Prediction of human intestinal metabolism of CYP3A substrates using the Advanced, Dissolution, Absorption and Metabolism (ADAM) Model

H.Misha1, M. Jamei1, K. Rowland-Yeo1, A. Rostami-Hodjegan1,2

1- Simcyp Ltd, Blades Enterprise Centre, John St, Sheffield, S2 4SU, UK
2- School of Pharmacy and Pharmaceutical Sciences, Manchester University, Manchester, UK

Objectives
To predict the fraction of dose escaping the gut first-pass metabolism (Fg) and its inter-individual variability using the ADAM model.

Introduction
Oral bioavailability (F) is defined as F = F2 × F3 × F4; where F2 is the fraction of the dose absorbed, F3 is the fraction escaping the intestinal first-pass metabolism; F4 is the fraction that escapes hepatic first-pass metabolism. For orally administered drugs, first-pass metabolism can be a limiting factor to get the desired bioavailability. As cytochrome P450 3A4 (CYP3A) comprise of a large percentage of intestinal CYP enzymes, CYP3A substrates are most affected by gut metabolism. However, at discovery stage, where metabolism of drug is not fully characterised & in absence of clinical data, Fg has to be predicted using pragmatic approaches such as the ‘Qgut’ model8, which combines the drug permeability (CLp_gut) and unbound gut intrinsic clearance (CLU_gut) which are estimated from appropriate in vitro systems.

Methods
The Advanced, Dissolution, Absorption and Metabolism (ADAM) model as implemented in Simcyp® Population-based Simulator® (v10) is used to predict the Fg values. The model divides the gut into nine anatomically defined segments from the stomach through to the intestine (Col) (Fig. 1). Drug absorption from each segment is described as a function of release from the formulation, dissolution, precipitation, luminal degradation, permeability, metabolism, gut-wall transport and transit from one segment to another.

Results
The predictions of ~55% of the studied compounds fall within 1.5 fold (and ~75% fall within two-fold, Fig. 2). The deviations are seen mostly (~80%) in compounds, with observed Fg values < 0.5. Using Simcyp data, the predictions for ~80% of the 11 compounds were within 1.5 fold. Fg for saquinavir and cyclosporine was over-predicted (Fig. 3).

Discussion
The Mean Fold Error (MFE) in predictions by the ADAM model was 1.68, slightly better than 1.84, for predictions by ‘Qgut’ model (Fg reported by Gertz et al.5). The Root Mean Square Error (RMSE) for both prediction sets was ~0.3. The predictions for the 11 compounds using Simcyp compound library data were better (MFE=1.3), when compared to same 11 compounds from the dataset generated by using ADAM model (MFE=1.38) and from reported data in Gertz et al.5 (MFE=1.64), using HIM2 CL_p_gut data, RMSE for all three datasets was ~0.2. The deviations (~25 % compounds, Fig. 2) in the predicted values of Fg might be due to a) the system used to determine the CLp_gut data i.e. the HIM2 system. As, although the clearance values were corrected for the CYP3A enzyme, activity in the ADAM model, the HIM2 system itself is not enzyme specific nor does it account for effect of transporters. b) Missing data for induction/inhibition effect of compounds such as, indinavir (CYP3A4 inhibitor), rifabutin (CYP3A4 inducer) or transporter data for compounds such as cyclosporine & saquinavir (both substrates for P-gp30).

In vivo, Fg can be estimated by conducting clinical studies involving concomitant administration of grapefruit juice with drug. It is known that furanocoumarins in grapefruit specifically inhibit intestinal CYP3A and not hepatic CYP3A4. So, a comparison of Area under the curve (AUC(oral)) after administration of the drug with and without grapefruit juice can provide Fg.

Reported Fg values for 25 compounds (Table 1) along with their CLp_gut values (measured in human intestinal microsomes system, prepared by elution method (HIM2), not reported here) were obtained from the review by Gertz et al.5. In vivo variability for Fg values for 15 out of the 25 compounds was calculated by meta-analysis & scrutinising the references of Gertz et al.5. These observed Fg values were compared against those predicted from ADAM model (with variability). Additional simulations were conducted using data from Simcyp compound library, for 11 out of the above mentioned 25 compounds, and Fg predictions (Table 1) for these were compared against the reported values5.

References
(1) Paine et al. 1997, JPET; 283:1552-62
(2) Yang et al. 2007, CDT; 8:676-84
(4) Greenblatt et al. 2003, CPT; 74:1219-9
(5) Gertz et al. 2010, DMD; 38: 1147-58
(6) Galatin & Houston 2006, JPET; 318:1220-29
(7) Kraft et al. 2004, JCP; 44: 305-13
(8) Lee et al. 2001, JCP; 41: 317-23
(9) Eagling et al. 1999, BJCP; 48: 543-52