Certara's Simcyp PBPK Achieves First FDA Virtual Bioequivalence Approval for 'Complex' Generic Drug

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PRINCETON, NJ – June 12, 2019 – Certara® the global leader in model-informed drug development, regulatory science, real-world evidence and market access services, today announced that its Simcyp® physiologically-based pharmacokinetic (PBPK) modeling and simulation technology was used to demonstrate bioequivalence (BE) for the US Food and Drug Administration (FDA) approval of a complex generic drug on the agency's abbreviated new drug application (ANDA) pathway.

"This drug approval represents a breakthrough for the industry and will help usher in a new era in which complex generic drugs and treatments with alternative delivery methods and formulations can be brought to patients more quickly, without compromising their safety. This approach also benefits patients by supporting the FDA's mission to provide affordable quality products through increasing competition and extending the playing field," said Simcyp President and Managing Director Steve Toon, PhD.

"Virtual bioequivalence represents an ideal application for Simcyp's PBPK modeling and simulation capabilities. It is also an excellent addition to the many scientific and regulatory accomplishments that the Simcyp team has achieved during the past 20 years," said Certara Chief Scientific Officer Professor Amin Rostami. "This approval demonstrates the boundless opportunities for innovation using PBPK across the entire spectrum of new, alternative and reformulated drug products."

BE studies are conducted to ensure that the rate and extent of absorption of test drug products are not significantly different from that of the comparable reference drug products. Changes in the manufacturing process/site, raw material supplier or minor adjustments to the drug formulation, also require evaluation of BE to demonstrate that such changes do not substantially change its *in vivo* performance.

Virtual bioequivalence leverages advanced modeling and simulation to not only demonstrate BE, but also provide additional insight into drug performance. These *in silico* studies are safer (removing the need for drug administration to, often, young healthy volunteers), faster and less expensive to conduct than clinical BE studies and represent an important advance for generic and innovator drug companies alike.

Simcyp MechDermA Model

Certara's innovative research into the *in-silico* evaluation of bioequivalence and bioavailability has been actively encouraged by the FDA. For example, Certara's Simcyp division was awarded an FDA grant in 2014 to further develop and verify the Simcyp Simulator's Multi-Phase Multi-Layer Mechanistic Dermal Absorption model, MPML MechDermA, specifically to assess the bioequivalence of drugs absorbed through the skin, while also factoring in variability in specific populations. In 2016, Simcyp was awarded an additional FDA grant to create and verify a PBPK modeling and simulation framework to predict the behavior of complex, supersaturating drug products in the human body.

In 2018, the FDA awarded Simcyp two additional virtual BE grants, one of which focused on the inclusion of skin disease states in PBPK models to help pharma companies develop non-Q1/Q2/Q3 formulations and simulate *in-vivo* performance in patient populations to further support their substitutability in diseased skin. When evaluating BE, the FDA uses Q1 to define qualitative equivalence (test and reference products contain the same active and inactive ingredients), Q2 for quantitative equivalence (test and reference products contain the same amounts of active and inactive ingredients), and Q3 for physicochemical attributes of a specific dosage form.

In addition to the grants, Simcyp's Senior Principal Scientist and Head of the Dermatological Research Group Professor Sebastian Polak was invited to present at the FDA's topical dermatological generic drug products workshop in October 2017 on the "Development and Validation of Dermal PBPK Model towards Virtual Bioequivalence Assessment." MPML MechDermA was featured as the result of an FDA-supported research initiative that created an alternative approach to evaluate bioequivalence for topical dermatological generic drug products that was more efficient and reproducible.

Certara's Simcyp Simulator is the most sophisticated platform for determining first-in-human dose selection, designing more efficient and effective clinical studies, evaluating and advancing new drug formulations, and predicting drug-drug interactions and PK outcomes in numerous virtual clinical populations. These include vulnerable populations, such as pediatric patients, pregnant women, and patients with impaired organ function. The Simcyp Simulator has now been used to inform drug label claims, removing the need for specific clinical investigation, for more than 50 new drugs approved by FDA, the European Medicines Authority, and Japan's Pharmaceuticals and Medical Devices Agency.

About Certara

Certara enables superior drug development and patient care decision-making through model-informed drug development, regulatory science, real-world evidence solutions and knowledge integration. As a result, it optimizes R&D productivity, commercial value and patient outcomes. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions,

and key regulatory agencies across 60 countries. For more information, visit www.certara.com.

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