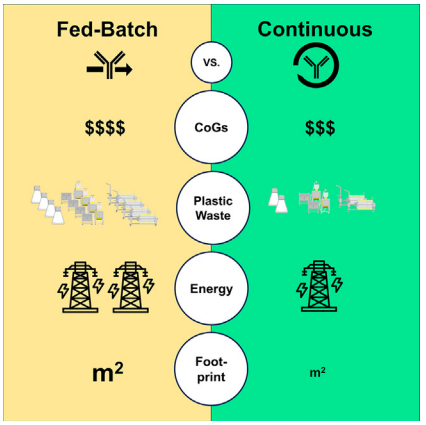
Trends in Biotechnology

Report

Advancing biopharmaceutical manufacturing: economic and sustainability assessment of end-to-end continuous production of monoclonal antibodies



The analysis in this report demonstrates that end-to-end continuous processing in a multiproduct monoclonal antibody (mAb) facility can reduce the cost of goods, plastic waste, and CO_2 emissions by up to 23%, 57%, and 54%, respectively. This could result in more equitable therapeutic access and reduce the ecological impact of mAb manufacturing.

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Highlights

Monoclonal antibodies (mAbs) have become key therapeutics to address various diseases and global healthcare needs.

The high cost of goods (CoGs) is the main barrier to universal access and equitable distribution of these therapeutics.

Sustainable production of biological products, including mAbs, is a key target for the pharmaceutical industry.

End-to-end continuous bioprocessing can significantly reduce the CoGs, increase manufacturing robustness, and reduce the ecological footprint of biopharmaceutical manufacturing of mAbs.

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Report

Advancing biopharmaceutical manufacturing: economic and sustainability assessment of end-to-end continuous production of monoclonal antibodies

Behnam Partopour [1,2,3,*] and David Pollard[1,2,3]

Monoclonal antibodies (mAbs) have become essential therapeutics for treating various diseases. The robust, cost-effective, and sustainable production of mAbs is crucial due to their growing clinical and commercial demand. Advances in bioprocessing, such as improved cell lines, perfusion bioreactors, multicolumn chromatography, and automation, can significantly increase productivity, making treatments more accessible. Streamlining the production process also aligns with environmental sustainability by reducing waste and energy consumption. This study quantifies the economic and environmental impacts of incorporating recent advances into end-to-end continuous bioprocessing of mAbs. The results demonstrate that, compared with an optimized best-in-class fed-batch process (with 15 g/l titer and multicolumn chromatography), continuous manufacturing can reduce the total annual production costs, facility footprint, plastic waste, and CO_2 emissions by up to 23%, 51%, 57%, and 54%, respectively, in a multiproduct facility producing clinical and commercial lots. Additionally, uncertainty analysis indicates that these gains are even more substantial under demand fluctuations.

Technology readiness

Technology platforms discussed in this report are available for implementation and utilization (Technology readiness level 8/9). However, moving industry toward adaptation is slow. There are two main challenges for full-scale implementation. First, manufacturers exhibit a cautious approach toward adopting emerging technologies, particularly in industries subject to stringent regulatory oversight. Second, the implementation of new technologies in a new facility necessitates significant capital investment. The analysis in this report highlights the significant economic and environmental impact of continuous processing and encourages manufacturers and regulatory agencies to move toward acceptance of this technology.

Introduction

The fast-growing landscape of biopharmaceutical manufacturing is marked by an ongoing pursuit of efficiency, sustainability, and quality. mAbs remain at the forefront of biological therapeutic innovation, necessitating the exploration of production methodologies that meet the increasing demand without compromising on these pillars of progress. More than 150 therapeutic mAbs have been approved globally by regulatory agencies [1,2]. As biopharmaceutical manufacturing evolves, a shift toward understanding and reducing production costs and footprint has emerged, achieving significant savings in operational expenses through process intensification and improved operational efficiency [3,4]. Currently, the industry is confronting new challenges, such as increased competition post-patent expiration, managing diverse and changing biologic portfolios, and expanding patient access globally [5]. These pressures have highlighted the need for greater manufacturing flexibility, sustainability, and cost reductions, while navigating a complex and dynamic market landscape [6]. Quantifying these improvements is essential to accelerate the advancement of processes and technologies, and to inform strategic decisions for the next generation of bioprocesses.

Continuous manufacturing is emerging as a key innovation in the biopharmaceutical sector, offering benefits such as reduced operational space, alongside enhanced product quality through improved process monitoring, which all translates into higher **productivity** (see Glossary) [7,8].

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Companies are gradually considering integrating these methods by using a hybrid approach, blending batch and continuous processes. This strategy has led to notable advances in both upstream and downstream processing, such as better cell expression, bioreactor control, and continuous techniques for product capture, purification, and formulation. These improvements, often utilizing **single-use (SU)** systems for efficiency and ease of operation, are paving the way for lower costs, minimization of human error, and consistently higher quality in biopharmaceutical production [3,7,9,10].

This study highlights the nuances of continuous mAb production within mixed-product facilities with clinical and commercial supply, delineating its economic viability, environmental implications, and operational adaptability compared with best-in-class fed-batch processing.

This report performs a rigorous economic efficiency assessment to evaluate the cost-effectiveness of continuous processing in mAb production. This critical analysis encompasses capital investment, operational expenses, and the overarching annual costs, providing a comprehensive economic perspective. The investigation extends to sustainability, scrutinizing the impact of continuous processing on energy consumption, waste generation, and resource utilization. Through this assessment, we endeavor to quantify its environmental footprint, thereby projecting the environmental alignment of this method with global sustainability goals. Further inquiry into process optimization for mixed-product facilities probes the adaptability and flexibility of continuous processing. Factors, such as changeover times and the operational intricacies of handling multiple product lines within single facilities, are examined. Scalability and adaptation are pivotal; thus, the scalability of continuous processing for varying production volumes and its integration potential into existing manufacturing frameworks are thoroughly assessed. The robustness of continuous processes is examined to understand the risks and uncertainties inherent in mAb production, especially within the complex environment of mixed-product facilities due to variance in therapeutic product demand.

This research report, assembled by an interdisciplinary team of experts from Sartorius and Just-Evotec Biologics, leverages extensive knowledge in continuous biomanufacturing. Through this exploration, we provide a data-driven foundation for policy and decision-making, augment process reliability, enhance risk management, and fortify industry confidence in continuous processing methods amid the complex challenges of biopharmaceutical production.

Three important features distinguish this report from previous studies. First, this study focuses on comparing current best-in-class technologies (i.e., SU intensified fed-batch processes with 15 g/l **titer**) with SU end-to-end continuous processing at 3–5 g/l/day productivity. Detailed comparisons between standard fed-batch processes in SU and stainless steel (SS) facilities can be found in previous publications [3,7], which quantified the advantages of SU systems (Table S1 in the supplemental information online). Furthermore, the most common current 10-kl or 15-kl SS bioreactors will not be optimal for high titers and a wide range of throughputs in a single mixed-product facility (3–750 kg demand range for each product). The results of these studies demonstrate that there will continue to be a shift from these traditional large production trains toward smaller and more robust SU technologies.

Second, we evaluate sustainability metrics, such as CO_2 emissions, plastic waste, and facility footprint, of the processes. Finally, unlike traditional four- or six-pack facilities with fixed bioreactor volumes, we investigate facilities with mixed production lines (e.g., 2 × 1000 l plus 1 × 500 l and 1 × 200 l production trains). With an increase in the number of approved therapeutic mAbs, a flexible facility with a range of production volumes will be required, from a few kilograms of products for

Glossary

Alternating tangential flow filter (ATF): cell separation technology that alternates the direction of fluid flow across a filter to enhance filtration efficiency.
Multicolumn: continuous processing technique in chromatography where multiple columns operate in parallel or sequentially to improve the efficiency and yield of capture and purification unit operations.
Multiproduct facility: biopharmaceutical manufacturing factory where multiple mAb products with different annual demands are produced.
Operating costs (OPEX): operating costs including, but not limited to, consumables, materials, reagents, labor, and utilities.
Perfusion bioreactor: continuous cell culture system where fresh media is constantly provided and waste and products are constantly removed, allowing for high cell density and extended culture duration.
Single-use (SU): disposable bioprocessing consumables, such as bags and filters designed for one-time use, reducing the need for cleaning, sterilization, and contamination risks in manufacturing processes.
Productivity: concentration of the product in the volume of the bioreactor (liter) per day (g/l/day).
Titer: final concentration of product (mAbs) in the bioreactor (g/l).
Total capital investments (CAPEX): capital investments including, but not limited to, design, construction, installation, equipment, automation, piping, and other initial investment costs.
Yield: percentage of the amount of product recovered in each unit operation compared with the amount of the product entered.

rare autoimmune diseases to several hundred kilograms for common infectious diseases. Such a range of production volumes for different products is difficult to support with large four- or six-pack SS bioreactors; thus, large SS platforms are not included in this report.

Our internal data points support all the input used for this study unless other publications are cited. The input values (titers, **yields**, etc.) are based on the most optimized processes available. Owing to the proprietary nature of the information, detailed process descriptions, such as flowrates, individual step configurations, price, and so on, are not reported here.

Results

Process descriptions

Figure 1 illustrates three different process configurations for biopharmaceutical production: standard fed-batch, intensified and optimized fed-batch (IO-FB), and end-to-end continuous processes, each with their respective stages from seed train to cryo-storage.

In configuration A, the standard fed-batch process is listed as the reference process. It begins with a seed train that includes vial thaw, two subsequent 3-day cell culture phases, and a final 3-day batch culture. Following this, the production bioreactor operates for 9.5 days and reaches 6 g/l titer. The downstream process (DSP) includes a single-column capture, viral inactivation in the mixing tank, polishing through single-column chromatography, viral filtration, and, finally, ultrafiltration/diafiltration (UF/DF) before the product is transferred to cryo-storage. The overall yield of this process is 67%. This means that 67% of mAbs produced in the bioreactor are recovered as drug substance after the purification steps.

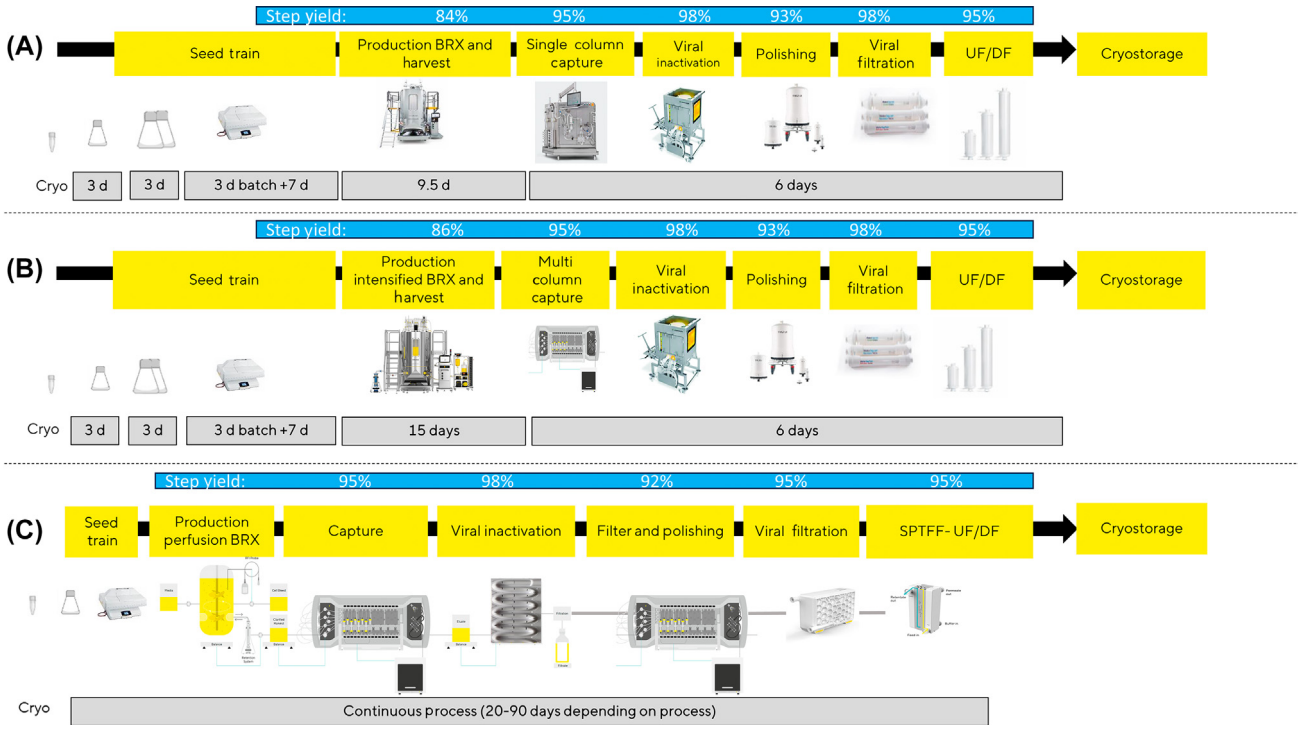

Figure 1. Fed-batch and continuous process descriptions. (A) Standard fed-batch with 6 g/l and 67% downstream process (DSP) recovery. (B) Intensified optimized fed-batch (IO-FB) process with 15 g/l and 70% DSP recovery. (C) Continuous process with 3–5 g/l/day and 75% DSP recovery. Abbreviations: BRX, bioreactor; DF, diafiltration; SPTFF, single-pass tangential flow filtration; UF, ultrafiltration.

Configuration B is an IO-FB process that is equipped with an **alternating tangential flow filter (ATF)** module. The intensified bioreactor runs for 15 days and yields 15 g/l product. Downstream processing includes **multicolumn** capture, which enhances purification efficiency at such high titers and allows higher resin utilization, followed by the usual steps of viral inactivation in the mixing tank, single-column polishing, viral filtration, and UF/DF, leading up to cryo-storage, all in batch mode. The overall yield of this process is 70%, representing a meaningful advantage over the standard fed-batch process.

The third configuration, C, represents a continuous process, which streamlines production by integrating a **perfusion bioreactor** that can operate for 20–90 days, depending on the specifics of the process. Independent of operation duration, the first 7 days are considered initial growth days. The capture phase is conducted in a multicolumn format. The number of columns can vary based on operation duration for better resin utilization up to a maximum number of cycles. The captured product is fed into a plug flow viral inactivation system followed by another multicolumn chromatography skid that hosts both polishing steps. The continuous nature of this process is highlighted using a single-pass tangential flow filtration (SPTFF) for UF/DF, before the product proceeds to cryo-storage. The overall yield of this process is 75% due to the high efficiency of the continuous DSP platform. This is a conservative estimate and higher yields for a continuous DSP process are achievable.

These configurations illustrate the evolution from traditional batch to state-of-the-art continuous processes, each with trade-offs in terms of complexity, duration, and, potentially, efficiency. In most industries, continuous processes (Figure 1C) are often preferred for their operational efficiencies and more consistent product quality. However, biopharmaceutical manufacturing has not yet fully adopted this technology, and standard- and intensified fed-batch processes remain ubiquitous.

Individual process train case studies

Figure 2A provides a cost analysis for different scales of mAb biopharmaceutical production, represented as cost per gram of annual production throughput (kg/year). Four different production scenarios are plotted against their associated costs, illustrating how economies of scale impact the cost-efficiency of bioproduction processes (Figure 2A). A standard fed-batch process with 6 g/l titer is compared with a 3 g/l/day continuous process as the benchmark for the rest of the analysis.

The simulation assumptions consider all relevant factors contributing to cost of goods (CoGs), including equipment, materials, consumables, and media for both IO-FB and continuous processes. However, it does not include facility-associated costs and labor, and focuses solely on process-only attributes. The number of employees and labor costs vary significantly among facilities, even for a given process, and can introduce significant noise into the calculations. This hinders the impact of core cost attributes in the context of this study.

The gray line in Figure 2A represents a 2000-l bioreactor operating in fed-batch mode with varying degrees of utilization, showcasing how cost efficiency improves with increased throughput and utilization. This trend is also observed by colored lines corresponding to a 500-l continuous bioreactor system at different run durations (30, 60, and 90 days) and utilization rates. Notably, the 500-l bioreactor operating continuously over longer durations (especially 60 and 90 days) shows a pronounced decrease in CoGs, indicating that longer duration runs at a medium scale can substantially drive down the cost per gram of protein produced.

Figure 2A also introduces break-even points for three production scales: 33 kg/year, 66 kg/year, and 150 kg/year. Each of these points corresponds to the capacity where the continuous

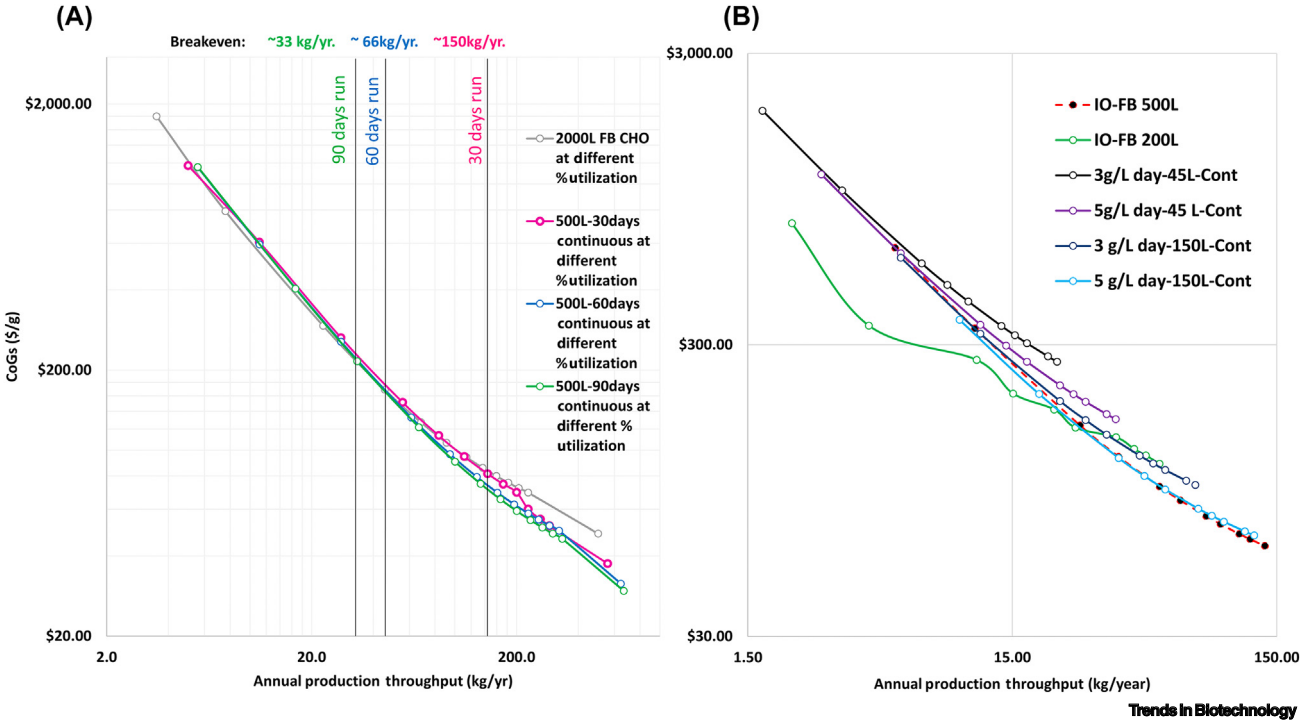

Figure 2. Impact of scale and technology on cost of goods (CoGs). (A) Comparison of a single 500-l continuous (Cont) process and 2000-l standard fed-batch (FB) process for small-scale production. (B) Comparison of a single 50-l or 200-l continuous process and 200-l or 500-l intensified optimized FB (IO-FB) process for small-scale production. In each graph, breakeven points represent the production volume for which the cost of goods becomes similar. CoGs correspond to process only and do not include labor.

process becomes more cost-effective compared with the fed-batch process. In general, batch processes are more cost-effective at lower production volumes. This is mainly due to higher capital investment in process equipment and automation for continuous processes at this specific scale.

Overall, the data suggest that optimizing run duration and bioreactor utilization is critical for achieving cost savings in protein production. Figure 2A provides a clear visual interpretation of how strategic operational decisions can influence production economics, particularly highlighting the advantages of continuous processing as plant capacity and utilization increase. Above a 150 kg/year capacity (regardless of production duration and utilization), continuous process becomes the cost-effective option.

Figure 2B presents a detailed analysis of the CoGs for mAb production on a scale <150 kg/year, comparing IO-FB processes with continuous bioprocessing methods, with a focus on the relationship between CoGs and throughput for small-scale mAb production. It shows various scenarios, including different yields for both fed-batch and continuous processes, juxtaposed against their respective costs. The assumptions made for this model exclude any facility-associated costs, allowing for a clear focus on process-specific expenses.

Two distinct fed-batch processes are considered: both with an ATF and a yield of 15 g/l in 15 days, but different bioreactor volumes of 200 l and 500 l. By contrast, the continuous process is based upon 50-l and 200-l bioreactors (working at 45 l and 150 l), with yields of 3 g/l/day and 5 g/l/day at a two-vessel volume per day (VVD) perfusion rate and 30-day run.

The results highlight that, for small-scale production volumes of 20–40 kg/year, both IO-FB and continuous processing methods have similar CoGs. However, when production volumes are <20 kg/year, the 200-l IO-FB becomes more economical due to lower equipment and operational expenditure. Advantages of continuous processing, such as the need for smaller equipment and reduced resin needs, are included but are not the primary cost drivers at this scale of production. At throughputs of 40–130 kg/year, IO-FB and 5 g/l/day continuous processes have similar CoGs even in small-volume bioreactors.

To summarize, the results in Figure 2B indicate that, when the annual production volume for an entire process is <130 kg/year, the IO-FB process with 15 g/l titer and a 30-day continuous process at 5 g/l/day productivity are very competitive, while IO-FB is favorable for <20 kg/year.

Figure 3 compares the CoGs for medium-scale protein production, contrasting IO-FB processes with fully continuous processes. It depicts CoGs against annual throughput (kg/year) at different plant utilization rates, providing a visual representation of costs across different production scales and methods. The IO-FB processes evaluated include those with ATF at 15 g/l in 15 days, and a working volume (WV) of 2000 l. Since the maximum capacity of a 1 × 2000-l bioreactor for this configuration is only 410 kg, an additional scenario of a 2 × 2000-l bioreactor was considered to cover the complete throughput range of interest. For continuous processes, perfusion bioreactors at scales of 500 l and 1000 l, with yields of 3 g/l/day and 5 g/l/day, and 30-, 60-, and 90-day runs were investigated.

For lower throughputs <200 kg/year, continuous processing costs are similar to IO-FB, which mirrors the findings for small-scale models. However, 60- and 90-day continuous runs consistently outperform IO-FB regarding CoGs. Furthermore, Figure 3 shows that fully continuous processes, particularly at the 1000-l scale with a 5 g/l/day yield over 60 days, offer substantial cost savings, especially >350 kg/year.

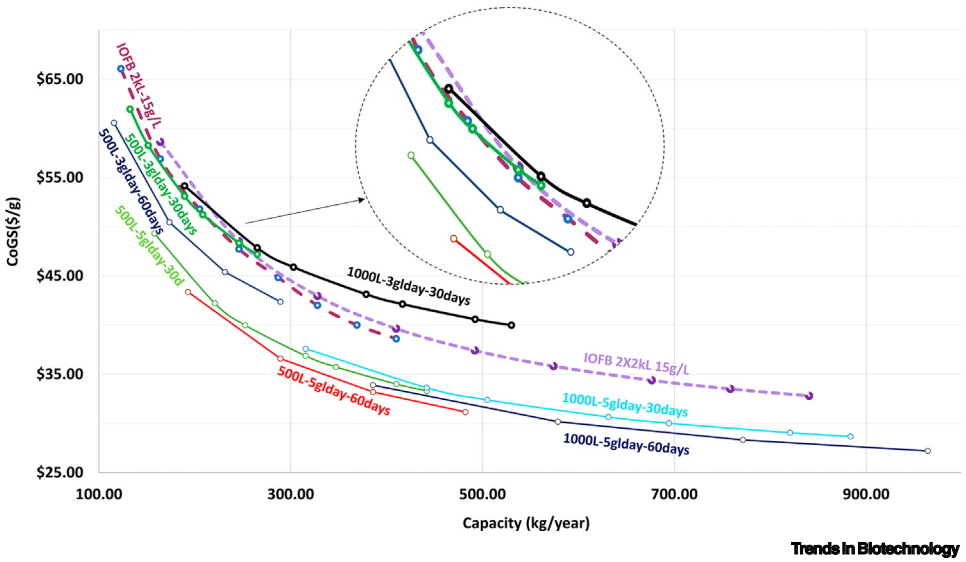

Figure 3. Cost of goods (CoGs) versus scale for large-scale monoclonal antibody (mAb) production. Comparison of single-line processes at different working volumes, productivity, and production duration for continuous and intensified optimized fed-batch (IO-FB) processes. The continuous process with 5 g/l/day productivity has the lowest costs for annual throughputs >160 kg. Unlike Figure 2 in the main text, all analyses are for 500-l and higher bioreactor working volumes. CoGs correspond to process only and do not include labor.

For a given productivity and process duration, large WVs are associated with higher costs under the same capacity (areas of overlap in Figure 3). This is due to higher overall utilization of the smaller scale system.

As the throughput increases, the benefits of continuous processing become more pronounced, indicating a trend where the economies of scale begin to favor the fully continuous methods over IO-FB for medium-scale mAb production. The results underscore the potential economic efficiencies that can be realized through the adoption of continuous bioprocessing at this scale. The main advantages of continuous processes over IO-FB become significant for longer process durations (>30 days) and 5 g/l/day productivity.

Mixed-product facility case study

The analysis, to this point, included direct process costs for a single production line (or train). Next, we investigated a facility for the biomanufacturing of multiple products with various throughputs at different clinical stages. The products of this facility were classified into three main categories: (i) clinical candidates for first-in-human (FIH) clinical studies: throughput range (3–10 kg); (ii) 12 candidates for Phase 2 and 3 clinical studies: throughput range (10–50 kg); and (iii) three commercial drug substances: throughput range (250–750 kg).

Based on our calculations, an IO-FB **multiproduct facility** that can process these products at given capacities at 90% utilization includes 1 × 200-l, 1 × 500-l, and 2 × 2000-l bioreactors to cover the low range, or 1 × 500-l, 1 × 1000-l, and 4 × 2000-l for the high range, all running at 15 g/l and 15 days per batch. By contrast, for a continuous process, 1 × 100-l, 1 × 200-l, and 1 × 1000-l bioreactors are required to cover the low range, or 1 × 500-l, 1 × 1000-l, and 1 × 2000-l bioreactors for the high range, all running at 5 g/l/day but for different durations (Table S2 in the supplemental information online). Each facility includes three designated lines for different production scales and each bioreactor has its own DSP trains. Further optimization for integrating multiple DSP trains could be carried out, but is out of the scope of this study.

Operating costs (OPEX) for the IO-FB are, on average, 8% more than for continuous processing. The large number of batches required to process the target products and the higher turnover results in more consumables for the IO-FB process, while a continuous process can run for longer durations without the frequent need to change most of the consumables.

Equipment costs are 9–28% higher for the IO-FB process, mainly due to requirements for a greater quantity of larger equipment (e.g., bioreactors). This also translates into process area calculations. Process area is calculated by factoring each equipment footprint as a percentage of total floor area. A smaller equipment footprint means less equipment is required for bioprocessing area, a 3–51% reduction. **Total capital investments (CAPEX)** are calculated by integrating equipment costs with overall facility costs (e.g., building, installation, cost of work, automation, etc.). The total upfront investment for the IO-FB process is 15–38% more than for the continuous process.

The total annual cost is calculated by the given OPEX and CAPEX, assuming a 15% capital charge and 8 years overall facility life span (constant for both IO-FB and continuous). The total annual cost represents the cumulative impact of all the other parameters mentioned earlier and is, on average, 12–23% higher for the IO-FB process compared with the continuous process.

The main reasons for the reduced costs of continuous processing are: their smaller unit operations and footprint; the longer duration of the process, which results in less changeover of SU consumables; and the higher overall process yield.

A more dramatic difference can be observed for the environmental metrics. Total kilograms of CO_2 and plastic were calculated for each line and then normalized based on total facility throughput (kg/kg). The continuous process, on average, produces 57% less plastic waste compared with IO-FB. The size and number of plastic bags used for IO-FB are major contributors to this difference. The higher number of batches required for IO-FB processes and the larger size of equipment both impact the size and number of plastic bag assemblies.

Furthermore, the continuous process, on average, has 54% lower CO_2 emissions compared with the IO-FB process. The electrical supply and building heating, ventilation, and air conditioning (HVAC) are the two main contributors to the CO_2 emissions of any facility. For continuous processes, smaller equipment size and a smaller facility footprint mean lower energy requirements for the process and building, and, therefore, a significant reduction in CO_2 emissions. These values can change dramatically based on the location of the facility and its sources of energy.

Uncertainty assessment for the mixed-product facility

A deterministic assessment of the mixed-product facilities based on lower and higher capacities shows significant leverage for continuous facilities based on the annual costs and environmental footprint. However, a facility rarely operates at up to 90% capacity. Many factors, such as drug withdrawals, new therapeutics, changes in patient population, supply change issues, and pandemics, can significantly impact the facility operations. Monte Carlo simulations with 100 000 different utilization scenarios over the lifespan of the facility can depict a more realistic picture of the uncertainties involved in the biomanufacturing of mAbs and the potential impact of continuous processing.

The product demand profile uncertainty curve utilized by Walther and colleagues [5] was used here to investigate the impact of 100 000 randomly generated scenarios on the annual cost difference between the two technologies. The curve suggests that actual demand has a 70% chance of matching the projection. There is a 15% chance of a 50% increase in demand and a 15% chance of a 20% reduction in demand. A continuous approximation of mixed normal distributions was used for the simulation. The mixture model combines different normal distributions weighted by their probabilities to form a continuous probability distribution.

The optimized facilities for the high-range capacity in Table 1 were used as the basis of the uncertainty analysis. In Table 1, low and high-range columns correspond to ranges reported for

Table 1. Multiproduct facility simulations for continuous and IO-FB processes

Feature	Continuous facility		IO–FB facility		Relative difference (IO–FB–continuous)/(IO–FB)	
	Low range	High range	Low range	High range	Low range	High range
OPEX (US$M)	32	58	34	63	8%	8%
Equipment (US$M)	36	51	40	71	9%	28%
Process area (m^2)	1020	1090	1472	2222	31%	51%
Total facility costs (US$M)	122	131	147	222	17%	41%
Total CAPEX (US$M)	159	182	187	293	15%	38%
Total annual cost (US$M)	67	99	76	128	12%	23%
Annual capacity (kg/year)	915.9	2136	898	2042	–2%	–5%
Estimated average annual process plastic waste (kg/kg mAb)	16		36.8		57%	
Estimated average process CO_2 emission (kg/kg mAb)	1414		3096		54%	

configurations A–C. The relative difference describes the percentage change moving from a continuous to fed-batch process. All the associated costs, such as OPEX and CAPEX, increase. Even greater differences are observed in the amount of plastic waste and CO_2 emissions.

The results when demand deviates from specific utilization (for which the facilities were designed and optimized) in Table 1 suggest that the continuous process becomes even more cost-effective than IO-FB. The cost difference depicted in Figure 4 suggests that, under uncertainty, the annual cost savings of the continuous process can be up to US$50 million, whereas, in the deterministic model, the annual cost difference was projected to be US$29 million (under the optimal utilization rate for both platforms). This indicates that the continuous platform is more robust under uncertainty. The main contributor here is the flexibility of the continuous process during each run. The production capacity for a fixed bioreactor volume for one batch can easily be adjusted by changing the duration of a run without turnovers. However, this capacity for the IO-FB process is fixed and, in some scenarios, extra lines need to be added to the IO-FB facility to meet the demand.

Discussion

Batch processes involve discrete steps, which can introduce variability due to changes during each batch. However, in continuous bioprocessing, the reactor operates continuously, leading to a more homogeneous output. This consistency minimizes variations in product quality and reduces the probability of out-of-specification drug substances. Within a continuous manufacturing platform, real-time monitoring allows for early defect detection, whereas, in batch processing, defects may not be identified until the entire batch is completed, making it harder to maintain consistent quality. Batch processes, while less demanding in terms of control, are more reliant on

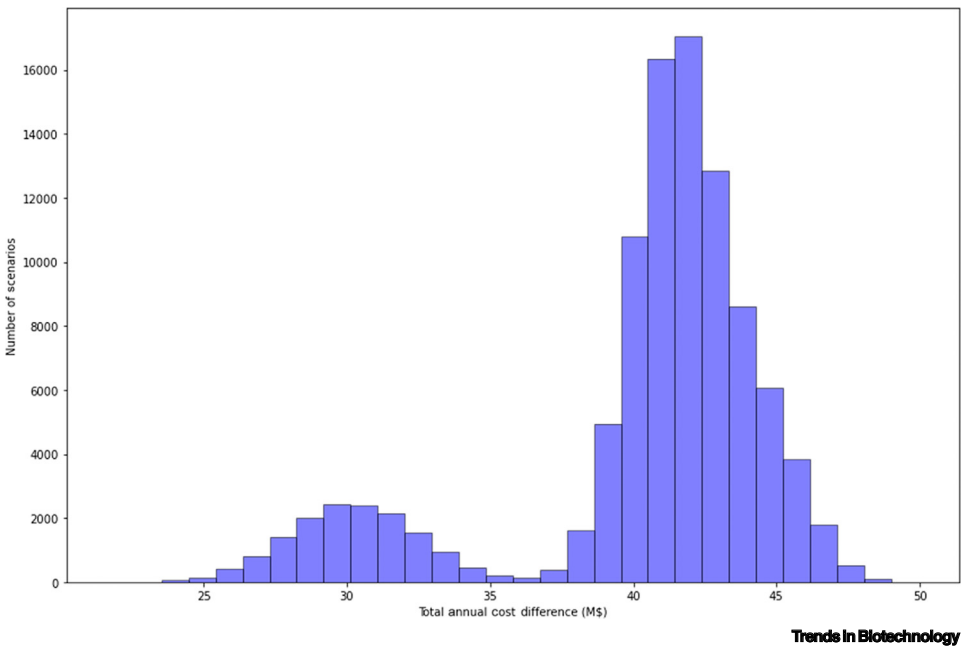

Figure 4. Uncertainty in annual costs. The distribution of annual cost difference for the two processes is based on the Monte Carlo simulation of 100 000 scenarios where annual demand could change based on the given distribution. The graph depicts the frequency and range of cost savings for the randomly generated scenarios. The results suggest that, in the real world with demand uncertainties, the annual cost savings of an end-to-end continuous process, due to flexible run duration, can be up to US$49 million. This is significantly more than the US$29 million estimated based on the ideal facility utilization assumption reported in Table 1 in the main text.

operators and, therefore, are more susceptible to operator error. Perhaps most importantly, continuous bioprocessing requires more automation and robust controls. Overarching control strategies of the complete drug substance production are implemented to control the flows and methods of each of the integrated unit operations [11]. This is supported by process analytical technology (PAT) tools, such as capacitance-triggered start-up of protein capture when perfusion reaches the required cell density [12], automated multicolumn switchover using actual antibody titers from an inline sensor [12], and Raman-triggered clearance of host cell proteins (HCPs) from flow-through chromatography [13]. In the coming years, these controls will be expanded with the application of hybrid mechanistic-model process-control algorithms that can enable self-correcting processes within a particular design space, such as real-time aggregate control at anion exchange from a short pH excursion during viral inactivation. Ultimately, overarching control can enable responsive supply-on-demand strategies, whereby purification method flow rates are automatically adjusted upon changing perfusion flow rates to respond to daily changing drug substance requests [11].

Concluding remarks

Currently, an increasing number of approved therapeutic mAbs, uncertainty in the global supply chain and demand, geopolitical considerations, and environmental concerns are the main challenges in biopharmaceutical manufacturing. This report shows that the continuous manufacturing platform has clear advantages in addressing these issues. The reported reductions in capital investment and annual costs reduce existing risks for biopharmaceutical manufacturers and would eventually result in a reduced cost of the therapeutics.

Flexibility in batch duration for the continuous platform enables a robust response to the uncertainties in supply chain and demand trends. Lower overall costs also reduce the impact of uncertainties from market fluctuations (e.g., biosimilars and withdrawals).

More compact facilities and higher process efficiency significantly reduce the environmental impact of biopharmaceutical manufacturing. The reported reduction in CO_2 emissions and plastic wastes (54% and 57%, respectively) aligns with the sustainability goals of every major biopharmaceutical manufacturer and most governments around the world, and elevates global health. Reduced footprint and initial investment also enable decentralized manufacturing concepts to address the unmet needs in low-income countries.

With significant increases in bioreactor productivity and process intensification, the DSP has become the main cost driver. To further reduce costs, prioritizing higher protein capture capacities, either through increased resin capacity or alternative methods, such as precipitation, is essential. Additionally, more efficient use of buffers and media is necessary to reduce water consumption. Implementing in-line buffer stock blending can significantly cut down on water and plastic waste [14]. Finally, the significant ongoing research and development work in continuous manufacturing would only elevate the importance and impact of this platform (see Outstanding questions).

Outstanding questions

Can all new mAbs be produced in continuous mode?

How would autonomous control transform continuous processing and the associated labor and facility costs?

What will it take for manufacturers with legacy fed-batch facilities to transition to continuous processes?

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- METHOD DETAILS
  - Cost analysis
  - Sustainability calculations
  - Uncertainty calculations

- RESOURCE AVAILABILITY
  - Lead contact
  - Material availability
  - Data and code availability

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Declaration of interests

Sartorius is a global biopharmaceutical technology provider, active in both fed-batch and continuous bioprocessing technologies.

Supplemental information

Supplemental information to this article can be found online at https://doi.org/10.1016/j.tibtech.2024.10.007.

References

1. Lyu, X. *et al.* (2022) The global landscape of approved antibody therapies. *Antibody Ther.* 5, 233–257
2. Walsh, G. and Walsh, E. (2022) Biopharmaceutical benchmarks 2022. *Nat. Biotechnol.* 40, 1722–1760
3. Pollard, D. *et al.* (2016) Standardized economic cost modeling for next-generation MAb production. *BioProcess Int.* 14–23
4. Yang, O. *et al.* (2020) Economic analysis of batch and continuous biopharmaceutical antibody production: a review. *J. Pharm. Innov.* 15, 182–200
5. Walther, J. *et al.* (2015) The business impact of an integrated continuous biomanufacturing platform for recombinant protein production. *J. Biotechnol.* 213, 3–12
6. Coffman, J. *et al.* (2021) A common framework for integrated and continuous biomanufacturing. *Biotechnol. Bioeng.* 118, 1735–1749
7. Garci, F.A. and Gefroh, E. (2023) Reducing biopharmaceutical manufacturing costs through continuous processing in a flexible J. POD facility. *Drug Discov. Today*, 103619
8. Mahal, H. *et al.* (2021) End-to-end continuous bioprocessing: impact on facility design, cost of goods, and cost of development for monoclonal antibodies. *Biotechnol. Bioeng.* 118, 3468–3485
9. Levine, H.L. *et al.* (2012) Efficient, flexible facilities for the 21st century. *BioProcess Int.* 10, 20–30
10. Coffman, J. *et al.* (2021) The design basis for the integrated and continuous biomanufacturing framework. *Biotechnol. Bioeng.* 118, 3323–3333
11. Pollard, D.J. *et al.* (2017) Progress toward automated single-use continuous monoclonal antibody manufacturing via the protein refinery operations lab. In *Continuous Biomanufacturing-Innovative Technologies and Methods* (Subramanian, G., ed.), pp. 107–130, Wiley
12. Kruse, T. *et al.* (2023) Advanced control strategies for continuous capture of monoclonal antibodies based upon biolayer interferometry. *Biotechnol. Bioeng.* 121, 771–783
13. Chen, J. *et al.* (2024) Application of Raman spectroscopy during pharmaceutical process development for determination of critical quality attributes in Protein A chromatography. *J. Chrom. A* 1718, 464721
14. Gibson, K. *et al.* (2023) Evaluation of the impact of buffer management strategies on biopharmaceutical manufacturing process mass intensity. *Processes* 8, 2242

STAR★METHODS

KEY RESOURCES TABLE

Software and algorithms	Company	Source
BioSolve version 9	BioPharm Services	https://biopharmservices.com/
Anaconda3	Continuum Analytics	www.anaconda.com/download

METHOD DETAILS

Cost analysis

The entire deterministic cost analysis is carried out within BioSolve Software (version 9). Detailed process descriptions were provided as input to the software by the authors. Critical input parameters for these calculations are

(i) Bioreactor productivity
(ii) Individual unit operations yield, sizing, and duration
(iii) Bill of material
(iv) Facility, utilities, and solution management descriptions
(v) Capital investment assumptions (e.g., inflation rate, interest rate, etc.)
(vi) Cost data for equipment, consumables, materials and reagents, labor, and construction.

Sustainability calculations

The sustainability calculations are based on a 'greenfield facility' located in the northeast of the USA. The equivalent CO_2 emission is derived from facility energy consumption. Providing the utility and equipment energy requirements for each unit operation, HVAC energy requirements (based on fan efficiency, area classification, and footprint), facility lighting, and geographical information, overall energy requirement was estimated. The equivalent CO_2 emission per kWh of US energy generation was estimated using publicly available reports from the US Department of Energy (DoE) and the US Environmental Protection Agency (https://www.epa.gov/energy/greenhouse-gases-equivalencies-calculator-calculations-and-references). All these values can be provided as inputs in the 'Facility' sheet of BioSolve software. Based on the process description, annual production volume, and facility-related user input values, the software will calculate the annual energy requirement and equivalent CO_2 emissions. Furthermore, the amount of plastic waste is calculated based on the Bill of Material, estimated weight (kg) of single-use consumables, and number of batches per year.

Uncertainty calculations

To calculate the probability distribution for the demand fluctuation scenario described in the text a continuous approximation of mixed normal distributions was used. Therefore, we created a mixture model that combines different normal distributions weighted by their probabilities. This includes the following steps:

1. Define the normal distributions for each scenario:
   (i) Scenario 1: Actual demand matches the projection.
   (ii) Scenario 2: 50% increase in demand.
   (iii) Scenario 3: 20% reduction in demand.
2. Assign probabilities to each scenario:
   (i) Scenario 1: Probability = 70% (0.7).
   (ii) Scenario 2: Probability = 15% (0.15).
   (iii) Scenario 3: Probability = 15% (0.15).

3. Combine these distributions into a mixed normal distribution:

The probability density function (PDF) of the mixed normal distribution is a weighted sum of the individual PDFs, where each PDF is:

$$f_1(x) = \frac{1}{\sqrt{2\pi\sigma}} \exp\left(-\frac{(x-\mu)^2}{2\sigma^2}\right) \quad [1]$$

$$f_2(x) = \frac{1}{\sqrt{2\pi\sigma}} \exp\left(-\frac{(x-1.5\mu)^2}{2\sigma^2}\right) \quad [2]$$

$$f_3(x) = \frac{1}{\sqrt{2\pi\sigma}} \exp\left(-\frac{(x-0.8\mu)^2}{2\sigma^2}\right) \quad [3]$$

Then a continuous approximation of demand probability will be:

$$f(x) = 0.7f_1(x) + 0.15f_2(x) + 0.15f_3(x) \quad [4]$$

Deducting the results of the Monte Carlo simulations based on this probability distribution for continuous and IO-FB platforms would result in the presented bi-modal distribution.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Behnam Partopour (Behnam.partopour@sartorius.com).

Material availability

This study did not generate new unique reagents.

Data and code availability

The underlying data cannot be deposited in a public repository due to confidentiality. This paper does not report original code. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.