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A HOLISTIC APPROACH TO THE SCALE-UP OF A MICROCARRIER-BASED PERFUSION CELL CULTURE PROCESS FOR THE PRODUCTION OF A THERAPEUTIC ENZYME

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This case study describes our holistic approach of scaling up a microcarrier-based perfusion cell culture process for the production of a therapeutic enzyme directly from a 12L benchtop glass bioreactor to a commercial scale stainless steel bioreactor. Besides conventional scale-up challenges such as mixing, shear stress and mass transfer, the scale-up of this microcarrier-based cell culture process posed its own challenges, e.g. the original design of the commercial scale stainless steel bioreactor had difficulty suspending microcarriers. Additional challenges included achieving effective cell attachment after seeding, balancing microcarrier stratification and culture turbulence, and minimizing bubble shear stress and foaming. To mitigate risks and maximize the chance of success in scaling up this process within an aggressive project timeline, we carried out a series of studies to systematically tackle these challenges.

First, physical modifications necessary to adapt the existing commercial scale stainless steel bioreactor for this microcarrier-based cell culture process, e.g. impeller, baffle and sparger designs, were implemented based on computation fluid dynamics (CFD) simulation, high speed imaging, and at scale bioreactor characterization. Second, 12L small scale bioreactor studies were performed in concert with simulation and mathematical modeling to define operating ranges for scale-dependent parameters for the commercial scale bioreactor. Third, strategies to mitigate potential negative effects of scale-dependent parameters on the commercial scale process such as stratification, turbulence and foaming were established and tested at the 12L scale.

Through our systematic work using CFD simulation, mathematical modeling, bioreactor characterization, and small scale bioreactor experimentation, we were able to achieve comparable bioreactor performance including product quality in the first large scale run; this allowed us to meet an accelerated project timeline.