Deciding on an Integrated Continuous Processing Approach

A Conference Report

by Miriam Monge

Biopharmaceutical manufacturers are increasingly investigating or implementing continuous processes, and industry experts are participating in vibrant and healthy discussions on a wide range of process approaches being adopted. We seem to have entered a phase within the biopharmaceutical industry (which is often described as conservative) of intense bioprocess innovation as manufacturers strive to lower costs and provide agile, responsive supply chains for "drug on demand" continuous manufacturing operations. Senior industry leaders met in Berkeley, CA, in late 2015 at ECI's Integrated Continuous Biomanufacturing Conference II to hear keynote presentations from both Alison Moore (senior vice president of process development at Amgen) and Janet Woodcock (director of the Center for Drug Evaluation and Research, CDER, at the US Food and Drug Administration) and discuss real-world challenges of implementing continuous biomanufacturing.

Keynote Presentations

Moore described Amgen's target of achieving a process delivering 5 g of product per liter of cell culture media per day with a sophisticated automation strategy for real-time process control. Process intensification will allow the company to develop a highly responsive biomanufacturing network that is optimized for speed, flexibility, and cost to seamlessly deliver Amgen's multimodal product portfolio. Recent advances have made such process intensification possible: e.g., developments in single-use cell culture bioreactors, growth media that can support high cell densities, robust retention devices, and stable cell lines capable of producing consistent product over many weeks. Integration of upstream and downstream process development teams under a single umbrella can help deliver processes with greater intensification by minimizing intermediate hold steps that do not add value. A significant amount of Amgen's continuous biomanufacturing effort is allocated to operating within the current regulatory landscape.

In her keynote presentation, Woodcock highlighted that CDER is keen to see improvements in quality and greater efficiency in biologics development and manufacturing. She would welcome changes to regulations that could facilitate quality and efficiency improvements. The FDA's "emerging technology team" is supporting continuous biomanufacturing by providing grants to specific research initiatives. An example of that approach is the agency's recognition that a prerequisite for continuous manufacturing is availability of suitable systems to allow dynamic process control. The emerging technologies team is providing contracts and grants to advance system engineering controls and allow a greater understanding of the performance of such technologies. Team leader Larry Lee (acting associate director for research policy and implementation) can be contacted by companies that wish to present their continuous concept to the FDA. The team can be a one-stop shop for communicating with the agency on regulatory aspects.

Perfusion Processing

One reason for the regulatory support of continuous processing in biomanufacturing has been the presumed quality improvement that can be gained by maintaining biological systems in a steady state. Veronique Chotteau (principal investigator at the KTH Royal Institute of Technology in Stockholm, Sweden) compared metabolic flux analysis modeling of mammalian cells grown in perfusion culture with those grown in fed-batch mode. She demonstrated that the perfusion culture showed a more consistent metabolic profile.

Not everyone in this field, however, agrees that steady-state processing is the right approach. Jon Coffman (director of engineering at Boehringer Ingelheim) described one outcome of his company's collaboration with Pfizer as being a dynamic perfusion process that does not use steady-state growth conditions. Such an approach overcomes the problem associated with steady-state perfusion processes: namely, that a time lag can run to weeks before a culture has high enough cell densities to achieve volumetric productivity targets. The dynamic perfusion approach can apply to existing fed-batch manufacturing assets, overcoming the challenge that Moore described of deploying flexible production within a legacy manufacturing network.

Integration and Implementation

Integration of continuous upstream processes with product capture is now well established, according to Thierry Ziegler (head of biopharmaceutics development at Sanofi in France). But he emphasizes that full integration of continuous downstream processing to perfusion processes still requires further investigation. As an alternative to fully continuous processing, Sanofi is developing a hybrid approach for downstream process intensification called "Accelerated Seamless Antibody Purification" (ASAP). ASAP processing allows three chromatography steps to run continuously, with no holding time or adjustments required to maximize process efficiency. This process performs antibody purification within hours instead of days.

Mark Brower (bioprocess development at Merck & Co) described how a single-use fully automated continuous bioprocessing suite has been established at his company with distributed control through the DeltaV control system (Emerson Process Management). The Protein Refinery Operations Lab (PRO Lab) system is a "sandbox" for continuous protein production and advanced process control. Its upstream process uses single-use bioreactors with the harvest occurring through a single-use tangential flow, cell-retention device with automated cell bleeding through online capacitance. The purification process is dominated by the use of simulated moving-bed chromatography steps. The PRO Lab concept adopts a single-use, closed-system methodology with automated control strategies for end-to-end lights-out operation using overarching supervisory control (Delta V control system). Sixty days of continuous automated processing have been demonstrated so far with some initial proof of concept for automated deviation control. Process analytical technologies (PAT) are being implemented for process monitoring and multivariate data analysis to allow adaptive control. That will allow Merck to transition from end-product testing to real-time release testing.

Which Is Right for Your Company?

Undoubtedly, each approach to integrated continuous biomanufacturing will have its relative merits. The process adopted by one organization will not necessarily be appropriate for another simply because of the context into which it will be implemented. According to BioPlan's 10th *Annual Report and Survey of the Biopharmaceutical Manufacturing Capacity and Production* (published 2013), Amgen's installed stainless steel bioreactor capacity far exceeds that of Merck's. Such legacy capacity positions will influence future strategies for continuous production, as both Moore and Brower indicated. Amgen's approach must be suitable for its multimodal product platforms, whereas Sanofi's ASAP process is designed to work specifically with antibodies. Steady-state perfusion suits commercial-scale production of labile products, but a dynamic perfusion manufacturing strategy can rapidly deliver toxicology material and shorten the time it takes to get to submission of an investigational new drug (IND) application. The question then is not which is the best approach to continuous biomanufacturing, but rather which is the best approach for your organization?

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