^{1}H NMR-based process understanding and biochemical marker identification methodology for monitoring CHO cell culture process during commercial-scale manufacturing

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Abstract

Controlling the process of CHO cell fed-batch culture is critical for biologics quality control. However, the biological complexity of cells has hampered the reliable process understanding for industrial manufacturing. In this study, a workflow was developed for the consistency monitoring and biochemical marker identification of the commercial-scale CHO cell culture process through ^{1}H NMR assisted with multivariate data analysis (MVDA). Firstly, a total of 63 metabolites were identified in this study object in ^{1}H NMR spectra of the CHO cell-free supernatants. Secondly, multivariate statistical process control (MSPC) charts were used to evaluate process consistency. According to MSPC charts, the batch-to-batch quality consistency was high, indicating the CHO cell culture process at the commercial scale was well-controlled. Then, the biochemical marker identification in the cell logarithmic expansion, stable growth, and decline phases were provided through orthogonal partial least square discriminant analysis (OPLS-DA) based S-line plots. L-glutamine, pyroglutamic acid, 4-hydroxyproline, choline, glucose, lactate, alanine, and proline were determined as biochemical markers of the logarithmic growth phase. Isoleucine, leucine, valine, acetate, and alanine were determined as biochemical markers of the stable growth phase. Acetate, glycine, glycerin, and gluconic acid were identified as biochemical markers of the cell decline phase. The workflow proposed in this study demonstrates that the combination of MVDA tools and ^{1}H NMR technology is highly appealing to the research of the biomanufacturing process, and applies well to provide critical guidance in future work on consistency evaluation and biochemical marker monitoring of the production of other biologics.

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