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INTEGRATING EMERGING TRENDS IN UPSTREAM PROCESS DEVELOPMENT: AUTOSAMPLING, NUTRIENT FEEDBACK CONTROL, AND SINGLE USE TANKS

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Key to effective upstream development is the presence of resource-efficient systems for examining complex process options. In this presentation, we report the design and characterization of a 3-L rigid single-use bioreactor (SUB), combined with a completely automated sampling and control system capable of evaluating different metabolic-based feed strategies.

Considerations in our development of a custom 3-L SUB, targeted to replace current workhorse glass reactors, encompassed proper technical functionality to flexibility and ease of use. Highlights include: vessel configuration details (impeller, sparger, baffles), perfusion readiness, agitation system design (magnetic bottom drive), and extra sensor ports and feed lines. The SUB was developed through multiple iterations to arrive at the final design, which was characterized experimentally for kLa and by CFD for mixing. The final engineering design is able to support cell density above $100x10^6$ cells/mL.

In parallel we pursued an automated system capable of investigating feed strategies tailored to real-time cell metabolite measurements, i.e. with feedback control based upon residual metabolite levels. In the end our customized automated sampling and feed control system allows programmed sampling of both cell-free and cell-containing retains from eight bioreactors, delivery to integrated analyzers, and control of nutrient feed pumps (2 per bioreactor). The system is capable of feedback control to implement individualized feed strategies that incorporate data inputs from the integrated analyzers.

Implementation of the custom 3-L SUBs and automated sampling and feed control system has enabled enhanced process development capability, by introducing technology to both improve operational efficiency and facilitate experiments of greater complexity.