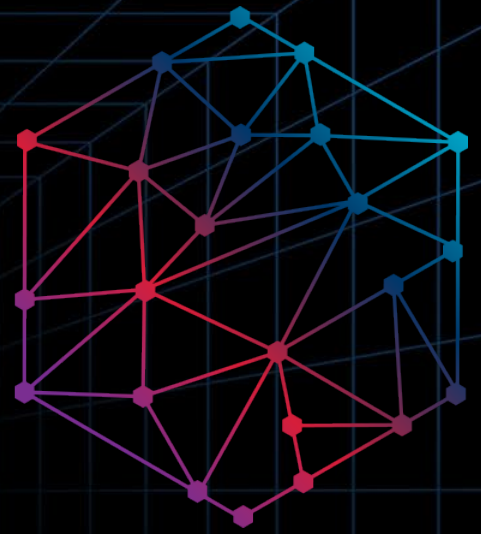
Model-Informed Drug Development

MIDD+

2021 Virtual Conference



GastroPlus® DDI Standards Update Project

Simulations Plus, DDI Task Force

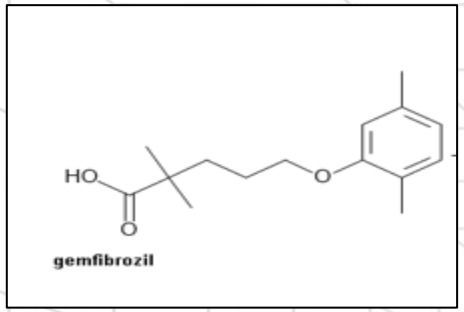
SimulationsPlus

Cognigen | DILIsym Services | Lixoft

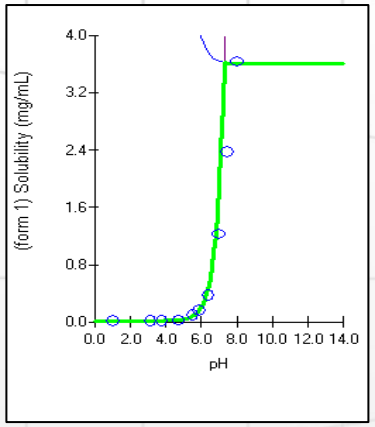
Outline of Process for Model Development and Documentation

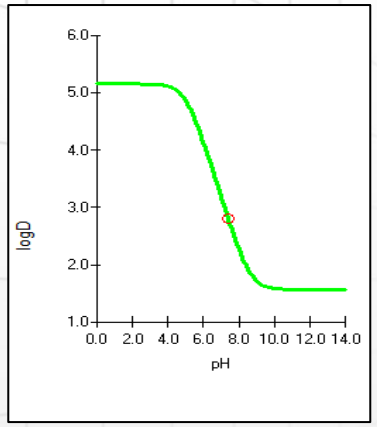
- Creation of GP a project starts with structure import using ADMET Predictor Module for both substrates and perpetrators.
  - Physicochemical, biopharmaceutical, and biochemical properties
  - Initial evaluation via “Chemistry Classification” with all aspects of ADMET
  - Extensive literature collection and spreadsheet documentation.
    - Workbook with multiple sheets for Compound Properties
    - DDI study data for multiple perpetration mechanisms.
  - First simulations for “Measured Properties” with parameter sensitivity analysis.
  - Model building for individual substrate and/or perpetrator simulations compared to observed data
    - 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 accuracy of AUC Ratios
  - Preparation of slides and written reports suitable for regulatory submission.

Gemfibrozil BCS II Physicochemical Properties



MW = 250.34





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

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 pKa = 5 (Luner et. al., Pharm. Res.11(12):1755 (1994)

S+Sw = 0.0826 mg/ml @ pH 4.24 (AP 10.0)
Exp Sw = 0.02 mg/ml @ pH 1 37 deg C (LOW) (Luner et. al., Pharm. Res.11(12):1755 (1994)
S+Solubility Factor = 276.89
S+FaSSIF = 0.42 mg/ml, S+ FeSSIF = 0.62 mg/ml (AP 10.0)
Exp FaSSIF = N.A

S+Peff = 7.33x 10^{-4} (cm/s) (AP 10.0) (HIGH)
Caco-2 Papp A->B = 5.89E-5 (Absorptions Systems Lighthouse Database)
Caco-2 Papp B->A = 4.73E-5 (Absorptions Systems Lighthouse Database)
Caco-2 Converted to Hum Peff = 5.60E-4 cm/s (From GeoMean =5.28E-5 cm/s from Abs Sys Caco-2)

S+hum_fup% = 5.18 %(AP 10.0)
Exp. Fup = 3.5%(Oprea and Benet Wombat database)
S+RBP = 0.67(AP 10.0)
Exp Rbp =0.75(Deguchi et. al., Drug.Metab.Dispos.39(5):820 (2011)

S+Enzyme Substrate: CYP2C9(48%), CYP2C19(71%), UGT1A1(68%), UGT1A3(97%), UGT1A9(76%), UGT2B7(93%)
S+Transporter Substrate: P-gp(75%), OATP1B1(99%), OAT1(87%),
Exp Enzyme Substrate: 2C9, 2C19, UGT1A3, UGT2B7
Exp Transporter Substrate: OATP1B1 (liver influx)

S+Enzyme Inhibitor: CYP2C9(77%)
S+Transporter Inhibitor: OAT1(95%), OAT3(76%),
Exp Enzyme Inhibitor: 2C8, 2C9
Exp Transporter Inhibitor: NTCP, OAT3, OATP1B1, OATP1B3

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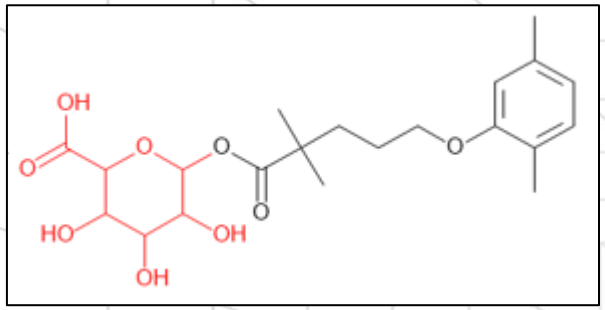
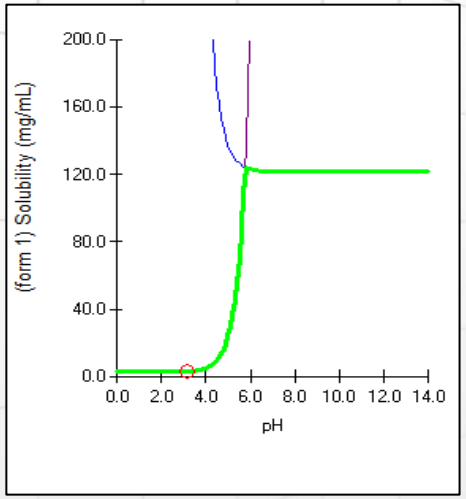
Gemfibrozil Glucuronide Physicochemical Properties



MW = 426.47



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

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

S+pKa = 4.12 (Acid)
Exp pKa = N.A

S+Sw = 3.0900 mg/ml @ pH 3.15 (AP 9.5)
Exp Sw =N.A
S+Solubility Factor = 43.48
S+FaSSIF = 1.13 mg/ml, S+ FeSSIF = 2.71 mg/ml
Exp FaSSIF =N.A

S+Peff = 4.0E-5 (cm/s) (AP 10.0)

S+hum_fup% = 11.2% (AP 10.0)
Exp. Fup% =11.5% (Shitara et al., J.Pharmacol. Exp.Ther. 311(1):228(2004)
NOTE: For all simulations Fup% = 5.0 to correct the Vdss for glucuronide

S+RBP = 0.65 (AP 10.0)
Exp Rbp =N.A

S+Enzyme Substrate:
Exp Enzyme Substrate: Hydrolase
S+Transporter Substrate: P-gp(99%), OATP1B1(99%), OATP1B3(93%), OAT1(65%), OAT3(97%), OCT1(76%)
Exp Transporter Substrate: OATP1B1 (liver influx), OAT3 (kidney influx), MRP2 (liver-bile efflux), MRP3 (liver-systemic efflux), MRP4 (kidney-tubule efflux)

S+Enzyme Inhibitor: CYP2C9(35%), CYP3A4(42%)
S+Transporter Inhibitor:
Exp Enzyme Inhibitor: 2C8, 2C9
Exp Transporter Inhibitor: NTCP, OAT3, OATP1B1, OATP1B3

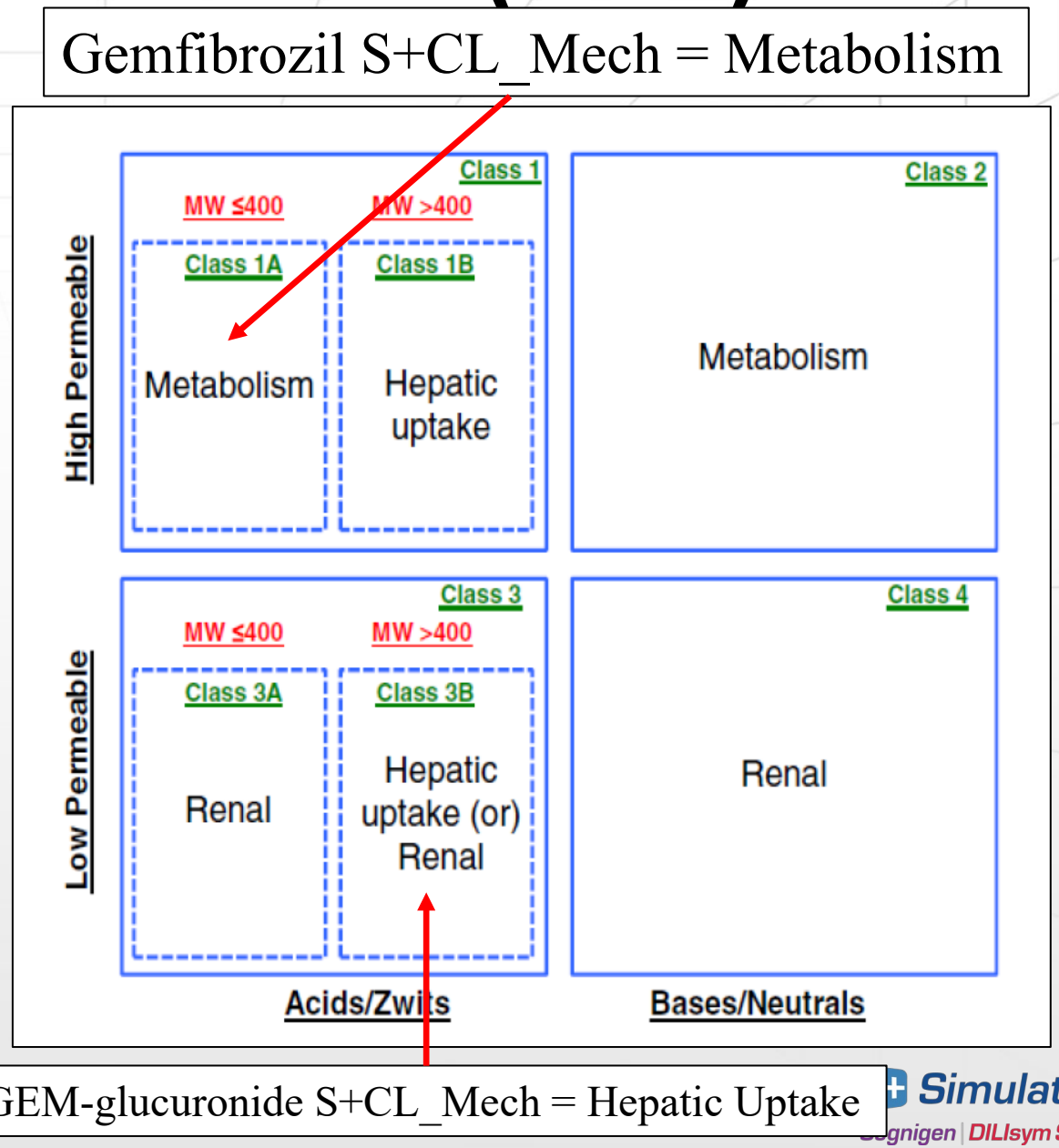
Extended Clearance CS (ECCS)

Compound are assigned to one of six classes based on:

1) High or low permeability
2) High or low MW (400 g/mol)
3) Ionization class: Acids/Zwitterions versus Bases/Neutrals

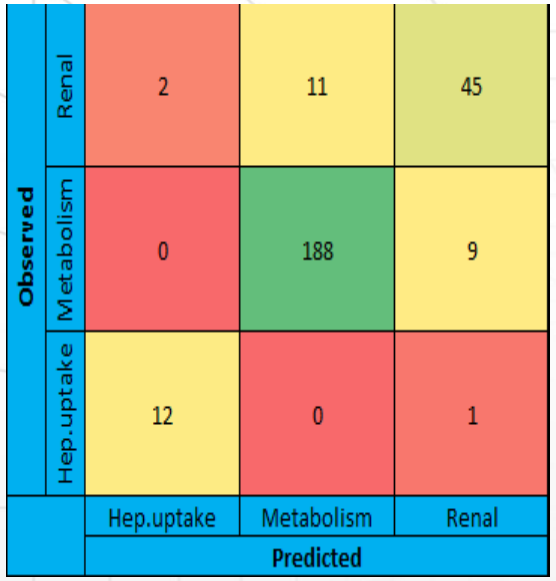
Class 1A and 2 are metabolism
Classes 3A and 4 are renal
Class 1B is hepatic uptake
Class 3B is hepatic uptake or renal

Varma M., et. al. Pharm. Res. 2015, 32, 3785.

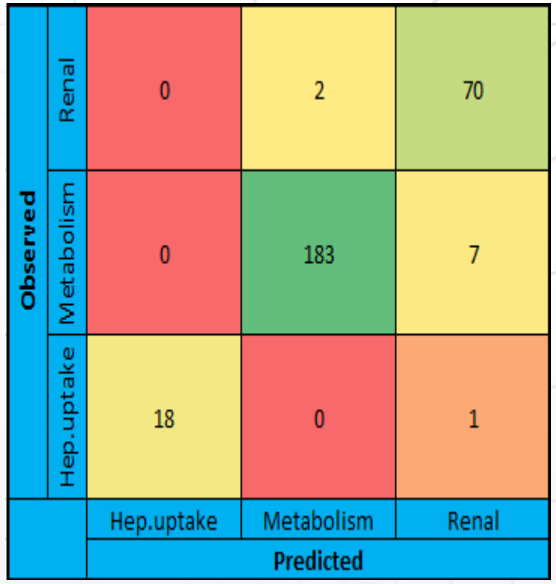


Varma and ADMET Predictor ECCS models

Varma ECCS



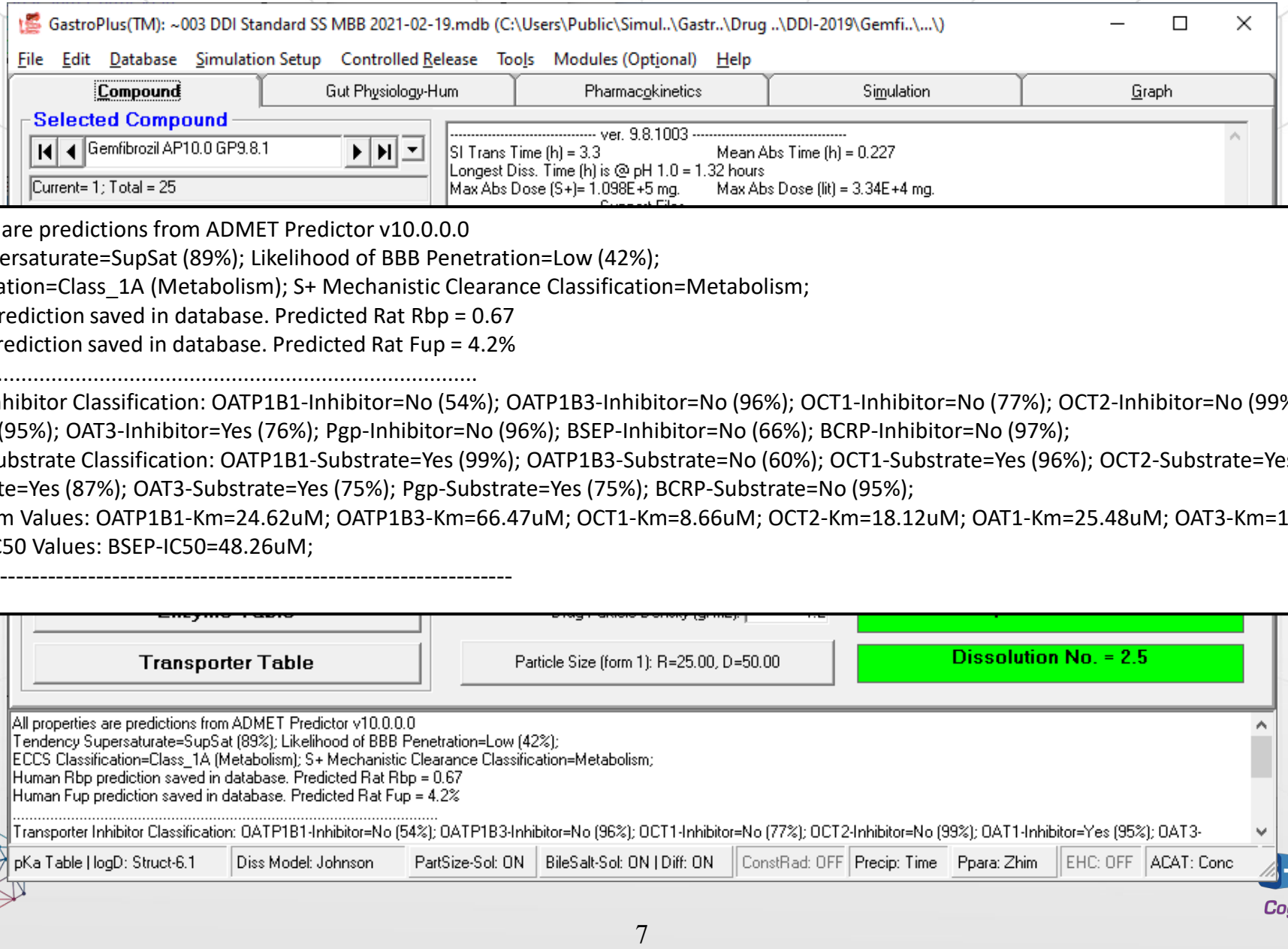
S+Hum CL Mech.



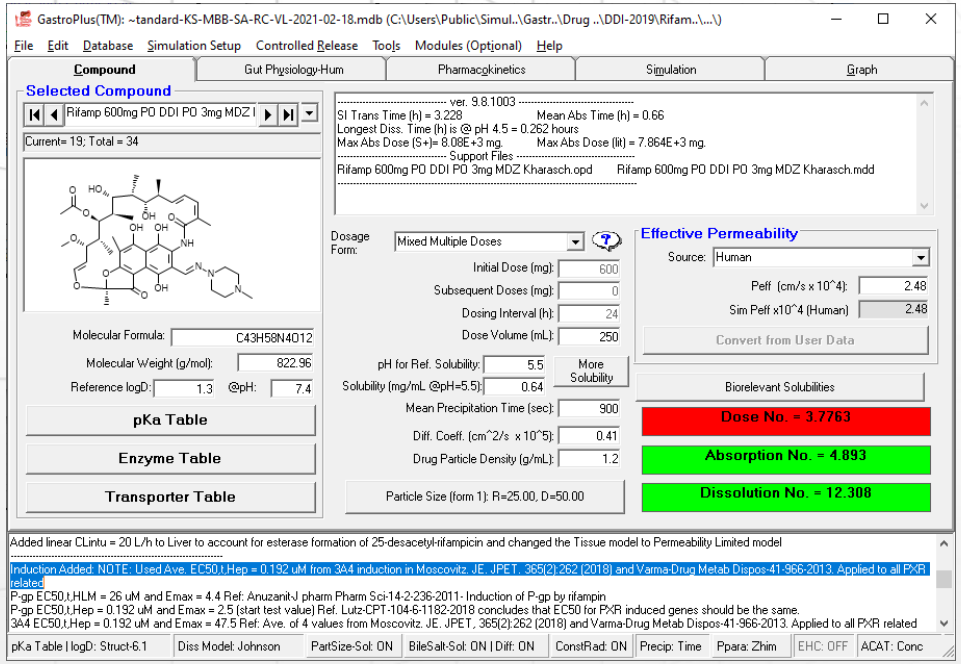
Statistic	ECCS	Hum CL Mech Bin
Concordance	91%	96%
Youden	0.78	0.94
Coverage	88%	92%

Varma M., et. al. Pharm. Res. 2015, 32, 3785.

Purely *in silico* model



Documentation directly in comment field of database



All properties are predictions from ADMET Predictor v9.5.0.0
Tendency Supersaturate=SupSat; Likelihood of BBB Penetration=Low (92%); Pgp-Inhibitor=Yes (97%); Pgp-Substrate=Yes (94%); OATP1B1-Inhibitor=Yes (91%); OCT2-Inhibitor=No (95%); BSEP-Inhibitor=Yes (83%); BCRP-Substrate=Yes (54%);
ECCS Classification=Class_4; High_MWt; S+ Mechanistic Clearance Classification=HepUptake;
Human Rbp prediction saved in database. Predicted Rat Rbp = 1.25
Human Fup prediction saved in database. Predicted Rat Fup = 11.27%

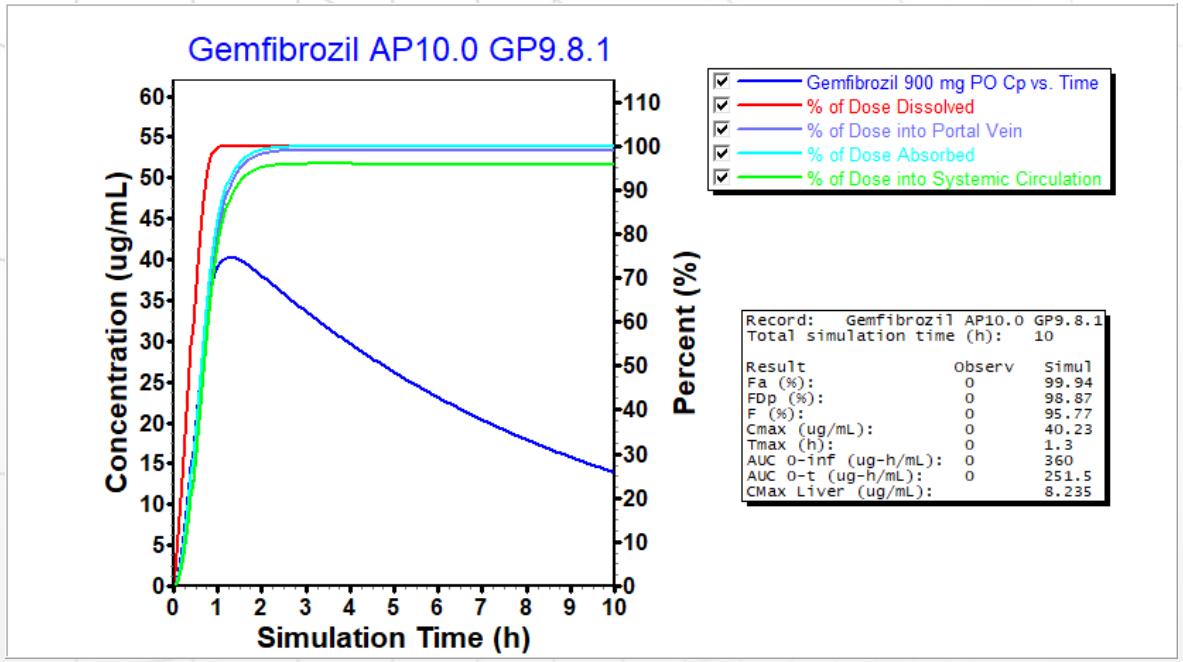
MBB, 4/5/2020, Updated 12/27/2020
Clinical data from
Changed log P to log D(7.4) = 1.3 Ref. Measured in Roche discovery assays: Baneyx-EurJPharmSci-56-1-2014-PBPK modeling of CYP3A4 induction by rifampicin
Used log P = 1.5 to calculate Kps and chnaged back log p= 1.3
Changed Solubility to 0.64 at pH 5.5 Ref. Becker-J Pharm Sci-98-7-2252-2009-Rifampicin Biowaiver monograph- pH Vs Solubility profile
Roche PAMPA based conversion to Peff = 0.4E-4 cm/s (a value determined from PAMPA. Ref. Measured in Roche discovery assays: Baneyx-EurJPharmSci-56-1-2014) was increased by 6.2-Fold to 2.48E-4 cm/s per Baneyx for all records.
Changed fup% = 7% Ref. Yoshikado-ClinPharmTherap-100-5-513-2016-Supplement
Changed Rbp = 0.8 to calculate Kps that match the Noncompartmental Vdss for healthy subjects.
etc.

Induction Added: NOTE: EC50.u = 64 nM Unbound 3A4 induction from Asaumi R, CPT Pharmacometrics Syst. Pharmacol. 7: 186 (2018). Applied to all PXR related genes.
P-gp EC50,t,HLM = 26 uM and Emax = 4.4 Ref: Anuzanit-J pharm Pharm Sci-14-2-236-2011- Induction of P-gp by rifampin
P-gp EC50,t,Hep = 0.064 uM and Emax = 2.2 Ref. Lutz-CPT-104-6-1182-2018 concludes that EC50 for PXR induced genes should be the same.
etc.
UGT1A1 EC50,t,Hep = 0.0.64 uM and Emax = 4.4 Emax is the average of 3 values from Moscovitz (Note: Same Emax as UGT2B7 which are in both Gut and Liver Ref. Moscovitz, 2018
etc.

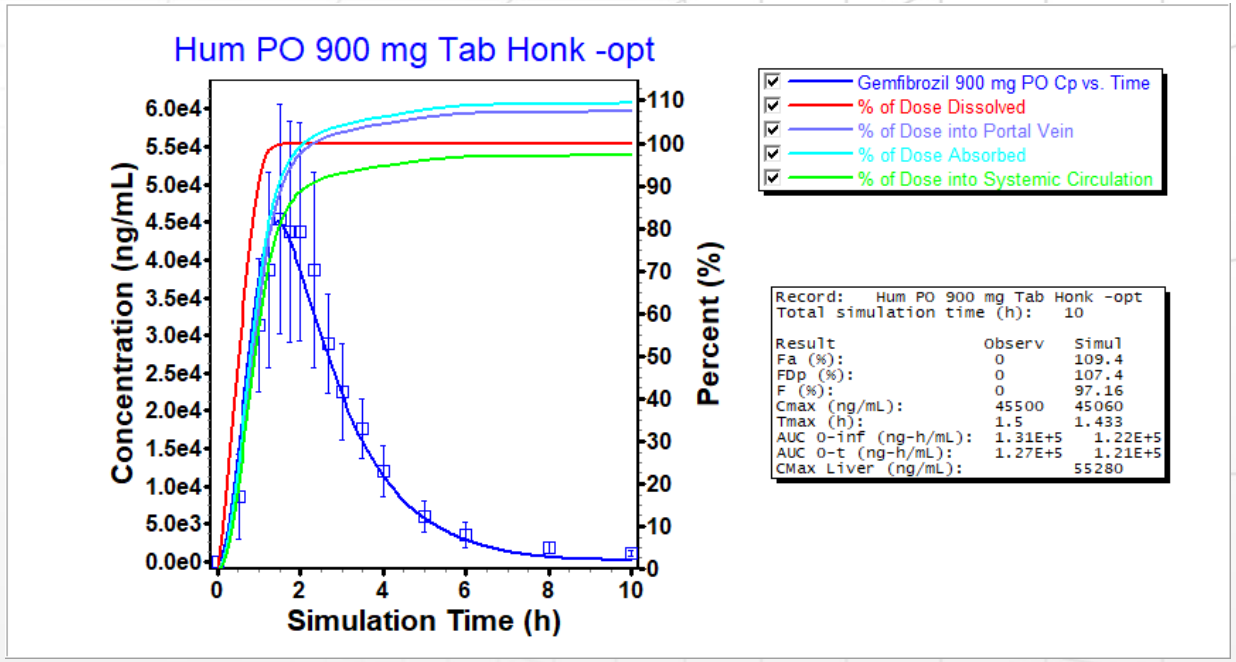
Inhibition Added:
P-gp inhibition Ki,t,HLM = 13.7 uM Substrate E17G and NMQ Ref. for HEK293 iinverted memb. vessicles Ave. Pedersen-EurJPharmSci-103-70-2017
OATP1B1 inhibition Ki = 0.62 uM Substrate = 3H-TIC Ref. Takashima T. J. Nucl. Med. 53:741 (2012)
3A4 inhibition Ki,u = 18.5 uM Ref. Kajosaari-BasicClinicalPharmacolToxicol-97-249-2005
etc.

Hum PO 900 mg Tab *in silico vs.* Honkalammi

Purely *in silico*



All mechanisms *in silico, in vitro, & fitted*



Physiology used: Healthy Male 23 years 73 Kg 23 BMI

All mechanisms PBPK Model: Liver and Kidney were assumed Permeability limited organs; the rest were assumed perfusion limited Kps for the Glucuronide record were calculated using the Poulin-extracellular method was used for both Perfusion Limited and for Permeability limited tissues.

Honkalammi et.al., Drug. Metab. Dispos. 39(10):1977(2011)

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.

Outline of Process for Model Development and Documentation

- Creation of GP a project starts with structure import using ADMET Predictor Module for both substrates and perpetrators.
  - Physicochemical, biopharmaceutical, and biochemical properties
  - Initial evaluation via “Chemistry Classification” with all aspects of ADMET
    - Solubility vs. pH, dissolution, absorption (w/ influx and efflux transporters), clearance (metabolic, biliary, and renal), distribution, excretion, and toxicity.
  - Extensive literature collection and spreadsheet documentation.
    - Workbook with multiple sheets for Physicochemical, Metabolic, Transporter, Preclinical, and Clinical single compound and DDI study data for multiple perpetration mechanisms.
  - 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.

Human Cp vs. time profiles before and after GEM and GEM-glucuronide DDIs

Subset of 13 references from a total of 83:

1. Hermening-JChromatogrBBiomedSci-741-2-129-2000-PK profiles-of-gemfibrozil-and-glucuronide-and-covalent-adducts-PO-900-mg
2. Hirano-DrugMetabDisp-34-7-1229-2006-DDI-Pitavastatin-Verapamil-Ki-hepatic-uptake-OAT1B1
3. Ho-Gastroenterology-130-6-1793-2006-Rosuvatatin-hepatic-uptake-OATP and NTCP-Vmax-Km transporters
4. Honkalammi-DrugMetabDispos-39-10-1977-2011-Human data-Repaglinide-Gemfibrozile DDI-2C8 activity
5. Kajosaari-Backmann-BasicClinPharmcolToxicol-97-249-2005-Metabolism-Repaglinide-Gemfibrozil-CYP2C8-Ki-CYP3A4
6. Nakagomi-Xenobiotica-37-4-416-2007_Inhibition of hOAT3 pravastatin transport by gemfibrozil and glucuronide human
7. Nakagomi-Hagihara-Xenobiotica-37-5-474-2007-Gemfibrozil-and-its-glucuronide-inhibit-OATP1B1
8. Ogilvie-DrugMetabDispos-34-1-191-2006-Gemfibrozil Glucuronide-HLM study-NADPH dependent inactivation-2C8
9. Schneck-ClinPharmacolTher-75-5-455-2004-Rosuvastatin and Gemfibrozil DDI
10. Wang-CPT- PharmacometSysPharmacol-6-4-228-2017-Transporter Based DDI Rosuvastatin PBPK model SimCyp
11. Wen-Neuvoven-DrugMetabDisposition-29-11-1359-2001-invitro-2C9 inhibition-Gemfibrozil
12. Yamazaki-Lin-Xenobiotica-35-7-737-2005-OATP1B1-MRP2-P-gp-mediated transport-Gemfibrozil-DDI-Fibric acid derivatives
13. Yoshida-ClinPharmTherap-91-6-1053-2012-Transporter-DDI-of-OATP-Substrates-from-in-vitro-studies-w-Supplements

Extensive Workbook for all DDI Standards

	A	B	C	D	E
1	Gemfibrozil Physicochemical Properties			MWt	
2	SS, 05\18\2020 Updated 09\22\2020			250.34	
3					
4					
5		**Property**	**Value**	**Units**	**Ref.**
6		S+logP	4		ADMET Predictor ver. 10.0
7		Exp log D (Oct/H2O)@pH 7.4	2.8		Luner-Radebaugh-PharmRes-11-12-1755-1994-Gemfibrozil-pH sol
8		Exp log P extrapolated from Log D	5.2		GP 9.7
9		**pKas**			
10		S+Acid pKa	4.92		ADMET Predictor ver. 10.0
11		Exp Acid pKa	5		Luner-Radebaugh-PharmRes-11-12-1755-1994-Gemfibrozil-pH sol
12		**Solubility**			
13		S+Sw	0.0826	mg/mL	ADMET Predictor ver. 10.0
14		S+pH	4.24		ADMET Predictor ver. 10.0
15		S+Solublity Factor	276.89		ADMET Predictor ver. 10.0
16		Aq. Sol from GSE	0.00213	mg/mL	Yalkowsky GSE
17		Exp. Solubility @ pH 1 @37 deg C	0.02000	mg/mL	Luner-Radebaugh-PharmRes-11-12-1755-1994-Gemfibrozil-pH sol
18		S+FaSSIF @ pH 6.5	0.4200	mg/mL	ADMET Predictor ver. 10.0
19		S+FeSSIF @ pH 5.0	0.6200	mg/mL	ADMET Predictor ver. 10.0
20		**Permeability**			
21		S+Peff	7.33E+04	cm/s	ADMET Predictor ver. 10.0
22		Caco-2 Papp A->B	5.89E-05		Absorptions Systems Lighthouse Database
23		Caco-2 Papp B->A	4.73E-05		Absorptions Systems Lighthouse Database
24		Ratio B->A / A->B	0.80		
25		GeoMean B->A and A->B	5.28E-05		Absorptions Systems Lighthouse Database
26		P-gp Substrate	No	Yes/No	
27		Caco-2 Converted to Hum Peff	5.60E-04	cm/s	Converted from GeoMean of Absorption Systems Caco-2
28		**Blood to Plasma Conc. Ratio**			
29		S+Rbp	0.67		ADMET Predictor ver. 10.0
30		Ex Rbp			
31		Fitted for PBPK			
32		**Fraction Unbound in Plasma**			
33		S+PrUnbnd	5.18	%	ADMET Predictor ver. 10.0
34		Ex fup	3.5	%	Oprea and Benet Wombat database
35		Ex fup	2	%	Miller-ClinPharmacokinet-34-2-155-1998-Clinical PK of Fibric Acid
36		**Melting Point**			

Estimated free base solubility using GSE Ref. Sanghvi-Yalkowsky-QSARCombSci-22-2-258-2003-Estima

log S = 0.5 – 0.01(m.p. °C – 25) – log P solution logS= 0.5 -0.01(122-25)-3.97= -4.45

Aq. Sol

-5.07E+00 Log Sol (M)

8.51E-06 **M**

0.002 g/L

ISIS/Base

File Edit Options Object Database Search List Window Help

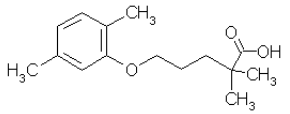
BIOBYTEMASTER-2008.DB/Main

ISIS/Base

File Edit Options Object Database Search List Window Help

ABS-SYSTEMS-LIGHTHOUSE-DATABASE-MBB-3-15-05.DB/Main

Forms Query Browse Update <Root> Search Domain: All 1 of 1

Structure	ID	LDS_PN
	186	L0186
	Compound_Name: Gemfibrozil	CAS_RegistryNumber: 25812-30-0
	*fmla_Structure: $C_{15}H_{22}O_3$	*mol.weight_Structure: 250.3408
	Selected	Therapeutic_Category: Antihyperlipoproteinemic

PctBound_HumanPlasmaProt_Log	PctBound_RatPlasmaProt_Log	OralBioavailability_LitValue: 98.0000	MolWeight_LDS_File: 250.3000
PctRemaining_HumanLiverMsomes: 35.3000	PctRemaining_RatLiverMsomes: 67.5000	Papp_Caco2_AB_Log (Papp x 10E6): 1.7699	Papp_Caco2_BA_Log: 1.6746
BrainPlasmaRatioRat_Log	Clearance_LitValue (L/h): 1.7000	Papp_MDR_MDCK_AB_Log	Papp_MDR_MDCK_BA_Log
DoseNumber_LitValue: 240.0000	EffluxRatio_Caco2_Log: -0.0953	pKa1: 4.8900	pKa2
EffluxRatio_MDR_MDCK_Log	HIA_LitValue	pKa3	HIA_LitValue
InVitroHalfLife_HumanLvrMsomes (min): 63.3000	InVitroHalfLife_RatLiverMsomes (min): 37.9000	Solubility_LitValue (mg/mL): 0.0100	Solubility_pH20 (mg/mL)
LogP_Predicted: 4.8000	LogP: 4.6370	Solubility_pH74	Uptake_RatBrainPerfusion_Log
MaximumDoseStrength_LitValue: 0.0100	VolumeOfDistribution_LitValue (L/Kg): 0.1400	CLint_uL_min_milCells	CLint_mL_min_mg
Papp_Caco2_AB_BCS_pH65	Recov_Caco2_AB_BCS_pH65	Papp_Caco2_AB_BCS_pH74	Recov_Caco2_AB_BCS_pH74

Gemfibrozil-Physicochemical | GGluc-Physicochemical | Metabolism-Hermening 2000 | Metab & CLint-UGT | Transporter-OATP1B1 | CYP E

Model-Inform

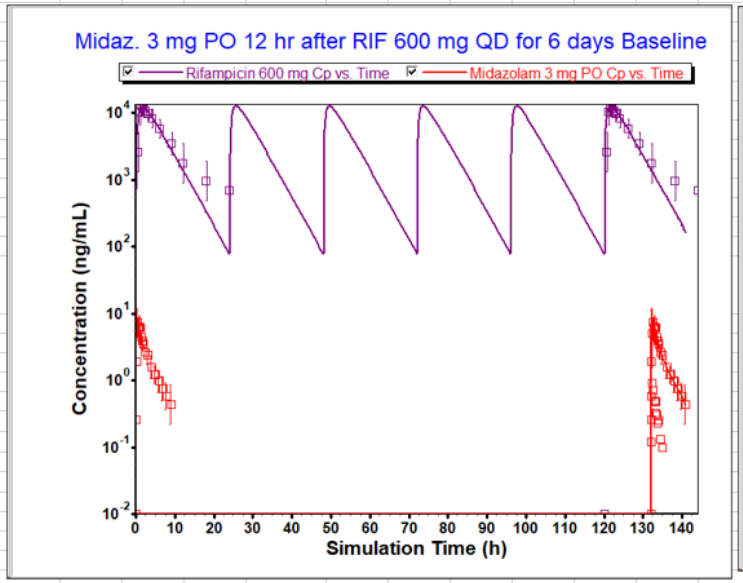
MIDD+

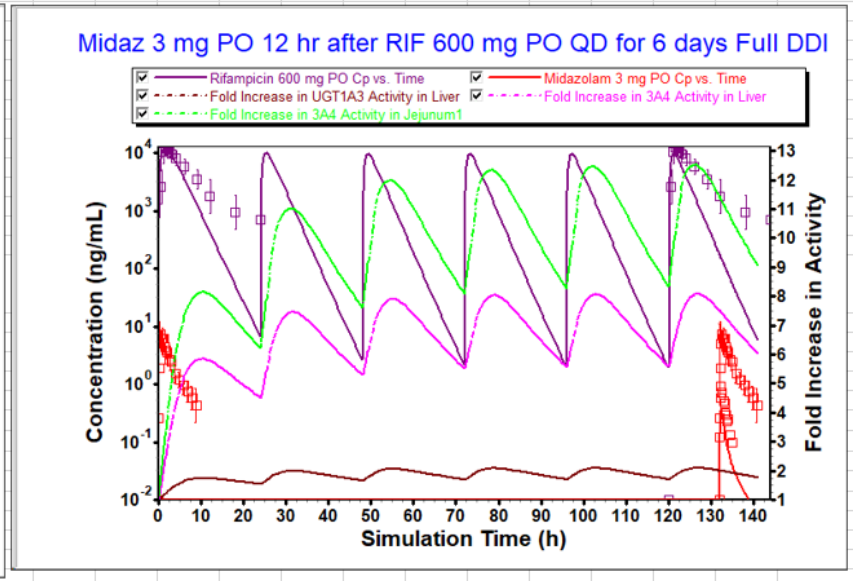
2021 Virtual Conference

Extensive Workbook for all DDI Standards

All subjects received 3 mg oral MDZ, followed by the indicated dose of oral ALF. Results are given as mean ± SD (N = 10).
ND, Not determined (the calculated F_G for MDZ after rifampin was either zero or indefinite because F_H was zero); CL/F, oral clearance; V_c/F, volume of central compartment; F_{oral}, oral bioavailability; F_G, intestinal bioavailability; CL_{mioniv}, effect clearance.
*Significantly different from same-dose control ($P < .05$).

GastroPlus(TM) 9.8.0008	12/23/2020	9:24:33 AM						
Compound 1:	Victim							
Database:	Midazolam-GP-9.7-DDI-Standard-VL-2020-09-07-MBB-2020-12-22.mdb							
Record:	Midaz PO 3.0mg vs RIF 600mg 5d Kharasch							
Compound 2:	**Perpetrator: 3A4 ind. & inh., UGT1A3 ind., MRP2 inh., and OATP1B1 inh.**							
Database:	Rifampicin-GP9.8-DDI-Standard-KS-MBB-SA-RC-2020-12-22.mdb							
Record:	Rifamp 600mg PO DDI PO 3mg MDZ Kharasch							
[NewTable]	Dynamic Simulation Results							
Compound	Fa [%]	FDp [%]	F [%]	Cmax [ug/mL]	Tmax [h]	AUC(0-t) [ng-h/mL]	AUC(0-inf) [ng-h/mL]	
Midaz PO 3.0mg vs RIF 600mg 5d Kharasch-baseline	99.99	27.94	15.15	0.00688	132.7	18.26	20.13	
Rifamp 600mg PO DDI PO 3mg MDZ Kharasch-baseline	99.95	97.86	90.54	12.76	121.6	473000	474000	
RIF-Gluc Metabolite-baseline	0	0	0	1.907	99.64	99900	100000	
Midaz PO 3.0mg vs RIF 600mg 5d Kharasch-DDI	99.99	5.487	0.756	0.00034	132.4	0.524	0.54	
Rifamp 600mg PO DDI PO 3mg MDZ Kharasch-DDI	99.97	86.52	75.92	12.18	1.5	251000	251000	
RIF-Gluc Metabolite-DDI	0	0	0	2.419	3.76	92500	92600	
Midaz PO 3.0mg vs RIF 600mg 5d Kharasch-ratio	1	0.196	0.05	0.05	0.998	0.029	0.027	
Rifamp 600mg PO DDI PO 3mg MDZ Kharasch-ratio	1	0.884	0.839	0.955	0.012	0.531	0.53	
RIF-Gluc Metabolite-ratio	0	0	0	1.268	0.038	0.926	0.926	





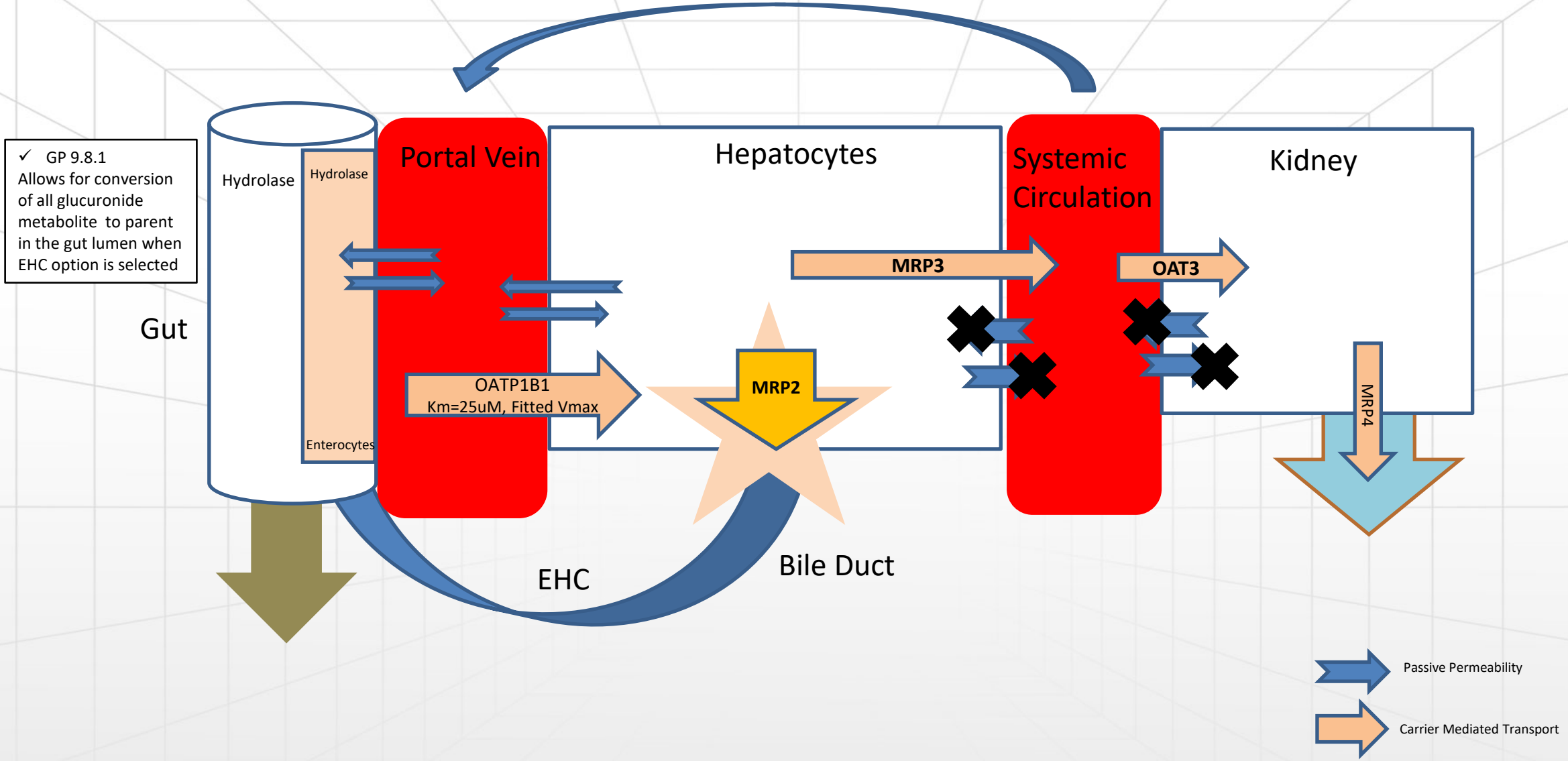
Peloquin 600mg PO Results | Acocella 600mg 900mg PO QD | Acocella 600mg 900mg Results | Kharasch 2011 600mg DDI Alf IV | Khar. 2004 600mg vs Midaz IV | **Khar. 2004 600mg vs Midaz PO**

Inclusion of a spreadsheet for fast editing of Perpetrator Table with new "Validated" Field

H58: Ogilvie-Parkinson-DrugMetabDispos-34-1-191-2006-Reversible Inhibition (IC50,t,HLM) of paclitaxel metabolism by gemfibrozil glucuronide in HLM.

	A	B	C	D	E	F	G	H	I	J	K	L	M
1		**Perpetrators Table**											
2	OrigOr	Generic	Enzyme	InhibitionConstant	InhibitionConstantUnits	InhibitionConstantType	Substrate	Reference	InVitroFu	InVitroFuType	InVitroProtConc	Kinact	Validate
84	82	Gem Gluc Tornio EC Kps	2C8	20	uM	IC50-irr-in vitro, T	Paclitaxel	Ogilvie-Parkinson-DrugMetabDispos-34	0.992	Calc(Hallifax)-HLM	0.1	0.21	TRUE
85	83	Gem Gluc Tornio EC Kps	2C8	24	uM	IC50-rev-in vitro, T	Paclitaxel	Ogilvie-Parkinson-DrugMetabDispos-34	0.826	Calc(Hallifax)-HLM	0.5	0	FALSE
86	84	Gem Gluc Tornio EC Kps	OAT3	9.9	uM	Ki-rev-in vitro, U	14C-Pravastatin	Nakagomi-Hagihara-Xenobiotica-37-4-4	-1	Unknown	0.5	0	TRUE
87	85	Gem Gluc Tornio EC Kps	OAT3	13	uM	IC50-rev-in vitro, U	Unknown	Yoshida-ClinPharmTherap-91-6-1053-20	-1	Unknown	0.5	0	FALSE
88	86	Gem Gluc Tornio EC Kps	OATP1B1	22.6	uM	Ki-rev-in vitro, U	3H-Pitavastatin	Hirano-Sugiyama-DrugMetabDispositio	-1	Unknown	0.5	0	FALSE
89	87	Gem Gluc Tornio EC Kps	OATP1B1	15.7	uM	Ki-rev-in vitro, T	14C-Pravastatin	Nakagomi-hagihara-Xenobiotica-37-5-4	0.987	Calc(Austin)-Hep	0.5	0	FALSE
90	88	Gem Gluc Tornio EC Kps	OATP1B1	7.6	uM	Ki-rev-in vitro, U	14C-Pravastatin	Nakagomi-hagihara-Xenobiotica-37-5-4	-1	Unknown	0.5	0	TRUE
91	89	Gem Gluc Tornio EC Kps	OATP1B1	14	uM	IC50-rev-in vitro, U	Unknown	Yoshida-ClinPharmTherap-91-6-1053-20	-1	Unknown	0.5	0	FALSE
92	90	Gem Gluc Tornio EC Kps	OATP1B3	74	uM	IC50-rev-in vitro, U	Unknown	Yoshida-ClinPharmTherap-91-6-1053-20	-1	Unknown	0.5	0	FALSE
93	91	GEM PO 600 mg DDI Repag Tornio	2C8	30.4	uM	Ki-rev-in vitro, T	Paclitaxel	Kajosaari-Backmann-BasicClinPharmcol	0.826	Calc(Hallifax)-HLM	0.5	0	TRUE
94	92	GEM PO 600 mg DDI Repag Tornio	2C8	120	uM	IC50-rev-in vitro, T	Paclitaxel	Ogilvie-Parkinson-DrugMetabDispos-34	0.826	Calc(Hallifax)-HLM	0.5	0	FALSE
95	93	GEM PO 600 mg DDI Repag Tornio	2C9	30	uM	IC50-rev-in vitro, T	Diclofenac	Ogilvie-Parkinson-DrugMetabDispos-34	0.826	Calc(Hallifax)-HLM	0.5	0	FALSE
96	94	GEM PO 600 mg DDI Repag Tornio	2C9	4	uM	Ki-rev-in vitro, U	Tolbutamide	Wang-JPET-302-1-43-2002-Unbound inhi	-1	Unknown	0.5	0	FALSE
97	95	GEM PO 600 mg DDI Repag Tornio	2C9	5.8	uM	Ki-rev-in vitro, T	Tolbutamide	Wen-Neuvoven-DrugMetabDisposition-	0.826	Calc(Hallifax)-HLM	0.5	0	TRUE
98	96	GEM PO 600 mg DDI Repag Tornio	NTCP	23	uM	IC50-rev-in vitro, U	Rosuvastatin	Ho et al-Gastroenterology. 2006-130(6)1	-1	Unknown	0.5	0	FALSE
99	97	GEM PO 600 mg DDI Repag Tornio	OAT3	3.4	uM	Ki-rev-in vitro, U	14C-Pravastatin	Nakagomi-Hagihara-Xenobiotica-37-4-4	-1	Unknown	0.5	0	FALSE
100	98	GEM PO 600 mg DDI Repag Tornio	OAT3	3.2	uM	IC50-rev-in vitro, U	Unknown	Yoshida-ClinPharmTherap-91-6-1053-20	-1	Unknown	0.5	0	FALSE
101	99	GEM PO 600 mg DDI Repag Tornio	OATP1B1	25.2	uM	Ki-rev-in vitro, U	3H-Pitavastatin	Hirano-Sugiyama-DrugMetabDispositio	-1	Unknown	0.5	0	FALSE
102	100	GEM PO 600 mg DDI Repag Tornio	OATP1B1	31.7	uM	Ki-rev-in vitro, T	14C-Pravastatin	Nakagomi-hagihara-Xenobiotica-37-5-4	0.645	Calc(Austin)-Hep	0.5	0	FALSE
103	101	GEM PO 600 mg DDI Repag Tornio	OATP1B1	15.1	uM	Ki-rev-in vitro, U	14C-Pravastatin	Nakagomi-hagihara-Xenobiotica-37-5-4	-1	Unknown	0.5	0	FALSE
104	102	GEM PO 600 mg DDI Repag Tornio	OATP1B1	4	uM	IC50-rev-in vitro, U	3H-Rosuvastatin	Schneck-ClinPharmacolTher-75-5-455-2	-1	Unknown	0.5	0	FALSE
105	103	GEM PO 600 mg DDI Repag Tornio	OATP1B1	12.5	uM	Ki-rev-in vitro, U	3H-E217BETAG	Yamazaki-Lin-Xenobiotica-35-7-737-200	-1	Unknown	0.5	0	TRUE
106	104	GEM PO 600 mg DDI Repag Tornio	OATP1B1	20	uM	IC50-rev-in vitro, U	Unknown	Yoshida-ClinPharmTherap-91-6-1053-20	-1	Unknown	0.5	0	FALSE

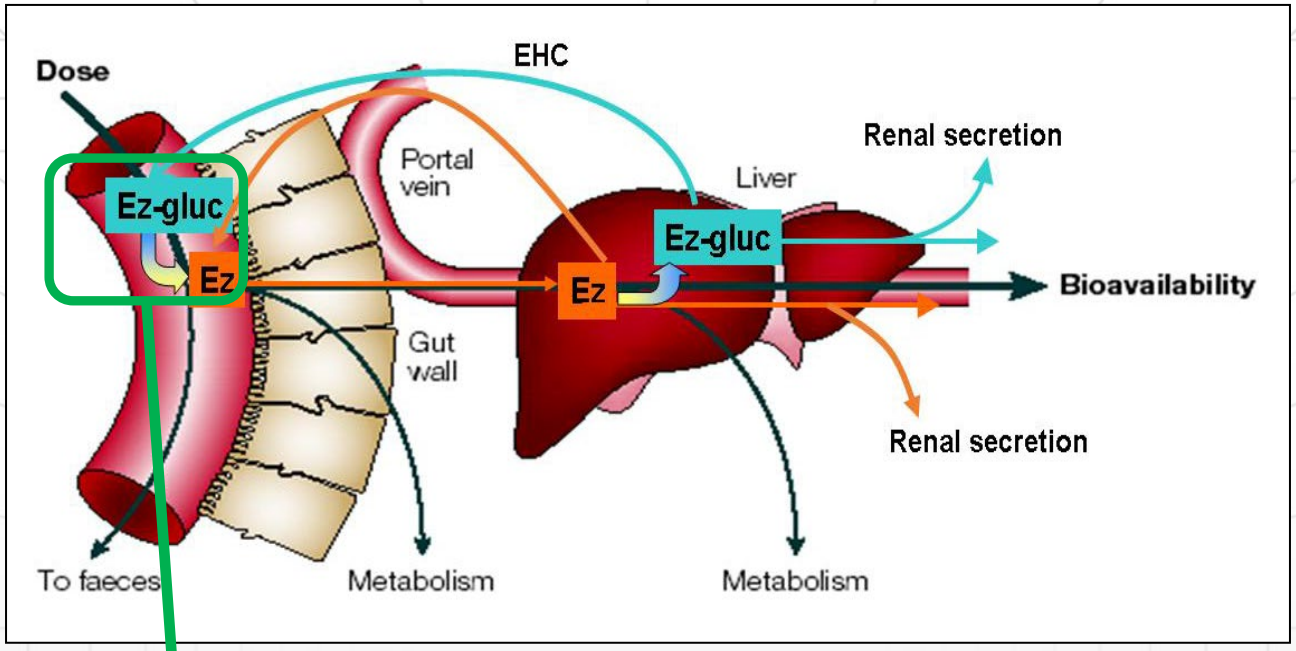
For example: the rifampicin perpetrator table has > 400 rows

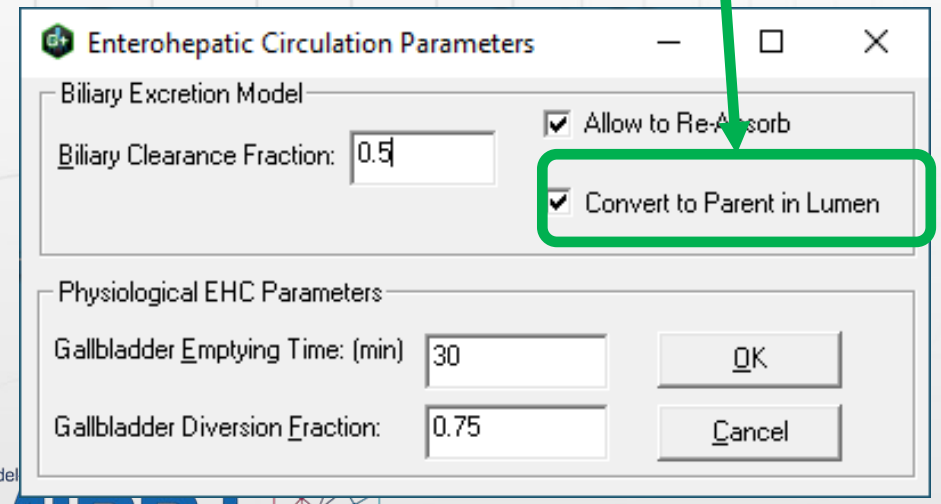


Metabolite- Gemfibrozil Glucuronide

16

Acyl-glucuronide Conversion to Parent in Gut Lumen



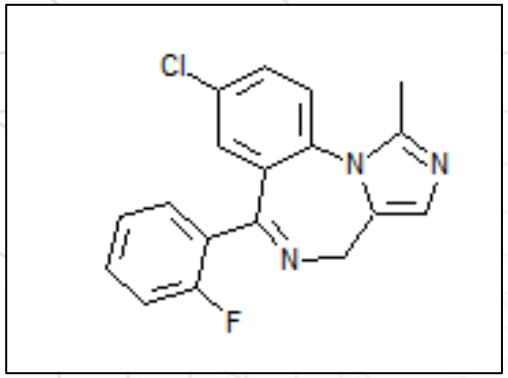


- This is not a general solution for compound metabolism in gut lumen (that is coming in GPX)
- It is applicable primarily for acyl-glucuronide metabolites
- It produces parent compound in the lumen for re-absorbtion
- Assumes breakdown of glucuronides so molecular ratio = 1

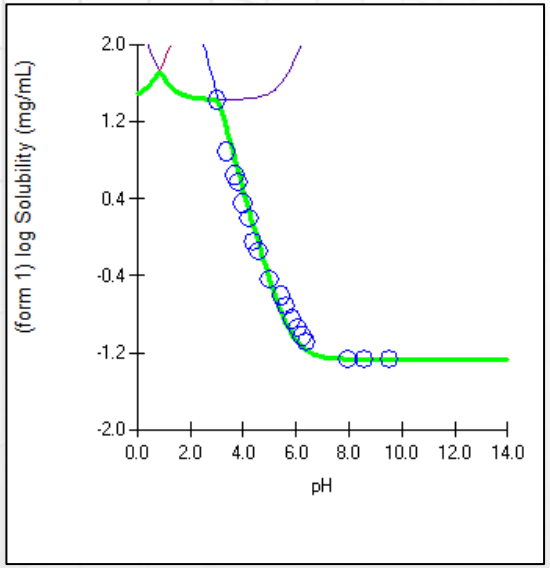
Outline of Process for Model Development and Documentation

- Creation of GP a project starts with structure import using ADMET Predictor Module for both substrates and perpetrators.
  - Physicochemical, biopharmaceutical, and biochemical properties
  - Initial evaluation via “Chemistry Classification” with all aspects of ADMET
    - Solubility vs. pH, dissolution, absorption (w/ influx and efflux transporters), clearance (metabolic, biliary, and renal), distribution, excretion, and toxicity.
  - Extensive literature collection and spreadsheet documentation.
    - Workbook with multiple sheets for Physicochemical, Metabolic, Transporter, Preclinical, and Clinical single compound and DDI study data for multiple perpetration mechanisms.
  - 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.

Midazolam BCS/BDDCS II Physicochemical Properties



MW = 325.77



AP 9.5 = ADMET Predictor v. 9.5
S+ = properties predicted with Simulations Plus models
S+Sw = native solubility in pure water
S+Peff = human jejunal permeability estimate

S+LogP = 3.56 (AP 9.5)
Exp LogP = 2.7 (Hoffmann-La Roche)

S+pKa = 4.57 (Base) and 0.84 (Base
Exp pKa = 6.04 (Andersin-JPharmaceutBioMedAnal-9-6-451-1991)

S+Sw = 2.1 μg/mL @ pH = 7.05 (AP 9.5)
Exp Sw = 54 μg/mL @ pH 9.5 Andersin, 1991) LOW

S+FaSSIF = 33 μg/mL, S+ FeSSIF = 210 μg/mL
Exp FaSSIF = 11 μg/mL, (personal communication ??)

S+Peff = 7.55 x 10^{-4} (cm/s) (AP 9.5) HIGH
Exp Ussing Papp = 3.8E-5 cm/s (Sjoberg-Ungel, 2013)
Conversion to Hum. Jej. Peff = 3.82E-4 cm/s

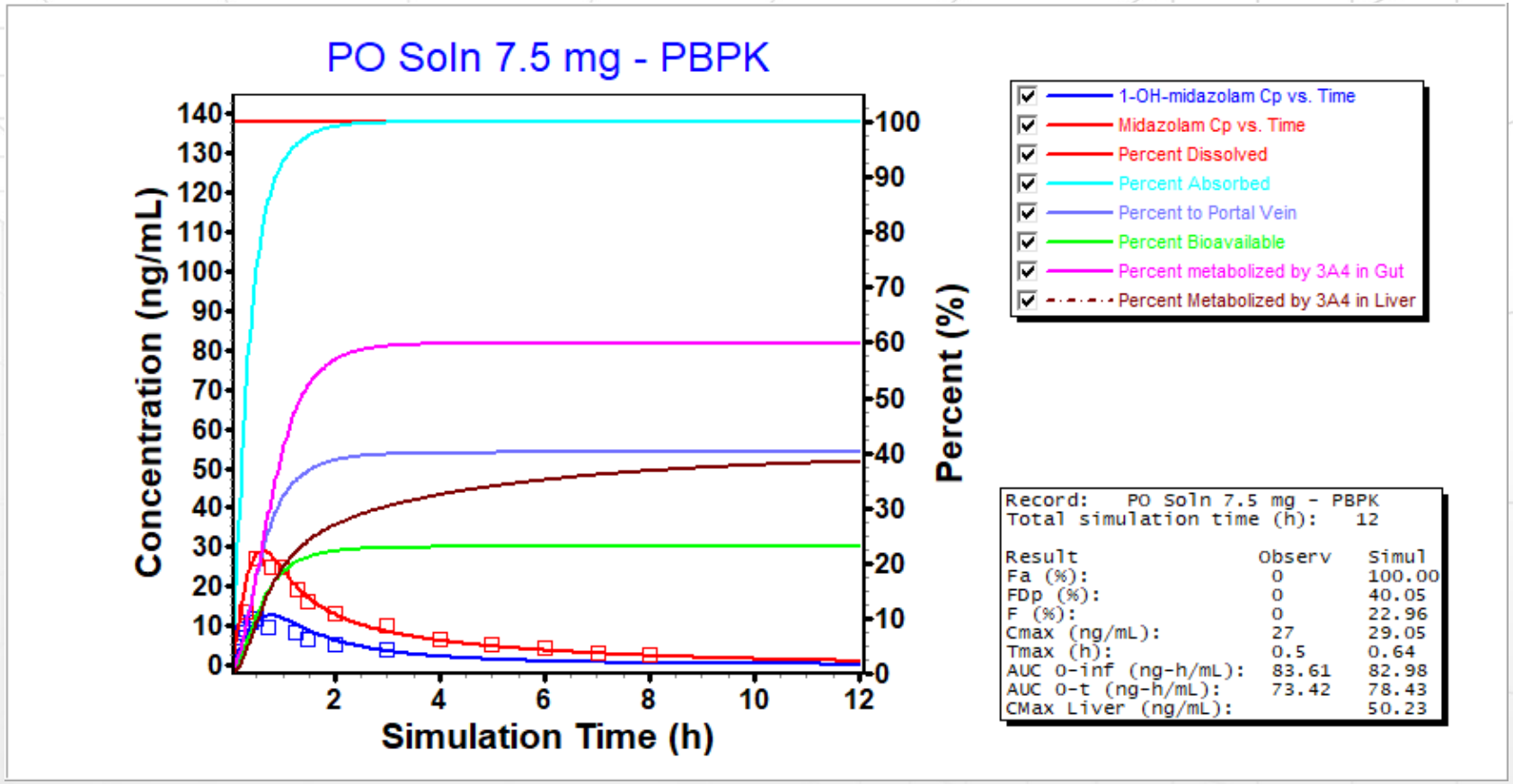
S+HLM-3A4 Km = 21 μM Vmax = 3.5 nmol/min/mg Prot. (AP 9.5)
Exp CYP3A4 Km = 3.7 μM (Paine, 1997)
Exp CYP3A4 Vmax = 0.85 nmol/min/mg Prot.
Exp CYP3A4 Km = 2.27 mM (Walsky, 2004)
Exp CYP3A4 Vmax = 1.22 nmol/min/mg Prot.

S+hum_fup% = 6.61 (AP 9.5)
Exp. Fup = 4.4% Ave. (de Vries, 199) and (Fisher, 1999)

S+RBP = 0.78 (AP 9.5)
Exp Rbp = 0.55 (Gertz, 2011)

PBPK Model for Midazolam 7.5 mg PO Solution Bornemann

- **Assumptions:**
  - Perfusion-limited midazolam
  - Permeability-limited liver and kidney for 1-OH-midazolam
  - Added MRP3 liver basolateral to efflux metabolite to systemic circulation for PO records only.
  - fu_{ent} = 4.4%
- **Clearance:**
  - Paine-J. Pharmacol. Exp. Ther., 283:1552 (1997) unbound K_m = 3.7 μM and V_{max} = 0.85 nmol/min/mg micro. Prot.
- **Distribution:**
  - Midazolam Lukacova default Kp calculation
  - 1-OH-midazolam reduced log P = 2.2 to calc. Kps and then ran simulation with log P = 2.57



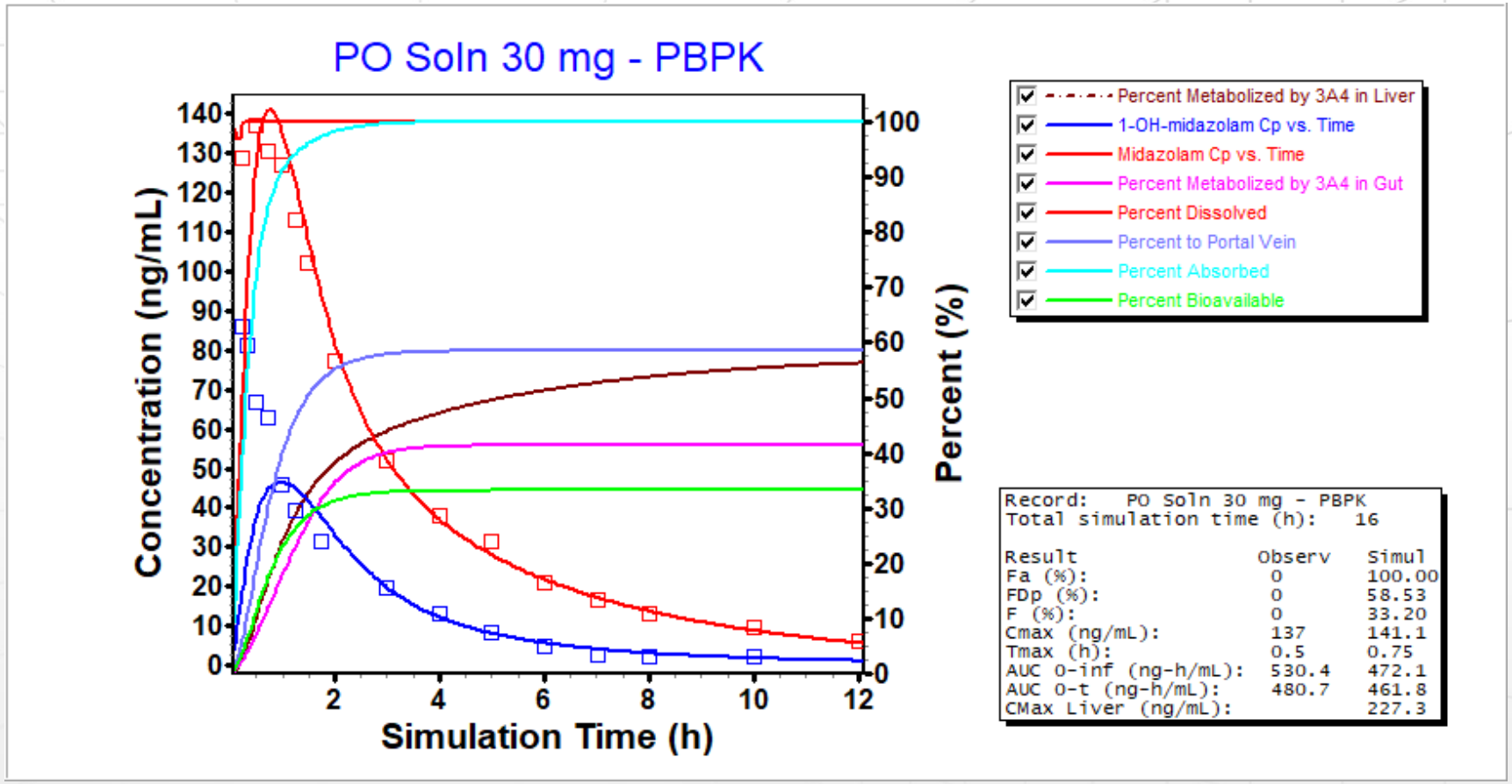
Record: PO Soln 7.5 mg - PBPK
Total simulation time (h): 12

Result	Observ	Simul
Fa (%):	0	100.00
FDp (%):	0	40.05
F (%):	0	22.96
Cmax (ng/mL):	27	29.05
Tmax (h):	0.5	0.64
AUC 0-inf (ng-h/mL):	83.61	82.98
AUC 0-t (ng-h/mL):	73.42	78.43
CMax Liver (ng/mL):		50.23

Clinical data from:
Bornemann-EurJClinPharmacol-29-1-91-1985

PBPK Model for Midazolam 30 mg PO Solution Bornemann

- **Assumptions:**
  - Perfusion-limited midazolam
  - Permeability-limited liver and kidney for 1-OH-midazolam
  - Added MRP3 liver basolateral to efflux metabolite to systemic circulation for PO records only.
  - fu_{ent} = 4.4%
- **Clearance:**
  - Paine-J. Pharmacol. Exp. Ther., 283:1552 (1997) unbound K_m = 3.7 µM and V_{max} = 0.85 nmol/min/mg micro. Prot.
- **Distribution:**
  - Midazolam Lukacova default Kp calculation
  - 1-OH-midazolam reduced log P = 2.2 to calc. Kps and then ran simulation with log P = 2.57

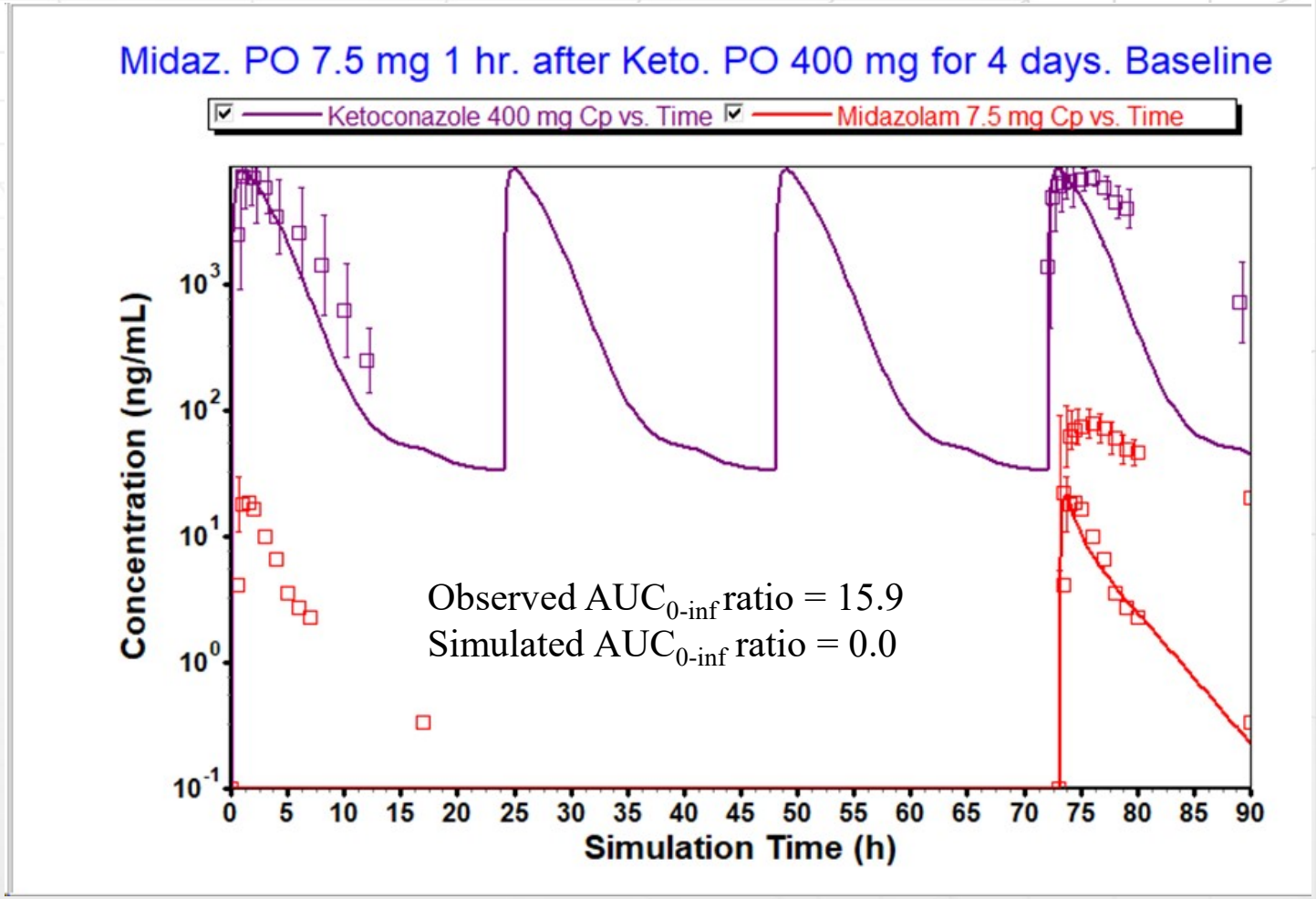


Clinical data from:
Bornemann-EurJClinPharmacol-29-1-91-1985

Midaz. 7.5 mg PO Tab DDI vs. Keto. 400 mg QD for 4 days: Olkkola

Baseline Simulation without DDI interactions

- **Assumptions:**
  - Perfusion-limited midazolam
  - Permeability-limited liver and kidney for 1-OH-midazolam
  - Ketoconazole: 3A4 total Rev. IC_{50} = 26 nM, 3A4 total Irrev. IC_{50} = 15 nM, Kinact = 0.001 min^{-1} and P-gp total IC_{50} = 5.6 µM
  - Reduced fu_{ent} = 4.4% (Ref. Trevaskis-PharmRes-28-9-2176-2011)
- **Clearance:**
  - Paine-J. Pharmacol. Exp. Ther., 283:1552 (1997) unbound $K_{m,u}$ = 3.7 µM and V_{max} = 0.977 nmol/min/mg micro. Prot. The 1.15-fold higher clearance was used due to the Olkkola population of 7 females and 2 male subjects.
- **Distribution:**
  - Midazolam Lukacova default Kp calculation
  - 1-OH-midazolam reduced log P = 2.2 to calc. Kps and then ran simulation with log P = 2.57



Midazolam clinical data from: Olkkola-ClinPharmacolTherap-55-5-481-1994
Ketoconazole clinical data from: Daneshmend-Antimicrobial agents and Chemotherapy-25-1-1-1984 and Olkkola-ClinPharmacolTherap-55-5-481-1994
Ketoconazole TDI parameters from: Haarhoff-Xenobiotica-47-6-470-2017

In vitro CYP3A Inhibition Parameters ($IC_{50,t,HLM}$) for Ketoconazole

Table 2. Evaluation of CYP3A inhibition with HLM and CLM.

	HLM			CLM		
	IC_{50} (μM)			IC_{50} (μM)		
Inhibitor	Non-preincubation (0 min)	Preincubation (30 min)	Ratio	Non-preincubation (0 min)	Preincubation (30 min)	Ratio
Amprenavir	0.55 ± 0.08	0.084 ± 0.025	6.5	0.3 ± 0.04	0.2 ± 0.03	1.7
Azithromycin	>100	>100	1.0	>100	>100	1.0
Bergamottin	>50	0.17 ± 0.04	>294.1	>50	1.3 ± 0.4	>38.5
Buspirone	>50	15.8 ± 2.9	>3.2	>50	>50	1.0
Cimetidine	>100	>100	1.0	>100	>100	1.0
Clarithromycin	>50	8.2 ± 0.3	>6.1	>50	15.1 ± 0.4	>3.3
Clozapine	>50	21.2 ± 3.7	>2.4	>50	27.2 ± 6.2	>1.8
Cyclosporin A	24.4 ± 5.8	5.8 ± 1.0	4.2	12.0 ± 2.6	7.0 ± 1.5	1.7
Dextromethorphan	>50	>50	1.0	>50	>50	1.0
Diltiazem	43.5 ± 8.6	7.7 ± 1.7	5.6	30.7 ± 4.8	1.4 ± 0.4	21.9
Erythromycin	>100	12.1 ± 3.3	>8.3	>100	54.2 ± 10.2	>1.8
Ethynylestradiol	41.7 ± 1.7	5.2 ± 0.5	8.0	31.4 ± 1.6	4.5 ± 0.8	7.0
Felodipine	4.1 ± 1.3	4.0 ± 0.4	1.0	4.5 ± 1.1	7.4 ± 2.2	0.6
Fluconazole	3.2 ± 0.6	3.7 ± 0.7	0.86	6.8 ± 0.9	6.9 ± 0.6	1.0
Fluoxetine	>50	>50	1.0	>50	>50	1.0
Fluvoxamine	>50	>50	1.0	>50	>50	1.0
Furafylline	>50	>50	1.0	>50	>50	1.0
Irinotecan	>100	>100	1.0	>100	>100	1.0
Isoniazid	>100	>100	1.0	>100	>100	1.0
Itraconazole	0.068 ± 0.017	0.017 ± 0.006	4.0	0.12 ± 0.02	0.054 ± 0.009	2.2
Ketoconazole	0.026 ± 0.010	0.015 ± 0.003	1.7	0.04 ± 0.006	0.056 ± 0.009	0.7
Mibefradil	0.67 ± 0.14	0.017 ± 0.004	39.4	1.0 ± 0.2	0.17 ± 0.04	5.9

- Optimized K_{inact} = 0.001 min^{-1} was used for irreversible inhibition

Publication supporting competitive and time-dependent inhibition by ketoconazole

Haarhoff-Xenobiotica-47-6-470-2017

Midaz. 7.5 mg PO Tab DDI vs. Keto. 400 mg QD for 4 days: Olkkola

Simulated AUC Ratio w/autoinhibition is accurate by adding: Irreversible IC_{50} for 3A4

- **Assumptions:**
  - Perfusion-limited midazolam
  - Permeability-limited liver and kidney for 1-OH-midazolam
  - Ketoconazole: 3A4 total Rev. IC_{50} = 26 nM, 3A4 total Irrev. IC_{50} = 15 nM, Kinact = 0.001 min^{-1} and P-gp total IC_{50} = 5.6 µM
  - Reduced fu_{ent} = 4.4% (Ref. Trevaskis-PharmRes-28-9-2176-2011)
- **Clearance:**
  - Paine-J. Pharmacol. Exp. Ther., 283:1552 (1997) unbound K_m = 3.7 µM and V_{max} = 0.977 nmol/min/mg micro. Prot. The 1.15-fold higher clearance was used due to the Olkkola population of 7 females and 2 male subjects.
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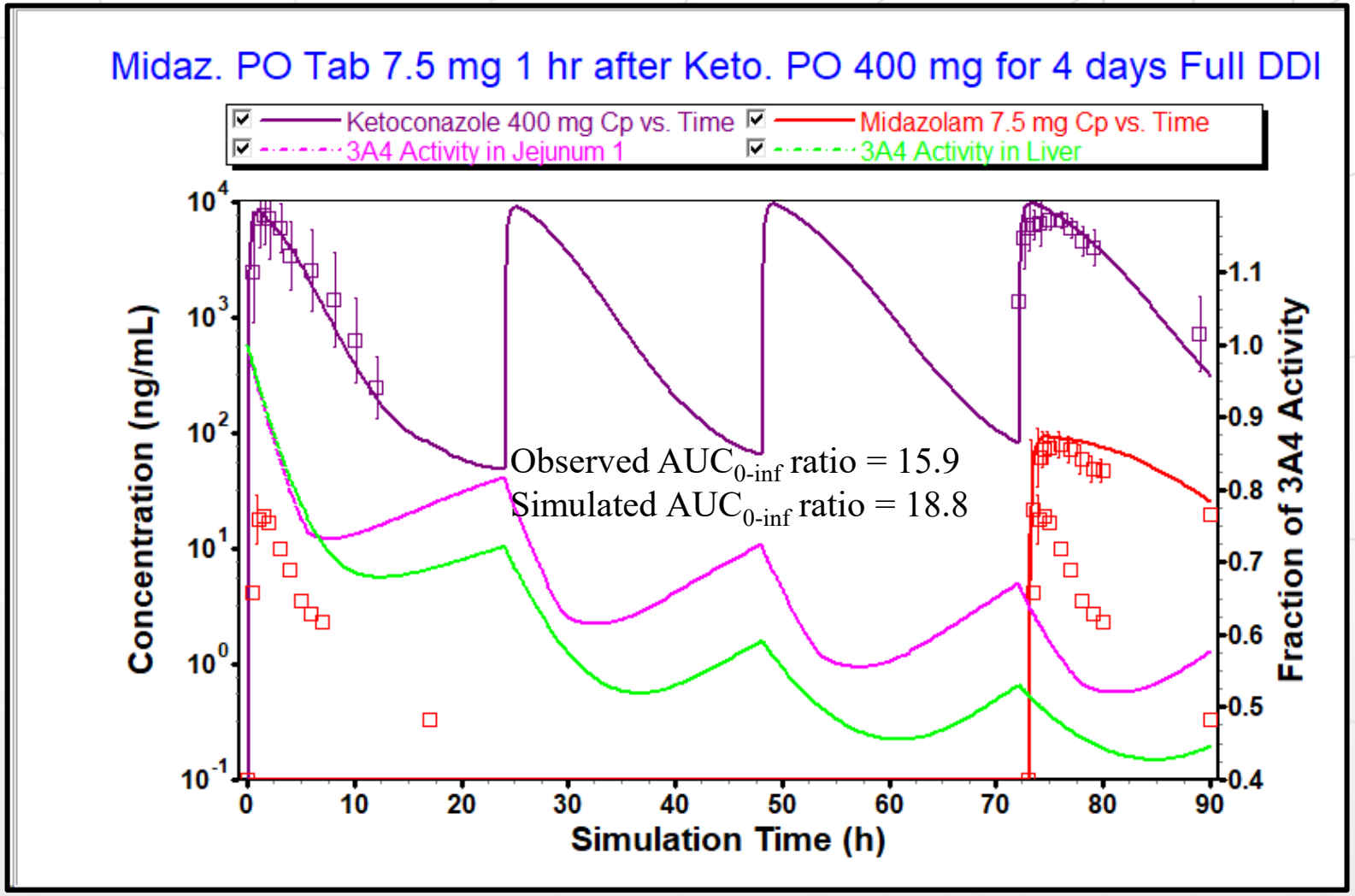
  - 1-OH-midazolam reduced log P = 2.2 to calc. Kps and then ran simulation with log P = 2.57



Midazolam clinical data from: Olkkola-ClinPharmacolTherap-55-5-481-1994
Ketoconazole clinical data from: Daneshmend-Antimicrobial agents and Chemotherapy-25-1-1-1984 and Olkkola-ClinPharmacolTherap-55-5-481-1994
Ketoconazole TDI parameters from: Haarhoff-Xenobiotica-47-6-470-2017

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  - Extensive literature collection and spreadsheet documentation.
    - Workbook with multiple sheets for Physicochemical, Metabolic, Transporter, Preclinical, and Clinical single compound and DDI study data for multiple perpetration mechanisms.
  - 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).
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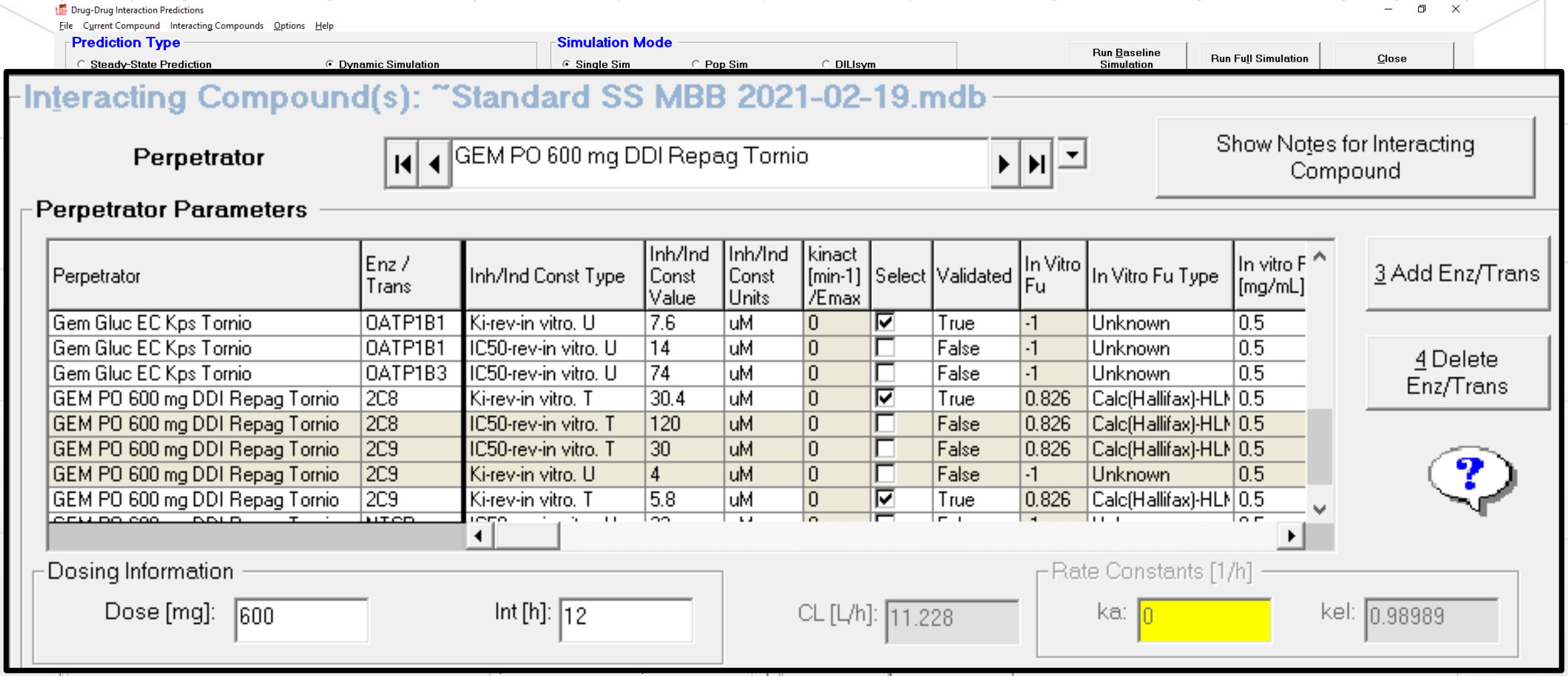
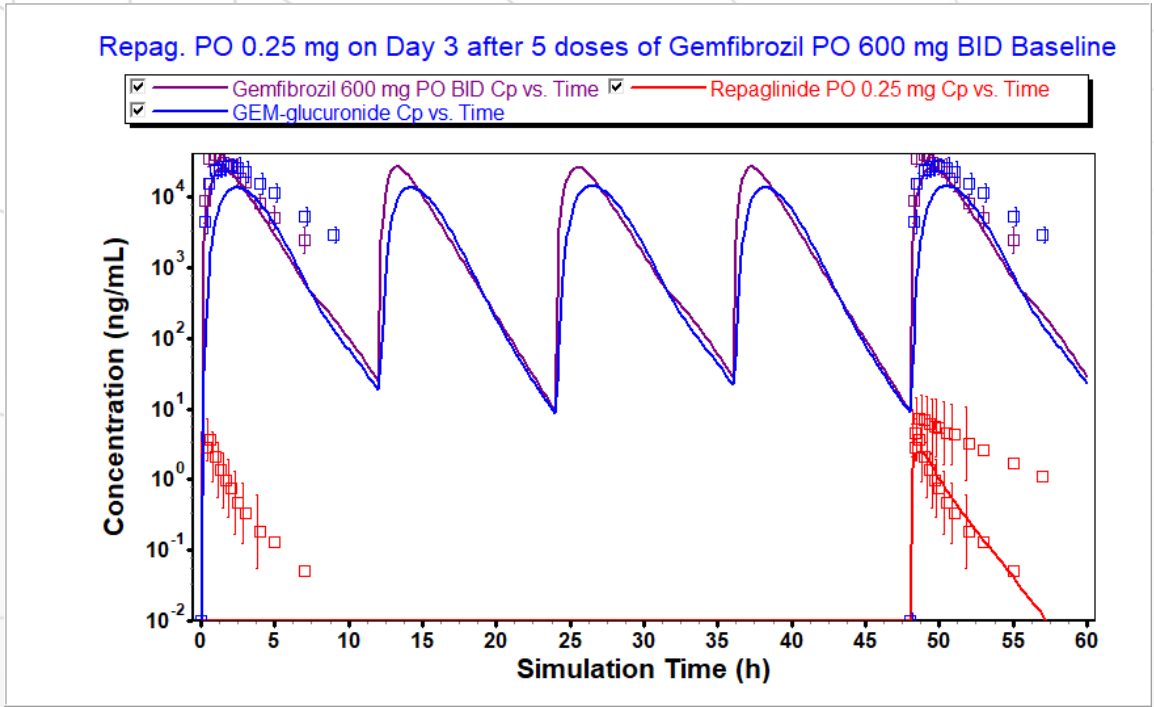
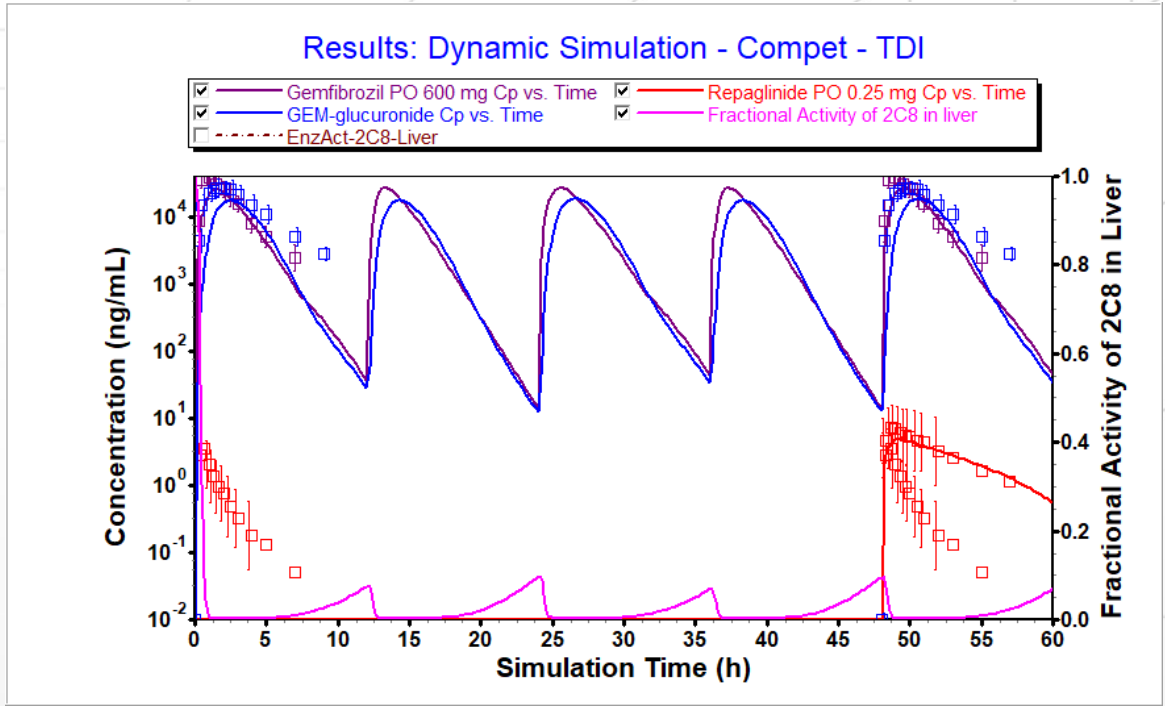
Newer DDI Module with “Validated” Field



Perpetrator	Enz / Trans	Inh/Ind Const Type	Inh/Ind Const Value	Inh/Ind Const Units	kinact [min-1] /Emax	Select	Validated	In Vitro Fu	In Vitro Fu Type	In vitro F [mg/mL]
Gem Gluc EC Kps Tornio	OATP1B1	Ki-rev-in vitro. U	7.6	uM	0	☑	True	-1	Unknown	0.5
Gem Gluc EC Kps Tornio	OATP1B1	IC50-rev-in vitro. U	14	uM	0	☐	False	-1	Unknown	0.5
Gem Gluc EC Kps Tornio	OATP1B3	IC50-rev-in vitro. U	74	uM	0	☐	False	-1	Unknown	0.5
GEM PO 600 mg DDI Repag Tornio	2C8	Ki-rev-in vitro. T	30.4	uM	0	☑	True	0.826	Calc(Hallifax)-HLM	0.5
GEM PO 600 mg DDI Repag Tornio	2C8	IC50-rev-in vitro. T	120	uM	0	☐	False	0.826	Calc(Hallifax)-HLM	0.5
GEM PO 600 mg DDI Repag Tornio	2C9	IC50-rev-in vitro. T	30	uM	0	☐	False	0.826	Calc(Hallifax)-HLM	0.5
GEM PO 600 mg DDI Repag Tornio	2C9	Ki-rev-in vitro. U	4	uM	0	☐	False	-1	Unknown	0.5
GEM PO 600 mg DDI Repag Tornio	2C9	Ki-rev-in vitro. T	5.8	uM	0	☑	True	0.826	Calc(Hallifax)-HLM	0.5

Repaglinide PO 2.5 mg on Day 3 after 5 doses of GEM 600 mg PO





Ki values selected are:
1.) 12.5 uM for OATP1B1 (Gemfibrozil parent)
2.) 7.6 uM for OATP1B1 (Glucuronide)
3.) 30.4 uM for the CYP2C8 (Reversible) for the parent and
4.) 20 uM for Irrev inhibition and Kinact= 0.21 min^{-1} of CYP2C8 for the Glucuronide
5.) 3.4 uM for the OAT3 (Rev inhibition) for the parent and
6.) 9.9 uM for the OAT3 (Rev inhibition) Glucuronide
7.) 5.8 uM for the CYP2C9 (Rev Inhibition) by Parent

Repaglinide record: Repaglinide_PO_0.25mg_Gem 600 mg
GEM Record:GEM PO 600 mg DDI Repag Tornio
GEM-Gluc record: Gem-Gluc EC Kps Tornio
Gemfibrozil was dosed with DDI module (600 mg, BID dosing interval)
Observed data for GEM and GEM gluc and Repaglinide before and after DDI in the plot is from Tornio et. al., 2008

Tornio et. al., Clin. Pharmacol. Thera. 84(3):403(2008)

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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).

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

Lower limit: R_o

$$\text{Limit} = \frac{1 + 2(R}{R_}$$

where R_{obs} represents $AUC_{+inhibitor}/AUC$ inhibition DDIs. The new predictive measu

fold. The trend of lower prediction accuracy at higher potency of DDIs reported in previous studies is no longer apparent when predictions are assessed via the new predictive measure. Thus, the study proposes a more logical method for the assessment of prediction success and its application for induction and inhibition DDIs.

To allow for uncertainty in the observed [illegible], 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

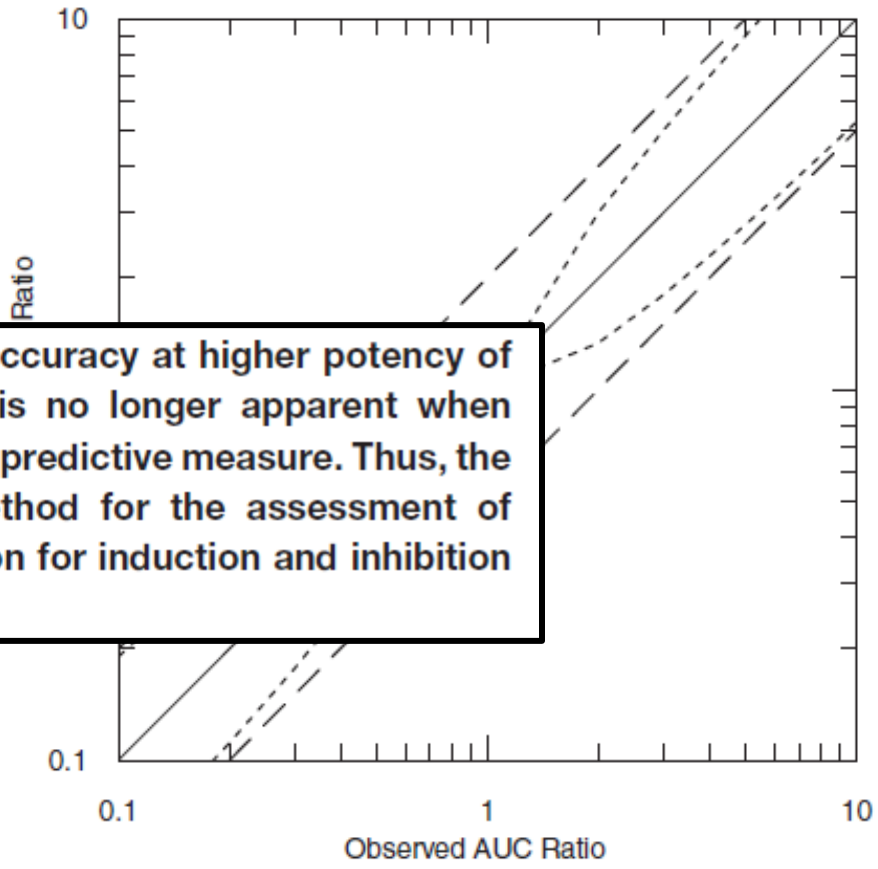


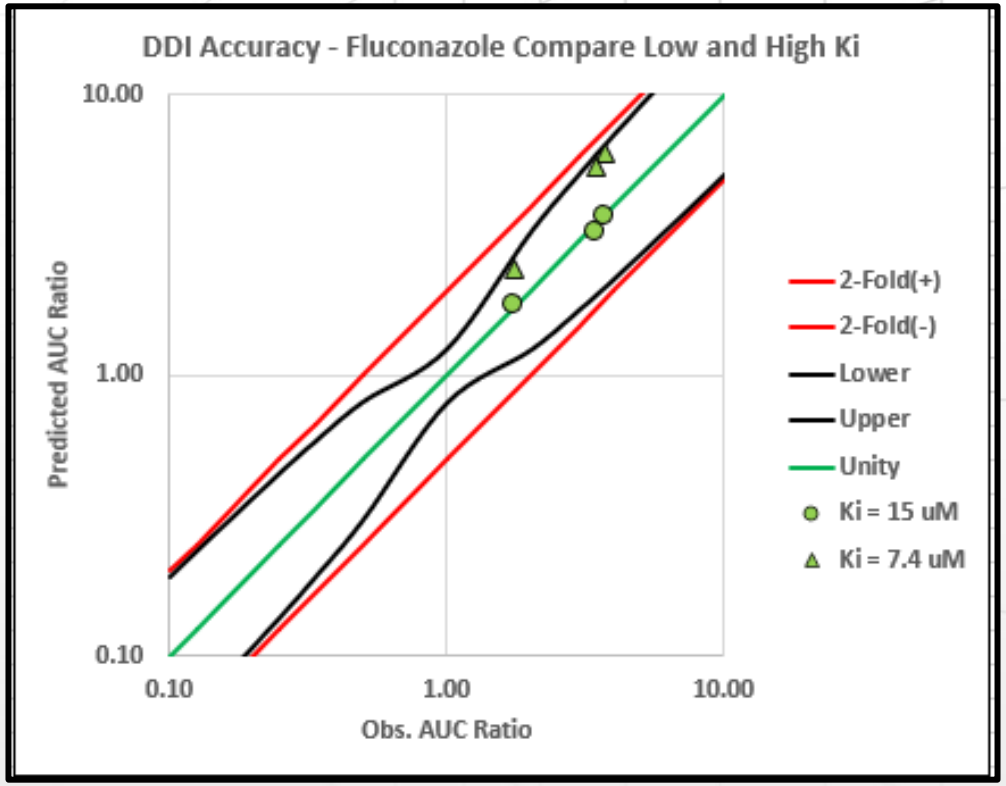
FIG. 1. Schematic graph displaying the limits of the different predictive measures; the traditional two-fold predictive measure (dashed lines) and the proposed new predictive measure (dotted lines). Observed AUC ratios include both induction and inhibition DDIs.

Midazolam DDI vs. Fluconazole

	Obs Ratio	Variability (CV)	1.25 Limit	Guest Limits Upper	Lower	Unity	2-fold(+)	2-fold(-)	log Limits UL	LL	Center
Reciprocal of ratio 2 -10	0.10	1.25	1.93	0.19	0.05	0.10	0.20	0.05	-0.28	0.28	0
	0.13	1.25	1.91	0.24	0.07	0.13	0.25	0.06	-0.28	0.28	0
	0.25	1.25	1.81	0.45	0.14	0.25	0.50	0.13	-0.26	0.26	0
	0.33	1.25	1.75	0.58	0.19	0.33	0.67	0.17	-0.24	0.24	0
	0.50	1.25	1.63	0.81	0.31	0.50	1.00	0.25	-0.21	0.21	0.00
	1.00	1.25	1.25	1.25	0.80	1	2.00	0.50	0.10	-0.10	0
	2.00	1.25	1.63	3.25	1.23	2	4.00	1.00	0.21	-0.21	0
	3.00	1.25	1.75	5.25	1.71	3	6.00	1.50	0.24	-0.24	0
	4.00	1.25	1.81	7.25	2.21	4	8.00	2.00	0.26	-0.26	0
	8.00	1.25	1.91	15.25	4.20	8	16.00	4.00	0.28	-0.28	0
	10.00	1.25	1.93	19.25	5.19	10	20.00	5.00	0.28	-0.28	0

Guest Criteria for Ki = 15 uM					Guest Criteria for Ki = 15 uM				
CV	Limit	Up Lim	Low Lim	Predicted	CV	Limit	Up Lim	Low Lim	Predicted
Cmax					AUC0-t				
1.25	1.67	3.84	1.37	2.07	1.25	1.80	6.70	2.07	3.69
1.25	1.58	2.82	1.13	1.86	1.25	1.78	6.13	1.93	3.23
1.25	-	-	-	-	1.25	1.57	2.73	1.11	1.79

Guest Criteria for Ki = 7.4 uM					Guest Criteria for Ki = 7.4 uM				
CV	Limit	Up Lim	Low Lim	Predicted	CV	Limit	Up Lim	Low Lim	Predicted
Cmax					AUC0-t				
1.25	1.67	3.84	1.37	2.57	1.25	1.80	6.70	2.07	6.19
1.25	1.58	2.82	1.13	2.32	1.25	1.78	6.13	1.93	5.50
1.25	-	-	-	-	1.25	1.57	2.73	1.11	2.37



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Written Report of Model Development and Validations

Table 6 **Baseline Simulations of Sensitive CYP3A4 Substrates: Simulated Versus Observed PK Parameters of Triazolam and Midazolam.**

Reference	Substrate Dose and Regimen	Observed#		Simulated	
		C_{max} (ng/mL)	AUC_{0-t} (ng*hr/mL)	C_{max} (ng/mL)	AUC_{0-t} (ng*hr/mL)
(Varhe, Olkkola et al. 1994)	**0.25 mg single dose triazolam tablet**	1.5 ± 0.2	5.9 ± 0.7	1.49	8.86
(Greenblatt, Wright et al. 1998)	**0.25 mg single dose triazolam tablet**	2.6 ± 0.3	10.6 ± 1.6$	1.82	11.06$
(Olkkola, Backman et al. 1994)	**7.5 mg PO midazolam**	22 ± 6	65± 10$	25	82.99$

#Observed values are from the average of individual values, and represent mean ± standard error; $represent AUC_{0-inf}

Table 7 **DDI Simulations of Sensitive CYP3A4 Substrates: Simulated Versus Observed PK Parameters of Triazolam and Midazolam With or Without Co-administration of Ketoconazole**

Reference	Substrate		C_{max} (ng/mL)	AUC_{0-t} (ng*h/mL)
(Varhe, Olkkola et al. 1994)	**Triazolam**	Observed baseline#	1.5 ± 0.2	5.9 ± 0.7
		Simulated baseline	1.49	8.86
		Observed DDI #	4.6 ± 0.5	48.1 ± 5.3
		Simulated DDI	4.24	55.82
		Observed DDI ratio#	3.07	8.1
		Simulated DDI ratio	2.85	6.3
(Greenblatt, Wright et al. 1998)	**Triazolam**	Observed baseline#	2.6 ± 0.3	10.6 ± 1.6$
		Simulated baseline	1.82	11.06$
		Observed DDI #	5.4 ± 0.4	145.4 ± 39.1$
		Simulated DDI	4.71	142.6$
		Observed DDI ratio#	2.1	13.7$
		Simulated DDI ratio	2.59	12.9$
(Olkkola, Backman et al. 1994)	**Midazolam**	Observed baseline#	22 ± 6$	65 ± 10$
		Simulated baseline	25	82.99$
		Observed DDI#	90 ± 7	1033.3$
		Simulated DDI	96	1300.7$
		Observed DDI ratio	4.09	15.9$
		Simulated DDI ratio	3.84	15.7$

#Parameters are from the average of observed individual values and represent mean ± standard error; $represent AUC_{0-inf}; the simulated DDI ratios were highlighted in green while observed DDI ratios were highlighted in blue.

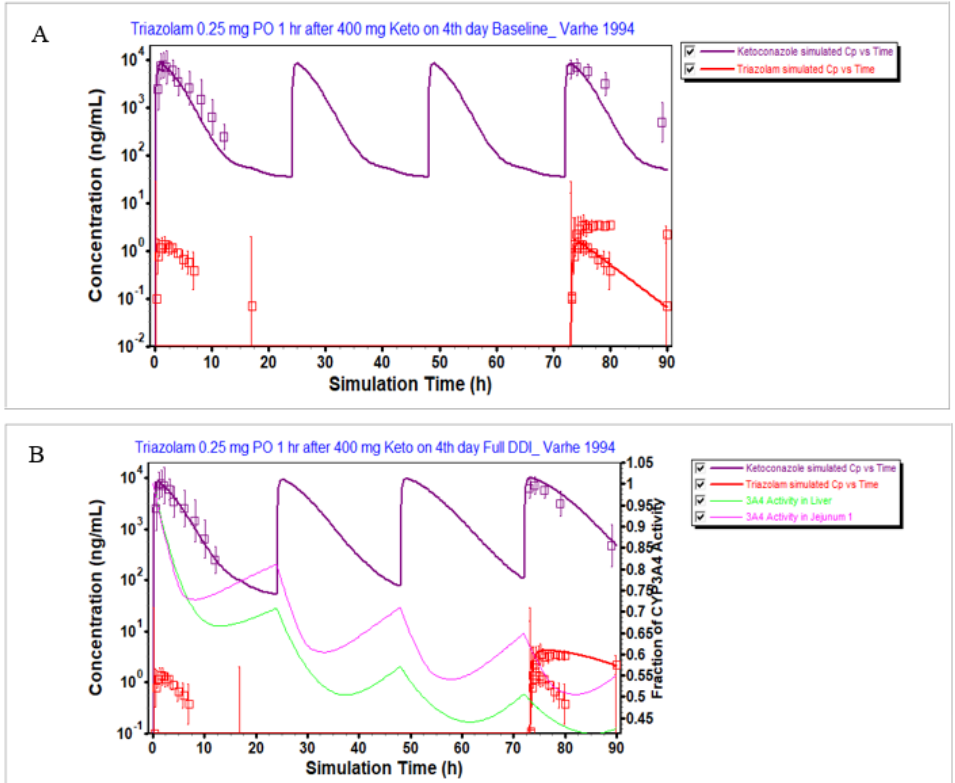

Figure 6 **Baseline Simulation Without a Drug-Drug Interaction (A, Top) and Full Dynamic Simulation With a Drug-Drug Interaction (B, Bottom) Between Ketoconazole and Triazolam**

Ketoconazole (400 mg) was administered for four doses, and 0.25 mg triazolam was given at 3 PM after the fourth dose of KCZ (given at 2 PM) (Varhe, Olkkola et al. 1994).

The open squares and error bars represent the mean observed data and coefficient of variation, respectively, and the simulated (line) C_P-time profiles for triazolam (red) and ketoconazole (purple). The simulated CYP3A4 activity in liver is highlighted in green, and the simulated

Conclusions

- The GP DDI Standard Update Project Team have made significant advances in the ability to simulate complex mechanistic drug-drug interactions involving enzymes, transporters, and enterohepatic circulation.
- Now DDI simulations will be accomplished with a full database of validation study records for both substrates and perpetrators
- We provide extensive literature references, data compilation, slides, and written documentation and GastroPlus model files that can be used for regulatory submissions
- When documentation is in a complete draft form, all components are 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

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