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CHO cell culture process impacts monoclonal antibody trisulfide modification and sulfhydryl-drug conjugation

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Abstract:

During the production of monoclonal antibodies using a CHO cell culture process, important parameters are generally controlled by a feedback mechanism (PID) in order to ensure consistency in both productivity and product quality. These parameters typically include pH, dissolved oxygen, and temperature. While most of these parameters are controlled very well within their specific dead band range, dissolved oxygen at times can be a little more difficult to control. Oscillations in dissolved oxygen concentration are not uncommon and these fluctuations can sometime be exacerbated when using an aeration strategy with a high mass transfer rate.

Recently, we observed a cell line that becomes lactogenic accompanied by a drop in product titer due to extreme fluctuations in dissolved oxygen concentration. It was also observed that the antibody lots with higher lactate production correlated with increase trisulfide formation between heavy-light chains. Consequently, the elevated trisulfide levels correlate to changes in the drug-to-antibody ratio (DAR), when used in sulfhydryl-targeted maleimide conjugation.

Experiments were conducted to determine if lactogenicity is triggered by low concentrations of dissolved oxygen or by fluctuations in dissolved oxygen concentration during the cell cultivation process. Further experiments were performed to evaluate if the elevated trisulfide is associated with the lactogenic status of the cells or any particular nutrient/metabolite. Results from these experiments will be presented and strategies for better control of the cell culture process and the product quality of antibody-drug conjugates will be discussed.