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Case Study for Improved Process Robustness at Manufacturing Scale for a Mammalian Cell Culture Process: Troubleshooting Medium Preparation and Gas Entrance Velocity Effects

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A case study is presented of the scale up of a mammalian cell culture process from 100 L to 2000 L scale. Upon scale up, decreased culture growth and productivity were observed, along with batch to batch variation. The reduced performance at 2000 L scale was attributed to two factors: early culture acidification, resulting from differences in medium preparation, and higher gas entrance velocity. Troubleshooting was performed at bench, pilot, and manufacturing scale for developing improved process understanding. The medium preparation time and the associated base titration were shown to be important factors impacting process performance. In addition, with the development of at-scale process history, sensitivity of the cell culture process to gas entrance velocity effects were also observed. Using 2 L and 100 L scale down models, it was established that higher gas entrance velocity leads to reduced cell density and titers. The medium prep control strategy and ways to minimize gas entrance velocity for implementation at production scales will be reviewed.