Understand & Control Product Quality Attributes in Cell Culture

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In preparation for commercialization of therapeutic protein manufacturing, cell culture process is developed and characterized to ensure consistent delivery of high quality protein. Drug substance and drug product quality attributes can be impacted by the cell culture process. Two case studies will be presented to demonstrate how Lilly developed new tools to understand and control critical quality attributes in cell culture.

In a fusion protein program, a protein cleavage form was considered as critical quality attribute due to its lack of potency. This cleavage form cannot be removed by downstream purification process and presented at relatively large percentage (10%) in drug substance. It is important to develop a robust cell culture process so that this product related impurity can be minimized and controlled. Traditional tools (i.e. protease inhibitors, pH and temperature etc) had limited impact on this cleavage. However, we found that osmolality and pCO_2 controls were important to reduce this impurity in drug substance. With implementation of the new control strategy, the cleavage level reduced by 50% and was successfully scaled-up.

For the second case study, , we will share our observations that cell culture process changes had a significant impact on high protein concentration (> 100 mg/ml) drug products stability profiles in several molecules. HMW aggregates growth rate in drug product increased significantly after the cell culture medium change though aggregates level in drug substance were similar. Lilly developed a surrogate assay for drug substance as an indicator to aggregates on drug product stability. By using this surrogate assay, a large number of cell culture factors were screened and a few levers (i.e. media components and process conditions) in cell culture were identified to impact drug product aggregates growth, which were later confirmed in real time stability studies.