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OVERCOMING SCALE-UP CHALLENGES WITH A NON-ROBUST CELL LINE

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Cell culture scale up success depends on robust cell line, process, and equipment. Mixing characteristics of bench scale through large scale bioreactors need to be well understood and a reliable scale up parameter needs to be used. The cell culture raw material lot to lot variability as well as hydration protocol reliability needs to be considered. The cell culture process parameter ranges need to be broad enough to account for system variability and the process should not run at the edge of failure. In our experience, greater than 95% of cell lines are robust and easily scalable. Cell line robustness and scalability is not as well understood as process and equipment robustness. Certain cell line platform and individual clones are inherently less robust than others. We will present a case study of a tech transfer process where client cell line had prior history of non-robustness. For identical process conditions, cell line titer varied 4x and peak cell density varied 2x. KBI carried out a series of bench scale (3L) bioreactor studies to identify the cause of the variability in performance and determined that small changes in pH (<0.05) led to large differences in cell culture performance. We identified that the base addition at lower end of pH deadband led to lactate production/ base addition cycle which profoundly impacted culture performance. In addition each feed addition led to a pH drop (0.05 – 0.2 units) even though the feed pH itself was neutral. Through optimization of initial pH, post-feed pH set-point, feed addition rate and CO_2 stripping strategies a significantly more robust and scalable process was created at KBI and the process was scaled up to 2000L scale. Hypothesis on the attributes of the cell line leading to inherent lack of robustness will be discussed.