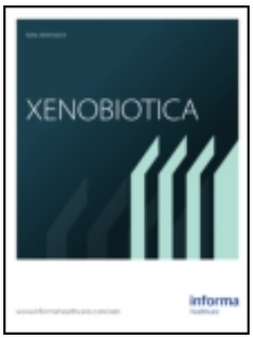

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Editorial

Modelling and simulation in prediction of human xenobiotic absorption, distribution, metabolism and excretion (ADME): *in vitro–in vivo* extrapolations (IVIVE)

Over the past three decades tremendous success has been gained in establishing various *in vitro* systems and connecting the output from such systems via different mechanistic models to *in vivo* consequences which should be expected for chemical entities upon administration to humans. Although many scientists are still within the confinement of simplistic/pragmatic cut-off approaches (such as desirable or undesirable values for solubility, metabolic stability, permeability, transporter affinity, receptor binding, etc.) in determining the suitability of new chemical entities for further development as a drug, the use and understanding of the value associated with more integrated modelling and simulation (M&S) approaches is gaining more recognition (Rostami-Hodjegan & Tucker 2007). These efforts can be seen as a parallel activity to attempts in other areas of science under the overarching umbrella of 'Systems Biology'. Thus, we may call quantitative *in vitro–in vivo* extrapolations (IVIVE) for characterizing absorption, distribution, metabolism and excretion (ADME) properties 'Systems Pharmacokinetics'; or when combined with the knowledge of receptors and pathophysiology, 'Systems Pharmacology'.

Inevitably, like any other evolving and active subject area, the interpretation and value of IVIVE efforts remain the subject of debate as the vital distinction between a useful 'simulation' and a precise 'prediction' is often not appreciated (Rostami-Hodjegan & Tucker 2004). However, it is also important to realize that as the applications of the models grow, many cases are identified where detailed knowledge of biological parameters of relevance to IVIVE are missing (we may call these 'known-unknowns' of the Systems Biology as applied to IVIVE). The current special issue of *Xenobiotica* focuses not only just on the models that are needed for M&S of IVIVE, but also on the efforts in gaining a better comprehension of the system and obtaining all the relevant biological values which helps with putting different pieces of the IVIVE jigsaw together.

In a recent commentary on the US Food and Drug Administration's (US FDA) Critical Path Initiative (Buckman et al. 2007), it was indicated that the task of incorporating new science into drug development requires the investment of all parties, including regulatory organizations, academia, and industry. The guiding principles of this type of initiative should be 'toolkit' development at a pre-competitive level rather than product-specific development to enable collaborations between different industrial partners. The papers comprising this special issue of the journal have been contributions from a number of distinguished speakers

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at four seminars in Philadelphia in Pennsylvania, USA (2006), in Basel, Switzerland (2006), in Baltimore, Maryland (2007), and Prague, Czech Republic (2007), sponsored by the Simcyp Consortium (http://www.simcyp.com). The consortium was formed in 1999 at the University of Sheffield in Sheffield, UK, addressing many of the objectives outlined in the US FDA's Critical Path Document (as applied to ADME). We are grateful for the opportunity that these seminars provided us to assemble a unique collection of valuable papers summarizing the status of IVIVE attempts in characterizing ADME and we hope readers will take advantage of this concise reference to the broad spectrum of activities in the area.

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