

INTEGRATION OF UPSTREAM AND DOWNSTREAM FOR A HYBRID CONTINUOUS PROCESS DEVELOPMENT AND MANUFACTURING FOR A STABLE MONOCLONAL ANTIBODY PRODUCED IN CHO CELL CULTURE

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Process intensification by continuous operation has been successfully applied in the chemical industry, when batch processes matured several decades ago. Fully integrated upstream and downstream continuous processing has also shown great potential for increased productivity and reduced cost in biomanufacturing using mammalian cell culture. After a few decades of development, continuous or perfusion cell culture has demonstrated for manufacturing of labile proteins or low-titer processes. Due to significant challenges implementing fully integrated continuous biomanufacturing and the fact that fed-batch cell culture has not yet matured, fed-batch cell culture and batch chromatography steps are still predominant for stable protein manufacturing in the industry. In comparison to perfusion cell culture, continuous or semi-continuous downstream processing for stable monoclonal antibodies (mAbs) has developed within less than a decade. Due to a high titer, e.g., 8-10 g/L, already achieved via fed-batch cell culture, which challenges the processing capacity for batch downstream commercial manufacturing, the demand of continuous chromatography operation dramatically increases. Here, we present a case study developing a hybrid continuous upstream and downstream as our next generation process for production of a stable mAb. For upstream, we implemented N-1 perfusion seed, which significantly increased the seeding density for fed-batch production. After media and process parameter optimization, the product titer for the intensified fed-batch process with high-seed increased more than 100% over the original fed-batch process. It should be noted that the original fed-batch process was optimized and used for clinical manufacturing at 1000-L scale. For next generation downstream, we developed multi-column chromatography for Protein A step, automated VI step and integrated pool-less polishing chromatography steps with increased productivity and reduction in resin requirement, buffer consumption and processing time. The next generation process with perfusion N-1 seed and continuous chromatography steps has been scaled up in 500-L bioreactor, and now has been demonstrated for full implementation in a GMP manufacturing facility at the 2000-L scale. We will present full set of data to compare the original optimized batch process at 1000-L scale and the next generation process at 2000-L scale for the stable mAb production using CHO cell culture. We believe that the hybrid continuous process is relatively easy to develop and implement in GMP manufacturing with significantly higher productivity than conventional fed-batch process for now, while the hybrid continuous process lays a good foundation for us to further develop and implement fully continuous upstream and downstream process in manufacturing with even higher productivity in future.