2023 DDI Standards Model Update

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Please note: this presentation, including questions from the audience, is being recorded and may be made available.

SimulationsPlus MIDD Model Informed Drug Development + 2023

SimulationsPlus

Outline

- **GastroPlus® DDI Module overview**
- DDI Standard Model development process
- Standard Model Examples
- Case Studies/Examples

GastroPlus DDI Module - Interaction Types

- Steady-state competitive inhibition
- Steady-state time-dependent inhibition
- Steady-state induction

(may include metabolites effect with simulated perpetrator concentrations)

- Dynamic competitive inhibition
- Dynamic time-dependent inhibition
- Dynamic induction

(include effect of parent and/or metabolites; include enzymes and transporters)

Steady-State Prediction - Equation

contribution of gut to DDI

$$\frac{AUC_{PO}^{inh}}{AUC_{PO}} = \frac{1}{F_g + (1-F_g)\cdot\left(\sum_{E=1}^{NumEnzymes} \frac{fm_E^g \times \left(1+\frac{E_{max}\times I_g}{EC_{50}+I_g}\right)}{\left(1+\frac{I_g}{Ki_E^{rev}}\right)\times\left(1+\frac{k_{inact,E}\times I_g}{k_{deg,E}^g\times\left(Ki_E^{irrev}+I_g\right)}\right)} + fm_{other}^g\right)}$$

contribution of liver to DDI

$$\times \frac{1}{\left(\sum_{E=1}^{NumEnzymes} \frac{fm_E^L \times \left(1+\frac{E_{max}\times I_L}{EC_{50}+I_L}\right)}{\left(1+\frac{I_L}{Ki_E^{rev}}\right)\times\left(1+\frac{k_{inact,E}\times I_L}{k_{deg,E}^L\times\left(Ki_E^{irrev}+I_L\right)}\right)} + fm_{other}^L\right)}$$

For clarity, effect of only one inhibitor/inducer is shown in the equation, but with the use of *simulated* concentrations, the effects of parent compound as well as its metabolites (if they have an effect and their constants are specified) can be included.

Wang Y-H., Drug Metab Dispos 2004, 32:259-266
Galetin A., Drug Metab Pharmacokinet 2010, 25:28-47

Steady-State Prediction - Required Inputs

1. f_m and F_g values for substrate (victim)
2. K_i (or IC_{50}) for inhibitor
3. K_{inact} [min^{-1}] for inhibitor for time-dependent inhibition
4. EC_{50} and E_{max} for inducer
5. Enzyme turnover rate (k_{deg} [min^{-1}]) for time-dependent inhibition
6. Inhibitor/inducer (perpetrator) concentration:
   a. Number of different calculated and simulated inhibitor/inducer concentration estimates are available
   b. Full PK model is required for simulated inhibitor/inducer concentration
   c. Additional inputs required for calculated inhibitor/inducer concentrations (Fa, FDp, F, k_a, k_{el}, etc.)

fm - fraction of total gut or total systemic clearance attributed to given enzyme
Fg – fraction of the dose that escapes gut metabolism
Default k_{deg} values for CYPs are included in program

Steady-State – Perpetrator Concentrations

DDI Module within GastroPlus offers number of ways to obtain 'effective' perpetrator concentration for prediction under steady-state assumptions

Calculated perpetrator concentrations are obtained from standard equations:

Systemic Average

$$[I]_{av} = \frac{D/\tau}{CL/F}$$

Systemic Cmin

$$[I]_{min} = [I]_{max} \times e^{-k_e \tau}$$

Systemic Cmax

$$[I]_{max} = \frac{[I]_{av} k_{el} \tau}{1 - e^{-k_{el} \tau}}$$

Liver Inlet

$$[I]_{in} = [I]_{av} + \frac{k_a \times FDp \times D}{Q_h}$$

Gut

$$[I]_g = \frac{k_a \times F_a \times D}{Q_e}$$

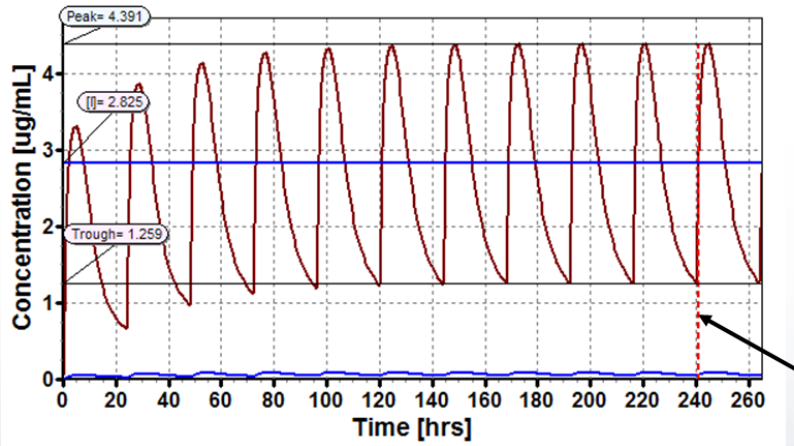
Corresponding unbound concentrations are calculated as:

$$[I]_U = [I] \times \frac{F_{up}[\%]}{100}$$

D-dose, τ-dosing interval, *CL*-clearance, k_{el}-elimination rate constant, k_a-absorption rate constant, *Fa*-fraction absorbed, *FDp*-fraction of dose getting to portal vein, *F*-bioavailability, Q_h-liver blood flow, Q_e-enterocytic blood flow, $F_{up}[\%]$ – percent of drug unbound in plasma

Ito K. Br J Clin Pharmacol 2004, 57(4): 473-486

Simulated perpetrator concentrations are obtained from simulated profile for perpetrator using full absorption and PK model saved in the database:



Dynamic Simulation – Equations

Competitive Inhibition

$$v = \frac{EnzAct_0 \times V_{max} \times [S]_u}{K_m\left(1 + \sum_{j=1}^{N} \frac{[A]_{u,j}}{K_{m,j}} + \sum_{i=1}^{M} \frac{[I]_{u,i}}{K_{i,j}}\right) + [S]_u}$$

Time-Dependent Inhibition & Induction

$$v = \frac{EnzAct_t \times V_{max} \times [S]_u}{K_m\left(1 + \sum_{j=1}^{N} \frac{[A]_{u,j}}{K_{m,j}} + \sum_{i=1}^{M} \frac{[I]_{u,i}}{K_{i,j}}\right) + [S]_u}$$

$$\frac{dEnzAct}{dt} = -\left(\sum_{t=1}^{TDI} \frac{k_{inact,t} \times [I]_{u,t}}{K_{i,t}\left(1 + \sum_{\substack{n=1 \\ n \neq t}}^{TDI} \frac{[I]_{u,n}}{K_{i,n}}\right) + [I]_{u,t}}\right) \times EnzAct + k_{\deg}\left(EnzAct_0 - EnzAct\right)$$

$$+ k_{\deg} \times EnzAct_0 \times \sum_{d=1}^{inducers} \frac{E_{\max,d} \times [I]_u}{EC_{50,d} + [I]_u}$$

Dynamic DDI Simulations – Required Inputs

1. K_i (or IC_{50}) for each inhibitor
2. K_{inact} [min^{-1}] for each time-dependent inhibitor
3. EC_{50} and E_{max} for each inducer
4. k_{deg} [min^{-1}] each enzyme's/transporter's turnover rate for time-dependent inhibition and induction (GastroPlus provides these for CYPs)
5. Full PK models for perpetrator and victim by themselves
6. (compartmental or PBPK, the same type of model required for both)
7. Only drug-dependent properties need to be adjusted for each compound in the system – physiological properties are the same

NOTE: The physiology for the current record will be used for both compounds

Dynamic DDI Simulations

Dynamic simulation makes no assumptions or simplifications beyond those already included in the PK models of interacting compounds:

- Need to build compartmental or PBPK model for victim and perpetrator.
- Accounts for interaction in **any tissue**
- Accounts for **competition between multiple substrates** of the same enzyme/transporter and for a possible effect of 'substrate' on 'inhibitor'/'inducer'
  - NOTE: if multiple compounds in the system have specified K_m and V_{max} values for the same enzyme/transporter, their competition for the binding sites of that enzyme/transporter will be accounted for using $K_i = K_m$
- Accounts for **competition between multiple irreversible inhibitors** for the binding to enzyme
- Accounts for possibility of **perpetrator acting as inhibitor and inducer** at the same time
- Default physiological parameters (expression levels, turnover rates) are available for CYP enzymes, but any enzyme/transporter may be included if user knows relevant parameter values

DDI Module –PBPK Models in various stages of validation: Probe Substrates, Inhibitors, and Inducers

Alfentanil	Dolutegravir	Metformin	Rifampicin	Warfarin
Atazanavir	Efavirenz	Midazolam	Rivaroxaban	
Atomoxetine	Fexofenadine	Omeprazole & Metab.	Rosiglitazone	
Bupropion	Fluconazole	Phenytoin	Rosuvastatin	
Caffeine	Fluvoxamine	Posaconazole	Theophylline	Atorvastatin
Cyclosporine	Gemfibrozil & glucuronide	Pravastatin	Tolbutamide	Simvastatin
Desipramine	Imipramine	Quinidine	Triazolam	
Digoxin	Itraconazole &Metab.	Raltegravir & Metab.	Verapamil	
Diltiazem & Metab.	Ketoconazole	Repaglinide	Voriconazole	

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- **DDI Standard Model development process**
- Standard Model Examples
- Case Studies/Examples

DDI Module –PBPK Models in various stages of validation: Probe Substrates, Inhibitors, and Inducers

Model building process for DDI Standards

- Literature collection complete and collated in spreadsheet
- Model building and validation of compound alone
- Validation for DDI mechanisms
- Reporting

The models are updated as new information becomes available in public domain

As we are prioritizing next batch of DDI standards to build and/or update, we welcome your feedback on compounds that would be most important for your projects.

Outline of Process for Model Development and Documentation

- Physicochemical, biopharmaceutical, and biochemical properties
- Initial evaluation via “Chemistry Classification” with all aspects of ADMET
- Extensive literature collection and spreadsheet documentation.
- First simulations for “Measured Properties” with parameter sensitivity analysis.
- Model building for individual substrate and/or perpetrator simulations compared to observed data for single escalating doses (for nonlinear dose dependence), multiple dosing (for autoinhibition / autoinduction).
- DDI simulations for all appropriate mechanisms on both substrate and perpetrator.
- Analysis of results using the “Guest”* criterion for different levels of accuracy cutoff for increasing AUC (inhibition) and decreasing AUC (induction).
- Preparation of slides and written reports suitable for regulatory submission.

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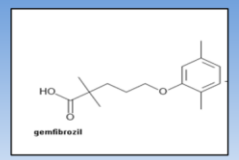
Initial *in silico* Evaluation

Gemfibrozil BCS II Physicochemical Properties



MW = 250.34

S+LogP = 4 (AP 10.0)
Exp LogD (Octanol/H2O) @ pH7.4 = 2.8 (Luner et. al., Pharm. Res.11(12):1755 (1994)
NOTE: Changed LogD (7.4) = 0.8 to calculate Kps then changed back to 2.8 to run simulations.

S+pKa = 4.92 (Acid) (AP 10.0
Exp pK

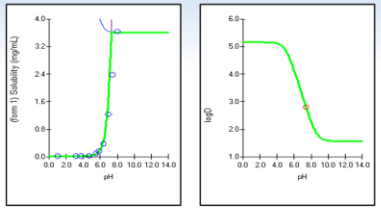
S+Sw =
Exp Sw
S+Solu
S+FaSS
Exp Fas

S+Peff
Caco-2
Caco-2
Caco-2

S+hum
Exp. Fu
S+RBP
Exp Rb

S+Enzy
UGT2B1
S+Trans
Exp Enz
Exp Tra

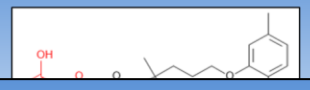
S+Enzy
S+Trans
Exp Enz



Estimated Solubility Factor after fitting pH
Vs solubility profile = 156.9
Adjusted Sol factor = 180

AP 10.0 = ADMET Predictor v. 10.0
S+ = properties predicted with Simulations Plus models
S+Sw = native solubility in pure water
S+Peff = human jejunal permeability estimate
N.A = Not Available

Gemfibrozil Glucuronide Physicochemical Properties



S+LogP = 1.67(AP 10.0)
Exp LogD (Octanol/H2O) @ pH7.4
Exp log P extrapolated from Log D

mg/ml

acol. Exp.Ther. 311(1):228(2004)
correct the Vdss for glucuronide

P1B1(99%), OATP1B3(93%), OAT1(65%), OAT3(97%), OCT1(76%)
r influx), OAT3 (kidney influx), MRP2 (liver-bile efflux), MRP3 (liver-
ux)

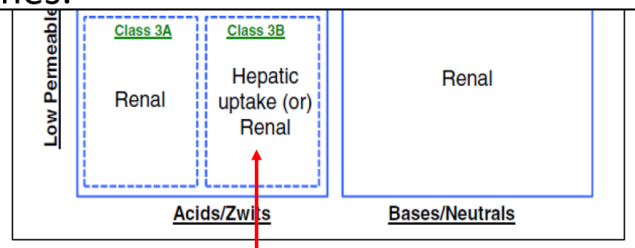
A4(42%)

Conclusions and Recommended Testing Based on *in silico* properties

- Low solubility in stomach probably won't reduce bioavailability but may result in slow dissolution and longer T_{max}.
- Low MWt, high permeability, and acidic pKa of parent GEM suggest mainly metabolic clearance by Phase I (2C9 and 2C19) and Phase II (UGT1A3 and UGT2B7) enzymes.
- AP10.0 transporter module suggests possible liver and kidney influx.
- High MWt, low permability, and acidic pKa of GEM-glucuronide suggests systemic clearance by hepatic and renal influx.
- Both parent and glucuronide metabolite may be involved in DDI inhibition of enzymes.

Gemfibrozil AP10.0 Transp

- Transporter Substrate Classific
  - **OATP1B1-Substrate=Yes (99%);** OATP1B3-Substrate=No
    Substrate=Yes (74%); OAT1-Substrate=Yes (87%); OAT3-
    BCRP-Substrate=No (95%);
- Transporter Km Values:
  - OATP1B1-Km=24.62uM; OATP1B3-Km=66.47uM; OCT1-
    Km=25.48uM; OAT3-Km=122.11uM;
- Transporter Inhibitor Classification:
  - OATP1B1-Inhibitor=No (54%); OATP1B3-Inhibitor=No (96%); OCT1-Inhibitor=No (77%); OCT2-Inhibitor=No (99%); **OAT1-Inhibitor=Yes (95%); OAT3-Inhibitor=Yes (76%);** Pgp-Inhibitor=No (96%); BSEP-Inhibitor=No (66%); BCRP-Inhibitor=No (97%);
- Transporter IC50 Values:
  - BSEP-IC50=48.26uM;



GEM-glucuronide S+CL_Mech = Hepatic Uptake

de AP10.0 Transporter Classification

Classification:

3-Substrate=Yes (92%); OCT1-Substrate=Yes (76%); OCT2-
es (65%); OAT3-Substrate=Yes (97%); Pgp-Substrate=Yes (99%); BCRP-

S:

4.53uM; OCT1-Km=6.99uM; OCT2-Km=2.99uM; OAT1-Km=24.36uM;

- Transporter Inhibitor Classification:
  - OATP1B1-Inhibitor=No (54%); OATP1B3-Inhibitor=No (49%); OCT1-Inhibitor=No (89%); OCT2-Inhibitor=No (99%); OAT1-Inhibitor=No (94%); OAT3-Inhibitor=No (83%); Pgp-Inhibitor=No (96%); BSEP-Inhibitor=No (99%); BCRP-Inhibitor=No (97%);
- Transporter IC50 Values:
  - BSEP-IC50=41.79uM;

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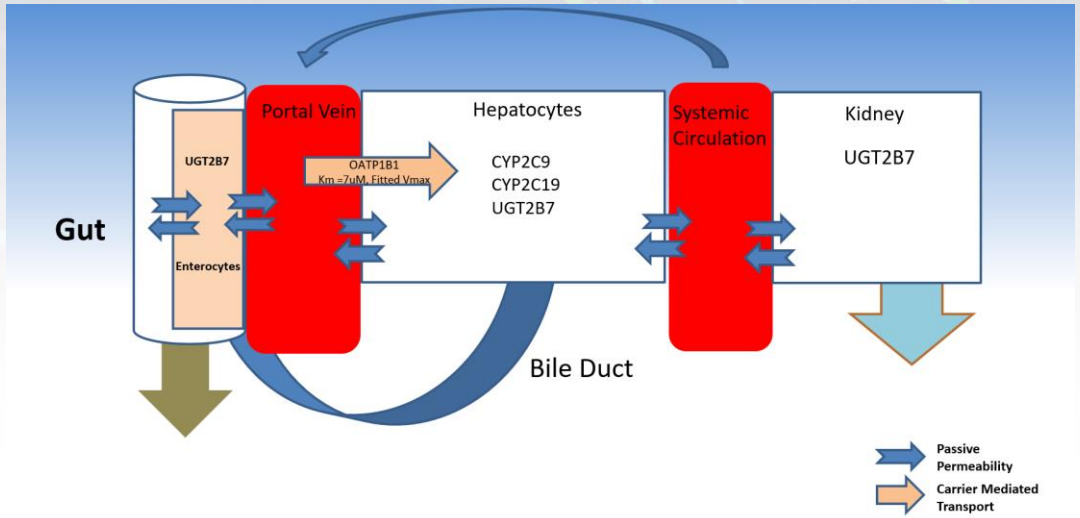
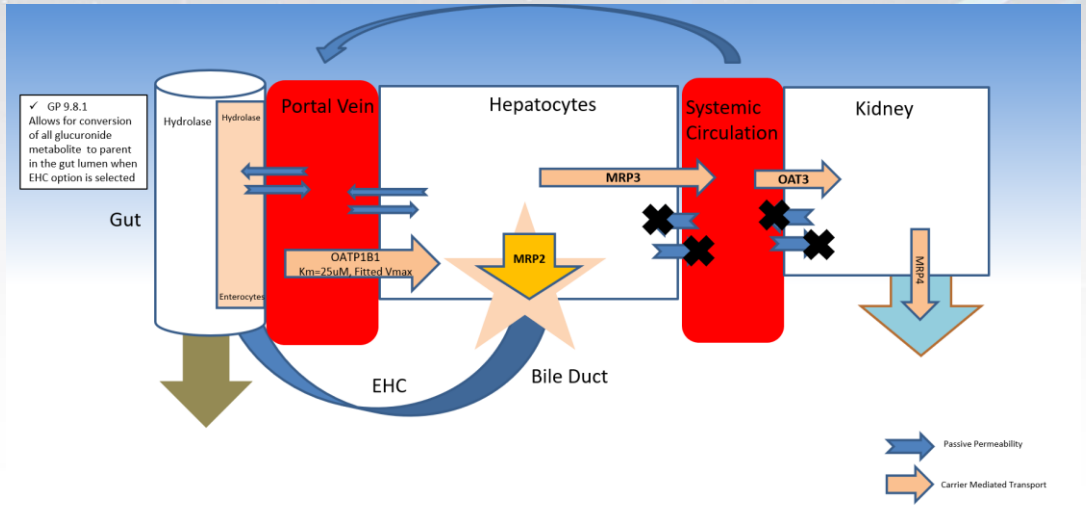
Build and Validate PK Model with All Relevant Mechanisms





Parent- Gemfibrozil

Metabolite- Gemfibrozil Glucuronide

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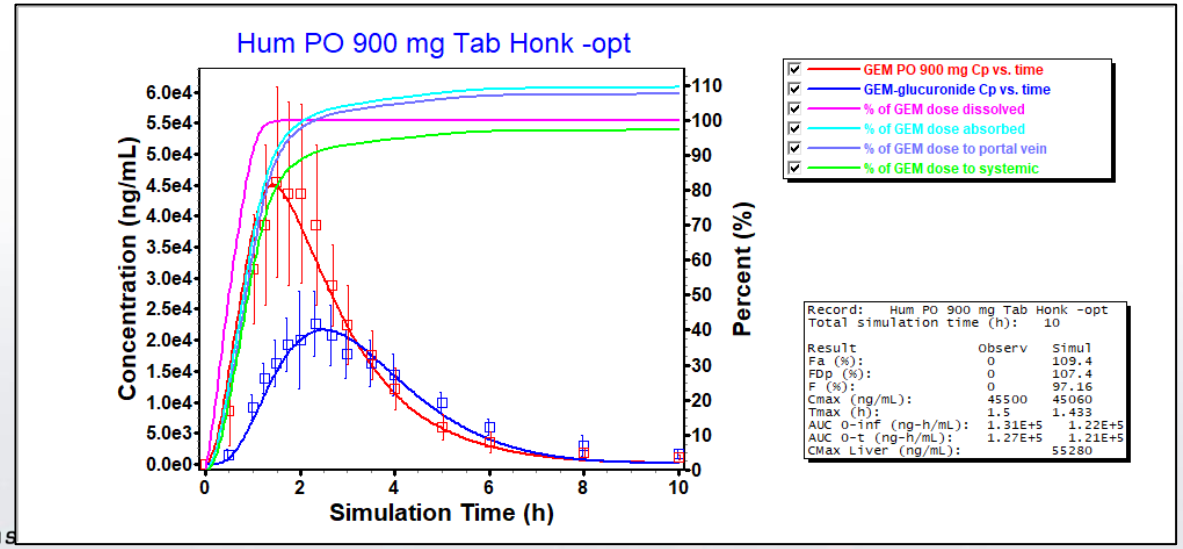

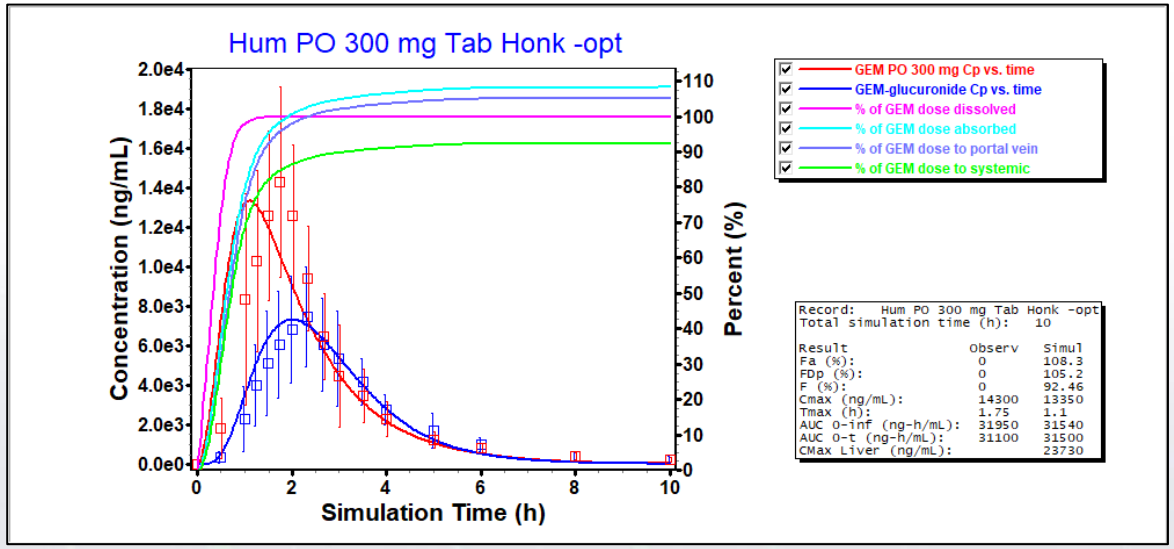

The model describes pharmacokinetics under different administration conditions (only two studies shown here)

Validate Model for DDI Predictions

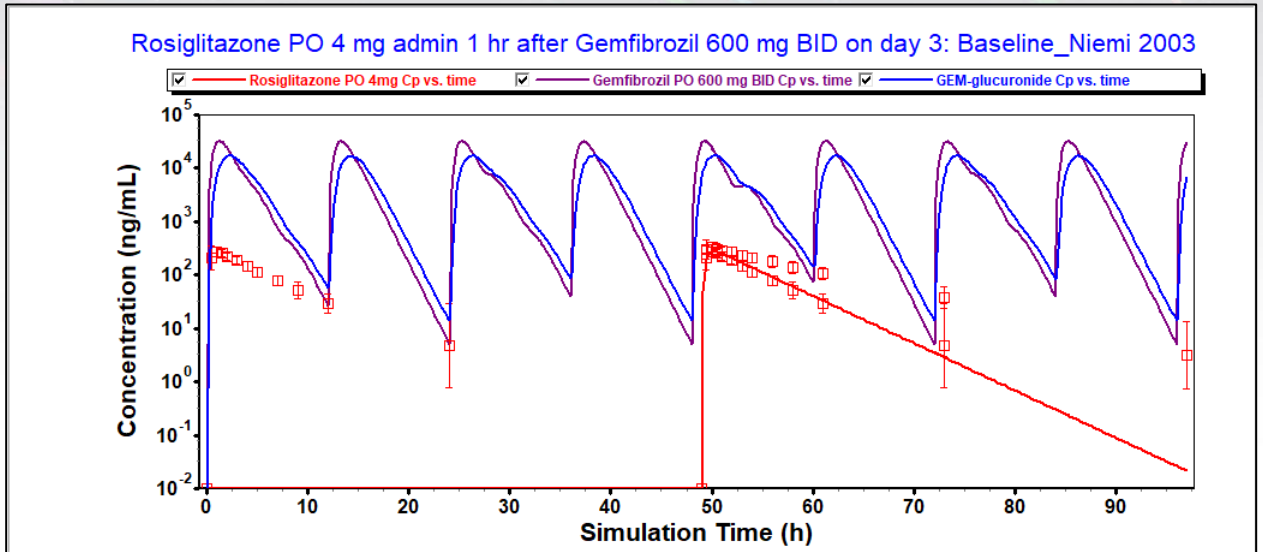

Table 9. DDI Simulation with Rosiglitazone: Comparison of Simulated and Observed PK Parameters of Rosiglitazone with or without Gemfibrozil (Strong CYP2C8 Inhibitor)

Reference	Perpetrator	PK Parameter	C_{max} (ng/mL)	$AUC_{(0-9)}$ (ng*h/mL)	$AUC_{(0-inf)}$ (ng*h/mL)
(Niemi et al. 2003)	Gemfibrozil and Gemfibrozil glucuronide	Observed baseline#	285 ± 50	1554 ± 336	1556 ± 368
		Simulated baseline	278	1689	1690
		Observed DDI #	349 ± 94	3499 ± 1001	3563 ± 1054
		Simulated DDI	322	3577	3605
		Observed DDI ratio#	1.2	2.3	2.3
		Simulated DDI ratio	1.2	2.1	2.1
		GUEST Limits for DDI ratios (LL-UL)	(0.88-1.69)	(1.35-3.75)	(1.37-3.83)

Guest (Guest et al. 2011) Criteria limits (i.e., lower limit and upper limit) for DDI ratios are highlighted in green

The model predicts DDI from different studies (only one study shown here)

Eleanor J. Guest et al. DMD, 39(2):170 (2011)

Materials and Methods

The traditional two-fold predictive measure is bounded two-fold above and below the observed value: any prediction within these boundaries is classed as a successful prediction (see Fig. 1). Therefore, if the observed ratio, $AUC_{+inhibitor}/AUC_{control}$, is 1, the boundaries would be from 0.5 to 2.0. As noted in the *Introduction*, this range is too wide for an interaction, which is in fact not present. As a result, we propose new limits, as shown in eqs. 1 to 3 below. The limits coalesce when the observed ratio is 1 and approach the traditional two-fold limits as the ratio becomes larger (Fig. 1).

$$\text{Upper limit: } R_{obs} * \text{Limit} \quad (1)$$

$$\text{Lower limit: } R_{obs}/\text{Limit} \quad (2)$$

$$\text{Limit} = \frac{1 + 2(R_{obs} - 1)}{R_{obs}} \quad (3)$$

where R_{obs} represents $AUC_{+inhibitor}/AUC_{control}) \geq 1$, i.e., in the case of inhibition DDIs. The new predictive measure is also applicable for induction

To allow for uncertainty in the observed ratio, the impact of variability was assessed by considering DDIs involving midazolam; a commonly used CYP3A4 victim drug (Bjornsson et al., 2003; Galetin et al., 2005). In this case, upper and lower limits are as defined in eqs. 1 and 2, respectively, but the variability is now introduced into the limit as shown in eq. 4.

$$\text{Limit} = \frac{\delta + 2(R_{obs} - 1)}{R_{obs}} \quad (4)$$

where δ is a parameter that accounts for variability. If $\delta = 1$, there is no variability and limits revert to those defined by eq. 3. If $\delta = 1.25$ and $R_{obs} = 1$, then the limits on R are between 0.80 and 1.25, corresponding to the conventional 20% limits used in bioequivalence testing (United States Food and Drug Administration, 2003). Note that these limits are symmetrical on the

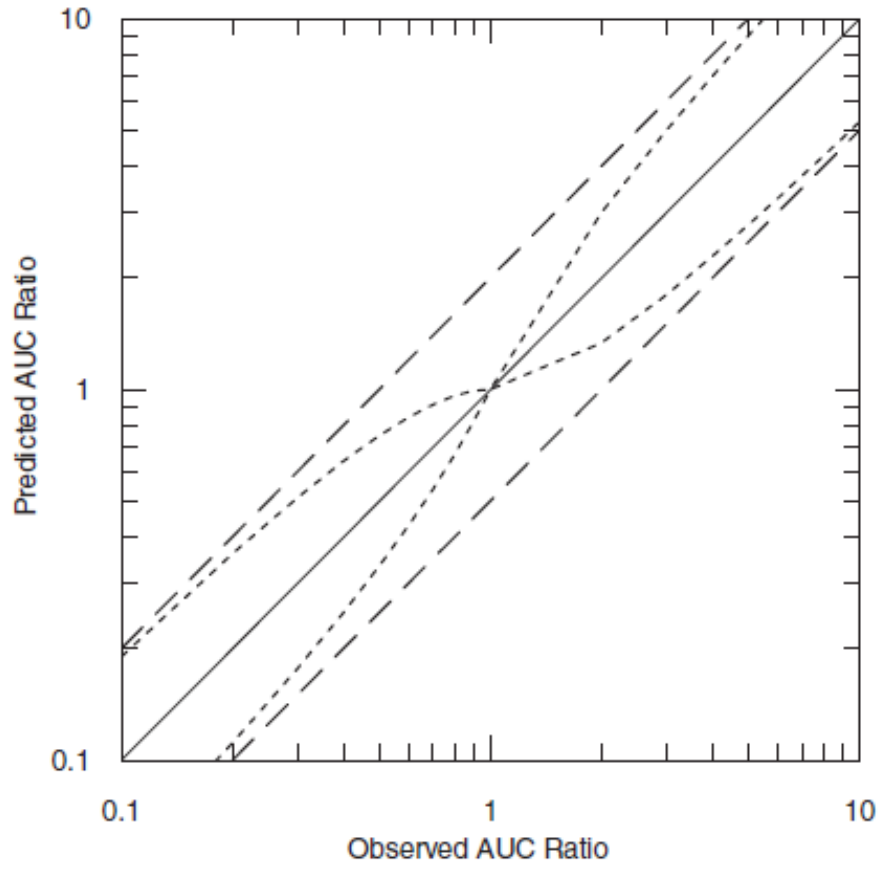

FIG. 1. Schematic graph displaying the limits of the different predictive measures; the traditional two-fold predictive measure (dashed lines) and the proposed new predictive measure (dotted lines). Observed AUC ratios include both induction and inhibition DDIs.

Written Report of Model Development and Validations

Development of a whole-body PBPK model of perpetrator and metabolite pair of gemfibrozil and its glucuronide and model validation with known drug-drug interactions (DDIs) (repaglinide and rosiglitazone)

Saima Subhani, Haiying Zhou, Viera Lukacova, Michael B. Bolger

1. Introduction

A physiologically based pharmacokinetic (PBPK) model for gemfibrozil (GEM) and its major glucuronidation metabolite gemfibrozil-1-O-β-glucuronide (GEM-glucuronide, or glucuronide) was built in GastroPlus® version 9.8.1003 (Simulations Plus, Inc.) and was validated by predicting known DDIs with repaglinide and rosiglitazone.

The PBPK model accounts for GEM metabolism by UGT2B7, UGT1A3, CYP2C9, and CYP2C19 and carrier-mediated hepatic uptake by OATP1B1. Hepatic disposition of the GEM-glucuronide was incorporated into the model by the addition of transporters MRP2 (hepatic secretion into the bile), MRP3 (hepatic basolateral efflux), and OATP1B1 (hepatic basolateral uptake). Renal disposition of GEM-glucuronide was modeled by the addition of carrier-mediated basolateral uptake into the kidney via OAT3 as well as apical efflux into the urine through MRP4.

The model was developed to capture the different *in vivo* mechanisms involved in the absorption, distribution, metabolism, and elimination of GEM and GEM-glucuronide. The model includes transporter- and enzyme-related mechanisms to account for nonlinear dose dependence of plasma concentration for GEM-glucuronide and accurate description of enterohepatic circulation (EHC). A new algorithm was added in GastroPlus version 9.8.1 to account for the complete hydrolysis of the GEM-glucuronide into the GEM parent compound in the lumen of the gastrointestinal tract. This new mechanism is particularly important for acyl-glucuronides (like gemfibrozil and the

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Integrating science and software **PBPK Model: Gemfibrozil & Gemfibrozil Glucuronide**

individual and population physiology. The PBPK physiologies used for simulations of all studies are summarized in Table 2.

Table 1. Clinical PK Data Used for Gemfibrozil and its Glucuronide PBPK Model Calibration and Qualification

Study Type	Description	Reference
Pharmacokinetics of Gemfibrozil and Gemfibrozil glucuronide		
Bioanalytical method development study with gemfibrozil and its glucuronide measured in hyperlipidemic patients	A single-dose 900 mg PO dose administration in young hyperlipaedaemic adults subjects. Cp vs. time for gemfibrozil and its glucuronide were measured.	(Hermening et al. 2000)
Dose-dependent interaction between gemfibrozil (30mg,100mg, 300mg, 900mg) and repaglinide in Humans	On the study day, a single oral dose of 0.25 mg of repaglinide was administered with 150 ml of water at 9:00 AM after an overnight fast and 1 h after a single 30mg, 100 mg, 300 mg, or 900 mg dose of gemfibrozil or placebo. The plasma concentration profiles of both parent and glucuronide were measured in 10 healthy volunteers (9 males and one female).	(Honkalammi et al. 2011a)
Investigation of time needed for inactivation CYP2C8 by gemfibrozil repaglinide as a probe drug.	On the study day, a single oral dose of 0.25 mg of repaglinide was administered with 150 ml of water at 9:00 AM after an overnight fast and 1, 4, or 6 h after a single 600 mg dose of gemfibrozil or placebo. The plasma concentration profiles of both parent and glucuronide were measured in 10 healthy volunteers (5 males and 5 females).	(Honkalammi et al. 2011b)
DDI studies used for the model verification		

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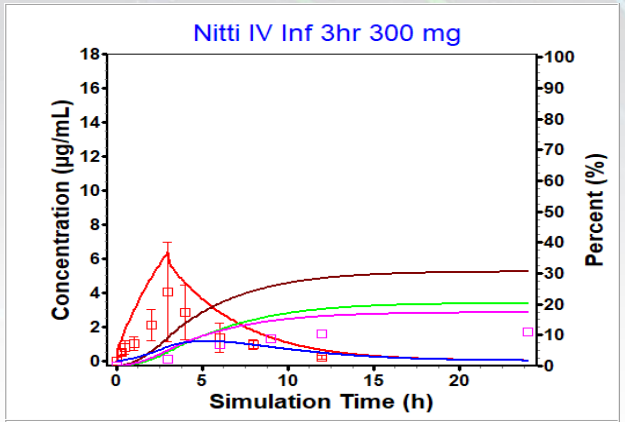
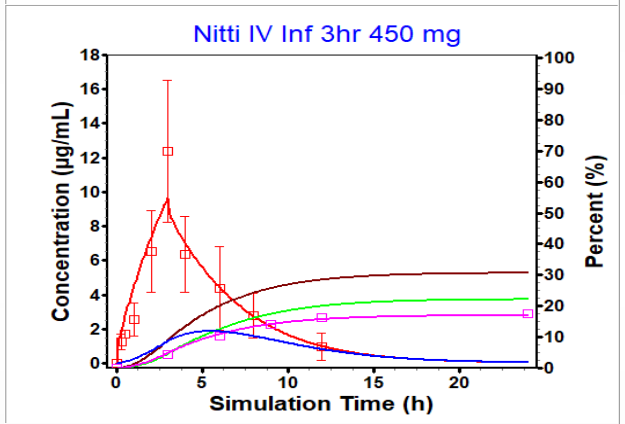
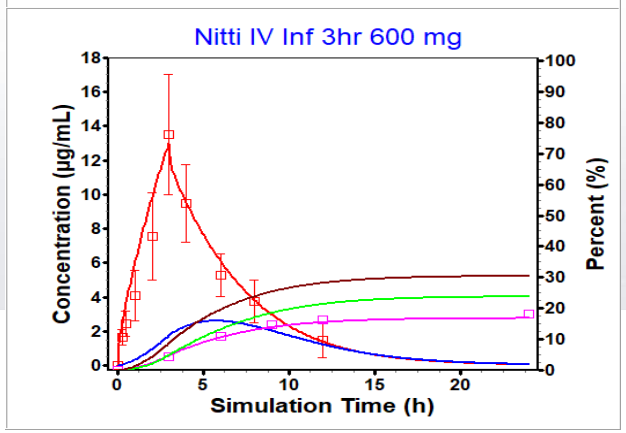
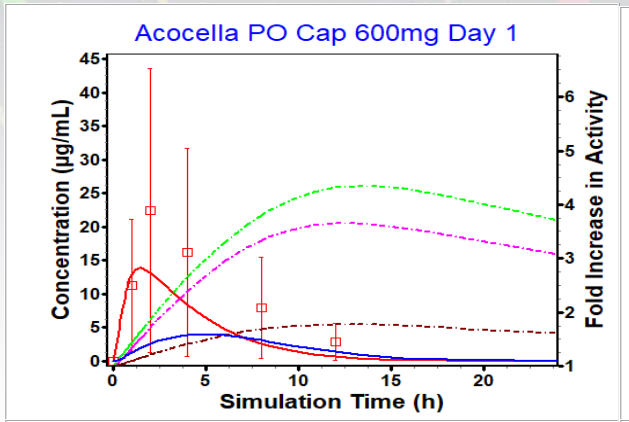
- DDI Standard Model development process
- **Standard Model Examples**
- Case Studies/Examples

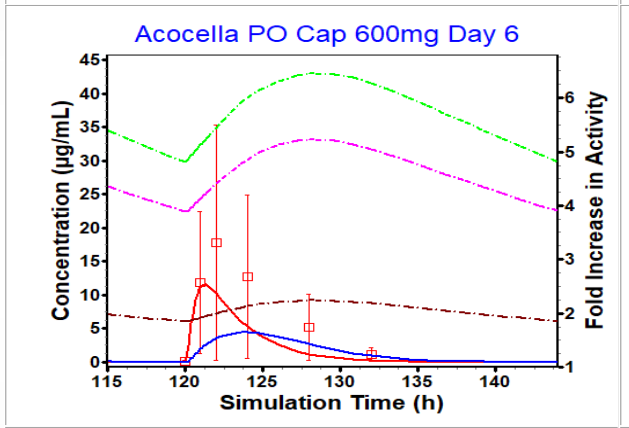
Rifampicin - Pharmacokinetics

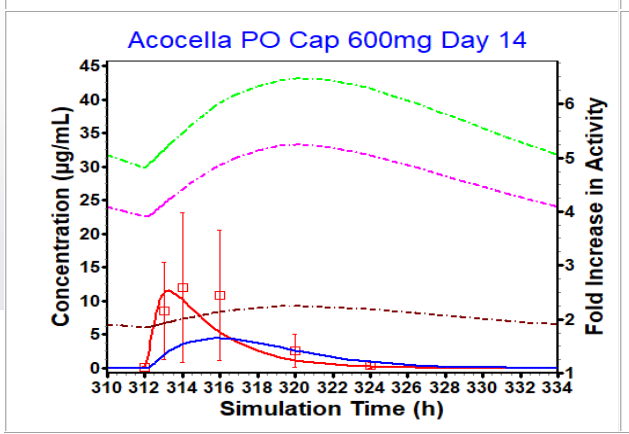


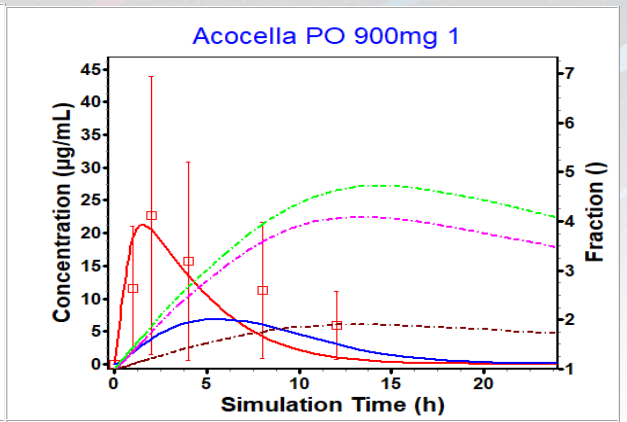


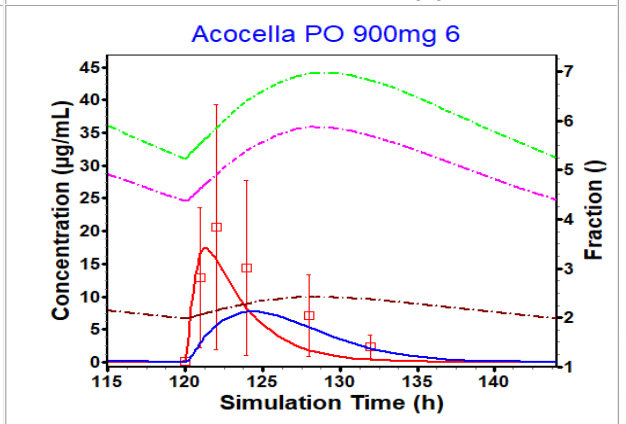


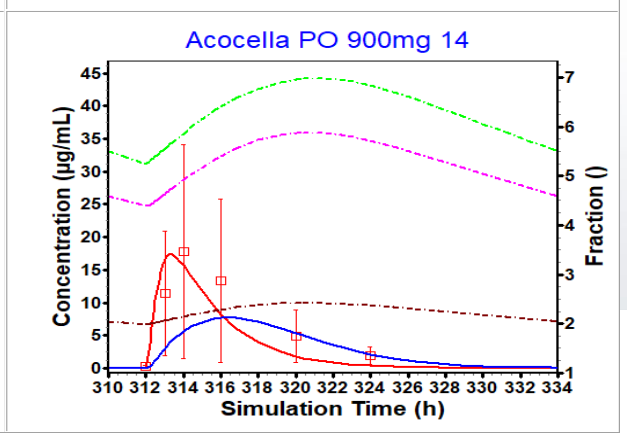






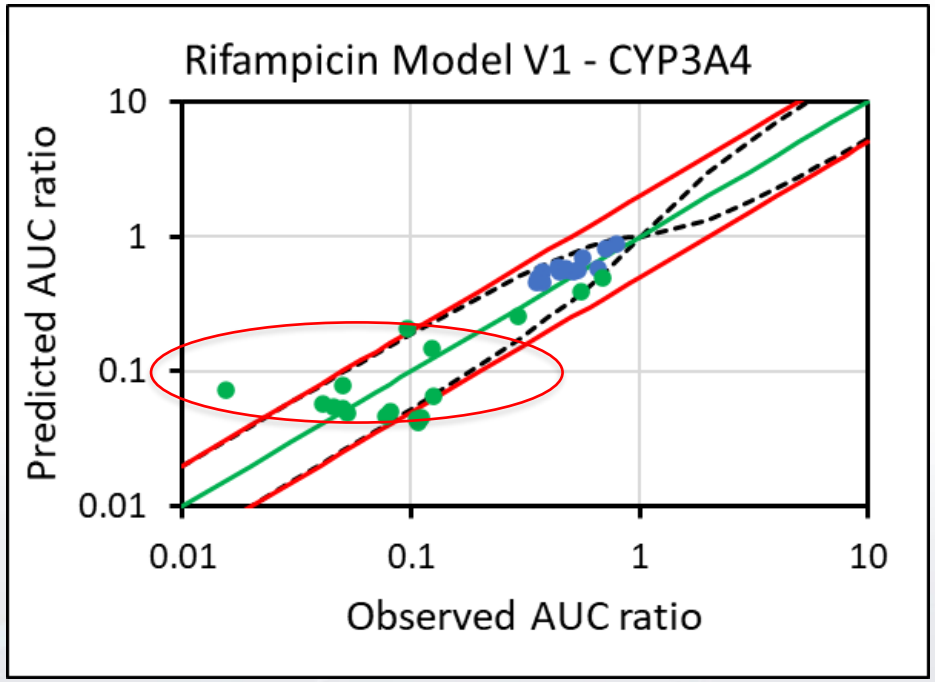


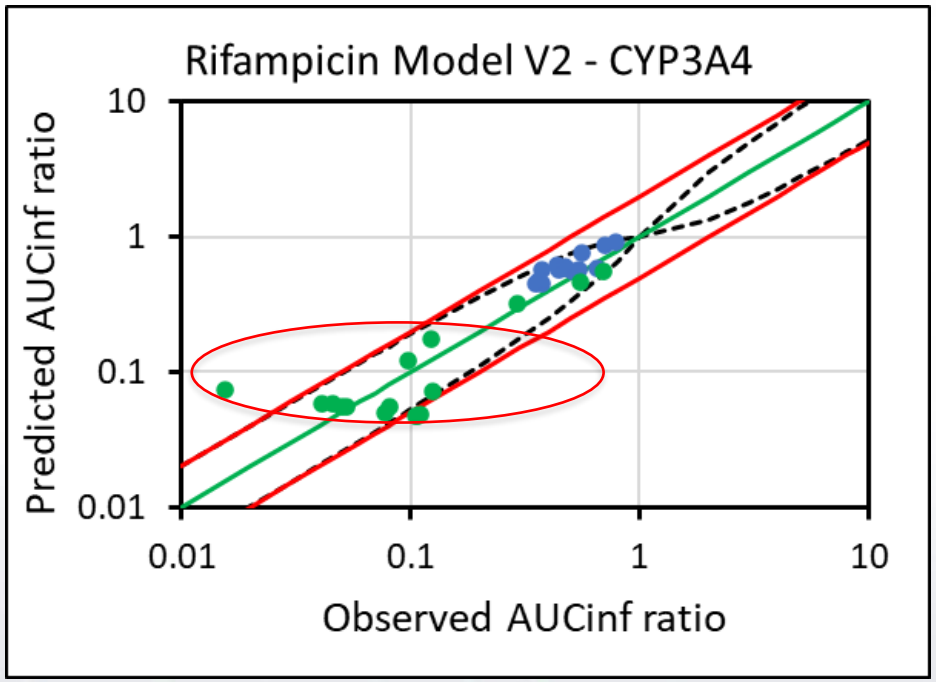




Rifampicin (V1 & V2) – CYP3A4-mediated DDI

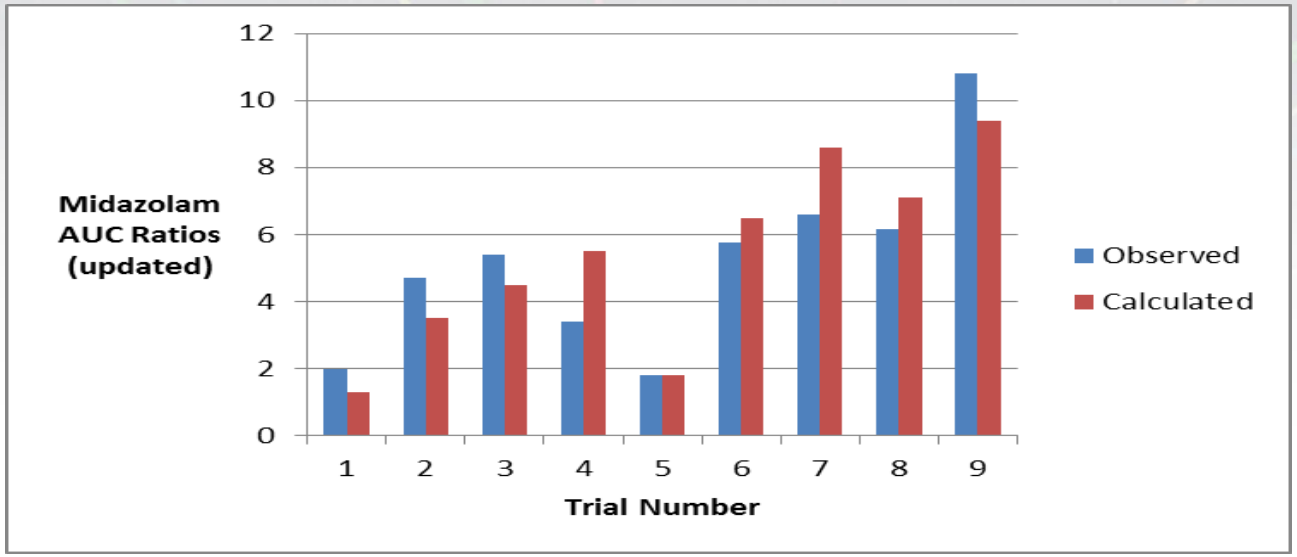
- DDI studies with alfentanil, midazolam, and triazolam
- The performance of the two model versions is similar
- Updated model includes additional mechanisms impacting rifampicin PK and is also being validated for rifampicin impact on other enzymes and transporters (CYP2C8, UGT1A1, OATP1B1, P-gp, etc.)





Keep in mind variability when using the models to validate other substrate models (for example, verifying correct contribution of CYP3A4 to metabolism of victim compound)

Itraconazole – Midazolam DDI (includes inhibitory effect of itraconazole and 3 metabolites)



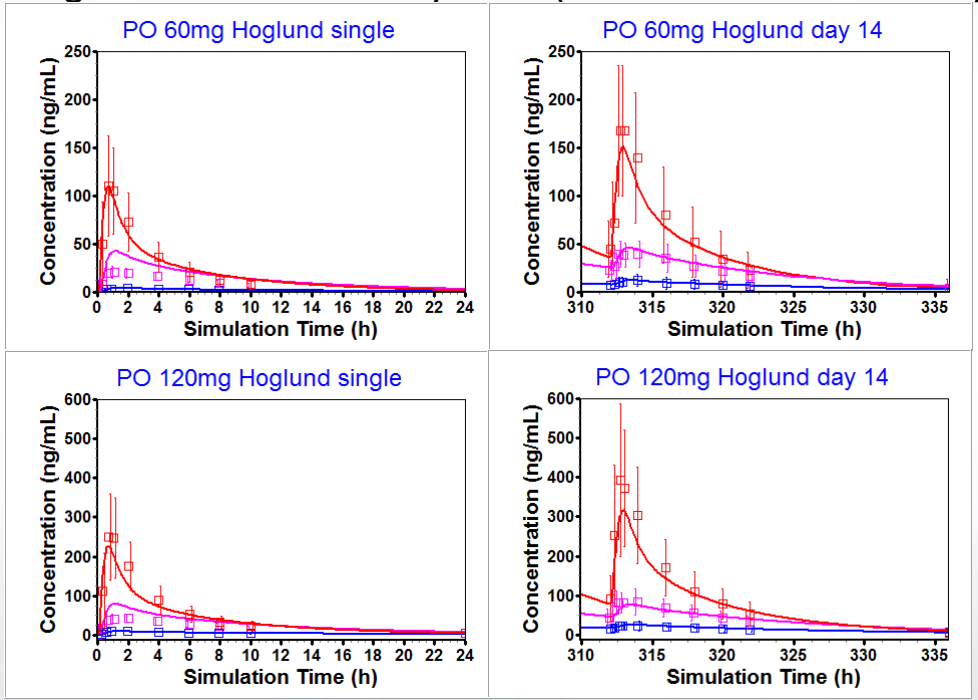
Szeto K., et al.
Poster W5237
AAPS Annual Meeting, 2015

Trial No.	1	2	3	4	5	6	7	8	9
ITZ	50 mg SD	200 mg SD	400 mg SD	200 mg SD	200 mg QD for 6 days	100 mg QD for 4 days	200 mg QD for 6 days	200 mg QD for 4 days	200 mg QD for 4 days
MID	2 mg PO taken 4 hrs after ITZ	2 mg PO taken 4 hrs after ITZ	2 mg PO taken 4 hrs after ITZ	7.5 mg PO taken 2 hrs after ITZ	0.05 mg/kg IV over 2 min given 2 hrs after ITZ on day 4	7.5 mg PO taken 2 hrs after ITZ on day 4	7.5 mg PO taken 2 hrs after ITZ on day 6	15 mg PO taken 2 hrs after ITZ on day 4	7.5 mg PO taken 1 hr after ITZ on day 4
Demog (M:F)	n=6 (5:1); 22-42 yrs	n=6 (5:1); 22-42 yrs	n=6 (5:1); 22-42 yrs	n=12 (7:5); 19-25 yrs; 57-95 kg	n=12 (7:5); 19-25 yrs; 57-95 kg	n=12 (4:8); 19-30 yrs; 54-98 kg	n=12 (7:5); 19-25 yrs; 57-95 kg	n=9 (4:5); 22-34 yrs; 55-78 kg	n=9 (2:7); 19-26 yrs; 52-85 kg
Study Protocol	Not defined - assumed fasted state	Not defined - assumed fasted state	Not defined - assumed fasted state	The volunteers fasted for 3 hrs before MID administration and had a standard meal 4 hrs afterwards	The volunteers fasted for 3 hrs before MID administration and had a standard meal 4 hrs afterwards	The volunteers fasted for 3 hrs before MID administration and had a light standard meal 4 hrs afterwards	The volunteers fasted for 3 hrs before MID administration and had a standard meal 4 hrs afterwards	The volunteers fasted for 2 hrs before MID administration and had light standard meals 4 hrs and 7 hrs after MID	The volunteers fasted for 3 hrs before MID administration and had a standard meal 4 hrs afterwards
Ref	Templeton et al. 2010	Templeton et al. 2010	Templeton et al. 2010	Olkkola et al. 1996	Olkkola et al. 1996	Ahonen et al. 1995	Olkkola et al. 1996	Backman et al. 1998	Olkkola et al. 1994

Diltiazem – CYP3A4 Inhibitor (Competitive and TDI)

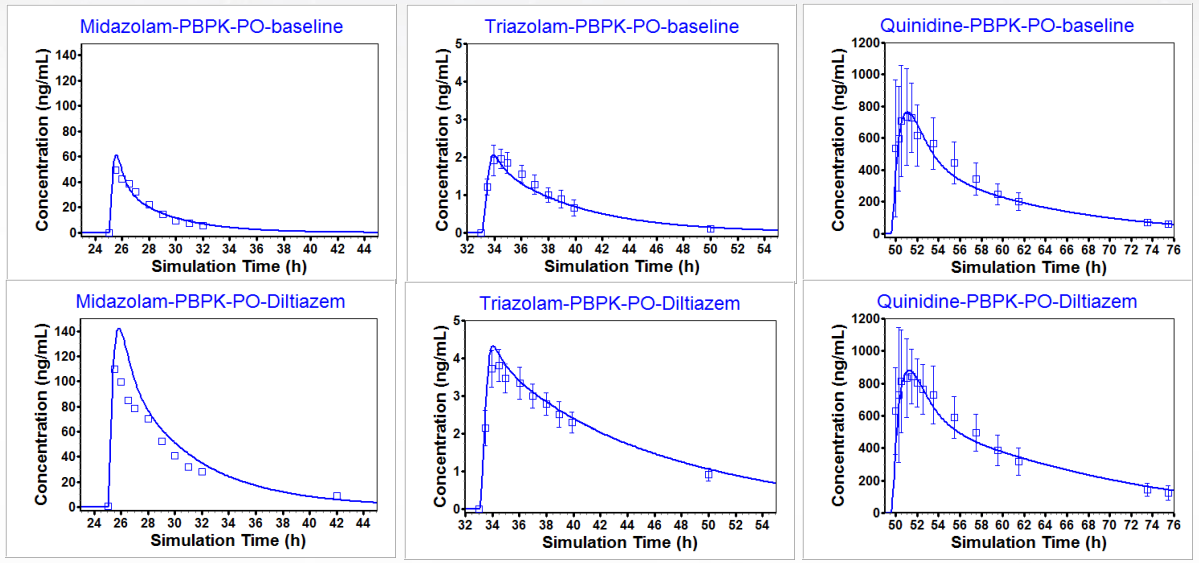
- The model describes pharmacokinetics under different administration conditions
- The model correctly predicts clinical DDI (time-dependent inhibition of CYP3A4) with different substrates

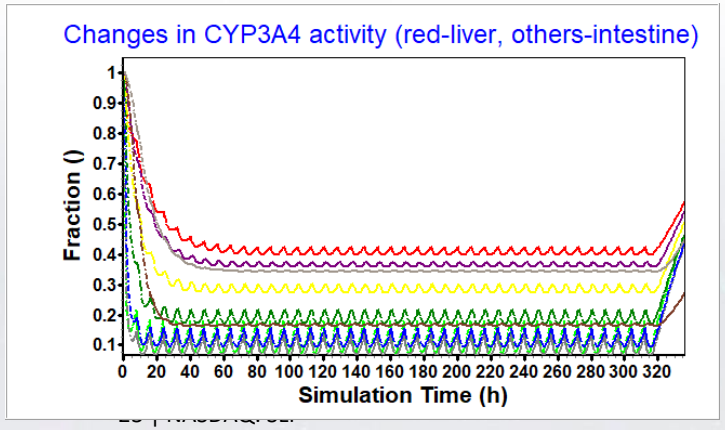
Diltiazem and metabolite PK for different doses after single dose and in steady state (**includes autoinhibition**)



red-diltiazem, magenta – N-demethyldiltiazem, blue-deacetyldiltiazem

Observed data from Hoglund P. – Ther Drug Monit 1989





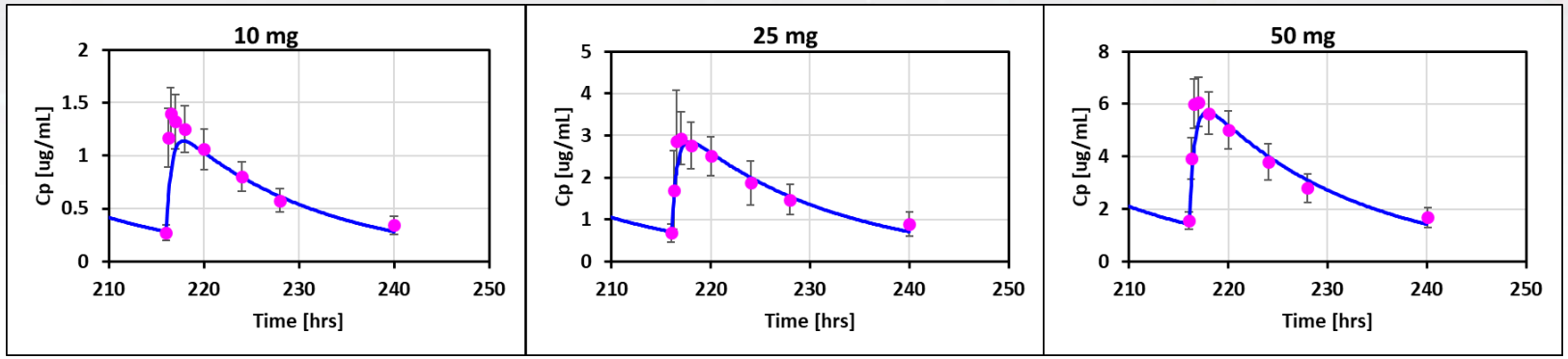
[observed data from: Backman JT-Br J Clin Pharmacol 1994, Varhe-Clin Pharmacol Ther 1996, Lagniere-Clin Pharmacol Ther 1996]

SimulationsPlus MIDD Model Informed Drug Development + 2023

SimulationsPlus

Dolutegravir – UGT1A1 Substrate

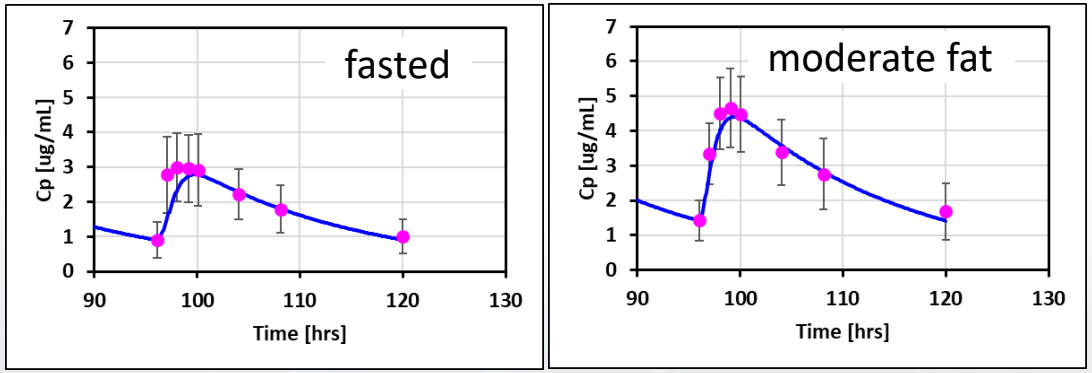
Dolutegravir suspension administration in fasted healthy subjects



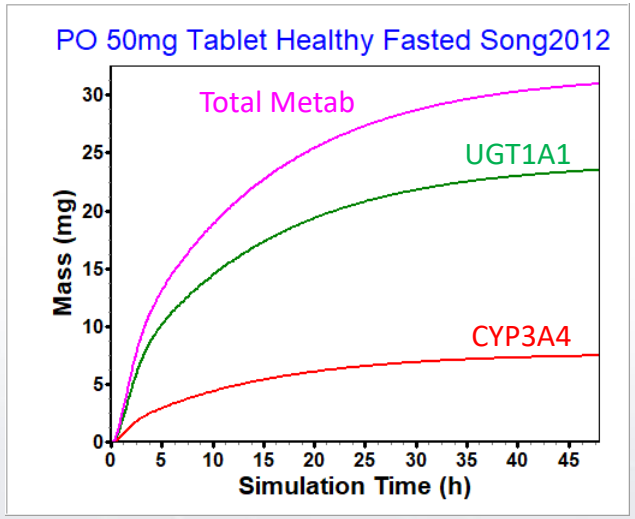
Observed data from Min S. – Antimicrob Agents Chemother 2010

- The model describes pharmacokinetics under different administration conditions (only some of the published studies shown here)
- Contribution of different enzymes to metabolism is captured correctly

Dolutegravir 50 mg dose in healthy subjects

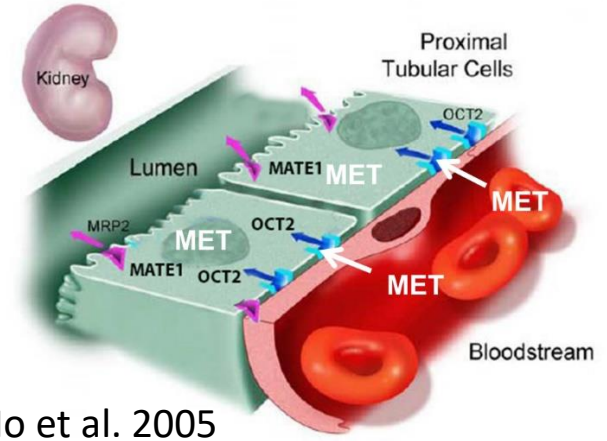


Observed data from Song I. – Eur J Clin Pharmacol 2015

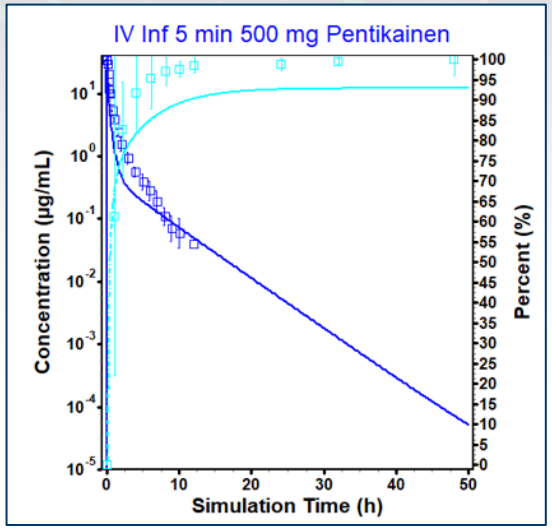


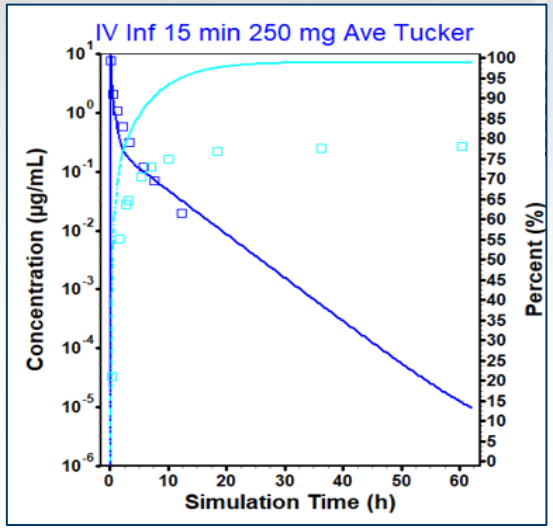
Reported contribution of CYP3A4 from *in vitro* and *in vivo* studies is ~25% [Reese MJ-Drug Metab Dispos 2013; Johnson M-Br J Clin Pharmacol 2014]

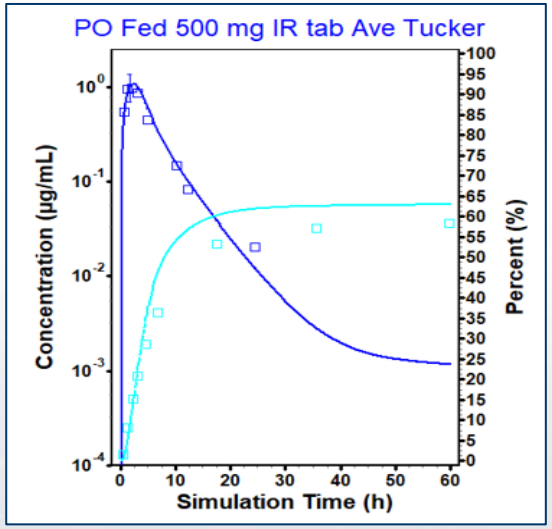
Metformin – OCT2/MATE2K Substrate

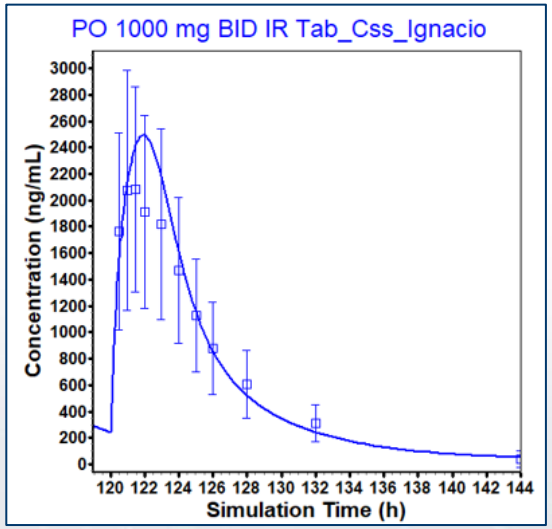


Ho et al. 2005

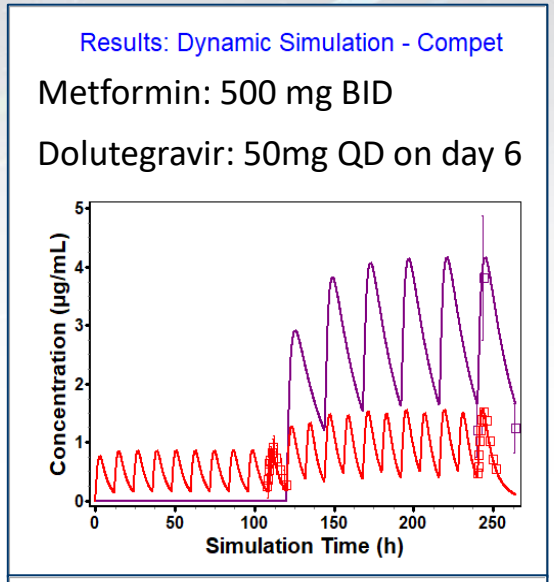


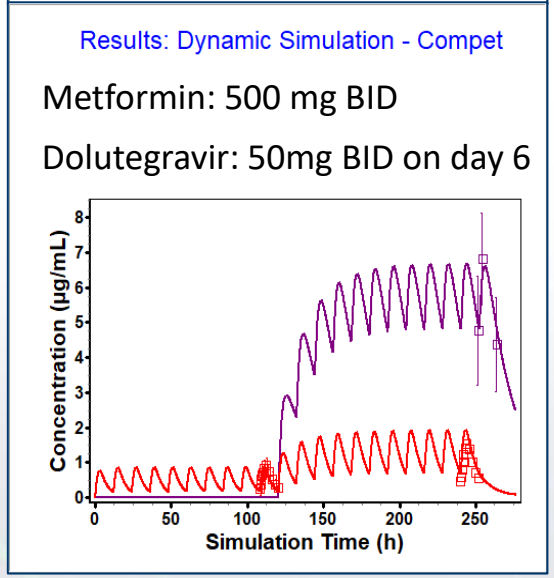






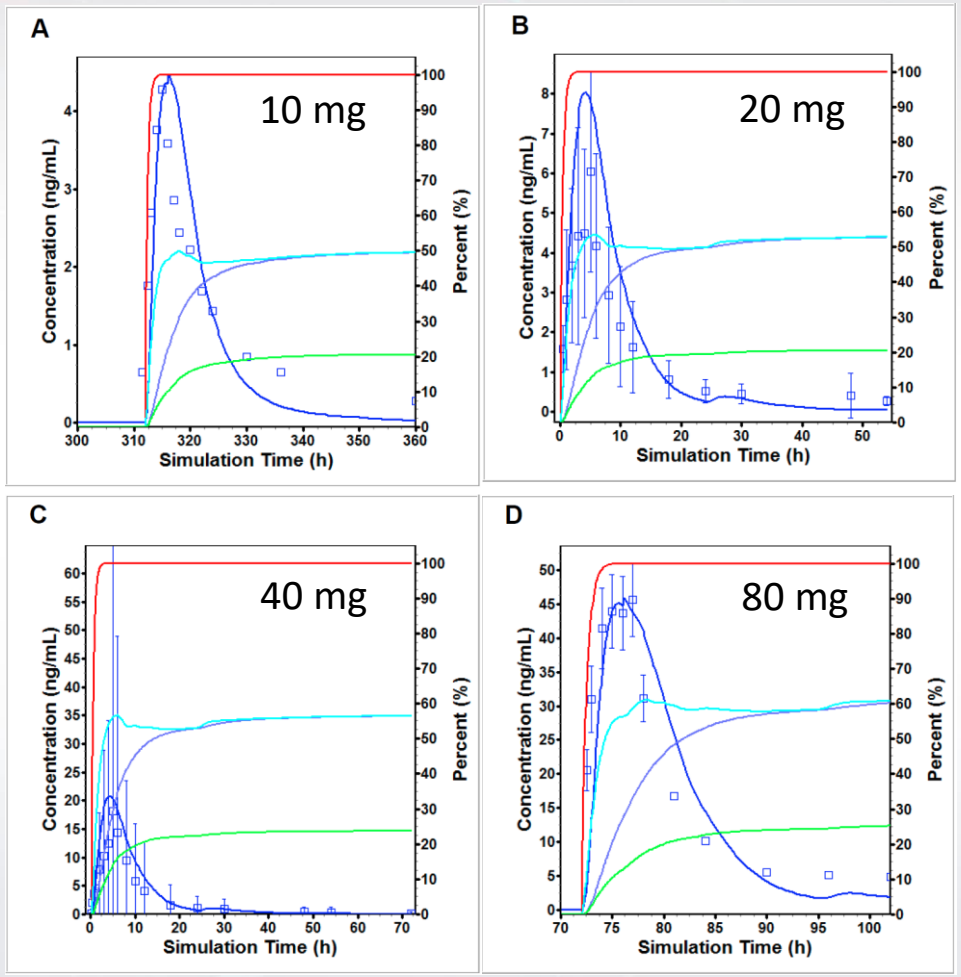
- The model describes pharmacokinetics under different administration conditions (only some of the published studies shown here)
- Model was validated as OCT2 substrate by simulating DDI with dolutegravir





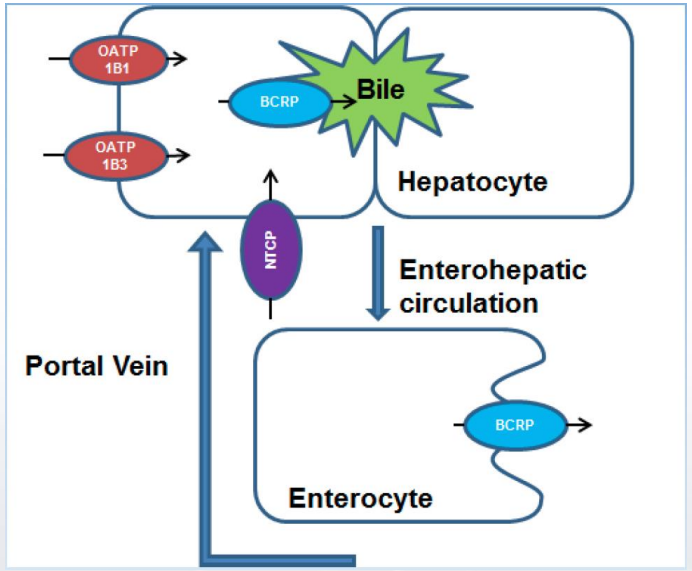
Rosuvastatin – OATP1B1/1B3 Substrate

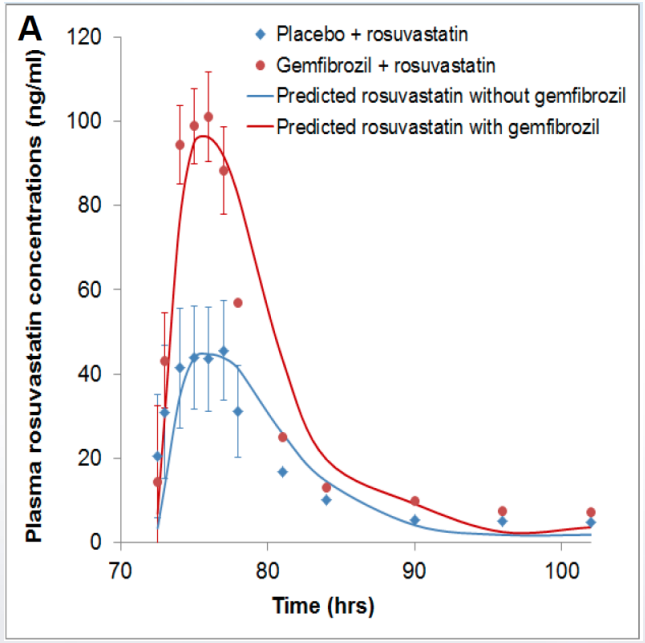
Rosuvastatin PK after different doses



Macwan – AAPS 2015

- The model describes pharmacokinetics under different administration conditions
- DDI with the inhibitor of uptake transporters (gemfibrozil) is predicted correctly





Outline

- GastroPlus® DDI Module overview
- DDI Standard Model development process
- Standard Model Examples
- **Case Studies/Examples**

DDI for Oxycodone (and Metabolites)

Received: 26 September 2019 | Revised: 2 January 2020 | Accepted: 8 January 2020
DOI: 10.1002/bdd.2215

ORIGINAL PAPER

WILEY

Physiologically based pharmacokinetic modelling of oxycodone drug–drug interactions

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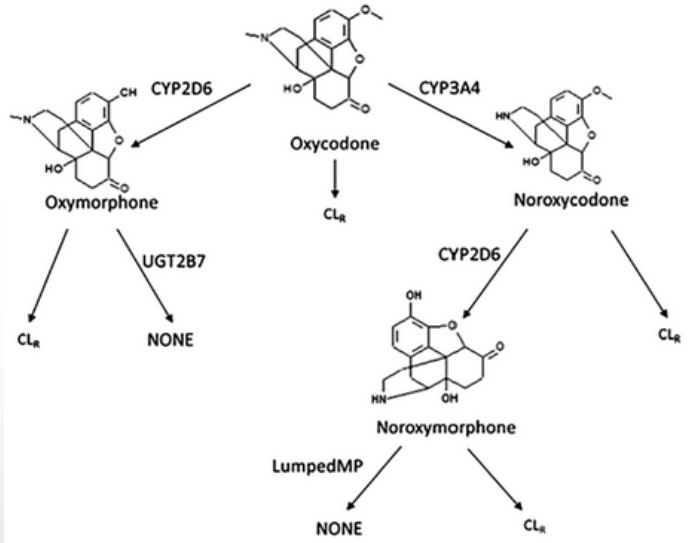


FIGURE 1 The elimination of oxycodone and its three main metabolites incorporated in the model. Noroxycodone and oxymorphone are formed from oxycodone via CYP3A4 and CYP2D6, respectively. Noroxycodone is further metabolized to noroxymorphone via CYP2D6. Oxymorphone and noroxymorphone are metabolized to "NONE", meaning that formed metabolites are not tracked, by UGT2B7 and liver microsomal enzymes (LumpedMP), respectively (Coffman, King, Rios, & Tephly, 1998; Lalovic et al., 2004; Lalovic et al., 2006)

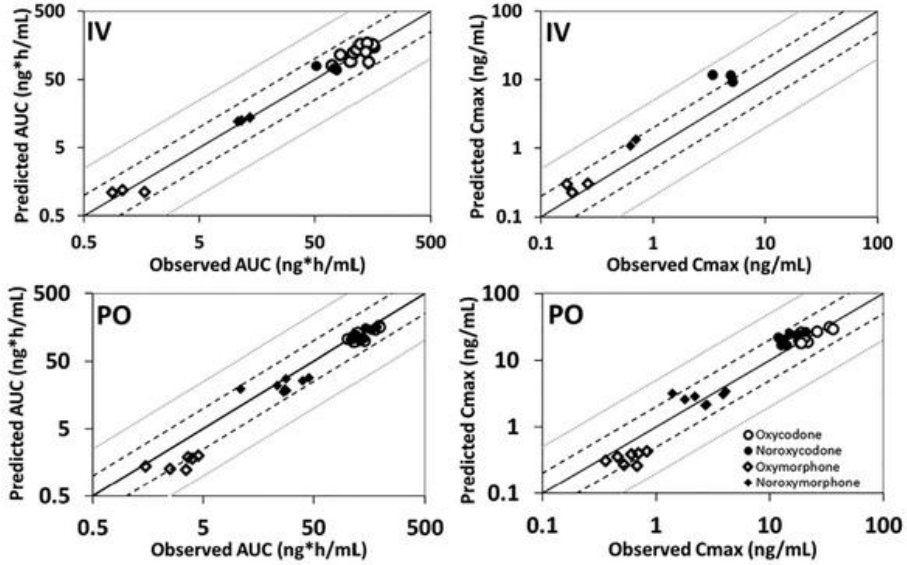


FIGURE 3 Observed versus predicted AUC and C_{max} for oxycodone and oxycodone metabolites after oral and intravenous oxycodone administration. Black and grey dotted line represents 2- and 5-fold limits, respectively. Black solid line represents the unity line

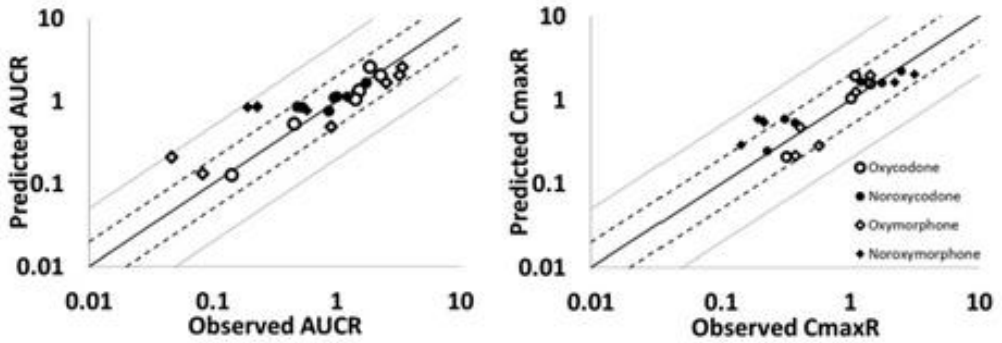


FIGURE 6 Observed versus predicted AUCR and C_{max}R values in DDI simulations. Black and grey dotted line represent 2- and 5-fold limits, respectively. Black line represents the unity line

Rytkonen, Biopharm Drug Dispos 2020

Predicted DDIs with ketoconazole, itraconazole, quinidine, rifampicin

Transporter Mediated DDI in Regulatory Submissions

Table 2 Examples of DDI PBPK analyses and their impact on drug development and regulatory decision

Drug	Key theme (impact level) and question(s)	Victim/perpetrator?	Brief description	Internal impact	Qualification dataset	FDA/EMA response
Trametinib (marketed) Chen *et al.*, 2015[61]	DDI (high) Requested to provide clinical studies to investigate the inhibition of intestinal BCRP. *In vitro* BCRP inhibition data flagged the potential risk of *in vivo* DDI according to the EMA regulatory guidelines.	Perpetrator: Weak BCRP inhibitor	*In vitro* Trametinib is a weak BCRP inhibitor, however based upon the EMA DDI guidance criteria the *in vivo* risk in the gut could not be excluded using *in vitro* data alone. Predicted intestinal concentrations were simulated using GastroPlus. Complete inhibition was predicted for the first 40 minutes post dose and partial inhibition was predicted up to 1.6 hours post dose and restricted to the duodenum and jejunum. Recommendation was to limit the co-administration of sensitive BCRP substrates to 2 hours post trametnib administration	Previously constructed GastroPlus Model of trametinib was developed for other applications, therefore minimal work was required to construct the model in response to the agency. Absorption was simulated and the outputs of the model (predicted concentrations vs. time) along the intestinal track were used as input in the DDI prediction guidelines, internal static modeling as well as cross referencing data in the Washington database to inform concomitant medications at risk. No clinical BCRP DDI study was conducted	*In vitro* BCRP inhibition data. Sponsor was requested to further discuss the interaction potential between trametinib and drugs mainly absorbed in the duodenum and jejunum. Outcome: Using the University of Washington database a list of BCRP substrates absorbed within 1-2 hours after oral administration was constructed. This list was further refined to exclude those substrates in which the DDI mechanism was known, leaving behind a list of substrates that may potentially be affected by BCRP inhibition.	FDA: Not submitted by the sponsor. EMA: Accepted.

Shebley Clin Pharm Ther 2018

Table 3 Examples of transporter-mediated DDI PBPK analyses and their impact on drug development and regulatory decision

Example number	Drug	Key theme Transporter (location function) Inhibitor – inh Substrate - sub	Victim/perpetrator/ and question(s)?	Brief description	Impact[a]	Qualification dataset	FDA/EMA response
4	Axitinib (marketed)	Intestinal transporter: P-gp (apical efflux) inhibitor	Does P-gp inhibition *in vitro* translate to clinical DDI liability unbound C_{max} of 0.0008 μM,	ACAT model using Gastroplus was built to simulate axitinib concentrations in segments of GI tract	High Impact: Agreement of HA that no formal DDI trial with P-gp substrate is needed		FDA: Accepted EMA: Not submitted

Taskar Clin Pharm Ther 2019

Case study: Ruxolitinib

- Ruxolitinib is metabolized by CYPs 3A4 (major), 2C9 and 1A2
- *in vitro* studies showed it is a weak inhibitor of Pgp
- PBPK model was developed to describe the essential ruxolitinib PK characteristics and validated by reproducing DDIs with three CYP3A4 perpetrators (competitive inhibitor, time-dependent inhibitor, and inducer)
- Validated PBPK model was used to predict DDI potential when coadministered with fluconazole (CYP 3A4 and 2C9 inhibitor) and digoxin (Pgp substrate).

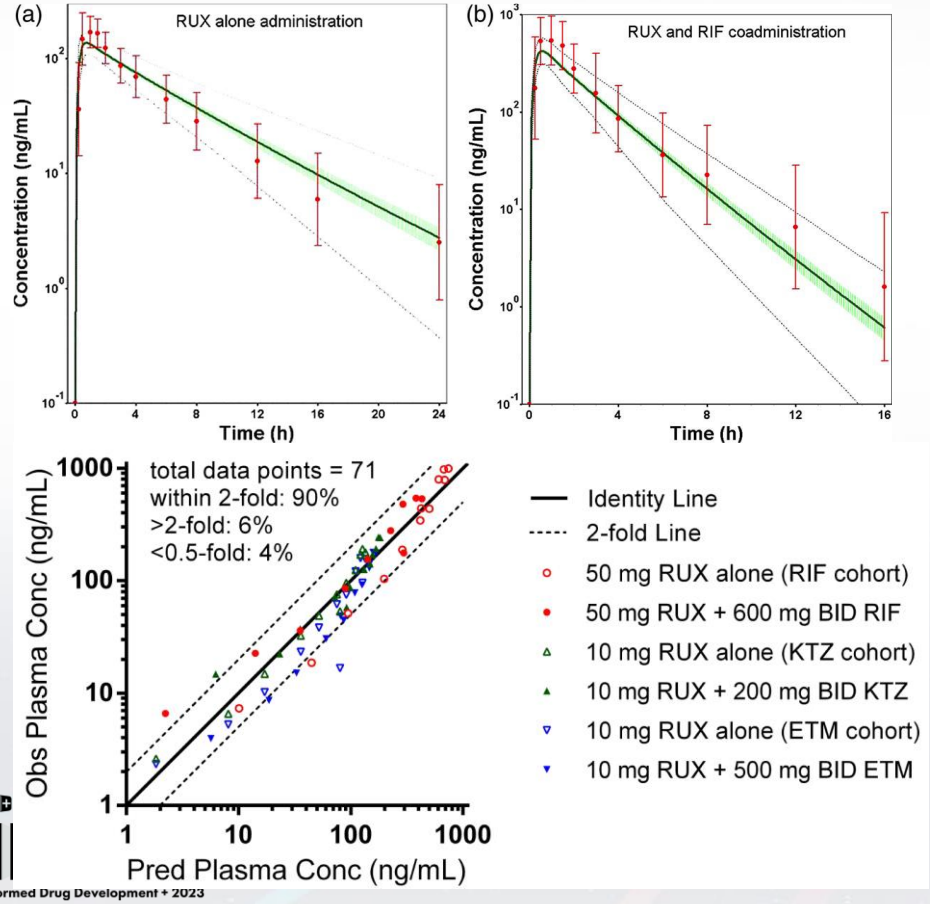


Table 1 Predicted versus observed $AUC_{0-\infty}$ and C_{max} ratios for drug–drug or drug–food interactions involving ruxolitinib

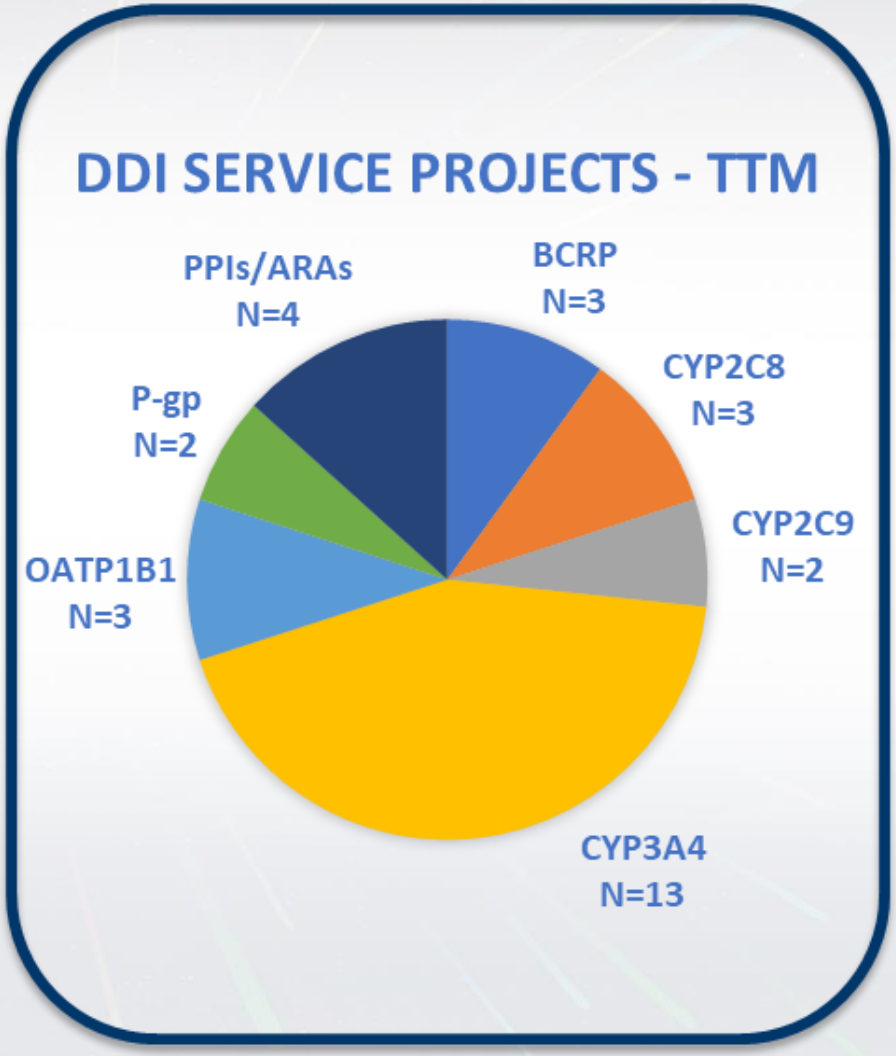
	—$AUC_{0-\infty}$ ratio—		—C_{max} ratio—	
Retrospective prediction	**Observed**	**Predicted**	**Observed**	**Predicted**
RUX + high-fat meal	1.05 (0.97–1.13)	0.94	0.76 (0.63–0.91)	0.74
RUX + 600 mg q.d. RIF	0.29 (0.21–0.40)	0.25	0.48 (0.36–0.64)	0.58
RUX + 200 mg b.i.d. KTZ	1.91 (1.72–2.12)	1.80	1.33 (1.18–1.49)	1.34
RUX + 500 mg b.i.d.ETM	1.27 (1.17–1.38)	1.56	1.08 (0.95–1.25)	1.22
Prospective prediction				
RUX + FLN 100 mg q.d.		1.87		1.26
RUX + FLN 200 mg q.d.		2.46		1.33
RUX + FLN 400 mg q.d.		3.47		1.39
RUX + FLN 100 mg b.i.d.		2.40		1.32
RUX + FLN 200 mg b.i.d.		3.43		1.39
Digoxin + RUX 25 mg SD		1.00		1.00
Digoxin + RUX 200 mg SD		1.01		1.01
Digoxin + RUX 200 mg SD[a]		1.02		1.05

$AUC_{0-\infty}$, area under plasma concentration-time curve extrapolated to infinity; b.i.d., dosing every 12 h; q.d., dosing every 24 h; C_{max}, peak plasma concentration; ratio, quotient of object drug's exposure with/without the presence of precipitator, presented in geometric mean (90% CI) for observed values; SD = single dose.
[a]Simulation conducted with RUX K_i for P-gp at 1/10 of observed value (21.5 μM).

Simulations Plus Consulting Services

Breakdown of DDI projects conducted by our Consulting Services Team

Busting Myths



Conclusions

- Our scientists, collaborators, and users continue developing **GastroPlus** models to simulate complex **mechanistic drug-drug interactions** involving enzymes and transporters, for use in **internal decision making** as well as **regulatory applications**.
- We provide complete **GastroPlus model files** and **written documentation** for the standard models built by our scientists.
- **Documentation** is scientifically reviewed and formatted as a complete package **for regulatory review** of novel compound results.
- All complete models will be available for download by registered GP license holders.

Acknowledgements

Michael Bolger (Founding Scientist)

Simulation Studies Team

Simulation Technologies Team

External Collaborators

With support from:

Neil Miller (VP Simulation Sciences)

Project Management Team

and other teams at Simulations Plus:

Computational Technologies

Cheminformatics

SimulationsPlus

MIDD+

Model Informed Drug Development + 2023

Q&A

Questions & Answers