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# Development of functionally closed downstream operations for continuous biomanufacturing of recombinant therapeutic proteins

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# DEVELOPMENT OF FUNCTIONALLY CLOSED DOWNSTREAM OPERATIONS FOR CONTINUOUS BIOMANUFACTURING OF RECOMBINANT THERAPEUTIC PROTEINS

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Traditionally, upstream processing in biologics manufacturing is performed in an aseptic and functionally closed manner while downstream processes are open operations designed to maintain a low-bioburden state. Consequently, the downstream process components such as skids, column hardware, and chromatography resins currently available have been designed for low bioburden rather than aseptic operations. One of the key design elements of Integrated Continuous Biomanufacturing (ICB) is the linkage of upstream and downstream operations and the capability of the system to run for prolonged durations at ambient temperature. Thus, a critical design criterion for ICB is the ability of the system to maintain a bioburden-free state. This study demonstrates the development of novel tools and methodologies to address the need for at-scale bioburden-free downstream operations for ICB.

Both engineering and operational solutions were identified to achieve bioburden-free integration of a bioreactor with a periodic counter-current (PCC) skid. The engineering/operational solutions included the construction of a SIPable and functionally- closed manufacturing scale PCC skid, disposable and functionally-closed chromatography columns coupled with an innovative strategy to render them bioburden-free, as well as the use of tubing welders. To this end, we have successfully demonstrated at-scale operation for integrated capture of both a stable (monoclonal antibody) and an unstable molecule (recombinant enzyme) for over 40 days each. Samples from different points of the system showed that the operation was bioburden-free for the duration of the campaign. Additionally, no indication of time based performance decline was observed for either the mAb or enzyme capture step. Overall, our findings demonstrate successful scale-up of a functionally-closed, integrated and continuous capture step operated for weeks in a bioburden-free state. Such principles and solutions can be further extended to subsequent downstream unit operations, enabling the development of an end-to-end biomanufacturing platform. Environmental control requirements for a functionally closed end-to-end cGMP facility can potentially result in dramatic reductions for both OPEX and CAPEX.