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TITLE

COMBINING POPULATION-BASED MECHANISTIC MODELLING OF ORAL ABSORPTION AND PARAMETER ESTIMATION ALGORITHMS TO OBTAIN RELIABLE PREDICTIONS OF BIOAVAILABILITY

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The bioavailability of drugs from oral formulations is influenced by many physiological factors including gastrointestinal fluid composition, pH and dynamics, transit and motility, and metabolism and transport, each of which may vary with age, gender, race, food intake, and disease. Therefore, oral bioavailability, particularly of poorly soluble and/or poorly permeable compounds and those that are extensively metabolized, often exhibits a high degree of inter- and intra-individual variability. The Simcyp Advanced Dissolution Absorption and Metabolism (ADAM) model is a mechanistic predictive tool which, not only provides an estimation of bioavailability purely from in vitro data, but also offers an assessment of inter-individual variability. The detailed description of this model together with the structure of the whole platform has been previously published. ADAM is capable of describing absorption as a function of release from the formulation, dissolution, precipitation, luminal degradation, permeability, metabolism and transport as well as transit in each segment. The use of in vitro dissolution profiles, through in vitro – in vivo correlation (IVIVC), to predict bioavailability is a common practice which commonly involves deconvolution. As an alternative, a time-mapping function between in vitro and in vivo dissolution profiles can be used to predict in vivo concentration-time profiles; this requires a fitting tool. The Parameter Estimation (PE) module within the Simcyp Simulator is a powerful new fitting tool that bridges typical physiologically-based pharmacokinetic (PBPK) models and common POP-PK analysis of clinical data. In this presentation the ADAM model and PE module are described and practical examples of their simultaneous applications in drug and formulation development are demonstrated.