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Assessing the Impact of Genetic Polymorphisms and Drug-drug Interactions on Exposure

Is a Clinical Study Necessary?

A recent paper—authored by scientists working at the US Food and Drug Administration (FDA)—describes the development and validation of physiologically-based pharmacokinetic (PBPK) models to assess the impact of pharmacogenetics and polypharmacy on drug disposition

Background

PBPK modeling and simulation is gaining increasing acceptance due to the enormous cost and time saving benefits that can be realized through its ability to address regulatory concerns without always defaulting to clinical study — particularly relating to the assessment of complex drug-drug interactions (DDIs). Independent validation of simulations against clinical data provides confidence in the results and guides users in adopting best practices.

Challenge

Although dedicated clinical pharmacology studies can quantify the impact of certain intrinsic or extrinsic factors on drug exposure, it is often not feasible to investigate every possible scenario, especially when there is complex interplay between multiple factors. Demonstration of PBPK modeling capabilities to assess these risks requires robust evidence that simulations can accurately predict the impact of multiple factors and provide meaningful data for both drug developers and regulators.

Solution

Using the Simcyp Simulator, researchers from the US FDA created PBPK models for four substrates of the key drug metabolism enzymes, CYP3A4 and CYP2D6. The models were assessed on the potential to predict the effects of decreased enzyme activities on drug concentrations as a consequence of co-administered inhibitors and/or genetic variation. The team reported high predictive accuracy against the clinical data, concluding that models can be used to understand the effects of individual or combined factors and might be used to support decisions on whether, when and how to conduct a clinical trial.[1]

Challenge

To quantify the effects of multiple combined factors on drug exposure, without conducting clinical studies for every scenario.

Solution

Scientists working at the FDA analyzed the predictive performance of Simcyp PBPK modeling and simulation for four drugs, eliminated via multiple pathways, using 20 different DDI and pharmacogenetic studies.

Benefit

There was high predictive accuracy of the PBPK modeling, demonstrating its role in supporting decisions on whether, when and how to conduct clinical trials to determine the effects of DDIs and genetic polymorphisms on the pharmacokinetic of drugs in development.

Benefit

This study provides further validation of the value of PBPK modeling and simulation in prospectively assessing the effects of genetic polymorphisms or DDIs on pharmacokinetics.

Impact

Optimizing clinical trials improves patient safety and reduces the risk of late-stage "surprises" due to unanticipated DDIs. By identifying those less informative trials that can be avoided altogether, pharmaceutical companies could potentially save around $1-2 million per study and accelerate the time to market by as much as two years.

References

1. Vieira MD, Kim MJ, Apparaju S, Sinha V, Zineh I, Huang SM, Zhao P. PBPK model describes the effects of comedication and genetic polymorphism on systemic exposure of drugs that undergo multiple clearance pathways. *Clinical Pharmacology and Therapeutics*. 2014; 95(5):550-7.

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