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DEVELOPMENT OF A QUALITY DRIVEN INTEGRATED CONTINUOUS BIOMANUFACTURING PROCESS

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The recent improvements of continuous up- and downstream processes in the production of therapeutic proteins suggest their final integration to a single process stream. Besides general benefits of continuous manufacturing, such as reduced equipment size, enhanced cost efficiency and high volumetric productivity, the steady state operation favors constant or even improved product quality. However, N-linked glycosylation, charge variants, aggregates and other critical quality attributes of therapeutic proteins depend on operating conditions in up- and downstream processing. The combination of long process durations and the accompanied lack of experimental high-throughput capabilities of continuous bioprocesses demand for model based optimization regarding product yield and quality.

In this study a perfusion bioreactor has been directly connected to a continuous protein A capture step. The effect of media components and different viable cell densities on product quantity and quality was investigated in the CHO cell process. A higher degree of modularity regarding the mAb glycosylation compared to fed-batch mode could be observed which was mainly due to the removal of byproducts and differences in the cellular metabolism. A mechanistic mathematical model was then developed to describe and predict the resulting N-linked glycosylation pattern as a function of the applied conditions in continuous cell culture. Furthermore, a second mechanistic model in combination with at-line monitoring of the harvest product concentration was applied for the model predictive control of the in-group developed capture SMB process. The chromatographic process was able to process fresh media from multiple viable cell density set points thereby demonstrating the high flexibility of the downstream process.

Adjustable yet consistent product quality can be achieved within a defined steady state in continuous bioprocessing. The model-based control and monitoring of a perfusion cell culture and the adaption of the subsequent downstream processes reveals that quality driven considerations are the real advantages of integrated bioprocessing over conventional batch-wise operation.