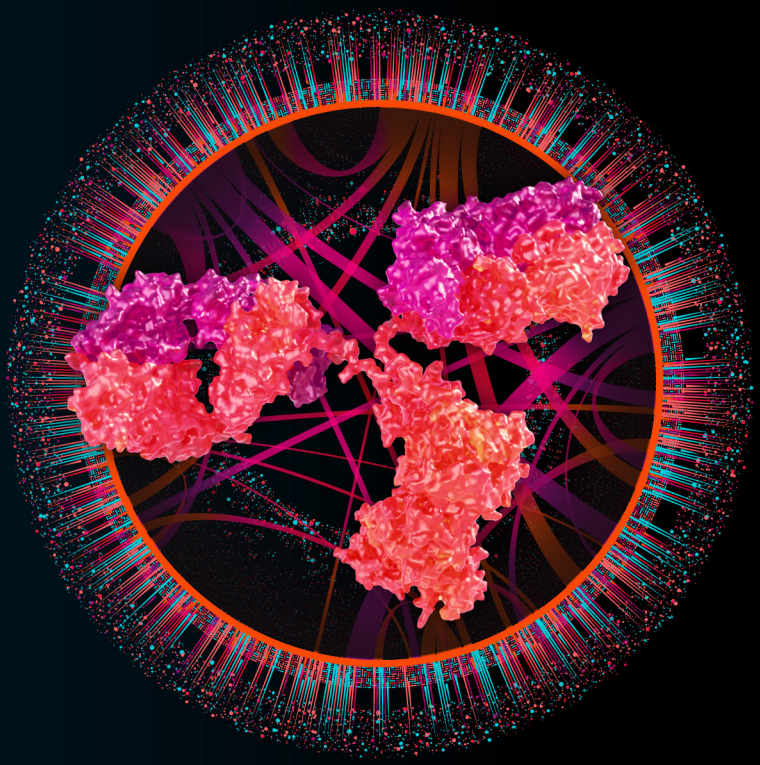
SCALE-UP EXPERTISE TO SUPPORT YOUR BIOLOGICS LIFE CYCLE



Pramthesh (Prem) Patel, Ph.D., Vice President of Process Development and MS&T, Avid Bioservices

The efficient scale-up of biopharmaceutical manufacturing processes can be quite challenging. Partnering with a service provider that can support projects from early development through commercialization facilitates scale-up, particularly if the contract development and manufacturing organization (CDMO) has the right organizational philosophies with respect to culture, experience, and collaboration. Avid Bioservices has nearly two decades of experience helping clients commercialize a considerable variety of biomolecules. With such extensive experience, a culture of collaboration, and facilities and equipment designed to facilitate seamless transfer from one scale to another, Avid can support the full biologics development life cycle.

Biologics Scaling Faces Unknown Unknowns

Any scale-up operation has its challenges. Scale-up in bioprocess development is one of the biggest challenges faced by the biopharmaceutical industry. Since biopharmaceutical production processes inherently involve biology, each process involves unique elements that impact scaling, introducing layers of complexity. Despite significant advances in our understanding of biopharma processes and the basic science and engineering, key aspects are lost during translation from small to large scale that cannot yet be explained.

Many factors impacting scale-up remain unexplained. Donald Rumsfeld famously parsed information in terms of *known knowns, known unknowns*, and *unknown unknowns*. Known knowns – such as temperature, pH, mixing, and mass transfer – can be addressed. For the many known unknowns, there is often nothing that can be done to resolve them, even with the best

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computational fluid dynamics (CFD) modeling solutions. Furthermore, many of the challenges to scaling of biologics processes are unknown unknowns that have a dramatic impact on scale-up but for which nothing is understood, and even workable hypotheses are lacking.

As the molecular complexity of biologic drug substances increases – such as in the case of heavily glycosylated proteins or bispecifics and trispecifics – scale-up challenges increase as well. For many next-generation drug substances, cell culture often results in the production of different yet highly similar versions of the desired biomolecule, making process development, scale-up, and tech transfer more complicated. More sophisticated posttranslational modifications (PTMs), such as glycosylation and fucosylation, have also added to scaling challenges. Biosimilars, meanwhile, must exquisitely match the quality specifications of their originator products. Developing the bioprocesses for these complex molecules is itself challenging but matching the originator's attributes at each scale of production multiplies these challenges.

Significant Progress, But a Long Way to Go

Progress has been made from the perspectives of engineering, raw materials, and biology. On the engineering side, newer impeller designs, sparging strategies, and mass transfer capabilities enable improved performance at larger scale. Increased knowledge has led to better CFD modeling systems and the development of mathematical models that help determine the optimal agitation approaches, impeller speeds, gassing strategies, and other parameters. There is greater understanding of mass transfer, bubble sizes, and other critical engineering considerations. All this progress has helped tremendously to better define scale-up.

On the raw material side, increasing use of chemically defined media has eliminated issues relating to the lot-to-lot variability associated with complex and non-defined materials. Some of the mammalian cells used for cell culture are well characterized and better understood, which also facilitates efficient scale-up. In fact, the industry is moving toward the use of a limited selection of CHO cells that behave similarly.

However, much still remains to be deciphered. Glycosylation pathways play important roles in the determination of product quality, but there is much that is not yet understood about these mechanisms. It is a very complex pathway of which only a few steps have been elucidated completely. Solutions for the hydrostatic pressure issue remain elusive.

Fortunately, as additional experience is gained with more complex biologics and key aspects of manufacturability – such as separation technologies for removing process-related impurities – many of these challenges will eventually be overcome. Advances in the design of biomolecules will also lead to increased selectivity of bioprocesses. Many forthcoming technologies will favor the formation of desired moieties and thereby also increase manufacturability.

Considering Scaling from the Beginning

An interface between process optimization and scaling is essential. Achieving high titers at lab scale is only a first step. High levels of expression must also be achieved at the 5,000-, 10,000-, or even 20,000-liter scale if drug candidates are to be commercialized. The ultimate goal is to reach patients – in some cases, as many as hundreds of millions of people around the world. If a drug substance cannot be produced at scale, it does not help anyone.

It is thus very important that biopharmaceutical scientists keep in mind that processes must work on the manufacturing floor – and not just from the perspective of scale-up. Every facet of every unit operation, such as the reagents and buffers, must be considered with respect to industrialization. If they are toxic to the environment, they are not practical from a sustainability perspective. Thus, all aspects of scale-up, not only the actual scale-up considerations but all issues that enable or prevent implementation of processes on the manufacturing floor, should influence bioprocess development.

In essence, process optimization can be looked at in two ways: (1) increasing productivity and improving product quality and (2) increasing manufacturability by simplifying protocols, enhancing supply chain security for critical raw materials, choosing sustainable reagents and process conditions, and so on. The first form of process optimization can potentially reduce scalability, while the latter can contribute to greater scalability. A fine balance must be struck between the two, with manufacturability and scale-up kept in mind throughout process development and optimization.

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Leveraging Modern PAT Tools

Comprehensive process characterization and understanding of cell culture processes is essential to developing robust and scalable biologics manufacturing solutions. Modern process analytical technology (PAT) tools enable process development and production scientists to "listen" to what cells in a bioreactor are "saying" regarding what they need (and when) in order to function as desired.

Online cell counters, dissolved oxygen and pH sensors, metabolite analyzers, and many other tools that have been introduced for several years have proven to be tremendously helpful for scaling processes. Scale-up is no longer performed "in the dark," with analytics only possible after completion of a manufacturing run. With access to data provided by PAT tools, even the average process today can be scaled up right the first time – something that was not previously possible. No longer are three or four large runs with tweaking between each one required; there is sufficient process experience, knowledge, and technical expertise to immediately dial in the optimal process parameters.

At the same time, it is important to acknowledge that processes for the production of engineered proteins and antibodies today are more intensive, with much higher cell densities and significantly higher productivities. More product quality attributes (PQAs) are monitored analytically, and more is understood about which process parameters are linked to those PQAs. The need to meet more requirements has further raised the bar with respect to scale-up. As a consequence, PAT tools are becoming essential.

Role of Strategic Leadership

How a company approaches scale-up represents one element of the organization's overall development and manufacturing philosophy. Senior leadership must set the appropriate tone with respect to strategic goals and the cultural environment, both of which impact individual expectations. Rewarding R&D for achieving high titers on the small scale rather than focusing on the importance of realizing those high titers in production will lead company scientists to strive for the former rather than the latter.

Senior management must set the right tone by emphasizing the end goal of the organization, which is to serve as many patients as possible at an acceptable cost of access. They must make it clear that any success at early stages that comes at the expense of success in production does not benefit the organization or patients. Presenting such a holistic problem statement changes how the company structure is designed, how goals are set, how rewards are administered, and other attributes.

Benefits of End-to-End Providers

Outsourcing partners that provide end-to-end services and have customer- and patient-centric cultures can have a direct impact on development timelines and cost. Collaborating with such partners facilitates scale-up and tech transfer because R&D and production scientists – both process and analytical – are co-located at the same site and are able to work closely together throughout the lifetime of a project.

It is particularly beneficial for scale-up, which is still an art form rather than a precisely ordered science. Much can be lost in the translation from a process development lab to a manufacturing floor. Even if the groups are part of the same company, silos can be built with walls that prevent the transfer of process nuances between them unless the right structure and organization are implemented.

The best outsourcing partners are those that provide end-to-end services within a framework designed to not only allow but encourage the free flow of information and even personnel between R&D, manufacturing, analytical, quality, engineering, sourcing, and any other relevant groups. This approach is further enhanced by installing the same equipment in the R&D labs and on the manufacturing floor.

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The Right Philosophies for Successful Scaling at Avid

As a contract development and manufacturing organization (CDMO), Avid Bioservices has been pursuing commercial biologics production since 2005 and has released over 200 commercial batches to the market. Three core philosophies have driven Avid's success: culture, experience, and collaboration.

Avid's culture is defined by our senior leadership and emphasizes a holistic approach, values every employee, and remains focused on our clients. Underlying all our efforts is the concept that Avid is not successful unless our clients are successful, and they are successful only when we provide high-quality product on time and in full. With this viewpoint, everyone is working together to achieve the same goal and always aware of how their efforts impact their colleagues, tracking the next unit operation or the next manufacturing scale. One aspect of this philosophy is reflected in the placement of the process development, analytical, and manufacturing, science, and technology (MSAT) groups under one roof, with a free flow of personnel between the teams and with MSAT personnel trained to function at a high level on the manufacturing floor when needed.

The scientists at Avid have extensive experience within the industry. Many have been with the company for 10 or more years; some for over 20. They have worked with a range of clients on many different types of molecules at all stages of development through commercialization. They bring different perspectives and have seen and together overcome many different kinds of problems and challenges. Close collaboration with clients creates further opportunities for learning and innovating.

The company's approach to facility design drives data sharing and collaboration. The equipment installed in the process development and scale-up labs are almost if not exactly identical to those on the plant floor from the perspective of control systems, brands, and specific models, including everything from bioreactors to protein separation technologies. The same is true for the analytical development and quality control (QC) labs, so that an assay developed for R&D can be seamlessly transferred for use in a GMP environment.

Potential for Future Reductions in Scaling Needs

With these core philosophies, Avid is not only well positioned to support clients with even the most complex biologics but is prepared to take proactive steps in preparation for future changes within the biopharma industry. That includes expectations for evolving scale-up needs, which for a variety of reasons could decline over the next several years.

Dramatic increases in productivity are also reducing the need for large stainless-steel bioreactors and leading to growing adoption of single-use technologies at the 2,000-L scale. Further enhancements in cell lines, increases in process understanding, advances in PAT capabilities, and higher performance of downstream purification systems will drive additional improvements. Mass spectrometers that can be employed on the manufacturing floor will also provide higher levels of process information not currently available. With all these developments, it is not unreasonable that commercial scales could ultimately decline to hundreds of liters.

In addition, the potency of candidate drug substances is increasing; consequently, dose volumes are declining. Greater targeting ability is increasing specificity as well, which is also enabling the administration of lower doses. Along the same lines, the rise of personalized medicine is contributing to a focus on the development of new drugs designed to treat smaller patient populations with specific attributes, leading to the need for smaller production volumes. Altogether, these trends will contribute to a future decline in the scale required for commercial manufacturing.

Novel technologies will also have an impact on scaling needs. The application of artificial intelligence, machine learning, big-data analytics, and other advanced digital technologies will provide tremendous insight into critical factors for effective scale-up. Similarly, the advent of cell-free manufacturing systems has the potential to drive the industry in an entirely new direction. Cell and gene therapies, meanwhile, have different production volume needs and are playing a growing role in the therapeutic landscape. ■

ABOUT THE AUTHOR

Pramthesh Patel
Vice President of Process Development and MS&T

Pramthesh (Prem) Patel has over 30 years of experience in the pharmaceutical industry spanning drug discovery and drug development. Over the past several years, Prem has served as the Senior Director of upstream process development activities for the entire biopharmaceutical portfolio at GSK. Prem has authored and reviewed six marketing applications, which have been approved for commercialization in all major global markets. Prem obtained his BS degree in microbiology and chemistry from the University of Bombay, India, his MS degree in microbial physiology from Southern Illinois University, and his Ph. D. from the University of Florida in cellular physiology and molecular biology, and he did postdoctoral training at Virginia Tech.

LinkedIn: www.linkedin.com/in/pramthesh/
Email: ppatel@avidbio.com