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CASE STUDY

SIMCYP SIMULATOR DEMONSTRATES BIOEQUIVALENCE (BE), ELIMINATING NEED FOR COSTLY CLINICAL STUDY

In the heavily regulated pharmaceutical industry, changes to the manufacturing process can be quite complex and costly. This is especially true when moving production from one location to another.

Per the FDA guidance, "Studies to establish bioequivalence (BE) between two products are important for certain formulation or manufacturing changes occurring during the drug development and post approval stages. In BE studies, the exposure profile of a test drug product is compared to that of a reference drug product."

In this case study, the sponsor's closing of a manufacturing site required that one of its top-selling products be made at a different facility, triggering FDA to request they demonstrate BE on that product. FDA suggested the sponsor might be able to leverage Physiologically based Pharmacokinetics (PBPK) to demonstrate BE versus re-running the original BE study.

Simcyp had recently completed a grant for FDA's Office of Generics that focused on enhancing PBPK models for orally dosed drug products. One innovation in that research, Particle Population Balance (PPB) recognizes that each particle in a formulation can be different and that this type of heterogeneity can have an impact on drug dissolution. For the drug in this case, the particle size was bimodal and changed over time. Simcyp scientists were able to use PPB to account for the particle size differences from the drug being manufactured at site A and site B.

In addition to the particle size challenge, the drug itself has a complicated pharmacokinetic (PK) profile, including multiple PK peaks, enterohepatic recycling (HER) considerations and food effects. The Simcyp scientists used the Simulator to perform in vitro to in vivo extrapolation, simulate food staggering, and verify the model against the original BE clinical data.

Manufacturing Site Closure Requires the Establishment of BE Before Green-lighting Move to Alternate Production Location

The FDA accepted the Simcyp Simulator PBPK model in lieu of the clinical BE study, saving the company an estimated $500,000 and several months.