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Advanced process monitoring and feedback control to enhance cell culture process production and robustness

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ADVANCED PROCESS MONITORING AND FEEDBACK CONTROL TO ENHANCE CELL CULTURE PROCESS PRODUCTION AND ROBUSTNESS

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Key Words: Mammalian cell culture; fed-batch; auto-feedback control; capacitance; glucose/lactate control

It is common practice in biotherapeutic manufacturing to define a fixed-volume feed strategy for nutrient feeds based on historical cell demand. However, once the feed volumes are defined, they are inflexible to batch-to-batch variations in cell growth and physiology and can lead to inconsistent productivity and product quality. In an effort to control critical quality attributes and to apply Process Analytical Technology (PAT), we demonstrated three different and novel approaches for implementing online monitoring and feedback control to improve the performance and/or robustness of cell culture processes. First, we describe the first reported fed-batch process utilizing online amino acid measurements (glutamate) to trigger automatic feedback control delivering complex nutrient feed. More importantly, the resulting feed strategy was translated into a manufacturing-friendly manual feed strategy without impact on product quality. Second, we increase the complexity of the control strategy by designing multiple feedback control loops for all feed solutions based on varied inputs (bio-capacitance for cell mass, Nova-Flex for glucose), resulting in a truly fully automatic cell culture process. We then demonstrate the utility of the feedback control system to rescue a batch without manual intervention by automatically adjusting the feed in response to an excursion that was intentionally introduced. Finally, we describe the implementation of a new online monitoring instrument in combination with a logic control module to simultaneously monitor and control glucose and lactate with high frequency, resulting in cell culture process improvement. Together, the three cases presented here illustrate an advanced process control toolbox which can be readily applied to various cell lines, media systems, and processes to significantly increase productivity and improve robustness in manufacturing, with the goal of ensuring process performance and product quality consistency.