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BioProcess International
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FOR THE GLOBAL BIOTECHNOLOGY INDUSTRY

Special Edition

The Best of BPI

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- Media-Optimization Strategies To Bring Down Costs
- The "Uberization" of Autologous Cell Therapies
- Accelerating AAV Development Workflows with Small-Molecule Yield Enhancers
- An Industry Perspective Toward a Harmonized Control Strategy for Polysorbates
- A New Regulatory Paradigm Amid Biosimilar Advances
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NANO PAUSE

Chris Spivey
Industry Relations and Strategic Partnerships Director, BPI

Proficiency in artificial intelligence, machine learning, and big-data analytics — capabilities that were considered specialized, perhaps "next-level" just five years ago — have become commonplace needs for the biomanufacturing workforce. "In pharma, the science evolves faster than the training, leaving too many people to learn on the job. We need to shift the paradigm, from reactive training to continuous capability-building," says Vincenzo Antignani, manager of global training technical services at ZOLL Medical Corporation.

An underlying reality is that it is hard for companies to find expert, fully trained staff as well as construct and conduct effective training themselves. Meanwhile, drug development is now a kaleidoscope of shifting technical targets and commercial priorities. One needs only to look at the explosion of GLP-1 demand to understand how shortfalls might arise. "We're building therapies that require people to understand machines, data, biology, and software simultaneously, then wondering why another two hours of SOP training isn't fixing the problem," says Brian Drapeau, cofounder of GxP Frame and Life Sciences AI Academy.

During COVID-19, training migrated to digital platforms. That shift exposed gaps in digital literacy, particularly among experienced professionals. Training delivery methods evolved and became younger facing. Virtual reality and gamified learning emerged for pharmaceutical education. Concomitantly, we moved away from one-size-fits-all training to personalized tailored programs — e.g., for hospital-based CAR-T production or mRNA manufacturing.

Baley Reeves, director at Texas A&M University's National Center for Therapeutics Manufacturing, points out, "As the US gears up to onshore much of its pharmaceutical manufacturing, talent shortages will be exacerbated, and manufacturers alone cannot afford to train the workforce needed to support new manufacturing facilities. A jointly funded effort between the private sector and federal/local government is required to ensure that the US has the human capital to support the onshoring of critical medicines." It remains unclear what the current administration is willing to do to support its clarion call for securing sovereignty over drug supply chains.

At Informa Connect, we aim to guide the next generation of bioprocessing scientists through our inaugural "Campus" component at Biotech Week Boston from September 22 to 25. In addition to some fun-for-the-young elements, like a quiz show, there are also presentations on "How To Navigate and Optimize Your Time in an Exhibit Hall," "How To Future-Proof Your Life Science Career — Early, Mid, and Late Stage," "From Bench to Leadership," and "Interview Tips for Life Science Jobs." Our hope is to foster the highly skilled workforce needed to realize the future of biotechnology.

EDITORIAL ADVISORS

Biosimilar Success in an Evolving Landscape

Development Considerations for Staying Competitive

Kimberly Salgado

The biosimilar landscape is shifting rapidly. Biosimilars are designed to emulate the mechanisms of action, safety profiles, and efficacy levels of reference biologic products for which patents have expired. Such drugs cost less to develop than their novel predecessors do and, as a result, help to expand treatment access for patients. Currently, increasing numbers of biologics are nearing patent expiration, creating vast opportunities for biosimilars developers.

However, evolving therapeutic modalities mean that biosimilar development is being challenged to move past standard monoclonal antibodies (mAbs). New biosimilar regulatory guidance is creating uncertainty about how to meet data requirements with fewer clinical studies than have been needed historically. Meanwhile, growing competition has created a challenging commercialization environment for emerging biosimilar products. Developers can set up their biosimilars for successful market entry by understanding the impacts of those changes to the landscape and creating an agile strategy from the outset.

Some innovator antibody–drug conjugates (ADCs) and bispecific antibodies (bsAbs, shown above engaging T cells) are scheduled to reach patent expiration in the near future, raising new opportunities and obstacles for biosimilars development.

Pivoting to Advanced Modalities

One key consideration for biosimilar developers is evolution among therapeutic modalities. Monoclonal antibodies have been mainstays of biosimilar development for some time, and they are expected to remain relevant. Nevertheless, as technology and biological understanding have advanced, therapies within newer modalities are becoming highly relevant to the biosimilars market. For instance, some innovator antibody–drug conjugates (ADCs) and bispecific antibodies (bsAbs) are scheduled to reach patent expiration in the coming years, and associated biosimilars are projected to have a high potential for revenue growth.

However, second-generation biologics also come with increased complexity in chemistry, manufacturing, and controls (CMC) that ensure drug-product quality and consistency. For example, to demonstrate sufficient similarity with a reference biologic, ADCs require careful structural characterization including drug/antibody ratio (DAR), consistency in drug-attachment sites, incidence of drug replacement by reaction by-products, and the presence of free linkers (**1**). Additionally, it is important to carefully assess the product's higher order structure to ascertain the effects of the conjugation process and the drug group characteristics on the final ADC because these elements have many variables that can impact site reactions, aggregation potential, or secondary/tertiary structure.

Bispecific antibodies have their own distinctive CMC considerations. Chemical and biological stability are paramount because the more complex structure of bsAbs greatly increases the risk of abnormal protein folding and impaired function and safety compared with other antibody-based therapeutics. Additionally, there are several different types of bsAb molecules, each requiring a different manufacturing approach, adding yet another layer of complexity. For instance, different formats require different purification strategies due to format-specific impurities (**2**).

Developers can stay ahead of the curve and be prepared to pivot successfully as markets shift by building CMC capabilities for advanced biologic modalities early, optimizing processes, and working out solutions to common stumbling blocks. The better established that CMC operations are, the more efficient development and manufacture will be and the more swiftly a biosimilar can be submitted for regulatory approval. In a therapeutic landscape with growing competition, the additional speed to market that early CMC preparedness imparts can make a significant impact on a biosimilar's success.

Adjusting to Regulatory Changes

Recent years have seen multiple biosimilar regulatory updates from the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), largely consisting of streamlined development processes. Perhaps the most significant change was one made by both agencies: In certain cases, comparative efficacy studies might no longer be required (**3, 4**). Traditionally, such studies would follow pharmacokinetic-similarity studies, thus playing a key role in assessing a biosimilar's similarity to the reference product. In specific contexts, however, regulatory authorities may determine that clinical comparative efficacy studies cannot be waived. Such larger-scale biosimilar comparative trials may remain necessary for biologics that are administered locally with minimal systemic exposure or for products with incompletely characterized mechanisms of action. Accordingly, it is essential for sponsors to engage proactively with regulatory agencies early in the development process to achieve alignment on the appropriate evidentiary pathway.

When comparative efficacy studies are not required, regulatory authorities will put more weight on comparative analytical assessment of a biosimilar's structure and function as well as process- and product-related attributes. The increased emphasis on analytical comparability, including CMC, means that the link between manufacturing processes and analytical attributes becomes more visible.

> By paying attention to landscape changes and being prepared to adapt, developers can give their biosimilars the **BEST POSSIBLE** foundation for market success.

To meet the rising level of scrutiny, developers will need to employ more extensive and in-depth physiochemical characterization, along with stronger process- and product-related characterization. In parallel, risk assessments must define clearly which analytical differences between a biosimilar and reference product are acceptable and which ones are not. For example, there might be minor disparities in clinically inactive components, but any differences that influence safety, purity, or potency would be unacceptable.

Another more recent regulatory shift was the FDA's fourth revision of the *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act* in March 2026 (**5**). This update allows a biosimilar candidate to be compared to a reference product that was approved in a country other than the United States without requiring a three-way pharmacokinetic study involving a US-approved reference product. However, the non–US-licensed comparator must be sufficiently similar to a US-licensed biologic as proven by robust analytical data, and developers must explain clearly why any analytical differences in quality attributes do not impact the comparator's relevance.

Overall, building a strong body of evidence will be critical to standing out and staying competitive when entering a crowded biosimilars market. Additionally, paying close attention to, and complying with, regulatory requirements will be an important element of avoiding delays in approval and reaching the market as soon as possible.

Standing Out in a Crowded Market

Numerous factors have made the biosimilars market increasingly competitive. The waiving of comparative efficacy studies, for example, removes a highly time-consuming and costly element of biosimilar development. With that barrier to entry lowered, growing numbers of small, agile organizations are entering the market.

International players also have been entering US and EU markets. Partnerships with global pharmaceutical organizations, for instance, have helped Chinese biotechnology companies to gain biosimilar approvals in multiple countries. An excellent illustration is the partnership between Shanghai Henlius Biologics and US-based Accord BioPharma, which facilitated the commercialization of a trastuzumab biosimilar in Canada, United States, and European Union (**6**).

Additionally, the newly increased flexibility for use of non–US-licensed reference products in FDA product submissions enables international developers to eliminate the high costs and complex logistics of procuring a US product. This empowerment of global development programs to seek biosimilar approval in the United States means that competition from international groups should continue to rise.

Succeeding in such a highly competitive environment will require agility. With the biosimilar market continuing to evolve, developers that can anticipate and respond dynamically will have a competitive edge over laggards. Furthermore, developers should aim to achieve first-mover advantage where possible. First entrants for a given biosimilar tend to have a lasting higher share of the market compared with those entering the market later. According to some estimates, first entrants can expect their share to be about 27% higher than the second entrant to a given biosimilar market (**7**).

Keeping an Eye on the Horizon

With capabilities expanding and regulatory authorities working to

*Continued on **page 20***

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Media-Optimization Strategies To Bring Down Costs

36% of Facilities Want Better Supplements for Increased Titer in Bioprocessing

Katrina Cordovado

Increasing expression titers and bringing down process costs have become commercial necessities across protein biologics, vaccines, and especially advanced modalities such as cell and gene therapies (CGTs); high productivity per batch correlates directly to cost competitiveness, effective facility use and speed to market. Although cell-line engineering and bioreactor design have progressed significantly over time, cell-culture media and supplements remain some of the most underappreciated drivers of titer improvement.

Need for cost control is reflected in findings from the BioPlan Associates *22nd Annual Report of Biopharmaceutical Manufacturing Capacity and Production*. Representatives from 36% of surveyed facilities report that media optimization will have the greatest impact on reducing cost of goods (CoG) — a striking signal that upstream inputs are now central to economic outcomes (**1**).

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The Culture-Media Landscape: From Baseline Input to Performance Driver

Historically, cell-culture media were treated as relatively standardized components that were selected early, modified incrementally, and rarely revisited once a process was established. Today, that paradigm is shifting rapidly.

Over the past two decades, the culture-media landscape has undergone a significant transformation, driven by advances in biopharmaceutical manufacturing, regulatory expectations, and process-optimization strategies. Historically, cell-culture systems relied heavily on complex and often undefined components such as serum, hydrolysates, and yeast extracts. Those materials provided robust cell growth and productivity but introduced process variability, supply constraints, and regulatory concerns related to traceability and contamination risks. As the biopharmaceutical industry matured, there was a strong shift toward chemically defined media. Such formulations offered improved consistency and simplified regulatory compliance. Large biomanufacturers increasingly adopted fully defined media systems to reduce variability and enable standardized platform processes across multiple products.

However, that transition introduced new challenges. Chemically defined media, though consistent, are expensive and do not guarantee optimal cellular performance under all conditions. As biomanufacturing has evolved toward complex processes such as high-density cultures, perfusion, viral-vector production, and expansion of gene-modified cell therapies, the limitations of chemically defined systems have become more apparent. As a result, the industry is entering a new phase: Manufacturers increasingly are seeking solutions that combine the consistency of defined systems with the functional

performance benefits of complex supplements. That has renewed interest in functional nutrient systems, enzyme-based tools, and performance-enhancing supplements that can improve yield, robustness, and cost-efficiency.

That evolution is occurring in parallel with broader trends in manufacturing-capacity expansion, process intensification, and demand for novel technologies. Together, such forces are placing media, and particularly supplementation strategies, at the center of upstream innovation.

Why Titer Drives the Need for Better Supplements

Expression titer remains one of the most important performance metrics in bioprocessing. High titers translate to smaller batch sizes for the same output, diminished facility-footprint requirements, reduced downstream-process burden, and improved overall process economics.

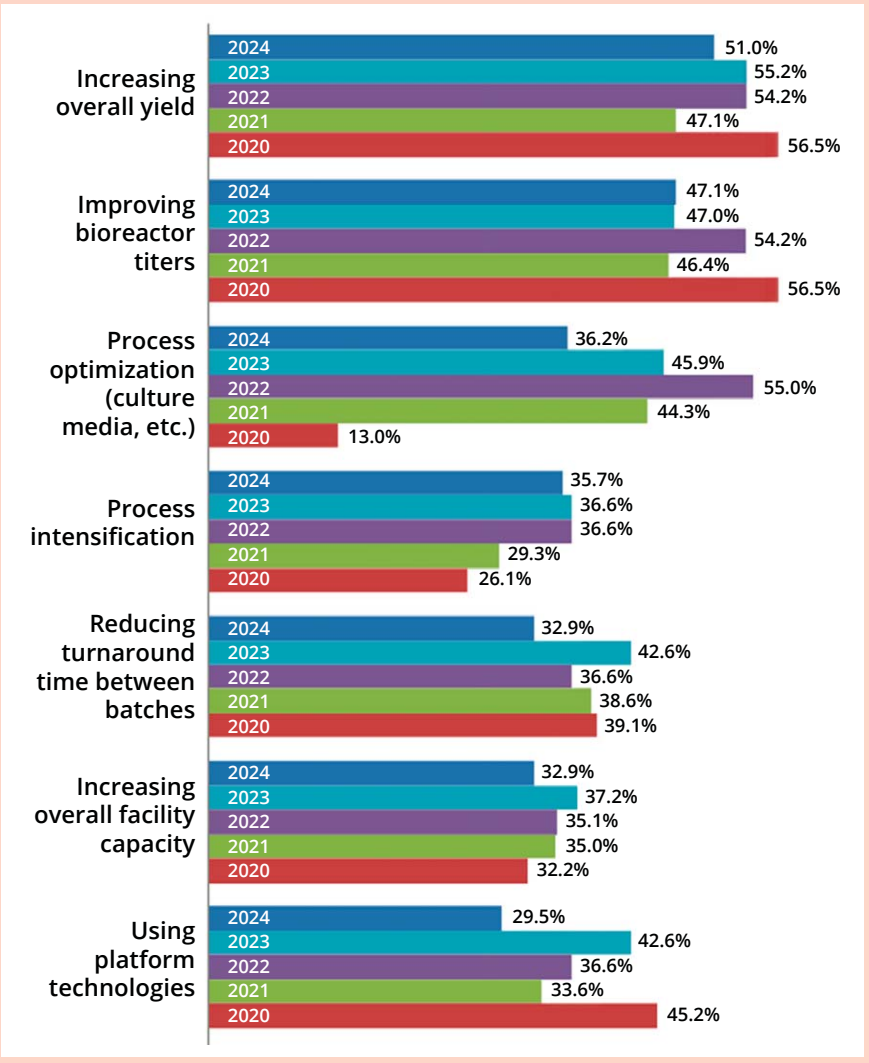
However, achieving increased titers is constrained by cellular limitations, including nutrient depletion, accumulation of metabolic by-products, and cellular stresses that reduce viability. This is where supplements play a critical role. Modern supplementation strategies are designed to provide targeted nutrients at optimal times, support metabolic balance, enhance protein-expression pathways, and stabilize cells under high-density conditions.

Despite key advances, many processes still rely on legacy feed strategies that were not designed for today's intensified culture systems. There is growing recognition that next-generation supplements, not just base media, are required to unlock further gains in upstream productivity.

Media Optimization as a Core Cost Lever

Media and supplements remain core cost levers for bioprocessing. According to BioPlan's survey, conducted in 2025, representatives from 36% of facilities identified process optimization as the single factor with the greatest potential impact on reducing CoG (Figure 1). Although cost-reduction efforts remain focused on downstream purification efficiency, the fact that media optimization ranks as the top factor for over one-third of surveyed facilities underscores a growing realization that upstream inputs still dictate downstream economics.

Figure 1: Selected factors that biomanufacturers believe will have the greatest influence on reducing cost of goods for biotherapeutics, 2020–2024; data come from the BioPlan *22nd Annual Report and Survey of Biopharmaceutical Manufacturing Capacity* (**1**). In the survey responses, improvements in upstream performance, cell-culture productivity, and media supplementation consistently rank among the most important contributors to lowering manufacturing costs.

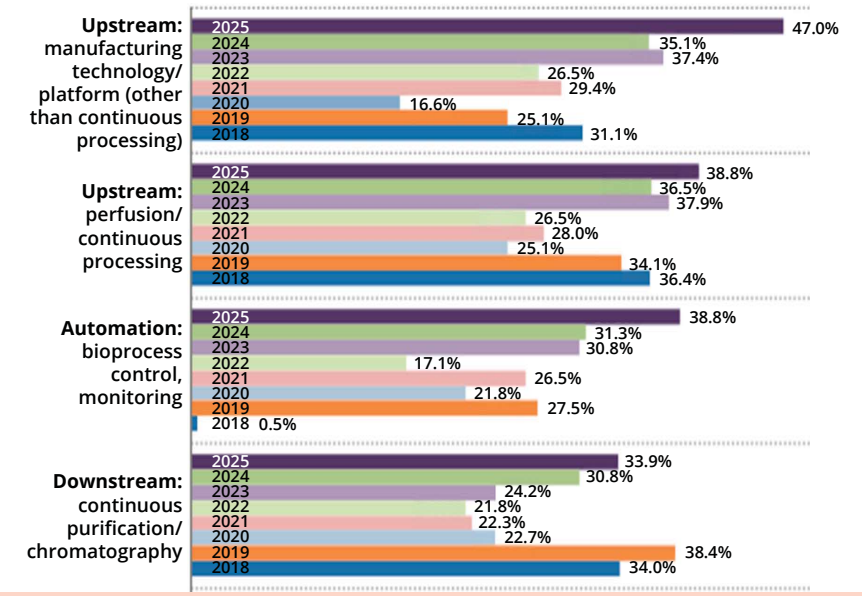


That recognition aligns with additional BioPlan findings showing that cost reduction and productivity remain top priorities for the industry. Over the past 10 iterations of our survey, about 30% of total respondents have identified those as key areas requiring improvement in a given year. The growing emphasis on culture media and supplements is a natural consequence of titer's direct influence on both CoG and process productivity.

Upstream Innovation Priorities Are Accelerating

BioPlan survey data also indicate that 47% of facilities identify upstream platforms and technologies as the top area to test or evaluate within the next 12 months (Figure 2). That finding reinforces the sense of industry-wide prioritization for upstream innovation as a pathway to improving process performance. Manufacturers not only are recognizing the importance of upstream factors, but also are investing actively in new approaches to enhance them. Within this context, media and supplementation strategies have an opportune position because they can be implemented more rapidly than many hardware or infrastructure changes can

Figure 2: BioPlan's annual survey asks respondents to report bioprocessing systems and innovations that they plan to evaluate or test in their facilities within the next 12 months. Pictured are data from 2018–2025.



be while still delivering meaningful gains in productivity and efficiency.

Taken together with the emphasis on CoG reduction, the near-term interest in upstream platforms reinforces a broader narrative: Improvements in upstream performance, including media optimization, increasingly are recognized as the most accessible and impactful levers for addressing technical and economic concerns in biomanufacturing.

Growing Demand for Improved Culture Media and Reagents

Areas of Opportunity: BioPlan has evaluated technologies that improve bioreactor yields, stabilize process conditions, and/or reduce downstream losses for over 25 years. Those areas can have a significant influence on the economics of biologics production. At the same time, emerging biomanufacturing platforms for mRNA production, synthetic biology, and cell-free protein expression are creating entirely new categories of biochemical inputs. Such technologies rely heavily on enzymes and specialized reagents, opening opportunities for suppliers that can develop new classes of bioprocess tools. Several new opportunities are emerging.

Expansion of Adherent Stem Cells: CGTs represent one of the fastest growing segments of the biopharmaceutical industry. Opportunities are particularly available for supporting expansion processes for adherence-dependent stem cells.

Continuous Biomanufacturing and Perfusion Cell Culture: One of the most important developments for recombinant-protein production has been the growing adoption of continuous biomanufacturing and perfusion cell-culture systems.

Serum Reduction and Replacement in Vaccine Manufacturing: For many years, fetal bovine serum (FBS) and related materials were common in vaccine production processes. However, the vaccine industry increasingly is eliminating serum from cell-culture processes.

Media-Cost Optimization in Biosimilar Manufacturing: Biosimilars compete with originator products primarily on price. That competitive dynamic creates strong pressure on manufacturing costs, creating opportunities for media optimization.

Viral-Vector Yield Enhancement: Gene therapies and other medicines based on viral vectors represent another rapidly growing sector of biotechnology. Yet vector yields are often low.

Functional Nutrient Systems: Historically, supplements such as hydrolysates, peptones, and yeast extracts were used as nutrient sources. Biomanufacturers increasingly expect modern supplements to influence cellular metabolism.

mRNA Manufacturing and Enzyme-Intensive Bioprocessing: RNA technologies have emerged as a critically important innovation in modern biotechnology. Manufacturing processes for mRNA molecules involve cell-free enzymatic reactions that synthesize RNA molecules from DNA templates. As a result, mRNA manufacturing is highly dependent on enzymatic tools.

Synthetic Biology and Cell-Free Biomanufacturing Platforms: Beyond traditional cell-based production, manufacturers can leverage cell-free expression systems. Such technologies remain nascent and have relatively niche applications, but in the future, they could be cost-competitive with traditional cell-based manufacturing.

Demand Mechanisms: Demand for improved supplements is being driven disproportionately by rapidly growing modalities such as CGTs. Cell therapy represents a field in particular need of media innovation given its use of primary and/or engineered cells — e.g., stem, T, and natural killer (NK) cells — and those materials' sensitivity to culture conditions. Cell-therapy production processes also emphasize phenotype and functionality rather than just growth. Therapeutic cells often require highly customized media and supplements to maintain cell identity and optimize expansion without inducing exhaustion.

Production of adenoassociated viruses (AAVs), lentiviruses (LVs), and other viral vectors presents its own set of challenges. Those include low productivity compared with workflows for monoclonal antibodies (mAbs), host-cell sensitivity to culture conditions, and complex transfection requirements. In this context, supplements play a critical role in enhancing transfection efficiency, supporting cell health during production, and increasing viral yield.

Opportunities for Innovation

One key area for innovation is metabolic control and precision feeding. Traditional feeding strategies based on fixed schedules or bulk nutrient additions are being replaced by approaches that dynamically adjust nutrient delivery based on real-time cell needs. Increased control over such conditions helps to minimize by-product accumulation and extend productive culture phases.

Continued on ***page 14***

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Distributed Biomanufacturing

Rethinking Production and Logistics for Autologous Cell Therapies

Cheryl Scott

After years of groundbreaking scientific advances in cell and gene therapies (CGTs), the advanced-therapies sector faces a fundamental challenge that has little to do with bioscience itself. The question of whether such therapies work has been settled, more or less: They do, and remarkably well. Many product approvals that demonstrated as much, however, have gone on to highlight the difficulties in manufacturing and delivering CGTs to patients who need them. That growing concern has sparked much debate about the future of related biomanufacturing models, from centralized facilities to point-of-care (PoC) production and many concepts in between.

Early in 2026, *BioProcess International* and IB Communications collaborated on a video roundtable discussion moderated by Claudia Zylberberg (Akron Bio, Kosten Digital), with industry leaders from across the CGT ecosystem: Liza Loidolt (Terumo BCT), Heather Purvis (Title21 Health Solutions), Josh Ludwig (ScaleReady), Becky Cap (Vitalant), and Carol Houts (Germfree). We brought them together to examine what many people in the industry are calling the "Uberization" of biotechnology, a fundamental rethinking of where and how biomanufacturing happens. This conversation brought together perspectives from manufacturing, clinical operations, regulatory affairs, and quality systems, revealing both the promise and complexity of distributed manufacturing models.

Background

The Uberization term for decentralized manufacturing models refers to the ride-sharing paradigm to describe distributed, on-demand service delivery through networked platforms. This represents a fundamental departure from traditional centralized biomanufacturing, bringing production closer to patients through PoC facilities and regional manufacturing hubs (**1–3**).

CGT organizations would establish multiple production facilities across defined geographical areas, enabling cells to be processed and distributed near medical centers and patients. This approach is particularly attractive for autologous therapy, in which a patient's own cells are collected, genetically modified, and returned under strict timelines. Such personalized treatments have significant shelf-life limitations and require fresh biological starting materials to achieve optimal cell numbers, dosing, and potency.

The distributed model typically involves a central control site that serves as the regulatory nexus, maintaining master files and ensuring consistency across multiple decentralized manufacturing units. That hub-and-spoke architecture mirrors platform-based coordination seen in ride sharing, where a central system orchestrates distributed operations while maintaining quality standards.

Several factors are propelling this shift. Centralized manufacturing has led to high costs of goods (CoG), limited throughput, variable quality, and accessibility challenges. Patients often face extended vein-to-vein times (from cell collection to treatment administration), which can be critical for those with rapidly progressing diseases. Decentralized production could shorten those timelines dramatically, with some models targeting treatment within five days of diagnosis.

The US Advanced Research Projects Agency for Health (ARPA-H) launched its Genetic Medicines and Individualized Manufacturing for Everyone (GIVE) program in September 2025 to establish distributed manufacturing combined with automated quality assurance. The intent is to make breakthrough treatments "accessible, affordable, and ready to dose within a week of diagnosis."

The Uberization trend relies heavily on automation and closed-system technologies. Such technologies minimize manual intervention, reduce contamination risks, and enable standardization across multiple sites — all of which are essential for maintaining comparability of therapies produced at different locations. Resolution Therapeutics, for one, has emphasized that distributed manufacturing is essential for achieving global patient access (**4**).

Despite its promise, decentralized manufacturing faces regulatory hurdles regarding product variability, comparability across sites, and compliance oversight mechanisms. Robust quality-management systems spanning distributed networks will be essential to making it work, along with advanced process analytical technologies (PAT) for real-time monitoring and control.

The Limitations of Centralized Manufacturing

For the first decades of commercial cell therapy, centralized manufacturing prevailed as processes were refined and good manufacturing practices (GMPs) were established. "I think centralized manufacturing was a critical necessity in the early stages of the industry, when we didn't know what GMP would look like," Cap said. "But we're still dealing with a 'boutique,' craftsman-like process [now]."

However, what worked in early development has become increasingly problematic as the industry attempts to commercialize. Loidolt noted that "after years of experience with these therapies, we still have an average US patient traveling to a qualified, accredited center to receive therapy some 30–50 miles away for the patients who receive therapy. Patients living more than 50 miles away from a treatment center have a dramatically reduced chance of receiving therapy. So an average patient spends more than an hour to get to the therapy that they need."

Geographic barriers represent more than mere inconvenience. Time is limited for patients with aggressive hematologic malignancies, for example. The logistics of centralized manufacturing can take weeks: collecting cells, shipping them to distant facilities, waiting for processing, and then coordinating delivery back to patients. As therapeutic indications expand beyond acute cancer settings into autoimmune diseases and beyond, such delays do not become more acceptable.

"At some point where you're trying to commercialize and really get to scale," said Cap, "the logistics and centralization of that one hub become almost impossible to manage."

Promise and Pitfalls: The theoretical appeal of PoC manufacturing is undeniable. Bringing production closer to patients and removing the work from a cleanroom setting could dramatically reduce vein-to-vein time, eliminate complex logistics and costs, and expand access to underserved communities. Yet the reality has proven to be far more complex than the vision.

Loidolt offered a sobering assessment: "When we think about PoC solutions, it becomes very clear that hospitals are optimized for clinical care but not for manufacturing robustness required to deliver these therapies at scale to large patient populations. What hospitals are not built for is consistent GMP execution: environmental controls, material segregation, even sustained operator training."

The fundamental mismatch between hospital capabilities and biomanufacturing requirements extends beyond physical infrastructure. Hospitals struggle with what she described as "staffing continuity, deviation management, quality control, and product release. These are simply not the capabilities that they have the muscle to deliver today, but will certainly be a regulatory requirement as PoC manufacturing gains scale."

Purvis has experience working with hospital systems and said they're good at standardizing processes. "That's how they operate, how they thrive and survive, that's how they receive their accreditations and reimbursements. But that rigid kind of adherence that we need often is not respected in the same way."

Quality systems are of particular concern. She explained that hospitals often aren't built for distributed accountability, but rather for centralized control in each location. "What emerges without a common standardized process and language is not flexibility; it's actually compliance ambiguity." With multiple sites interpreting standard operating procedures (SOPs) differently, documentation and quality controls are inconsistent, often with unclear authority for release decisions.

The Standardization Imperative

If distributed manufacturing is to succeed, the roundtable participants all agreed, then standardization becomes a critical requirement. Achieving that across multiple sites — each with its own culture, systems, and personnel — represents a formidable challenge.

Ludwig approached the question from a perspective of manufacturing technology, identifying process definition as a primary failure point when companies attempt to scale down manufacturing processes for PoC applications. He described the industry's reluctance to standardize: "Whether it's in the academic medical centers or even centralized manufacturing facilities, we want to design for flexibility. In theory, you want a flexible process that can add in the best new technologies as they come along."

He argued that pursuit of flexibility can backfire, however. "We hear people talk about it as multiple ways to do the same thing." Undocumented workarounds are a danger in an industry not too far removed from pure research. "Maybe key people understand what to do, but it's not written down, and if it's not documented, then it's really not followed."

The solution, Ludwig suggested, may be counterintuitive. "When you have standardized very clear processes that don't leave things up to the imagination, then you actually enable flexibility going forward because you really know the characterization of your process, and you're going to understand the failure points. You can make improvements from there." That philosophy extends to selection of manufacturing technologies themselves. Ludwig emphasized "choosing tools and steps within a process that allow and lend themselves to simple training, and maybe the less-is-more aspect of manufacturing anything."

The challenge of standardization is compounded by a diversity of approaches across the industry. Ludwig noted that although major players with years of experience understand their processes well, "from my perspective and getting to see a lot of different protocols, there are so many variations from company to company that it's difficult to get the scale that we want in our industry because everyone's chasing a unique way to make cell therapies consistently."

Building an Infrastructure

Houts brought a regulatory and quality-systems perspective, emphasizing that

successful distributed manufacturing requires thinking beyond cleanroom operations. "Cleanrooms are important," she acknowledged. "But if the systems and the strategy for GMP are not being built alongside them, that's going to catch everyone off guard." She advocated for parallel development. "What we recommend is building your operational framework at the same time you're building your cleanroom. These things should run in parallel, and when multiple sites are working together, then you take that opportunity to bring those teams together and build the systems together."

Houts pointed out that many concepts needed for distributed manufacturing already exist. "When I worked in pharma, it was very much a centralized manufacturing structure, but we had outsourced manufacturing." She worked with both contract manufacturing and development organizations (CMOs and CDMOs). "We had those philosophies around technology transfer and process equivalents out there for a long time. I think there's a lot that we can borrow from the pharma space and apply to how we're thinking about bringing hospitals online."

However, she emphasized a critical difference between PoC and outsourcing approaches. "When you're looking at the teams that are going to perform these processes, they are fundamentally unfamiliar with GMP, whereas we've had decades to get familiar with this on the pharma side."

The panel highlighted community programs associated with the California Institute for Regenerative Medicine (CIRM) as a promising model. "They're relying on their alpha clinics," said Houts. "They have nine very experienced sites in California. I think that that's how you do it. With mentorship in place, you can build quality systems from the ground up."

Rethinking Speed and Predictability

The industry has long operated under an assumption that faster is always better. "Over the past decade, especially autologous cell therapies have been administered in patients with acute diseases such as hematologic malignancies," said Loidolt, "where speed was everything. The faster, the better — that was the mantra." But that may be too simplistic a view. She argued that as the field matures and expands into new indications, the calculus changes.

Chimeric antigen receptor (CAR) T-cell therapies are a good example. "If you think about speed as we transition into the fifth wave of CAR-T therapies, and where that field is going, it becomes a little tricky to talk about speed in that one-dimensional way. If it compresses training, oversight, quality control, and decision making, then that isn't the right speed we should be chasing."

Then she proposed an alternative priority. "The real goal here is to use those predictable, reliable speed elements that deliver consistent process and outcomes every time for every patient. Speed alone isn't as important, I think, as it was a decade ago. What is more important today is the predictability, the process control, and the digital infrastructure that actually controls the outcome."

That shift from speed to predictability represents a maturation of the field. Loidolt noted that "speed is becoming table stakes. Many therapy developers have gotten there. But speed alone isn't what we should be chasing to make this therapy standard of care for more patients who need it — predictability of outcomes is that new north star."

The Accountability Question

One of the most difficult aspects of distributed manufacturing is determining accountability when things go wrong. In centralized models, such responsibility is clear. For distributed systems with multiple stakeholders, the lines blur considerably.

Purvis offered the following analogy: "You can equate it to how a nurse might feel. Orders come from a physician who has seen the patient and drives what needs to happen, but the nurse is executing those orders. And if something goes wrong with a patient, the immediate spotlight is always on the nurse, the last person in the process chain and the first one who's facing the patient." She compared that with the current view of PoC processing. "That's where the spotlight is, with the organizations that are executing right next to the patients — whether that's accurate and should be or not."

The problem extends beyond blame assignment to proactive ownership, Purvis noted. "We have a lot of folks in this industry who make suggestions about what should happen, but without proactive ownership to make that happen." And she said the digital infrastructure challenge compounds accountability issues. "A struggle remains in connecting organizations, with the digital infrastructure they currently house, to keep costs down and patient access high. But distributed models multiply interfaces. And every interface is a potential accountability gap."

Regulatory Considerations

Meanwhile, the regulatory framework for distributed manufacturing is only beginning to evolve. "There's no regulatory framework for this," said Houts. "But what does exist in our current regulations is a framework for administrative procedures around establishment licenses, and drug master files that can provide a mechanism for decentralized manufacturing."

The question of acceptable variability across sites remains, and she recommended proactive engagement. "We're seeing this play out in a really good way," she said. "Comparability protocols are submitted to regulators around the world with the equivalent of type C meetings where hospitals can present their strategies and what their quality systems will look like." She emphasized the importance of standardization for managing variability. "Whether it's the environment, the procedures, or process, standardization really does limit the variability."

Trade-Offs and Practical Realities

The panelists identified specific trade-offs that the industry understands intellectually while resisting practical implementation. Cap highlighted as critical areas clinical training and cleanroom requirements.

In relation to the former, she challenged conventional wisdom. "I've heard a lot of physicians from academic

centers say there's no way that all of these people out here in the community can learn how to manage patients if you include all the necessary logistical implementation. Maybe that's the case. But as we understand how these products work and how patients react, I think a lot of training can go to support clinical staffs — especially if, they are allowed to focus on clinical care rather than trying to become a therapeutic manufacturer."

Regarding cleanroom requirements, Cap drew on her blood-center experience. "Over the past eight decades, blood centers have been manufacturing transfusible products in closed systems within controlled (not classified) spaces. From that history, we can loosen our grip just a bit to say that not every process has to be in cleanroom. There has to be a cleanroom environment for some of what we're doing in CGT, but what can we transition away from that to enable access? People might nod when you say that, but they're not ready to do it."

The Hub-and-Spoke Model

Cap described her company's approach as an example of practical distributed logistics that can build toward manufacturing. "We have started focusing on leveraging that hub-and-spoke model, where we have built in flexibility in our nurse corps into hubs where we can provide apheresis that are closer to where patients live." This model allows for strategic distribution of capabilities. "If we have a hospital in a fairly remote location, and they have multiple patients to be collected, then we can support that site and do the collections efficiently and effectively."

The approach requires gradually expanding capabilities. "Right now," said Cap, "our laboratories are receiving finished product for hospitals that don't have the infrastructure to store those products. We're holding onto them in a controlled GMP environment under a centralized quality management system. And when patients are ready, we prepare and thaw the product then bring it to the bedside. Sometimes we prepare product at the bedside, then hand it over to a nurse for infusion."

She emphasized the incremental nature of transitioning to such a model. "We have all kinds of things in our vision for how to enable that — cellular starting material collection and product delivery and working toward the middle to leverage some of the tools that suppliers are bringing to the market. But it's a process, and change management is hard. We have to be patient and deliberate."

10 Key Discussion Points

Centralized manufacturing is no longer sufficient at scale. As autologous therapies in particular scale up/out, centralized hubs introduce logistical bottlenecks, extended vein-to-vein times, and growing patient burdens.

Point-of-care (PoC) manufacturing is conceptually attractive but operationally fragile. Gaps include environmental controls, deviation management, operator training continuity, quality oversight, and real-time product release.

Hybrid and distributed models are emerging by necessity. Such models reduce patient travel and logistics complexity while preserving oversight and consistency.

Process standardization is the primary failure point in decentralization. When manufacturing is scaled down or distributed, process (not people or facilities) fails first.

Quality systems are built for centralization, not distribution. Early issues emerge in chain of custody, deviation consistency, batch-record standardization, and release authority.

Infrastructure is more than cleanrooms. Successful distributed models build compliant manufacturing strategy, digital controls, and training frameworks alongside physical infrastructure, often borrowing proven approaches from outsourcing experience.

Digital orchestration is the missing coordination layer. The cell and gene therapy (CGT) industry lacks a unified digital orchestration framework that can enforce standardized workflows, real-time quality oversight, deviation visibility, and product release across sites.

Speed must be reframed as predictability. It remains critical in acute settings, reducing patient deterioration and reliance on bridging therapies.

Decentralization shifts rather than eliminates risk. Manufacturing near patients can improve starting-material quality and reduce logistics risk while increasing pressure on facility footprint, throughput, workforce training, and operational discipline.

Accountability remains ambiguous. Clear ownership models supported by centralized governance and digital enforcement will be critical to sustainable decentralization.

A Call for Collaboration

Panelists offered some final perspective on what the CGT industry must do to advance distributed manufacturing. Ludwig emphasized open knowledge sharing. "We have some real-world examples and groups working on this right now — efforts that are funded through government grants and agencies so that whatever we learn is published and known and shared. A lot of our manufacturing progress in the centralized realm was kept centralized as well. So if we're going to do a distributed model, we probably have to distribute the learning in a larger, broader, more open way than we've done before."

Cap highlighted the Uber analogy. "What did Uber do that was so incredible? They centralized and standardized a process for delivering transportation. We're not all going to the same place, and we don't all take the same type of vehicle, but this notion of breaking down the process into components is critical. Distributed manufacturing doesn't mean just one thing; it needs to be 'customized standardization' to meet the needs of each disease, community, and manufacturing process."

Loidolt cautioned against oversimplification. "The one assumption that we need to stop repeating is that distributed manufacturing is inherently simpler, and it's going to solve all of the problems. I don't think it's going to pan out that way; it's more complex but in different ways. Success will come from acknowledging complexity early on and designing for it, not pretending that any particular technology will solve it alone."

She also emphasized partnership and collaboration. "It's going to be institution by institution, designing a blueprint that works for one academic center, and then

scaling it and offering it to other centers. We're going to learn together by small steps and connecting the different aspects of this value chain in novel ways."

Purvis focused on practical support, "putting our words into action and proactively supporting people doing the work, being able to give these organizations the tools that they need to be successful. We need to do that through education to our frontline teams, digital support and platforms, engagement with our academic centers and replicating their action goals — whatever it looks like. We need to take that template, get it approved and accredited, and then ensure that it is readily available to the people who are ready to do the work. That's where the passion lies, and they just want this for their patients, so we need to deliver."

Smarter, Not Simpler

The path from centralized CGT manufacturing to distributed models represents more than a logistical shift; it requires fundamental changes in how the industry thinks about quality, standardization, training, and accountability. The promise of bringing life-saving therapies to patients is real, but so are the complications of maintaining consistency and quality across multiple sites with different capabilities.

Success will require the CGT industry to move beyond aspirational statements about distributed manufacturing and engage in the hard work of building manufacturing and logistics systems, training personnel, establishing clear accountability, and creating the digital infrastructure necessary to connect disparate sites into coherent networks. As Zylberberg noted in closing, "There is a lot to keep talking about, because this is here to stay. And we need to take this challenge and move to the next level. I know that we will be able to do it, so many more patients can take advantage of these amazing therapies."

The "Uberization" of biotechnology is not about simplifying CGT manufacturing; it is about making it smarter, more standardized, and ultimately more accessible than before — and thereby providing transformative therapies to the patients who need them most.

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Continued from ***page 8***

Another important area is the development of functional supplements that go beyond basic nutrition to modulate cellular pathways, reduce stress responses, and enhance protein folding and secretion. This paradigm treats supplementation as a tool for active process control rather than a static input.

There is also growing demand for modality-specific formulations tailored to particular cell types or applications. Those include transfection enhancers and exosome production boosters. The emergence of such offerings reflects a broad move from applying generalized solutions to use of highly specialized products. At the same time, regulatory pressures concerning process reproducibility are driving adoption of chemically defined and animal-component–free media, requiring elimination of serum and undefined components and increasing reliance on fully characterized ingredients.

Beyond High-Quality Ingredients

Biomanufacturers increasingly consider media optimization with innovative supplements to be a strategic differentiator. In the past, gains in upstream productivity were driven largely by cell-line engineering and bioreactor design. But future gains are likely to depend increasingly on media formulation, supplement design, and feeding strategies. The fact that over one-third of facilities surveyed for the BioPlan 22nd annual report now consider media optimization as the primary lever for reducing CoG highlights the centrality of the industry's shift in mindset.

Improved supplements could enable titer increases, improve cell performance, and support complex modalities. Media formulation and supplementation are no longer background variables; rather, they are recognized as key drivers of performance, cost, and scalability. And as bioprocessing continues to evolve, the need for innovation in media optimization and supplementation will only accelerate.

Technologies that improve yield, stabilize process conditions, and/or reduce downstream losses can influence bioprocess economics significantly. Emerging platforms for mRNA production, synthetic biology, and cell-free protein expression are creating entirely new categories of biochemical inputs. Those technologies rely heavily on enzymes and specialized biochemical reagents, opening opportunities for suppliers capable of developing new classes of bioprocess tools.

Taken together, the trends outlined here suggest that bioprocess suppliers should focus not just on supplying high-quality ingredients, but more importantly on enabling improvements in bioproduction and process economics.

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Accelerating AAV Process Development and Productivity

Using High-Throughput DoE and Small-Molecule Process Intensification

Arinjay Sarma, Andrea Vervoort, Abigail Fernandes, Katelyn Badham, Stacia Dolliver, Sarah Wootton, Piriya Yoganathan, Jennifer Quizi, and Jondavid de Jong

Adenoassociated virus (AAV) gene therapies have shown strong clinical promise across a growing number of genetic diseases, yet concerns with upstream manufacturing continue to limit scalability, process robustness, cost-efficiency, and patient access. In systems based on transient transfection, volumetric productivity is often modest, and reliance on plasmid DNA (pDNA) remains a major driver of upstream cost of goods (CoG).

Compounding those difficulties, vector production is governed by complex interactions among process parameters including cell density, plasmid loading, transfection-reagent ratios, and media composition. Multidimensional effects are difficult to resolve using traditional one-factor-at-a-time (OFaT) development approaches, which typically result in low process throughput, high reagent consumption, and slow iteration cycles.

Such challenges are especially evident in manufacturing AAV-based therapies for rare and ultrarare diseases such surfactant protein B (SP-B) and adenosine triphosphate–binding cassette subfamily A member 3 (ABCA3) deficiencies, rare genetic disorders that lead to severe respiratory failure in neonates. AAV-mediated gene replacement represents a compelling therapeutic strategy for this disease. Among AAV serotypes, AAV6 is particularly well suited for pulmonary delivery because of its strong tropism for airway epithelial cells. However, robust manufacturing of AAV6 vectors at clinical and commercial scales requires careful upstream optimization.

Virica Biotech, Inspire Biotherapeutics, and the Ottawa Hospital Research Institute (OHRI) Biotherapeutics Manufacturing Centre (BMC) are collaborating to develop an optimized, suspension-based production process using the National Research Council Canada's (NRC's) HEK293SF-3F6 human embryonic kidney cell line and an engineered AAV6.2FF capsid. The AAV6.2FF capsid has demonstrated better transduction of respiratory epithelial cells than wild-type AAV6. Virica further applied a high-throughput process-development platform combining miniaturized vector production, automated analytics, design of experiments (DoE) assessment, and proprietary Viral Sensitizers (VSEs), small molecules that temporarily reduce host cell defenses to boost viral vector production, enabling rapid, data-driven optimization with direct relevance to scalable manufacturing.

VSEs encompass a proprietary collection of small molecules that enhance the growth of viruses by transiently and efficiently dampening cellular antiviral defenses. Leveraging high-throughput methods, Virica has assembled a library of over 100 small molecules that enhance viral production by transiently antagonizing a broad range of cellular innate antiviral pathways. Owing to their diversity in structure and unique molecular targets, VSEs can be used alone or in tandem to

target multiple pathways to increase viral-vector yield.

Although this work applies an engineered AAV6 capsid developed for treatment of SP-B and ABCA3 deficiencies, the process-development framework described herein is broadly applicable to transient AAV production systems across multiple serotypes and therapeutic programs.

Process Development Strategy

We divided upstream process development into two phases. Phase 1 used high-throughput DoE screening to optimize baseline transfection conditions in the NRC HEK293SF-3F6 suspension platform across four parameters: media formulation, cell density at transfection, total pDNA loading, and transfection reagent:DNA ratio. Phase 2 evaluated VSE formulations under the optimized baseline conditions to improve vector productivity further.

Phase 1 — Optimizing Baseline Production: To identify optimal core transfection conditions for AAV6.2FF production, Virica combined DoE with high-throughput viral-vector production workflows. We selected that approach considering the biological complexity of AAV manufacturing. DoE enables efficient identification of key drivers and critical parameter interactions by using statistical methods to evaluate multiple factors simultaneously.

Key platform elements — including cell line, transfection reagent, and plasmid system — were held constant to maintain compatibility with good manufacturing practice (GMP)–oriented manufacturing and downstream scale-up.

The initial DoE campaign evaluated four experimental variables:

- production media (two commercially available formulations)
- cell density at time of transfection (0.1×10^6 to 3×10^6 cells/mL)
- total plasmid input per culture volume (0.5–3 µg/mL)
- transfection reagent:DNA ratio (0.5–3).

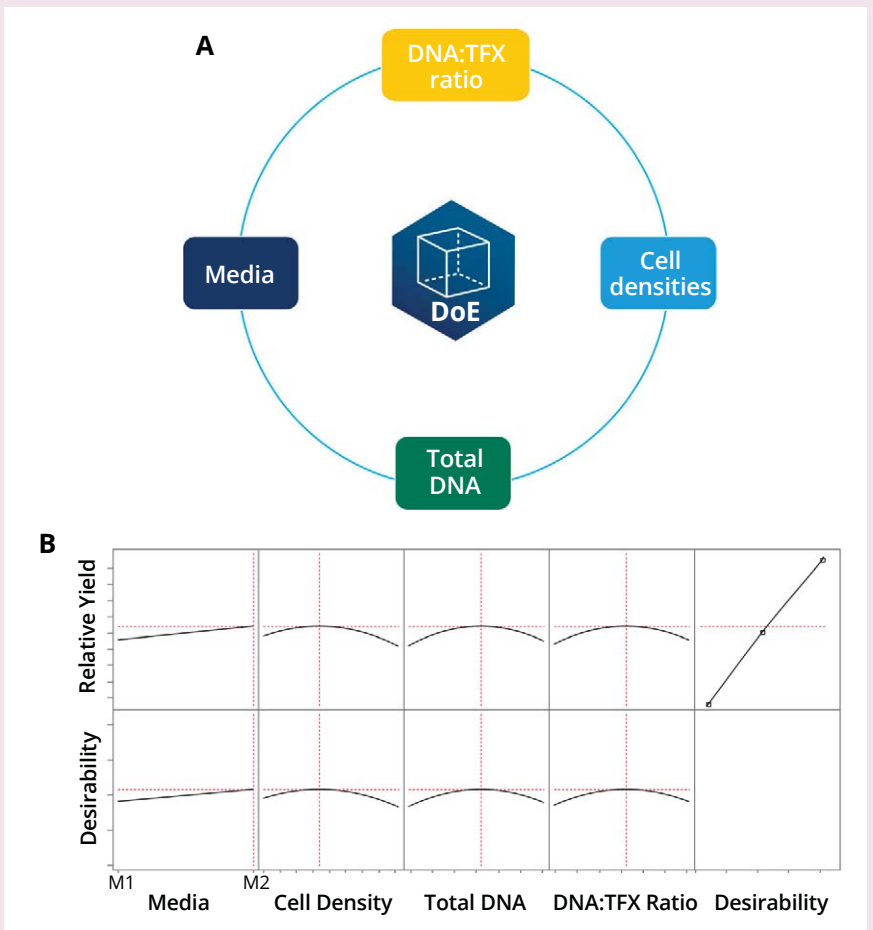
Leveraging a high-throughput platform, we assessed >360 unique experimental conditions in technical triplicate for each DoE iteration, enabling rapid identification of key drivers of AAV productivity and efficient refinement of the production design space. Three sequential DoE campaigns were conducted to refine parameter ranges iteratively and identify optimal process conditions (Figure 1).

Importantly, candidate conditions selected for iterative validation were based on more than just maximal vector yield. Process conditions were prioritized based on a balance between productivity and projected manufacturing economics. Because pDNA is a major contributor to upstream CoG in transient-transfection–based AAV production, we deemed conditions requiring significant plasmid input to be less attractive for manufacturing translation. Accordingly, we advanced experimental conditions that showed strong vector productivity while maintaining manufacturing-compatible pDNA input levels for further evaluation.

Altogether, the three DoE campaigns assessed >1000 unique conditions. Several clear trends emerged. Media formulation had a strong effect on vector productivity, with substantial differences in titer observed across conditions. Vector yield was sensitive to both pDNA loading and DNA:transfection reagent ratio, underscoring the need to balance productivity against plasmid consumption. In addition, optimal productivity was observed within a relatively narrow cell density range, indicating a constrained operating window for efficient transfection.

The top four conditions identified through DoE study advanced to shake-flask validation studies. Results were

Figure 1: Four design-of-experiments (DoE) interactions were executed using high-throughput virology assessment (96-well plates) to optimize production parameters for enhanced yield of AAV6.2FF vectors from HEK293SF-3F6 cells; (A) schematic representing variable factors assessed; (B) outputs from final DoE iteration identifying optimal media, cell density, total DNA, and DNA:transfection reagent (TFX) ratio in relation to relative yield. The desirability plot reflects how well each condition meets the defined optimization goal. In this case, desirability mirrors relative yield (measured in relative luminescence units, RLU), which was the only response optimized. Conditions that maximize yield achieve the highest desirability.



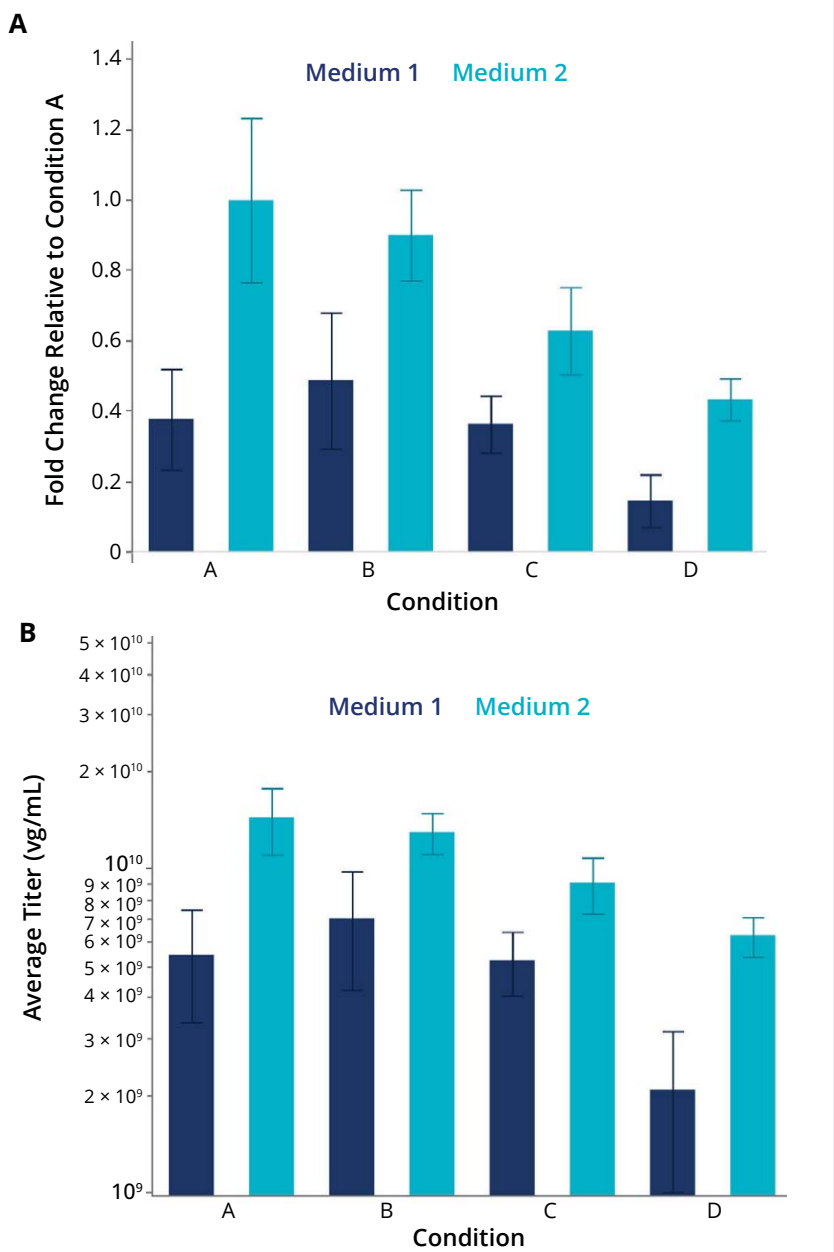
reproducible across two independent biological replicates, each with two technical replicates per condition. Condition A with Media 2 produced the highest average titer, as measured by quantitative polymerase chain reaction (qPCR) assays. However, Condition B (Media 2) used half as many cells while keeping the same amount of DNA and transfection reagent. Because its results were not statistically different from those of Condition A, we chose Condition B as the optimized baseline condition for future studies (Figure 2).

Phase 2 — Optimizing Use of Small-Molecule Production Enhancer: Virica maintains a curated library of VSE media additives that are designed to improve viral-vector manufacturing by modulating cellular pathways involved in functional virus production. Those compounds can be incorporated into existing production workflows without major changes to underlying transfection processes. The CellVantage AAV-suspension kit includes three molecules from the AAV library with distinct modes of action that experimentally have enhanced vector yield both individually and in pairwise combinations. Residual assay methodologies to support detection and characterization of VSE compounds are available and will be described in future work. Following identification of optimized baseline transfection conditions, we initiated a second phase of process development to evaluate the impact of CellVantage AAV production enhancers on AAV6.2FF vector yield.

To optimize our media formulation, we performed a combinatorial DoE assessment of components in the three-molecule kit, evaluating single-compound and pairwise-compound activity across multiple doses. A transduction-based AAV quantification assay with a luciferase reporter and relative luminescence unit (RLU) readout provided high-throughput assessment of functional AAV-particle production. Initial VSE hits and optimal concentration ranges were identified based on RLU outputs, with high RLUs corresponding to large numbers of functional AAV particles. As shown in the heat map, all single compounds provided dose-dependent enhancement over baseline conditions, and some of the strongest effects observed came from VSE-component pairing (Figure 3).

The top candidate formulations advanced to shake-flask validation studies to confirm that productivity gains observed in the miniaturized platform translated to larger suspension-culture systems. Most formulations consistently enhanced expression titers relative to baseline and control conditions (as ascertained by qPCR, data not shown). The top three formulations from the initial shake-flask study were confirmed in two additional biological replicates, with two technical replicates per iteration. Figure 4 presents the pooled data. We included baseline production and vehicle (dimethyl sulfoxide, DMSO) control conditions to assess solvent effects. Results did not

Figure 2: Shake-flask validation of design-of-experiments (DoE) outputs; the four highest-yielding conditions identified by the DoE (across two media types) advanced to shake-flask assessment. Condition A with Medium 2 provided the highest yield as measured by quantitative polymerase chain reaction (qPCR). However, Condition B with Medium 2 used half as many cells at the same quantity of plasmid DNA and transfection reagent. We selected B as the optimized baseline condition for subsequent studies because it was not statistically different from condition A. Panel (A) depicts change in titer relative to the highest-yielding condition, A. Panel (B) shows average titers (viral genomes (vg)/mL) for conditions A–D, as measured by qPCR.



differ significantly, yielding average titers of 2.88 × 10^{10} vg/mL and 2.11 × 10^{10} vg/mL, respectively. By contrast, the three top VSE formulations (003 + 008, 007 + 008, and 008 alone) each produced statistically significant increases in vector productivity as measured by qPCR, with average improvements of 3–6× over baseline.

The highest-performing formulation was a combination of CellVantage AAV compounds VSE-007 and VSE-008, which consistently produced titers exceeding 10^{11} vg/mL and achieved an average titer of 1.5 × 10^{11} vg/mL across all biological replicates.

Discussion

High-throughput experimentation integrated with DoE modeling provides an efficient framework for viral-vector process development. Unlike traditional OFaT approaches, which are time- and reagent-intensive and offer limited insight into parameter interactions, the high-throughput DoE platform enabled rapid exploration of a multidimensional process space and efficient identification of key drivers for AAV productivity.

A key advantage of such an approach is its ability to converge on manufacturing-relevant conditions quickly. In transient AAV-production systems, pDNA is a major upstream cost driver, and yield gains that require substantially greater plasmid input might offer limited value at scale. By incorporating manufacturability into our optimization strategy, we prioritized candidate conditions for strong productivity at moderate, manufacturing-compatible plasmid input levels, thus supporting more economically viable GMP production.

Small-molecule VSE technology provided a complementary route to process intensification by targeting cellular bottlenecks that influence AAV yield. Using a combinatorial DoE strategy, VSE formulations drove substantial gains in vector productivity, with top candidates achieving 3–6× increases in viral-genome titer over baseline without requiring increased pDNA input or major changes to our production workflow.

A small molecule enabling a 3–6× increase in upstream AAV yield fundamentally reshapes the economics of viral-vector manufacturing by directly reducing CoG per dose (by 46–63% depending on the strategy). Given that upstream production — encompassing pDNA, media, labor, and facility use — is a primary cost driver in AAV manufacturing, increased yields should help to distribute fixed and semivariable costs across significantly more doses, substantially

Figure 3: Output from final 96-well combinatorial design of experiment (DoE) assessing single and pairwise combination of three proprietary Viral Sensitizer (VSE) small-molecule yield enhancers; results demonstrate activity in the tested HEK293SF-3F6 cell line across increasing concentrations. This heatmap depicts relative luminescence units (RLUs) reported based on an internal transduction-based quantification assay. A high RLU per condition corresponds to a large number of functional adenoassociated virus (AAV) particles produced. Several formulations provided significant benefit relative to baseline, and the top three formulations were selected for validation at the shake-flask level.

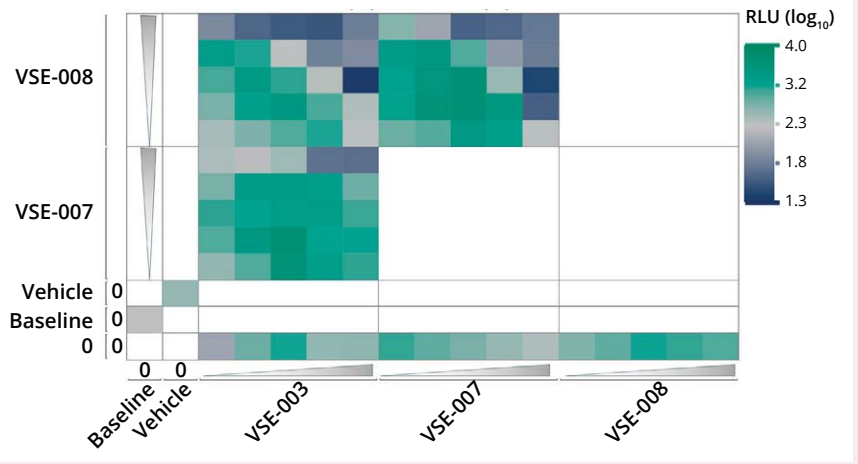
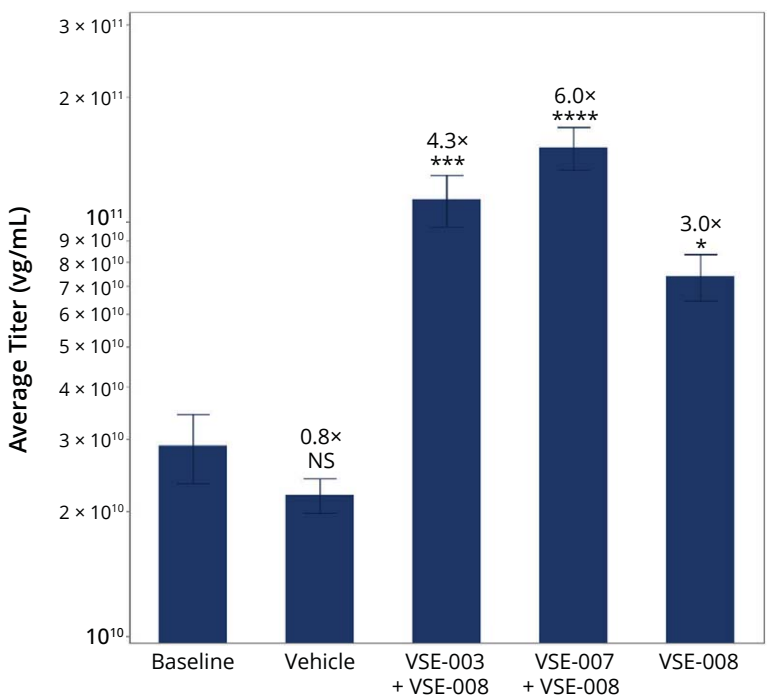


Figure 4: Shake-flask validation of optimized Viral Sensitizer (VSE) enhancer formulations; the three highest-yielding conditions identified in a combinatorial design of experiments (DoE) were assessed at the shake-flask level. The control and vehicle (dimethyl sulfoxide, DMSO) conditions did not differ significantly from each other, yet all VSE formulations provided statistically significant increases in titer relative to baseline control. The top formulation (007 + 008) improved overall titer by an average of 6.0×. NS indicates a result that is not statistically significant. Asterisks represent *p*-values, with *, **, ***, and **** indicating <0.05, <0.01, <0.001, and <0.0001, respectively.



reducing cost per dose. Such gains should extend downstream because high titers improve purification efficiency, reduce processing cycles, and lower consumables use, collectively amplifying overall manufacturing efficiency.

Beyond direct cost savings, yield enhancement introduces meaningful strategic flexibility into process design and capacity planning. Biomanufacturers can choose to reduce the number of batches required to meet demand, downscale bioreactor volumes to lower capital and operational expenditures, or maintain existing infrastructure to expand output as needed. Such flexibility diminishes operational complexity and risk while improving facility throughput and responsiveness to changing clinical or commercial needs.

For the biopharmaceutical industry, improved upstream productivity addresses a central bottleneck in gene-therapy manufacturing: limited supply. By expediting production of clinical and commercial material, small-molecule yield enhancers shorten development timelines, facilitate larger or multiple-indication trials, and improve companies' ability to meet market demand at launch and beyond. In aggregate, those benefits position biomanufacturers to achieve sustainable economics, increase scalability, and a establish a strong competitive footing in the evolving gene-therapy sector.

For rare-disease and ultrarare indications, such gains will be especially meaningful. Accelerated process development can shorten the path from vector design to clinical evaluation, and improved process productivity supports sustainable manufacturing while broadening patient access.

Our results demonstrate that integrating high-throughput virology, DoE, and small-molecule production enhancers is an effective strategy for upstream AAV process intensification, enabling robust, scalable, and economically practical manufacturing for clinical and commercial applications.

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Continued from page 4

streamline and promote biosimilar development, this landscape is likely to continue shifting in notable ways. By paying attention to such changes and being prepared to adapt, developers can give their biosimilars the best possible foundation for market success. Because many high-selling biologic originator products are expected to lose patent exclusivity with no associated biosimilars currently in development, biosimilar developers still have a tremendous opportunity to gain a share of the global market.

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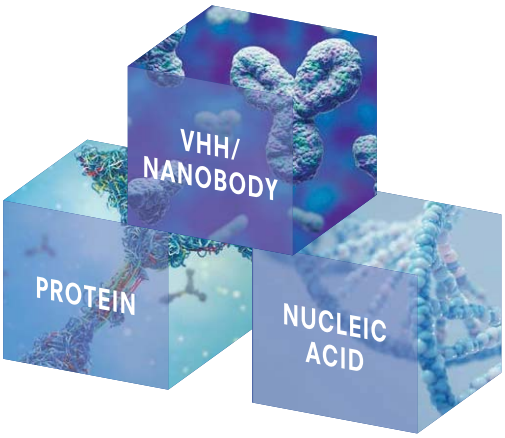

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An Industry Perspective Toward a Harmonized Control Strategy for Polysorbate in Biopharmaceuticals

Vanessa Auquier, Dilbir Bindra, Katrin Husmann, Juliana Kretsinger, Alice Lindsay Newman, Renuka Thirumangalathu, Houjun Yang, and Qi Zeng

Polysorbate (PS), specifically PS20 and PS80, is a critical excipient in biopharmaceutical formulations (**1–3**). As a surfactant, PS helps to stabilize proteins and prevent aggregation, which extends product shelf life and maintains overall quality. However, changes in PS levels and degradation have been areas of industry focus regarding potential detrimental impacts on critical quality attributes (CQAs) for drug substances and products (DSs, DPs). Although PS loss from degradation or through adsorption and associated control strategies are well documented in literature (**1–3**), a cross-industry discussion indicates that a harmonized approach to PS control strategy is still lacking. Our commentary explores current trends and challenges and provides strategic recommendations around PS specifications, informed by recent literature and industry discussions.

The Challenge of PS Control

Suboptimal PS levels can cause protein aggregation, increased turbidity, and particle formation in biopharmaceutical products. PS-degradation pathways primarily are driven by chemical and enzymatic degradation (**3–8**). Oxidative degradation of PS is influenced by multiple factors, such as light exposure, residual trace metals, peroxide impurities, and storage temperature. Enzymatic degradation of PS often is catalyzed by hydrolytic enzymes (e.g., lipases and esterases) that were carried in as residual host-cell proteins (HCPs) from a manufacturing process. PS levels also can decrease through physical processes such as adsorption or retention during filtration steps that occur during manufacturing or clinical use. In most cases, control of PS degradation and adsorption is possible through appropriate mitigation strategies to prevent impact on CQAs (**3–10**). To develop such strategies, manufacturers must define the criticality of PS levels based on the potential impact to product CQAs (**9, 11, 12**).

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Industry Insights and Evolving Regulatory Expectations: Regulatory expectations have shifted over the past few years concerning PS specifications. Agencies are asking manufacturers to apply increasingly stringent controls and specifications, even during early development, when commercial formulations and primary container closures are not fully defined. That trend reflects increased scrutiny of product quality and safety throughout a product's development. It is necessary to build a strong understanding of the connection between PS controls and specifications to product quality and safety.

Strategy for PS Specification

In our view, PS specification for a **DS** is not necessary when it is stored long term under frozen conditions. Frozen storage of biologics is recognized as a standard practice across the industry and thus is accepted as an optimal strategy for maintaining adequate shelf life (**13**). For frozen DS, both the active ingredient and PS remain chemically and physically stable; a DS specification for PS at release or on stability would provide limited value beyond established controls. That view aligns with recent literature showing that PS degradation and particle formation are concerns for liquid storage (e.g., 2–8 °C) and at other elevated temperatures; thus, those concerns are unrelated to frozen DS storage, which supports a rationale for reliance on process controls over a DS PS specification (**8, 9, 12**). Companies instead should consider appropriate procedural controls and/or in-process testing for PS during DS manufacturing. Furthermore, any testing performed at the DP level would provide additional assurance of control for the DS.

Approaches to establishing a **DP** PS specification strategy are complex. Drawing from the framework outlined by Jones et al. (**1**) and discussion among industry experts (**10–12**), the DP PS specification strategy should involve a phase-appropriate approach.

Early Phase (Clinical Phases 1–2): Directly controlling PS levels through specifications is not recommended in early development phases due to limited data. Instead, testing should be conducted to evaluate PS reduction trends and potential impacts on product quality. PS levels can be tested internally for investigational purposes only (FIO) to generate data and support

late-phase control strategies. During early development, PS specifications for release and/or DP stability typically are not required. PS levels are maintained by process controls, with critical controls for visible and subvisible particles and soluble aggregates in place to ensure clinical use and safety.

As clinical development progresses, a robust PS characterization strategy can determine the level of PS in a DP that provides sufficient protection from exposure to different stressors during manufacturing, transportation, storage, and in-use preparation. PS characterization during stability studies provides an evaluation of any significant reduction in PS levels and enables correlation of trends with known product CQAs to understand potential safety and efficacy impacts.

Late Phase (Phase 3 and Commercialization): When a commercial DP presentation is defined, a comprehensive PS control strategy specific to that product is implemented. Specifications might become necessary if there is demonstrated impact on safety- and efficacy-related CQAs. For cases in which PS reduction is not observed (or reduction is observed but shows no impact to CQAs), then a PS release/stability specification is unnecessary. A recent survey collected data on products that observed significant PS content loss during storage at 2–8 °C and documented that, in most cases, no impact to CQAs occurred (**12**). In only eight cases, subvisible and/or visible particles formed, and manufacturers found that such problems often could be mitigated through formulation or purification optimization (**12**). During phase 3 clinical development and process validation, potential correlations of PS content to CQA impacts must be monitored.

For cases in which a control strategy requires a PS specification (e.g., when PS reduction cannot be mitigated and is shown to impact CQAs), then specification limits can be developed with a risk-based, scientifically justified approach. Such an approach should consider relevant information from formulation-development studies, robustness testing, and agitation studies to establish surfactant concentrations in a DP (**14**). The specification limits should be defined based on impacts to CQAs and requirements for product stability rather than maintenance of the target level added to the formulation. It is also important to define a minimum surfactant concentration to maintain target-molecule stability; therefore specification limits should ensure that those levels are maintained throughout product shelf life.

End-to-End PS Control Strategy Considerations

As with any CQA assessment, whether PS content is needed in final DP release and stability specifications should be based on an end-to-end control strategy starting at the DS stage and leveraging a science-driven approach.

PS Quality: Selecting excipients of appropriate quality is a key aspect of critical material assessment (CMA). Because PSs are heterogeneous mixtures of fatty-acid esters, they require stringent controls to ensure batch-to-batch consistency and suitability for use in biologic products (**1, 10, 15, 16**). Material controls for PS include strict supplier qualification, compliance with pharmacopeial standards, controlled storage conditions (e.g., temperature, light, and humidity), use of compatible packaging, and appropriate management of in-use period (**1, 10**).

A manufacturer may consider using PS of a specific quality level to reduce the presence of impurities and degradation products further. It is recommended to dispense PS from freshly opened containers under a nitrogen overlay to help maintain PS quality and minimize the formation of degradation products such as free fatty acids, polyoxyethylene sorbitan, peroxides, and aldehydes (**1, 10**).

DS: A starting point for evaluating PS-related impacts is to assess hydrolytic enzymes in a DS that could cause PS degradation (**17**). HCPs can be carried over into a DS by two mechanisms: copurification with target proteins and nonspecific interaction with target proteins. Although purification steps are typically effective controls in the former scenario, the presence of residual HCPs in a final DS cannot be fully eliminated. Because hydrolytic enzymes can carry over into a DS, a comprehensive control strategy for the impact of DS manufacturing processes on PS is recommended. That starts with evaluation of a cell-line development process. For example, genomic knockout approaches can be used to disrupt the coding sequence of a target hydrolase (**18**). If a cell line is established already, there might be no opportunity for such optimization, and controls would need to be implemented at upstream and downstream process steps. Listed below are some well-established process controls that could be evaluated to reduce or remove HCPs, including lipases and esterases, in DS (**19**):

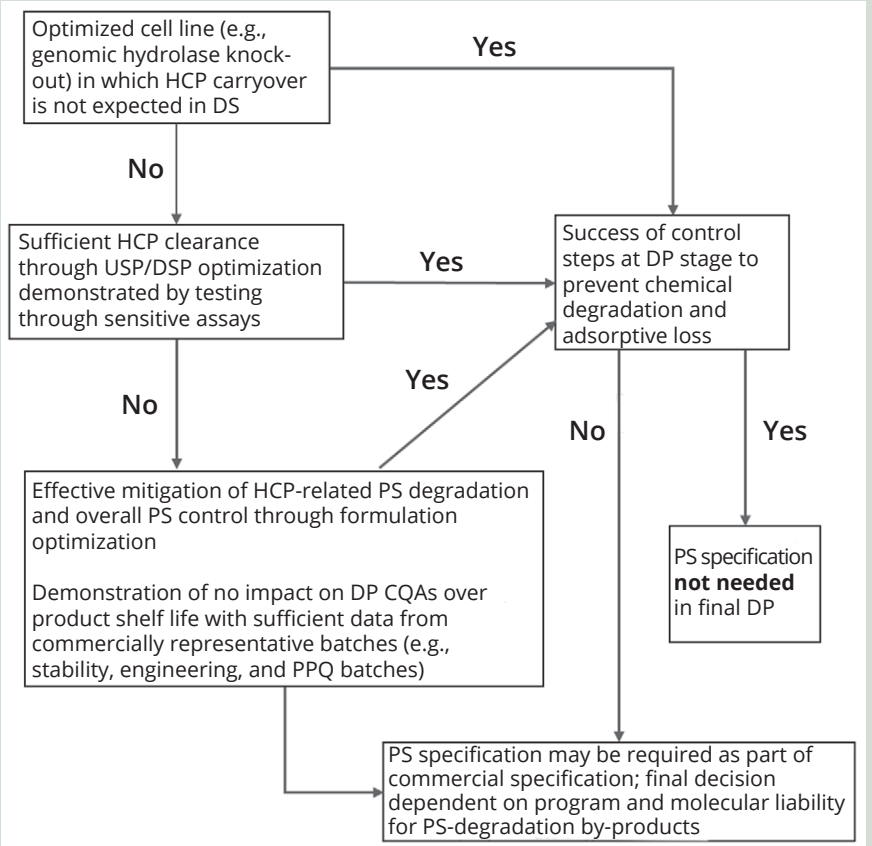
- temperature control of a cell-culture broth
- low-pH flocculation during harvest
- enhanced purification steps — e.g., protein A affinity, anion-exchange (AEX), cation-exchange (CEX), and/or hydrophobic-interaction (HIC) chromatography processes — and associated wash steps
- temperature and hold-time optimization during ultrafiltration/diafiltration (UF/DF).

To understand the effectiveness of the controls mentioned above, selective and specific analytical assays should be used to quantify HCP levels, especially for lipases and esterases, in a DS (**20**). Through appropriate process control, characterization, and sensitive analytical quantification, impurity control can be achieved.

Forced-Degradation Study: A *forced-degradation study* evaluates worst-case scenarios for the types of stresses that a final DP might experience and provides a forecast of possible degradation conditions. CQAs of DPs are measured during the study to trend PS and DP degradations under stressed conditions. Typically, a forced-degradation study is initiated during early phase development. To accommodate evolving process or formulation changes that are not considered during early phases, additional forced-degradation studies in the late phase often are recommended.

DP: PS degradation should be well defined for a given DP, whether such degradation occurs during shelf life, manufacturing, filtration or in-use. Potential effects on DP CQAs are key considerations for whether a specification is warranted on a final DP (**1, 9, 10**). Generalizations cannot be made about the

Figure 1: Polysorbate (PS) specification decision framework; in this context, host-cell proteins (HCPs) include only those related to PS degradation. (CQA = critical quality attribute, DP = drug product, DS = drug substance, DSP = downstream processing, PPQ = process performance qualification, USP = upstream processing)



risk and severity of PS losses from degradation or adsorption; the same goes for resulting impacts to product quality. Therefore, risk and severity should be assessed for individual products. When defining a commercial quality target product profile (QTPP) for PS-containing biotherapeutics, a control strategy should begin with DS CQAs and PS raw-material characteristics, as noted previously. Focus then shifts to the DP through optimizing a formulation design (especially around protein concentration and PS ratio). That involves monitoring development batches on stability and assessing the correlation of PS levels and degradation on DP CQAs.

During product development, selection of appropriate PS levels in a formulation is critical. Minimum and target PS concentrations must be justified for DP through multiple studies performed during development. PS levels are established and optimized through systematic development studies, such as agitation or interfacial-stress testing, freeze–thaw stress studies, simulated shipping/transport experiments, primary-container or contact-material compatibility studies, and formulation robustness studies to evaluate performance of surfactants in stabilizing the molecule of interest. Appropriate formulation-screening studies should be considered to understand the potential for PS chemical degradation (including metal-mediated degradation) during manufacturing, handling, and storage.

Controls implemented during DP manufacturing constitute a critical component of an overall PS control strategy. During process development, each DP unit operation (e.g., solution compounding, mixing, sterile filtration, holding, and filling) is evaluated for its potential to affect PS levels or quality, including losses and degradation associated with light exposure, temperature excursions, air–liquid interfaces, and adsorption to product-contact materials (**21–23**). Based on those risk assessments, specific control measures should be established and justified as part of the PS control strategy. Those could include defined light-protection requirements, qualification of low-binding single-use components, controlled hold times and temperatures, and appropriate line conditioning or priming to reduce PS adsorption (**10–12**).

For DP that undergoes dilution before intravenous administration, a minimum surfactant concentration should be specified for a finished DP to ensure adequate interfacial protection and stabilization of the product following clinical dilution and under intended use conditions (e.g., up to 24 hours at 2–8 °C followed by a limited period at room temperature) (**3, 24, 25**). In situations where in-use conditions result in PS levels below those explored during formulation screening, in-use stability studies are warranted to monitor relevant product quality attributes (e.g., aggregation, visible and subvisible particulates, and biological activity) and demonstrate that product quality and clinical performance are not compromised (**9, 26**).

Figure 1 outlines an approach to setting PS DP specification using PS-degradation data. To make a data-driven decision on PS use in final DP specifications, we recommend establishing a baseline by testing PS levels in representative, commercially relevant DP batches on stability to monitor PS degradation (if any) and other DP CQAs. Based on those data, PS specification at release/stability should be defined.

Future Directions

A clear need exists for harmonization regarding PS specifications as part of a holistic control strategy. Such coordination will help to build standardized expectations from health authorities and enable an aligned PS-control strategy across industry. A scientifically justified and risk-based approach will help to navigate complexities, providing a robust framework adaptable to new and emerging modalities.

A robust control strategy for PS should be based on scientific understanding of PS fate (through degradation pathways, adsorption during manufacturing and clinical in-use, and other such losses) and relevant impacts to DP CQAs. Specification strategies should be driven by empirical evidence and product-specific risk assessments. The overarching objective

remains ensuring patient safety and product stability; decisions to include — or not include — PS-related specifications should be supported by scientific data and risk management.

PS specification in biopharmaceuticals requires an understanding of regulatory guidance, molecular interactions, PS fate, and related influences on CQAs. As product development progresses, aligning strategies with both scientific rationale and regulatory expectations will be key to managing PS-related challenges. Our commentary adds to the ongoing discussion around PS control strategy, encouraging further research and cross-industry collaboration to develop cohesive strategies that reflect the diverse and dynamic nature of biopharmaceutical development. A strategy for PS specifications should be defined based on a detailed understanding of the factors described above. The ultimate goal is to safeguard product quality and patient safety by ensuring control of CQAs.

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Rationalizing Biological Drug Development

Biosimilar Science, Modality-Specific Pathways, and the Bioprocessing Revolution, Part 1

Sarfaraz K. Niazi

Regulatory frameworks governing biological medicines have developed incrementally over several decades, influenced by accumulating experience with recombinant-DNA technology and its associated manufacturing complexities. Unlike small-molecule pharmaceuticals, which can be characterized fully through structural determination and synthesized reproducibly using defined chemical reactions, proteins produced in living systems exhibit variability attributable to host-cell biology, culture conditions, purification processes, and posttranslational modifications (PTMs) (**1**). Such variability is not merely an imperfection to be minimized, but a fundamental characteristic of biological manufacturing that requires regulatory oversight.

The European Medicines Agency (EMA) established the inaugural comprehensive biosimilar pathway in 2005, acknowledging that follow-on biologics necessitated a distinct regulatory approach from generic small molecules (**2**). The core premise was that, although exact structural replication was unachievable, comparative evidence could substantiate that residual differences would not lead to clinically significant divergence. That evidentiary framework generally comprised three levels:

- exhaustive analytical characterization to confirm physicochemical and biological similarity
- nonclinical evaluations concerning pharmacology and toxicology, where scientifically justified
- clinical trials demonstrating comparable pharmacokinetic (PK) properties, immunogenicity, and, in numerous instances, therapeutic efficacy (**3**).

The United States implemented the Biologics Price Competition and Innovation Act of 2009, establishing a statutory framework that similarly prioritized a stepwise demonstration of biosimilarity (**4**). The US Food and Drug Administration (FDA) articulated a totality-of-evidence standard that provided flexibility regarding the nature and extent of data required; however, early implementations tended to adopt a conservative approach, favoring comprehensive clinical-development programs (**5**). The cautious stance reflected genuine uncertainty about whether analytical tools available at that time could identify all clinically relevant differences reliably, particularly for complex glycoproteins and monoclonal antibodies (mAbs) with intricate structure–function relationships. As analytical science has advanced, such concerns have diminished gradually, with modern techniques achieving resolutions that significantly reduce the epistemic gap that clinical trials were intended to bridge (**6, 7**).

The Empirical Record of Biosimilar Development: Two decades of biosimilar experience have generated an extensive empirical record that warrants careful examination. Across hundreds of biosimilar approvals worldwide, comparative clinical-efficacy trials have rarely identified differences between biosimilars and corresponding reference products that were not already apparent from analytical or PK data (**8, 9**). Multiple retrospective analyses have

documented that when analytical similarity is robustly established and PK bioequivalence is demonstrated, confirmatory efficacy studies function primarily as verification exercises rather than sources of new discriminatory information.

That pattern has prompted increased scrutiny of whether routine clinical confirmation is the most efficient use of resources. Each comparative efficacy trial requires significant financial investment, generally tens or hundreds of millions of dollars depending on the therapeutic area and indication (**10**). Such trials randomly assign patients to products whose similarity has been previously established using more direct and sensitive analytical techniques. The opportunity costs extend beyond individual development projects to encompass broad effects on market competition, pricing strategies, and global accessibility to biological therapies (**11, 12**).

Regulatory agencies have begun explicitly acknowledging those considerations. The World Health Organization's (WHO's) revised biosimilar guidelines adopt a risk-based framework, recognizing that clinical PK and pharmacodynamic (PD) studies may be sufficient when analytical and functional similarity are comprehensive and when exposure–response relationships are well characterized (**13**). Similar perspectives have been articulated by the EMA, which has expressed intentions to streamline biosimilar development through tailored clinical approaches (**14**). Those regulatory advancements reflect an increasing consensus that evidentiary requirements should be calibrated to genuine scientific uncertainty rather than applied categorically irrespective of product characteristics (**15, 16**). Importantly, the rationale for reducing clinical confirmation does not dismiss in vivo biology; PK studies conducted in humans constitute an inherently in vivo integrative measure that captures the cumulative effects of absorption, distribution, metabolism, elimination, and immune engagement, all of which influence therapeutic exposure. It is the comparative efficacy trial, rather than the PK study, whose redundancy is in question once exposure equivalence has been demonstrated (**8, 17**).

Analytical Advancement and the Shifting Basis of Uncertainty: The scientific rationale for reducing reliance on comparative efficacy trials largely rests on advances in analytical characterization, which have revolutionized our understanding of biological products prior to clinical testing. Techniques such as mass spectrometry (MS) now enable peptide mapping at resolutions that can identify single amino-acid substitutions, deamidation events, and oxidative modifications with high sensitivity (**6**). Higher-order structural methodologies, including hydrogen–deuterium exchange, analytical ultracentrifugation, and cryogenic electron microscopy, offer orthogonal validation of conformational similarity. Furthermore, functional assays with enhanced dynamic range and specificity allow for precise quantification of binding kinetics, effector functions, and biological activity, capabilities that were unattainable with earlier technologies (**1**).

Those capabilities fundamentally modify the epistemic landscape in which biosimilarity determinations are conducted. When structural attributes can be characterized thoroughly and functional properties measured directly, the residual uncertainty that clinical trials aim to mitigate decreases correspondingly (**18**). This advancement does not eliminate the role of human studies but instead redefines their position within an evidentiary hierarchy. Their comparative advantage now lies in identifying unforeseen safety signals or verifying exposure–response relationships rather than in providing redundant confirmation of efficacy.

Glycosylation analysis effectively illustrates this progression. In the early days of biosimilar development, challenges frequently arose with glycan heterogeneity because constraints in analytical methodologies hampered comprehensive characterization of carbohydrate structures that could influence PK properties, immunogenicity, and effector functions. Modern glycan-mapping techniques, including hydrophilic-interaction chromatography, capillary electrophoresis, and MS sequencing, enable detailed profiling that significantly reduces uncertainty about the functional implications of glycoform distributions (**7**).

Evidence Proportionality as Regulatory Principle: The concept of evidence proportionality posits that regulatory requirements ought to be calibrated to genuine scientific uncertainty rather than to a categorical classification of products. Although that principle is implied within totality-of-evidence frameworks, it has been explicitly articulated in recent guidance documents (**14, 15**). Its practical implications transcend biosimilar streamlining, extending to the adaptation of evidence standards as scientific knowledge advances and analytical capabilities broaden.

Proportionality functions across several dimensions. Products with well-understood mechanisms warrant a different evidentiary emphasis compared with those involving novel pathways or newly characterized targets. Modalities with inherently lower variability may justify a reduced clinical burden compared with those in which manufacturing complexity introduces increased uncertainty. Follow-on products for molecules with extensive postmarket experience benefit from accumulated knowledge that new therapeutic classes do not possess (**13, 16, 19**).

The regulatory challenge concerns the practical implementation of the proportionality principle, ensuring against arbitrary decision-making that would compromise predictability and fairness. It is imperative to establish clear criteria that differentiate scientifically justified cases warranting streamlined processes from those that require clinical confirmation due to residual uncertainty. Such criteria should be transparent, applied consistently, and based on a clear assessment of the sources of uncertainty and their clinical significance (**19**).

Emerging Modalities and Challenges to Classification

The Expanding Therapeutic Universe Beyond Recombinant Proteins: Biologics are undergoing significant diversification in modalities, challenging existing regulatory frameworks that were tailored for recombinant-protein therapeutics. Messenger RNA (mRNA) technology, exemplified dramatically

through the deployment of COVID-19 vaccines, is merely the most conspicuous indication of a broader transition toward nucleic-acid–based therapeutics that can direct protein expression within patient cells (**20**). That shift has considerable implications for how therapeutic equivalence should be conceptualized and demonstrated.

The fundamental distinction between traditional biologics and nucleic-acid therapeutics resides in their respective sites of protein synthesis. Recombinant proteins are produced ex vivo in bioreactor systems, where cellular machinery, culture conditions, and purification procedures collectively influence a final product's attributes (**1**). The heterogeneity observed, though manageable within certain parameters, reflects the inherent biological characteristics of the production system and cannot be eliminated. Conversely, nucleic-acid therapeutics deliver genetic instructions that enable patient cells to synthesize functional proteins using endogenous biosynthetic machinery (**21**). The therapeutic agent is the nucleotide sequence rather than a protein product; however, the agent's clinical efficacy ultimately depends on the expression and activity of the resultant proteins.

That "architectural" difference bears regulatory implications that current frameworks do not address comprehensively. Therapeutics whose informational core is digitally characterized and can be duplicated accurately at the nucleotide level do not fit seamlessly within categories that were designed for products with inherent and analytically complex manufacturing variability.

Messenger RNA Therapeutics — Structure, Variability, and Regulatory Implications: Therapeutics based on mRNA achieve clinical effects by transiently expressing encoded proteins following delivery to target cells. The RNA molecule comprises several functional domains whose design critically influences their performance:

- a 5′ cap structure that protects against degradation and facilitates ribosomal recognition
- untranslated regions that modulate translation efficiency and mRNA stability
- the coding sequence itself, typically optimized through codon selection to enhance expression
- a polyadenylated tail that contributes to stability and translational activity (**22**).

Chemical modifications, particularly incorporation of modified nucleosides such as pseudouridine or N1-methylpseudouridine, are designed to reduce innate immune activation and improve protein expression (**23**).

From a regulatory perspective, the sources of variability in mRNA products differ substantially from those of recombinant proteins; however, variability is not entirely absent. Two distinct layers of variability must be considered for mRNA follow-on products. The first is the informational layer: A sequence identity can be verified directly through standard molecular-biology techniques, ensuring that the product's instructional content is accurately and completely defined. The second is the delivery-system layer: Lipid nanoparticle (LNP) attributes — including particle-size distribution, polydispersity index, encapsulation efficiency, lipid molar ratios, and surface charge — can vary considerably across batches and manufacturing platforms. Such differences can significantly influence biodistribution, cellular uptake, endosomal-escape efficiency, and ultimately protein expression. Delivery-system characteristics necessitate comprehensive physicochemical characterization. They are not automatically interchangeable solely because the encoded sequence is identical. Both layers must be addressed. Although characterization is considerably more manageable for mRNA products than it is for complex glycoproteins, it remains a complex endeavor (**20**).

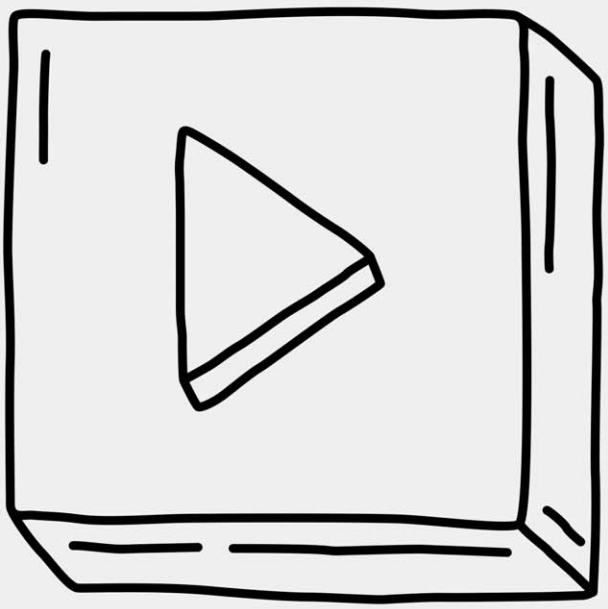
An RNA-delivery system introduces complexity that warrants careful consideration. LNP formulations must protect RNA during systemic circulation, facilitate cellular uptake, and enable endosomal escape for cytoplasmic delivery. Particle-size distribution, encapsulation efficiency, surface charge, and lipid composition all influence biodistribution and expression kinetics (**22**). However, those parameters can be characterized using established physicochemical methods, and their effects on expression profiles can be evaluated through manageable-scale PK/PD studies.

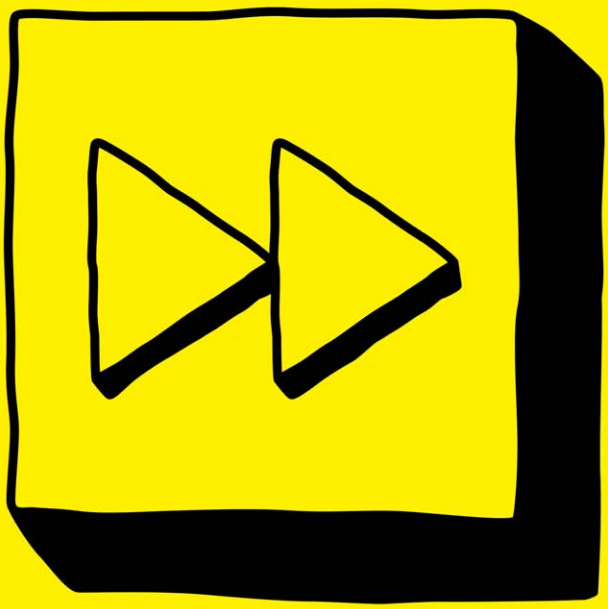
Self-Amplifying and Circular RNA Constructs: Self-amplifying RNA (saRNA) expands the traditional mRNA paradigm by incorporating viral-replicase components that facilitate intracellular amplification of the RNA template. Upon cellular uptake, the replicase produces multiple copies of the messenger sequence. That approach could result in higher or more sustained protein expression from lower administered doses than what can be achieved with standard mRNA therapeutics (**21**). The saRNA methodology introduces further design considerations, including replicase immunogenicity, amplification kinetics, and potential for prolonged expression, which may or may not be advantageous depending on the therapeutic context.

Circular RNA (circRNA) offers an alternative strategy to enhance the stability and longevity of expression. By eliminating free RNA termini that are susceptible to exonuclease degradation, circular constructs resist exonucleolytic pathways that constrain the half-life of linear mRNA, thereby facilitating more sustained intracellular expression from a given dosage (**24**). Expression may occur through internal ribosome entry sites or mechanisms that are subjects of active research. Manufacturing processes for circRNA differ from those for linear mRNA because they necessitate additional enzymatic or chemical circularization steps; however, the fundamental principle of sequence-defined instructional content remains unchanged.

Both approaches share with conventional mRNA a key characteristic: Therapeutic instruction is encoded in a nucleotide sequence amenable to precise analytical characterization (**25**). The regulatory question is whether products that differ primarily in stability and expression kinetics, but are used for encoding identical proteins, should be evaluated through frameworks developed for products whose variability arises from fundamentally different sources.

In Vivo Expression Systems for Antibodies and Complex Proteins: Perhaps the most conceptually





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challenging development involves systems designed for sustained in vivo expression of complex proteins, including mAbs. Rather than delivering purified antibodies via periodic infusions, in vivo approaches provide genetic instructions that enable continuous or long-duration antibody production within a patient (**26**). Medicines delivered by viral vectors, LNPs, and other such platforms could achieve therapeutic-antibody levels with reduced administration frequency compared with conventional biologics.

From a biosimilarity perspective, such systems raise fundamental questions regarding the definition of a therapeutic product and the methodology for evaluating comparability. If two platforms produce different vectors encoding the same antibody sequence, then the resulting proteins should be identical in primary structure; however, their PTMs would be influenced by the (in vivo) expression environment rather than bioreactor conditions. The pertinent comparison may involve not the administered product itself, but rather the protein expressed in vivo, as evaluated through systemic concentrations and biomarker responses.

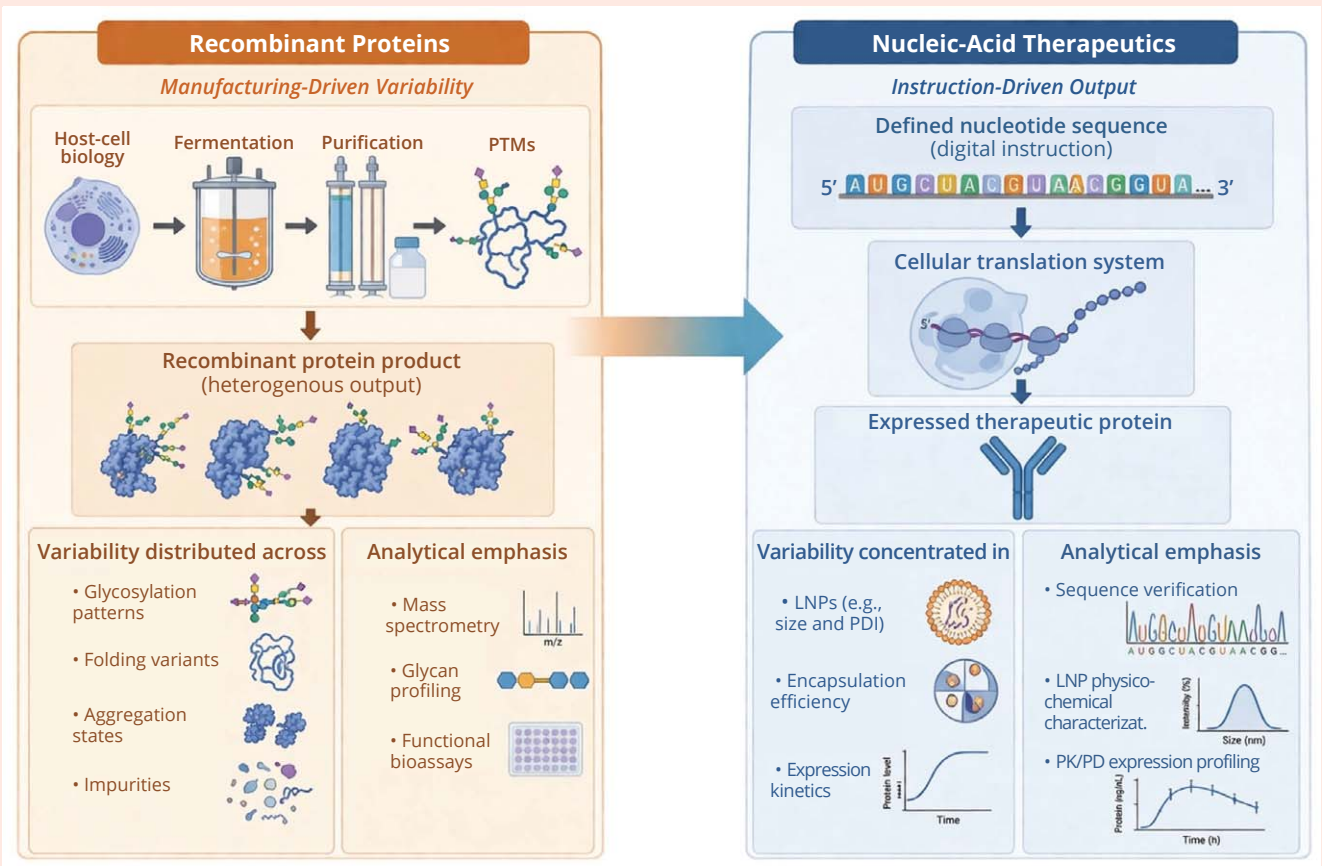
Such reorientation toward expressed-protein equivalence rather than administered-product identity signifies a substantial conceptual shift with practical implications for drug-development pathways and regulatory expectations.

Regulatory Classification Challenges: Existing regulatory categories inadequately address emerging modalities. Messenger RNA products encoding proteins identical to those in approved recombinant biologics are classified as neither biosimilars nor generics under current definitions despite producing the same active protein through different routes (**26**). Considering such products as entirely new biological entities would overlook the extensive knowledge related to the encoded protein's mechanism of action, safety profile, and exposure–response relationships. At the same time, classifying those products as biosimilars would apply a framework intended for different types of uncertainty.

The practical consequences of categorical misalignment include development burdens that may exceed scientific justification, regulatory timelines that do not reflect actual risk profiles, and competitive dynamics that entrench existing products against follow-on competition (**12**). Those outcomes harm rather than protect patients by limiting therapeutic options and perpetuating high prices.

A more coherent approach would focus regulatory attention on the actual sources of uncertainty for each modality rather than applying categorical requirements developed for different product types. For instance, evaluation of nucleic-acid therapeutics would emphasize sequence characterization, delivery-system attributes, expression PKs, and mechanism-based activity

Figure 1: Conceptual shift from manufacturing heterogeneity to instructional determinism; callout annotations indicate which analytical methods are most sensitive for characterizing variability at each point along the continuum, reinforcing the connection between modality characteristics and appropriate regulatory emphasis. (LNP = lipid nanoparticle, PDI = polydispersity index, PK/PD = pharmacokinetics/pharmacodynamics, PTM = posttranslational modification)



assessments. It would also calibrate clinical requirements to residual uncertainties that cannot be resolved by such studies (**13**).

Figure 1 illustrates a continuum depicting the relationships among biologic modalities and their primary sources of variability. On the left, classical recombinant proteins are presented with multiple upstream arrows symbolizing host-cell biology, fermentation conditions, purification processes, and PTM systems, which collectively influence a final product's attributes (**1**). Variability is distributed across these biological variables, each introducing uncertainty that affects the final product.

Progressing along the continuum, mRNA and other nucleic-acid therapeutics are depicted with an instructional sequence as a singular, well-defined element that feeds into the cellular translation machinery (**20**). Variability primarily relates to the performance of delivery systems and expression kinetics rather than the informational content itself. The visual representation emphasizes that sequence-defined products exhibit a fundamentally different relationship between manufacturing inputs and therapeutic outputs compared with recombinant proteins.

Mechanistic Foundations for Regulatory Differentiation

The Mechanistic Heterogeneity of Therapeutic Proteins: Therapeutic proteins exert clinical effects through a variety of mechanisms, each with distinct implications for how structural variability influences functional outcomes. Such mechanistic heterogeneity has not been integrated comprehensively into regulatory frameworks, which often consider biologics as a single category governed by uniform evidentiary standards. Nonetheless, the scientific rationale for differentiated treatment is supported by well-established pharmacological principles that distinguish direct molecular interaction from receptor-mediated signal transduction.

Receptor agonists and antagonists initiate intracellular-signaling cascades that amplify and diversify an initial binding event through multiple downstream effectors. Small differences in receptor-binding kinetics, affinity, or selectivity can propagate through nonlinear amplification to produce tissue-specific effects that may be difficult to predict from binding measurements alone. Signal-transduction pathways exhibit feedback regulation, crosstalk with parallel cascades, and context-dependent modulation that introduce complexity into structure–activity relationships.

A distinct subset of therapeutic proteins functions through mechanisms that do not encompass signal transduction (hereafter called *nonsignaling proteins*). Such agents achieve clinical benefit by intercepting molecular targets before they engage biological pathways, effectively removing pathogenic factors from circulation or tissues without initiating downstream signaling (**27, 28**). The pharmacological implications of this mechanistic distinction merit judicious regulatory evaluation.

Nonsignaling Protein Therapeutics — Definition and Characteristics: Nonsignaling protein therapeutics constitute a coherent mechanistic category characterized by direct biochemical interception rather than receptor-mediated cellular activation (**8, 9, 26**). Representative mechanisms include

- *ligand neutralization*, in which antibodies or fusion proteins bind soluble mediators to prevent receptor engagement
- *cascade blockade*, in which terminal pathway components are inhibited to prevent downstream effector functions
- *substrate sequestration*, in which pathogenic molecules are bound and cleared without initiating cellular responses.

The defining characteristic of these products is bounded pharmacology: the therapeutic effect directly correlates with the degree of target suppression, which in turn correlates with drug exposure at the site of action. Unlike receptor-mediated systems, where small binding differences can cascade into larger functional divergence, nonsignaling mechanisms exhibit predictable exposure–response relationships amenable to direct quantification (**28**). A *validated exposure–response relationship*, as used throughout this article, is one for which a quantitative link between drug concentration and pharmacological effect has been prospectively characterized, confirmed in at least two independent datasets or study contexts, and shown to be sufficiently stable across the patient population that equivalent exposure can serve as a surrogate for equivalent therapeutic performance. That is a substantive evidentiary standard, not a default assumption. The immediate and strongest regulatory case for exposure-anchored equivalence concerns precisely this class of products with bounded pharmacology and validated exposure–response relationships. The previous section discusses extension of similar reasoning to emerging modalities such as mRNA therapeutics, saRNA, and in vivo expression systems as a framework for future regulatory-pathway design, not as a claim that those modalities are currently ready for waiver of comparative efficacy requirements.

Clinical examples encompass a variety of therapeutic domains. For example, some agents neutralize circulating tumor necrosis factor (TNF) proteins before they engage membrane receptors, thereby preventing downstream inflammatory signaling. In ophthalmological contexts, antibodies are used to sequester vascular endothelial growth factor (VEGF) to inhibit receptor activation and subsequent neovascularization. Complement-cascade inhibitors obstruct terminal-pathway activation without triggering cellular signaling (**27**). In each of those instances, functional assays that directly measure target neutralization accurately reflect the mechanism underlying clinical benefit.

Regulatory Experience with Nonsignaling Biosimilars: The biosimilar experience concerning nonsignaling protein therapeutics offers empirical validation for mechanism-based regulatory differentiation. Biosimilars of anti-TNF agents, anti-VEGF antibodies, and other nonsignaling products have consistently demonstrated that thorough analytical and functional similarity predicts clinical equivalence. Confirmatory efficacy studies

infrequently alter regulatory determinations (**8, 9**).

That pattern exemplifies the mechanistic features that distinguish nonsignaling products. When a therapeutic effect relies on target neutralization and neutralization capacity can be measured directly through validated functional assays, the residual uncertainty that clinical trials are intended to address diminishes accordingly. The sensitivity of functional assays to detect significant differences generally surpasses that of clinical-efficacy endpoints, which are affected by patient heterogeneity, disease variability, and measurement noise (**28**).

A retrospective analysis of biosimilar switching studies further substantiates this stance. Extensive observational datasets investigating outcomes after transitions between reference products and biosimilars have not revealed clinically significant differences for nonsignaling agents where analytical and functional similarity has been confirmed (**9**). Such real-world evidence complements the theoretical argument for mechanism-based regulatory calibration.

From Advocacy to Regulatory Action — The Elimination of Comparative Efficacy Studies

Four peer-reviewed publications helped to make the scientific case against mandatory comparative efficacy testing for biosimilars before regulatory agencies imposed that requirement. Cataloging this publication record helps to contextualize subsequent regulatory modifications.

The first publication documents that, across all biosimilar approvals on record, comparative efficacy trials have not detected clinically meaningful differences beyond those already evident from analytical or PK data (**29**). The second applies Bayesian reasoning to demonstrate that, when prior analytical and PK data establish a high probability of equivalence, a confirmatory efficacy trial cannot yield a significantly different posterior estimate (**16**). The third illustrates that comparative PK studies, which are currently mandated for every biosimilar, are statistically analogous to the bioequivalence studies that are accepted as sufficient for the approval of generic drugs, thereby rendering the additional efficacy requirement redundant (**12**). And the fourth analysis explores how the FDA's January 2026 Bayesian guidance formalizes a justification-first framework: Clinical testing is justified only when it can meaningfully augment existing evidence, a threshold that analytically well-characterized biosimilars seldom approach (**30**).

In September 2025, the FDA approved an application for a ustekinumab biosimilar (reference product: Stelara) without requiring performance of clinical-efficacy studies, marking the inaugural waiver of this nature granted for a mAb biosimilar (**31**). The agency concluded that comprehensive analytical characterization combined with a PK similarity study was adequate to establish biosimilarity. The related draft guidance issued on 29 October 2025, titled "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Updated Recommendations for Assessing the Need for Comparative Efficacy Studies," extended that stance to encompass therapeutic-protein biosimilars broadly (**32**). It asserts that a comparative analytical assessment, alongside PK and immunogenicity data, generally will suffice for products derived from highly purified, well-characterized clonal cell lines. Furthermore, the draft guidance explicitly acknowledges that analytical methods are often more sensitive than clinical-efficacy trials are for detecting differences that could impede demonstration of biosimilarity.

The FDA's January 2026 draft guidance on Bayesian methodology in clinical trials provides a statistical framework that offers the necessary theoretical coherence for biosimilar waivers (**33**). Bayesian inference formalizes the principle that a study is scientifically justified solely when it can meaningfully update the posterior probability of the hypothesis under investigation. For biosimilars with comprehensive analytical, functional, and PK similarity already established, the prior probability of clinical equivalence is sufficiently high that no realistically powered efficacy trial will produce a materially different posterior estimate. The FDA guidance reinforces the notion that biosimilar reform exemplifies a broader principle applicable throughout drug development: Clinical testing must be justified by the information it contributes, rather than being applied categorically.

The batch-release analogy, although imperfect, effectively illustrates the problem of informational redundancy. When two samples from the same lot are tested, their structural identity is confirmed analytically, thereby rendering a clinical trial unlikely to provide additional insight. A biosimilar, in contrast, differs because it is produced through a distinct process, so the analogy is not exact. Nonetheless, it encapsulates the fundamental issue: Once analytical and PK comparability are established through rigorous assessment, the residual uncertainty that a clinical trial might address becomes sufficiently narrow. In such cases, the trial is unlikely to be sensitive enough to detect any remaining differences. A successful outcome in the trial offers minimal additional value, whereas a failed outcome is more plausibly indicative of a gap in the analytical program rather than a genuine clinical disparity. This perspective aligns with retrospective findings that the outcomes of comparative efficacy trials have not provided decisive information for biosimilarity determinations in the EMA's review records. That does not imply that clinical confirmation is never necessary; rather, its application should be reserved for situations for which residual uncertainty cannot be resolved by lower-tier evidence.

The persistence of efficacy-trial requirements reflected a well-documented pattern: Evidentiary frameworks established under early technological conditions can survive long after those conditions have changed. Drug-development practice established clinical trials as proof that a product works, and biosimilars, despite being required only to show equivalence rather than efficacy, inherited that framework. Clinical data carry institutional weight that analytical data do not, regardless of comparative

sensitivity. Overcoming that attachment required building an approval record large enough to make the pattern undeniable.

The EMA's reflection paper, adopted in March 2026, reaches a broadly compatible practical conclusion (**14**). It asserts that biosimilars may be approved without need for comparative efficacy studies where analytical characterization is comprehensive and PK similarity is demonstrated. The tailored approach is anticipated to apply to most biosimilars. The paper maintains the requirement for efficacy studies in cases where the mechanism or structure–function relationships are not fully understood, where analytical methods lack sufficient sensitivity, or where negligible systemic absorption renders PK comparison infeasible. Such exceptions are scientifically justifiable.

A significant distinction between the FDA and EMA frameworks pertains to their default assumptions. The EMA considers comparative efficacy as the primary expectation, from which exceptions must be justified; by contrast, the FDA guidance prioritizes analytical and PK data as the primary standards, with clinical efficacy serving as an exception that requires justification. The practical implications of that difference in framing for biosimilar developers, and the extent to which it diminishes as postguidance experience accumulates, will become clearer as both frameworks are implemented during evaluation of forthcoming applications.

Exposure-Anchored Equivalence for Nonsignaling Products: For nonsignaling protein therapeutics, exposure-anchored equivalence presents a scientifically justifiable alternative to standard comparative clinical-efficacy trials (**8, 13, 26**). This argument is based on mechanistic first principles: If therapeutic benefit is contingent upon target suppression, and if target suppression is governed by drug concentration at the site of action, then establishing equivalent exposure provides direct evidence of comparable therapeutic effectiveness.

PK studies aimed at establishing bioequivalence in exposure metrics are considerably more sensitive in identifying significant differences than are clinical efficacy trials powered for binary therapeutic endpoints. Statistical criteria for demonstrating bioequivalence within predefined margins are well established and can be met with relatively modest sample sizes compared with those needed for efficacy trials. Consequently, patient burden decreases, along with development timelines and associated costs (**16**).

Such an approach does not entirely relinquish requirements for clinical data; rather, it repositions those requirements within an evidentiary framework that emphasizes mechanistic relevance. The assessment of immunogenicity remains indispensable. Safety surveillance conducted through appropriately designed studies is likewise required. What is modified is the function of efficacy endpoints, which shift from a confirmatory gatekeeper to a conditional instrument used when significant uncertainty remains after analytical, functional, and PK evaluations (**15**).

Therapeutic Substitution Beyond Molecular Mimicry: The mechanistic perspective extends beyond biosimilar development to encompass therapeutic substitution, in which nonbiologic alternatives achieve comparable clinical outcomes through convergent pathways (**34**). Small molecules targeting identical biological processes as therapeutic proteins, RNA interference (RNAi) agents that suppress disease-driving gene expression, and targeted protein-degradation systems that eliminate pathogenic proteins constitute alternatives that could offer advantages in convenience, manufacturing scalability, and cost (**35, 36**).

The clinical validation of therapeutic substitution encompasses various disease domains. For hemophilia treatment, RNAi therapies targeting antithrombin have demonstrated efficacy comparable to bypassing agents and factor replacement (**37**). In complement-mediated conditions, small-molecule and peptide inhibitors have demonstrated clinical activity on par with mAb therapies. In the context of inflammatory diseases, oral Janus kinase inhibitors offer alternative mechanisms for achieving therapeutic success that are traditionally associated with biologic administration.

Those examples demonstrate that clinical equivalence does not necessitate molecular identity. When disease pathophysiology is comprehensively understood and therapeutic mechanisms converge on shared biological outcomes, diverse modalities may attain comparable clinical benefits through distinct molecular strategies. Regulatory frameworks that place excessive emphasis on structural similarity may unintentionally disadvantage alternative modalities, potentially limiting therapeutic options and access (**34**).

Looking Ahead

Thus far, I have explored the scientific and regulatory foundations for a reconsideration of biosimilarity. I identify a shift from current regulatory frameworks, which were designed to address clinical and mechanistic uncertainty for recombinant-protein products given the use of now-legacy analytical capabilities, to a framework that focuses regulatory attention on the sources of uncertainty for each modality rather than applying categorical requirements developed for different product types. First, I addressed the expanding biologic landscape, including the emergence of nucleic-acid–based therapeutics that require a different regulatory framework than that used for recombinant proteins. Then, I developed the mechanistic case for nonsignaling-protein therapeutics as a product class for which exposure-anchored equivalence, established through analytical characterization and PK similarity, would be sufficient to demonstrate biosimilarity without necessitating clinical-efficacy confirmation.

Available online in September 2026, Part 2 of this article moves into practical implications of a regulatory paradigm shift. I examine how artificial intelligence, quantum-mechanical methods, and four emerging manufacturing approaches — continuous bioprocessing, *Escherichia coli* expression, cell-free protein synthesis, and reduced process qualification lots under ICH Q5E — collectively could reduce total biosimilar development costs substantially, with estimates suggesting a pathway from the current range of US$100–300 million toward $20 million per program under optimistic assumptions. I also analyze practical and policy consequences of the differences between the FDA's and EMA's proposed framings of biosimilar assessment.

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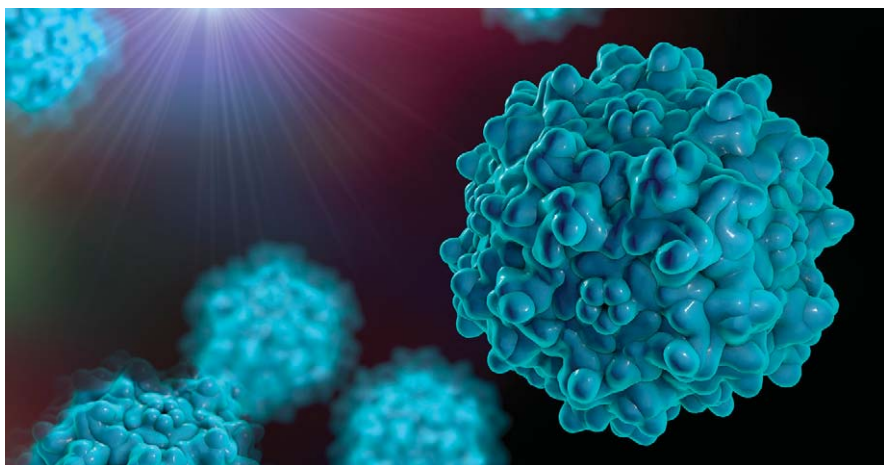
Advancing AAV Process Control with Continuous In-Line Monitoring and Orthogonal At-Line Validation

Paul Mania, Jeisa Pelet, Teva Smith, and Erik Hughes



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Accurate quantification of recombinant adenoassociated virus (AAV) genomes is essential for gene-therapy safety, efficacy, and consistency. However, downstream process development remains slow, resource-intensive, and dependent on multiple optimization cycles, largely due to the absence of rapid in-process analytics and the long delays of laboratory testing. Current methods include Droplet Digital polymerase chain reaction (ddPCR, Bio-Rad Laboratories), enzyme-linked immunosorbent assay (ELISA), transmission electron microscopy (TEM), analytical ultracentrifugation (AUC), and Gyrolab automated immunoassay (Gyros Protein Technologies). Emerging methods include high-performance liquid chromatography (HPLC), capillary electrophoresis (CE), dynamic light scattering (DLS), and ultraviolet–visible (UV-vis) spectroscopy. All of those methods are constrained by either narrow dynamic ranges, extensive sample preparation, long turnaround times, or low throughput. Those concerns underscore the need for robust, manipulation-free assays that enable high-throughput, real-time titer measurement.

To overcome such limitations, we evaluated integration of variable pathlength technology (VPT) with the PATsmart FlowVPX spectrophotometer and KrosFlo KR2i Real-time Process Management (RPM) system for continuous, in-line monitoring of AAV concentration during purification, complemented by PATsmart SoloVPE milestone sampling in concentration–diafiltration–concentration (CDC) workflows (all technologies from Repligen). The FlowVPX system enables direct nucleic-acid quantification during tangential-flow filtration (TFF) processes, delivering actionable, real-time data for process control.

We present a rapid, reproducible method for determining AAV titer, which is a critical quality attribute (CQA). The method is designed specifically to enable true in-process monitoring and real-time concentration targeting during AAV manufacturing. The Slope Spectroscopy method and KrosFlo RPM system not only mitigate batch-failure risk, but also support proactive process control for late-stage clinical and commercial manufacturing while accelerating raw-material characterization, reducing development cycles, conserving resources, and shortening manufacturing timelines.

Slope Spectroscopy Method

The Slope Spectroscopy method enhances conventional UV-vis spectroscopy by deriving concentration values from the linear relationship between absorbance and optical pathlength, as defined by the Beer–Lambert law.

Linear regression yields a coefficient of determination (R^2) value indicating the linearity of up to 10 absorbance readings at different pathlengths, verifying compliance with the Beer–Lambert law and ensuring measurement accuracy. The method requires a minimum of five data points for absorbance versus pathlength.

The pathlength can be adjusted to steps as small as 5 µm on the SoloVPE

Table 1: Operating parameters (mPES = modified polyethersulfone, NA = not applicable)

Parameter	KR2i RPM System	
Mode	Concentration – Diafiltration – Concentration (CDC)	
Diafiltration volumes	8	
Flow rate	106 mL/min	
Filter	mPES 100 kDa 115 cm^2 (D02-E100-05-S)	
Tubing	Platinum-cured silicone, size #16	
Parameter	**FlowVPX**	**SoloVPE**
Sample volume	NA	100 µL
Starting pathlength	3.0 mm	8.0 mm
Step size	0.5 mm	1.0 mm
Data points	6	6
Averaging time	1.0 s	1.0 s

system and 1 µm on the FlowVPX system, and the instruments have maximum pathlengths of 15 mm and 3 mm, respectively. That capability enables users to capture absorbance behavior across a broad dynamic range. The system then calculates slope-based concentration with a quality threshold of $R^2 \geq 0.999$. Because no dilution or manipulation is required, the method is rapid, precise, reproducible, and nondestructive, enabling efficient AAV quantitation.

AAV Quantitation

To quantify AAV genome and capsid titers, slope-based absorbance measurements are acquired at 260 nm (A_{260}) and 280 nm (A_{280}). Nucleic acids (i.e., the AAV genome) absorb maximally at 260 nm, whereas capsid proteins absorb at 280 nm. Four extinction coefficients (ECs) are necessary to quantify both genome and capsid titer simultaneously because each material has a different EC at each wavelength.

Because capsid-protein and nucleic-acid spectra overlap at 260 nm and 280 nm, calculations must account for the absorbance contribution from each substance. Thus, the total slope at a particular wavelength ($m_{\lambda,full}$) is the sum of the capsid-protein slope ($m_{\lambda,c}$) and the DNA slope ($m_{\lambda,d}$):

$$m_{280,full} = m_{280,c} + m_{280,d}$$

$$m_{260,full} = m_{260,c} + m_{260,d}$$

According to the Slope Spectroscopy equation, in which the slope equals the EC multiplied by the concentration ($m = \varepsilon \times conc$), those equations can be written as:

$$m_{280,full} = (\varepsilon_{280,c} \times conc_c) + (\varepsilon_{280,d} \times conc_d)$$

$$m_{260,full} = (\varepsilon_{260,c} \times conc_c) + (\varepsilon_{260,d} \times conc_d)$$

Solving those equations for $conc_c$ and $conc_d$ results in:

$$conc_d = \frac{R \times m_{280} - m_{260}}{\varepsilon_{260,d} \times (R \times K - 1)} \times N_A$$

$$conc_c = \frac{m_{280} - K \times m_{260}}{\varepsilon_{280,c} \times (1 - R \times K)} \times N_A$$

where $R \equiv (\varepsilon_{260,c} \div \varepsilon_{280,c})$, $K \equiv (\varepsilon_{280,d} \div \varepsilon_{260,d})$, and N_A is Avogadro's constant.

Those equations are built into PATsmart ViPER ANLYTX control software for VPT instruments such as the SoloVPE and FlowVPX systems. Users need only to enter the genome EC, and they can choose to change the capsid EC from the default value, which was determined experimentally by Sommer et al. (**1**).

Materials

- SoloVPE system:
  - SoloVPE instrument
  - Cary 60 UV-vis spectrophotometer
  - ViPER ANLYTX control software
- KrosFlo KR2i RPM system:
  - KrosFlo KR2i TFF system
  - FlowVPX instrument
  - Cary 60 UV-vis spectrophotometer
  - KrosFlo RPM software
- Vector product: AAV serotype 2 bearing a green fluorescent protein transgene (AAV2-GFP)

The FlowVPX system is a good manufacturing practice (GMP)–enabled, in-line UV-vis spectrophotometer designed for real-time concentration monitoring during processes such as TFF. Using VPT, the instrument adjusts optical pathlengths from 0.001 mm to 3.000 mm for accurate measurement of capsid proteins and nucleic acids using A_{260}/A_{280} ratios. The system offers automated, closed-loop control through open platform communications unified architecture (OPC UA) connectivity, supports compliance with Title 21 *US Code of Federal Regulations* Part 11, and provides rapid, automated analytics that make it a strong process analytical technology (PAT) for gene-therapy manufacturing.

The KrosFlo KR2i benchtop TFF system is designed for volumes from 10 mL to 10 L, a common range in AAV purification. The system includes a low-shear peristaltic pump, modular filters, automated control modes, and an automatic backpressure valve to stabilize transmembrane pressure (TMP) and reduce membrane fouling.

The KrosFlo KR2i RPM system integrates the KR2i TFF system with the FlowVPX spectrophotometer to enable automated, in-line concentration monitoring with real-time endpoint control. Operated through KrosFlo RPM software, the system manages filtration settings and data acquisition. It can run complex TFF workflows according to user-defined setpoints informed by data from the VPT system, auxiliary pumps, scales, and backpressure valve.

Experimental Design

An AAV2-GFP product served as a model vector for this proof-of-concept evaluation. Purified AAV2 material with an initial concentration of 10^{13} vector genomes (vg)/mL underwent prefiltration through a 0.2-µm membrane. TFF was conducted in a CDC sequence, incorporating 8 diavolumes (DV) during the diafiltration step (DF). The first and second concentration phases (C1 and C2) each targeted a twofold increase to yield an expected final titer of 4×10^{13} vg/mL. After final concentration, material underwent filtration for bioburden control and further purification to remove potential aggregates.

The FlowVPX system provided real-time, in-line monitoring of vector

Table 2: Analytical method comparison, viral genome (vg) titer; C1 = concentration step 1, C2 = concentration step 2, ddPCR = Droplet Digital polymerase chain reaction, DF = diafiltration, NA = not applicable

	Concentration (vg/mL)			|%Difference|		
Stage	ddPCR	SoloVPE	FlowVPX	ddPCR v. SoloVPE	ddPCR v. FlowVPX	SoloVPE v. FlowVPX
Load	1.0×10^{13}	1.1×10^{13}	1.2×10^{13}	9.5%	18%	8.7%
Post-C1	1.8×10^{13}	2.2×10^{13}	2.3×10^{13}	20%	24%	4.4%
Post-DF	2.0×10^{13}	2.2×10^{13}	2.2×10^{13}	9.5%	9.5%	0.0%
Post-C2	4.4×10^{13}	4.6×10^{13}	4.7×10^{13}	4.4%	6.6%	2.2%
Filtered retentate	4.2×10^{13}	4.2×10^{13}	NA	0.0%	NA	NA

Table 3: SoloVPE system intermediate precision results for viral genome (vg) titer; C1 = concentration step 1, C2 = concentration step 2, DF = diafiltration, RSD = relative standard deviation, SD = standard deviation

Stage	Analyst	SoloVPE Results (vg/mL, $\times 10^{13}$)	Average (vg/mL, $\times 10^{13}$)	SD (vg/mL)	%RSD
Load	1	1.12	1.13	2.1×10^{11}	1.9%
		1.12			
		1.10			
	2	1.13			
		1.16			
		1.14			
Post-C1	1	2.25	2.18	4.8×10^{11}	2.2%
		2.21			
		2.21			
	2	2.13			
		2.14			
		2.15			
Post-DF	1	2.14	2.16	4.1×10^{11}	1.9%
		2.15			
		2.10			
	2	2.19			
		2.22			
		2.17			
Post-C2	1	4.50	4.56	1.2×10^{12}	2.6%
		4.46			
		4.72			
	2	4.51			
		4.48			
		4.70			
Filtered retentate	1	4.28	4.24	7.9×10^{11}	1.9%
		4.29			
		4.29			
	2	4.23			
		4.09			
		4.28			

concentration to help determine transition points between TFF stages. Samples corresponding to the load, post-C1, post-DF, and post-C2 stages were collected for at-line analysis using the SoloVPE system. Post-C2 filtered retentate was sampled and analyzed as well, though that material was not monitored in real time using the FlowVPX system. At-line samples were submitted for orthogonal quantification by ddPCR assay (for genome titer) and Gyrolab immunoassay (for capsid titer) to compare the analytical methods. Percent differences between methods were calculated relative to the average of the two results.

Reported capsid ECs were 3.72×10^6 $M^{-1}cm^{-1}$ at 260 nm and 6.61×10^6 $M^{-1}cm^{-1}$ at 280 nm (**1**).

Table 4: Relative standard deviation (RSD) comparison for off-line viral genome (vg) titer; C1 = concentration step 1, C2 = concentration step 2, ddPCR = Droplet Digital polymerase chain reaction, DF = diafiltration

Stage	ddPCR	SoloVPE
Load	3.2%	1.9%
Post-C1	6.5%	2.2%
Post-DF	2.4%	1.9%
Post-C2	2.1%	2.6%
Filtered retentate	4.3%	1.9%
Average	3.7%	2.1%

The Flow VPX system captured the short recirculation step during which retained material was released back into the retentate, highlighting the system's ability to capture **DYNAMIC** changes in real time.

Genome ECs of 27 $(mg/mL)^{-1}cm^{-1}$ were derived from the single-stranded DNA (ssDNA) insert-gene coefficient at 260 nm and scaled by genome molecular weight to molar units. Genome ECs at 280 nm were calculated as $0.555 \times \varepsilon_{260}$, which is consistent with the A_{260}/A_{280} ratio of 1.8.

At-line measurements were conducted on a single SoloVPE system by two independent analysts. At each process step, a sufficient sample volume was collected for each analyst to prepare three distinct aliquots, and each aliquot was measured in triplicate. This procedure yielded 18 individual concentration determinations per process step (nine per analyst), providing a structured dataset for evaluating the method's repeatability and intermediate precision. Methods performed by the SoloVPE and FlowVPX systems were optimized for low absorbance samples using a fixed slope algorithm for measurement (Table 1).

Figure 1: FlowVPX system viral genome (vg) titer profile, with average SoloVPE and Droplet Digital polymerase chain reaction (ddPCR) measurements overlaid; C1 = concentration step 1, DF = diafiltration, C2 = concentration step 2

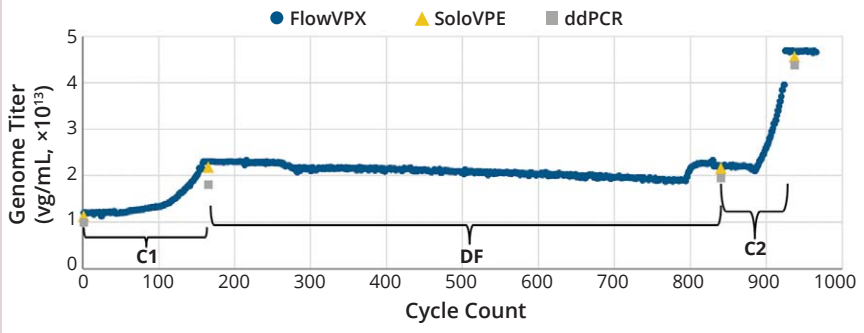


Table 5: Analytical method comparison, capsid (cp) titer; C1 = concentration step 1, C2 = concentration step 2, DF = diafiltration, NA = not applicable

	Concentration (cp/mL)			|%Difference|		
Stage	Gyrolab	SoloVPE	FlowVPX	Gyrolab v. SoloVPE	Gyrolab v. FlowVPX	SoloVPE v. FlowVPX
Load	2.1×10^{13}	2.1×10^{13}	2.2×10^{13}	0.0%	4.7%	4.7%
Post-C1	3.6×10^{13}	3.9×10^{13}	3.8×10^{13}	8.0%	5.4%	2.6%
Post-DF	3.3×10^{13}	4.1×10^{13}	3.7×10^{13}	22%	11%	10%
Post-C2	7.2×10^{13}	7.4×10^{13}	7.4×10^{13}	2.7%	2.7%	0.0%
Filtered retentate	7.1×10^{13}	7.1×10^{13}	NA	NA	NA	NA

Results

Genome Titer: Comparability across methods was strong. Results from the SoloVPE and ddPCR methods differed by <20%, and FlowVPX and ddPCR results differed by <24% (Table 2). The closest alignment was observed between the SoloVPE and FlowVPX measurements, with differences consistently <9%.

Intermediate precision testing demonstrated excellent reproducibility for the SoloVPE method, with variation between analysts below 3% (Table 3). Compared with ddPCR, the SoloVPE method showed better precision across all stages of the process (Table 4).

Process monitoring with the FlowVPX instrument provided a complete concentration profile throughout the CDC run (Figure 1). Overlaying results from the SoloVPE and ddPCR methods with FlowVPX data confirms overall alignment across the methods. Figure 2 compares concentration measurements at each process stage, with results reinforcing strong correlation across the platforms.

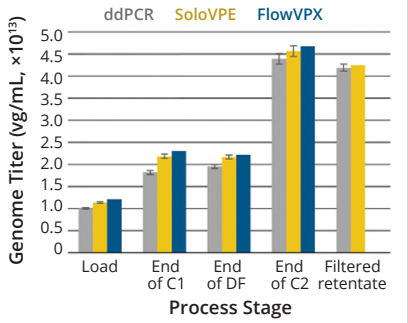
Figure 1 shows concentration decreasing during the DF phase, which is expected as material accumulates on the filter membrane. Toward the end of DF, a short recirculation step occurred before C2, during which retained material was released back into the retentate, causing a small, sharp increase in measured titer. That behavior is normal and represents a valuable insight uniquely captured by the FlowVPX system. In that regard, the system enables users to deepen their understanding of what occurs during their processes.

Capsid Titer: Capsid quantification showed similar trends to those observed for genome titer. As shown in Table 5, SoloVPE and Gyrolab results differed by up to 22%. The FlowVPX instrument yielded results within 10% and 11% of the SoloVPE and Gyrolab platforms, respectively.

Intermediate precision remained robust with <6% variation between analysts (Table 6). Assessment of repeatability again favored the SoloVPE platform (3.5% average relative standard deviation, RSD) over the Gyrolab platform (5.2% average RSD) at all stages of the process.

The FlowVPX system also provided continuous, in-line capsid concentration data for the full CDC process. In Figures 3 and 4, data from the SoloVPE and Gyrolab assays align closely with the FlowVPX data. Like Figure 1, Figure 3 shows the expected decline in capsid titer as material collects on the membrane. Again, that temporary retention and subsequent release at late stages is characteristic of the process and highlights the FlowVPX system's ability to capture dynamic changes in real time, offering valuable insight into capsid handling during purification.

Figure 2: Comparison of viral genome (vg) titer at defined process stages; C1 = concentration step 1, C2 = concentration step 2, ddPCR = Droplet Digital polymerase chain reaction, DF = diafiltration



Conclusion

The KrosFlo RPM system enables real-time capture of dynamic changes throughout AAV concentration workflows, providing critical insights into TFF process behavior. Continuous, in-line monitoring by the FlowVPX instrument generates a detailed concentration profile across each stage of a CDC process, allowing detection of transient events such as membrane interactions or material retention that are often missed by endpoint assays. By delivering immediate feedback, the FlowVPX system enhances process understanding and supports proactive decision-making during both process development and manufacturing. Although our work demonstrates the utility of the platform for monitoring purified material during TFF, broader applicability across earlier or less-purified process streams warrants further evaluation.

Likewise, the SoloVPE system delivers rapid, slope-based absorbance measurements at 260 nm and 280 nm, enabling samples to be withdrawn from the process stream and analyzed within minutes.

Figure 3: FlowVPX system capsid (cp) titer profile, with average SoloVPE system and Gyrolab immunoassay measurements overlaid; C1 = concentration step 1, DF = diafiltration, C2 = concentration step 2

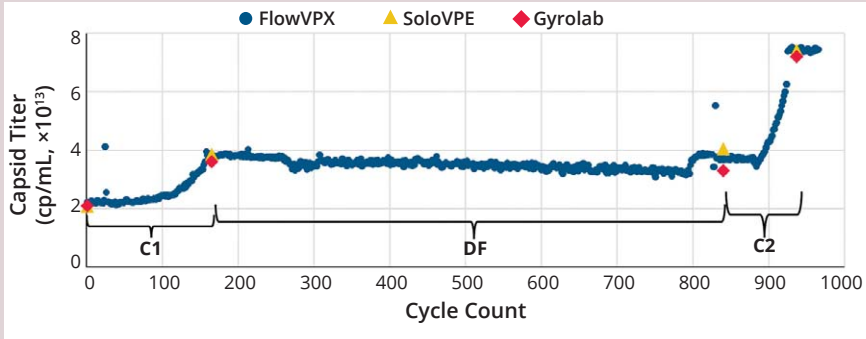


Figure 4: Comparison of capsid (cp) titer at defined process stages; C1 = concentration step 1, C2 = concentration step 2, DF = diafiltration, PCR = polymerase chain reaction

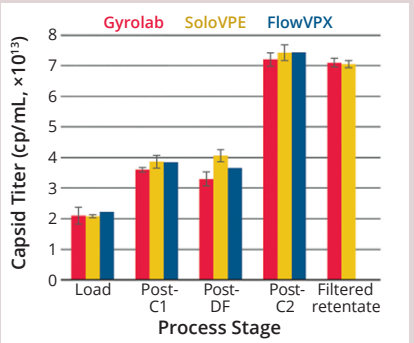


Table 6: SoloVPE system intermediate precision results for capid (cp) titer; C1 = concentration step 1, C2 = concentration step 2, DF = diafiltration, RSD = relative standard deviation, SD = standard deviation

Stage	Analyst	SoloVPE Results (vg/mL, ×10¹³)	Average (vg/mL, ×10¹³)	SD (vg/mL)	%RSD
Load	1	2.08	2.08	4.5 × 10¹¹	2.2%
		2.04			
		2.10			
	2	2.10			
		2.15			
		2.03			
Post-C1	1	3.78	3.86	2.1 × 10¹²	5.4%
		4.26			
		3.68			
	2	3.79			
		3.91			
		3.77			
Post-DF	1	4.12	4.06	2.0 × 10¹²	4.9%
		4.17			
		4.02			
	2	4.01			
		4.31			
		3.72			
Post-C2	1	7.66	7.42	2.6 × 10¹²	3.5%
		7.18			
		7.44			
	2	7.19			
		7.25			
		7.79			
Filtered retentate	1	7.19	7.05	1.1 × 10¹²	1.6%
		7.09			
		7.07			
	2	6.85			
		7.05			
		7.05			

By contrast, ddPCR assays can be a costly, time-consuming approach for AAV quantification, with consumables and reagents totaling up to US$1000 per plate. A workflow typically requires 24–48 hours from sample preparation through data analysis, significantly delaying feedback. Additionally, ddPCR assays can fail because of inhibition, droplet generation issues, amplification variability, and other such factors, requiring an assay to be repeated.

When performing ddPCR assays, maintaining consistency across analysts requires training and strict procedural controls. By comparison, intermediate precision is virtually nonexistent for the SoloVPE and KrosFlo RPM systems because measurements are highly reproducible and require minimal operator intervention.

Together, the FlowVPX and SoloVPE systems provide a fast, cost-effective, and highly reproducible analytical framework that delivers real-time quantification of AAV genome and capsid titers as well as exclusive process insights. The VPT platform and method strengthen confidence in quantification while enhancing overall process understanding and control.

Reference

1 Sommer JM, et al. Quantification of Adeno-Associated Virus Particles and Empty Capsids by Optical Density Measurement. *Mol. Ther.* 7(1) 2003: 122–128; https://doi.org/10.1016/s1525-0016(02)00019-9.

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Buffer Outsourcing

Enabling Flexible Biopharmaceutical Manufacturing Through High-Concentration Buffer Technologies

Gearoid O'Rourke

Buffers are fundamental to virtually every stage of biopharmaceutical manufacturing, including upstream processing, chromatography, viral filtration, tangential-flow filtration, formulation, and final fill operations. Although buffer solutions are essential, their preparation consumes significant manufacturing resources: dedicated preparation suites, mixing vessels, water for injection (WFI), single-use mixing systems, storage capacity, quality-control resources, and skilled manufacturing personnel.

Historically, many biomanufacturers produced buffers in house because that was considered the most straightforward means of ensuring supply security and process control. However, with increasing demand for biologics and advanced therapies, facilities are under unprecedented pressure to maximize use of good manufacturing practice (GMP) production space. Every square meter dedicated to something other than product manufacturing represents lost capacity for higher-value activities.

Brenntag Pharma good manufacturing practice (GMP) hub with dedicated class C cleanrooms for biobuffer manufacturing.
(HTTPS://WWW.BRENNTAG.COM/EN-GB/INDUSTRIES/PHARMA/PHARMA-GMP-HUB)

Why Buffer Outsourcing Is Growing in Popularity

Outsourced buffer manufacturing has become increasingly attractive for organizations seeking operational flexibility without compromising quality. Specialist chemical and pharmaceutical suppliers possess the technical expertise, analytical capability, and GMP manufacturing infrastructure required to produce highly controlled buffer concentrates that can be diluted at the point of use.

The advantages of outsourced buffer manufacturing are manifold: increased production capacity, reduced capital investment, diminished inventory requirements, improved supply-chain efficiency, simplified operations, increased production flexibility, and reduced operational risk. Rather than investing in additional buffer-preparation infrastructure, companies can redirect capital and personnel toward production activities.

Development of High-Concentration Buffers

Although outsourcing standard buffer formulations is relatively straightforward, developing highly concentrated buffer systems presents significant scientific and engineering challenges. Many common bioprocess buffers approach their limits of solubility under standard manufacturing conditions. Increasing concentration by a factor of 10 is not simply a matter of adding raw material.

Successful concentrate development requires extensive research and development (R&D) to understand

- component solubility limitations
- pH behavior at elevated concentrations
- ionic-strength effects
- temperature-dependent crystallization
- long-term chemical stability
- compatibility of buffer components
- effects of concentration on filtration performance
- storage stability over the intended shelf life.

Each formulation must be carefully engineered to prevent precipitation during manufacture, storage, and transport while ensuring that, after dilution, the final working buffer remains chemically identical to the original formulation. That requires iterative laboratory development, analytical verification, and pilot-scale manufacturing before commercial production can be achieved.

Analytical characterization of buffer concentrates typically involves verification of pH, osmolality, and conductivity, as well as assays of individual components, impurity profiling, evaluation of microbial control, and accelerated stability studies. Such activities demonstrate that concentrate performance will remain consistent throughout the intended shelf life. Thus, a buffer-development program represents a significant investment in formulation science, process engineering and quality-by-design principles.

Unlocking Capacity Through Buffer Concentrates

One recent project undertaken by Brenntag demonstrates how outsourced buffer manufacturing can deliver benefits extending well beyond supply-chain optimization. A global biopharmaceutical company was experiencing increased demand for manufacturing capacity and required a pilot-scale GMP area on site. Buffer preparation occupied valuable manufacturing space and equipment that otherwise could have been dedicated to finished-drug production. Brenntag's technical development team collaborated with the customer company to design and qualify a suite of 10× concentrated buffer formulations suitable for commercial manufacture.

Developing such concentrates required an extensive R&D program to overcome formulation challenges associated with high-concentration buffer chemistry. The work involved optimization of formulation composition, manufacturing parameters, analytical methods, and storage conditions to ensure that the concentrates remained stable throughout production, transportation, and storage. Buffers also needed to perform consistently following dilution.

The resulting products were manufactured under GMP conditions in a class C cleanroom and supplied as validated 10× concentrates. At the customer's site, concentrates were diluted with WFI immediately before use, producing the required working-strength process buffers without need for extensive in-house preparation.

Manufacturing Benefits: By transferring buffer manufacture to Brenntag, the customer was able to repurpose the area previously dedicated to buffer production for pilot-plant infrastructure. That capacity was later redeployed for finished-drug production. Outsourcing buffer manufacturing reduced operational complexity while improving manufacturing flexibility, enabling the company to respond effectively to increasing product demand. Rather than expanding its facility or investing in additional buffer-preparation equipment, the customer maximized its existing manufacturing assets.

Sustainability Advantages: The benefits extended beyond manufacturing efficiency. Traditional buffer supply often relies upon large volumes of ready-to-use solution stored and transported in single-use bioprocess bags. Supplying a 10× concentrate significantly reduced the transport volume required to deliver the same amount of usable buffer. Final dilution with WFI at the customer's facility minimized transportation requirements while reducing packaging demand.

The project also substantially reduced the number of single-use bags entering the manufacturing process. To support the customer's sustainability objectives, Brenntag implemented a rigid outer-container system that was designed for repeated use. That measure reduced plastic consumption and packaging waste, diminished transportation volumes, improved logistics efficiency, and progress toward corporate sustainability objectives. As environmental considerations become increasingly important within pharmaceutical manufacturing, such operational improvements are becoming significant drivers of outsourcing decisions.

A Collaborative Development Model

The success of high-concentration buffer outsourcing depends on more than manufacturing capability alone. Effective programs require close technical collaboration between supplier and customer throughout formulation development, scale-up, validation, and commercial supply.

By combining formulation science, analytical expertise, GMP capability, and supply-chain management, specialist partners can deliver custom solutions that align with both manufacturing and sustainability objectives. This collaborative model allows biopharmaceutical companies to focus internal expertise on drug development and manufacture while relying on experienced partners to manage increasingly sophisticated buffer-supply requirements.

Simplifying Operations While Releasing Capacity

Buffer manufacturing is evolving from a routine support activity into a strategic component of biomanufacturing operations. As production capacity becomes an increasingly valuable resource, outsourcing buffer preparation offers manufacturers an opportunity to improve operational efficiency while maintaining the high quality standards required for GMP manufacturing.

The development of high-concentration buffer technologies demonstrates how formulation science can create value far beyond a buffer itself. Through significant investment in R&D, specialist suppliers such as Brenntag can engineer robust concentrate formulations that simplify manufacturing, release valuable production capacity, and contribute to an organization's sustainability goals.

The case study presented here illustrates how a program for a carefully engineered 10× buffer concentrate enabled a biomanufacturer to repurpose pilot-plant capacity for finished-drug production while reducing packaging waste, lowering transportation requirements, and supporting environmental objectives. As biologics manufacturing continues to grow, such collaborative approaches are likely to become an increasingly important element of efficient and sustainable production.

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Consistency Is Key

Managing Complexity When Scaling Out Adherent-Cell Cultures

Brian Gazaille with Tom Bongiorno

Adherent-cell culture remains a cornerstone of biological research and commercial biopharmaceutical manufacturing. For viral vaccines, production in anchorage-dependent cell lines has largely surmounted egg-based methods because of advantages for scalability and product quality (see Figure 1 for a sample workflow). Therapies based on mesenchymal stem cells generally depend on expansion steps in adherent cultures. And applications continue to proliferate.

With demand surging for such products, upstream scientists find themselves under pressure to increase production. But adherent processes have distinctive scalability limitations compared with stirred-tank cultures of suspension-adapted cells — hence the age-old question of whether to scale up or out. Scaling up creates complex engineering demands regarding surface-area optimization, nutrient delivery, and shear-stress management; however, scale-out introduces concerns for process consistency and operations.

As Tom Bongiorno (senior support scientist at Corning) explained to me, there are ways to manage such concerns and maximize the productivity of adherent processes. We explored practical difficulties that come with scaling out and running multiple reactors in parallel. Bongiorno highlighted strategies and technologies that can help scientists to improve consistency across cultures while alleviating pressure on technicians.

Options Abound

How do you determine whether to scale adherent cultures up or out?

There are several trade-offs in the decision. Scale-up favors robustness and long-term cost reduction but requires more extensive optimization, whereas scale-out favors shorter timelines but requires more labor and manual processing. I recommend beginning your decision-making by considering what you expect the production-scale process to be.

What vessels and configurations support scale-out, and how do you determine which systems are best for a given process? Standard, fed-batch cultures can be performed with multilayer products such as Corning CellSTACK culture chambers and HYPERStack vessels. Recirculation of conditioned media is available with the Corning CellCube system and Ascent fixed-bed bioreactor systems. The CellSTACK technology is ideal for researchers who are most experienced with traditional planar cell culture and can accept a relatively low surface area per vessel. HYPERStack systems require moderate training and expertise but offer about triple the surface area per vessel footprint. The CellCube system is modular, offering flexibility to scale up or out, and it must be paired with a recirculation bioreactor. Ascent products combine a concentration mesh bearing an ultrahigh surface area with built-in media conditioning and recirculation.

What Could Go Wrong and What Should Go Right

Let's say that we have chosen to scale out. What problems might arise when operating multiple cultures? Over the duration of a passage, cell densities can vary, so your vessels might be optimal to passage at different times. A potential effect of the differences in cell densities is that cell phenotype can drift, resulting in distinct cell profiles in each vessel.

What process parameters and product-quality attributes are most important to monitor and maintain across cultures? For scale-out in any vessel type, it is probably most critical to keep cell identity constant across cultures. Though it may be impractical in adherent processes to assess cell identity in situ, sampling between passages offers a straightforward

approach to confirm cell identity and other attributes at regular intervals. At the beginning of each passage, cell density should be kept constant across vessels. Doing that will encourage consistency in other various product characteristics, including cell identity.

Cell density is especially important for stem-cell cultures because increased localized cell densities can prompt unexpected differentiation. A single cell suspension should be used to seed each vessel, and operators should ensure a homogenous mixture before every seeding step and to add an equal volume of cell suspension to each vessel. For multilayer vessels, additional steps must be taken to distribute cells evenly across layers. As the number of vessels increases, uniform seeding can become operationally challenging, emphasizing the need for detailed standardized procedures and training. For cell types that are prone to clumping, a cell strainer (e.g., a Corning or Falcon strainer) can help to ensure a single cell suspension.

What operational complexities come with scale-out? The chief challenges are increased labor and the associated complexities for operations. Finite labor constrains the extent to which a process can be scaled out. Timing trade-offs must be considered, too. For extensively scaled-out processes, a medium exchange or harvest step can take half of a day or longer, which is sufficiently long to influence your process. Given the labor availability and applicable biology, it is important to design processes based on the answers to these questions:

- Across your vessels, is it more critical to match the media exposure time for each exchange (facilitated by staggered seeding) or the total time from seeding to harvest (facilitated by synchronized seeding)?
- Are cells amenable to refrigeration and other interventions that temporarily slow underlying biochemical reactions?
- What are the operational limits of subsequent steps — e.g., the volumetric capacity of available centrifuges?

Answers to those questions can differ even within a process. For instance, the timing of a pretransfection medium exchange may be critical to coordinate across vessels, whereas precise timing of routine media exchanges may be less important.

How do scientists generally recover material from adherent cultures? How does scale-out complicate that process? For such processes, adherent cells typically are harvested using standard dissociation reagents at room temperature (for operational simplicity) and without mechanical intervention (which can cause aggregation). Specifically for scale-out processes, it is recommended to optimize dissociation-reagent incubation time, taking into account vessel-volume requirements and the properties of the static, room-temperature processing environment.

Large scale-out processes often are processed in sub-batches. For instance, cells may be harvested from two or three vessels at once and pooled for centrifugation and passaging. Considering the trade-offs that we discussed, sub-batching offers a convenient middle ground when navigating scale-out complexities.

Tech Talk and Reflections

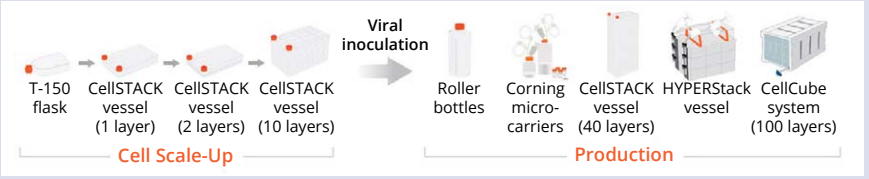
How might automation address operational concerns? Automation can drastically reduce the labor constraint associated with scale-out. Automated culture platforms, such as the Ascent fixed-bed reactor and CellCube system (with its third-party bioreactor), also can improve consistency in timing, media-exchange flow rates, and other such parameters. Enhanced process consistency is generally associated with improved yields and product quality — e.g., by increasing the uniformity of cell densities and the concentrations of media nutrients and waste products that cells experience during a process.

What do you think are the best and worst ways to apply automation in a scale-out strategy? Automation is best applied to scale-out when labor and/or bioprocessing expertise are limited and would otherwise constrain the size of a full-scale process. As with any implementation of automation, there is a risk with scale-out that automation simply magnifies a poorly designed process. Use a stepwise approach, starting at a small scale and validating critical quality attributes and process parameters (CQAs, CPPs) along the way.

Before evaluating a platform, you should robustly quantify the CQAs of cells cultured in your current, manual process. You can compare those attributes with those obtained using the automated platform under evaluation. Initial testing on the smallest available automation platform is recommended to minimize process development costs and to enable like-to-like comparison between a manual and automated process.

What was your most memorable scale-out experience? I recall a customer who was using a large number of HYPERStack vessels connected via closed-system tubing. The customer leveraged the modularity of the HYPERStack technology to tune the total surface area as needed for the process. However, in an effort to reduce the risk of contamination by minimizing the number of closed-system connections, the customer attached all of their HYPERStack vessels together. We identified several complications with that approach, including the total processing time and the required weight and size of the media bag. By switching to the sub-batching strategy that I described before, we optimized the process.

Figure 1: Scale-up solutions — vaccine-production workflow using adherent cell lines



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Advancing High-Concentration mAb Processing Through Improved TFF Cassette Design

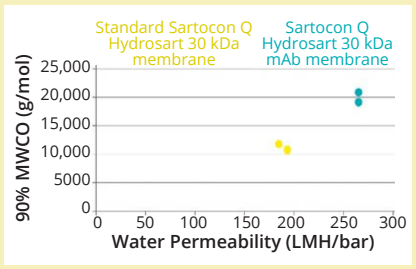
Anika Manzke and Katy McLaughlin

Monoclonal antibody (mAb) therapeutics are increasingly formulated at high concentrations, driven by escalating upstream titers, the shift toward personalized treatment, and growing use of subcutaneous administration (**1**). Thus, downstream concentration steps require scalable and robust tangential-flow filtration (TFF) solutions that can achieve high protein concentrations while maintaining product retention, flux, and operational stability.

As the only operation that simultaneously separates and concentrates target molecules, TFF's most critical application is the ultrafiltration and diafiltration (UF/DF) step before sterile filtration and filling. At that stage, mAbs are processed to a final target concentration, often with exchange into a formulation buffer. Yet UF/DF performance is challenging at high mAb concentrations. High solution viscosities reduce mass transfer; concentration polarization and gel-layer formation at the membrane surface can restrict operating windows. In practice, high-viscosity solutions can create operational challenges, including long process times, high pressures, and increased risk of performance drift during the final UF phase.

As a result, cassette design becomes a decisive factor in whether high-concentration targets can be reached efficiently without compromising scalability and operational stability. Wider channels can accommodate more viscous solutions but require increased pump capacity to maintain effective crossflow. Narrower channels require lower flow rates but can reach pressure limits sooner as viscosity increases. The selected cassette design must balance pressure, flow, processing time, and shear exposure.

Figure 1: The optimized Sartocon Q Hydrosart 30 kDa mAb membrane combines high water permeability with a retention profile ideal for high-yield mAb processing. (LMH = liters per square meter per hour, MWCO = molecular-weight cutoff)



Membrane selection is equally important. Although a 30 kDa molecular-weight cutoff (MWCO) is typical for processing standard mAbs, differences in membrane pore structure and permeability can affect product retention, flux stability, and overall process efficiency.

The Sartocon Q Hydrosart 30 kDa mAb cassette has been developed specifically to address those challenges. It is optimized for mAb concentration steps and designed to improve process efficiency while maintaining scalability and operational robustness. Here, we introduce key elements in the cassette's design and explain how those features apply in mAb processing workflows.

Optimized Membrane Design

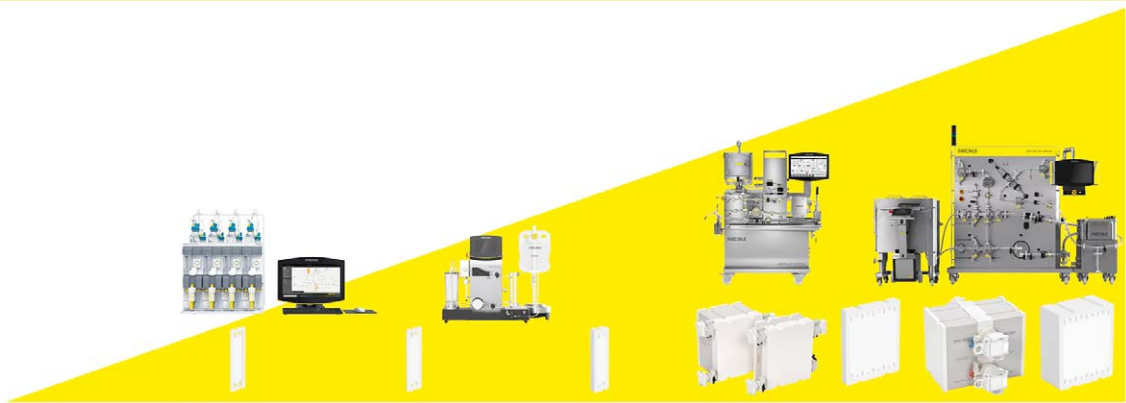
At the core of the Sartocon Q Hydrosart 30 kDa mAb cassette is a membrane optimized for mAb processing rather than general UF. Stabilized, cellulose-based Hydrosart membranes are well established in the biopharmaceutical industry. The membranes' high hydrophilicity and negligible protein adsorption make them virtually nonfouling, supporting high product recovery and sustained flux throughout processing. Hydrosart membranes are also stable across a broad pH range. Unlike other membranes on the market, they can withstand cleaning with up to 1 M NaOH, even at elevated temperatures, without loss of performance over repeated cleaning cycles. As mAb concentrations and protein loads increase, effective and reproducible cleaning becomes essential to maintaining consistent performance across multiple cycles. This combination of sustained filtration performance and efficient cleanability supports a long product life cycle.

The Sartocon Q Hydrosart 30 kDa mAb membrane was further optimized for mAb applications, combining higher water permeability with a retention profile suitable for mAb processing (Figure 1). That optimization provides 30–50% higher buffer flux than the standard Hydrosart 30 kDa membrane while maintaining mAb retention.

New Screen Design

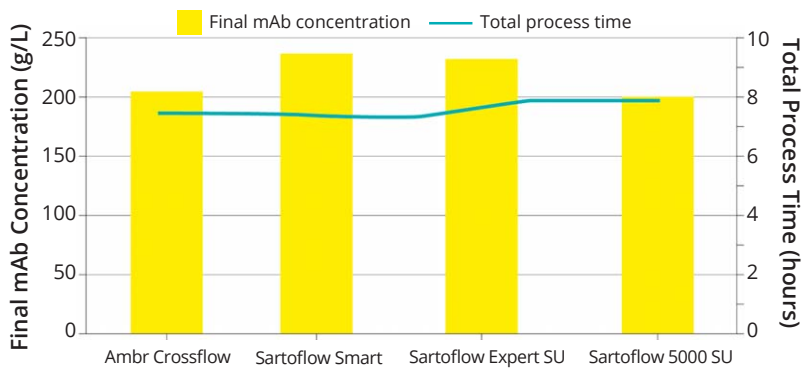
In addition to an optimized membrane, the cassette incorporates a new screen configuration intended to support viscous solutions. Compared with legacy systems, Q-Screen technology combines a fine-mesh design with a more open flow path, maintaining higher flux as solution viscosity increases. That feature supports high

Figure 2: Sartocon Q Hydrosart 30 kDa mAb modules for tangential-flow filtration (TFF) are available in five configurations offering different effective filtration areas and compatibility with multiple TFF systems.



Format	Sartocon Q Slice 100	Sartocon Q Slice 200	Sartocon Q Slice	Sartocon Q	Sartocube Q
Effective filtration area	86 cm²	172 cm²	0.13 m²	0.63 m²	3.09 m²
System	Ambr Crossflow	Sartoflow Smart		Sartoflow Expert SU	Sartoflow 5000 SU

Figure 3: Total process time and final monoclonal antibody (mAb) concentration achieved with Sartocon Q Hydrosart 30 kDa mAb cassettes at different scales



final mAb concentrations while limiting shear exposure, reducing the need for extended process times and operation close to pressure limits.

Scalability

The Sartocon Q Hydrosart 30 kDa mAb cassette is available in multiuse formats and self-contained units. Those offerings range in size from small-scale Sartocon Slice cassette formats, such as the Sartocon Slice 100 cassette (with an effective filtration area of 86 cm²), to conventional cassette formats up to 0.63 m² and larger Sartocube and self-contained single-use configurations of up to 6.18 m² (Figure 2). The small-scale Sartocon Slice 100 cassette enables process development and optimization using low volumes, which is critical in early phases, when material is limited.

The smaller devices are designed to scale to larger formats, so parameters established during development can be transferred to manufacturing without redefining a process. In a study performed using a customer's mAb feed, small configurations showed performance consistent with larger formats (Figure 3) (**2**). At a loading density of 1000 g/m², final mAb concentrations exceeded 230 g/L with 99% recovery. Results were largely unchanged across scales and comparable with those achieved using other filters on the market.

Process duration — encompassing initial UF, DF, and final UF steps — remained within an eight-hour production shift across all device sizes. Being able to finish an entire UF/DF process within a single shift helps to minimize the risk of product degradation and allows more batches to be processed within the available manufacturing schedule.

Facilitating TFF Workflows

Fast, reliable, and scalable TFF solutions are increasingly important as high-concentration mAb formulations become more common. The Sartocon Q Hydrosart 30 kDa mAb cassette offers a balanced solution that combines high performance with operational efficiency. Its optimized membrane, advanced screen design, and built-in scalability are intended to fit seamlessly into demanding mAb processing workflows without compromising development flexibility or operational consistency.

Learn more about the Sartorius TFF portfolio and request a sample at *https://www.sartorius.com/en/products/process-filtration/tangential-flow-filtration/tff-cassettes#id-1821194*.

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Preparing for Viral Clearance Studies

How Manufacturing Readiness Supports Successful Downstream Validation

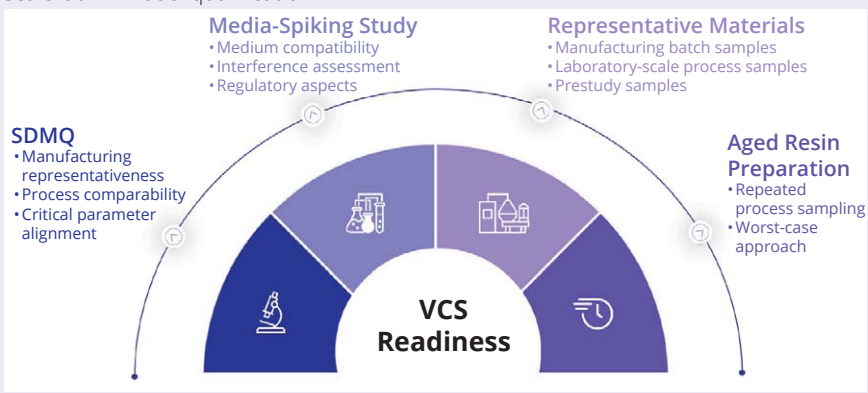
Donggu Oh

Viral safety is a nonnegotiable regulatory expectation for biologic drug substances manufactured using mammalian cell culture. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q5A guidelines mandate appropriate viral clearance studies (VCSs) to demonstrate removal or inactivation of potential viral contaminants (**1**). VCSs help establish the overall viral safety strategy in downstream processing expected by global regulatory authorities.

Much of the industry discussion surrounding viral clearance focuses on virus-filtration technologies, low-pH viral inactivation, chromatography, or the design of validation studies themselves. However, successful VCSs rely on a series of manufacturing activities that begin well before any virus is introduced into a laboratory model. From developing representative scale-down models to preparing manufacturing materials and conducting supporting studies, manufacturing teams help ensure that VCSs can be executed efficiently and generate meaningful, representative results.

The Samsung Biologics manufacturing science and technology (MSAT) team has developed standardized approaches to recurring manufacturing support activities, translating experience accumulated across diverse downstream validation studies into workflows that promote consistency, facilitate knowledge transfer, and strengthen downstream validation preparation across client programs.

Figure 1: Validation activities to ensure viral-clearance study (VCS) readiness; SDMQ = scale-down model qualification



Why Manufacturing Preparation Matters

Validation determines whether downstream processes perform as intended under manufacturing conditions. Whether supporting VCSs, process characterization, or chromatography resin life-cycle assessments, laboratory studies must accurately reflect commercial manufacturing operations to generate meaningful data. Such validation studies begin with qualified laboratory-scale process models that appropriately represent a manufacturing process.

Process scale cannot simply be reduced for validation studies. Manufacturing parameters, chromatography behavior, material characteristics, and process consistency must all be carefully reproduced to establish representative study conditions. Without this preparation, even technically well-designed validation studies may generate results that are difficult to interpret or apply to commercial manufacturing.

Readiness with Scale-Down Model Qualification

Scale-down model qualification (SDMQ) is a critical component of downstream validation. Such models link laboratory-based validation studies to commercial manufacturing. By demonstrating that laboratory-scale processes accurately represent manufacturing performance, they provide a reliable platform for subsequent technical studies.

Samsung Biologics has used accumulated project experience to create standardized execution workflows that cover major activities such as sample preparation, experimental protocol development, laboratory execution, data analysis, and report generation. As a result, technical teams can leverage proven frameworks while incorporating product-specific requirements where appropriate. This standardization allows scientists to focus on technical evaluation and process understanding rather than building supporting documentation from scratch. Beyond

improving operational efficiency, this approach promotes greater consistency across projects and facilitates knowledge sharing throughout the organization.

Media-Spiking Studies for Validation Readiness

Another important aspect of Another important aspect of manufacturing readiness involves supporting studies performed before formal VCSs. During these preparatory studies, viruses are intentionally introduced into process materials to evaluate removal capability. Because those viruses are delivered in a liquid medium, teams must confirm that the carrier solution itself does not influence downstream process performance. Media-spiking studies help evaluate whether this additional liquid changes process behavior, verifying that the spiking material does not introduce artifacts or interfere with unit operation performance. Such studies are a key component of viral clearance preparation and support regulatory confidence in study design.

At Samsung Biologics, media-spiking has been standardized using predefined protocols and execution procedures, enabling efficient preparation before formal VCSs. Using samples generated from manufacturing or laboratory-scale material, these studies provide critical data that help partners execute a VCS efficiently. Rather than an isolated experiment, media-spiking serves as a scientific readiness assessment that verifies matrix compatibility before virus-spiking and strengthens confidence in subsequent VCS results.

Preparing Representative Process Materials

Supporting VCSs also requires the preparation of representative manufacturing materials. Depending on the study objectives, samples may be generated from manufacturing batches or produced using qualified laboratory-scale models. In addition to materials intended for virus-spiking studies, appropriate samples for pre-study assessments, such as cytotoxicity and interference testing for viral-titer analysis, are also prepared based on accumulated study experience.

Those materials must accurately reflect manufacturing conditions because the validity of downstream VCSs depends on the quality and representativeness of the starting materials. Manufacturing teams generate suitable process samples, maintain process consistency, and provide the technical foundation on which external viral clearance laboratories perform their validation studies. Although virus handling itself is performed by specialized laboratories with appropriate biosafety capabilities, manufacturing preparation remains an essential prerequisite for successful execution.

Supporting Resin Life-Cycle Evaluation

A third preparatory activity involves preparing aged chromatography resins for life-cycle VCSs. Because resins are reused throughout commercial manufacturing, regulators require manufacturers to demonstrate that viral clearance performance holds throughout a validated resin lifetime. Consequently, these studies use representative aged resins to confirm that resin aging does not adversely affect viral-removal capability.

External laboratories conduct virus-spiking experiments, and manufacturing teams generate representative aged resins by performing repeated processing cycles using qualified scale-down models that simulate long-term manufacturing. Depending on life-cycle requirements, resins corresponding to approximately 100–200 manufacturing cycles are prepared to support VCSs under representative worst-case operating conditions.

Because generating representative aged resins requires substantial processing over an extended period, proactive planning and standardized operating procedures are essential to ensure suitable materials are available when life-cycle VCSs begin. At Samsung Biologics, standardized resin-aging strategies enable timely preparation of representative aged resins while maintaining consistency with commercial manufacturing conditions, providing scientifically justified materials for downstream evaluation.

Turning Experience Into Standardized Execution

Many of these supporting activities are well-established throughout the biopharmaceutical industry. The difference lies in consistency of execution across programs rather than in the studies themselves. As organizations accumulate experience, recurring technical activities naturally evolve into standardized workflows. These workflows incorporate lessons learned into protocol templates, reporting formats, documentation practices, and technical guidance, allowing future programs to build upon established knowledge.

Samsung Biologics has refined its standardized approaches with data from numerous downstream validation support studies. By transforming experience into repeatable workflows, project teams can leverage existing technical knowledge while maintaining flexibility for client- and product-specific requirements. This approach supports consistent execution, promotes efficient knowledge transfer across teams, and provides a strong technical foundation for downstream validation preparation.

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Data Issues and Regulatory Hurdles Are Stopping AI from Driving Real Value in Pharma

James Colley

The pharmaceutical industry is beguiled with the promise of artificial intelligence (AI), but industry insiders reveal a significant disparity between executive vision and operational readiness. Although AI adoption is progressing across the sector, it remains highly uneven; current success is largely limited to speeding up documentation and compliance. The dreams of autonomous factories are still some way off.

BioPhorum, a collaborative industry network, has consolidated benchmarking data across its members (collected throughout 2025) to analyze themes, use cases, and limitations of AI tools in the pharmaceutical industry. We found the following:

- AI was live and embedded in only four of the 30 use cases recorded. Those use cases sat within quality, information-technology (IT), and data-science functions.
- 13 out of 30 use cases were still in the pilot or development phase, whereas 12 were still under consideration.
- Within drug development, three out of 21 responding organizations noted that they were scaling pilots successfully, and none had fully embedded workflows.
- Members within advanced therapies showed the slowest uptake of AI, with no use cases live or in the pilot stage.

So where is AI actually adding value? AI is being adopted primarily for deviation management, documentation review, compliance checking, and complaints management. Organizations are finding quick wins by deploying AI to assist with standard operating procedure (SOP) authoring, audit-trail reviews, and annual product-quality reviews. In one notable instance, AI was used to reduce manufacturing execution system source-code review time from 16 hours to under a single hour.

Beyond paperwork, more advanced applications are beginning to emerge in predictive analytics and in silico modeling. Predictive analytics are now actively optimizing drug yields and acting as early warning systems on the factory floor by detecting abnormal states in bioreactors before costly failures occur. AI is also shifting trial-and-error experimentation out of physical laboratories and into virtual simulations, acting as an advanced assistant that simplifies data workflows and drastically accelerates the scientific test and learning cycle.

However, broad transformative gains have yet to progress because of a data problem. *Data readiness* — specifically, questions of data access, availability, formatting, and lineage — has emerged as the single largest barrier to AI deployment across the industry. Before organizations can reap the rewards of such technologies, they must spend years cleaning and connecting fragmented, inaccessible datasets. Currently, over half of surveyed organizations admit that they have not harmonized their unstructured data, relying instead on manual extraction and transformation. Without clean, structured data as a precursor, meaningful validation of advanced AI models is simply impossible.

Despite such hurdles, many pharmaceutical companies are not buying off-the-shelf AI software. BioPhorum's benchmarking shows a distinct preference across the industry for building AI capabilities internally rather than purchasing commercial tools. This trend is perfectly illustrated in quality operations: Out of 19 recently implemented tools, 12 were developed entirely in house, seven were codeveloped with a vendor, and none were purchased directly as off-the-shelf solutions. That build preference is driven by high data sensitivity, the need to encode bespoke proprietary processes, and a lack of maturity among commercial vendor offerings. Greater maturity is needed to meet strict compliance needs in a highly regulated industry.

Regulation is another key barrier to AI progress. For decades, the pharmaceutical industry has relied on strict validation processes to guarantee safety. Those processes, built for traditional software, are designed to be perfectly predictable. But modern AI isn't traditional software; it is designed to learn, adapt, and shift its behavior based on new data. The industry's current rulebooks simply are not built to handle tools that constantly evolve. Right now, regulatory expectations for those models remain clouded at best, leaving companies guessing how to formally prove that an AI tool will not drift off course.

Ultimately, the vision of fully agentic and autonomous systems that independently manage complex workflows is still a long way off. Across all industry groups evaluating such technologies, there is consensus that AI tools must be audit-ready and compliant by design. AI models lack a true semantic understanding of manufacturing intent or clinical context, and thus human-in-the-loop oversight remains essential for all scientific and operational decision-making.

Although the pharmaceutical industry is finding ways to build its own tools for administrative wins and early-warning alerts, organizations are still wrestling with the unglamorous groundwork. Until such deep-rooted data issues are fully rectified and regulators write a new playbook for adaptive technology, the sector cannot use the technology to drive real, transformative value. We may be in the age of AI, but the human expert is not leaving.

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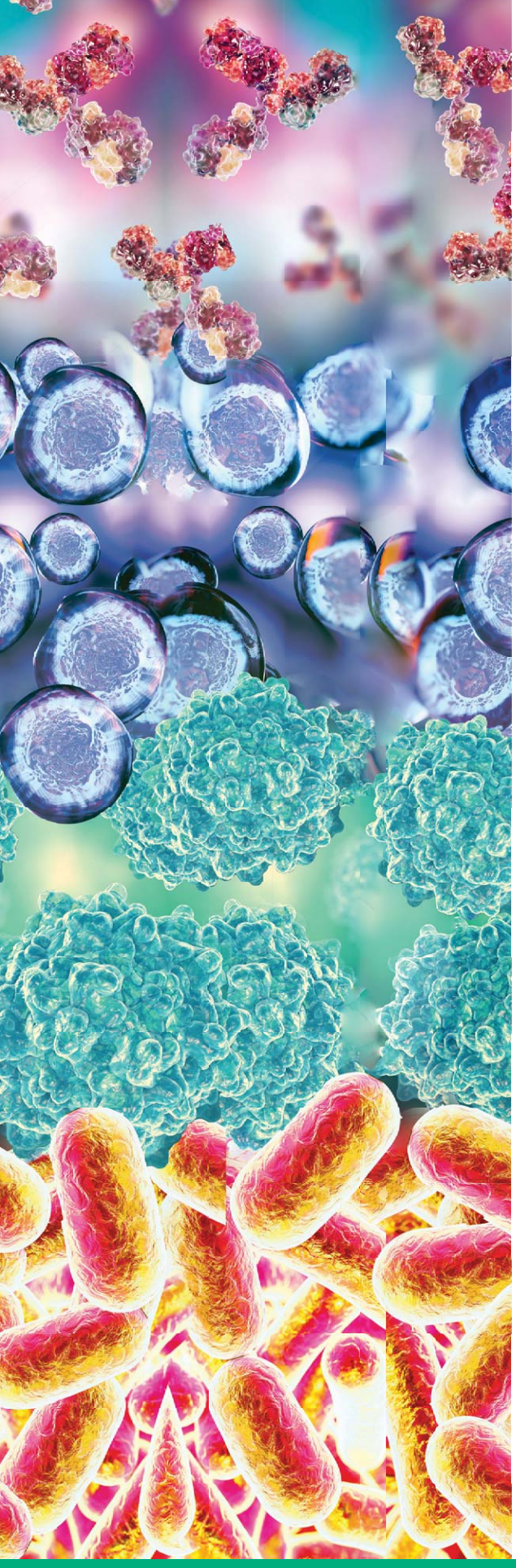

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