

USE OF BIOCAPACITANCE PROBES FOR OPTIMIZED PROCESS CONTROL AT LARGE-SCALE MANUFACTURING

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Monoclonal antibody production is moving towards high-titer processes. Development of such processes often requires pushing cell densities much higher which can amplify process sensitivity to nutrient feed addition amounts with regards to titer and to product quality. As such, these processes require tightly controlled feed additions during the process to balance nutrient consumption. Legacy manufacturing fed-batch processes have typically applied fixed-volume bolus feeds, which in combination with small variations in seed density and/or growth rates can result in significant variation in feed amount per cell. Therefore, for high-titer fed-batch processes, Biogen has moved to variable-volume biomass-dependent feeding via online biocapacitance for biomass measurement. The use of online biocapacitance enables monitoring of the batch performance real-time and has the potential to reduce the dependency on offline sampling and operator interactions as well as eliminate offline biomass analysis variation. This strategy has enabled Biogen to develop robust fed-batch processes with titers in the 7-10 g/L range.

In Biogen's Large-scale manufacturing facilities online biomass monitoring by biocapacitance is applied in all bioreactors including seed train reactors, which enables the use of online biomass measurement for calculation of bioreactor-to-bioreactor transfer amounts. Data from a high-cell density, high-titer monoclonal antibody process applying online biocapacitance both at 3 L laboratory scale and at 15,000 L manufacturing scale are presented. The data demonstrates how online capacitance probe measurements were used for tight control of bioreactor-to-bioreactor transfers and for biomass dependent complex feed additions. Furthermore, the use of online biocapacitance for process decisions has shown reduced process variability when compared to the use of offline biomass analysis. The advantages and challenges of applying online biocapacitance are discussed.