An Evaluation of the Utility of Physiologically Based Models of Pharmacokinetics in Early Drug Discovery

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ABSTRACT: Generic physiologically-based models of pharmacokinetics were evaluated for early drug discovery. Plasma profiles after intravenous and oral dosing were simulated in rat for 68 compounds from six chemical classes. Input data consisted of structure based predictions of lipophilicity, ionization, and protein binding plus intrinsic clearance measured in rat hepatocytes, single measured values of aqueous solubility, and artificial membrane permeability. Log*P* of compounds was high with a mean of 3.9 while free fraction in plasma (mean 9%) and solubility (mean 37 μg/mL) were low. Predicted and observed clearance and volume showed mean fold-error and R^2 of 1.8, 0.56, and 1.9, 0.25 respectively. Predicted bioavailability showed strong bias to under prediction correlated to very low aqueous solubility and a theoretical correction for bile salt solubilization *in vivo* brought some improvement in average prediction error (to 31%). Overall, this evaluation shows that generic simulation may be applicable for typical drug-like compounds to predict differences in pharmacokinetic parameters of more than twofold based upon minimal measured input data. However verification of the simulations with *in vivo* data for a few compounds of each compound class is recommended since recent discovery compounds may have properties beyond the scope of the current generic models. J Pharm Sci 94:2327–2343, 2005

Keywords: pharmacokinetics; physiological model; simulations; computational ADME; absorption; GastroPlus; drug discovery

INTRODUCTION

During drug discovery, considerable resources are required to assess the pharmacokinetic properties of potential drug candidates *in vivo* in animals and there is interest in optimizing the use of such testing by applying simulation.[1–5] Physiologically based pharmacokinetic (PBPK) models take *in vitro* and *in silico* data inputs and can predict concentration versus time profiles before any *in vivo* experiment is performed. If sufficiently reliable, such simulations could decrease the turnaround time for delivery of information to medicinal chemists during the optimization phase and could also be used to prioritize compounds for the more costly *in vivo* testing. Equally importantly, the mechanistic framework provided by a PBPK model can integrate all available predictive data on a compound. Then, if comparison of simulation to *in vivo* data shows a large discrepancy, the need for further experiments to quantify additional processes may be indicated. Such integrative capabilities and mechanistic insights are not provided by the more commonly used noncompartmental or compartmental analysis and while pharmacokinetics in the rat is obviously not of ultimate interest for the pharmaceutical industry there is evidence that PBPK models are superior to other more empirical methods for interspecies scaling and prediction of human pharmacokinetics.[6,7]

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Thus a verified PBPK model in rat can be scaled to human to provide a basis for the rational selection of compounds for clinical development and if combined with a pharmacodynamic model allows prediction of the effective human dose.[6,7]

However, before such tools are routinely used they need to be extensively validated to define their accuracy and limitations. Here we assess the ability of generic PBPK models to predict plasma profiles in the rat for a set of 68 compounds taken from six chemical classes undergoing medicinal chemistry optimization in different drug discovery projects. The simulations are based upon minimal *in vitro* and *in silico* inputs such as are available at this early stage and the compounds were selected purely based on the availability of *in vivo* data. This study focuses on the practical utility of generic PBPK simulations and also discusses the required functionality of software for application in pharmaceutical drug discovery.

METHODS

Strategy

The steps taken are described below and are illustrated in Figure 1.

1. The data needed as input for the models are loaded into the simulation tools (experimental details are given below).
2. Use of the PBPK whole body disposition model involves:
   a. Prediction of model parameters using established *in vitro* to *in vivo* scaling for clearance and mechanistic models of tissue distribution (described below).
   b. Simulation of the concentration versus time profile of the compound after an intravenous bolus dose.
3. Simulation of plasma concentration versus time after an oral dose involves.
   a. Simulation of the absorption versus time with a PBPK model of the GI tract.
   b. Combining the predicted absorption with a compartmental disposition model fit to the simulated intravenous profile from 2b.
4. Comparison of simulated and observed plasma profiles and derived PK parameters.

Simulation of Disposition Profiles

A previously described whole body PBPK simulation tool has been developed for generic

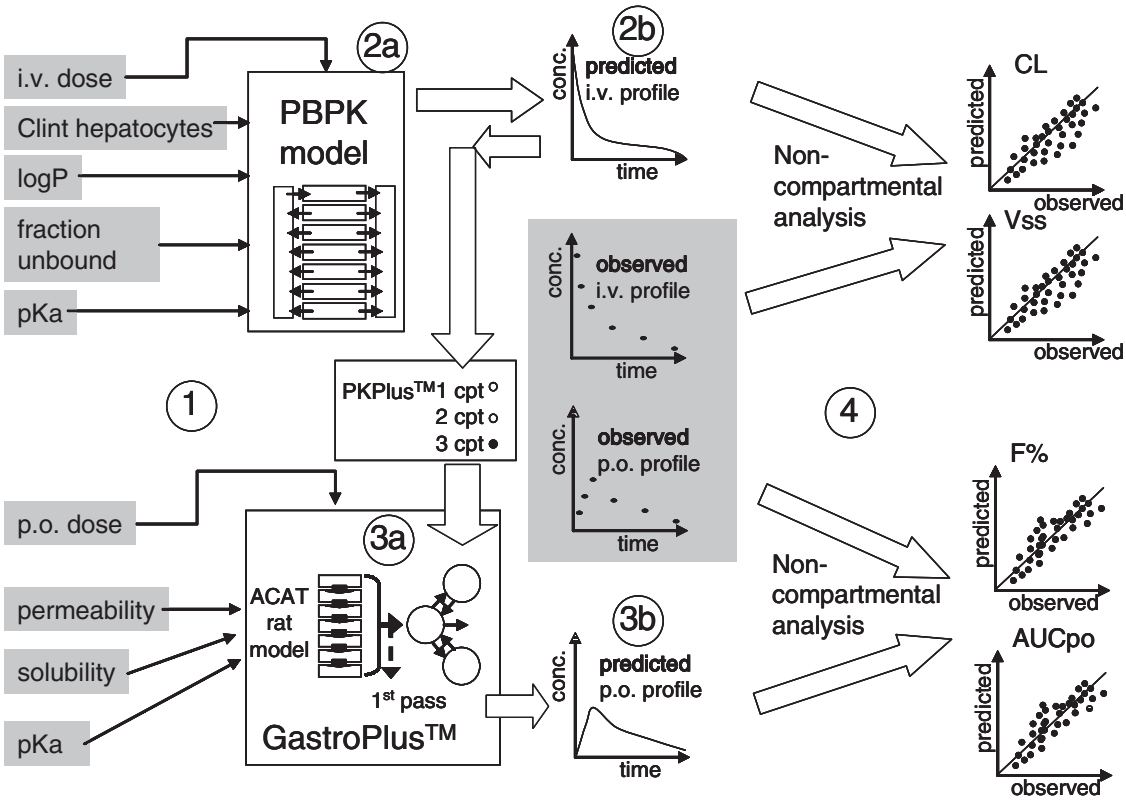

Figure 1. Steps taken in this evaluation.