

Mechanistic PBPK simulation in place of in vivo drug-drug interaction (DDI) studies for compliance with regulatory requirements of EMA and FDA

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Purpose

To highlight the application and validation of PBPK DDI simulation results obtained using GastroPlus™ in compliance with newly proposed European Medicines Agency (EMA) and US FDA guidelines for the investigation of drug interactions.

Methods

Both EMA and FDA guidance documents specify the applicability of simulation results in regulatory submissions regarding special (e.g. pediatric) populations and for predicting the effect of complex drug-drug interactions (EMA, April 2010; FDA Guidance, 2006). The GastroPlus v.7.0 (Simulations Plus, Inc., Lancaster, CA) DDI Module was used in conjunction with its internal Population Estimates for Age-Related (PEAR™) Physiology to model the static and dynamic interactions between pairs of drugs, including their metabolites. The validation examples include: fluvoxamine interacting with omeprazole and its metabolites via CYP 3A4, 2C9, and 2C19 in extensive and poor metabolizers; fluvoxamine interacting with theophylline via CYP 1A2; fluoxetine and norfluoxetine interacting with alprazolam, desipramine, imipramine, amitriptyline, clozapine, tolterodine, and propafenone via CYP2D6; ketoconazole interacting with alprazolam, loratidine, midazolam, nisoldipine, sirolimus, tacrolimus, and triazolam via CYP3A4; and quinidine interacting with atomoxetine via CYP2D6 in extensive and poor metabolizers.

Results

We developed extensive data on the validation of DDI simulations in support of the ability to quantitatively predict drug-drug interactions via inhibition of specific enzymes. The validation set of drugs included a large number of inhibitors for which high quality *in vitro* data were available. Most DDI predictions (expressed as AUC ratios) for these examples were accurate to within 30% of the values observed *in vivo*.

Conclusions

Regulatory guidance documents suggest the application of modeling and simulation in support of waivers for *in vivo* DDI studies. The GastroPlus DDI module and PEAR physiology have been demonstrated to provide accurate predictions of known drug-drug interactions involving Cytochrome P450 enzymes with and without taking polymorphic expression into consideration.

For more detail on theophylline and cilostazol as substrates and diltiazem as an inhibitor, please visit the following posters at this conference. Observed vs. Predicted AUC Ratios for Various Substrates
Poster #: T2374, T2375, and T2365.

The GastroPlus (Version 7.0) Drug-Drug Interaction Module was used to predict the severity of drug-drug interactions based mostly on equations for steady-state competitive inhibition. The theophylline and cilostazol studies were based on dynamic simulations for competitive inhibition, while studies with diltiazem as the inhibitor were based on dynamic simulations with time-dependent inhibition. The largest outlier was a study of midazolam's interaction with diltiazem. For this model we considered deactivation of 3A4 by both diltiazem and its metabolites. One explanation for the over-prediction of AUC ratio would be if the turnover of 3A4 was faster than the default value of $5 \times 10^{-4} \text{ min}^{-1}$ reported in the literature. Since this poster is focused on prediction and not parameter fitting we are reporting the results without changing turnover rate.

The inhibitor concentrations in gut (I_g) and liver (I_l), fraction of total clearance due to metabolism by individual enzymes (f_m), and fraction of drug that escapes intestinal metabolism (F_g) were calculated by the simulation. The severity of the drug interaction is classified by the FDA using the change in area under the curve (AUC) due to coadministration with the inhibitor (strong inhibitor > 5 fold, moderate inhibitor 2-5 fold, and weak inhibitor 1.25-2 fold increase in AUC).

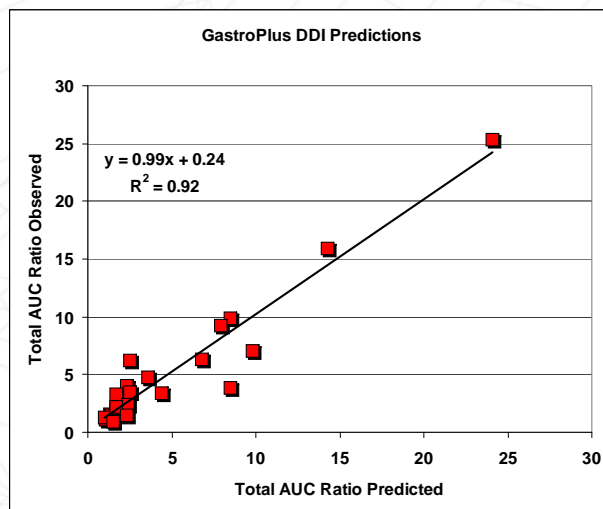


Table of results for predictive DDI studies.

Substrate	Inhibitor	Enzyme	Simulated AUC Ratio Gut	Simulated AUC Ratio Liver	Simulated Total AUC Ratio	Observed AUC Ratio	Class
Omeprazole	Fluvoxamine	2C19 Poor		1.4	1.4	1.23	Weak
Omeprazole	Fluvoxamine	2C19 Exten.		1.7	1.7	2.08	Weak
Theophylline	Fluvoxamine	1A2		1.6	1.6	2.0	Weak
Alprazolam	Fluoxetine Norfluoxetine	2D6		1.0 1.1	1.1	1.1	Weak
Alprazolam	Ketoconazole	3A4	1.0	2.3	2.3	4.0	Moderate
Desipramine	Fluoxetine Norfluoxetine	2D6		2.6 5.6	6.8	5.3-7.4	Strong
Imipramine	Fluoxetine Norfluoxetine	2D6		1.4 1.7	1.7	3.3	Moderate
Amitriptyline	Fluoxetine Norfluoxetine	2D6		1.5 1.6	1.7	1.8	Weak
Clozapine	Fluoxetine Norfluoxetine	2D6		1.2 1.3	1.3	1.6	Weak
Tolterodine	Fluoxetine Norfluoxetine	2D6		1.4 3.2	3.6	4.8	Moderate
Propafenone	Fluoxetine Norfluoxetine	2D6		1.2 1.3	1.4	1.5	Weak
Loratidine	Ketoconazole	3A4	1.2	2	2.5	3.5	Moderate
Midazolam	Fluconazole	3A4	2.2	2.0	4.4	3.4	Moderate
Midazolam	Ketoconazole	3A4	2.4	5.9	14.3	15.9	Strong
Midazolam	Itraconazole	3A4	2.4	1.0	2.5	6.2	Strong
Midazolam	Diltiazem	3A4	1.7	5.0	8.5	3.8	Moderate
Nisoldipine	Ketoconazole	3A4	7.6	3.2	24.1	25.3	Strong
Sirolimus	Ketoconazole	3A4	2.4	3.5	8.5	9.9	Strong
Tacrolimus	Ketoconazole	3A4	1.5	1.7	2.4	2.4	Moderate
Triazolam	Ketoconazole	3A4	2.1	3.8	7.9	9.2	Strong
Atomoxetine	Quinidine	2D6 Exten.		9.8	9.8	6-8	Strong
Atomoxetine	Quinidine	2D6 Poor		1.5	1.5	1.0	Weak
Cilostazol	Omeprazole	3A4	1.0	1.0	1.0	1.3	Weak
Cilostazol	Quinidine	3A4	1.0	1.5	1.5	0.9	Weak
Cilostazol	Ketoconazole	3A4	1.1	1.6	1.7	2.2	Moderate
Quinidine	Diltiazem	3A4	1.0	2.3	2.3	1.5	Weak

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