DEVELOPMENT OF CONTINUOUS PRODUCTION AND PURIFICATION PROCESSES FOR THE INTEGRATED MANUFACTURE OF MONOCLONAL ANTIBODIES

Fabian Steinebach, Institute for Chemical and Bioengineering, ETH Zürich
fabian.steinebach@chem.ethz.ch
Daniel Karst, Institute for Chemical and Bioengineering, ETH Zürich
Nicole Ulmer, Institute for Chemical and Bioengineering, ETH Zürich
Moritz Wolf, Institute for Chemical and Bioengineering, ETH Zürich
Sebastian Vogg, Institute for Chemical and Bioengineering, ETH Zürich
Massimo Morbidelli, Institute for Chemical and Bioengineering, ETH Zürich

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Continuous integrated manufacturing is a novel paradigm in the production of therapeutic proteins. It is considered to not only decrease capital and operating cost, but also improve product quality and therefore alleviate regulatory issues. These advantages have increased interest in continuous unit operations and their integration. Herein, we evaluate the performance of multi-column downstream processes as part of an end-to-end integrated production stream. The following steps were operated in an integrated manner: A perfusion bioreactor equipped with an external hollow fiber device, a continuous two column capture process, a virus inactivation step, a semi-continuous polishing step (twin-column MCSGP) and a batch-wise flow-through polishing step. In each unit, internal recycle loops allow to improve the performance: Increased volumetric productivity and capacity utilization are obtained in the bioreactor and capture step, respectively; furthermore, the purity-yield trade-off typically encountered in batch-wise bind-elute polishing steps can be overcome. A commercial monoclonal antibody was continuously produced and purified in this setup. The end-to-end integration was carried out for 17 cycles yielding uniform product quality. The steady-state operation was fully characterized in terms of product titer and quality considering both product (aggregates, fragments) and process (HCP, DNA, leached Protein A) related impurities; this analysis was done at the outlet of each of the units.