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From Strain Readiness to Systems Readiness in Industrial Bioprocessing

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Abstract

Industrial biotechnology can now generate new hosts, pathways, feedstocks, and product concepts with unprecedented speed. Yet promising laboratory performance often fails to become credible manufacturing performance. This article argues that the gap cannot be addressed by strain readiness alone. It also requires systems readiness: the extent to which a biologically promising process can be observed, controlled, transferred, and supported by evidence beyond proof-of-concept. This is especially important between strain development, upstream process development, and scale-up, where weak observability and fragmented system architecture can turn promising biology into uncertain industrial performance. Analytics, automation, sampling, digital models, and infrastructure should therefore be treated as essential parts of scalable process development.

1. Industrial biotechnology is generating possibility faster than it is learning to scale

Industrial biotechnology has become highly effective at producing promising biological starting points. It is increasingly expected to support applications across food, feed, enzymes, chemicals, materials, therapeutics, circular manufacturing, and reduced dependence on fossil-derived inputs. Synthetic biology, metabolic engineering, genome editing, computational design, and high-throughput screening have expanded both the range of molecules that can be made biologically and the range of organisms that can be engineered to produce them [1,2]. This progress is real, but it sharpens an important distinction: a strain that performs in a controlled laboratory setting is not automatically a process that can be manufactured reliably.

Biological performance becomes industrially meaningful only when it can be observed, controlled, reproduced, and interpreted under realistic process conditions. A strain may show attractive productivity in early experiments, yet still remain difficult to scale, stabilize, monitor, or troubleshoot. Such problems are often described as late-stage scale-up failures, but many originate earlier, when development decisions are made with insufficient visibility into the biological and process states that will later determine performance.

This article focuses on emerging and translational industrial bioprocesses at the interface of strain development, upstream process development, and scale-up. Mature biopharmaceutical, enzyme, food, feed, precision-fermentation, or bio-based manufacturing processes may already benefit from substantial process knowledge and established manufacturing discipline. The concern here is narrower, but increasingly important: newer or less characterized processes are often assessed primarily on biological promise before the surrounding process system is mature enough to support that promise.

Recent investment cycles in precision fermentation and related industrial biotechnology areas have made this tension more visible [1,3]. They have shown how difficult it can be to convert compelling biology into production systems that meet expectations for cost, volume, robustness, and timeline. These outcomes cannot be attributed to technical scale-up alone. Capital availability, infrastructure access, regulatory pathways, commercial demand, and techno-economic assumptions also matter [1,3,4]. However, weak process understanding amplifies uncertainty across all of them. When the causes of performance changes remain unclear, it becomes harder to refine cost projections, de-risk scale-up, and build confidence in manufacturing claims [1,4,5].

Industrial biotechnology therefore needs a sharper translational question. Strain readiness asks whether the cell can perform in principle. Systems readiness asks whether the process around the cell is mature enough to make that performance visible, controllable, transferable, and credible beyond proof-of-concept.

2. A wider design space creates a larger learning burden

The biological design space for industrial bioprocessing is widening. Established hosts such as *Escherichia coli* and *Saccharomyces cerevisiae* are increasingly complemented by filamentous fungi, cyanobacteria, and other nontraditional or less extensively characterized organisms [2]. Feedstocks are also diversifying beyond refined sugars toward lignocellulosic hydrolysates, industrial side streams, waste-derived inputs, food-processing residues, gas streams, and substrates such as methanol, carbon monoxide, or carbon dioxide [6,7].

These directions may enable broader product portfolios, alternative input streams, improved carbon use, and stronger circularity claims, but they also increase the burden on process learning. Some nontraditional hosts may have limited industrial history or remain incompletely characterized under production-relevant conditions [2]. At larger scales, cells may also encounter oxygen, substrate, and pH gradients whose physiological consequences must be characterized for the selected host and process [8]. Circular or waste-derived feedstocks may likewise vary in composition and may contain impurities or inhibitory components that become relevant during repeated operation [6,7].

Scale-up adds another layer of uncertainty. Large bioreactors are not simply larger versions of laboratory vessels. Mixing behavior, oxygen transfer, and the spatial distributions of substrate, dissolved oxygen, and pH change with scale [8,9]. Cells may move through zones of substrate excess, oxygen limitation, acid or base exposure, and, depending on the vessel and organism, other localized stresses, such as hydrodynamic shear or hydrostatic pressure. A pathway that appears stable in a well-mixed laboratory reactor may impose a different physiological burden in a production vessel [8].

A wider biological design space does not automatically create a wider manufacturing-ready design space. As hosts, feedstocks, products, or operating conditions become more diverse, it becomes increasingly important to observe relevant process states, connect measurements to decisions, and support controlled learning across scale.

3. Limited process visibility slows bioprocess learning

Bioprocess development commonly draws on core bulk and process-state measurements, including biomass, pH, dissolved oxygen, base addition, metabolite measurements, and endpoint product assays [10,11]. These measurements remain useful and often indispensable. In some emerging processes, however, they may provide insufficient biological resolution or deliver insight too late to guide intervention.

Bioreactor populations are rarely uniform. Cells within the same vessel may differ in viability, physiological state, stress response, metabolic burden, productivity, or adaptation to local gradients [12,13]. Bulk measurements can obscure these differences. A culture may appear acceptable by optical density while a relevant subpopulation has already shifted toward a less productive or more stressed state. By the time the change becomes visible through titer, yield, or product quality, the most useful point of intervention may already have passed.

When process performance depends on heterogeneity, stress adaptation, viability shifts, or transient physiological states, cell-state analytics and population-resolved monitoring can provide additional insight [12–14]. Such methods are not universally necessary. Mature and robust processes may already be controlled adequately through conventional process variables and established strategies.

Label-free approaches such as impedance flow cytometry can complement fluorescence-based and other optical methods by enabling rapid, preparation-light assessment of cell populations and heterogeneity, with potential value for repeated or automated bioprocess monitoring [15]. Their usefulness is greatest when the biological question, required specificity and resolution, sampling strategy, and deployment context are appropriately matched.

Cell-state analytics are only one part of the broader process analytical technology (PAT) landscape. Spectroscopy, off-gas analysis, automated sampling, at-line metabolite analytics, flow cytometry, image-based methods, soft sensors, and process data models each provide a different view of process behavior [10,11]. Reliable and sufficiently frequent data streams from complementary modalities can improve process observability and support data-driven or AI-assisted interpretation of biological responses. The value of analytics increases when measurements are connected to one another and to the process decisions they are intended to support. A stand-alone assay may explain what happened after the run. An integrated measurement loop can shape decisions during the run.

This is where analytics become infrastructure. Sampling design, measurement frequency, data continuity, operator burden, and compatibility with existing infrastructure all determine whether information supports learning. Biopharmaceutical PAT and quality by design (QbD) provide a useful precedent for linking process understanding with control and regulatory confidence [5,10]. Industrial biotechnology should not copy biopharma uncritically, but the broader lesson remains: stronger manufacturing claims often depend on stronger process knowledge, not only stronger biological design.

4. Systems readiness is the bridge between biology and manufacturing

Improved analytics alone will not solve translation. A process may generate more data and still fail if sampling, analysis, interpretation, control, and decision-making remain disconnected. The challenge is not only measurement, but also the architecture of the process-learning system.

In development environments, this architecture can be weakened by fixed equipment assumptions, fragmented workflows, and uneven digital connectivity. Sampling, analysis, interpretation, and response may occur across different tools, timepoints, and organizational boundaries, slowing the rate at which processes become understandable and controllable [1,10,11].

Systems readiness is defined here as a qualitative process-development framework rather than a numerical readiness-level score. It describes whether a biologically promising process is sufficiently mature to be observed, controlled, transferred, and supported by evidence beyond proof-of-concept. It does not replace strain development, techno-economic or life-cycle analysis, regulatory strategy, or market validation. Rather, it connects them by asking whether biological performance can be made visible, reliable, and interpretable under conditions resembling the intended manufacturing context. **Figure 1** summarizes the four dimensions of systems readiness and the practical development question associated with each.

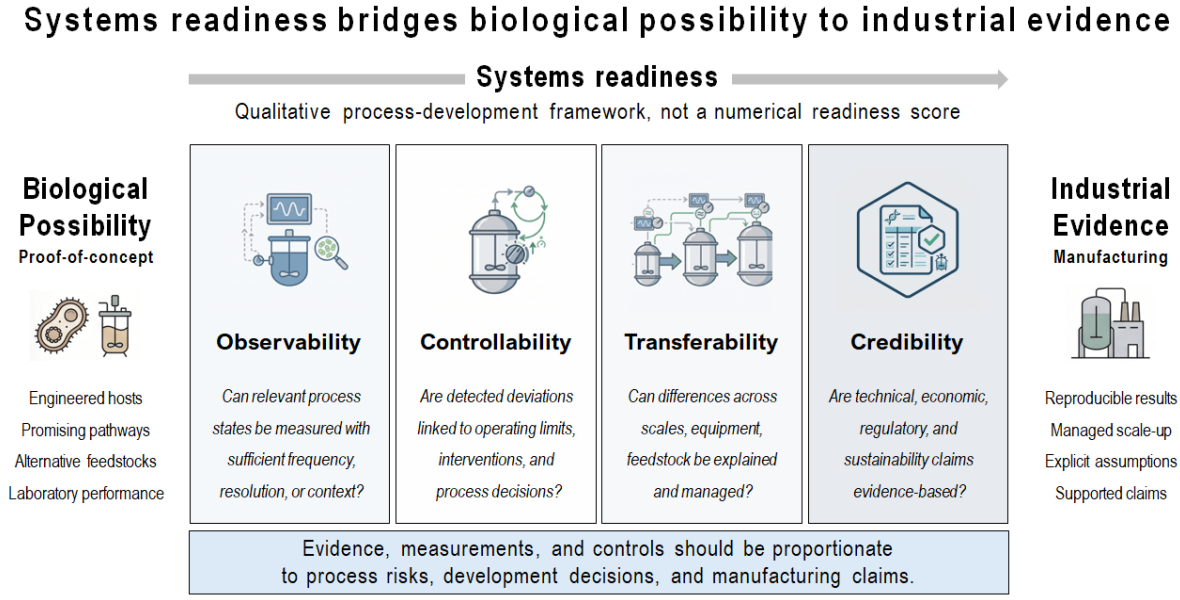


***Figure 1**. Systems readiness bridges biological possibility to industrial evidence through observability, controllability, transferability, and credibility. Each dimension represents a practical development question rather than a numerical readiness score. Evidence, measurements, and controls should be proportionate to process risks, development decisions, and manufacturing claims.*

The first dimension is **observability**: whether relevant biological or process states can be measured with sufficient frequency, resolution, and context to support learning. This may include pH, dissolved oxygen, temperature, agitation, gas flow, feed rate, off-gas composition, substrates, products, metabolites, impurities, viability, stress, and other cell-state information [10,11,14].

The second dimension is **controllability**. Visibility has limited value if it is not connected to action. Oxygen-transfer limitations, pH excursions, substrate fluctuations, and shifts in cell physiology need to be linked to operating windows, control strategies, intervention rules, and development decisions [5,8–10]. During scale-up, gradients matter because their consequences must be anticipated, bounded, or mitigated.

The third dimension is **transferability**. A process rarely moves from bench to manufacturing without changing. Transferability means that differences between scales, vessels, sites, or feedstock lots can be explained well enough to guide adaptation. Scale-down models, comparable sampling strategies, standardized interfaces, and digital records can reduce friction between discovery, development, piloting, and manufacturing [1,8].

The fourth dimension is **credibility**. Here, credibility refers to the quality and sufficiency of the evidence supporting process claims, not to reputation. In precision fermentation, cost and sustainability claims cannot be inferred from strain productivity alone; they depend on process design, scale-up assumptions, feedstock and energy inputs, downstream operations, capital and operating costs, regulatory constraints, and market context [3,4]. Systems readiness does not make a process economically attractive. It clarifies whether the available evidence is sufficient to support economic, regulatory, partner-facing, or customer-facing claims.

Systems readiness does not require every process to use the same analytical tools or achieve the same level of sophistication; rather, it requires that the evidence, measurements, and controls be proportionate to the process risks, development decisions, and claims being made.

These four dimensions are not a layer added after biology. They are how biological performance becomes industrial evidence.

5. Outlook: from promising cells to credible processes

Reframing translation around systems readiness changes the development question. It moves industrial biotechnology beyond a primarily biology-design narrative toward a more integrated engineering discipline. Programs should ask earlier which process states must be observed, which deviations must be controlled, which scale effects must be tested, and which claims must ultimately be supported by evidence. The objective is not to add measurement or complexity for its own sake, but to improve learning and decision-making before uncertainty becomes expensive or difficult to reverse.

For process development teams, observability and controllability should be treated as early design questions rather than late troubleshooting tools. Stress tests, feedstock-variability studies, scale-down models, sampling strategies, and appropriately integrated analytics can help expose uncertainty while it is still actionable. The appropriate level of analytical sophistication will differ between processes; the goal is to generate information that is relevant to the risks and decisions at hand.

For technology providers, analytical tools should be designed as components of the broader process architecture, not only as increasingly sensitive instruments. Their practical value lies in shortening the loop between process state, biological interpretation, and operational response while fitting the sampling, automation, and decision-making realities of the development environment.

For infrastructure builders, shared pilot facilities, modular upstream platforms, automated sampling systems, and connected data environments are valuable when they help developers compare conditions, test scale effects, and learn before committing to fixed manufacturing configurations. For investors, systems readiness can provide a more disciplined basis for assessing whether technical, economic, and scale-up claims are supported by process evidence.

For regulators and customers, better process visibility can strengthen confidence in manufacturing claims, particularly when processes depend on new hosts, variable feedstocks, unfamiliar products, or ambitious cost and sustainability assumptions.

Industrial biotechnology does not lack compelling biology. What many emerging processes still lack is the systems discipline required to evaluate and operate that biology convincingly under industrial conditions. The next phase will depend not only on what cells can be engineered to do, but on whether biological, analytical, digital, engineering, and organizational layers can be aligned so that performance becomes visible, controllable, transferable, and credible.

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