

OVERCOMING SCALE-UP CHALLENGES FOR A FIRST-IN-HUMAN (FIH) ANTIBODY PRODUCTION PROCESS AT THE 2000L SCALE: SUCCESSFUL OPTIMIZATION OF BIOREACTOR EQUIPMENT AND HARVEST CONDITIONS TO IMPROVE PROCESS PERFORMANCE AND PRODUCT YIELD

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During the development and scale-up of a FIH fed-batch cell culture process, we have encountered two major challenges that impacted culture performance and harvest process yield significantly. The first challenge relates to the oxygen requirement for this particular process, where a higher oxygen demand was observed compared to our platform processes. The high oxygen demand is met by increasing agitation and sparging of air and oxygen in bioreactors, but also negatively impacted cell health due to higher gas entrance velocities (GEV) from the higher sparging rate. The observation is exemplified in the manufacturing scale which significantly impacted cell culture performance and antibody production. Further exacerbating this issue, many sparger holes were later found to be plugged leading to a theoretical GEV as high as 300 m/s. Extensive troubleshooting studies were carried out at small scale to confirm the impact of high GEV on this antibody production process and led to the re-design of the sparger for the manufacturing scale. Once implemented, the new sparger successfully mitigated the issue. The second challenge was relating to harvest operation, where the final membrane filter was clogged at the manufacturing scale. Studies were performed at the pilot scale to evaluate different solutions including increasing depth filter area, testing different types of the final filter, and changing the chase buffer at the manufacturing scale. In the end, successful implementation of the new sparger design and optimized harvest conditions led to comparable process performance between the manufacturing scale and the pilot scale. The final process resulted not only in an increase in the overall product yield, but also prevented the need of filter change-outs during the harvest operation, therefore, significantly improving manufacturing ease.

Key words: Scale-up, optimization, sparger, harvest