USP/BioPhorum Joint Workshop on Continuous Manufacturing of Biologics

Executive Summary

Continuous manufacturing (CM) is an exciting frontier in drug manufacturing with the capacity to increase process efficiency while reducing costs. Manufacturers are now looking at ways to apply CM to make biologics. Biopharmaceutical continuous manufacturing (BCM) could increase product quality and productivity, enhance the process and product control, and increase flexibility, while also decreasing certain fixed costs associated with facility size and equipment maintenance, thereby reducing the environmental impact. There are barriers to the widespread adoption of BCM, however.

Compared to traditional fed-batch and discrete unit operations manufacturing, a continuous process runs as an end-to-end operation with uninterrupted medium exchange and perfusate flow supply from upstream unit operations into a fully connected downstream process. Implementing BCM, therefore, requires connecting discrete unit operations in ways that make it difficult to stop the process at any point to assess the quality of the product. The continuous flow of production puts particular emphasis on real-time monitoring and controls. Making this switch does not come without certain risks that must be considered by any manufacturer thinking about moving in this direction. The business risks can be even more significant for smaller companies representing many developers in emerging markets. To help the industry grapple with how best to approach these challenges, USP and BioPhorum held a Joint Workshop on Continuous Manufacturing of Biologics, Addressing Barriers to Adoption, at USP headquarters in Rockville, MD, on December 7th & 8th, 2022. The workshop brought together industry, academic, and regulatory experts to discuss the hottest topics in BCM and exchange their latest scientific findings. The workshop included sessions on Control Strategies, Lessons Learned and Case Studies, Manufacturing Platforms, Regulatory Considerations, and Novel Technologies, followed by robust and engaging panel discussions.

Several factors are contributing to the push toward BCM. There is pressure to lower the costs of many biologics. There is also uncertainty around the demand for specific therapies that can be mitigated with flexible or just-in-time approaches to manufacturing. Finally, increasing competition forces stakeholders to explore innovations that result in more efficient production. BCM can address these issues through an intensified, high productivity, longer duration cell culture process combined with the design of a flexible and modular cGMP manufacturing facility incorporating continuous downstream processing. Several companies discussed their innovations in enabling technologies and strategies for BCM. These presentations demonstrated how continuous systems enable much higher volumetric productivity than traditional batch or fed-batch fixed facility processes. Many companies are already successfully producing monoclonal antibodies at 500 L scale using perfusion bioreactors connected to continuous downstream operations. Some of these processes implement novel technologies like continuous tangential flow filtration (TFF) technology which has advantages in BCM because of the reduced pump passes for shear-sensitive products.

Viral clearance through steps like filtration is another important area of concern for manufacturers using BCM, as it is a critical step in ensuring biopharmaceutical products' safety. Some manufacturers are integrating viral filters after continuous column chromatography processes. Other companies are modeling the impact of contamination by performing small-scale, in-line virus spiking studies and using the data to develop validation strategies for large-scale viral filtration processes. All of these efforts have provided critical insights into viral filtration for BCM, but there are still physical limitations on existing filters that make it challenging to balance throughput capacity and flow rate across the system.

Control over BCM processes is essential for developing a successful continuous process. Several applications and models are being developed and optimized to improve process control and increase efficiency. For example, cutting-edge process analytics methods, such as real-time multi-angle light scattering (RT-MALS), are used to monitor mAb quality during manufacturing and improve monomeric protein yield by at least 5% while maintaining product quality. Digital twins of an integrated and continuous biomanufacturing process is another approach being developed to model the impact of expected disturbances, deviations, and uncertainties like process start-up, shut-down, and pauses on product quality.

Also, discussions of regulatory uncertainty acknowledged that there are valid reasons why small companies may want to avoid BCM at his time. However, representatives from small companies demonstrated why BCM could be advantageous for producing their drug candidate. Regulatory agencies, including the FDA, are also making a concerted effort to help spur the adoption of advanced manufacturing technologies such as BCM. Regulators also discussed guidance demonstrating a general understanding of critical aspects/risks associated with key unit operations. By understanding the risks, one can design representative small-scale models for critical studies like viral clearance, ensuring the viral safety of the continuous manufacturing process.

USP is making significant progress in understanding manufacturers' needs regarding BCM. Through our workshops and roundtable discussions, USP has engaged with leaders in the field. These discussions have shown us how the industry addresses some of the barriers to adoption and how we can help overcome those barriers. USP also has many opportunities for collaboration and invites qualified candidates to join one of our volunteer expert panels (EP). USP standards are continuously reviewed and revised based on new evidence, emerging public health concerns, and requests for revision. The EPs play a crucial role in this process by advising on how best to update our standards or by guiding the development of new standards and best practices. For more information or to apply to volunteer, go to https://www.usp.org/about/volunteer-experts.