MANAGING TRANSFER AND SCALE-UP OF A PROCESS WITH ATYPICAL IMPACT OF DISSOLVED OXYGEN CONCENTRATION ON PRODUCTIVITY AND PRODUCT QUALITY

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Dissolved oxygen (DO) is a routinely measured and controlled process parameter in mammalian cell cultures for monoclonal antibody production in stirred tank bioreactors. For typical Chinese hamster ovary (CHO) cell lines, DO is controlled around a specific set-point, but growth, productivity, and product quality are relatively independent of DO over a wide range relative to controller capability. Thus DO control is primarily used to ensure sufficient oxygen is provided to the cells to support their metabolism during growth and antibody production. Such processes can be transferred from one facility or scale to another with limited concern for detailed analysis of potential DO gradients within the bioreactor or differences in probe handling and pressure compensation methods.

This paper describes challenges associated with DO impact to productivity and product quality in a low-density CHO fed-batch process executed at 15 mL, 2 L, 12 kL, and 20 kL bioreactor scales. The work was initially motivated by unexpectedly low productivity at the 20 kL scale. Due to gradients within the 20 kL bioreactor and differences in pressure compensation strategies, the actual DO concentration during the run was up to 175% of the concentration at the 2 L process development scale. Subsequent experiments at the 15 mL and 2 L scales showed an inverse correlation between titer and DO set-point over the range of 10% to 60% air saturation. For the 2nd run at the 20 kL scale, the set-point was lowered and pressure compensation methods were adjusted, resulting in a significantly higher titer. The lower effective DO concentration was also applied at a second manufacturing facility, where a higher titer was again achieved.

While product quality was acceptable for the large scale runs with lower DO, process characterization studies demonstrated that DO set-point was correlated with the charge heterogeneity profile (Figure 1). The ideal DO range for higher productivity was correlated with higher likelihood of a charge heterogeneity profile outside of the target performance range. This presentation describes how statistical models generated from process characterization data, along with considerations of bioreactor configuration, mixing, and gassing strategies can be applied to develop a manufacturing process to simultaneously deliver acceptable product quality and meet productivity requirements.

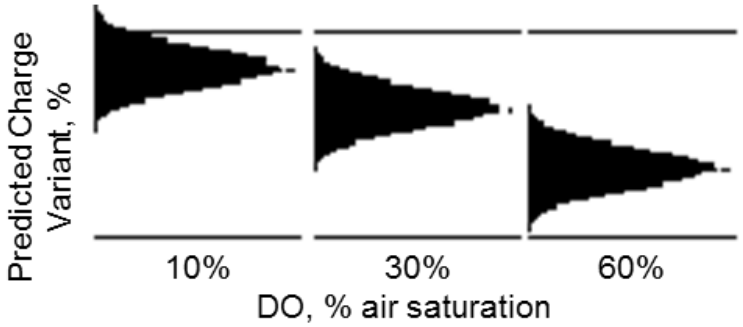

Figure 1 – Predicted charge variant abundance for the process executed at various DO set-points. Solid black lines: target performance range.