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CHALLENGES IN THE USE OF SCALE-DOWN MODELS FOR UNDERSTANDING AND MITIGATING PROCESS VARIATIONS OF A MONOCLONAL ANTIBODY PRODUCTION PROCESS

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Scale-down models are commonly used to execute process characterization studies, as well as to screen raw materials and to conduct investigations in support of manufacturing operations. During the clinical manufacture of a monoclonal antibody, consistent product quality was maintained; however, large variations in bioreactor harvest titer (> 2X) were observed between lots. Root cause analysis of this variation did not establish a linkage between culture performance and manufacturing execution or deviations. Further, small scale satellite reactor performance displayed lesser variability; thereby eliminating seed train and raw materials as potential root causes. Small scale investigations, using multiple scale-down models, were not able to reproduce the variability in product titer, and other cell culture metrics, observed at large scale. However, these studies were able to establish a correlation between cellular metabolism, feeding strategy and harvest titer. As a result, process modifications have successfully been developed to obtain a more robust production bioreactor process while maintaining product quality.