From Fed-Batch to Perfusion: Unlocking ROI and Capacity in Monoclonal Antibody Manufacturing

White Paper

Introduction

Therapeutic monoclonal antibodies (mAbs) are the predominant class of biopharmaceuticals, driven by their success in treating cancer, autoimmune disorders, and chronic inflammatory diseases. In recent years, the number of FDA-approved mAbs has steadily increased, reflecting both clinical demand and technological advances. Of the 50 new drugs approved by the FDA in 2024, sixteen were biologics, and momentum continues to build[1]. The global mAb market is projected to reach USD 494.53 billion by 2030, with a compound annual growth rate (CAGR) of 11.04% from 2023 to 2030[2].

With significant market expansion, biopharmaceutical manufacturers face increasing pressure to accelerate time to market and improve process efficiency and sustainability, while also reducing production costs. They must manage facility capacity constraints and remain cost-competitive in a crowded therapeutic landscape. At the same time, the increased number of marketed and pipeline products requires manufacturers to operate flexible multiproduct facilities that can switch efficiently between different therapies without compromising quality or timelines. Consequently, manufacturing platforms must be flexible enough to support not only a diverse portfolio of products, but also a wide range of production scales—from a few kilograms for rare autoimmune diseases to hundreds of kilograms for more prevalent indications—often under compressed timelines.

While biopharmaceutical manufacturers continue to rely on fed-batch for upstream mAb production due to its longstanding track record, platform familiarity, and regulatory precedent, this approach has several limitations. These include the need for larger bioreactors, fixed culture durations, lower volumetric productivity (grams of product per liter per day [g/L/day]), and long changeover times between runs, all of which contribute to higher capital (CAPEX) and operating (OPEX) expenses. For example, CAPEX for a fed-batch facility can reach up to $293 million, with annual OPEX as high as $63 million[3].

In contrast, process intensification strategies, such as perfusion and continuous manufacturing, offer technical, economic, and operational advantages. The same analysis (above) found that continuous biomanufacturing facilities could operate with significantly lower capital and operating costs, with CAPEX estimates up to $182 million and $58 million in annual OPEX[3]. These reductions are driven by smaller equipment and facility footprints, higher volumetric productivity, and greater use of single-use technologies. Continuous manufacturing has also been associated with 10% – 30% reductions in commercial cost of goods (COG). These figures make a compelling case for manufacturers to invest in upstream process intensification using perfusion to improve efficiency, support their diverse portfolio, and meet a wide range of demand under compressed timelines, which maximizes return on investment (ROI) in mAb production[4].

Advantages of Perfusion Cell Culture in Upstream Bioprocessing

Efforts to improve upstream productivity through cell line development and media optimization can involve substantial time and resource investments, often with limited results and a high risk of failure. Developing a high-producing, stable Chinese hamster ovary (CHO) clone can take 6 to 12 months, with costs typically ranging from $500,000 to over $1 million USD[5,6,7]. These timelines and expenses can vary due to factors such as cell line complexity, target expression levels, and whether the work is done in-house or outsourced. While optimized fed-batch cultures have achieved mAb titers exceeding 10 g/L, these processes are still constrained by cell density limits and fixed culture duration, placing a ceiling on further productivity gains[6].

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To overcome these limitations, manufacturers seek alternative approaches in upstream bioprocessing to break the titer ceiling without the inherent constraints of fed-batch processing. Upstream process intensification using perfusion and continuous bioprocessing can achieve 5 – 10X higher volumetric productivity by enabling significantly higher cell densities (Figure 1). Cells are maintained in a steady state of growth, supported by the constant exchange of fresh culture medium and removal of spent medium. Technologies such as XCell® ATF (alternating tangential flow) Systems play a critical role in perfusion culture by providing precise perfusion control and efficient cell retention with minimal filter fouling.

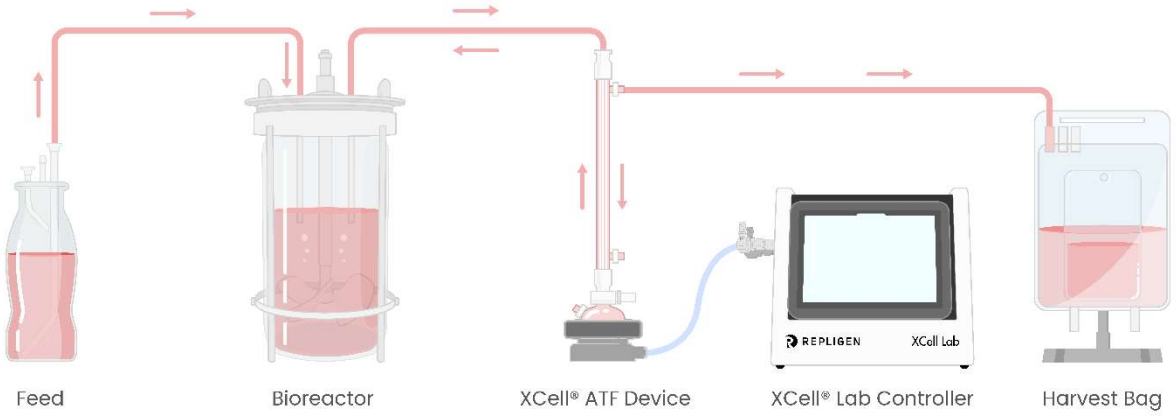

Figure 1. Example of a perfusion bioreactor setup using the XCell ATF System. A single-use stirred tank bioreactor is integrated with the XCell ATF single-use cell retention device and operated via the XCell Lab Controller. The system includes appropriate sterile tubing sets and fluid management components to enable continuous closed-loop perfusion for efficient cell retention and product harvest.

The ability to sustain high viable cell densities (VCD) over extended culture durations enables significantly higher mAb productivity per reactor volume per day compared to fed-batch processes. This elevated productivity allows manufacturers to meet output targets using smaller-volume, single-use bioreactors (SUB), which, in turn, reduce CAPEX and OPEX expenditures, and lower raw material consumption on a per-gram basis[3,4,8]. These efficiencies make perfusion-based processes well-suited for modern-day multi-product facilities where operational agility and space efficiency are critical.

From a sustainability perspective, continuous perfusion enables more compact, smaller footprint facilities, and enhanced process efficiencies that reduce the overall environmental impact. Recent modeling data show a potential 54% reduction in CO_2 emissions and 57% decrease in plastic waste compared to traditional fed-batch processes[3].

In addition to economic, operational, and sustainability benefits, continuous perfusion offers clear advantages in product quality. The stable culture environment reduces cellular stress responses that can lead to variability in critical quality attributes (CQA), such as glycosylation patterns, aggregation, and charge variants. For unstable molecules, continual waste removal helps preserve structural and functional integrity[9].

However, continuous perfusion does introduce additional considerations to the upstream cell culture process, including higher media consumption and longer run durations that can impact labor costs. To better understand the value of process intensification, the following section presents a comparative cost analysis of fed-batch and continuous perfusion upstream production (USP) across different production scales.

Cost Analysis of Continuous Perfusion

A theoretical upstream cost analysis was performed based on modeling assumptions and methodology adapted from Mahal et al.[4] This analysis modeled four USP scenarios in which both fed-batch and continuous perfusion processes targeted both 200 kg and 500 kg of mAb output per year. This cost analysis focuses solely on upstream operations and assumes similar downstream production (DSP) yield and cost.

A standard 30-day perfusion run was used to represent the continuous production model. The analysis incorporates standardized cost inputs—including media consumption, labor requirements, and indirect costs such as depreciation and facility utilities—providing a comparison of upstream cost drivers and demonstrating how continuous perfusion can impact the cost of goods at different production scales.

1. Cost Analysis Model Inputs

Table 1. Cost Analysis Model Assumptions

Parameter	Fed-batch 200	Fed-batch 500	ATF Perfusion 200	ATF Perfusion 500
Annual production target (kg)	200	500	200	500
Total harvest volume (L)	60,000	152,000	160,000*	400,000*
Titer	5 g/L	5 g/L	2.25 g/L *(45% of fed-batch)*	2.25 g/L *(45% of fed-batch)*
Cell density (million cells/mL)	10	10	50	50
Production bioreactor duration (days)	14	14	30	30
Lag phase (days)	-	-	5	5
Overall downstream process (DSP) yield	65%	65%	65%	65%
Batches per year	22	22	5	5
Number of bioreactors	1 × 5,000 L	1 × 10,000 L	1 × 1000 L	1 x 2000 L
Working volume ratio	80%	80%	80%	80%
Working volume (L)	4000	8000	800	1600
Perfusion rate (VVD)	-	-	1	1
Volumetric productivity (g/L/day)	0.36	0.36	2	2
Runs needed for target kg	15	19	8	10
Plant utilization (% annual capacity)	80%	80%	80%	80%

*Reflects continuous processing with integrated USP and DSP

Table 2. Direct Cost Inputs

Cost Category	Fed-batch	ATF Perfusion
Media cost (per L)	$33	$19
Buffer cost (per L)	$3	$3
WFI cost (per L)	$1.50	$1.50
QC release (per batch)	$35,000	$35,000

Table 3. Labor Cost Inputs

Labor Category	Fed-batch	ATF Perfusion
Operators per shift (USP/DSP)	6/6	3/3
# Shifts per day	3	3
Bioreactors per team	4	2
FTE cost per year	$150,000	$150,000

Table 4. Indirect Cost Inputs

Cost Component	Fed-batch 200	Fed-batch 500	ATF Perfusion 200	ATF Perfusion 500
Fixed CAPEX	$41M	$56M	$32M	$40M
Maintenance, tax, insurance	13% CAPEX	13% CAPEX	13% CAPEX	13% CAPEX
Depreciation period	10 years	10 years	10 years	10 years
Utilities (per m^2 footprint)	$525	$525	$525	$525

2. Cost Calculations
    a. Direct Cost Calculations
    Direct costs include media, buffers, WFI, and batch-level QC release testing. For fed-batch, a one-time media change equal to the working bioreactor volume (80% of nominal volume) per run was assumed. For perfusion, media usage was based on 1 volume-volume per day (VVD) for 25 days (excluding 5-day lag). Buffer and WFI costs were constant across scenarios.
    b. Labor Cost Calculations
    Labor costs were calculated based on the number of operators per shift, shifts per day, and bioreactor runtime. Cost calculated for USP only assuming 260 days per FTE.

$$FTE\ per\ run\ = Total\ operators\ \times\ Shifts\ per\ day\ \times Bioreactor\ runtime/260$$

    c. Indirect Cost Calculations
    Indirect costs exclude fixed CAPEX and were calculated based on depreciation, maintenance/taxes/insurance (MTI), and utilities (per m^2). Facility size was assumed based on Mahal *et al*. estimates for single-use facilities. All indirect cost components were multiplied by an 80% plant utilization factor to reflect annual facility use.

Table 5. Indirect Cost Assumptions

Bioreactor Size	Typical Facility Footprint (m^2)	Assumption for Calculations (m^2)
5,000L	2,000 – 2,500	2200
10,000L	3,000 – 3,500	3200
1,000L	600 – 800	700
2,000L	1,000 – 2,000	1100

3. Total Cost Across Production Scenarios
    The total cost per campaign across the four production scenarios is shown in Table 6 and summarized in Figure 2.

Table 6. Total Costs

Scenario	Direct Costs	Labor Costs	Indirect Costs	Total Cost	Cost/gram
Fed-batch 200	$684,188	$554,734	$8,468,000	$9,706,922	$49
Fed-batch 500	$967,734	$693,417	$11,648,000	$13,309,152	$27
ATF Perfusion 200	$739,231	$499,260	$6,182,000	$7,420,491	$37
ATF Perfusion 500	$1,276,538	$624,075	$7,822,000	$9,722,614	$19

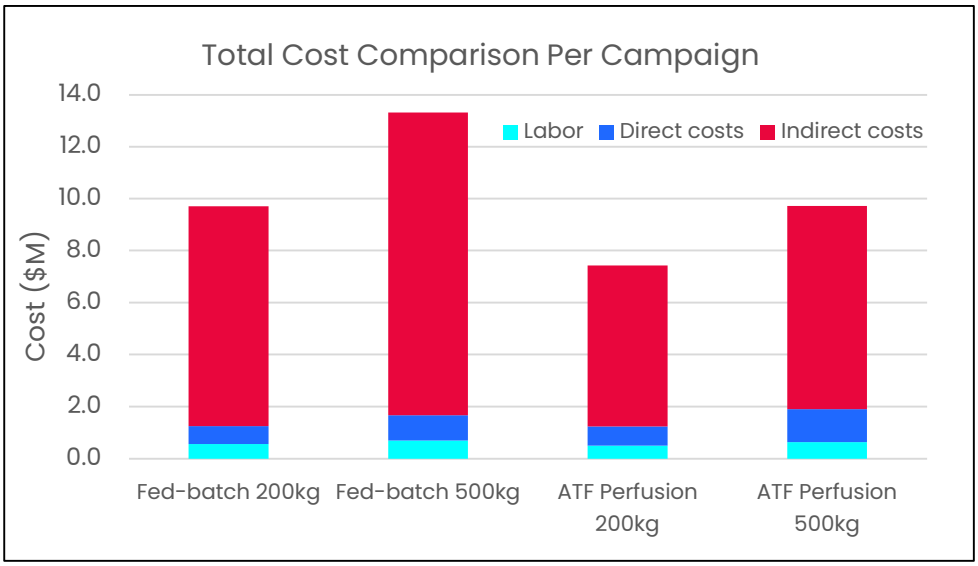

Figure 2. Total cost analysis across the four production scenarios: fed-batch (200 kg), fed-batch (500 kg), perfusion (200 kg) and perfusion (500 kg). While the direct costs for perfusion were higher than fed-batch, perfusion in both scenarios outperformed fed-batch due to reduced facility footprint and the ability to execute fewer bioreactor runs at higher volumetric productivity.

The cost analysis demonstrates that ATF perfusion culture provides a compelling economic advantage over traditional fed-batch upstream processes at both mid- and large-scales. At a 500 kg output, perfusion achieves the lowest cost per gram at $19/g, compared to $27/g for fed-batch, a 20% cost reduction. At 200 kg, perfusion also outperforms fed-batch with a cost per gram of $37/g versus $49/g, representing a 24.5% reduction. These cost advantages are driven by improved volumetric productivity and reduced indirect (facility-related) costs, which offset the higher media consumption associated with perfusion.

Importantly, perfusion achieves target outputs using smaller bioreactors and fewer production runs. As a result, while the labor cost per run may be higher, the overall cost per campaign is lower compared to fed-batch. The improved facility utilization frees up capacity that can be used to manufacture more of the same product or to manufacturing other products, providing greater scheduling flexibility in multi-product or multi-client facilities.

The 2.25 g/L titer used in this cost analysis reflects a conservative estimate for perfusion processes operating at VCD of 50 million cells/mL. However, many organizations are exploring 2 – 4X higher VCD than what is modeled, which can drive titers significantly above 2.25 g/L. These advancements suggest that the economic advantages of continuous perfusion could be even more pronounced as improved cell culture strategies lead to higher productivity and potentially lower COG.

While this cost analysis focused only on the USP, the data are aligned with modeling by Mahal et al., reinforcing the economic and operational advantages of perfusion-based manufacturing platforms.

Real-World ROI of Continuous Manufacturing Platforms

The economic models provide valuable insights into the potential benefits of perfusion, but real-world implementation provides validation to these analyses. Enzene Biosciences, a biopharmaceutical company and CDMO, has demonstrated the advantages of continuous manufacturing through its proprietary EnzeneX™ platform, which aims to improve quality, efficiency, and flexibility while reducing costs and timelines for biologics development and manufacturing. The platform streamlines the entire process, from cell line development to fill and finish, incorporating intensified perfusion using the XCell ATF System and automated multi-column chromatography to achieve continuous production.

According to company estimates, the EnzeneX platform delivers ~10X higher productivity and up to 80% lower production costs compared to fed-batch[10]. Additionally, EnzeneX reduces the carbon footprint (CO_2 emissions) by up to 50% compared to traditional

fed-batch processes. Enzene has also demonstrated that continuous perfusion leads to substantial increases in viable cell concentration (VCC), viability, and product quality for unstable molecules. For example, in a complex bispecific antibody program, the proteolytic clipping and product heterogeneity observed in fed-batch were significantly reduced under perfusion conditions, owing to the continuous removal of metabolic byproducts that minimized product exposure to degradative enzymes. A single 20 L perfusion run on the EnzeneX platform yielded 27 grams of high-quality, purified protein compared to just 3 grams obtained from a 50 L fed-batch process—a 9-fold increase in productivity. This output translated to over 500,000 doses of drug product from a single 20 L perfusion run. The commercially viable manufacturing process was developed and successfully transferred to a cGMP facility in under six months, demonstrating not only cost savings, but also a dramatic reduction in development timelines.

In another example, WuXi Biologics has integrated the XCell ATF system into their fully continuous manufacturing platform, WuXiUP™, for a monoclonal antibody therapeutic at pilot scale[12]. The platform achieved an average daily productivity of 6 g/L/day during the 18-day production phase, resulting in a total volumetric productivity of 105 g/L over the 25-day continuous run. A key advantage of this integrated continuous setup is the ability to perform real-time downstream processing as product is generated, eliminating the need to wait until the end of a batch run, as is required in fed-batch processes. This not only shortens overall processing timelines but also enables more efficient facility utilization and faster time to release.

Perfusion using the XCell ATF System offers manufacturers flexibility in scaling because it can support scale-up, scale-out, or scale-on, (also referred to as scale-by-time, Figure 3). Each approach carries trade-offs regarding capital investment, facility build time, consumables, process complexity, and scalability. For example, scaling up using larger bioreactor vessels provide economies of scale but come with capital investment and facility build time considerations. Scaling out, by running multiple bioreactors in parallel, provides flexibility for multi-product manufacturing but increases operational complexity and consumable usage[11].

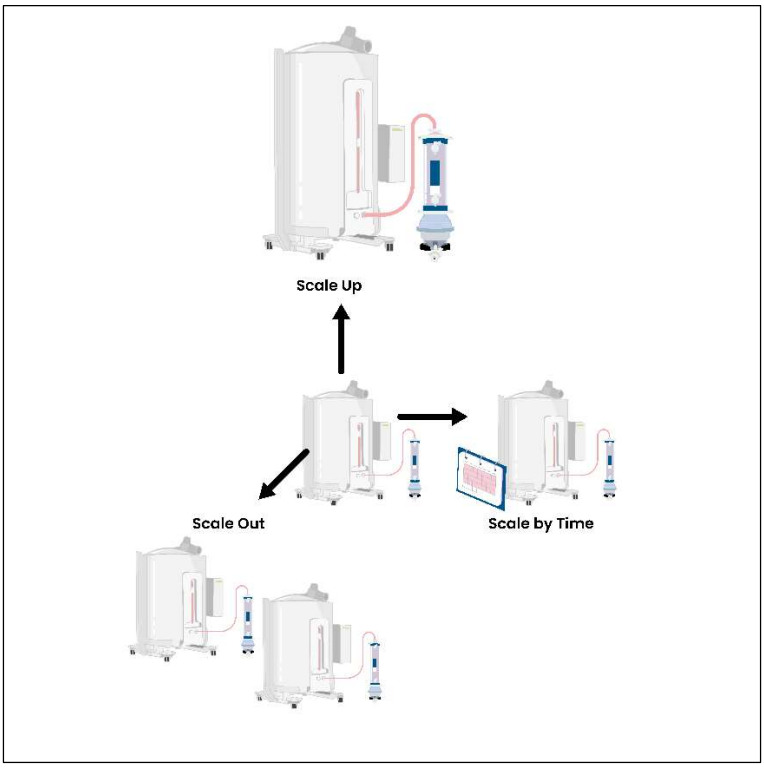

Figure 3: Scaling strategies for mAb production: Scale Up (increasing bioreactor size), Scale Out (increasing the number of bioreactors), and Scale on or Scale by Time (extending the duration of a run). Each approach comes with considerations for capital investment, facility build time, consumable cost, scalability from development to commercial stages, and process complexity.

Instead of adding larger bioreactors or additional infrastructure, manufacturers can use a scale-on approach, which is unique to perfusion processes, to increase output by extending the duration of a continuous run using existing bioreactors with cell retention

devices. The XCell ATF System is well suited for scale-on strategies, as its alternating tangential flow and low-shear cell retention technology support high cell viability and stable culture conditions over prolonged bioreactor runs. This makes extended campaigns feasible, enabling manufacturers to achieve higher productivity without compromising product quality. As a result, perfusion is well suited to meet fluctuating product demand scenarios without increasing capital and facility costs, enabling manufacturers to better meet the dynamic needs of today's therapeutic pipelines.

Making the Switch: Perceived Barriers to Implementation

For manufacturers accustomed to fed-batch operations, the prospect of switching to continuous manufacturing can raise questions around logistics and regulatory acceptance. While the transition from fed-batch does require upfront investment in equipment, facility modifications, and workforce training, these changes are supported by an increasingly well-defined path to implementation. Importantly, the long-term gains from improved volumetric productivity and improved facility utilization can offset initial costs to deliver significant cost savings over time.

One practical strategy is N-1 perfusion, where only the seed train (N-1 stage) is run in continuous mode to deliver a high-density inoculum to the production (N-stage) bioreactor. Because this approach leaves the N-stage fed-batch process unchanged, it offers a lower-risk and easily integrated entry point to continuous processing while still enabling meaningful gains in efficiency. The combination of implementation ease and productivity increase makes N-1 perfusion the most common starting point for upstream intensification with minimal process modifications and regulatory edits. Further improvements are possible by transitioning to a fully continuous processing scheme.

From a regulatory standpoint, the FDA and EMA have demonstrated strong support for continuous manufacturing strategies, recognizing their potential to improve product quality, consistency, and supply reliability. For example, the FDA Q13 Continuous Manufacturing of Drug Substances and Drug Products guidance outlines best practices for developing, implementing, and managing continuous processes throughout the product lifecycle[13]. Approved commercial products are produced using continuous processes, and the guidance document provides an example of a continuous process that integrates perfusion cell culture[14]. These examples demonstrate that there are no substantial regulatory hurdles to adopting continuous perfusion for commercial mAb production.

Conclusion

Fed-batch processes are giving way to process intensification strategies that improve productivity, efficiency, and sustainability. The theoretical cost analysis and real-world example outlined here support the adoption of continuous perfusion as a strategic investment for biomanufacturers seeking to intensify upstream operations, lower manufacturing costs, enhance production flexibility, and drive long-term value. The Repligen XCell ATF technology is a key enabler of this evolution, providing scalable and robust solutions that allow manufacturers to realize the full benefits of continuous perfusion bioprocessing.

Although perfusion processes may incur higher media and labor costs, these are offset by gains in volumetric productivity, reduced bioreactor volume, and fewer production runs required to achieve target outputs. This enables manufacturers to unlock capacity, maximize facility utilization, reduce COG, and accelerate time-to-market. At the same time, the approach supports industry sustainability goals by lowering carbon emissions and plastic waste. In real-world implementation, Enzene Biosciences achieved 10-fold higher productivity and 80% reduction in total production costs compared to traditional fed-batch processing. Building on this success, the company is now advancing EnzeneX 2.0, a continuous manufacturing platform capable of producing 10 – 15 kg of monoclonal antibody per month, within a 1,500 sq. ft. footprint, to drive even greater productivity and further reduce COG[10].

As biologics pipelines become increasingly complex and include a greater variety of therapeutic modalities, continuous perfusion offers a future-ready platform that delivers enhanced control, improved consistency, and higher product quality. The net result is measurable ROI, reducing upstream cost per gram while increasing efficiency, operational agility, and overall facility productivity, which enables manufacturers to better position themselves to meet future challenges and maintain competitiveness in the highly dynamic biopharmaceutical market.

To discuss how these economics apply to your upstream process, request a conversation with a Repligen technical specialist.

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