Pharmaceutical BIOPROCESSING

Biopharmaceutical manufacturing and flexible design: what does the future hold?

"Quality, safety and efficacy will continue to be the primary focus of the biopharmaceutical manufacturer."

Keywords: continuous processing • flexible facility • platform manufacturing process • single-use equipment

The biopharmaceutical manufacturer of the future is nimble by design to rapidly adapt to new products and improved processes. The facility is primed with technical proficiency to anticipate consequences of process improvements, characterization of their current capabilities, flexibility to rapidly introduce new technology and expertise to mitigate risk.

Recombinant protein manufacturing to date has primarily been orientated for timely delivery of exclusive large-volume products, 'blockbusters' to patients with access to the highest standard of care. Process development for the most part has focused on the regulatory requirements for quality, safety and efficacy. Thus, manufacturing science has evolved around issues such as elimination of animal-derived products, extractable leachables, and process qualification for viral and prion safety. Process development has achieved culture titers and recovery yields needed for a commercially viable process [1]. Thus, in the interest of speed to market, single-product facilities were built and more complex manufacturing efficiency issues were given secondary consideration. The future of recombinant protein products will include biosimilars, regional manufacturing and smaller volume, specialized products in multiproduct facilities, as biopharmaceutical manufactures strive to deliver drugs to a more diverse patient population at cheaper cost. As with most maturing industries, manufacturing efficiency will become more important.

The biotechnology facility of the future will probably not be a 'green field' new installation. It could be an existing facility owned by a biopharmaceutical manufacturer, a facility acquired through merger or acquisition, or one rented from a contract manufacturing organization. It will probably be a hybrid with a layout suitable for single-use equipment, and piping and utilities for installed stainless steel equipment with reduced clean-in-place (CIP) and steam-in-place (SIP) systems [2]. Selection of the facility will depend on modifications required, portfolio of products manufactured and the new process fit. Facility modification will continue with adjacent areas such as warehouses and lobbies being added to the clean area of the facility and closed systems being installed in uncontrolled space. In addition, the demand for each product and facility staffing will often determine the best value along with the process flow diagram and regulatory requirements. Equipment selection to optimize return on investment will require analysis of each unit operation. For example, selecting a new bioreactor would need consideration of at least three options: single-use plastic, automated stainless steel or hybrid stainless steel surrounded by single-use auxiliary equipment to simplify CIP and SIP. For a multiproduct facility, each option will need analysis of the capital, component, raw material and utility costs for four operating modes: production, turnaround between batches, product changeovers and idle. The best decision could be different in a facility that operates one shift 5 days a week with a high value to minimizing the time to turnaround equipment than in a 24 × 7 operation where CIP and SIP can be accomplished

Joseph McLaughlin
Author for correspondence:
Bioprocess Research & Development, Manufacturing, Pfizer Inc., 700 Chesterfield Parkway, St Louis, MO 63017, USA
amit.banerjee@pfizer.com

Amit Banerjee
Bioprocess Research & Development, BioTherapeutics Pharmaceutical Sciences, Pfizer Inc., 700 Chesterfield Parkway, St Louis, MO 63017, USA

FUTURE SCIENCE part of fsg

overnight. When process robustness and equipment reliability are included, additional complexity is introduced to the value-based decision. However, facilities that make the commitment to developing the expertise and knowledge base for making value-based decisions are more likely to manufacture the future products.

In the past, a new product would be anticipated years in advance with facilities being built, validated and started up only to wait in anxious anticipation of completion of clinical trials and regulatory approval. Future products with smaller demand, competition and cost constraints will be unable to support costly idle facilities. The single-use equipment manufacturers propose that facilities can be built quicker at lower cost and therefore reduce time to market. However, this still requires speculative construction and staffing of a facility. In addition, expired single-use components are also expensive. An alternative is to adapt existing facilities to multiproduct/multimodality operations. Single-use equipment will be important owing to its ability to reduce product change over time and support process adaptation [2]. However, characterization of processes, equipment and operations will also be beneficial. Characterization of the process, using Quality by Design (QBD) principles will enable defining a design space that can be used to adapt a process at the facility with a high degree of confidence [3]. Equipment characterization will enable rapid technology transfer and aid in value-based decisions on equipment selection: installed stainless steel, equipment modification, new installation or single-use component. Characterization of facility operations will facilitate trouble shooting and elimination of constraints for manufacturing product changeover and operations. Well-characterized facilities will be able to quickly make the modifications and adjustments to successfully manufacture a portfolio of products.

> "The biotechnology facility of the future will probably not be a 'green field' new installation."

Multiproduct facilities will derive additional value from platform processes, which require minimal adaptation to facility, equipment or supply chains. However, the unique nature of each product, process, purity profile and market demand will continue to require product-specific development and facility flexibility. Flexibility needs will include a wide range of scales, unit operations and operating modes. The decisions made during process development will be more complex as they begin to consider impact on existing facility operation. However, including an assessment of facility-specific value will guide process adaptation with an appropriate and balanced impact on upstream, downstream and operations.

The modality of products the biopharmaceutical manufacturer makes will be more diverse and complex with protein combinations such as antibody–drug conjugates. The complex nature of the products will demand a more sophisticated technology transfer process. However, to succeed, the technology transfer will need to be flexible and introduce learning's from other industries, which have already passed through the gates of maturing products and technology. For the last 30 years, biopharmaceutical manufacturers have adapted technology from other industries such as medicinal extracts and antibiotics. Many aspects of equipment and facility design have origins from the food and dairy industries. We continue to learn from the electronics industry on clean room and high-purity water design. Continuous improvement principles developed by Deming in the 1950s enabled the automotive industry to survive globalization and are being applied by the biopharmaceutical manufacturer. There is significant discussion trying to capture the advantage of continuous processing used by the paper and petrochemicals industries [4]. However, process-selective integration, simplification and automation may prove more beneficial to the biopharmaceutical manufacturer. A few examples would be the use of perfusion culture, buffer concentrates or elimination of product hold steps. However, their impact will require analysis of both facility and process impact. For example, installation of perfusion culture process would probably be constrained by media preparation capability in a facility designed for batch culture. The biopharmaceutical manufacturer that learns from other industries will have an advantage as the industry matures.

Quality, safety and efficacy will continue to be the primary focus of the biopharmaceutical manufacturer. As facilities introduce new products and technology, risk analysis needs to be performed to determine the impact of introducing new technologies, so as not to compromise product quality. The future biopharmaceutical manufacturer facility will need to accommodate a variety of modalities in a very capital constraint environment.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 Pohlscheidt M, Kiss R. Recent advances and trends in the biotechnology industry; development and manufacturing of recombinant proteins and antibodies. *Am. Pharm. Rev.* 16(6), 48–50, 52–53 (2013).

2 Eibl R, Eibl D. *Single Use Technology in Biopharmaceutical Manufacture.* John Wiley and Sons, NJ, USA (2011).

3 Banerjee A. Designing in quality: approaches to defining the design space for a monoclonal antibody process. *BioPharm Int.* 23(5), 26–40 (2010).

4 Warikoo V, Godawat R, Brower K *et al.* Integrated continuous production of recombinant therapeutic proteins. *Biotechnol. Bioeng.* 109(12), 3018–3029 (2012).