

OVERCOMING MANUFACTURING CHALLENGES FOR AN EARLY PHASE DEVELOPMENT PROGRAM

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Speed to clinic often does not allow for in-depth manufacturing process development and understanding of early phase clinical programs; however, this may be necessary when inconsistencies in process performance or product quality are observed. For a recent Phase 1 fed-batch process, drug substance manufacturing process variability was observed during development and manufacturing scale productions. Process performance variability was observed during upstream process with ending viability ranging from 90% to 60% and end product neutral glycan profile ranging from 15% to 50%. To mitigate future performance variability, two approaches were taken: 1) improve cell culture performance robustness and 2) probe the relationship between cell culture performance and product quality attributes. Using ambr®15 as a high-throughput screening tool, a series of risk-based process parameter screening studies were conducted to eliminate potential root causes for culture viability decline. Small scale studies, both at ambr®15 and benchtop bioreactor scales, offered insights suggesting shear sensitivity and raw material variability were potential contributors to inconsistent cell culture performance. Strategic process-specific alterations, such as changing aeration method and lowering the agitation intensity, resulted in culture health improvements. Small scale results also indicated high-risk medium lots may be identified and mitigated with additional shear protectants. Large scale manufacturing in-process data suggest glycosylation pattern may not be directly linked to cell culture viability. Further studies may be useful to identify other process steps that contribute to product quality variations. Learnings from this presentation highlight strategies to improve cell culture performance robustness and the need to establish the relationship between in-process attributes and end product quality.