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MEDIUM OPTIMIZATION CASE STUDY FOR CONTINUOUS UPSTREAM PROCESS

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Based on other mature industries, continuous upstream process is a logical replacement for current fed batch operations. However most industrial medium development has focused on the biological requirements for fed batch and therefore focused on the needs of stationary phase production. There is not an a priori expectation that growth and stationary phase requirements are identical. Yet an ideal continuous upstream process requires some combination of both. An optimal continuous upstream process requires a high cell density similar to fed batch operations. There is also some minimum growth rate required in order to match the combined death and cell removal rate at steady state. Hence, medium optimization yielding high productivity and sustaining sufficient growth is critical. In our work, we first established the minimum metabolic requirements to exceed high cell density at high viability based on our existing cell culture medium platform. Furthermore, the cells were able to reach a high cell density within only a few days post inoculation. Optimization was still required in order to shift from such a rapid growth process to a desirable high productivity continuous process. Fortunately, a continuous system is an ideal setup within which to evaluate multiple effects sequentially. An individual component can be spiked into the culture, and the direct impact can be monitored on cell growth and productivity. As the continuous system will continually wash out the component, the individual component impact is temporal and eventually the system returns to steady state in the absence of the spiked component. This process can be repeated iteratively until an optimal result is obtained. In our case, multiple positive effects were combined into one medium composition specifically optimized for a continuous upstream process.