DEVELOPMENT OF AN N-1 PERFUSION PROCESS AND OPTIMIZED SCALE-DOWN MODELS FOR IMPLEMENTATION IN A PLATFORM CHO CELL CULTURE MANUFACTURING PROCESS.

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The use of N-1 perfusion, coupled with high-inoculum fed batch in CHO cell culture manufacturing processes, has been shown to increase volumetric productivity and shorten the duration of the fed-batch production phase. Implementation of N-1 perfusion as part of a platform process requires the ability to screen multiple clones and to optimize media and process parameters in a high-throughput manner. We have developed an N-1 perfusion process, along with a series of scale-down models for N-1 perfusion using shake flasks, cell culture tubes, and deep-well plates. Process parameters for scale-down models were optimized to maximize comparability of growth profiles and cell culture performance relative to 5L N-1 perfusion bioreactors. Scale-down models were used to inoculate fed-batch experiments in Ambr15 micro-bioreactors at high seeding density, in order to compare growth and productivity profiles to those observed in 5L bench scale bioreactors. Multiple cell lines derived from different CHO hosts were evaluated in order to verify the robustness of the scale-down models. Results demonstrated that cell growth and viability in the optimized scale-down models were comparable to those observed in 5L N-1 perfusion bioreactors. Furthermore, growth, productivity, and product quality profiles from high-inoculum fed-batch experiments were comparable regardless of inoculum source. Optimized scale down models of N-1 perfusion, coupled with Ambr15 fed-batch production micro-bioreactors, have now been integrated into a high-throughput and robust workflow to enable DOE and screening experiments for clone selection, media development and parameter optimization in a platform N-1 perfusion process for monoclonal antibody manufacturing.