

CONTINUOUS BIOPROCESSING & PROCESS ANALYTICAL TECHNOLOGIES: A PATH TOWARDS QUALITY BY DESIGN

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Recent success in monoclonal antibody based immuno-oncology therapeutics such as Keytruda® has initiated a revolution within the Biopharmaceutical Industry. Development efforts to support this class of molecules include single-use technology, continuous production, process analytical technology (PAT), information technology (IT), multivariate data analysis (MVDA), and efforts towards real time release testing (RTRT). Merck's vision for a next-generation large molecule production facility aligns with these six key principles, as demonstrated by the construction of a continuous monoclonal antibody (mAb) production pilot plant named the Protein Refinery Operations lab (PROLab) within Merck Bioprocess Development.

Quality-by-Design (QbD) principles are maturing for the development of standard batch-based therapeutic protein manufacturing processes. Outside of the insight gained through similar techniques applied to unit operations run in a continuous mode, similar approaches for the dependencies created by connected and continuous processes are still in their infancy. Previously, a methodology for characterizing holistic downstream process performance through real time perturbation analysis, where the response to an upstream stimulus is monitored at several unit operations simultaneously was presented to start applying QbD principles to continuous bioprocessing.

Here, the authors build upon the concept of perturbation analysis by presenting case studies where advanced PAT tools have been embedded in PROLab operation. At-line and off-line process and product quality data from continuous upstream and downstream production will be presented over the course of long term perfusion cell culture with variable production rates. Specific emphasis will be placed on the performance of bioreactor cell retention and clarification trains, and post-chromatographic ultrafiltration unit operations. This process understanding can then be utilized to place PAT tools at the appropriate locations in the process to achieve product attribute control and ultimately to assure uninterrupted supply of therapeutic proteins to patients.