Cell Culture Processing Continually Advances

The growing use of automation and digitalization technologies push cell culture bioprocessing forward.

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Enhanced media, selective starting materials, genetically enhanced cell lines, and even animal-free cell culture parameters have all been working toward optimizing product output in the bioreactor. The cell culture process has come a long way with the common utilization of these process-optimizing tools and techniques.

LATEST CELL CULTURE TRENDS

The biopharmaceutical market is seeing fast growth, and two expression systems are competing for market dominance, mammalian cells and microorganisms, says Daniel Kopec, manager of Cell Culture Technologies at Sartorius. Kopec notes that, in recent years and based on the rise of antibody-based therapeutics, new biotherapeutic approvals have favored mammalian host cells. Emerging biotherapeutic molecules, however, have been facilitating the use of microbial host cells, he observes.

"Microbial platforms are capable of delivering, in a scalable and affordable manner, a range of functional recombinant therapeutics such as vaccines, hormones, interferons, and growth factors as well as non-pharma products, such as industrial enzymes," Kopec states.

Meanwhile, for mammalian cell applications, there has been a trend in past years toward serum-free, xeno-free, and chemically defined cell-culture media and intensified processes. "Serum-free, xeno-free, and chemically defined media represent a huge advantage in comparison to traditional serum requiring media, in terms of costs of goods (qualified serum is very expensive), time to market (consistent media yields predictable, reproducible results), and biosafety (not using serum rules out the risk of contamination by viruses and adventitious agents)," says Catherine Buchere, product manager Virus-based Therapeutics, Sartorius.

With process intensification, the aim is to increase the final product yield by optimizing the use of resources, whether it be a physical footprint, consumables, and/or time. Kopec points out examples of how processes could be intensified, which include perfusion operation with cell-retention devices reaching high cell densities, a shortened seed-train expansion, and continuous and integrated upstream and downstream processing.

Moreover, in addition to significant cell/media advancements as well as the momentum toward process intensification methods, Kopec observes that there are clear trends

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that continue to revolve around the ease of scale up, commercial flexibility, and advanced automation. "All of these promote much needed increases in development and processing efficiencies—especially for biotherapeutics, where a strong quality-by-design (QbD)/process analytical technology (PAT) approach will surely enable speed-to-market and higher success rates," he states.

CURRENT STATUS

The current status of cell culture processing owes its advancement to several influences, including cell-culture media considerations, the quality of raw materials, a push for sustainable processes, and concerns over inherent contaminants present in animal-derived materials.

Chemically defined media, as opposed to serum-based media (which can give rise to batch-to-batch variation issues), allow high cell densities in suspension cultures and reduce the risk of cells contracting human viruses, says Buchere. "Over the past two decades, major improvements in media composition, production strategies, and cell-line development resulted in the achievement of higher cell densities and product titers, leading to an overall reduction in production costs," Buchere states.

Furthermore, there is increasing customer interest in less complex media. "'Complexity' in media refers to the number of components and the complexity of the components themselves. A trend we are seeing is the development of a minimal set of well-balanced components to achieve a lean, robust, and flexible medium basis while maintaining highest performance in the cell culture step," notes Buchere.

With raw materials, meanwhile, variability is a key concern in the biopharmaceutical manufacturing process. Understanding the behavior of each raw material is crucial to reducing the risk of variation, Buchere adds. "Moving to chemically defined media is already an improved step, nevertheless, there are still some components that can introduce variation in the performance of the cell culture," she explains.

Buchere also explains that the source and production process for cell culture media would also be evaluated in terms of sustainability. "Many of the more common sources of culture media are not necessarily produced in a highly sustainable manner. The most popular media component, serum, is often produced from bovine and porcine sources, and production is energy-intensive and can result in significant emissions of CO_2 [carbon dioxide]," she says.

The quality and purity of biotherapeutics are influenced by many factors in the development and commercialization cycle, notes Kopec. These factors all play a significant role in the product's ultimate success. "In recent years, we have seen a number of products on the market that enable a much better approach to cell-line development and media optimization," Kopec says. He points out that, for example, automated bioreactor systems (e.g., Ambr 15, Sartorius) offer "groundbreaking levels of efficiency and visibility to the process."

In the meantime, software-based scaling tools are now coming into play, which are helping the industry to eliminate much of the guesswork in the scale up of manufacturing processes, Kopec adds. "Continuous and comprehensive data collection and analysis equip process engineers with in-depth process understanding. Advanced sensors now deliver more precise measurements at every stage of the process, generating vast quantities of information. Seamless data connectivity is now critical to translating in-line monitoring into actionable, real-time insights derived from data analysis," he says.

Ultimately, leveraging data collected across the workflow leads to greater process knowledge and can help reduce failure rates and, thus costs, Kopec asserts. Process consistency is the key process output—achieved with a QbD scale-up approach and advanced automation—to fully enable smart process development.

A BRIGHT FUTURE

The growing use of automation during expansion to increase product consistency and reduce failure rate is a rising trend in the biopharma industry, Kopec adds. "Highly automated bioreactors will require integration from various sensors, software, and interconnectivity via digitalization technologies such as MTP (module type packages). Interconnectivity is also a steppingstone for future scalability by ensuring larger consistent yields with larger bioreactors," he says.

Any manually controlled process holds a high level of risk, low output potential, and difficulty monitoring critical process parameters and critical quality attributes (CQAs). Interconnectivity across the workflow, together with automation, will enable more control and a more consistent output, Kopec explains. "Bringing together inline sensors, continuous monitoring, and advanced real-time analysis will require 'next-gen' automated bioreactors to enable finer, holistic control of the process. This next level of automation will result in a tighter design space and pushing the process to maximum output," he states.

Kopec also notes that next-generation, advanced bioreactor systems and variants are now entering the market, and these will offer true "off-the-shelf" setup and operation. These systems are well designed for emerging biotherapeutic process modalities. "The next-generation single-use bioreactors will integrate the latest advances in QbD/PAT technologies, such as advanced sensors, software (for automation/data analytics/scaling), and plant-level integration," he explains.

In addition, in the near term, Kopec expects that the biopharma industry will see strong momentum toward automated sampling for online CQA monitoring, which will help move the industry closer to real time release testing. Overall, there is heavy investment in the development of these technology integrations to support new biotherapeutic applications, Kopec observes. ◆