BIOREACTOR SCALE DOWN MODEL CASE STUDY: ENSURING NUTRIENT FEED STRATEGY IS REPRESENTATIVE OF CLINICAL AND COMMERCIAL SCALE

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Key Words: Fed-batch, nutrient feed, scale down model, sequence variant, amino acids.

Scale down or bench scale models (SDM) are critical for the development of biologics in that they are used in all phases of process development. SDM's are used during early clinical campaigns to select the final clone for clinical manufacturing and for optimization and characterization to support market authorization. It is imperative that the SDM be predictive of manufacturing scale in order to provide a robust, consistent, and well-understood process. During commercial process development, statistical methods are used to qualify the SDM, specific to the cell line and commercial process. SDM qualification can be done at this time due to the increased amount of data at both the bench and commercial scale to support equivalence testing. However, during early stage process development, there is little to no time to qualify scale down models for each cell line as speed to the clinic is the key imperative. As such, most companies leverage the same platform SDM for the majority of the pipeline programs. It is typical that only a single clone screen experiment is executed during this phase prior to the process being scaled up for clinical manufacturing. As such, it is critical that the SDM at this stage is predictive of the clinical scale, particularly the product quality.

This case study highlights an early phase program where as the process was scaled up, a significant increase in sequence variants was detected that was not observed in the SDM. This prompted further SDM experiments to understand this phenomenon. The root cause was identified to be minor differences in total feed volume delivered between the SDM and the at-scale run. This was because sampling of the SDM bioreactors removes a greater proportion of the total bioreactor volume, relative to large scale bioreactors. This minor difference had otherwise no impact to the cell culture performance or other product quality attributes. Due to these data and experience, the process platform was updated to further improve our SDM.