Synthetic Challenges Spanning Grams to Kilograms for Early Process Development of Small Molecule and Conjugate Drug Candidates

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Each phase of synthetic process development and each type of molecular modality bring with them unique challenges as drug candidates advance from research to pre-clinical studies and beyond. These challenges are highlighted in two vignettes from our process chemistry laboratories. In the first, a multi-kilogram-scale synthesis of a small molecule immunology-targeted ligand was achieved. Successful synthesis of this active pharmaceutical ingredient (API) required optimization of a difficult late-stage carbon-nitrogen coupling, as well as execution of a heterogeneous sultam alkylation on scale. Other process design considerations, such as robust isolations for nitrogen-rich intermediates, are discussed. In the second example, from our therapeutic antibody conjugate research program, the synthesis of a complex and highly cytotoxic linker-drug necessitated chemistry efforts across a fast-moving and dynamic supply chain. Several synthetic approaches toward a reactive, difficult-to-crystallize payload intermediate were explored. The process to dimerize this payload (a cyclopropabenzindolone pro-drug) onto a carefully engineered linker scaffold was developed and executed on gram scale to support downstream conjugation and key pre-clinical testing.