DEVELOPMENT OF SCALABLE SEMI-CONTINUOUS DOWNSTREAM PROCESSES

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Key Words: MAb process intensification, Multi-column capture, Low-pH viral inactivation, Integrated pool-less polishing

The goal of this work is to establish an intensified downstream scheme for stable, high-titer monoclonal antibody (mAb) processes to achieve increased manufacturing productivity with short cadence, reduced cost, and small facility footprint. Several continuous manufacturing technologies including multi-column chromatography for capture, automated low-pH viral inactivation (low-pH VI), and integrated pool-less polishing steps were evaluated following consistent development methodologies for several mAbs. This presentation aims to provide an overview of the approaches to developing and integrating these discrete technologies in one cohesive process flow that fits manufacturing requirements in a flexible manner. Development efforts are illustrated in three major areas. First, twin-column continuous capture chromatography (CaptureSMB) was evaluated systematically for equivalency assessment comparing to traditional batch operation for different molecules. Development data showed overall comparable chromatography performance, while certain trends were found to be molecule/process specific. For executing viral clearance studies, scalable models were developed using CaptureSMB and a surrogate system employing standard batch chromatography with flow path modifications to mimic the loading strategy of CaptureSMB. We also introduce a model-assisted process characterization approach toward validation of continuous twin-column capture chromatography owing to increased process understanding. Second, experimental studies and computational fluid dynamics (CFD) modeling were used to reduce the risk of product aggregation in low-pH VI manufacturing operation. For various mixing systems, localized low-pH zones were characterized quantitatively to avoid the undesirable conditions that could cause severe aggregate formation during acid adjustment. The modeling tool integrated with mAb aggregation measurements facilitates the optimization of operating parameters (e.g., titrant addition rate, impeller agitation) and automation strategy to ensure robust VI scale-up performance. Third, various scenarios of integrated pool-less polishing steps operated in flowthrough-flowthrough (FT-FT) or flowthrough-bind/elute (FT-B/E) mode were evaluated with or without inline adjustment between the two steps. Performance and quality attributes are compared for integrated and decoupled polishing steps, with an example describing the development and optimization workflow for a specific mAb process. Finally, implication to process development timelines, scale-up performance and practical challenges to process implementation in the new 2000-L manufacturing facility will be discussed.