ORGANIC SEMINAR

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AMGEN

Development of a Commercial Manufacturing Process for Sotorasib, a First-in-Class KRAS G12C Inhibitor

Atropisomeric molecules have recently gained significant attention in pharmaceutical discovery research. Due to their increased complexity, atropisomeric active pharmaceutical ingredients (APIs) pose a significant challenge for the development of efficient, large-scale manufacturing processes. LUMAKRAS^{TM} (sotorasib), an atropisomeric API, was the first KRAS^{G12C} inhibitor to enter clinical trials and receive FDA accelerated approval. The Amgen process development team developed a chromatography-free preparation of sotorasib by leveraging high-throughput experimentation, kinetic analysis, and modeling. The final process enabled the preparation of an atropisomeric precursor to sotorasib with >99.95% enantiopurity on a multi-hundred-kilogram scale. Optimization of the downstream processing steps reduced impurity formation and improved manufacturing cycle times, which resulted in improved API quality and manufacturing efficiency. These efforts resulted in the rapid development of a manufacturing process that enabled commercialization of sotorasib at an industry-leading speed while improving environmental sustainability.