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Implementation of a recirculating TFF N-1 perfusion system at manufacturing scale: Conquering process hurdles and scaling challenges

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IMPLEMENTATION OF A RECIRCULATING TFF N-1 PERFUSION SYSTEM AT MANUFACTURING SCALE: CONQUERING PROCESS HURDLES AND SCALING CHALLENGES

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In order to increase the output of a traditional large scale stainless steel fed-batch manufacturing facility without major engineering work, we investigated the implementation of N-1 perfusion technology to feed a more intensified fed-batch production process. Perfusion N-1 enables cells to grow to high densities in the seed train bioreactor. By shifting cell growth from production to seed train, we can increase seed train occupancy per batch and reduce production bioreactor occupancy per batch, which improves facility throughput by bringing the run duration ratio of N-1/N closer to unity. Instead of using the popular ATF technology, an in-house TFF system was developed to provide more flexibility during process development and optimization of all perfusion parameters.

We will share a case study of how two different filtration technologies (open channel and hollow fiber) were developed and scaled from pilot scale to manufacturing scale while maintaining consistent cell growth performance at high cell densities, >40x106 vc/mL. We will discuss the comparison of the two filter technologies, recirculation pump type selection, recirculation flow path design, filter area, skid/bioreactor design, and perfusion media volume challenges. Additional efforts were made in regards to SIP and sterility of these systems at pilot and manufacturing scale to safeguard the system from any potential contamination events. Sparger optimization work was also performed to solve mass transfer and cell damage challenges at pilot and manufacturing scales. Last but not least, a story of developing a scale-down model using peristaltic pump will be shared. Our work culminated in an engineering run at 17,000-L manufacturing scale using both technologies, which generated a high volumetric productivity of 750 mg/L/day and resulted in a 40% increase in facility output.