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EFFORTS TO REDUCE IMPACT OF MEDIA VARIABILITY ON PRODUCT QUALITY FOR A COMMERCIAL PERFUSION PROCESS

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Strict control of raw materials used in bioprocesses is necessary to ensure consistent product quality. However, use of poorly characterized complex components makes achieving such strict control difficult. A strong correlation between product quality variability among bulk drug substance lots and changes in a complex medium component was observed in a commercial perfusion process. This correlation was subsequently confirmed experimentally at both large and small scales. A multifaceted strategy was applied to investigate and mitigate the impact of the media variability on product quality, which included (1) studies in small scale perfusion bioreactors; (2) development of a simple cell based assay to screen different media component lots; and (3) utilization of advanced analytical techniques to identify components that impact product quality. Small-scale perfusion bioreactors were cultured using media lots whose large-scale performance were known, and results were consistent to large-scale performance, supporting the use of small-scale cultures to resolve large-scale media effects. Given the difficulty of utilizing small-scale perfusion bioreactors to screen media lots, an effort was also made to develop a shake flask protocol capable of resolving large-scale media impact on product quality. To simplify testing even further, proteomic and metabolomic analyses through LC-MS were also performed on media and soy retains. Multivariate analysis identified a number of species that could be used as a chemical fingerprint of desirable large-scale performance, which would simplify media qualifications even further. The continued development of new platforms and assays for screening undefined components improves responsiveness to raw material variability and, in turn, enables better control of product quality of commercial products.