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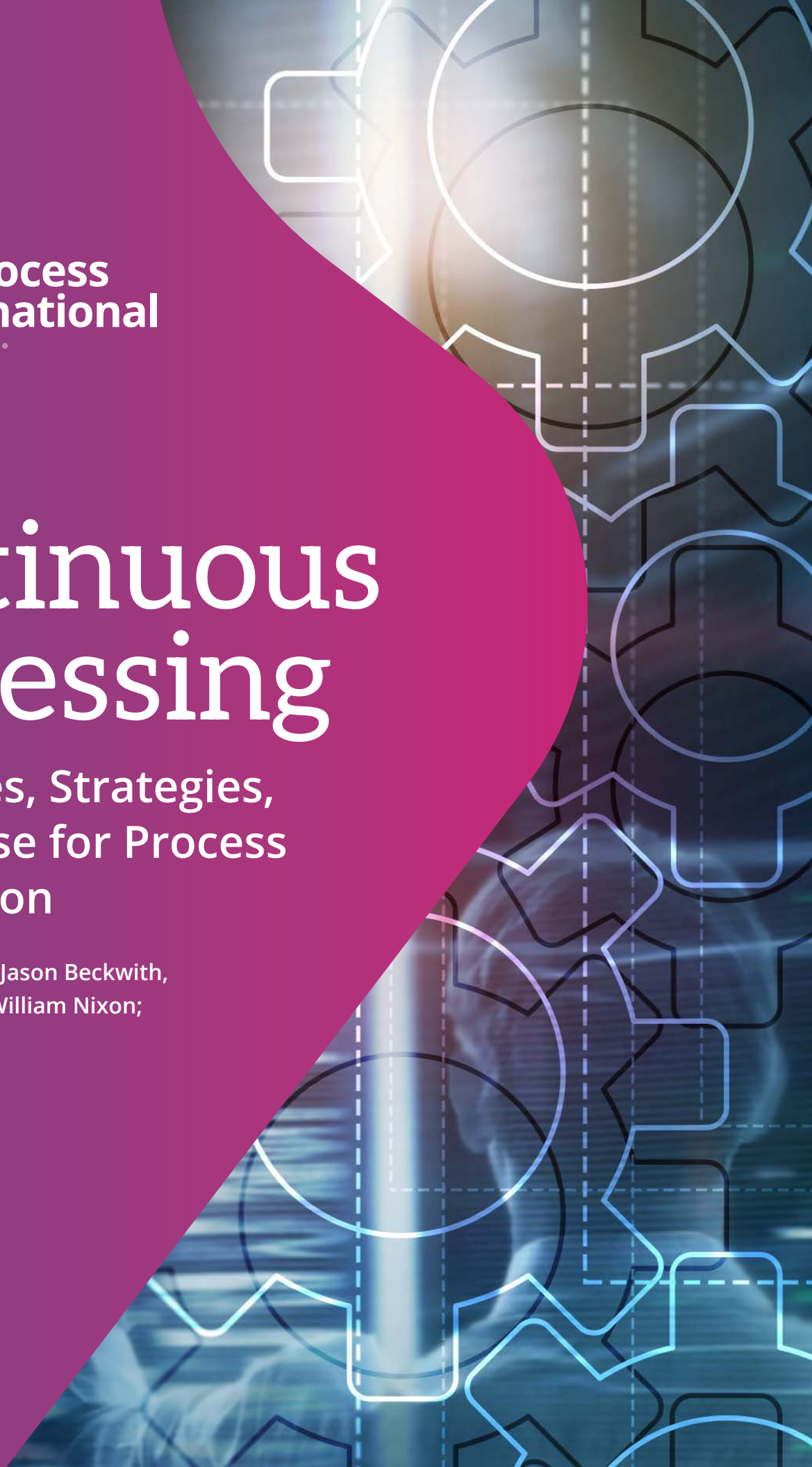
Technologies, Strategies, and Expertise for Process Intensification

by Renaud Jacquemart; Jason Beckwith, Stephen Goldrick, and William Nixon; and Charles Heise



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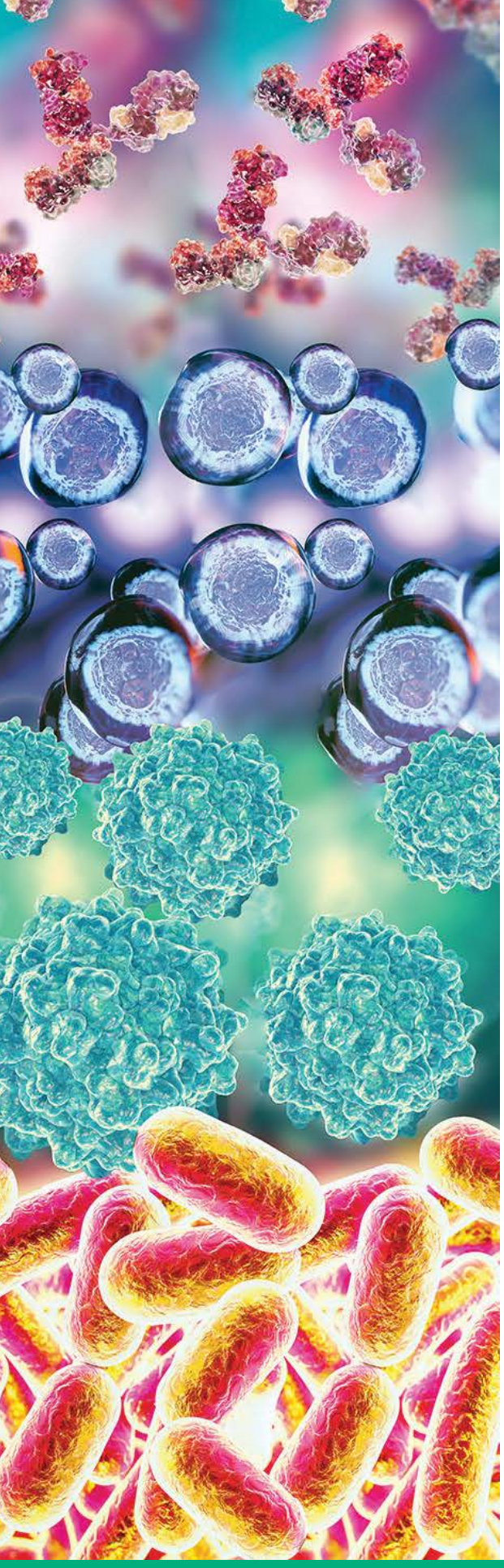
The biopharmaceutical industry is transitioning from experimental exploration to selective integration of continuous processing. Enabling technologies include perfusion bioreactors, continuous chromatography, and single-use platforms supported by advanced automation and real-time monitoring. However, workforce realities lag behind technological advances. Current challenges include managing tightly coupled operations, decision bottlenecks, and knowledge concentration. The industry is recognizing that sustainable intensification depends equally on technical capability and organizational readiness.



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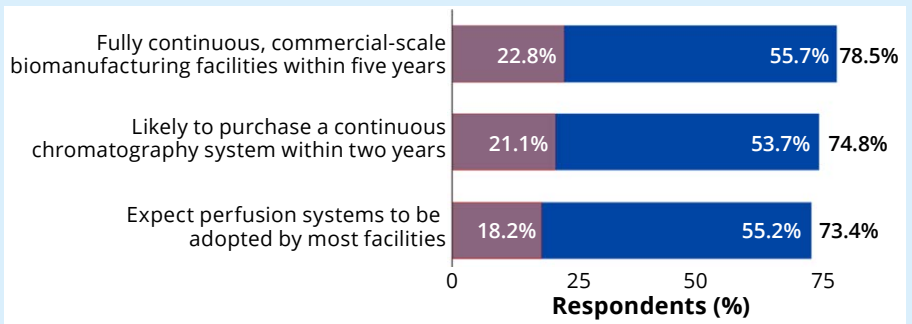
Continuous Bioprocessing for the Future

Enabling Factors and Driving Forces Across Biologic Modalities

Renaud Jacquemart

For over a decade, continuous bioprocessing (CBP) has been described as the future of biomanufacturing. In fact, 78.5% of respondents in the 22nd annual report on biopharmaceutical manufacturing capacity from BioPlan Associates said that the "industry will see fully continuous commercial-scale manufacturing facilities within 5 years" (**1**).

Figure 1: Future of continuous bioprocessing (**1**); percentage of survey respondents agreeing (blue) or strongly agreeing (gray)



CBP has been used at some level in the biopharmaceutical industry for decades, so it is no longer viewed as experimental. Figure 1 illustrates our data showing that over a third of all bioprocess facilities surveyed are evaluating continuous platforms seriously, and some have begun implementing elements of it already. Adoption for late-clinical or commercial-scale operations, however, remains slow and differs across product modalities.

The scientific rationale for adoption of this technology is clear: increasing volumetric productivities, decreasing facility footprints, improving process control, and offering the potential to enhance manufacturing efficiencies and economics. Yet the shift from batch to continuous manufacturing has not occurred abruptly; it has progressed gradually and unevenly through the biopharmaceutical industry.

Mapping the Transition: Where We Are Today

Our survey results suggest that the industry has moved beyond the question of whether continuous manufacturing should be explored. Over a third (37.1%) of responding organizations report that they are "evaluating or considering" continuous upstream technologies actively, and 29.1% are "informally evaluating" them

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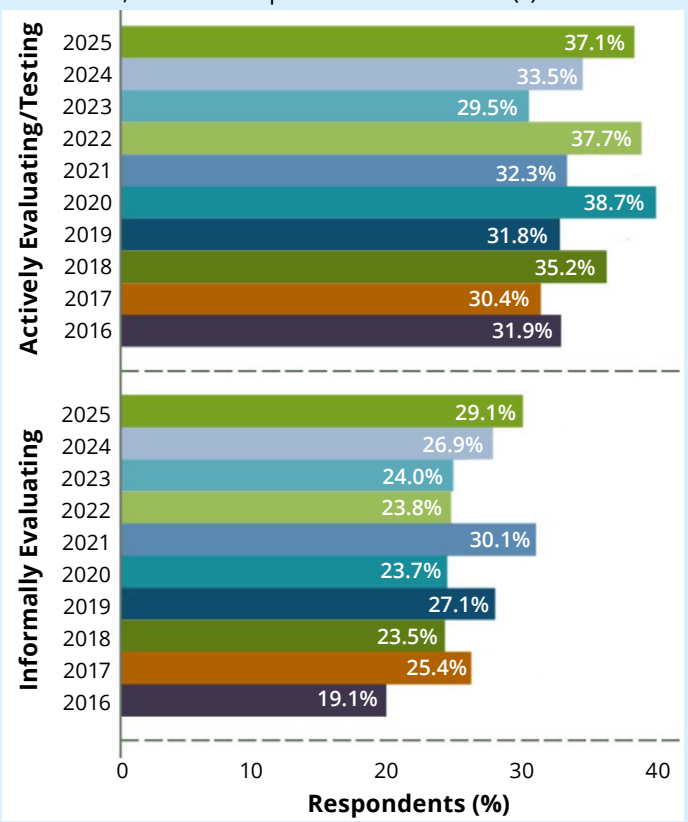
(**1**). CBP has become part of routine strategic planning. This is not a transient trend; we've tracked steady growth in the percentages of respondents evaluating or testing it over the past 10 years (Figure 2).

At the same time, testing does not translate directly into implementation. Many companies remain in an assessment phase, evaluating where continuous approaches can offer practical advantages, rather than broadly replacing batch manufacturing. Many are approaching continuous adoption as a staged transition rather than a simple switch from batch to continuous operations. Over the past decade, the field has progressed through a number of stages as technologies have matured and organizations have accumulated operational experience with intensified manufacturing approaches.

Figure 2: Facilities reported to be evaluating upstream continuous bioprocessing technologies over the following 12 months, results compared for 2016–2025 (**1**)



Phase 1 — Experimental Exploration: Early industry efforts focused on technical exploration and proof-of-concept demonstrations. Researchers and early adopters have investigated perfusion cell culture for multiple decades. Companies investigated continuous chromatography technologies such as simulated–moving-bed systems and integrated upstream–downstream pilot processes. The objective was to confirm that continuous operation could deliver stable product quality, reliable process control, and regulatory compliance. Most work took place in development laboratories and pilot facilities, often in collaboration with technology vendors and academic groups. Those early studies established a technical foundation for broader industry evaluation.

Phase 2 — Structured Evaluation: As technologies matured, biopharmaceutical companies began more systematic internal assessments of continuous and intensified manufacturing approaches. Perfusion-based upstream processes and continuous downstream purification became subjects of detailed evaluation. The focus shifted from technical feasibility to operational integration. Manufacturing science and technology (MSAT) teams examined how such systems could fit within existing operations, facility designs, and regulatory frameworks. Process-control strategies, integration of upstream and downstream operations, and monitoring requirements became central questions. During

this phase, advances in automation and digital monitoring began to support increasingly sophisticated control strategies. Continuous technologies no longer were seen as experimental, but rather as part of structured process development and manufacturing planning.

Phase 3 — Selective Integration: Now the industry appears to be entering a stage in which continuous technologies are implemented selectively where they have been confirmed to provide clear advantages. Because commercial adoption has been successful only in certain unit operations, the true value of a fully continuous process has not yet been realized. Rather than replacing batch processes across entire facilities, companies are integrating continuous elements into specific production steps. Examples include perfusion-based upstream production for high-productivity antibody processes, continuous chromatography to address downstream capacity limits, and hybrid approaches that combine batch and continuous operations. Adoption decisions increasingly depend on whether continuous processing can improve productivity, facility efficiency, supply reliability, and/or operational flexibility compared with established batch processes. Some biopharmaceutical companies and contract development and manufacturing organizations (CDMOs) are promoting their mastery of CBP as a strategic differentiator.

Phase 4 – Platform Integration (Future): A later stage will emerge in which continuous manufacturing integrates unit operations and becomes a standard feature of new facilities and production platforms. Such technologies will be incorporated during facility design rather than introduced into existing processes. Modular facilities built to house intensified production systems, integrated upstream and downstream workflows, and digital control environments optimized for steady-state operation will become common. Advanced-therapy platforms will benefit from such architectures, such as one that my company developed over 10 years ago with Natrix Separations (now part of MilliporeSigma) in collaboration with Univercells and Batavia Biosciences. However, the timing of this shift will depend on continued technological progress and regulatory experience.

Taken together, BioPlan Associates survey results suggest that the industry is moving from structured evaluation (phase 2) toward selective integration (phase 3). Continuous bioprocessing has progressed beyond experimental demonstrations, but it has not replaced batch manufacturing as the dominant model. Instead, many companies are adopting it deliberately in areas where the operational or economic advantages are clear.

Adoption decisions increasingly depend on whether continuous processing can **IMPROVE** productivity, facility efficiency, supply reliability, and/or operational flexibility compared with established batch processes.

Different Modalities Are at Different Points on the Adoption Path

The transition toward CBP has not been uniform across biologic modalities. Product characteristics, manufacturing scale, and process architecture all influence how quickly continuous technologies can be evaluated and adopted. Taken together, the following differences suggest that CBP is likely to progress along different paths across biologic product classes.

Monoclonal antibodies (mAbs) remain the most mature biopharmaceutical modality and thus provide a useful starting point for evaluating new manufacturing approaches. For mAb production, continuous processing often represents a path to optimization rather than a fundamental change in manufacturing strategy. Over the past two decades, the industry has developed well-established platform processes based on fed-batch Chinese hamster ovary (CHO) cell culture followed by protein A affinity chromatography capture and other downstream polishing steps. Such processes are robust and well understood from both technical and regulatory perspectives.

In that context, the main motivation for exploring continuous approaches is improved manufacturing efficiency and reduced cost of goods (CoG). Perfusion-based upstream processes can increase volumetric productivity relative to traditional fed-batch cultures, providing greater output from the same bioreactor volume. Continuous chromatography can improve resin-use efficiency and reduce column-size requirements. Together, those improvements should reduce facility footprints and increase throughput. Most batch antibody processes already are highly optimized, however, so companies tend to adopt continuous approaches only when the expected gains justify adding process complexity, making integration effort, and spending capital. Hybrid strategies that combine intensified upstream processing with partially continuous downstream operations thus are becoming common.

Non-mAb Recombinant Proteins: The situation is somewhat different for other biologics. Many non-mAb products lack standardized platform processes and thus require customized development strategies. Differences in molecular structure, stability, and purification behavior can complicate the manufacture of such proteins. In some cases, low expression levels and/or challenging purification steps create strong incentives to investigate intensified processes and continuous modes to improve productivity. At the same time, the absence of universal platform approaches often makes it necessary to evaluate continuous-processing implementation case by case.

Most batch antibody processes already are highly optimized, so companies tend to adopt continuous approaches only when the expected gains **JUSTIFY** adding process complexity, making integration effort, and spending capital.

Cell therapies represent a very different manufacturing paradigm. Their production processes are often small scale by comparison — even patient-specific in the case of autologous therapies. Both allogeneic and autologous approaches involve substantial biological variability and multiple processing steps including cell isolation and activation, genetic modification, expansion, and formulation. Those steps typically occur in closed systems with extensive quality monitoring. In such a setting, classical continuous manufacturing concepts such as long steady-state production runs are less applicable. Process improvements for cell-therapy manufacturing currently focus more on automation, closed-system processing, and improved control of cell expansion. Although perfusion-like strategies for maintaining cell cultures have been explored, fully continuous production of cell-therapy products remains unlikely.

Gene-therapy manufacturing, particularly for viral-vector production, does offer clearer opportunities for continuous or otherwise intensified processing, by contrast. Viral-vector processes often use suspension cell-culture systems such as human embryonic kidney (HEK293) or the baculovirus expression-vector system (BEVS) in insect cells and thus share many features with conventional recombinant-protein manufacturing. Their upstream culture, transfection or infection steps, and downstream processing resemble traditional bioprocessing workflows. Continuous and intensified approaches developed for antibody manufacturing therefore are adaptable to viral-vector production.

Perfusion-culture systems such as the Repligen's Alternating Tangential Flow (ATF) technology or fixed-bed bioreactors such as iCELLis (Cytiva) or scale-x (Univercells Technologies) systems can increase vector productivity and improve facility-use efficiencies. Continuous purification technologies could help companies address downstream bottlenecks associated with high vector loads. Several groups have investigated integrated manufacturing approaches that combine upstream perfusion culture with continuous downstream purification for viral-vector production (**2–6**). Such studies illustrate how continuous concepts could improve scalability and manufacturing efficiency for gene-therapy products.

Continuous and intensified approaches developed for antibody manufacturing are **ADAPTABLE** to viral vector production.

Operational Challenges Inhibiting Adoption

Continuous bioprocesses must maintain stable operating conditions for extended periods, which increases their demands for process analytical technologies (PATs) and real-time control systems over those of traditional batch operations. Emerging multiparameter single-use sensor platforms could help to address those needs by

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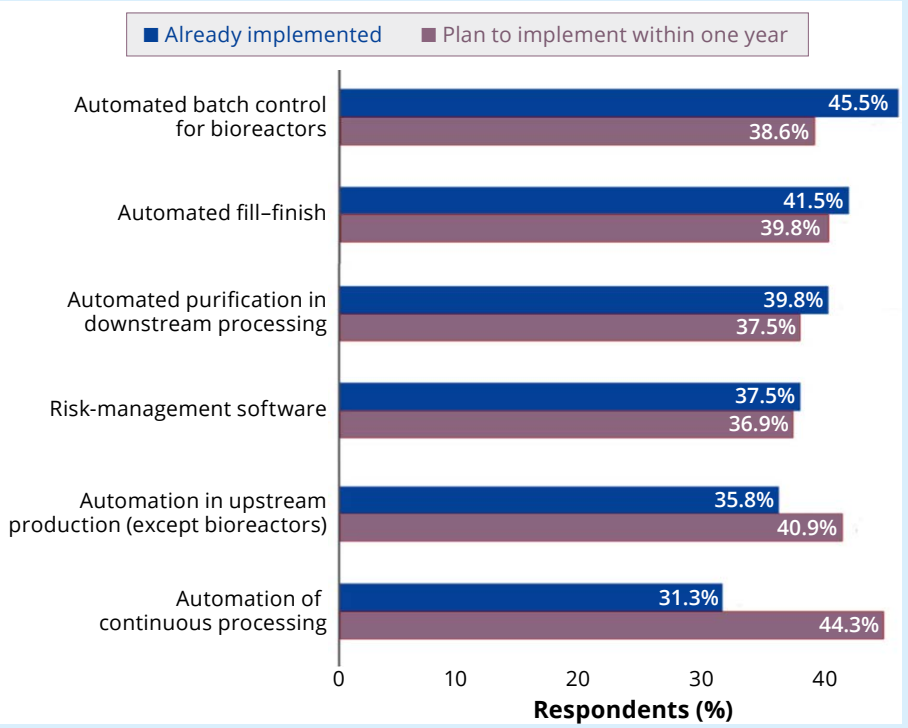
enabling simultaneous measurement of several critical process parameters (CPPs) directly within disposable bioprocess systems. That should improve both process monitoring and control-system responsiveness to move biomanufacturing closer to self-regulated operation.

Integration across the process train is another key issue. In batch manufacturing, individual unit operations can be optimized somewhat independently and connected through defined material transfers. Continuous systems require tightened coordination between steps. Instability or variability in one unit operation can propagate rapidly through the entire process if not managed effectively. As a result, companies evaluating continuous approaches must consider the robustness of their full integrated processes rather than the performance of individual operations alone.

Figure 3: Automation technologies implemented in bioprocessing facilities (**1**)



Automation To Facilitate CBP Implementation: Advances in automation and digital monitoring are helping to address some challenges in CBP integration and adoption. Our survey results (Figure 3) show increasing implementation of automated control systems and digital monitoring tools across biomanufacturing facilities. Such technologies provide the real-time data and control capabilities needed to operate continuous processes reliably. As automation systems mature, the operational burden associated with maintaining steady-state production decreases.

Demand for Supplier CBP Innovation: Adoption also depends on what technologies are available from equipment suppliers. Continuous unit operations such as perfusion cell-retention devices, continuous chromatography systems, and integrated monitoring tools have advanced substantially over the past decade. However, continued progress from suppliers and technology providers will be important to future progress. New equipment must introduce innovation while also demonstrating reliability, scalability, and ease of integration for existing manufacturing environments.

Sponsors and CDMOs also will play an essential role. Their willingness to test, evaluate, advise, and implement new technologies will determine how quickly those approaches become routine manufacturing practice.

Strategic Implications

Our survey data suggest that cost is not the most influential factor when companies consider continuous manufacturing. Instead, organizational readiness, operational risk management, and compatibility with long-term manufacturing strategies appear to play larger roles in decision making. That finding reflects how companies approach manufacturing technology adoption.

CBP can contribute to improved productivity and decreased manufacturing costs, but it is rarely adopted solely as a cost-reduction measure. More often, it is evaluated as part of broad manufacturing planning. Companies consider whether these technologies will support goals such as increased facility flexibility, improved asset efficiency, enhanced process control, and facilitated scale-up (or scale-out).

Continuous manufacturing therefore represents an evolution in both facility design and process strategy rather than a universal replacement for batch production. In most cases, continuous technologies are incorporated only where they offer clear advantages.

Driving Forces and Enablers

CBP is no longer a speculative idea in biopharmaceutical manufacturing. Our annual survey data indicate that the industry has moved beyond early experimentation and is now evaluating and implementing continuous technologies in selected applications.

The transition is happening unevenly across product modalities, with mAb manufacturing serving as the natural starting point for exploring such process-intensification strategies. Developers of other recombinant proteins are likely to adopt such approaches when product characteristics justify them. Advanced therapies introduce additional complexities. Cell-therapy manufacturing remains largely incompatible with most continuous architectures, but options are emerging. And viral-vector production may be the greatest beneficiary from intensified and integrated processing concepts.

Operational considerations continue to shape technology adoption. Continuous manufacturing requires advanced process control, monitoring infrastructure, and integrated process design. Progress in automation, digitalization, and analytical technologies therefore will be an important enabling factor.

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Continuous manufacturing therefore represents an **EVOLUTION** in both facility design and process strategy rather than a universal replacement for batch production.

Overall, CBP should not be viewed as a simple transition away from batch manufacturing. It represents a set of technologies that will be incorporated gradually into biomanufacturing systems where they provide clear technical or operational advantages. Hybrid processes that combine batch and continuous elements are likely to represent the most practical near-term path forward.

The industry appears to be in a stage of selective integration. The central question is no longer whether continuous bioprocessing will play a role in future manufacturing, but where it will deliver the greatest benefit as technologies mature and operational experience grows.

Continuous bioprocessing should not be viewed as a simple transition away from batch manufacturing. It represents a set of technologies that will be incorporated gradually into biomanufacturing systems where they provide clear technical or operational **ADVANTAGES**.

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About the Author

Renaud Jacquemart, *PhD, MBA, is senior advisor at BioPlan Associates in Rockville, MD, 1-301-921-5979, rjacquemart@bioplanssociates.com. He is a strategic commercial leader and biopharmaceutical product development expert with 25 years of international experience. His expertise spans the full life cycle of biologics, from early stage development to commercialization, with a focus on cost-effective, scalable solutions for go-to-market strategies, operational excellence, and competitive advantage in a complex, regulated landscape. As chief executive officer of Omnium Global, he played pivotal roles in driving strategic growth, fundraising, and market expansion for biopharmaceutical companies, contributing to successful acquisitions by major industry players.*

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Continuous Biologics Manufacturing for Modular and Sustainable Operations

Delivering Continuous Biomanufacturing Within a Novel Ecosystem

Charles Heise

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Global biologics demand is increasing faster than manufacturing capacity can keep up, while expectations for agility, resilience, and sustainability rise. But capacity alone cannot satisfy those constraints; biomanufacturers need a unified operating philosophy that standardizes science, technology, facility design, and governance across a manufacturing network. The FUJIFILM Biotechnologies kojoX™ ecosystem provides that structure by aligning scale-up, scale-out, and continuous-manufacturing strategies with functionally equivalent facilities, standardized equipment and automation, harmonized quality systems, and data-centric control.

Life-Cycle Manufacturing Supported by a Bioproduction Ecosystem

Biologics portfolios encompass diverse modalities, from high-volume monoclonal antibodies (mAbs) to potent, low-volume biotherapeutics. As indications evolve and regional launches proceed asynchronously, manufacturers must supply material quickly, securely, and cost-effectively while maintaining compliance and reducing environmental impact. Life-cycle–aligned strategies can address pipeline volatility, scale-up for high-volume established markets, scale-out for targeted or uncertain demand, and continuous processing for flexible production capacity without major facility expansion.

However, combining those strategies across modalities and geographies increases complexity in process design, technology selection, facility architecture, data management, and regulatory control. The kojoX bioproduction ecosystem can make that complexity manageable and processes repeatable.

A Revolutionary Operating Ecosystem

The kojoX ecosystem is a standardized yet flexible modular biomanufacturing system that is designed to shorten timelines,

improve scalability, and enhance product quality while reducing costs and environmental impact. By aligning processes, equipment, and digital systems across a global network, the kojoX system ensures seamless technology transfer, derisks supply chains, and provides the agility that biopharmaceutical companies need to deliver innovative therapies quickly and reliably.

Supply Resilience and Flexibility Delivered Through Facility and Functional Equivalence

FUJIFILM Biotechnologies operates facilities that are bound by common blueprints and operating systems. Large-scale assets use multipack stainless-steel bioreactors of up to 20,000 L, which provide high-volume supply for large patient cohorts. Mid- and small-scale assets are single-use, multidrug facilities optimized for potent products, clinical-stage, and smaller patient populations. The kojoX ecosystem guides and links operating capabilities for each manufacturing scale to the design space during process development. That alignment makes it feasible to move a product from single-use clinical suites to either single-use or stainless-steel commercial suites with minimal redesign of unit operations while maintaining the same core control strategy.

Functional equivalence is achieved through modular suite layouts, standardized utility and environmental specifications, and consistent automation interfaces. Those factors reduce the scope of revalidation during technology transfer to verifying equivalence instead of redeveloping control logic. They also support parallel qualification across multiple jurisdictions when dual-site supply is needed.

Robust, Risk-Based Control Strategies To Last a Life Cycle

An effective control strategy must link facility design, equipment capability, process characterization, and data integrity. The kojoX system implements a scientific, risk-based framework that defines the operational design space for each unit operation and for the integrated train, including environmental classification, closed-system boundaries, and acceptable ranges for critical parameters and material attributes. The same strategy is intended to be valid in early and late life-cycle stages, with scope to tighten ranges and increase automation authority as characterization data accumulate.

Mechanics and Implications of Integrated Continuous Processing: In practice, *continuous bioprocessing* is process intensification under tight integration rather than the pursuit of truly uninterrupted mass flow. For upstream production, perfusion typically is selected for productivity gains

An **EFFECTIVE** control strategy must **LINK** facility design, equipment capability, process characterization, and data integrity.

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For more information on the kojoX ecosystem, please visit https://fujifilmbiotechnologies.fujifilm.com/cdmo-services/kojox/.

and steady-state operation. Downstream processing must be configured to sustain constant volumetric flow, variable flow, and varying mass flow without violating capacity constraints in bind–elute chromatography steps. Such processes require careful flow matching and explicit debottlenecking strategies.

Buffer logistics has become a vital design variable. Unlike batch processing, in which buffers are consumed in discrete time windows, integrated trains impose quasisteady buffer-demand profiles. Ensuring compositional stability and on-time replenishment requires automated inventory monitoring, validated make-up sequences, and redundancy in distribution. Changeover plans must account for carryover risks, dead legs, and connection integrity inside a closed-system architecture that satisfies current good manufacturing practice (CGMP) environmental controls. Failure modes such as valve misalignment, level sensor drift, or filter fouling must be identified/modeled in advance, with automation responses that prioritize product quality and containment before throughput.

Environmental control is anchored in closed-system operation, reducing reliance on high-grade cleanroom classifications and supporting single-use efficiency. However, closure does not eliminate the need for environmental monitoring; it changes what is monitored and how deviations are triaged. Integration concentrates risk into fewer, more complex automation nodes compared with those of isolated systems. Alarm philosophies, interlocks, manual override procedures, and recovery recipes must be defined with the same rigor as process setpoints. Operator interaction decreases in frequency but increases in consequence, so human–machine interface design and training are part of the control strategy.

Data volume increases significantly during continuous monitoring across connected units. Such processes generate larger granular datasets that enable superior control but demand disciplined data management. Signal alignment, timestamp coherence, and context (e.g., which column was used in a specific phase) must be preserved to make data analyzable. Those structured datasets then are leveraged for adaptive control, predictive maintenance, and lot-release strategies that exploit trend consistency.

A Single-Use Platform for Continuous Bioprocessing

The MaruX™ fully automated continuous manufacturing platform performs integrated continuous processing in multidrug, single-use

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For more information on the MaruX platform, please visit https://fujifilmbiotechnologies.fujifilm.com/capabilities/biologics/mammalian-cell-culture/downstream-process-development/continuous-manufacturing/.

environments. The platform unifies perfusion upstream with continuous-ready downstream unit operations on standardized, multifunctional equipment. The same downstream system executes a full purification sequence under a common automation and data model, simplifying training and qualification. Closed-system design and robust environmental controls support CGMP operation while maintaining the flexibility required for multiproduct facilities (Figure 1).

The MaruX design overlays continuous integration on top of established unit operations, preserving batch steps where appropriate, then adding orchestration layers to coordinate flows and transitions. This reduces the incremental development burden compared with reinventing a process as "fully continuous," thus making it feasible to introduce continuous elements during phases 2 and 3. Because data structures and control logic are consistent with batch operations, the validation path remains traceable. Figure 2 provides results of a 500-L perfusion bioreactor run over 24 days using the MaruX design.

Standardization enables a three-step capacity strategy: **EXPAND** within a line, **DUPLICATE** lines within a facility, and **REPLICATE** additional sites.

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Life-Cycle Strategy: When To Transition to Continuous Manufacturing

Early clinical manufacturing often favors fed-batch processing due to its low complexity and small volume requirements. However, the advantages of continuous operation — productivity

Figure 1: Benefits of the MaruX fully automated continuous manufacturing platform; GMP = good manufacturing practice

improvement, data richness, and tight control — become compelling by the end of phase 3. A dual-mode cell-bank strategy reduces bridging risk, enabling a measured transition: Begin with fed-batch in phase 1, then introduce perfusion and harvest elements in phase 2 to build operator familiarity and data, and finally move to integrated continuous as demand and regulatory strategy justify the added automation. Within the kojoX ecosystem, that transition is planned from the outset so that the same control strategy can be tightened over time rather than replaced. Additionally, the same unit-operation equipment and data models are retained across the product life cycle.

The end state is flexible: Products can run in stainless-steel reactors at very large scales when demand justifies it, or they can remain in single-use trains when agility and multisite replication are needed. With facilities that are functionally equivalent under the kojoX framework, manufacturing pathways can be selected or revised based on evolving market signals without invalidating prior development work.

Technology Transfer and Networked Learning

Standardization enables a three-step capacity strategy: expand within a line, duplicate lines within a facility, and replicate additional sites. The kojoX ecosystem leverages the same suite layouts, equipment capabilities, automation interfaces, and data models across the network. As such, each step emphasizes equivalent verification rather than redevelopment. Through this approach, partners have accelerated regulatory filings, with regional nuances being handled within the harmonized quality system.

Knowledge transfer is bidirectional and continuous. The "living standard" approach requires tight coordination between

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Figure 2: Results of 500-L perfusion bioreactor run for 24 days using the MaruX platform; mAb = monoclonal antibody, VVD = vessel volumes per day

- 600 L of perfusate per day
- Cell density of 1.2×10^8 cells/mL
- Viability >90%
- ApolloX™ cell densities of 1.2×10^8 cells/mL

- Quality comparable to 50-L pilot run
- Consistent glycan profiles, with man-5 <3%
- Volume-exchange rate of 1.2 VVD

- 1.8 g full-length mAb/L/day titer
- ≈1 kg mAb/day supplied downstream
- Overall process yielded 0.54 kg/day of purified mAb

*suitable for Apollo and other perfusion-ready cell lines

engineering, process design, and data-science teams while enabling the most reliable means of propagating best practices without disrupting ongoing operations.

Sustainability Considerations

Single-use operations support sustainability goals by reducing utility consumption associated with cleaning and steam sterilization and by enabling small operational footprints for equivalent output. Adoption of energy-efficient supporting utilities — such as cold water for injection (WFI) where appropriate — can further reduce energy use. Such gains must be balanced with responsible single-use material management and local infrastructure capabilities. The kojoX system embeds those considerations during facility and process design so that sustainability advances do not compromise CGMP control or agility.

A Holistic Design To Meet Demand

Scaling biologics supply to meet global demand requires a system-level solution. The kojoX ecosystem provides a standardized, modular framework that unifies scientific understanding, technology selection, facility design, and digital governance throughout a global network. Within that framework, the MaruX single-use platform makes integrated continuous processing practical, allowing organizations to "scale on" over time through replication rather than only by vessel size. By preserving functional equivalence between mid-scale single-use and large-scale stainless-steel facilities, the kojoX system enables seamless movement between fed-batch, perfusion, and integrated continuous operations as products progress through their life cycles.

About the Author

Charles Heise *is associate director in the Bioprocessing Strategy & Development group at FUJIFILM Biotechnologies (Billingham, UK), working on developing connected, integrated processes. He has over 15 years of experience leading the development of CGMP processes for clinical and commercial recombinant-protein manufacture and academic research collaborations. He is co-inventor of the award-winning SymphonX™ purification skid and the downstream technical lead for the MaruX continuous biomanufacturing platform. Heise holds degrees from the University of Oxford (BS) and the University of York (PhD).*

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Biomanufacturing Process Intensification

Present State, Future Trajectory, and the Workforce System Required To Deliver It

Jason Beckwith, Stephen Goldrick, and William Nixon

Biomanufacturing process intensification (PI) has moved beyond theory into routine operational practice. Demand for biologics and advanced therapies has grown alongside sustained cost pressure, strict regulatory expectations, and practical limits on manufacturing capacity. As a result, organizations are rethinking how production systems function by shifting toward tightly coupled operations, rapid and controlled production cycles, and digitally supported quality oversight. The intent is to extract improved value from existing assets by increasing productivity, reducing time to release, maintaining quality, and strengthening capital efficiency.

Much of the discussion about PI concerns technology and infrastructure, yet delivery outcomes increasingly are shaped by the workforce system that is responsible for designing, operating, and governing intensified processes. As biomanufacturing becomes more tightly integrated and operates at higher speed with reduced tolerance for variability, the underlying talent model must evolve accordingly. In this context, talent-science modeling provides a quantitative and predictive way to understand how a workforce behaves under operating conditions, making it a critical enabler of sustained PI at scale.

The Current State of PI in Biomanufacturing

PI in biomanufacturing traditionally has been pursued as a means of increasing output while reducing physical footprints and operating costs (**1, 2**). For upstream production, that shift has been driven by dense and productive cell-culture systems, tight control of feeding and media exchange, and high reliance on advanced bioreactor control to stabilize performance at increasing operating limits. Downstream processing has followed a similar trajectory, with purification strategies evolving to manage high titers through compact, integrated, and throughput-efficient configurations.

At the same time, adoption of single-use technologies has reshaped facility design by enabling fast deployment, smooth changeovers, and

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low validation burden; modular and flexible manufacturing concepts have compressed development and scale-up timelines further. Those structural changes have reduced capital intensity and shortened the path from development to commercial supply.

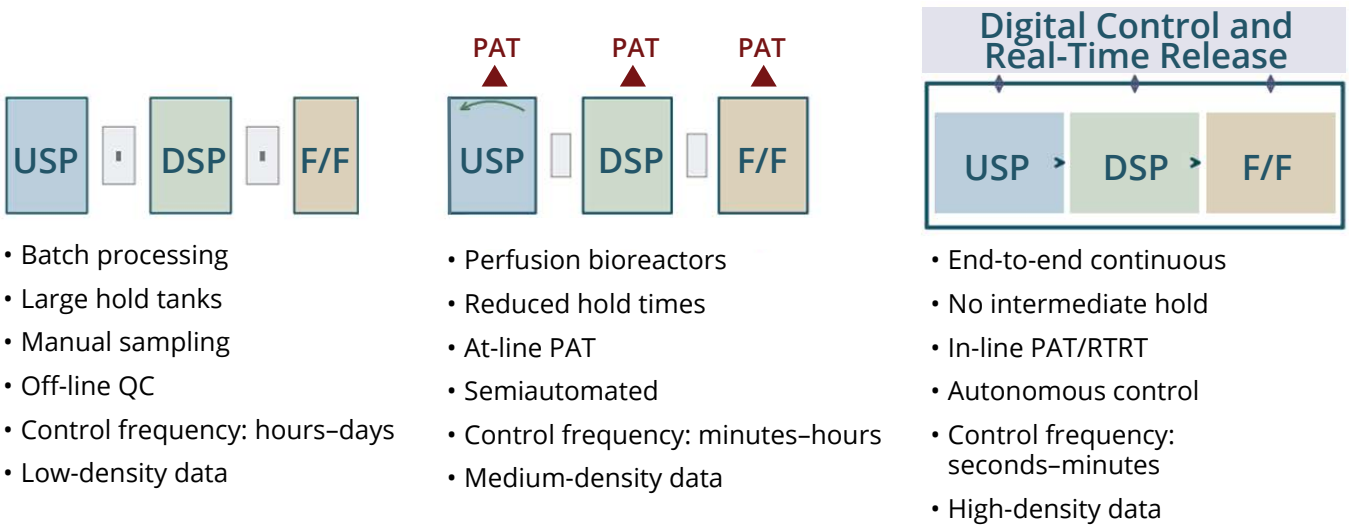
Digitalization has accelerated that trend by embedding deep process understanding into day-to-day operations (**3, 4**). Use of in-process data, predictive control, and real-time quality signals has shifted reliance away from endpoint testing and manual review, whereas integrated manufacturing and laboratory systems have expanded data continuity across development, production, and quality oversight.

Despite such advances, many organizations encounter diminishing returns as intensification increases. As processes operate closer to their limits, execution becomes increasingly sensitive to review delays, fragmented knowledge, and governance friction. Those constraints rarely originate within a unit operation itself, but instead emerge from interactions among process design, organizational structure, decision authority, and the distribution of skills across a manufacturing system.

PI steadily has increased the degree of coupling between unit operations and functional domains. Whereas early intensification focused on isolated productivity gains, current and emerging models link upstream, downstream, quality, and control systems into tightly coordinated manufacturing environments. That evolution fundamentally alters how variability propagates through a system and increases sensitivity to delays and errors in decision-making. Figure 1 illustrates that shift from loosely

Continuous and hybrid biomanufacturing models are moving beyond early adoption as control strategies **INCREASINGLY EXTEND** across upstream, downstream, and fill–finish activities.

Figure 1: Evolution of biomanufacturing process intensification (PI) and system coupling; DSP = downstream processing, F/F = fill–finish, PAT = process analytical technology, QC = quality control, RTRT = real-time release testing, USP = upstream production



coupled batch processes to highly integrated, data-driven manufacturing systems.

As such coupling increases, tolerance for latency, misalignment, and/or manual intervention decreases. Small disruptions in one part of a system propagate rapidly across operations, placing new demands on how decisions are made, reviewed, and executed. That scenario sets the context for why technical intensification alone is insufficient without corresponding evolution in workforce design and governance.

Emerging Future of Intensified Biomanufacturing

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The next phase of biomanufacturing intensification is characterized by a shift toward tightly coupled processes that operate with significant dependence on real-time data and little tolerance for manual intervention. Continuous and hybrid biomanufacturing models are moving beyond early adoption as control strategies increasingly extend across upstream, downstream, and fill–finish activities (**1, 4**). Meanwhile, advanced therapies introduce additional complexity through high variability.

Regulatory expectations are evolving in ways that reinforce that shift (**5, 6**). Agencies are emphasizing life-cycle management, ongoing process verification, and scientific justification of control strategies, with digital evidence increasingly supplanting static documentation as the basis for regulatory confidence.

Under those conditions, a manufacturing system begins to function less as a set of loosely connected operations and more as a tightly integrated network in which small disruptions propagate rapidly. Delays in decision-making, ambiguity in accountability, or gaps in capability can affect throughput, quality, and compliance on much shorter timescales than with traditional operating models.

Therefore, sustaining future intensification depends on the ability to manage complexity dynamically. That skill extends beyond technical capability and requires a workforce capable of rapid sense-making through well-defined distributed decision authority, and effective flow of knowledge across functional boundaries.

The Changing Nature of Talent in Intensified Biomanufacturing

PI and continuous processing reshape the role of talent across the value chain. Traditional functional boundaries among process development, manufacturing science and technology (MSAT), manufacturing, quality, and digital teams become blurred. Engineers and scientists increasingly operate at the interface between design and execution. Operators interact directly with advanced control systems and data-driven decision support tools.

Quality professionals engage early and frequently with process changes.

Skill requirements evolve as PI increases and manufacturing systems become interconnected. Deep technical expertise remains important, yet performance increasingly depends on understanding how unit operations interact, how control strategies behave under variation, and how failure propagates across tightly coupled systems. The ability to interpret data streams and apply model-based reasoning becomes part of routine operational practice, embedded within day-to-day decision-making rather than confined to specialist functions. Cross-functional coordination and clarity of decision authority will have direct impact on throughput, quality consistency, and regulatory confidence.

Leadership expectations must shift accordingly. Managers operate within environments where cycle times shorten and the margin for error narrows. Decision sequencing, resource allocation, and escalation pathways influence system stability as much as technical design. Leaders must maintain awareness of interdependencies across MSAT, manufacturing, quality, and digital systems while ensuring that accountability structures support timely action. Their effectiveness is reflected in how smoothly information moves and how consistently decisions translate into controlled execution.

As manufacturing platforms intensify, organizations frequently depend on a limited number of highly experienced individuals who understand both technical detail and system interactions. Those individuals often bridge functional boundaries and provide informal integration across process development, operations, and compliance. Such reliance can accelerate early implementation, yet it creates structural vulnerability as scale increases. Concentrated knowledge, expanding decision queues, and limited succession depth can undermine organizational resilience, particularly when throughput rises or regulatory pressure intensifies.

Workforce Complexity as a Limiting Factor

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In intensified/continuous biomanufacturing, workforce-related constraints often appear before traditional performance metrics shift. Decision queues lengthen, and reviews become serial rather than parallel. Technical specialists spend increasing time in coordination rather than in value creation. Projects compete for the same scarce expertise. Deviations recur around the same process interfaces.

Such signals indicate that a workforce system is approaching a complexity threshold. An organization remains staffed and engaged, yet its ability to absorb further intensification diminishes. Financial metrics and batch-output figures often lag those signals by months.

Conventional workforce metrics struggle to capture that dynamic. Headcount, vacancy rates, training completion, and engagement scores provide descriptive information, but they do not explain how work flows through a system. They do not reveal where decisions slow down, where accountability overlaps, or where skill coverage becomes brittle under stress. Such a gap between descriptive metrics and operational reality is increasingly costly in intensified manufacturing environments.

The earliest indicators of strain appear within the workforce system rather than in output or financial metrics. Those signals are operational in nature and relate to how work flows through people and decisions, rather than whether processes are scientifically sound. Figure 2 shows how workforce stress signals precede traditional indicators of underperformance.

When deviations increase or milestones slip, underlying causes often are already embedded in a system. Recognizing these early signals creates an opportunity for intervention while options remain available. That highlights the importance of measuring workforce behavior dynamically rather than relying on retrospective performance data.

Talent-Science Modeling as a Flow-Based Measurement Framework

Talent-science modeling addresses such gaps by evaluating the workforce as a dynamic system of interacting elements rather than a

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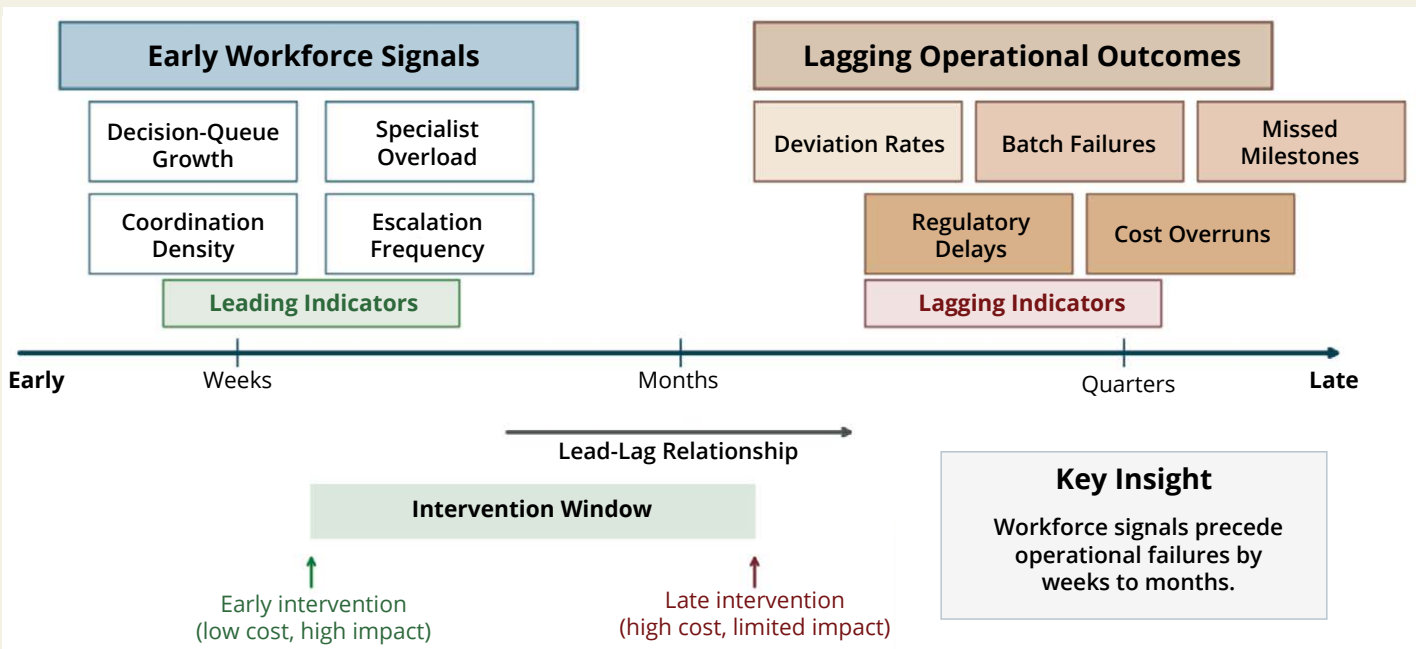
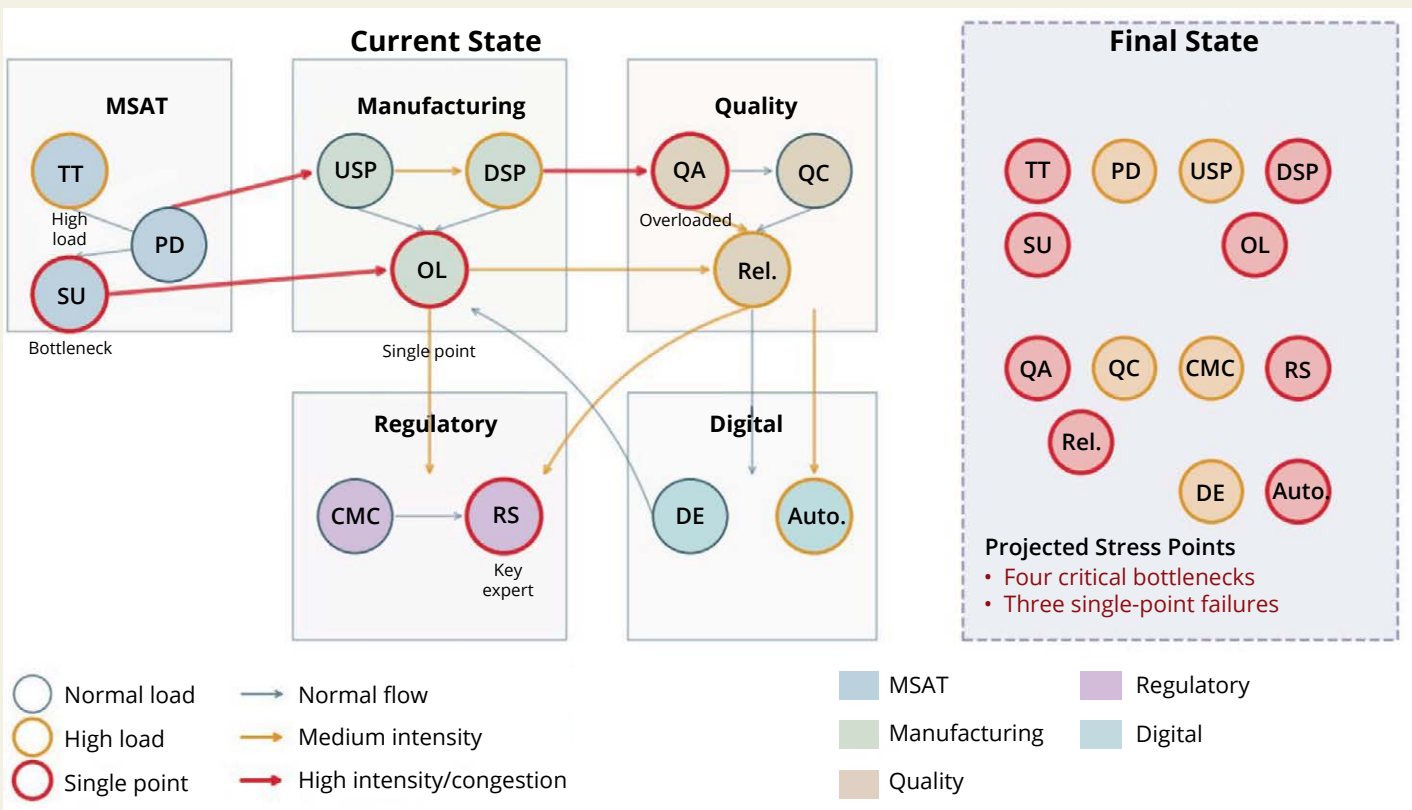
Figure 2: Workforce-system stress emerges before traditional performance indicators.



static set of roles. This approach draws on principles from systems engineering, complexity science, and predictive analytics to measure how work, decisions, and expertise move through an organization over time (**7**). At its core, talent science represents roles, teams, and decision points as nodes in a flow network. Workload, decision demand, and coordination requirements are treated as dynamic variables rather than averages. Skills coverage is measured in terms of effective availability under real operating conditions, considering competing demands, escalation patterns, and governance structures. This approach allows organizations to simulate how the workforce system responds to increased throughput, tight control strategies, and/or organizational change. Doing so can reveal where bottlenecks emerge, where overload accumulates, and where minor changes in demand produce disproportionate effects.

To manage intensified and continuous manufacturing systems effectively, workforce measurement must move beyond static structures and describe how work and decisions move through the organization. Talent science addresses that need by modeling the

Figure 3: Talent-science flow model for intensified biomanufacturing systems; Auto. = automation, CMC = chemistry, manufacturing, and controls, DE = data engineering, DSP = downstream processing, MSAT = manufacturing science and technology, OL = operations lead, PAT = process analytical technology, PD = process development, QA = quality assurance, QC = quality control, Rel. = release, RS = regulatory strategy, RTRT = real-time release testing, SU = scale-up, TT = technology transfer, USP = upstream production



workforce as a flow system subject to changing demand and constraints.

Figure 3 presents a simplified representation of that approach. A flow-based type of model enables predictive analysis rather than retrospective reporting. Leaders can assess whether current capability and governance structures will remain stable as processes intensify, and then evaluate interventions such as role redesign, decision redistribution, or capability investment before implementation. Talent science thus becomes a practical tool for sustaining PI at scale. Those predictive capabilities enable leaders to assess whether a workforce can sustain continuous processing, real time release, and/or rapid scale-up before such changes are implemented.

Table 1: Projected workforce stress indicators under intensification scenario

Metric	Baseline	Projected 25% Throughput Increase	Post-Redesign Project
Deviation approval concentration (top five individuals)	58%	61%	34%
Validation review concentration (top five individuals)	64%	68%	38%
Mean deviation review-cycle time	18 days	25.6 days (±42%)	19.2 days
Batch-release latency variability	Moderate	High	Moderate
Inspection readiness exposure score	Stable	Elevated	Stable

Predictive Workforce Stress Modeling in an Intensified Network

In one multisite biomanufacturing network of ≈1400 personnel, flow-based modeling was applied during preparation for a 25% throughput increase driven by continuous upstream operations and shortened release timelines. Baseline analysis revealed that 58% of deviation approvals and 64% of validation-review decisions were concentrated within five senior individuals across MSAT and quality functions.

Simulation under increased batch frequency projected a 42% increase in review cycle time within nine months, despite no change in headcount. Further modeling indicated that decision congestion, rather than technical capacity, would become the dominant constraint on release velocity.

Targeted redistribution of approval authority, structured delegation frameworks, and capability expansion in two specialist domains reduced projected cycle-time exposure by 36% prior to implementation of intensified operations. Following process redesign, deviation closure timelines stabilized despite increased throughput, and inspection readiness metrics remained consistent.

That example illustrates how workforce-flow constraints can be quantified, stress-tested, and redesigned before operational degradation occurs. In intensified systems, organizational modeling becomes a preventative control mechanism rather than a reactive response. In such systems, organizational modeling

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becomes a preventative control mechanism rather than a reactive response (Table 1).

Application of Talent Science to Intensified Manufacturing Environments

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As biomanufacturing platforms become more integrated and cycle times compress, execution stability depends increasingly on how a workforce system is structured and governed. Talent science provides a predictive framework for assessing whether organizational capability, decision flow, and leadership capacity can sustain intensified operating conditions before performance degradation occurs.

In late-stage development and technology transfer, talent-science modeling evaluates whether review bandwidth, validation capability, and decision authority are proportionate to accelerated timelines. It detects where review processes become serial rather than parallel, where informal escalation pathways influence outcomes, and where governance density may slow progression toward commercial readiness.

Within manufacturing and quality operations, the talent-science approach maps responsibility distribution for control strategies, deviation investigation, and inspection management. Thus, companies can quantify exposure created by concentration of expertise and identify where workload intensity or approval bottlenecks could compromise throughput or regulatory preparedness. Such insight supports targeted capability reinforcement and refinement of governance structures to strengthen resilience.

At a product-portfolio level, talent science introduces capacity realism into prioritization decisions. It measures how intensified programs draw upon shared technical and leadership resources, revealing where concurrent initiatives exceed available execution bandwidth. The results inform sequencing decisions grounded in delivery capacity rather than forecast ambition.

Across digital and automation initiatives, a talent-science framework evaluates whether organizational decision velocity aligns with system acceleration. Intensified-process data flows and automated control architectures increase the frequency and complexity of operational judgments (**3, 8**). Leaders can identify where human oversight capability requires reinforcement to maintain process stability and compliance confidence.

In succession and workforce stability planning, a talent-science model reveals knowledge concentration and structural fragility within critical domains. Early identification of such patterns

facilitates deliberate knowledge transfer, structured role evolution, and strategic capability development that preserve system continuity during growth or turnover.

Enabling Sustainable Intensification Through Workforce Design

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The future of biomanufacturing intensification depends on synchronizing technology, process, and talent evolution. Equipment and digital platforms can increase theoretical capacity, but realized performance depends on how effectively a workforce system can adapt.

Talent-science modeling provides a way to design such adaptation deliberately. By measuring workforce flow and stress points, organizations can evolve roles, decision rights, and governance structures in parallel with process changes. Companies can invest in capability where it protects system stability rather than where it appears attractive on paper.

Shifting to such an approach enables a transition from individually dependent delivery to performance grounded in structured operating systems. It reduces exposure created by concentrated expertise and strengthens organizational resilience with increasing scale and complexity. The new approach also reinforces regulatory confidence by demonstrating that intensified and continuous processes are sustained by coherent, scalable governance and capability frameworks.

An Intensified Future

Biomanufacturing PI has entered a phase in which organizational design influences performance as directly as process engineering. As manufacturing platforms become more tightly integrated, data-rich, and speed dependent, the workforce system becomes a determining variable in throughput stability, regulatory readiness, and cost control.

Technical capability enables intensification; and continuous processing sustains them. When decision flow, skill coverage, and governance density are misaligned with system complexity, performance degradation emerges despite sound process science. When workforce design evolves in parallel with technological advancement, intensified and continuous systems operate with stability rather than with fragility.

Sustainable PI therefore requires predictive insight into how work moves, how decisions accumulate, and how expertise is distributed under real demand conditions. Flow-based workforce modeling provides that insight. It allows leaders to intervene before review latency expands, before expertise concentration

creates risk exposure, and before execution strain appears in financial metrics.

PI without workforce modeling increases systemic vulnerability. Instead, it must be supported by predictive organizational design for scalable resilience. In the next generation of biomanufacturing, both dimensions must advance together.

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