Automated framework for global sensitivity analysis for the GastroPlus™ physiologically-based pharmacokinetic model

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Objectives: Develop a global sensitivity analysis to establish the critical model input influencing physiologically-based pharmacokinetic (PBPK) predictions by GastroPlus™ according to the Biopharmaceutical Classification System (BCS).

Methods: The capabilities of GastroPlus™, a commercially available PBPK software, were expanded by developing an integrated framework to perform an advanced global sensitivity analysis in MATLAB® and to control the GastroPlus™ graphical user interface with AutoIt. Morris’s screening method was implemented to analyze the behavior of GastroPlus™ for acetaminophen (BCS I), valproic acid (BCS II), propranolol (BCS III), and furosemide (BCS IV).

Results: Pharmacokinetic parameters tended to have greater significance than ACAT parameters for acetaminophen and valproic acid whereas ACAT parameters had a greater influence on propranolol and furosemide predictions (Figure 1). In all cases, the ACAT parameters showed decreasing sensitivity over time while pharmacokinetic parameters revealed increasing significance.

Conclusions: BCS I and II drugs are often associated with higher bioavailability whereas BCS III and IV drugs are associated with lower bioavailability due to the physiological implications of low solubility and permeability that limit dissolution and absorption from the gastrointestinal tract [1]. The Morris results reflected this behavior, revealing absorption and drug exposure were highly sensitive to gastrointestinal physiology for BCS III and IV drugs. In contrast, BCS I and II drug exposure were controlled by parameters related to drug distribution, metabolism, and elimination. Although more computationally expensive than a local sensitivity analysis, the Morris method informs model development and unveils the underlying physiology driving drug behavior in complex PBPK models, particularly when limited understanding is available about a drug and/or patient population of interest.

References: