DECREASING DRUG DEVELOPMENT TIMELINE VIA UPSTREAM PROCESS INTENSIFICATION

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A scalable, high-intensity perfusion process was developed at Boehringer Ingelheim, Fremont Inc which is 10x more productive for producing recombinant proteins than comparative fed batch processes in the same 14-day run duration. By eliminating wasteful cell bleed we were able to achieve cell densities up to five times greater than standard “steady state” perfusion culture previously used. In order to sustain such large cell masses at manageable media exchange rates, concentrated media feeds were developed which effectively allow for optimization of nutrient delivery and dilution rate. We believe this system is scalable up to 1kL; the process has already been demonstrated successfully at the pilot scale (100L), where bioreactor productivities averaging over 5 g/L/day have been demonstrated.

We begin development with new cell lines for the high intensity perfusion process by adapting spin-tube and shake flask models that others have used for fed batch. These methods are used to test for important control parameters to allow full development in a 2L bioreactor. AMBR250 bioreactors can be used, though not optimal, as will be discussed. Due to the simplicity of the process design, the integrated downstream is developed at small scale using classical batch chromatographic techniques, including high throughput process development and standard chromatographic steps. The virus inactivation step is developed by accounting for viscosity and titration of the product and buffer in the Protein A elution peak, which differ slightly from product to product. With these simple development techniques, we believe the highly productive process could be commercially viable at Phase I, with limited to no Phase III process development.