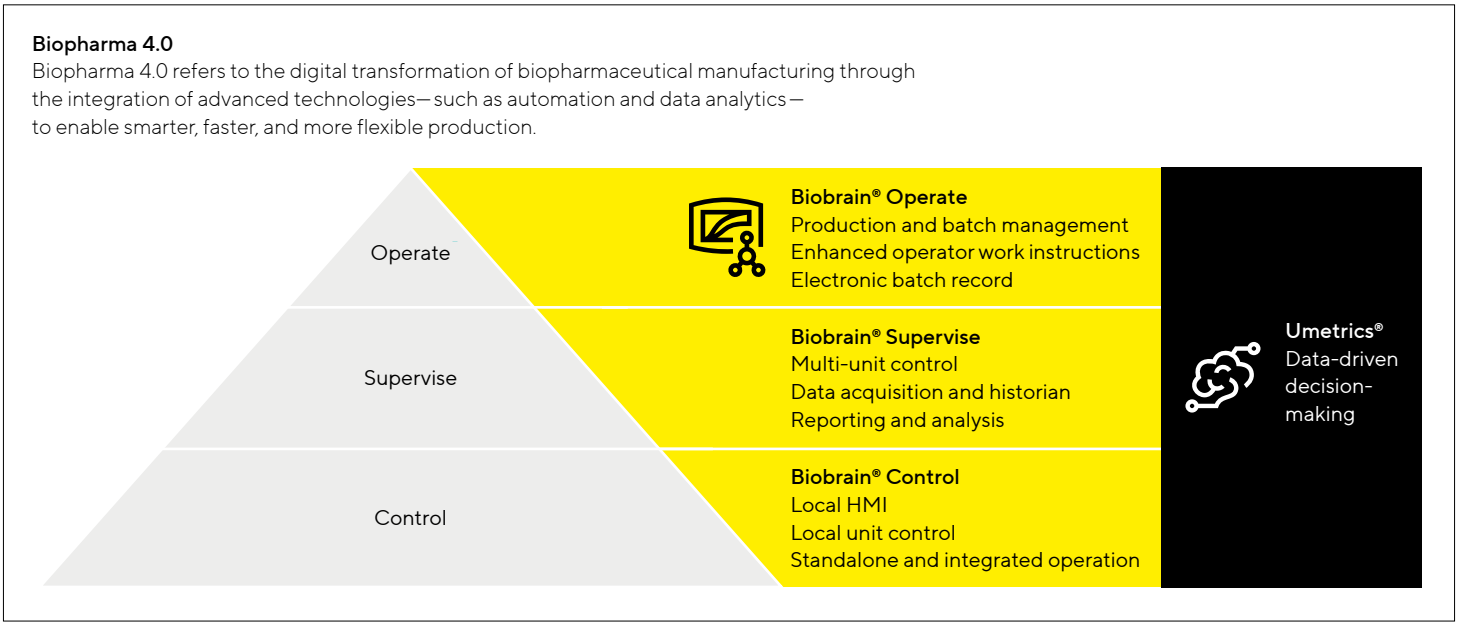
- **Seamless connectivity across layers:** Control and operation layers that integrate seamlessly into external DCS and manufacturing execution systems (MES).
- **Cross-platform interoperability:** Interoperability with third-party equipment through open protocols such as Open Platform Communications Unified Architecture (OPC UA), ensuring efficient cross-platform communication.
- **Standardized and validated interfaces:** Interfaces that follow industry standards help reduce project risks, shorten implementation timelines, and lower complexity across operations.

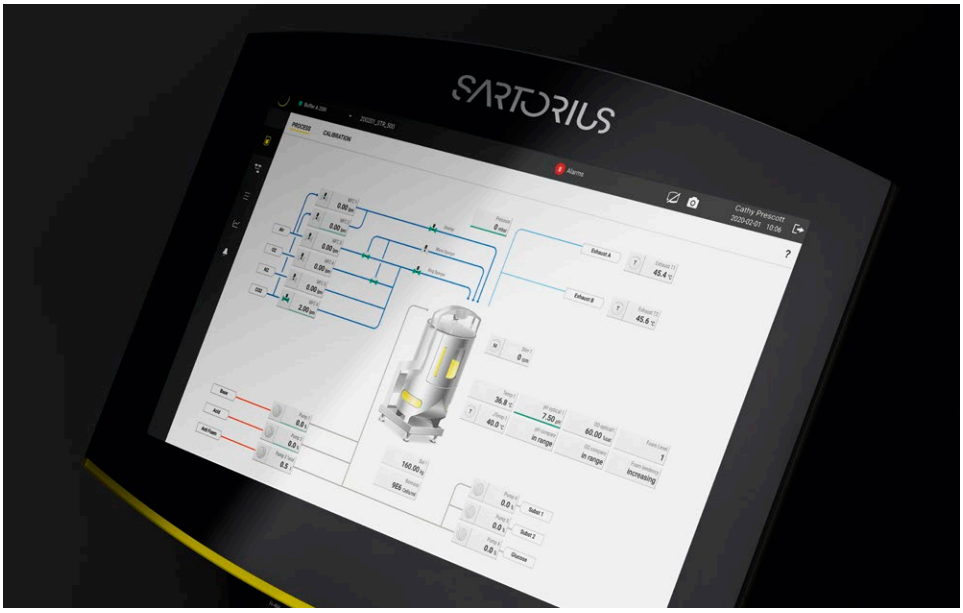
This modular capability enables efficient integration into existing or new manufacturing environments, accelerating deployment, improving synchronization, and minimizing overall project costs and risks. A prime example of this philosophy is Pionic®, a platform fully based on the Biobrain® control automation architecture, offering native, multi-layer integration and orchestration capabilities specifically tailored for the demands of PI.

By embedding modular, interoperable digital solutions from the outset, biopharmaceutical manufacturers can transform PI from a technical challenge into a competitive advantage—achieving faster, more reliable, and more flexible production.

Figure 26 illustrates the digital solution platform designed to simplify Biopharma 4.0. Predictive data analytical tools, PATs, automation software, and services are key enablers for PI. They help lower costs, shorten timelines, reduce the risk of lost batches, improve productivity, and ensure product quality during both process development and manufacturing. Together, these solutions form a robust, integrated, and scalable digital ecosystem, specifically designed to simplify and accelerate the digital transformation journey in biopharma.

Figure 26: *Digital Solution Platform to Simplify Biopharma 4.0*





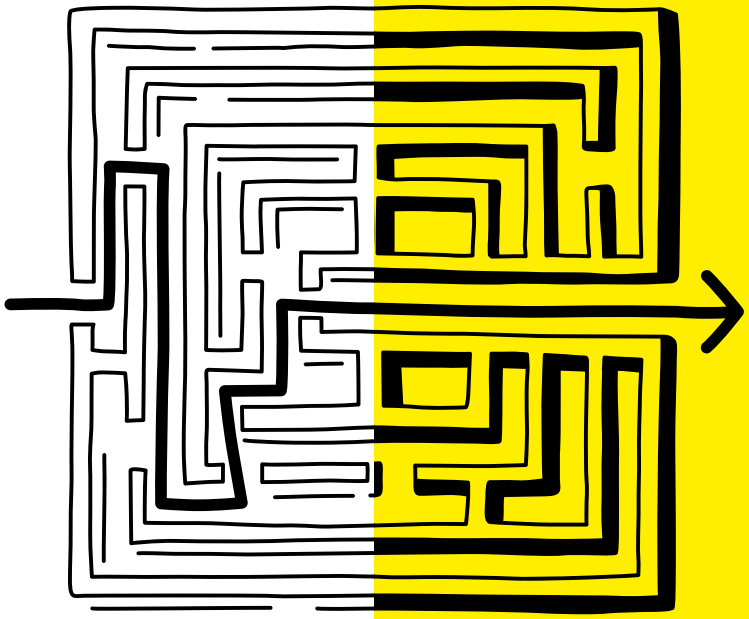
End-to-End PI Consultancy

Bioprocess Tools and Services for PI From Development to Commercial Manufacturing

Process Design and Cost Modeling Tools

Engaging in PI requires dedicated and skilled resources, which can make it both costly and time-consuming. With multiple strategies available for intensifying biopharmaceutical processes, selecting the right approach from the outset ensures the journey is worthwhile, maximizing cost, time, productivity, and throughput benefits (Figure 27).

Advanced process design and cost-modeling tools are essential for predicting the impact of PI and technology choices on overall process throughput and COGs. These tools assess the commercial viability of future or existing processes and forecast the effects of transitioning to alternative intensified configurations. They facilitate data-driven decision-making, helping users choose between fed-batch or perfusion USP, batch, connected, or continuous DSP, and multi-use or single-use facilities.



"Expert tools and consultancy simplify intensification from concept to execution."

Learn more at:
sartorius.com/process-intensification

ExCIT is a consultancy-driven tool designed to help end users navigate the complexity of DSP intensification. Grounded in real-world customer workflows, ExCIT provides expert guidance in selecting the most effective DSP intensification strategies and appropriate technologies.

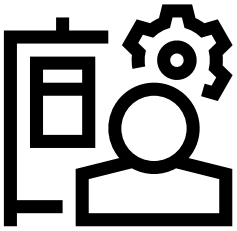
It supports clients in designing lab-scale experiments and enables data-driven decision-making by predicting critical factors such as total COGs, processing times, buffer usage, productivity, and throughput across the entire chromatography workflow. These insights help customers accelerate development, reduce risk, and scale confidently from laboratory to full production.

While the ExCIT tool covers all three chromatography steps and requires expert guidance, we have also created a simple version of the ExCIT tool, the Capture Intensifier Application. This web-based application allows end users to evaluate and predict the cost savings and productivity gains obtained with intensifying the Protein A capture step under specific process conditions.

Figure 27: Process Design and Cost Modeling Tools Help Users Navigate the Complex Landscape of PI

Technology	Batch upstream	Continuous upstream	Resin (batch)	Multi-column chromatography (resins)	Membranes (batch)	Multi-membrane chromatography
Upstream Process	Fed-batch	High-intensity fed-batch	Concentrated fed-batch	Perfusion unstable molecule		
Downstream Process	Batch	Connected	Continuous			
Fluid Management	Multi-use	Single-use				
Producer Profile	CDMO with multiple products	Large-scale process development; large pipeline	Small-scale process development; few molecules			
Drug Life Cycle	Clinical	Low-demand commercial	High-demand commercial			

Note. Increase in the number of feasible DSP batches per year, meaning higher outputs (kg of mAb) with the same facility and equipment. Biosolve software helps users select the right overall PI strategy. ExCIT helps users select the right chromatography workflow.



Bioprocess Consulting and Technical Services for PI

Implementing PI is often complex and resource-intensive, requiring the appropriate expert tools, knowledge, technical support, and consultancy services from USP and DSP and from conceptual design to facility build-outs.

PI is a stepwise journey beginning with initial process optimization, application development, process modeling, and conceptual design. It progresses through detailed engineering, validation, and regulatory support, culminating in final project execution (Figure 28).

Validation and Regulatory Support Services

Working in collaboration with suppliers allows users to obtain the required validation services for all process components essential for PI, including bioreactors, bags, container closure systems, mixing systems, sterile filters, transfer systems, membrane adsorbers, virus filters, and more. Leveraging Sartorius' Confidence® Validation Services, our deep understanding of the regulatory landscape, and extensive experience in PI and continuous manufacturing, we can assist in designing the appropriate validation master plan and ensuring compliance with the latest regulatory requirements.

Figure 28: *Technical, Consultancy, and Validation Services to Simplify PI*

PI Strategy and Technology Choice		PI Design and Establishment of Process Performances		Scale-Up, Validation, and Project Execution	
Process Optimization	**Process Design and Cost Modeling**	**Process Consulting and Conceptual Design**	**Process Engineering and Cost Calculation**	**Validation, Regulatory Support, and Training**	**System Installation, Factory Acceptance Testing, Site Acceptance Testing, and Installation Qualification and Operational Qualification**
Application Specialist ▪ Optimize process ▪ Generate data for process and cost modelling ▪ Base for scale up	**Process Consulting** ▪ PI design ▪ Technology choice ▪ Impact on COGs, timelines, footprint, throughput, buffers	**Integrated Solution Engineer** ▪ Mass balance ▪ COGs modeling ▪ Process flow diagram and layout ▪ Automation	**Process Engineer** ▪ Technical user requirements specification ▪ Piping and instrumentation diagrams and process flow diagrams ▪ 2D and 3D CAD design drawings ▪ Detailed COGs	**Validation Experts** ▪ Virus clearance ▪ Extractables and leachables ▪ Filtration and single-use systems' validation ▪ Particle validation	**Service & Manufacturing Engineers** ▪ Assembly ▪ Commissioning ▪ Factory acceptance testing and site acceptance testing ▪ Training ▪ Post-sales services

Note. Process modelling tools support the selection of the optimal overall PI strategy (USP batch vs. perfusion, DSP batch vs. continuous, single-use vs. multi-use). ExCIT supports the selection of the right chromatography workflow (membrane adsorbers vs. resins, batch vs. connected or continuous, bind and elute vs. flow-through).

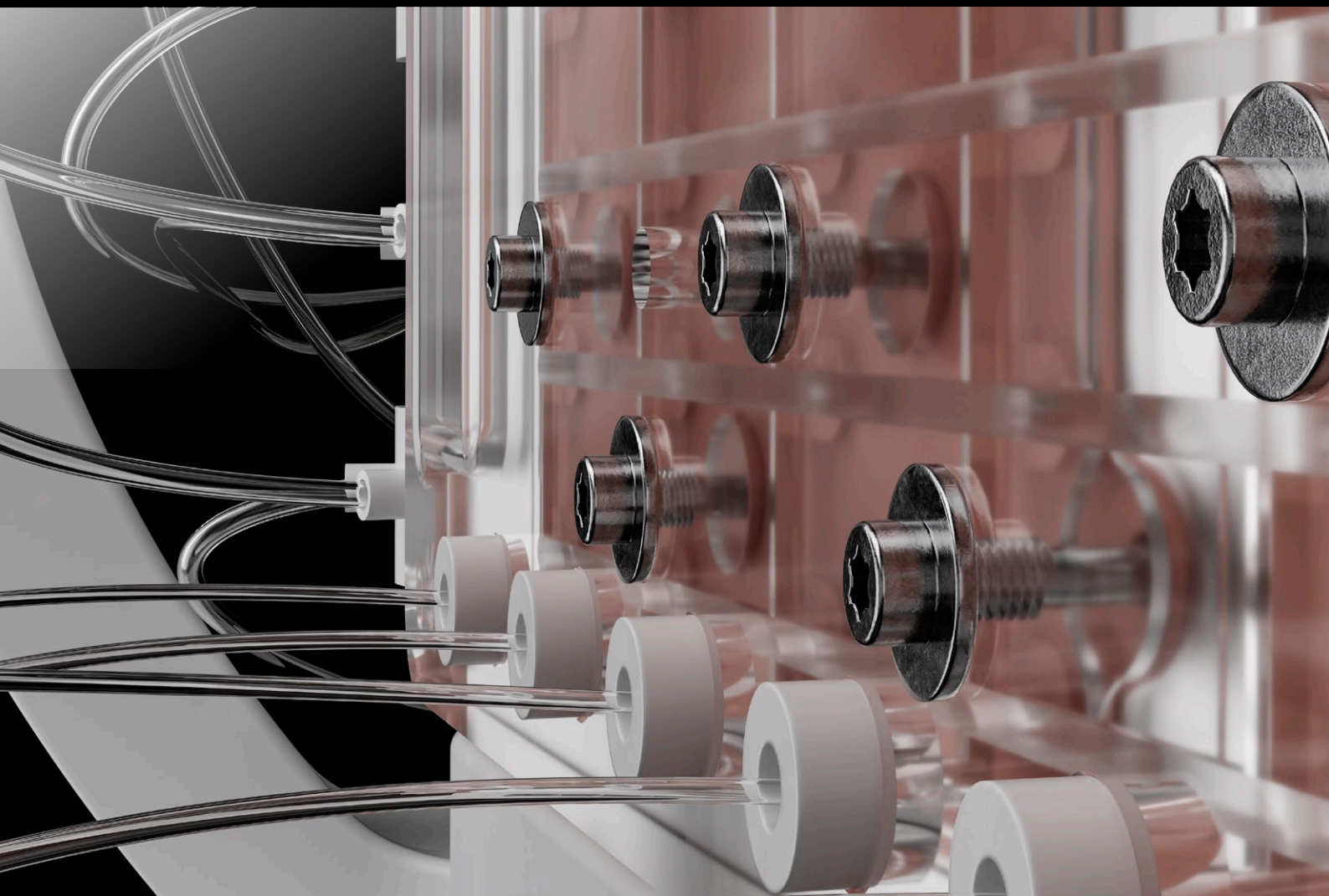
Conclusion

PI is essential for addressing the growing demand for mAb therapies, aiming to reduce costs, increase throughput, and minimize environmental impact. While advancements in upstream processes have boosted mAb titers and productivity, they have also shifted bottlenecks to DSP, necessitating comprehensive intensification across the entire manufacturing process.

This white paper demonstrates that intensifying upstream processes through intensified fed-batch or dynamic | continuous perfusion bioreactors, coupled with a fully integrated membrane chromatography workflow for downstream purification, offers a cost-effective alternative to traditional platforms. Membrane chromatography, particularly with Sartobind® Rapid A, enables faster purification cycles and efficiently purifies large quantities of antibodies using smaller consumables, significantly reducing overall downstream costs and process footprint. This approach benefits both low-demand and large-scale production, maintaining yield, purity, and product quality attributes.

As a partner in biopharmaceutical development, Sartorius supports the transition to intensified processing. Our suite of process and cost modeling tools, process technologies, digital solutions, and services to facilitate PI, ensure efficient, cost-effective, and sustainable mAb production, enabling the development of new and better therapies and more affordable medicine. It's time to intensify.

For more information, visit
sartorius.com/process-intensification



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Gerben Zijlstra is a leading expert in process intensification, integration, and continuous biomanufacturing, with over 25 years in the biopharma industry. He holds a Ph.D. from the University of Wageningen, focusing on process integration in animal cell culture. At Patheon, he developed commercial biotherapeutics and advanced process intensification projects with single-use bioreactors. Zijlstra invented the XD® Concentrated Fed-Batch technology, boosting productivity fivefold, and facilitated its scale-up to the Brisbane site, recognized by ISPE for process innovations. At Xendo, he worked on single-use continuous biomanufacturing and gene therapy.

Currently, he is a Bioprocess Solutions Expert at Sartorius.

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Jean-Marc Cappia is Head of Market Development Intensified Chromatography at Sartorius, based in Aubagne, France. With a biotechnology engineering degree from the INSA of Toulouse and more than 35 years of experience, Mr. Cappia supports the global biopharmaceutical industry, particularly with process design, process intensification, validation, training, and the implementation of single-use filtration, purification, and fluid management technologies.

Since joining Sartorius in 2006, he has been responsible for marketing, product management, and business development for emerging single-use technologies. In his current position he supports customers with their down-stream process intensification, with a focus on chromatography and with the objective to produce safer and cheaper biologics in more sustainable manufacturing facilities.

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