Applying QSAR and PBPK Modeling to Bridge Discovery and Assessment of Clinical Potential

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Agenda

- Brief overview of PBPK
- Case Studies
  - Estimation of Oral Bioavailability Using *in silico* or *in vitro* : *in vivo* Extrapolation (ISIVE and IVIVE)
  - Prediction of Cp Versus Time by Extrapolation From *in silico* and *in vitro* for Risperidone
  - *In silico* Prediction of Drug-Drug Interactions With Itraconazole and Midazolam
  - Halofantrine and Risk of QT Interval Prolongation
- Culture and Process Implications
- Wrap-up

Modeling and Simulation *in silico*
Part 1:
QSPR / QSAR and
Physiologically Based
Pharmacokinetic Modeling

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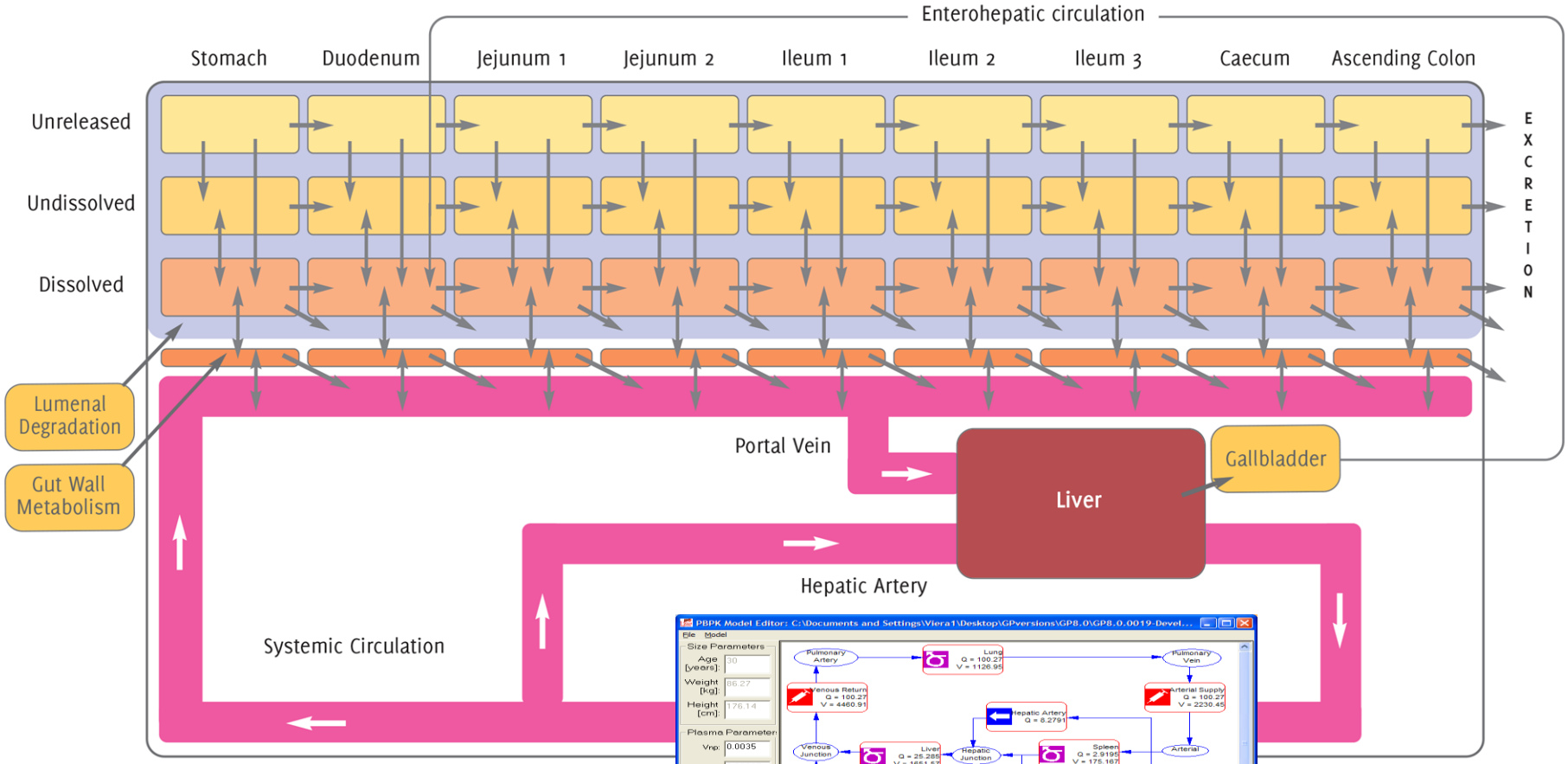
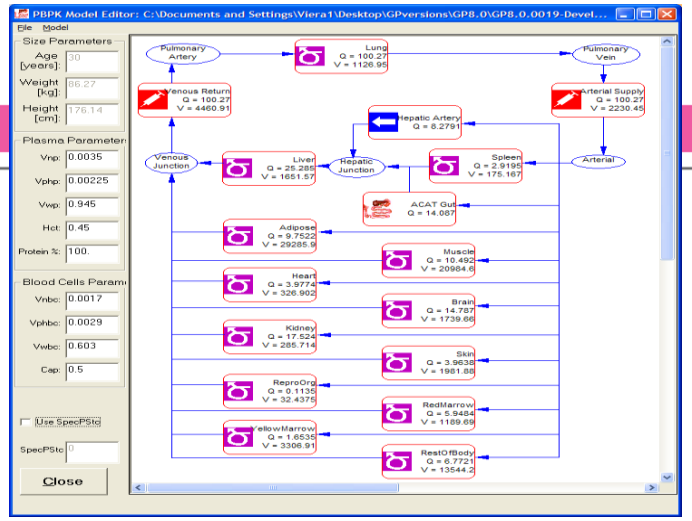
What Is Mechanistic Absorption/PBPK Model?

- Mathematical model that integrates drug properties with systems physiology data to simulate PK profiles in plasma and tissues
  - Glomerular filtration rate, hepatic clearance, plasma protein binding, gut and liver enzymes, and transporter expression and distribution patterns (passive diffusion versus active transport)
  - Tissue compartments and unbound concentrations are defined by volume, blood flow rate, and lipid composition as function of species, sex, age, ethnicity, and disease state
  - Gastrointestinal absorption requires species-specific values for fluid volume, surface area, gastric emptying, intestinal transit times, bile salt concentration, and pH that vary dynamically after dosing and with prandial state
- Required compound-specific parameters vary with ADME properties and question of interest

Jones HM, et al. Clin Pharmacol Ther. 2015;97(3):247-262.

Advanced Compartmental Absorption and Transit Model (ACAT™)





- Each compartment represents a tissue
  - Specific volume(s)*
  - Blood perfusion rate*
  - Enzyme/transporter expression levels*
  - Volume fractions of lipids and proteins*
  - Tissue:plasma partition coefficient (Kp)

Applications of PBPK Modeling

- Discovery and candidate selection
- First-in-human dosing
- Food effects
- Formulation and alternative route optimization
  - Ocular, pulmonary, dermal, oral cavity, and intramuscular long acting injectable microparticles (LAI)
- Virtual bioequivalence testing
- Virtual toxicity screening
- Drug-drug interactions (DDIs)
- Special populations
  - Pediatrics, pregnancy
  - Disease-specific changes in physiology
    - Hepatic and renal impairment, dehydration

Case Study: Estimation of Oral Bioavailability Using *in silico* or *in vitro* : *in vivo* Extrapolation ISIVE and IVIVE

Lawless M; DiBella J; Bolger MB; Clark RD; Huehn E;
Waldman M; Zhang J; Lukacova V.

Poster presented at
International Society for the Study of Xenobiotics (ISSX):
Prediction of Oral Bioavailability in silico, 2015.

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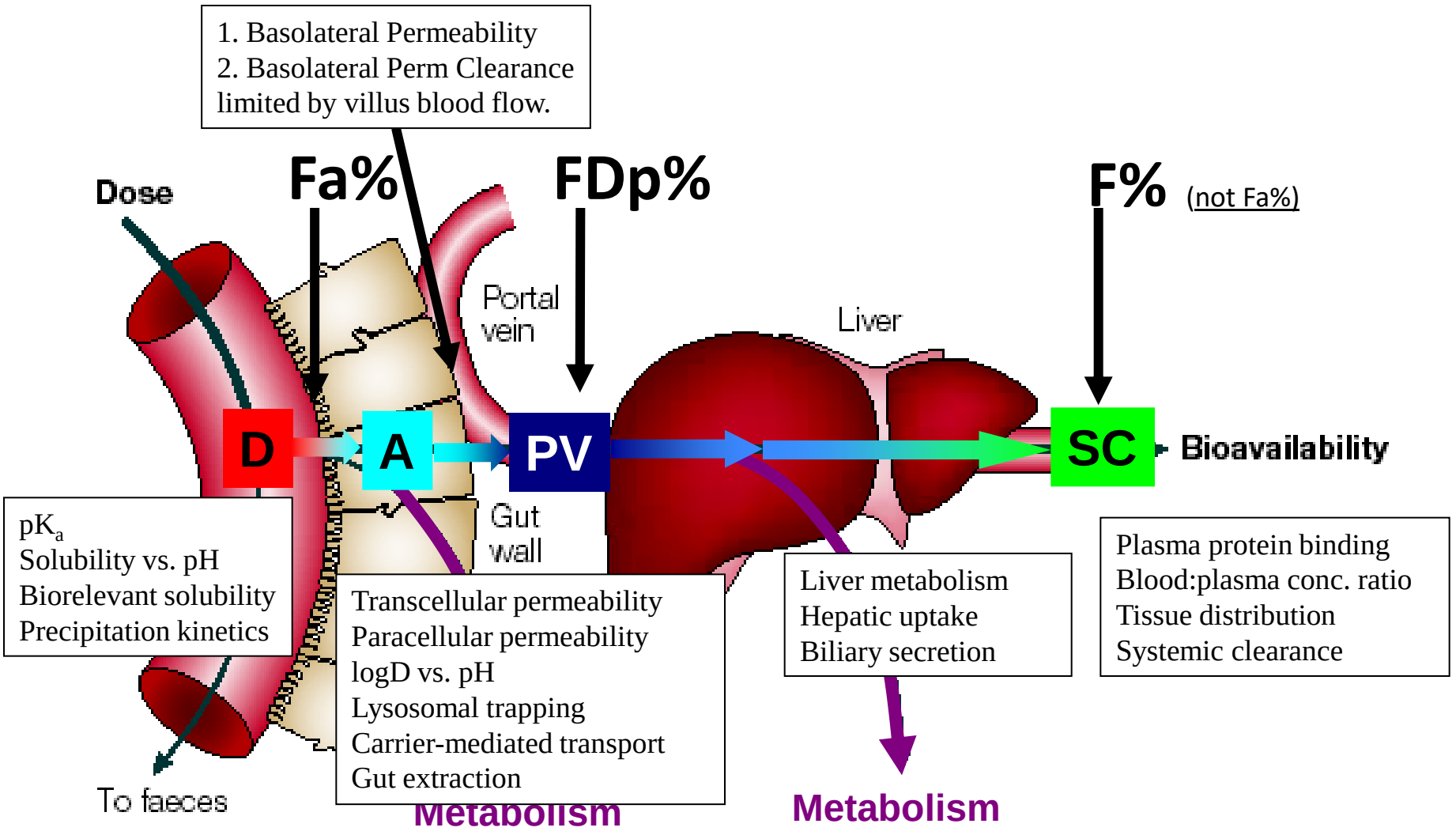
What's Happening *in vivo* During Absorption?



* Modified from van de Waterbeemd H, Gifford E. Nat Rev Drug Disc. 2003;2:192-204.

Confidence, Limitations, and Challenges for Preclinical and Clinical PK Prediction

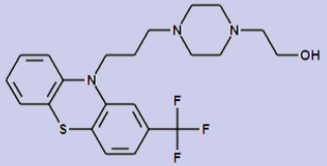
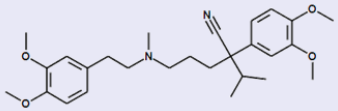
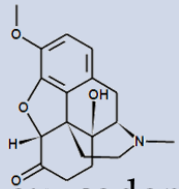
	Level of confidence	Limitations and challenges
CYP cleared substrates	Moderate to high	No significant limitations or challenges for liver metabolism from *in vitro* systems for BCS I and II drugs. Intestinal metabolism is more challenging.
Non-CYP metabolically cleared substrates	Low to moderate	Hepatocytes predictive for glucuronidation and some other non-P450 processes. Expression patterns and scaling factors for many non-CYP enzymes poorly defined.
Clearance/absorption by active transport	Low	Transporter abundances and activity scaling factors poorly understood.
Elimination by combination of metabolism and transport	Low	Interplay of multiple transporters and metabolic enzymes very challenging.
Passive distribution/absorption processes	High	No significant limitations or challenges.

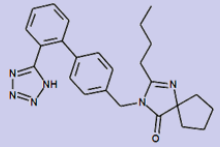
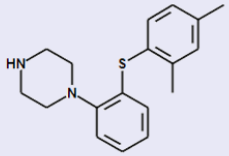
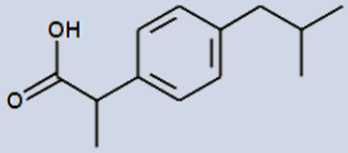
Jones HM, et al. Clin Pharmacol Ther. 2015;97(3):247-262.

Estimation of Bioavailability *in silico*

- Database of 62 drugs including oral bioavailability (F%) and dose was constructed
  - All compounds' reported major clearance pathways (MCPs) were CYP-mediated
  - For 43 drugs with more than one reported value of F%, average experimental CV% was 29%
- Reported F% values varied from 3% (fluphenazine) to 99% (diazepam, galantamine, glimepiride, indomethacin, and tamsulosin), with an average of 60%
- F% was predicted by integrating quantitative structure activity relationship (QSAR) model predictions and PBPK simulations
  - 35-year-old American male physiology was used for simulations

Examples of Drugs in Dataset Along With Their Dose, F%, and MCP

Drug	Dose [mg]	F%	MCP
 fluphenazine	5	3.1	2D6
 verapamil	80	22	3A4
 oxycodone	15	42	3A4

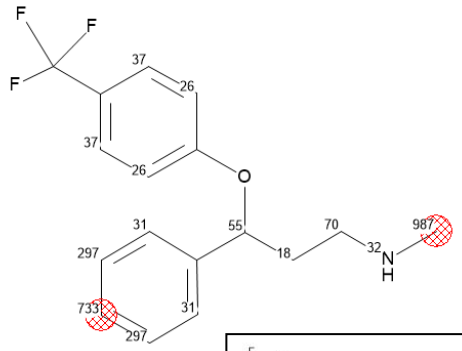
Drug	Dose [mg]	F%	MCP
 irbesartan	150	70	2C9
 vortioxetine	10	75	2D6
 ibuprofen	400	85	2C9

Estimation of CYP Metabolism *in silico*

CYP Substrate Classification

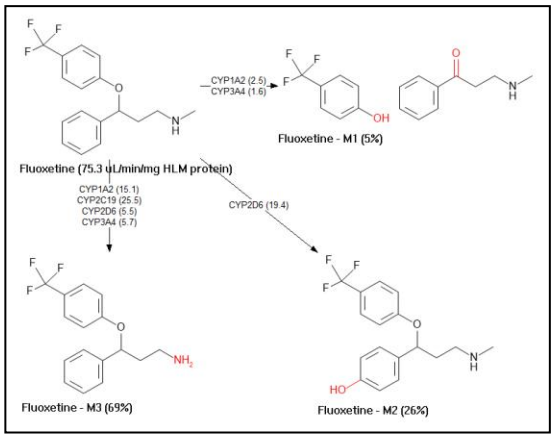
1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4

Sites of CYP Metabolism



K_m, V_{max}, CL_{int}

Metabolites



Clark RD, et al., J Cheminform. 2014;6:34.

K_m = concentration at 1/2 maximum metabolic velocity

V_{max} = maximum metabolic velocity

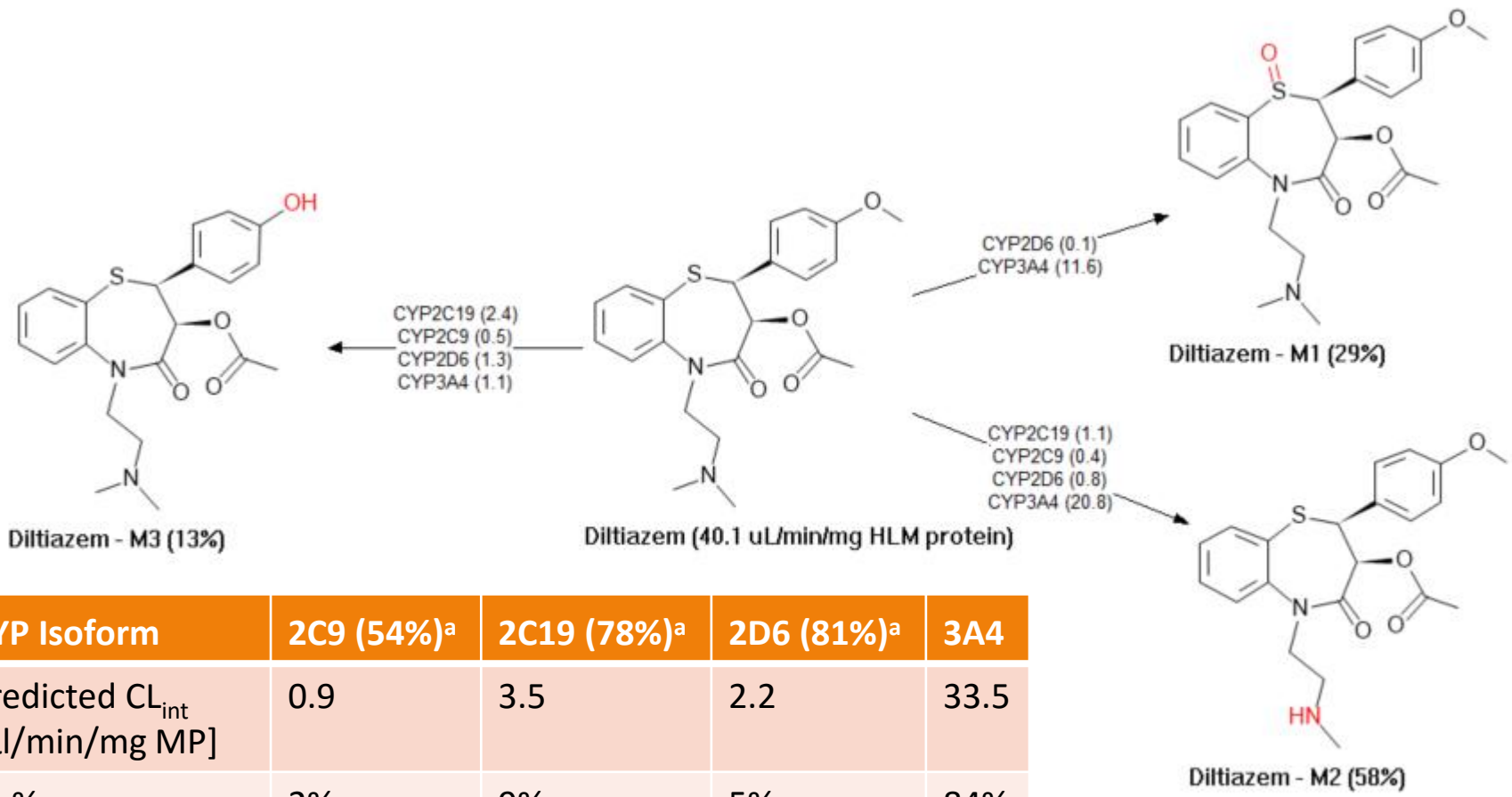
CL_{int} = intrinsic clearance

QSAR Models Used in PBPK Simulations

QSAR Model	Description
S+Sw	aqueous solubility
S+Sp	aqueous solubility at specified pH
S+FaSSGF	solubility in simulated fasted state gastric fluid
S+FaSSIF	solubility in simulated fasted state intestinal fluid
S+FeSSIF	solubility in simulated fed state intestinal fluid
S+logD	logD at specified pH
S+pKa	pK_a (single or multiple)
S+Peff	effective human jejunal permeability
S+PrUnbnd	percent unbound to plasma proteins
S+RBP	blood-to-plasma concentration ratio
DiffCoef[a]	molecular diffusion coefficient in water
MET_XXX_Km	kinetic Michaelis-Menten K_m constant (5 CYP isoforms)
MET_XXX_Vmax	Michaelis-Menten V_{max} constant (5 CYP isoforms)

[a] Hayduk W, Laudie H. AIChE J. 1974;20:611.

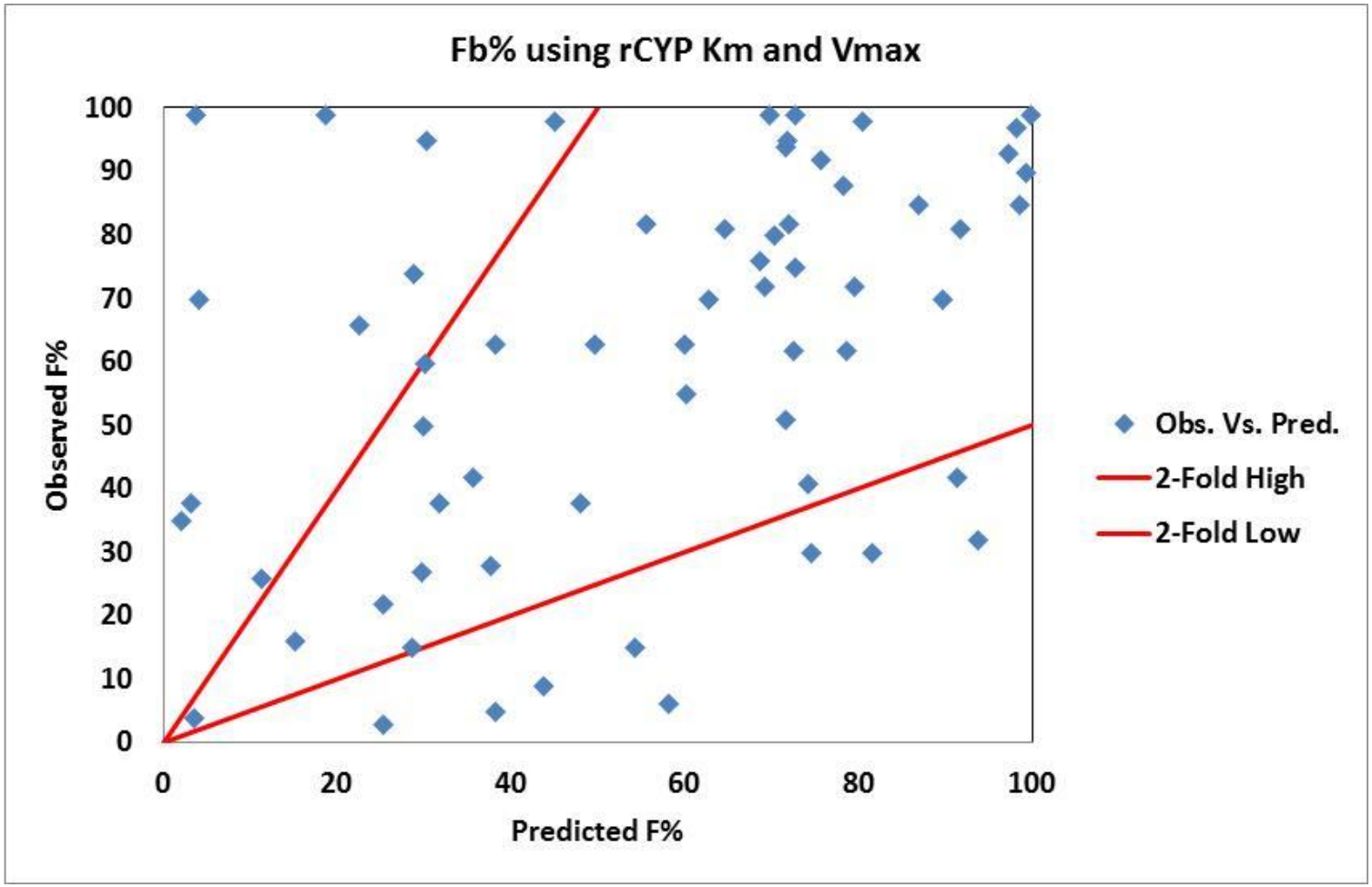
Example of Metabolite Predictions for Diltiazem



CYP Isoform	2C9 (54%)[a]	2C19 (78%)[a]	2D6 (81%)[a]	3A4
Predicted CL_{int} [µl/min/mg MP]	0.9	3.5	2.2	33.5
fm%	2%	9%	5%	84%

[a] Percent confidence in substrate classification model.

Observed Versus Predicted F% for 62 Compounds (69% Within 2-Fold)



Chaudhuri SR et al., AAPS Newsmagazine, June 2016

Results

- All molecules were predicted to be substrates of CYP associated with their MCP
- In 42 of 62 molecules, CYP isoform with highest predicted intrinsic clearance (CL_{int}) was same as MCP
- Overall, 58% of predicted oral bioavailability values were within 1.5-fold of observed oral bioavailability and 69% were within 2-fold
- Scaling V_{max} by CYP substrate model's confidence estimate resulted in fewer underpredictions

ADMET Predictor™ Version 7.2, Simulations Plus, Inc., Lancaster, CA 95354 USA.
GastroPlus™ Version 9.0, Simulations Plus, Inc., Lancaster, CA 95354 USA.

Case Study: Prediction of Cp Versus Time by Extrapolation From *in silico* and *in vitro* for Risperidone

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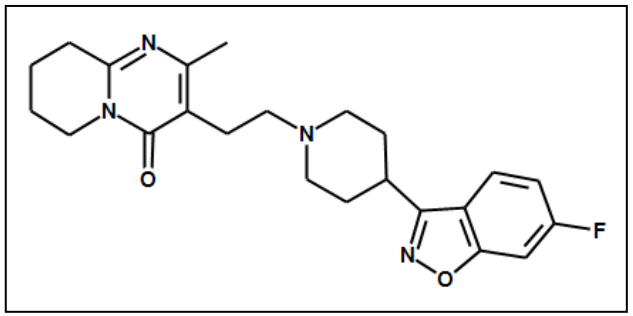
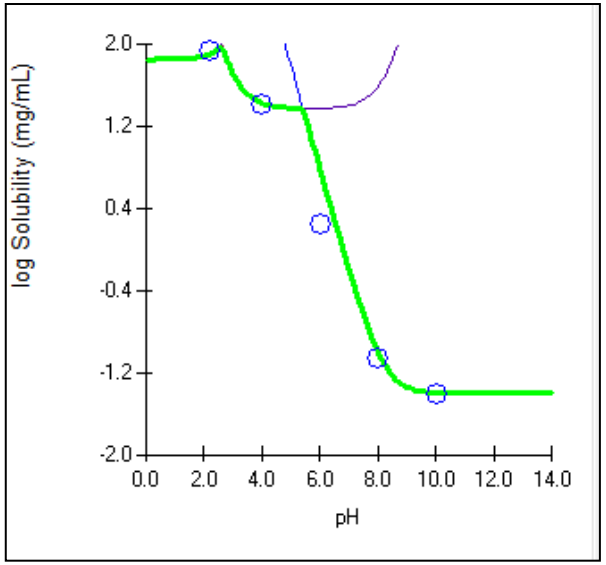
Risperidone BCS/BDDCS II Physicochemical Properties



MW = 410.49



AP 7.2 = ADMET Predictor, Version 7.2
S+ = properties predicted with Simulations Plus models
S+Sw = native solubility in pure water
S+Peff = human jejunal permeability estimate

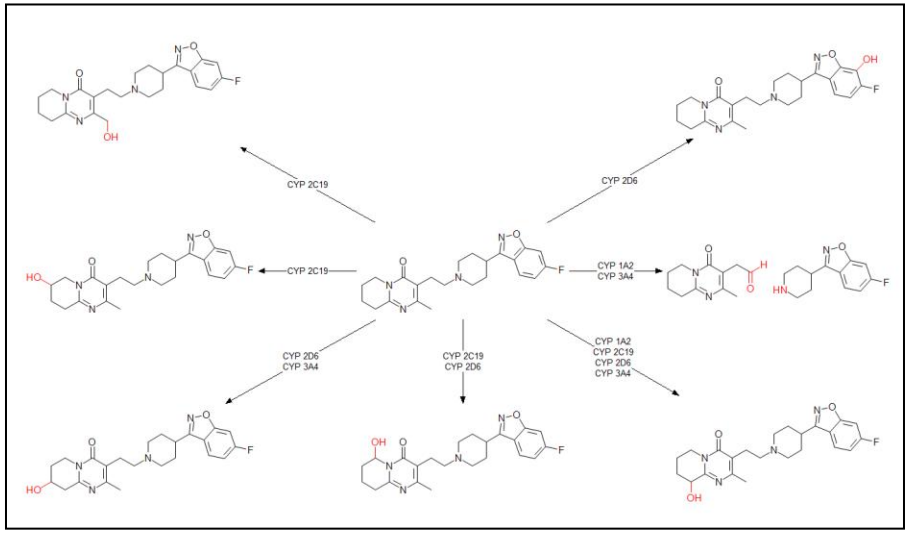
S+LogP = 3.23 (AP 7.2)
Exp LogP = 3.04 (Mannens 1994)

S+pKa = 7.8 (Base), 3.0 (Base)
Exp pKa = 8.2 (Base), 3.1 (Base) (Mannens 1994)
Potential for lysosomal trapping

S+Sw = 83.4 μg/mL (AP 7.2)
Exp Sw = 42.0 μg/mL (Brewster, 2010) LOW

S+FaSSIF = 92.5, S+ FeSSIF = 74.5 μg/mL
Exp FaSSIF = ??

S+Peff = 3.35 x 10^{-4} (cm/s) HIGH



Metabolized by: CYP3A4 & 2D6

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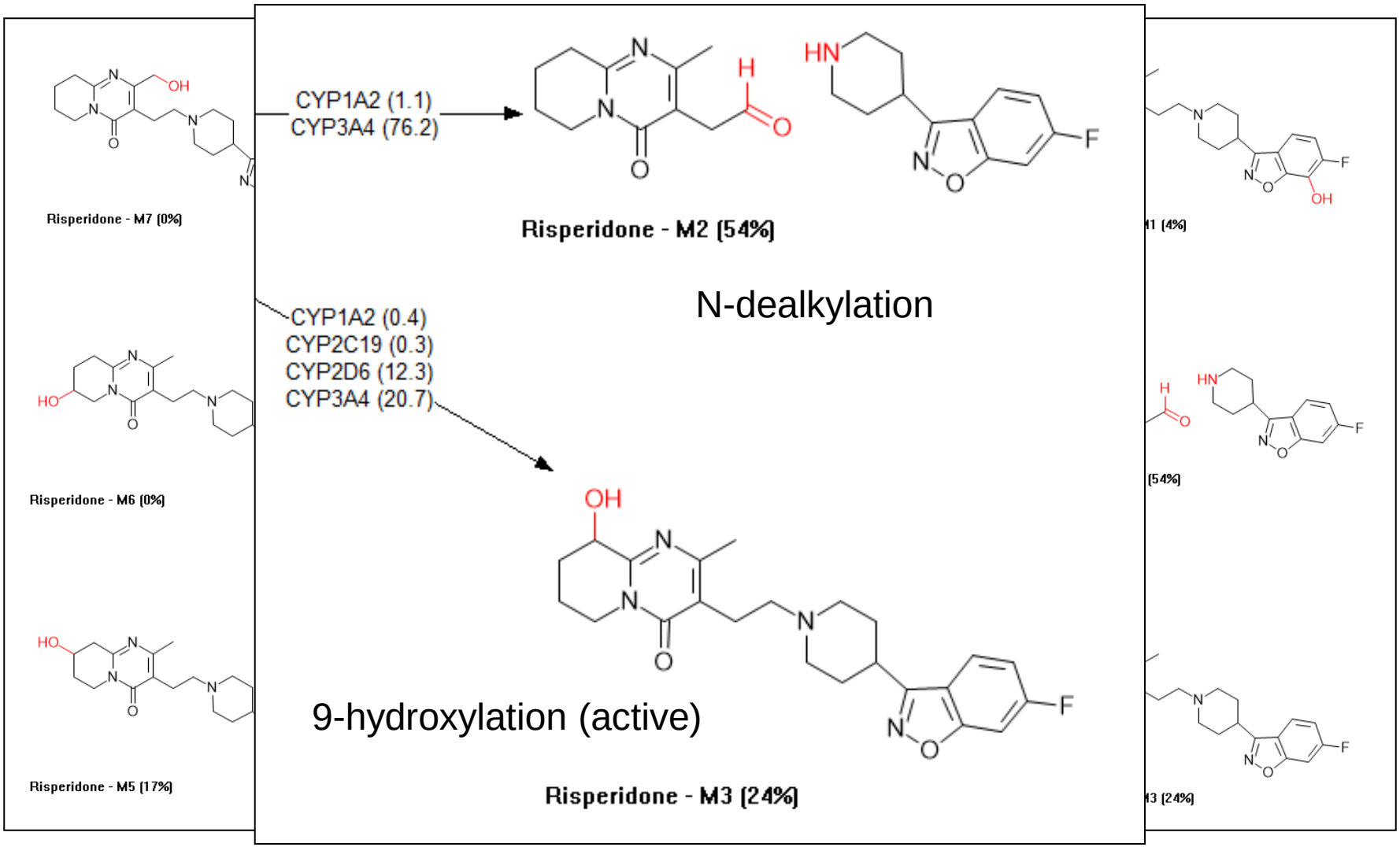
AP 7.2 Estimated Phase 1 Metabolic Products



AP 7.2 = ADMET Predictor, Version 7.2

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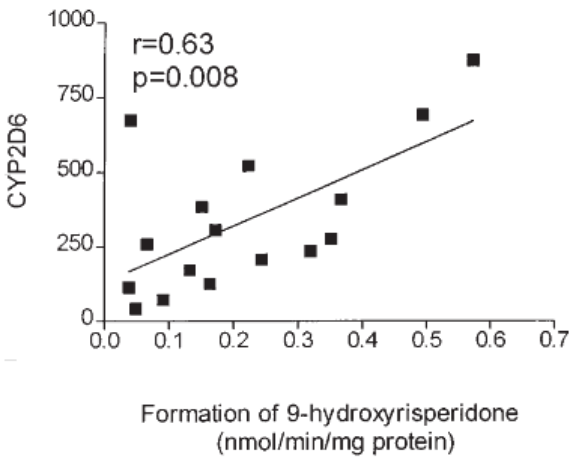
Observed Metabolism

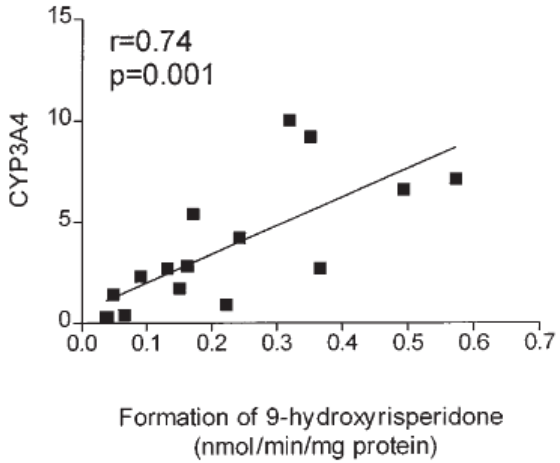
Naunyn-Schmiedeberg's Arch Pharmacol (1999) 359: 147–151

ORIGINAL ARTICLE

Jim Fang · Michel Bourin · Glen B. Baker

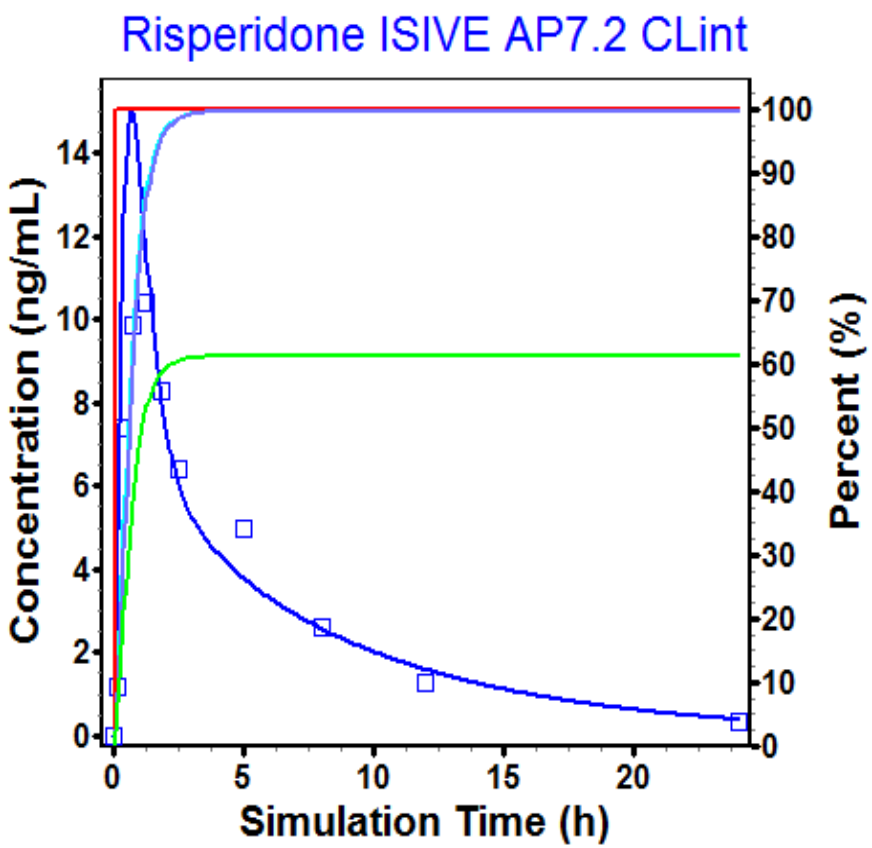
Metabolism of risperidone to 9-hydroxyrisperidone by human cytochromes P450 2D6 and 3A4

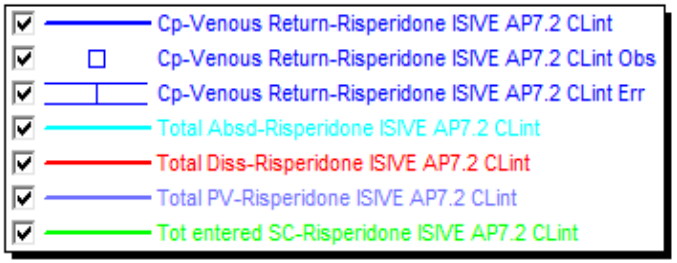




Formation of 9-OH metab. by human liver microsomes from 16 subjects: Correlated with enzyme activity (pmol/min/pmol CYP) against specific substrates.

Discovery *in silico* / *in vivo* PBPK Extrapolation...





Record: Risperidone ISIVE AP7.2 CLint
Total simulation time (h): 24

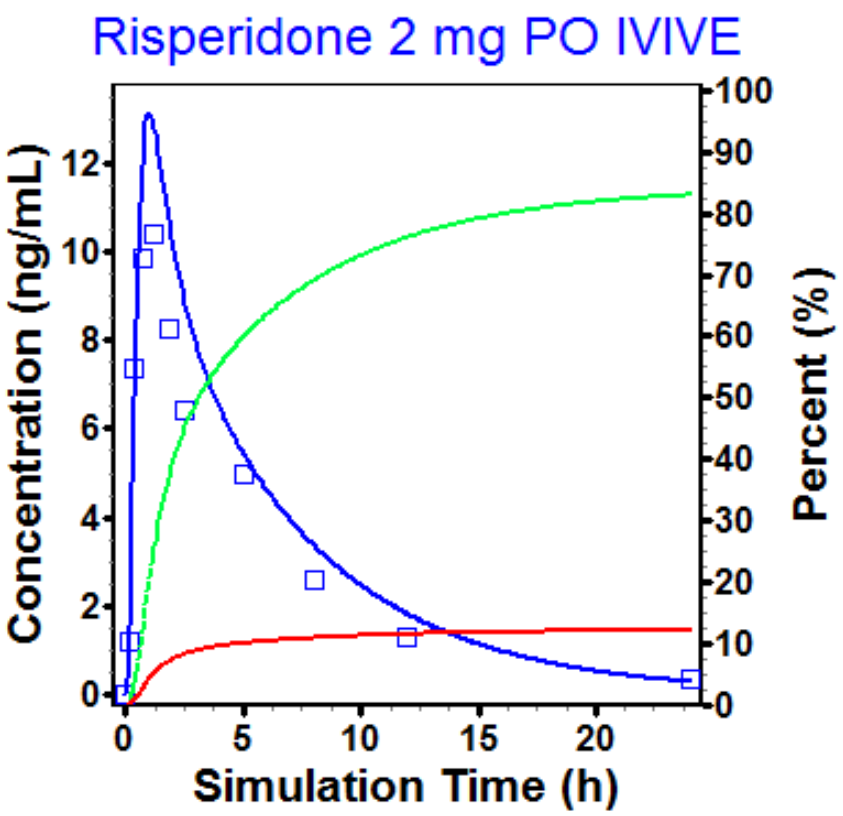
Result	Observ	Simul
Fa (%):	99	99.99
FDp (%):	0	99.99
F (%):	69	61.41
Cmax (ng/mL):	10.4	15.84
Tmax (h):	1.24	0.71
AUC 0-inf (ng-h/mL):	66.67	67.25
AUC 0-t (ng-h/mL):	63.07	63.80
CMax Liver (ng/mL):		116.8

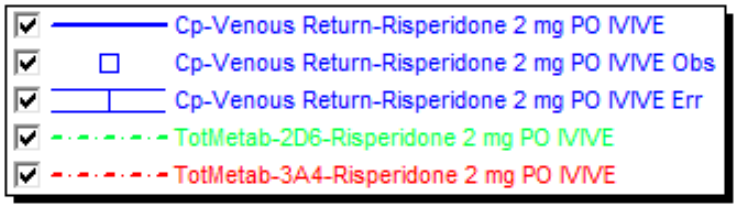
Purely *in silico* estimation of Cp versus time using ADMET Predictor 7.2 estimation of:

CL_{int} = 148 µL/min/mg Prot. applied to liver.

Chaudhuri SR et al., AAPS Newsmagazine, June 2016

Discovery *in vitro* / *in vivo* PBPK Extrapolation...





Record: Risperidone 2 mg PO IVIVE
Total simulation time (h): 24

Result	Observ	Simul
Fa (%):	99	99.98
FDp (%):	0	90.57
F (%):	69	60.26
Cmax (ng/mL):	10.4	13.13
Tmax (h):	1.24	1.04
AUC 0-inf (ng-h/mL):	66.67	76.35
AUC 0-t (ng-h/mL):	63.07	74.55
CMax Liver (ng/mL):		66.28

Estimation of Cp versus time using updated properties; including *in silico* 3A4 and 2D6 K_m, experimental *in vitro* solubility, permeability, Rbp, fup, and CYP clearance. CYP2D6 V_{max} = 7.5 pmol/min/pmol Enz. and 3A4 V_{max} = 0.6 pmol/min/pmol Enz.

Chaudhuri SR et al., AAPS Newsmagazine, June 2016

Case Study: PBPK Prediction of Drug-Drug Interactions With Itraconazole and Midazolam

Ke Szeto, Viera Lukacova, and Michael B. Bolger
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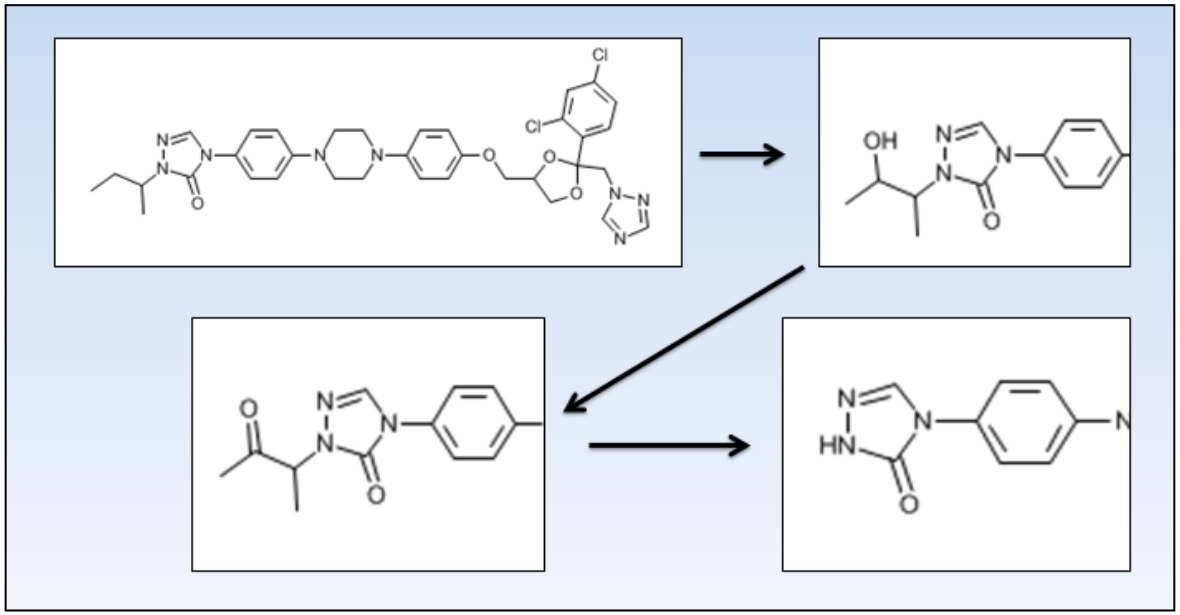
Overview of PBPK Model

- Itraconazole (ITZ) is BCS Class II weak base with low solubility and high permeability
- ITZ and its metabolites are both substrates and inhibitors of CYP3A4
- Key component of model is to accurately model dissolution, precipitation (mechanistic nucleation and growth), and absorption processes in gastrointestinal tract including food effects
- PBPK model incorporated a series of metabolic reactions from parent to downstream metabolites including V_{max}, K_m, and K_i for each moiety

ADMET Predictor™ Version 7.2, Simulations Plus, Inc., Lancaster, CA 95354 USA.
GastroPlus™ Version 9.0, Simulations Plus, Inc., Lancaster, CA 95354 USA.

Introduction

- Itraconazole is substrate and potent inhibitor of CYP3A4
- Primary metabolite, hydroxy-itraconazole (OH-ITZ), and 2 other downstream metabolites, keto-itraconazole (keto-ITZ) and N-desalkyl-itraconazole (ND-ITZ), are also substrates and inhibitors of CYP3A4
- Purpose was to develop mechanistic absorption model (MAM)/PBPK model for ITZ and its metabolites which accounts for all relevant mechanisms (dissolution, precipitation, absorption, distribution, metabolism, and auto-inhibition) after intravenous and oral ITZ administration



Previous PBPK DDI Calculations
Model Using ITZ, OH-ITZ Only

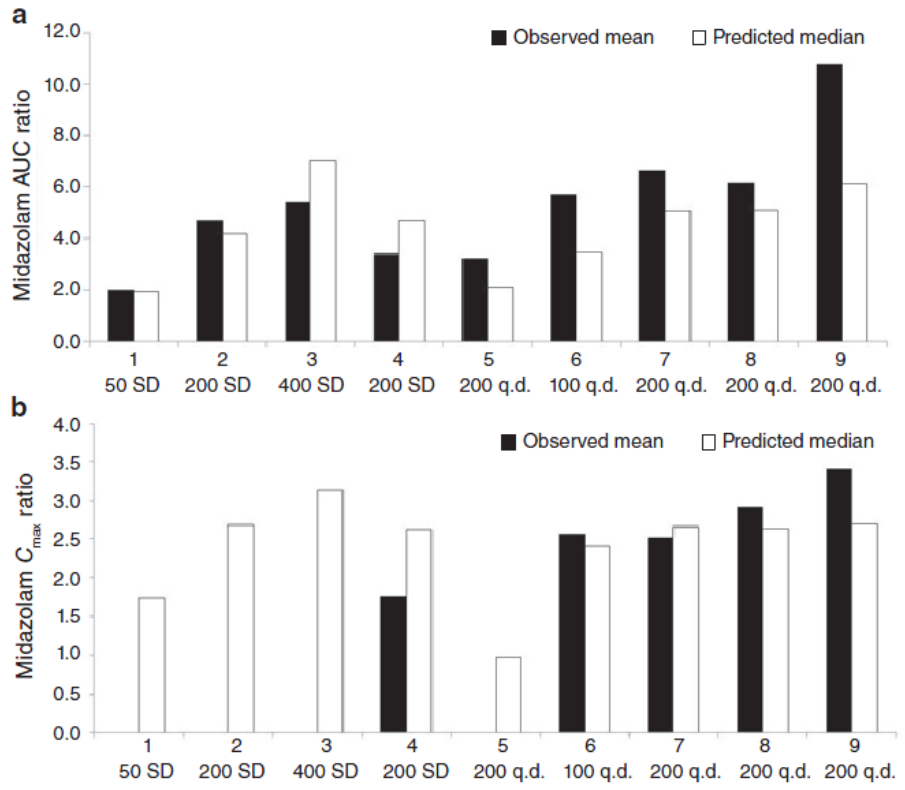


Figure 2 Predictive performance of the modified SimCYP itraconazole model, in which the major modification to the input parameters was reduction of hydroxyitraconazole volume at steady state (V_{ss}). (**a**) The black bars represent the observed mean AUC ratio; the white bars represent the predicted median AUC ratio for the respective trial (trials 1–9). (**b**) The black bars represent the observed mean C_{max} ratio; the white bars represent the predicted median C_{max} ratio for the respective trial. See **Supplementary Table S2** for full details of dosing regimens. q.d., once daily; SD, single dose.

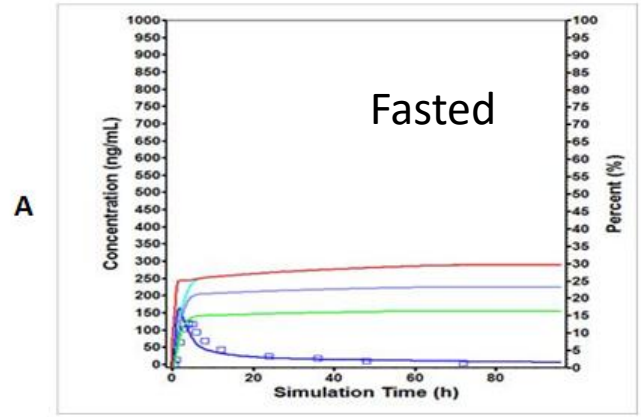
Ke AB. Clin Pharm Ther. 2014;95(5):480.

Results: Model Validation

Capsule 200 mg:

Solution 200 mg:

The results of selected doses are shown below:



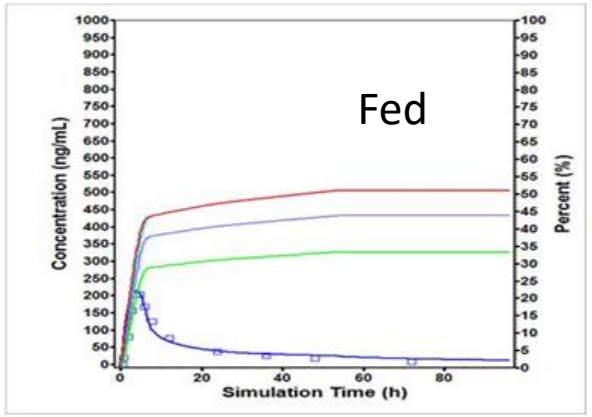
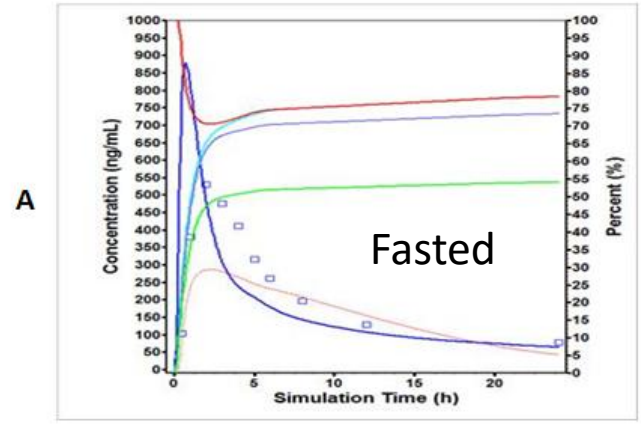


Figure 1: Mean simulated (line) and observed (points) pharmacokinetics profiles for ITZ after **capsule** administration of 200 mg ITZ to a 23-year-old male of 70.9 Kg under fasted (A) and fed (B) condition. Dark blue colored lines and data points represent plasma concentration (y-axis on the left). The remaining lines represent cumulative amount of ITZ dissolved, absorbed, entering portal vein, entering systemic circulation, and total precipitated, all shown as percent of the administered dose (y-axis on the right)



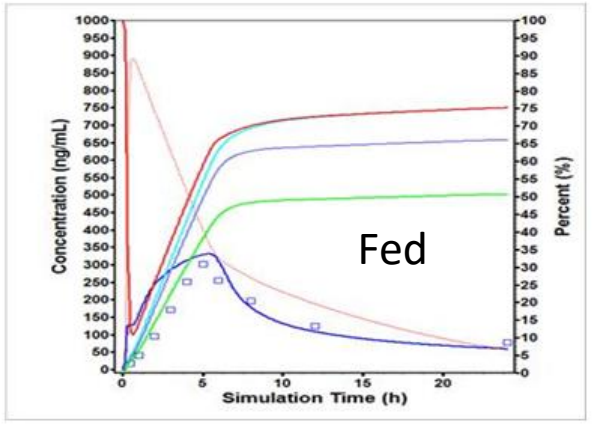


Figure 2: Mean simulated (line) and observed (points) pharmacokinetics profiles for ITZ after **solution** administration of 200 mg ITZ to a 23-year-old male of 70.9 Kg under fasted (A) and fed (B) condition. The color-coded lines follow the same definition as in Figure 1.

Itraconazole – Midazolam DDI

(Includes Inhibitory Effect of Itraconazole and 3 Metabolites)

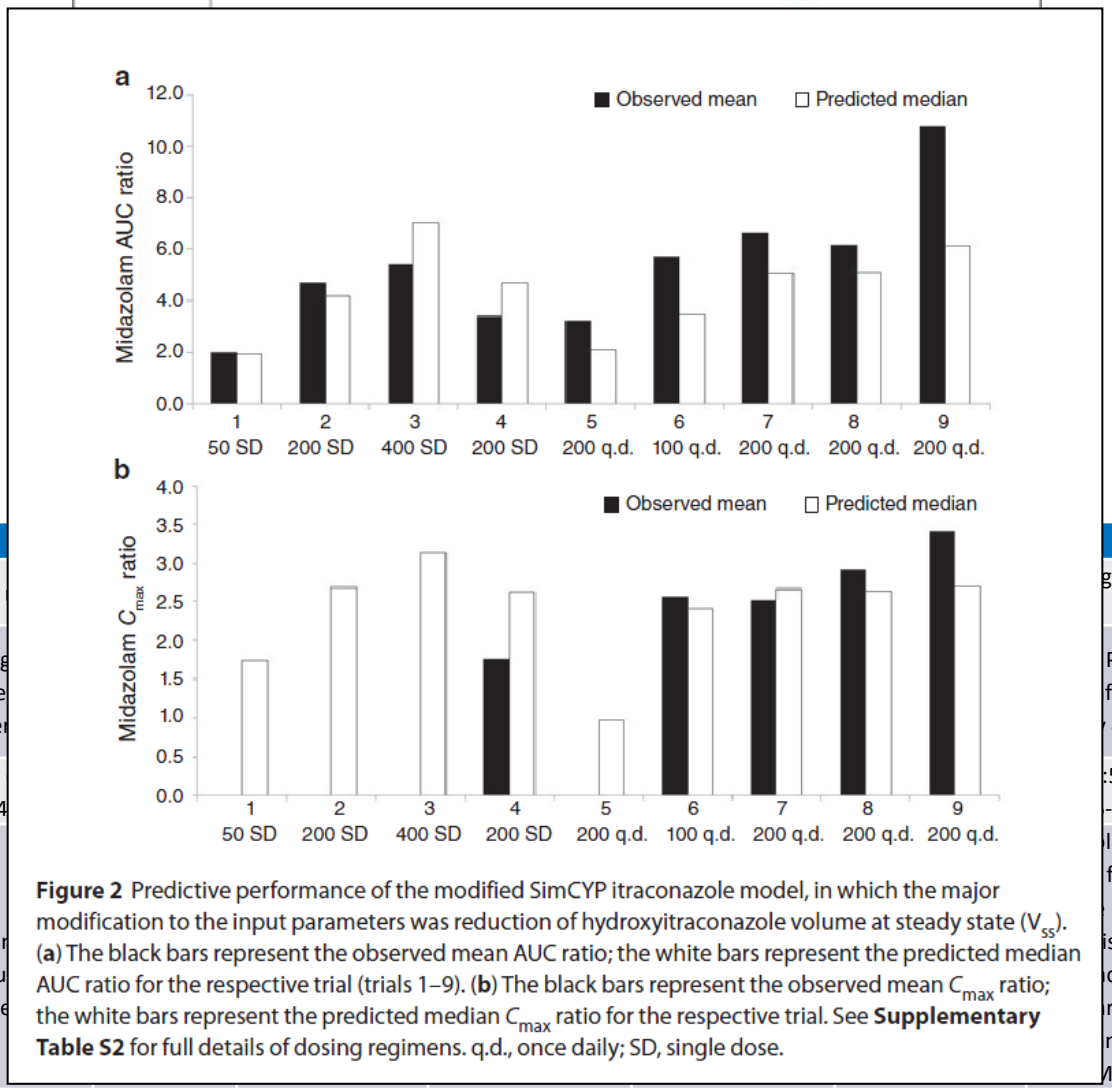


Figure 2 Predictive performance of the modified SimCYP itraconazole model, in which the major modification to the input parameters was reduction of hydroxyitraconazole volume at steady state (V_{ss}). (**a**) The black bars represent the observed mean AUC ratio; the white bars represent the predicted median AUC ratio for the respective trial (trials 1–9). (**b**) The black bars represent the observed mean C_{max} ratio; the white bars represent the predicted median C_{max} ratio for the respective trial. See **Supplementary Table S2** for full details of dosing regimens. q.d., once daily; SD, single dose.

Trial No.	1							8	9
ITZ	50 mg SD	200						g QD for	200 mg QD for 4 days
MID	2 mg PO taken 4 hrs after ITZ	2 mg take after						PO taken fter ITZ 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 22-4						:5); 22-34 -78 kg	n=9 (2:7); 19-26 yrs; 52-85 kg
Study Protocol	Not defined - assumed fasted state	Not defi assu faste						lunteers for 2 hrs MID istration d light rd meals nd 7 hrs 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

Results: Perpetrator = ITZ Victim = Midazolam

MDZ tablet (7.5 mg) With MDZ Administered 2 Hours After ITZ on Day 4 of ITZ 100-mg Once-a-Day Administration

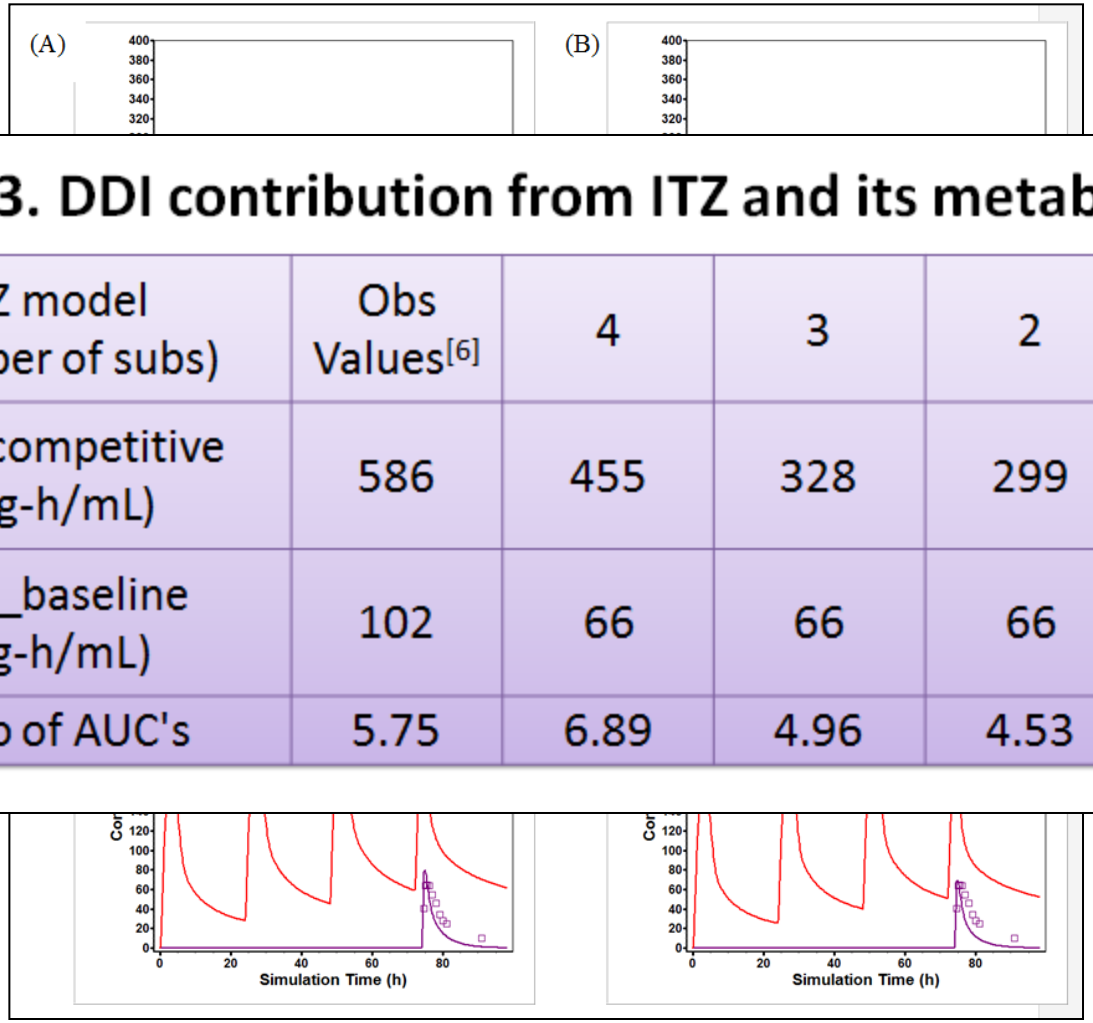


Table 3. DDI contribution from ITZ and its metabolites.

ITZ model (number of subs)	Obs Values[6]	4	3	2	1
AUC_competitive (ng-h/mL)	586	455	328	299	245
AUC_baseline (ng-h/mL)	102	66	66	66	66
Ratio of AUC's	5.75	6.89	4.96	4.53	3.71

Clinical data from: Ahonen J. Eur J Clin Pharmacol. 1997;51:415.

Tools to Assess Drug Safety *in silico*

Halofantrine and Risk of QT Interval Prolongation

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Simulations Plus, Inc.

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SCIENCE + SOFTWARE = SUCCESS

Merging PBPK and Pharmacodynamics
Halofantrine Case Study

- Early assessment of toxicology potential is critical to improving productivity
- PBPK can be used to predict drug concentration at site of action and provide realistic assessment of drug safety

Halofantrine Case Study
Background

- Halofantrine hydrochloride is useful for treatment of uncomplicated malaria
- Administered orally as racemic mixture and undergoes N-debutylation in liver by CYP3A4 to its major metabolite N-desbutylhalofantrine
- Parent and metabolite blocked hERG K+ channels in concentration-dependent manner with IC_{50} of 21.6 nM and 71.7 nM, respectively
- Slower elimination of metabolite results in accumulation with multiple dosing
- PBPK model developed for parent and metabolite
  - Used to predict tissue concentrations in heart
  - Tissue concentrations used to predict effects on QT interval prolongation

Physicochemical, Metabolism, and Toxicity Properties of Halofantrine

Physicochemical Properties	Value	Reference
Log P (Octanol/Water)[a]	7.58	ADMET Predictor[b]
Aqueous Solubility at pH 5.5 (µg/mL)	1.3	Humberstone, A.J.; Cowman, A.F.; Horton, J.; Charman, W.N., Effect of altered serum lipid concentrations on the IC50 of halofantrine against Plasmodium falciparum, J Pharm Sci (87) (1998) 256–258.
FaSSIF (µg/mL)	2.1	
FeSSIF (µg/mL)	264	
pKa Base	9.2	ADMET Predictor[b]
Percent Unbound in Plasma (%)[c] - Human	0.7	
Percent Unbound in Plasma (%) - Rat	0.038	Brocks, D.R., Stereoselective halofantrine and desbutylhalofantrine disposition in the rat: cardiac and plasma concentrations and plasma protein binding, Biopharm Drug Dispos (23) (2002) 9–15.
Blood/Plasma Concentration Ratio	1.5	Klein, K.; Aarons, L.; Ter Kuile, F.O.; Nosten, F.; White, N.J.; Edstein, M.D.; Teja-Isavadharm, P., Population pharmacokinetics of halofantrine in healthy volunteers and patients with symptomatic falciparum malaria, J Pharm Pharmacol (64) (2012) 1603–1613.
Metabolism		
In vitro CYP3A4 Km Halofantrine (µM)[d]	48	Baune, B.; Flinois, J.P.; Furlan, V.; Gimenez, F.; Taburet, A.M.; Becquemont, L.; Farinotti, R., Halofantrine metabolism in microsomes in man: major role of CYP 3A4 and CYP 3A5, J Pharm Pharmacol (51) (1999) 419–426.
In vitro CYP3A4 Vmax Halofantrine (pmol/min/mg protein)[d]	215	
In vitro CYP3A4 Km N-desbutylhalofantrine (µM)	71.7	ADMET Predictor[b]
In vitro CYP3A4 Vmax N-desbutylhalofantrine (pmol/min/mg protein)	1410	ADMET Predictor[b]
Toxicity		
hERG IC_{50} Halofantrine (nM)	21.6	Mbai, M.; Rajamani, S.; January, C.T., The anti-malarial drug halofantrine and its metabolite N-desbutylhalofantrine block HERG potassium channels, Cardiovasc Res (55) (2002) 799–805.
hERG IC_{50} N-desbutylhalofantrine (nM)	71.7	
Hill Coefficient Halofantrine	0.62	
Hill Coefficient N-desbutylhalofantrine	1.36	

Abbreviations: FaSSIF, fasted-state simulated intestinal fluid; FeSSIF, fed-state simulated intestinal fluid; IC_{50}, concentration resulting in 50% of the maximum inhibition; Km, concentration at 1/2 maximum metabolic velocity; Log P, octanol water partition coefficient; Vmax, maximum metabolic velocity.

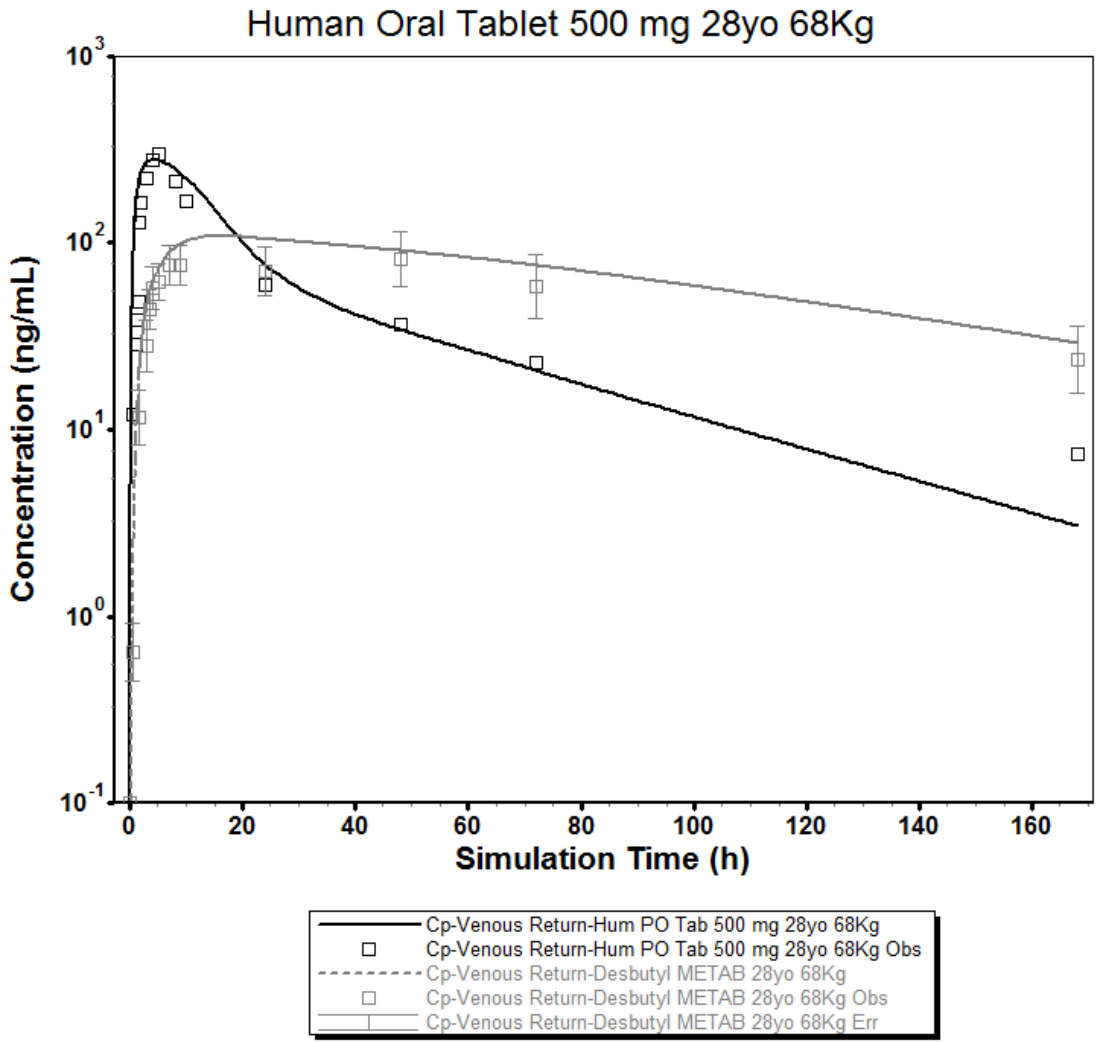
[a] Experimental log P not determined due to low aqueous solubility.

[b] ADMET Predictor. Version 7.2. Lancaster, CA: Simulations Plus, Inc.; 2015.

[c] Assumed fraction unbound in enterocytes to be 1% to account for lysosomal trapping.

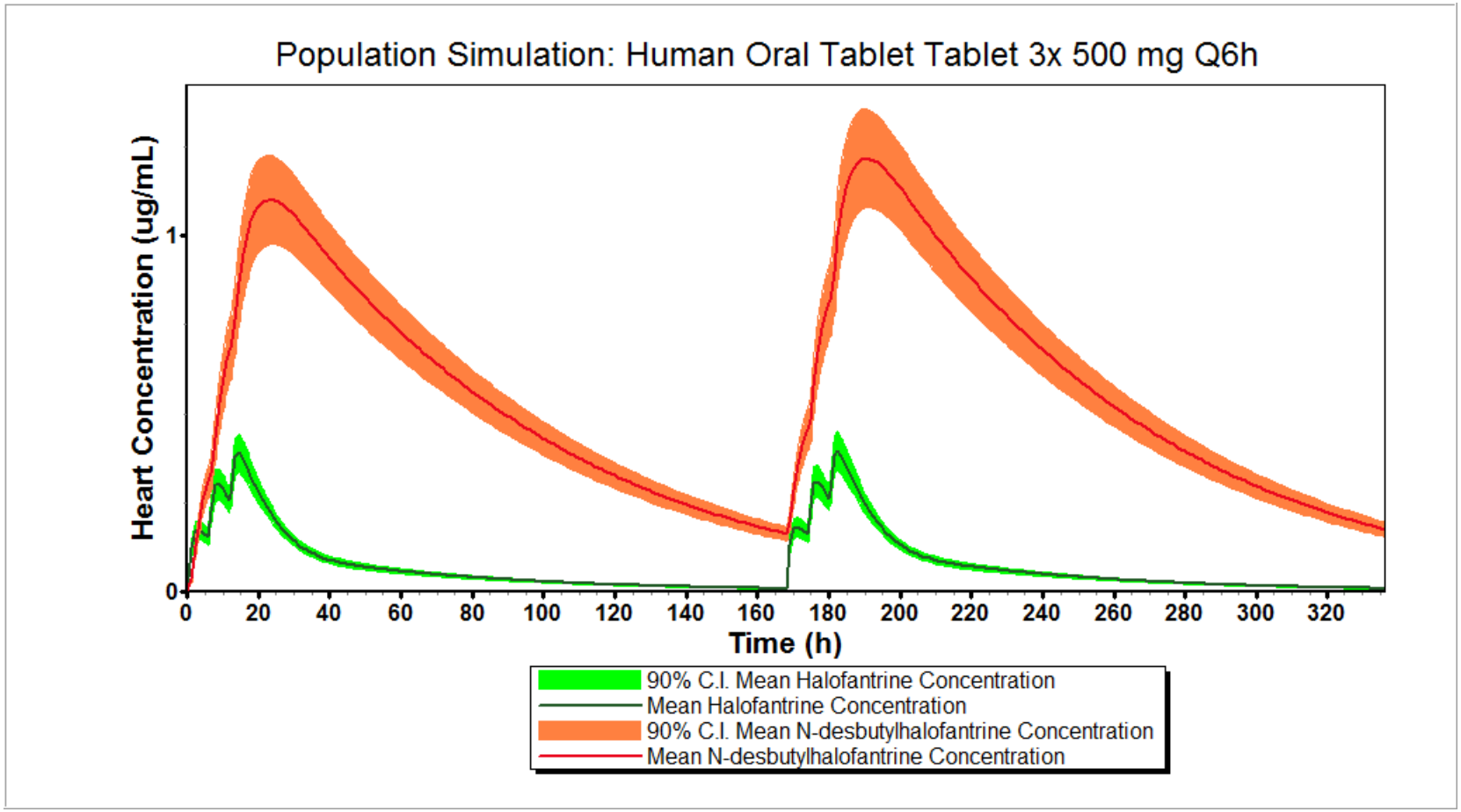
[d] *In vivo* V_{max} and K_m calculated using the Halifax Fu calculation method and GastroPlus default values for CYP3A4 microsomal content and molecular weight.

Plasma Concentration-Time Profiles for Parent and Metabolite Following a 500-mg Single Oral Dose



From GastroPlus™.

Heart Concentrations From Population Simulation Using Recommended Dosing Regimen for Treatment of Malaria



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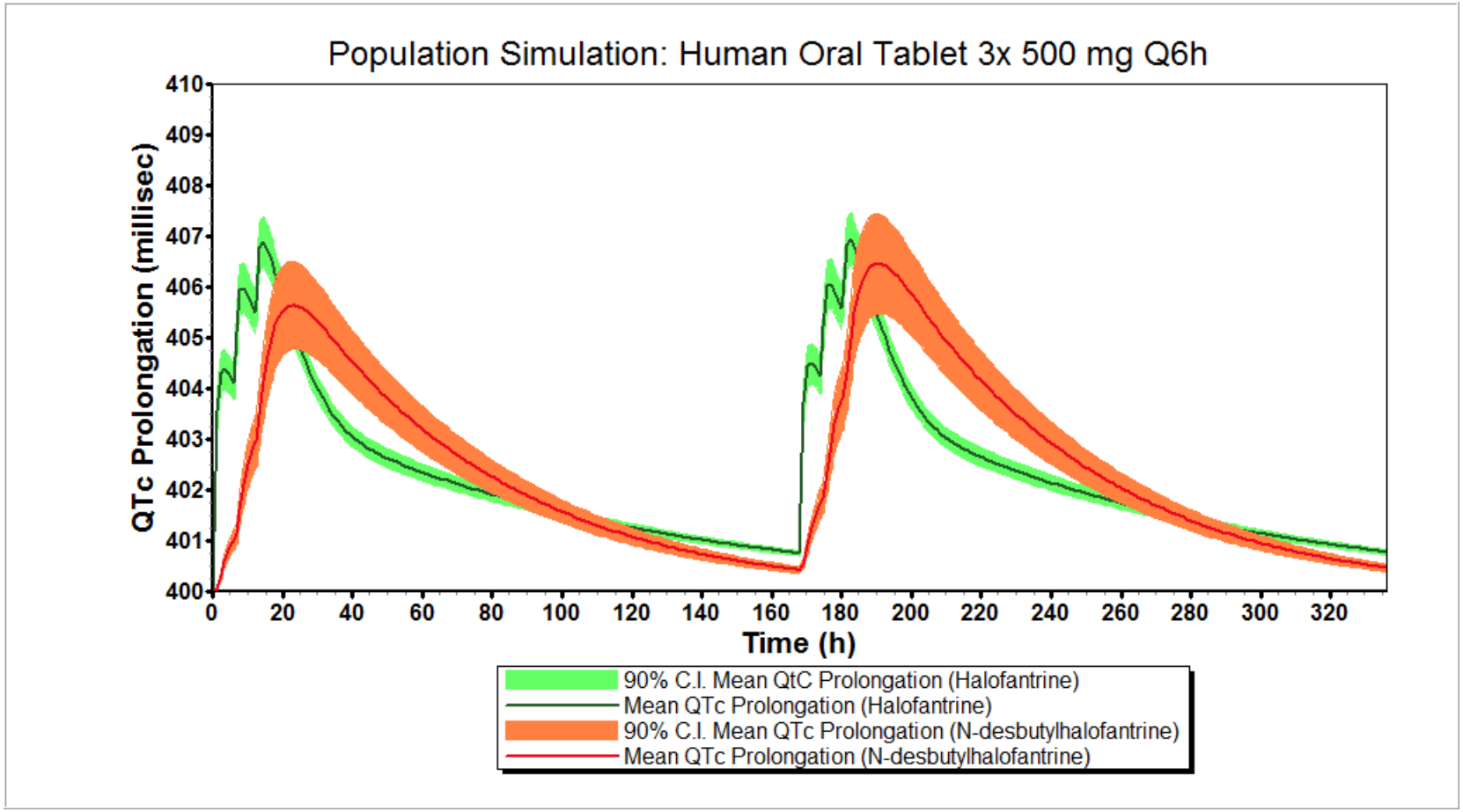
Effects on QTc Interval From Population Simulation Using Recommended Dosing Regimen for Treatment of Malaria



From GastroPlus™.

Halofantrine Case Study
Conclusions

- N-desbutylhalofantrine has been suggested to be safer antimalarial agent compared to halofantrine
- Our results suggest that gain in safety margin for QT interval prolongation-related cardiotoxicity is minimal
- With chronic dosing, higher concentrations of N-desbutylhalofantrine are likely to be associated with concentrations considerably higher than IC_{50} for HERG blockade
- Consequently, metabolite can play substantial role in cardiotoxicity of halofantrine

Modeling and Simulation *in silico*
Part 2:
Cultural and Process Implications

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Culture Changes of *in silico*-Based R&D
Interdisciplinary Collaboration

- Successful use of *in silico* tools requires interdisciplinary collaboration
  - Discovery scientists – Drug Metabolism and PK scientists – Formulation scientists – Clinical Pharmacologists
- PBPK modeling requires knowledge of physicochemical characteristics, physiology, and formulation science
  - Important information resides within various functional groups and needs to be disseminated efficiently and completely

Culture Changes of *in silico*-Based R&D
Management of PBPK Modeling Process

- Managing disagreements over model input parameters and interpretation of results
- Change control over time – Who has access to model/data?
- Time commitment – Who sets schedule and assigns responsibility for completing tasks on time?
- Interdisciplinary interactions – How does availability of model result in changes in relations between departments?

Culture Changes of *in silico*-Based R&D
Input Data Availability

- Data repository is living document/file
  - Should travel with compound through various stages of development
- Data availability and modeling goals change over time
  - What data are we missing to support modeling effort?
- How do we define expectations for model in different phases of R&D as more data become available?

Value of PBPK Model - Summary

- Well-verified PBPK model that is consistent with all collected data provides repository of knowledge
  - Mechanism-based extrapolation
  - Predict unstudied scenarios
- Predictions can be incorporated into regulatory submissions, product labels, post-approval studies, and next generation follow-on drugs
- Explore “what if” scenarios in which *in vivo* or clinical studies are not feasible
- Simulations to inform better study design and extrapolate across species, populations, and different modes of drug administration

Jones HM, et al. Clin Pharmacol Ther. 2015;97(3):247-262.

Summary

- Quantitative mechanistic framework for prediction of systemic and tissue exposures
- Increasing availability of *in silico* and *in vitro* systems, which act as surrogates for *in vivo* ADME processes
  - Advancements in *in vitro* – *in vivo* correlation of these data
- Expanding application from discovery to post approval
- Regulatory guidances suggesting use of PBPK modeling for DDI assessment and hepatic impairment

Jones HM, et al. Clin Pharmacol Ther. 2015;97(3):247-262.

Thank you.

Questions?

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