MEDIUM DEVELOPMENT STRATEGIES AND SCALE DOWN MODELS FOR A HIGH DENSITY HIGH PRODUCTIVITY CELL LINE

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Medium Development at Regeneron continues to enhance fed batch culture productivity. These efforts have been enabled through the development of high throughput scale down models in shake flasks and the ambr® 250. Design of Experiment (DOE) approaches have been applied to optimize the operating conditions in the small scale models leading to performance for growth and titer that match benchtop bioreactor with no off-set. The development of these representative scale down models and our approach to medium development will be described.

A medium development case study will be presented from a recent Regeneron fed batch process with a cell line achieving high cell densities and depleting the culture of key amino acids. The traditional medium development approach of supplementing the culture with the depleted nutrients was unsuccessful: high amino acid consumption rates required large amounts of amino acids resulting in significantly increased culture osmolality and reduced productivity. Leveraging high throughput culture systems and multifactor DOEs, multiple medium composition factors in combination were rapidly evaluated. Mathematical models relating medium input factors to process outputs are generated that allow for process optimization. Using this approach, a new feeding strategy was developed that limits increases in osmolality and yields titers approaching 10g/L in both the scale down systems and a process that has been implemented for clinical scale manufacturing of a monoclonal antibody.