

Commentary

**Prediction of Human Pharmacokinetics in 2013 and Beyond**

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Running Title: In vitro-in vivo prediction

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Document Statistics:

Number of text pages:

Number of references: 19

Number of words-abstract: 132

**Abbreviations:** BDDCS, Biopharmaceutical Drug Disposition Classification System; DDI, drug-drug interaction; IVIVE, in vitro-in vivo extrapolation; P450, cytochrome P450; PBPK, physiologically-based pharmacokinetic; UGT, UDP-glucuronosyltransferase

## ABSTRACT

The utility of in vitro generated kinetic data to provide quantitative prediction of in vivo pharmacokinetic behaviour is well established and forms a corner stone of many research projects in Drug Metabolism and Disposition, particularly within the Pharmaceutical Industry. This issue provides several excellent examples of the use of in vitro techniques for prediction of human PK. The general area of in vitro-in vivo extrapolation (IVIVE) covers many aspects and hence the spectrum of topics covers various aspects drug clearance and distribution and drug-drug interactions. Some articles were commissioned whereas others were identified during the reviewing process. Overall they provide a snapshot of activity at the end of 2013. They document that whereas the translation of some in vitro approaches is now established, others are areas in their infancy needing more development.

Prediction of metabolic clearance is an example of a mature IVIVE area. Di et al., (2013a) provide here an overview of best practices illustrating wide application. It is dominated by examples of hepatic cytochrome P450 (P450) but application beyond P450 enzymes to UDP-glucuronosyltransferases (UGTs) and aldehyde oxidase are now evident. Clearance prediction, and IVIVE in general, is increasingly coupled with physiologically-based pharmacokinetic (PBPK) models to allow prediction not limited to specific parameters but to generate a time course which can further inform quantitative aspects of drug absorption, distribution, metabolism and excretion processes (as outlined here by Shardlow et al., 2013). The dynamic rather than static approaches with a time dimension rather than a time averaged estimate results in far more comprehensive usage of the in vitro data. An excellent example is contained in this issue (Xu et al., 2013) where the importance of CYP2B6 polymorphisms is explored in defining efavirenz clearance.

Prediction of transporter hepatic clearance is an area of great interest and contrasts markedly with the state of play with metabolic hepatic clearance. The complexity of this is becoming evident when delineating the interrelationships between not only enzymes and transporters but also between transporters and between transporters and passive processes is acknowledged (Parker and Houston, 2008; Yabe et al., 2011; Menochet et al., 2012). It would appear that multiple in vitro models are required, and to integrate these different sources of data requires PBPK modelling procedures. This and other aspects of best practices for transporter related parameter estimations and predictions have been collated by the International Transporter Consortium (Zamek-Gliszczynski et al., 2013).

The balance of active and passive processes in membrane transport of drugs is often helped by consideration of the Biopharmaceutical Drug Disposition

Classification System (BDDCS) (Wu and Benet, 2005). Here Kikuchi et al., (2013) review the evidence for the utility of the BDDCS in predicting brain penetration from in vitro derived P-gp efflux ratios.

A limitation of standard in vitro methodologies for obtaining drug clearance, whether metabolic or transporter mediated, is the relatively short lifetime of enzymes in the in vitro incubation. The particularly short time of microsomal incubations is one of several reasons why hepatocytes have become more widely employed. However even hepatocytes in traditional culture (suspension or monolayer) can only be useful for a few hours. The need to measure the metabolic clearance of low turnover drugs is becoming increasingly important with the design of new drugs which do not use the well characterised enzymes (P450 and UGTs). Hence the articles by Di et al., (2013b) and Chan et al., (2013) concerned with evaluating novel approaches to hepatocyte incubation which provide increased longevity for hepatocyte incubations should be of great interest to many.

The importance of the gut to clearance of certain drugs and also drug-drug interactions (DDIs) has been appreciated for some time. However the most useful way of building this in with liver has received limited attention. Karlsson et al., (2013) provide a useful analysis of the current position in this area.

Prediction of metabolic DDI has also been an IVIVE area that has been extensively studied. This has particularly benefitted from the use of PBPK and the availability of commercial software. We now appreciate the potential of metabolites' contributions to metabolic DDI and here Callegri et al. (2013) provide a retrospective analysis of this complexity. Fuelled by the regulatory adoption of Metabolites in Safety Testing (Smith and Obach, 2010), this has become routinely investigated. Ways in which we

can adapt existing models for parent drug perpetrator to include metabolites are explored here by Lutz et al., (2013).

Enzyme (particularly P450) induction as a DDI mechanism for increased clearance has received much attention. In contrast other mechanisms for increased clearance such as activation (for example through CYP3A4 allosteric effects) are less studied and regarded by many as purely an in vitro phenomenon. Blobaum et al., (2013) provide an interesting case example for in vivo relevance using a rat model which will lend itself to wider use to explore the wider application of this potential player in DDIs.

Beyond 2013 there is little doubt that the in vitro kinetics of transporters and the factors controlling intracellular drug concentrations will continue to be a major focus for achieving successful in vivo human prediction. Clearer understanding and maturation of approaches, both experimental and modelling, together with integration into the existing metabolic clearance and DDI strategies will be achieved to keep pace with the drugs of the future. As the in vitro toolbox continues to expand and PBPK models are refined, our ability to make valuable in vivo predictions of complex events from comparatively simple in vitro experiments will continue to grow and provide a holistic view of the processes involved in Drug Metabolism and Disposition.

## **Authorship Contribution**

Wrote or contributed to the writing of the manuscript: BH

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