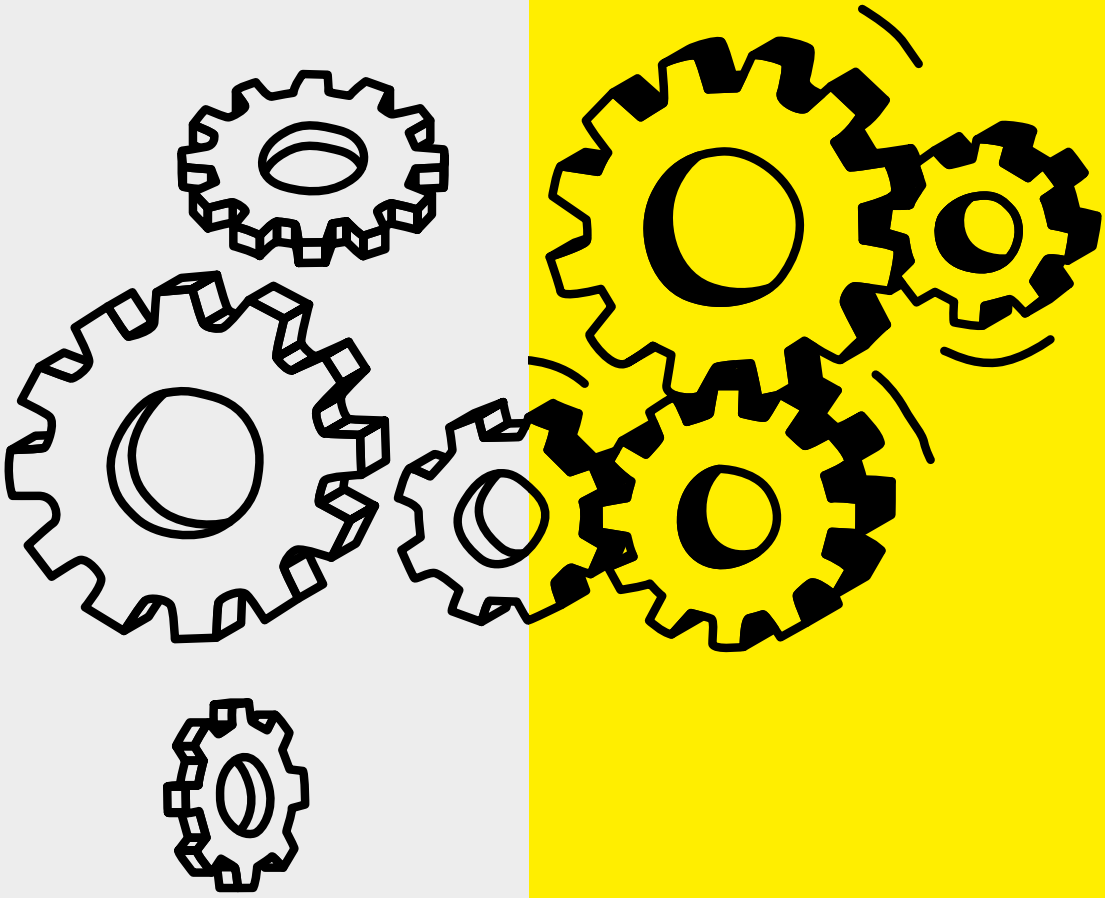


Simplifying Progress

Simplifying the Path to Autonomous Bioprocess Control

October, 2026 | Steve Miller, Gerben Zijlstra, Louis Crowley, Amine Djeffal, Cyril Mak, Beatrice Claverie, Vincent Lam, Sherwin Ting

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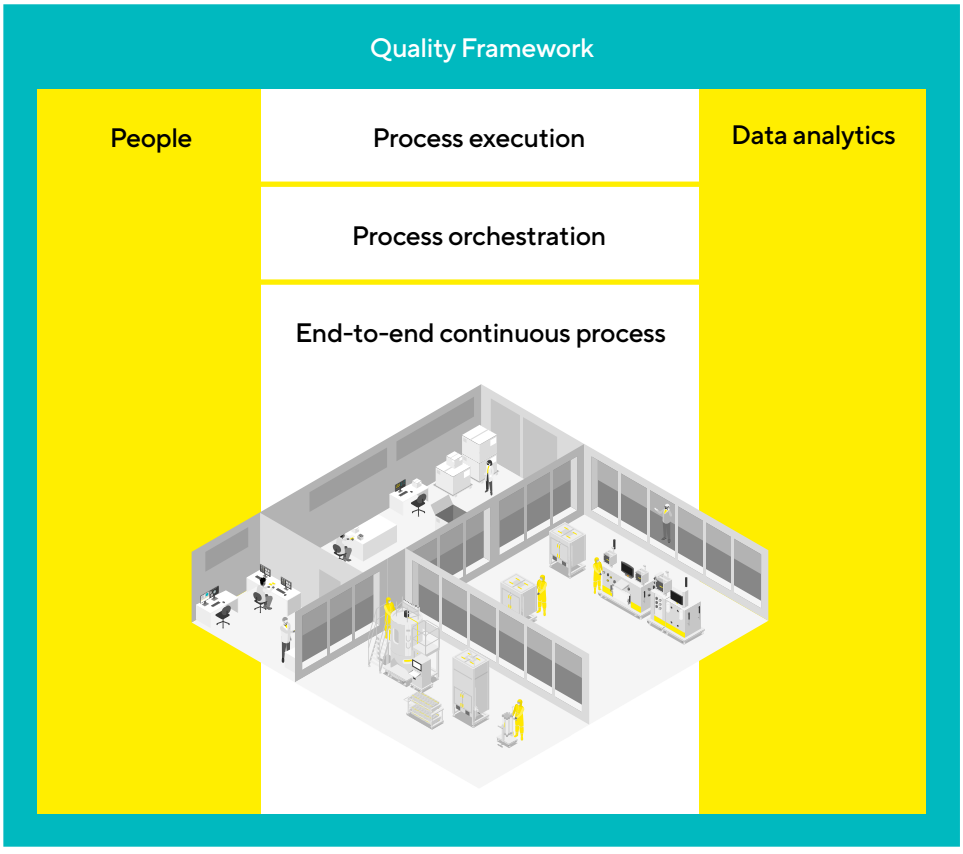
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Introduction

For decades, industries such as semiconductor manufacturing have used lights-out manufacturing. These industries adopted lights-out manufacturing to increase yield while reducing cost, and the advantages are clear for such high-volume precision manufacturing, where production tolerances are at the nanometer scale. However, in biopharmaceutical manufacturing, where products and processes are inherently more variable, removing human involvement in activities such as offline testing and the release of intermediate products to subsequent unit operations has been more challenging.

To ensure patient safety and product efficacy, product quality has always been the top priority in the biopharma industry, but with increased competition, greater emphasis has been placed on reducing cost and decreasing time to market, which must be achieved without compromising quality. Lights-out manufacturing has the potential to address a number of these challenges.

Figure 1: *Key components of an autonomous bioprocess control framework. The end-to-end continuous process line forms the physical foundation. The orchestration layer coordinates individual unit operations, while the process execution layer connects process activity with material, production, and compliance records. Data analytics support process monitoring, prediction, and optimization across these layers, and people provide the expertise and governance needed to develop and maintain the system. All components operate within a quality framework that supports consistent, compliant operation across the process lifecycle.*



Lights-out manufacturing, or "autonomous bioprocess control" (ABC), as defined in a paper published by BioPhorum,[1] refers to a fully automated biologics facility with a control system that can monitor, predict, and autonomously control the running process (Figure 1). These facilities are more cost-efficient, enable a deeper understanding of processes, and facilitate continuous optimization that drives up quality, while decreasing cost of goods in a more environmentally sustainable manner. However, achieving this state requires all elements to be connected, the design space to be characterized, and the appropriate expertise and understanding of regulatory requirements to be in place.

As such, biopharma companies face several barriers to achieving autonomous bioprocess control. These challenges extend beyond technology to include organizational structures, data governance, regulatory compliance, and legacy infrastructure. Implementing changes within existing infrastructure is perhaps the toughest challenge, as it is impractical to replace all infrastructure simultaneously.

There is no single path to autonomous bioprocess control, but maintaining momentum is key. Established practices from other industries can help organizations prioritize improvements. For example, Weighted Shortest Job First (WSJF), used in the Scaled Agile Framework, prioritizes work by weighing the cost of delay against the estimated duration.[3] This methodical process helps identify improvements that deliver business value early, helping sustain progress toward autonomous bioprocess control.

The goal of this paper is to show that there is a realistic pathway toward ABC and that the remaining gaps that prevent its broad implementation could be closed within the next five years. To explore this pathway, we follow a hypothetical monoclonal antibody (mAb) from discovery to commercial manufacturing over a seven-year development period, based on the assumptions outlined on this page.

The paper examines various technologies needed to support this journey, including whether established tools are fit for future requirements. Figure 1 shows the main blocks of an autonomous bioprocess control facility and provides a framework for discussing the remaining challenges. We will also reference the Digital Plant Maturity Model (DPMM®; Table 1), which describes the capabilities of the ABC facility and its supporting enterprise.[4]



Assumptions

- **Process design:** As discussed in our previous publication *The New Economics of Biologics: Breaking the $50/g Barrier—Now,*[2] a fully connected and intensified commercial manufacturing process is implemented from production bioreactor to bulk drug product, achieving the lowest cost of goods. Single-use systems are employed to increase flexibility, reduce footprint, and minimize environmental impact.

- **Tech transfer:** Phase I clinical production uses the same family of systems as commercial manufacturing. Where a scale-out strategy has been defined, both stages use systems of the same scale.

Organization

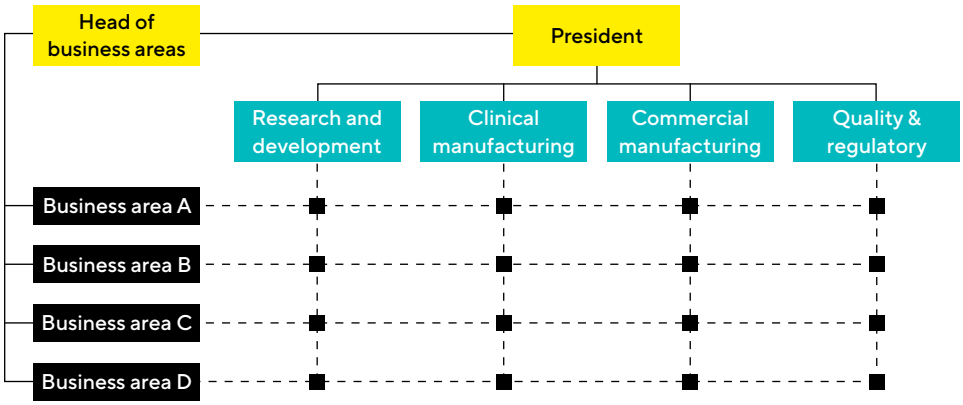


Sartorius can support workforce capability development through structured training and enablement programs focused on process intensification, data analytics, and advanced process control, including hands-on use of SIMCA® and MODDE® software. These programs combine software, training, and expert support to build internal capability in model development, interpretation, and lifecycle management. Sartorius also partners with the National Institute for Bioprocessing Research and Training (NIBRT) on a new facility expected to provide more than 1,000 scientists, engineers, and students each year with hands-on experience in intensified upstream and downstream processes.[5]

Many biopharma organizations operate in silos across the molecule lifecycle, with research and development activities separated from manufacturing operations (Figure 2). In larger organizations, these divisions are often even more granular, further complicating efforts to establish common standards for data, automation, and equipment.

Addressing these organizational barriers is the first step toward implementing autonomous bioprocess control. This requires top-down support and an organizational structure and culture that empower people to work across functions. A practical starting point would be to establish a cross-functional team with authority to make decisions across process development and manufacturing.

Figure 2: *Example of a matrix organizational structure across business areas and functional departments*



Alongside an appropriate structure and culture, companies may need to adapt their workforce skills to support continuous processing. Automation and data analytics expertise, for example, must be available as early as process development to establish continuous control strategies. New departments may also be needed to manage data governance across the different phases of a molecule's journey to commercial production.

The shift to 24/7 downstream processing, as already established upstream, also has implications for staffing and training. Working hours may need to be adjusted to support continuous operation, and cross-training may be needed to enable operators to handle issues across the process train.

Legacy Infrastructure

Many large companies have invested billions in their infrastructure, yet much of the industry remains concentrated around Levels 2 and 3 on the DPMM® (Table 1). Adapting this infrastructure for autonomous bioprocess control presents a major hurdle. However, the seven-year development period assumed for our hypothetical mAb therapeutic provides an opportunity to introduce changes progressively. Beginning in process development, new technologies can be deployed and refined for each new molecule that enters the clinical phase, carrying these capabilities forward into commercial manufacturing. Sanofi is taking this approach with its collaboration with Sartorius on a new connected and intensified downstream processing line.[6]

Table 1: *Definitions of levels in the DPMM®*

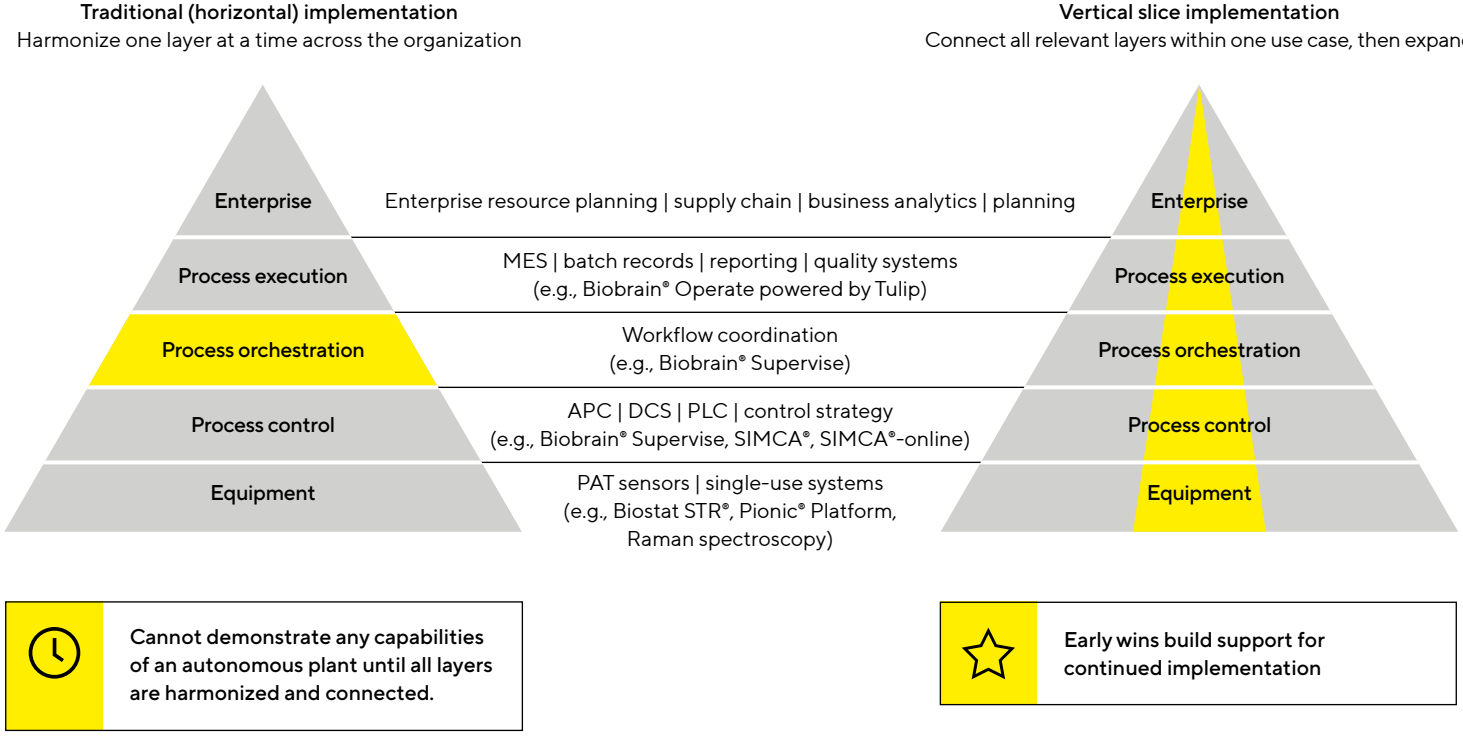
Level 1	Level 2	Level 3	Level 4	Level 5
Pre-digital plant	**Digital islands**	**Connected plant**	**Predictive plant**	**Adaptive plant**
Largely manual, paper-based processes with basic automation and minimal system integration.	Isolated automation and digital systems, with limited integration and substantial manual effort for analysis.	Integrated plant systems and electronic batch records, with automated analytics and some real-time process monitoring.	Enterprise-wide integration, real-time process analytics, and predictive modeling to anticipate events and improve processes.	Fully integrated, autonomous operations with continuous process verification, adaptive analytics, and integration across the value chain.

Implementation Approach

Implementation is arguably the most challenging aspect of autonomous bioprocess control. Assuming the transition has senior management support and a team empowered to make organizational and technology decisions, the next step is to create a roadmap that demonstrates business value throughout the transition, rather than only at its conclusion.

In a typical enterprise, harmonizing a single layer such as the distributed control system (DCS) is generally accepted to bring significant savings from economies of scale. However, in a siloed biopharma company, a digital platform fit for commercial manufacturing may not be suitable for Phase I clinical production. This is particularly true of traditional large manufacturing execution systems (MES) or DCS, which typically prioritize robustness over flexibility.

Figure 3: *Horizontal and vertical slice approaches to implementation. Horizontal implementation harmonizes one layer at a time across the organization. A vertical slice connects all relevant layers within a single process or use case, allowing business value to be demonstrated before implementation expands to additional unit operations, products, and sites.*



An alternative to harmonizing one layer across the enterprise is to connect all relevant layers within a single process or use case, i.e., a vertical "slice," from equipment and automation to data and process execution. For the molecule considered here, this would begin during process development. Examples include an orchestrated, intensified seed train followed by concentrated fed-batch production, or a perfusion bioreactor connected to a continuous capture step.

These connected capabilities can be tested and their value demonstrated before being carried forward into clinical manufacturing. Implementation can then expand to additional process steps as the molecule progresses toward commercial manufacturing, leveraging the full value of the dataset generated during process development and optimization.

Regardless of the implementation approach, current platforms and regulatory frameworks are not yet ready to support autonomous bioprocess control. Customers and suppliers must develop joint roadmaps for implementation, while partnering with quality teams and regulators to address the current gaps. The vertical slice approach allows this engagement to begin within a limited scope, so challenges associated with new capabilities, such as autonomous control strategies, can be addressed before broader implementation.



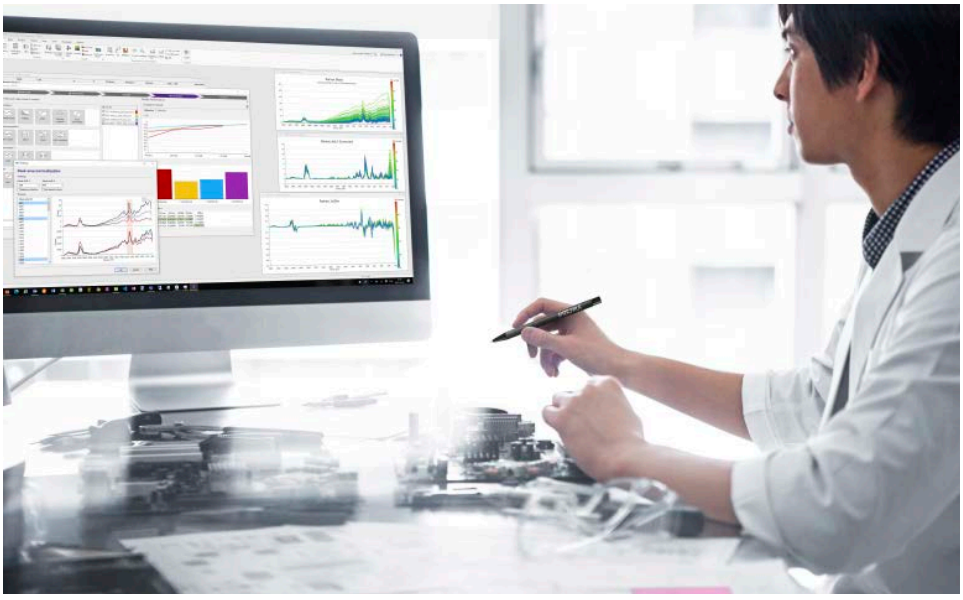
The Sartorius Process Intensification Forum provides a platform for industry alignment and knowledge sharing. Held in Asia, Europe, and the United States, these forums bring together thought leaders to share experience and discuss progress toward process intensification and autonomous bioprocess control. The 2026 European forum, held in Göttingen on September 16-17, 2026, brought together more than 200 experts from process development, manufacturing, and technology innovation. Representatives from the European Medicines Agency (EMA) and industry organizations such as BioPhorum, alongside industry leaders, presented advances in process intensification and continuous biomanufacturing and shared their perspectives on the path toward autonomous bioprocess control.

Data Model

The data model is the basis for creating a digital twin. It defines how data are standardized and characterized, and how they relate to one another. For example, it specifies how pH is described, which units are used, and how a measurement is linked to a process unit, such as a bioreactor or chromatography system, or to a sample analyzed offline using a blood gas analyzer. Without this foundation, including a shared ontology that defines concepts and their relationships, comparing data across systems is very time-consuming, requiring many hours of data pre-processing. If the data from process development, clinical phases, and commercial manufacturing are not comparable—as is currently the case in many molecule development journeys—this creates a significant barrier to developing digital twins early in development and evolving them through to commercial manufacturing.

Existing commercial standards can help establish this common data foundation. For example, the Allotrope Simple Model (ASM)[7] is a human- and machine-readable text format for representing standardized laboratory data. Its ease of integration with programming languages, tools, and workflows can support the implementation of autonomous bioprocess control. However, its primary application is in laboratory settings rather than commercial manufacturing.

The vertical slice implementation model allows organizations to begin with the data needed for a single process or use case, establishing the corresponding data model, governance, and infrastructure before extending them to additional process steps. In our hypothetical development journey, this means establishing the data model for the initial process development use case and building on it through clinical phases and into commercial manufacturing. Partnering with a company that understands the full stack—from process equipment through automation, MES, and data analytics—is a key success factor.



Automation Integration and Standards

A significant challenge in the biopharma industry is the compatibility of established and emerging standards. Legacy standards, such as ISA-88[8] and ISA-95[9], are well understood and provide a framework for describing process control and existing infrastructure. However, newer standards such as Module Type Package (MTP),[10] which uses Open Platform Communications Unified Architecture (OPC UA) to enable faster integration within a modular ecosystem, can conflict with these established frameworks. Much of this conflict stems from the shift away from the traditional stack of MES-DCS(-PLC)-IO for unit operations toward a process orchestration layer connected to a smart package unit. The International Society of Automation is working on ISA-113 to address these conflicts, but the standard will take several years to finalize.[11]

In addition, extensions to MTP such as Discover Negotiate Pair (DNP)[12] promise to enable industrial plug-and-play integration that could transform the biopharma industry. DNP could allow sensors to be dynamically added to or removed from process equipment, much like connecting or disconnecting a mouse or camera from a PC. This capability will be essential in flexible facilities that are reconfigured after each campaign. As our hypothetical molecule progresses, compatible interfaces would allow new sensors and process units to be introduced without redesigning the automation architecture at each stage. Partnering with companies actively involved in developing and implementing these standards will be essential to achieving autonomous bioprocess control.

Process Analytical Technology

Process analytical technology (PAT) covers a broad range of tools and approaches, but here we focus on process measurements and analysis.

Autonomous bioprocess control cannot rely on manual sampling and the delays associated with sending samples to a laboratory to measure critical process parameters. These measurements must be performed inline or at least at-line. As technologies evolve, new analytical methods can be tested in process development. This testing should include calibration strategies to mitigate sensor drift during the extended operating periods required for continuous manufacturing. If successful, these methods can then be transferred to commercial manufacturing. Standards such as DNP-enabled MTP will be critical to incorporating new technologies without redeveloping unit operations and automation systems each time.

In addition to measuring critical process parameters for process control, new sensing technologies are needed to monitor critical quality attributes, such as glycosylation, inline and as close to real time as possible. With sufficient data, soft sensors could provide indirect estimates of these attributes, for example, by using relationships between residence time distribution and glycosylation. Integrating these measurement and prediction capabilities into the process creates new requirements, as illustrated by the growing use of Raman spectroscopy.

Raman spectroscopy is increasingly used to monitor critical process parameters in upstream applications, such as glucose and lactate concentrations, and critical quality attributes, such as protein titer, in real time during production. Newer downstream applications include predicting how many more cycles are required to reach the desired protein concentration during ultrafiltration. In our mAb development scenario, introducing Raman spectroscopy early requires consideration of both its immediate measurement capabilities and the transferability of the system and its models through clinical phases into commercial manufacturing.

This raises several questions:

- Can the system's data be integrated into the existing automation infrastructure?
- Have the data been integrated into the organization's data model?
- Were the data collected and stored in compliance with 21 CFR Part 11?[13]
- Are the models generated in process development transferable to Phase I clinical production and ultimately commercial manufacturing?
- Has fluidic integration been considered across scales? Will measurements in a 50 L process development bioreactor be comparable to those in a 2,000 L commercial manufacturing bioreactor?

Unit Operations

While the industry has mature technologies and processes for producing mAbs in fed-batch mode, continuous downstream processing has not been readily adopted across biomanufacturing.[14] Upstream processing therefore provides a practical starting point for our vertical slice approach, using well-established single-use systems that can operate in perfusion or fed-batch mode. In the development scenario defined here, we assume these systems are already in place, limiting the impact on existing infrastructure and allowing a common platform to be used from process development through commercial manufacturing. Connecting the bioreactor to downstream capture or upstream seed train steps allows the solution to expand, progressively increasing the complexity of fluidics and process orchestration.

Although continuous downstream processing is less mature, solutions are emerging that support its gradual implementation. For example, Pionic® Platform combines modular downstream systems with integrated automation and orchestration via Biobrain® Supervise, allowing individual unit operations to be intensified separately or connected as implementation expands.[14]

Process Orchestration

Connecting unit operations through modular platforms requires automation that coordinates their operation and can be adapted as the process evolves. This process orchestration reduces the need for human intervention and helps minimize the risk of batch failure, making it an essential step toward autonomous bioprocess control.

In process development and early clinical manufacturing, individual unit operations or groups of equipment are often automated independently, creating islands of automation with limited connectivity between them. A different automation approach is usually adopted for commercial manufacturing, limiting the reuse of any existing process control strategies or digital twins and requiring substantial redevelopment.

Traditional automation platforms require users or system integrators to write application-specific code. This process is time-consuming and poorly suited for the flexibility needed during process development and early clinical phases. Some companies have developed extensive code libraries to make these platforms more configurable. However, libraries built around existing processes may not readily accommodate the increasingly complex continuous downstream processing platforms entering the market.

Selecting suppliers that offer configurable automation platforms following guidelines like GAMP 5 category 4[15] with flexible, open integration strategies will be critical. Applying the vertical slice approach to our mAb would establish coordinated control within a limited scope during process development. This orchestration strategy could then be adapted through clinical manufacturing and extended as additional unit operations are connected, rather than rebuilt for commercial production.



Process Management Automation

The Sartorius systems portfolio could support an end-to-end continuous bioprocess train, with a Biostat STR® bioreactor operating in perfusion mode connected to a Pionic® Platform for continuous downstream processing from capture to final product concentration. The Celsius® FFT Platform would provide bulk product freezing, with the overall process orchestrated by Biobrain® Supervise and managed by Biobrain® Operate.

Beyond real-time process data, autonomous bioprocess control requires non-automation data such as molecule information, batch campaign ID, information on raw materials used (including filters and media composition), and offline sampling data. Traditionally, these data are captured in MES platforms, but their costly deployment has typically limited their use to commercial manufacturing facilities producing blockbuster drugs. Developing advanced, data-driven strategies requires cost-effective and flexible solutions for process development and clinical phases.

No-code MES platforms have been available in the biopharma industry for several years, and their capabilities continue to expand. These platforms offer the potential to combine the flexibility needed in process development and clinical phases with the compliance required for scaling to commercial manufacturing. For our mAb, introducing this capability during process development would allow material and process execution data to be captured consistently through the clinical phases and into commercial manufacturing. Connecting these records with real-time data from process orchestration systems would build a more complete basis for developing and refining digital twins.



Digital Twins

In this paper, digital twins are defined as dynamic, virtual representations of physical bioprocesses that continuously synchronize with real-time process data. Combining mechanistic and | or data-driven models with live inputs, they simulate behavior, predict outcomes, test scenarios, and support monitoring, control, and optimization across the product lifecycle, from development through commercial manufacturing and tech transfer. For many years, the largest players in the biopharma industry have employed the basics of a digital twin by using multivariate data analytics (MVDA) to monitor and predict processes.[16-21] Well-established standards, such as ASTM E2891-20,[22] cover validation and lifecycle management, but the biggest gap is establishing the data foundation, data governance, and data science expertise needed to widely adopt MVDA capabilities across the industry.

For the mAb considered here, the vertical slice approach could begin with MVDA applied to the bioreactor during process development, using proven technology and established validation strategies. Models could then be refined using data generated through the clinical phases and adapted for commercial manufacturing. As additional process units are connected, the scope of monitoring and modeling could expand to include them, providing a basis for evaluating predictive and, ultimately, autonomous control.

Despite advancements in both upstream and downstream processing, a critical limitation remains: the lack of fully integrated, end-to-end process models. Most organizations still rely on fragmented modeling approaches, developed independently across units and lifecycle stages.

Developing end-to-end models requires data from multiple campaigns, with systems operated at steady state for the maximum anticipated duration. Deliberate process perturbations are also needed to characterize responses to anticipated disturbances, allowing the digital twin to predict their effects during operation. This exploration of the process design space can be made more efficient by using design of experiments principles that guide the selection of conditions to test.

The resulting models will then enable scenario simulation, process optimization, and development of operational strategies across the full product lifecycle. In process development environments, these tools already support the journey with applications including:

- Cell line selection for process intensification
- Media development and feeding strategy optimization[23]
- Upstream scenario-based design (e.g., prediction of perfusion performance based on fed-batch data) and in silico optimization (e.g., of fed-batch or perfusion strategies)[24,25]
- Upstream autonomous perfusion control[26]
- Development of downstream startup and shutdown strategies
- Semi-automated experimentation through adaptive design of experiments



The Sartorius Umetrics® Data Analytics Ecosystem supports process exploration through MODDE® design of experiments software. Data generated by these experiments can then be analyzed in SIMCA® software to develop models for process monitoring and prediction using SIMCA®-online.

Technology Transfer

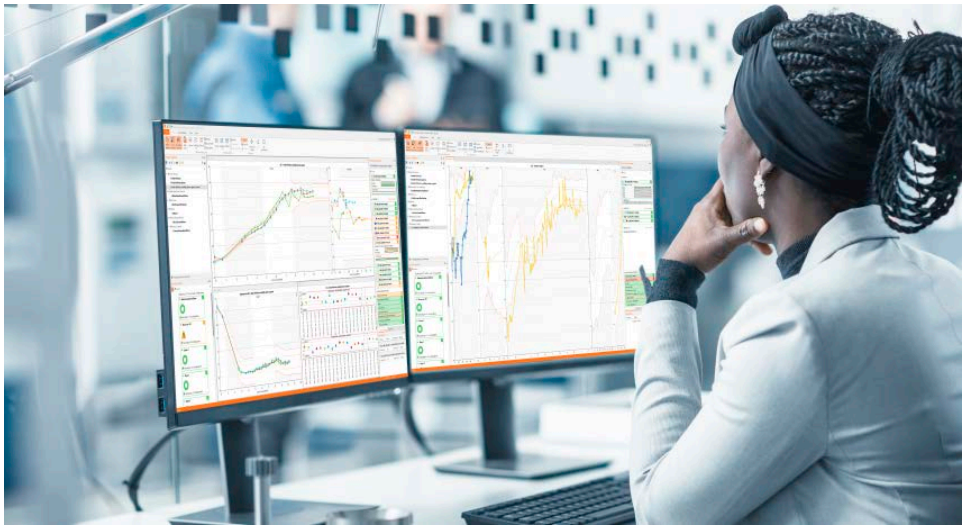
During technology transfer from Phase I clinical production to commercial manufacturing, core elements such as the cell line, cell culture media, or filtration materials may remain unchanged. However, equipment scale, suppliers, and system formats may change. For example, technology transfer may require transitioning the process from single-use to stainless-steel equipment or adopting a different automation platform. These changes can prolong technology transfer by requiring further process development. Achieving autonomous bioprocess control requires a consistent platform approach to be established much earlier, beginning in process development, to achieve fast and cost-effective technology transfer.

For the mAb considered here, this would mean characterizing the process design space during process development and generating sufficient data to predict behavior in larger-scale systems, define process limits, and establish the maximum duration of a campaign. This would mean a significant upfront investment in small-scale campaigns to build the models, followed by multiple verification runs throughout Phase I clinical production and commercial manufacturing to generate data to validate the approach.

Maintaining this platform approach throughout the molecule's development, supported by data generated at each stage, could minimize redevelopment efforts during technology transfer and support progression toward autonomous bioprocess control.

Key elements to establish consistency across this journey include:

- Data governance
- Analytical technologies
- Critical process materials, such as media, resins, and filters
- Process units
- Process modeling platforms
- Automation strategies



Regulatory

Regulatory development and support are critical to achieving autonomous bioprocess control. This covers many areas, from validation and model lifecycle management to the potential use of process simulation to reduce physical testing of long-duration processes.

For prospective and concurrent validation, ICH Q7 recommends three consecutive successful production batches as a guide, while recognizing that additional runs may be needed for complex processes or those with prolonged completion times. Generating this evidence for long-duration continuous processes could make validation particularly costly during Phase I clinical production, while the full benefits of autonomous bioprocess control may not be realized until Phase III or beyond.

New online technologies, such as Raman spectroscopy for measuring metabolites or substrates, also require appropriate validation and traceability to the guidelines developed by the National Institute of Standards and Technology (NIST). Process-specific models and validation strategies are currently needed, adding to the work required to implement these technologies.

It is important to note that regulators recognize the value of autonomous bioprocess control and have created dedicated teams to work with suppliers and drug developers on the associated challenges. The U.S. Food and Drug Administration's (FDA) Emerging Technology Program (ETP)[27] and the European Medicines Agency's Quality Innovation Group[28] have been established to support the introduction of novel technologies and encourage early engagement.[29] In our mAb development scenario, these discussions would begin during process development, helping define the evidence needed as the models and control capabilities progress through clinical phases toward commercial manufacturing.

The transition to autonomous bioprocess control will be incremental, rather than a single transformation of the entire facility. One approach is to update the approved manufacturing process for an existing biological product at the same site. This requires assessing the applicable post-approval change requirements, supported by a comparability assessment aligned with ICH Q5E and, for continuous processes, ICH Q13.[30,31] The comparability protocol must define the critical quality attributes and process parameters to be monitored, statistical acceptance criteria, and the scope of process performance data to be generated at the site before the change is implemented commercially.

The approach to defining a batch and the proposed commercial batch size or range should be described in the regulatory submission, as outlined in ICH Q13.[31] Later changes beyond the approved batch size range require supporting data and regulatory approval | notification. The regulatory pathway should be determined early: a Prior Approval Supplement or Changes Being Effected in 30 Days (CBE-30)[32] supplement in the United States, or a Type II or Type IB variation[33] in the European Union, depending on the nature and classification of the change.

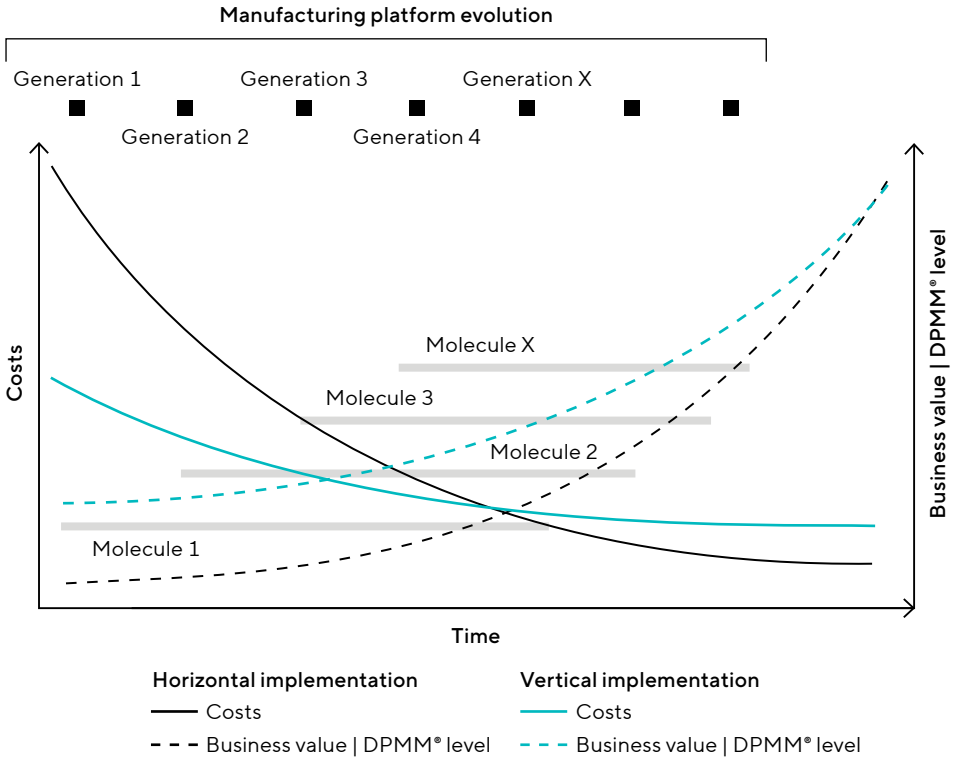


Sartorius actively engages in cross-industry initiatives such as BioPhorum, contributing to shared learning, benchmarking, and alignment on best practices across the biopharmaceutical industry. Its solutions and practices are aligned with widely recognized regulatory guidance and industry standards, including ICH Q13 on continuous manufacturing[31] and ASTM E3326-22 on biopharmaceutical continuous manufacturing.

An alternative approach is to introduce platform improvements with successive molecules while maintaining the established process for molecules that have passed Phase I clinical development.[29] Each new molecule would begin development using the latest manufacturing platform iteration, allowing improvements to be introduced progressively across the portfolio (Figure 4). Updates could follow an annual cycle aligned with maintenance or occur more frequently where the benefits justify them. This would allow the organization to progress through the DPMM® while delivering business value at each stage. This approach requires substantial upfront investment but delivers cumulative value with each new molecule and platform iteration. These improvements should substantially accelerate technology transfer and shorten each successive molecule's overall journey to commercial manufacturing, even though the duration of individual clinical trials remains unchanged. Figure 4 shows only those molecules that reach commercial manufacturing; many entering clinical Phase I will not progress through all subsequent stages.

In February 2026, the FDA issued updated guidance on Computer Software Assurance for Production and Quality Management System Software.[34] Although its implications are not yet widely understood by biomanufacturers and suppliers, it has the potential to accelerate the adoption of new digital technologies, shifting the focus from computer systems validation to a more risk-based approach to software adoption.

Figure 4: *Platform approach to autonomous bioprocess control. The value of autonomous bioprocess control increases with subsequent molecules as investments dilute and development time and costs fall.*



Conclusion

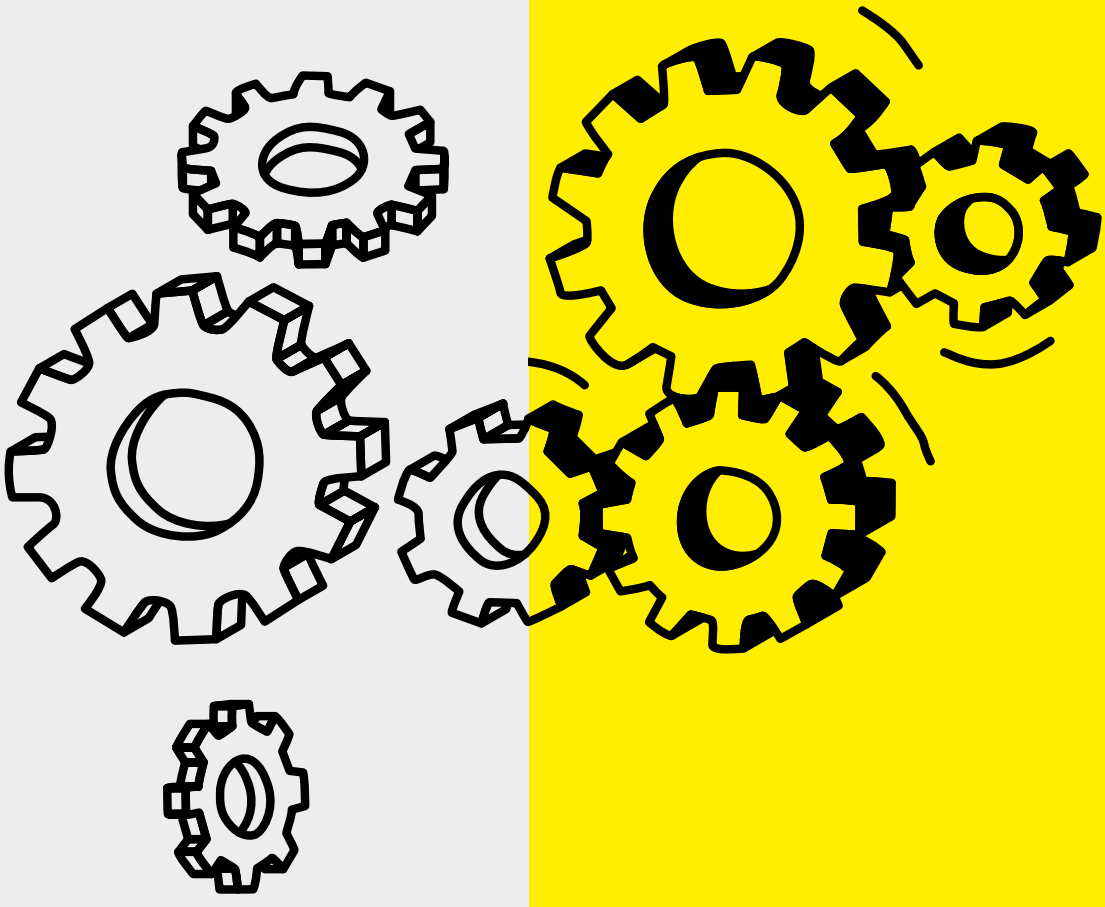
Autonomous bioprocess control offers clear potential benefits. The challenge is establishing a practical pathway to make it standard across the biopharmaceutical industry.

Large biopharmaceutical companies have invested billions in custom systems and infrastructure to deliver high-quality, life-changing medicines. Competitive pressures and sustainability requirements are now increasing the need to reduce manufacturing costs and shorten the time it takes to bring new molecules to market. While it is clear that a move toward increasing digitalization is essential to achieving these goals, large, often expensive, digitalization programs face scrutiny when their business value is unclear.

The development journey described in this paper provides a framework for incremental implementation. Beginning with a vertical slice, manufacturers can establish connected processes, data, and automation early in development and extend these capabilities as the molecule progresses toward commercial manufacturing. Successive molecules provide opportunities to introduce further platform improvements.

This approach requires collaboration across functions and sustained partnerships with suppliers and regulators. Measuring business value at each stage will be essential to ensuring that the journey toward autonomous bioprocess control is as valuable as the goal.

Learn more about how Sartorius can support your journey toward autonomous bioprocess control: sartorius.com/process-intensification



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