SCALE-DOWN MODEL QUALIFICATION STUDY IDENTIFIES PARAMETERS TO IMPROVE FULL-SCALE ROBUSTNESS

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Key Words: process control, process characterization, product quality, scale-down

In this case study, the small-scale model qualification of a Chinese Hamster Ovary (CHO) 2000L fed-batch process assisted with understanding observed variations in cell growth and product quality. The robustness issues were replicated at development scale (250mL and 2L) and our approach to identifying the root cause and optimizing process control are described for our representative scale-down models.

Full-scale lots exhibited variable peak viable cell density (VCD) which impacted productivity, and slightly impacted some quality attributes. Two main discrepancies identified at the 2000L production stage: high initial dissolved oxygen (DO) or more rapid cell growth, potentially leading to nutrient depletion and more rapid viability decline.

The high initial DO and slow cell growth was later reproduced in the scale-down model. At both scales, the slow cell growth led to reduced peak viable cell density (VCD) but higher end of culture viability and titer.

The 2000L lots with high initial cell growth rates, high peak VCD and a more rapid decline, produced lower titer with slight variations in basic and acidic variants, although other product quality attributes remained consistent. The same rapid VCD decline was reproduced at development scale during small-scale qualification runs and was determined to be linked to nutrient depletion with the aid of amino acid analysis. The amino acid analysis revealed more frequent depletion of asparagine in cultures with higher peak VCD and this correlated with a subsequent reduction in amino acid uptake and a slightly reduced culture pH within the control deadband.

The peak VCD variation was related to the VCD at temperature shift. Temperature shift was initiated at a VCD of at least 3×10^6 viable cells(vc)/mL but in practice, GMP and development lots were shifted in a wide range with those lots shifted closer to 4×10^6 vc/mL experiencing the detrimental higher peak VCD. Additional runs at small-scale were able to confirm that temperature shifting cells at a VCD closer to 3×10^6 vc/mL resulted in consistent and improved process performance with no impact to product quality attributes. Increased nutrient addition was also explored to compensate for asparagine depletion and high peak VCD, but no consistent process performance improvement resulted and additional variation in basic and acidic variants were noted.

The small-scale models were successfully qualified for use in late-stage development with this additional process understanding and with the accurate reproduction of full-scale responses to process variation. Process characterization studies are planned to study and potentially implement an improved control strategy needed for this fed-batch process with one objective being to consistently control initial cell growth to optimize process performance.