Flexible, continuous manufacturing technologies

Benefits for biologics from clinical to commercial phases

Response to an evolving biologics market
As an increasing number of biologics are approved each year, new trends have appeared in the industry. A major one is the emergence of precision medicine approaches to provide potent, targeted therapies for small patient populations.

While blockbuster monoclonal antibody therapeutic demand is in the range of metric tons of drug product per year, many next generation biologics, including bi/multi-specific antibodies and fusion proteins, have smaller mass demands ranging from tens to a few hundred kilograms.

A second trend is the focus on rapid response due to unpredictable market needs or pandemics, as seen with COVID-19. This market evolution highlights a need for flexible manufacturing platforms capable of producing a variety of products instead of a single blockbuster.

As a consequence, the Biopharma industry is shifting towards intensified, continuous processing in a flexible manufacturing format for their next-generation pipeline.

The Just - Evotec Biologics approach: Process intensification with flexible, continuous manufacturing
Just – Evotec Biologics uses an intensified, continuous process platform that connects high-performance, perfusion cell culture with intensified downstream processing. Perfusion cell culture maximizes bioreactor productivity by using high cell densities, and Just – Evotec Biologics has developed specific chemically-defined perfusion culture media that supports several commercial CHO lines as well as Just – Evotec Biologics' robust, high titer cell lines. To process mass that is continuously produced by the bioreactor, the downstream process is also intensified. This includes the use of continuous multi-column protein A capture connected directly to the bioreactor to purify the product as it is being expressed. Other steps have been optimized to maximize loadings while maintaining high yields. The entire process is designed to operate either in a fully continuous mode from bioreactor to drug substance, or in a semi-continuous mode using continuous capture and viral inactivation, with batch operation for subsequent steps.

A significant advantage of intensified, continuous processing is the opportunity to reduce manufacturing footprint, since a process that operates 24/7 in a connected, continuous manner does not require large processing equipment. To this end, Just – Evotec Biologics has designed and built a small-footprint, highly-automated cGMP manufacturing facility, J.POD®, that leverages single use systems and reconfigurable cleanroom pods for maximum flexibility. J.POD® can operate clinical or commercial processes in semi- or fully continuous mode with 500-1000L bioreactors. Instead of scaling up, a process can be scaled by bioreactor duration to deliver anywhere from a few kilograms of drug substance to metric tons.

Enhanced productivity vs traditional fed-batch
Intensified, perfusion processes typically outperform traditional fed-batch process yields by factors of 5 to 15x, due to higher cell densities and the ability to extend the bioreactor culture duration from 15 to 30 days or more. Just – Evotec Biologics' cGMP perfusion processes typically generate 2-4 g of product/L/day for well-behaved monoclonal antibodies. This translates into drug substance batches of 4-8 kg for a 15 day-500L bioreactor scale, or 25-45 kg for a 25 day-1000L scale process.

Better product quality
Another advantage of continuous processing over traditional fed-batch is the potential for improved product quality. Instead of the product remaining in the bioreactor until harvest as cell health declines, the Just – Evotec Biologics process ensures that the product is continuously removed from the bioreactor and purified. Product contact with cell culture fluid components, including proteases and other unwanted host cell proteins, is minimized. Thus, product aggregation, degradation by clipping, and other unwanted modifications such oxidation, deamidation, and glycation can be reduced. This is particularly advantageous for less stable proteins such as IgG fusions, Fc fusions, bispecific antibodies, and other non-traditional mAbs.

Ensuring speed to clinic …
For clinical processes, we leverage our 15 day semi-continuous process platform to reduce time for process development and transfer to manufacturing. This platform is well suited to early and later stage clinical programs, which require speed and flexibility in mass demand.

…while de-risking path to BLA
For products approaching commercial stage, a proven, fully continuous process platform housed in our J.POD® cGMP facility is available to maximize productivity and cost of manufacturing.

The process can be tailored to precisely meet our Biopharma partners' needs by applying a combination of scale-on (process duration) and scale-out (operating multiple manufacturing trains at the same scale) strategies instead of traditional but more challenging scale-up approaches.

Achieving greater cost-efficiency for commercial supply
There is a critical need to reduce biologics manufacturing costs (whether for a novel or biosimilar product) to favor wider patient access to high-quality biotherapeutics. At Just – Evotec Biologics, we strive to optimize commercial supply costs by focusing on process intensification and end-to-end continuous manufacturing in relatively small cGMP facilities designed for maximum flexibility and rapid deployment.

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