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### **In Vitro-In Vivo Extrapolation in PK from Known Knowns to Unknown Unknowns**

The *in silico* chemical and the virtual human are gradually being incorporated into the processes of drug discovery and development. In part, this trend is in response to the paradigm of 'high throughput screening' and an increasing use of human *in vitro* systems (e.g. liver microsomes, hepatocytes, expressed enzymes and transporters), creating large amounts of information that need to be integrated in parallel and subject to rapid and efficient extrapolation and scale-up. We have been developing algorithms and software incorporating demographic, physiological, genetic, enzymatic and other information that simulate and predict *in vivo* drug clearance and the extent of drug-drug interactions in populations of virtual patients (Simcyp®). A key feature of the approach is to identify the often complex mix of individual characteristics that predispose to extreme outcome. Complexities that have to be taken into account include the interplay between enzymes and transporters, irreversible (mechanism-based) enzyme inhibition, sequential gut and hepatic metabolism, the impact of genetic polymorphism, combined enzyme inhibition and induction and inter-ethnic and developmental aspects of ADME processes. The importance of variability in pharmacokinetics may be assessed by further linkage to pharmacodynamic models and clinical trials simulation.