A Process Development Strategy Providing Flexibility While Balancing Cost and Speed without Sacrificing Quality

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Platform process development approaches work well for large molecule therapeutics including monoclonal antibodies (mAbs). Pfizer's large molecule pipeline includes a variety of modalities ranging from mAbs to antibody drug conjugates to fusion proteins and native molecules. To efficiently prosecute this diverse portfolio we apply approaches that balance risk, timeline pressures, and cost without sacrificing quality. To accomplish these objectives we first assess the manufacturing risks associated with each therapeutic candidate molecule by conducting a molecule assessment, a combination of experimental and *in silico* evaluations designed to provide an early understanding of the fit for our Phase 1 process development platform.

For mAbs deemed "well behaved" we can apply a minimalist process development strategy designed to progress the therapeutic candidate to manufacturing for IND enabling toxicology studies as rapidly as possible. In these cases we apply a defined cell culture platform, a well-established 2-column purification process and platform analytical and formulation approaches. Initiation of cell line development activities well in advance of final candidate identification further reduces the timeline from candidate selection to manufacturing. This is accomplished by employing a targeted integration expression strategy. The targeted integration strategy allows parallel development of multiple molecules in a resource sparing manner, but may suffer from less than optimal expression requiring post-Phase 1 process optimization. To address this liability, we aspire to further increase efficiency by establishing a next-generation targeted integration host cell line that we expect will increase expression and reduce resource utilization.

For molecules deemed "not well behaved" we apply more extensive process development strategies with extended timelines and increased costs. In all cases, however, we apply lessons learned from previous experience to reduce or eliminate potential issues, including amino acid sequence liabilities and DNA sequences known to be prone to mis-splicing. Additionally, we apply robust genetic and biochemical sequence variant analysis to ensure the amino acid sequence fidelity for each therapeutic candidate. Taken together these strategies enable an early understanding of the most efficient process development approach that balances cost, speed, and quality of the product and the process.