

SUPPLEMENTARY FIGURE LEGENDS

Supplementary Figure 1. Observed and simulated fluoxetine and norfluoxetine plasma concentration versus time profiles. The simulated multiple dosing concentration versus time curves are shown in (A). The accuracy of the simulated multiple dosing accumulation was assessed by comparing the simulated data to single and multiple dosing data in the literature. Observed concentrations of fluoxetine and norfluoxetine enantiomers following a single dose of fluoxetine in CYP2D6 extensive metabolizers were within the 95% confidence interval of the predicted curve (38). (R)-fluoxetine and (R)-norfluoxetine are predicted to approach steady state by day 13 while the (S)-enantiomers are not, which is consistent with literature data (43). The observed versus predicted concentration versus time curves on day 12, following 12 daily doses of fluoxetine are shown in (B). Closed circles and error bars represent mean and standard deviation of observed values. Solid lines represent simulated values.

Supplementary Figure 2. Variability in simulated concentration versus time curves between separate trials. Shown are the day 1 and day 12 simulated concentration versus time profiles of dextromethorphan (A and D), omeprazole (B and E) and midazolam (C and F). The black circles and error bars represent the mean and standard error of the observed data. The grey lines represent the concentration versus time profiles in each of 10 trials and black lines represent the mean concentration versus time profile of the 10 trials. Each trial included 10 subjects.

Supplementary Figure 3. CYP3A4 activity in the liver and intestine in presence and absence of induction. The simulated percent of control CYP3A4 activity over time in the liver and intestine when only CYP3A4 inhibition is incorporated into the model is shown in A and B. The simulated percent of control activity in the liver and intestine when both inhibition and induction are incorporated into the model is shown C and D.