ENABLING COMMERCIAL-SCALE PERFUSION MANUFACTURING USING SINGLE-USE BIOREACTORS AND TANGENTIAL FLOW FILTRATION

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There is an increasingly urgent need to expand the manufacturing capacity of biopharmaceuticals, demonstrated by an increase in the development of new therapies concurrently with the limitations of existing fed-batch facilities. The cost and timeframe of designing and constructing new commercial (> 10 kL) fed-batch facilities ($400 – 800 M and five years respectively [1]), along with limited availability at Contract Manufacturing Organizations (CMOs), warrants the development of an alternative manufacturing strategy to the historical fed-batch standard. In this work, we propose a solution to the upstream component of this manufacturing dilemma: a single-use bioreactor and tangential flow filtration (TFF) cell culture process which enables perfusion processing capable of yielding titer 5x greater than a fed-batch culture at the same working volume (40 L).

This process is enabled by a TFF membrane composed of numerous hollow fibers capable of efficiently separating antibody product from CHO cells, where the latter are recirculated back into bioreactor, and a magnetically levitated centrifugal pump capable of maintaining required recirculation rates without significantly damaging cells via shear forces through the pump. The cell densities required to make this strategy advantageous at commercial scale (> 90 M cells/mL) are supported by a customized single-use bioreactor, including impeller and sparger designs capable of providing sufficient pO_2 and stripping of deleterious pCO_2 without generating unmanageable foam or exhaust filter fouling.

Novel control strategies were developed to maintain the high cell density in parallel with the required recirculation, nutrient feed, and permeate rates, including the delicate balance of minimizing shear stress through the recirculation pump by limiting pumping rate and minimizing hypoxia in the recirculation loop due to an insufficiently low pumping rate (i.e. high recirculation loop residence times). This balance was achieved both by building on success of the 3 L and Ambr250 TFF perfusion processes also developed at AstraZeneca, as well as novel computational fluid dynamics (CFD) simulations which generated pump shear profiles not readily accessible from experimental means.

This work demonstrates for the first time a single-use, high cell density, TFF perfusion cell culture process that is potentially scalable to the commercial scale (2 – 6 kL). Through establishing the success of this 40 L process with respect to maintaining high cell densities and significant titer increases compared to fed-batch processing, we have established a platform to study the challenges of scaling TFF perfusion to the commercial scale to ultimately enable the design of a single-use facility that will serve as a less expensive and more efficient alternative to presently available fed-batch manufacturing platforms.

[1] Jagschies, G. (2020). *Hierarchy of high impact improvements in bio manufacturing*. Paper presented at Workshop on Innovations in Pharmaceutical Manufacturing. National Academies of Science, Washington, DC.