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Using definitive screening design to effectively assess the combinatorial impacts of media supplements on monoclonal antibody production in mammalian cells

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Using Definitive Screening Design to Effectively Assess the Combinatorial Impacts of Media Supplements on Monoclonal Antibody Production in Mammalian Cells

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Process understanding is an essential component of QbD principles. Cell culture media composition can impact many process performance parameters such as viable cell density, product yield and product quality attributes. In order to enhance process understanding and exert better process control, numerous media supplements have previously been tested. However, their combinatorial effects on process and product quality have largely been unexplored. This is partially due to the resource and efforts required to execute relatively large size of experiment and data analysis.

Recent advancement in modern design of experiment methodology has alleviated this issue. The definitive screening design (DSD) allows for screening a large number of main effects unaliased with two-factor interactions, estimating some quadratic effects, and differentiating two-factor interactions that are only partially aliased with a significantly reduced experiment size compared to traditional fractional factorial and alphabetic-optimal designs. With 15 factors, the DSD only requires 33 runs. In comparison, the 33-run D-optimal design with 1 center point will have aliases among the 15 main effects and two-factor interactions. Although the 33-run 2^{15} fractional factorial with 1 center point does allow estimating the main effects independently, most of the two-factor interactions are confounded with other two-factor interactions and no independent quadratic effects can be estimated.

Leveraging the DSD allows us to effectively test the impact of 15 media supplements on cell culture performance and product quality using the shake flask model. The resulting statistical models for each critical response were further verified using bench-top stirred-tank bioreactors and multiple cell lines. The knowledge gained from this experiment not only enhances our process-to-product understanding, but also serves as a tool to manipulate critical cell parameters to achieve desired product quality.