Simulation of the Nonlinear PK of Gabapentin and Midazolam in Adult and Pediatric Populations

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Goals

- Demonstrate the application of physiologically based pharmacokinetic (PBPK) modeling methods for nonlinear metabolism and transport

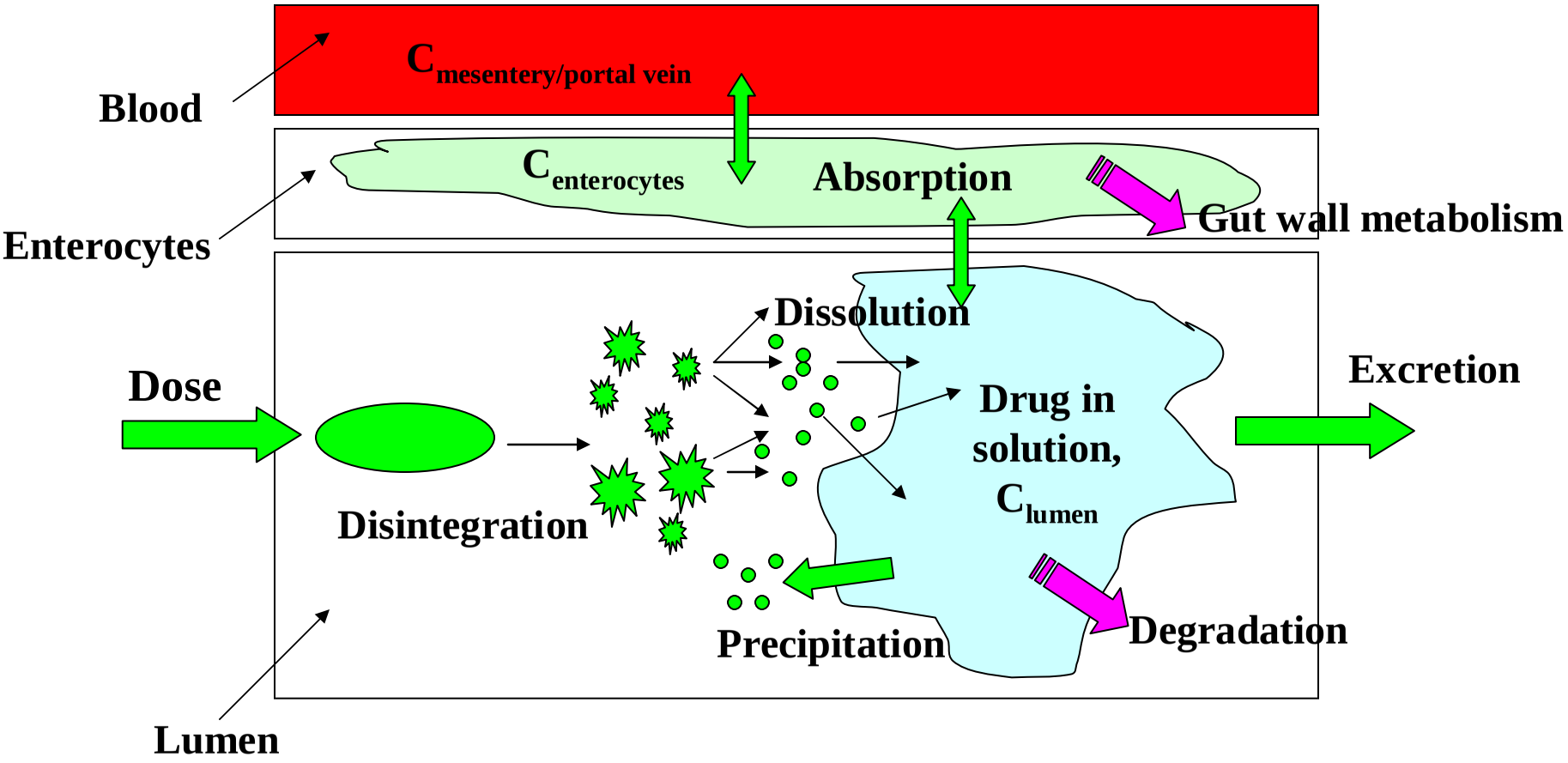
- Demonstrate the ability of PBPK modeling to predict PK for a pediatric population from adult and *in vitro* data

Methods – Physiological Models

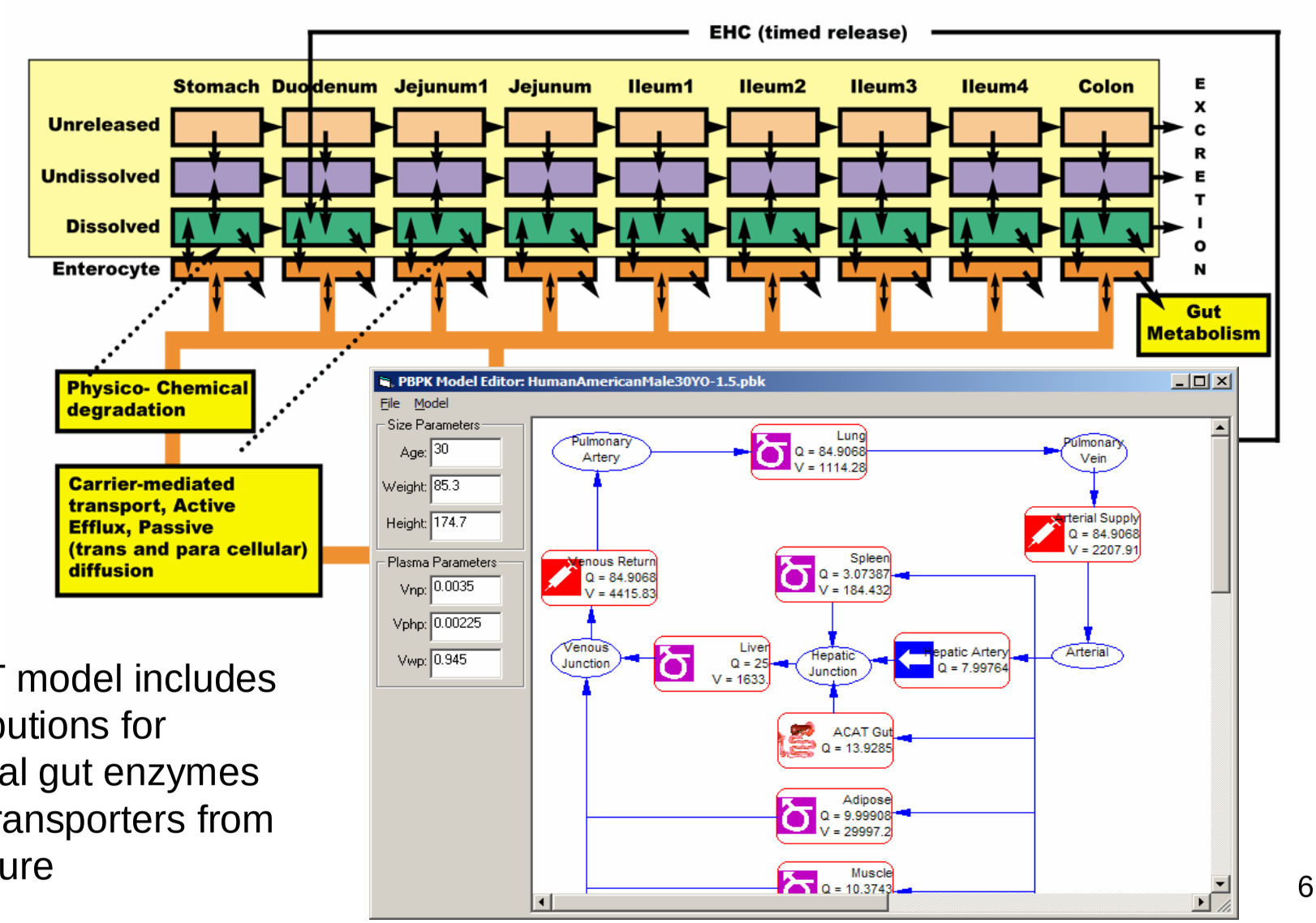
- Gut: ACAT (Advanced Compartmental Absorption and Transit) model[1,2]
- PBPK: Based on Roche PK-Predictor, as modified in a collaboration between Simulations Plus and Roche
- Tissue-plasma concentration ratio (Kp) calculations using method of Rodgers & Rowland[3]
- Physiologies: PEAR™ (Population Estimates for Age-Related Physiology) module within GastroPlus™

[1]Yu, L.X. and Amidon, G.A., Int. J. Pharm. 186:119 (1999)
[2]Agoram et al, Adv. Drug Deliv. Rev. 50:S41 (2001)
[3]Rodgers et al, J. Pharm. Sci. 94:6:1259 (2005)

Processes Involved in Oral Absorption



ACAT-PBPK Combined Model



ACAT model includes distributions for several gut enzymes and transporters from literature

PEAR™ Physiology

Population Estimates for Age-Related (PEAR) Physiology generates body weight, height, body mass index, tissue weights and volumes, and tissue perfusion rates, for male or female, Western or Asian, at any age between 1 and 85 years.

Correlation models were fitted to data from the U.S. National Health and Nutrition Examination Survey (NHANES)[1] database for American (Western) physiologies and from a Japanese database[2] for Japanese (Asian) populations. Allometric scaling is used to scale individual tissue weights and perfusion rates.

Tissue volumes and perfusion rates are calculated for each tissue for each generated physiology[3,4]

[1] http://www.cdc.gov/nchs/nhanes.htm
[2]Ogiu et al, Health Phys. 72(3):368 (1997)
[3]Price, P.S. Crit. Rev. Toxicol. 33(5):469 (2003)
[4]Haddad S., et al., J. Tox. Envir. Health 64:453 (2001)

Methods – Midazolam PK

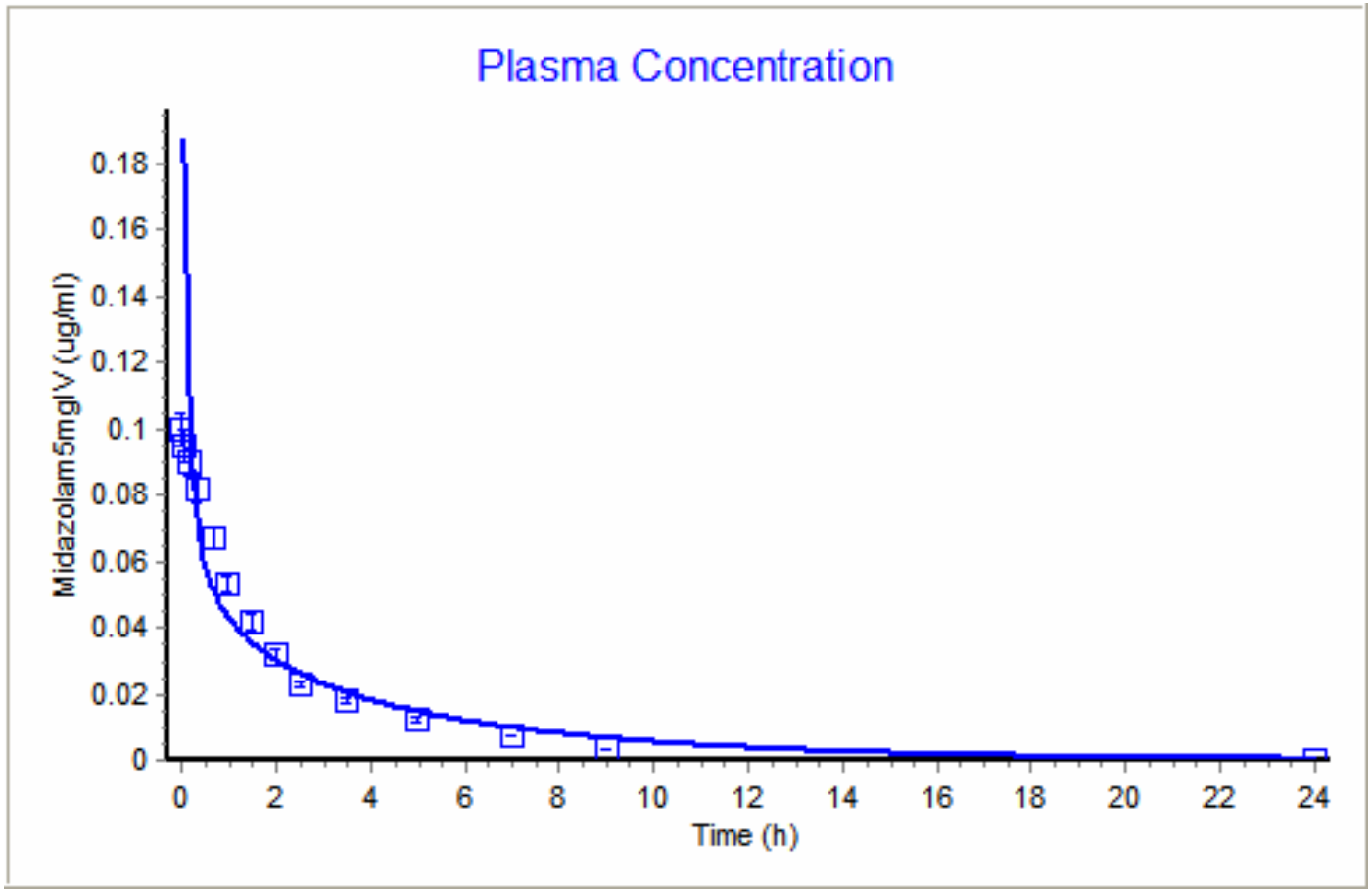
- Obtain *in vitro* data for metabolism of midazolam in human liver microsomes from the literature
- Calculate *in silico* midazolam tissue partition coefficients (K_ps) using published method of Rodgers & Rowland
- Generate *in silico* physico-chemical properties when experimental values were not available using ADMET Predictor™
- Assess default adult model for midazolam iv and po doses using nonlinear gut and liver clearance
- Adjust effective permeability (Peff) to improve adult fit for oral dose
- Reduce 3A4 metabolism (V_{max}) for pediatric populations using published data for enzyme expression levels
- Conduct Virtual Trial for pediatric population and compare to observed results

Midazolam Data

- In vitro metabolism (microsomes)[1]:
  - Vmax = 850 pmol/min/mg msp
  - Km = 3.7 µM
- Fup = 4%, logP = 2.7, pKa = 6.15
- Intravenous plasma concentration-time in adults[2]
- Plasma concentration-time data after oral doses in adults[2]
- Expression levels of 3A4 in children[3]
- Plasma concentration-time data after oral dosing in children[4]

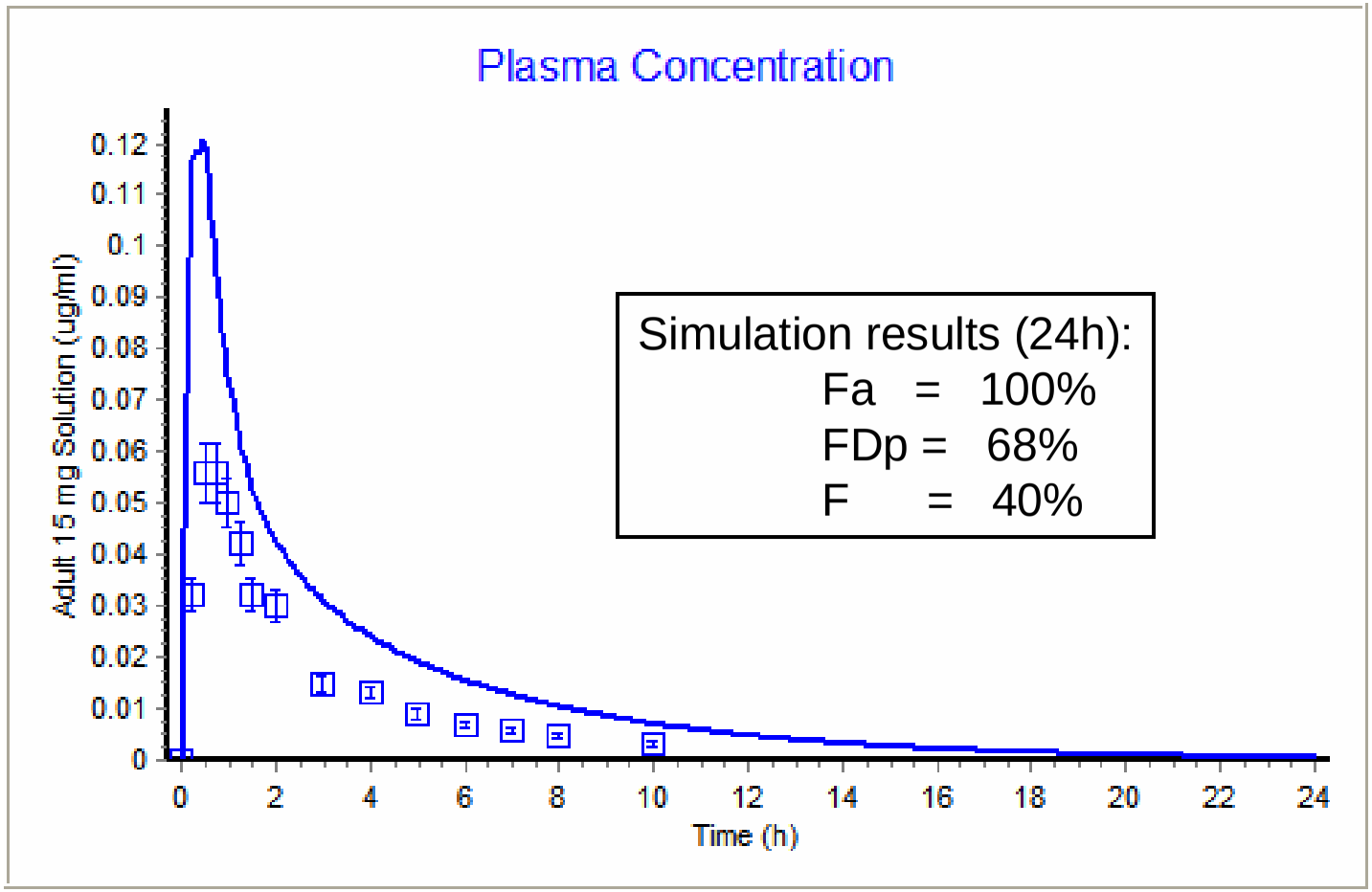
[1]Paine, M. J. Pharmacol. Exp. Therap. 283(3):1552 (1997)
[2]Kupferschmidt,H.H. et al, Clin. Pharmacol. Therapeut. 58:20 (1985)
[3]Johnson, T.N. et al, Br. Clin. Pharm. 51(5):451 (2001)
[4]Johnson, T.N. et al, Br. J. Anaesth. 89(3):428 (2002)

Results: Midazolam Adult 15 mg Oral Solution – Default iv Model



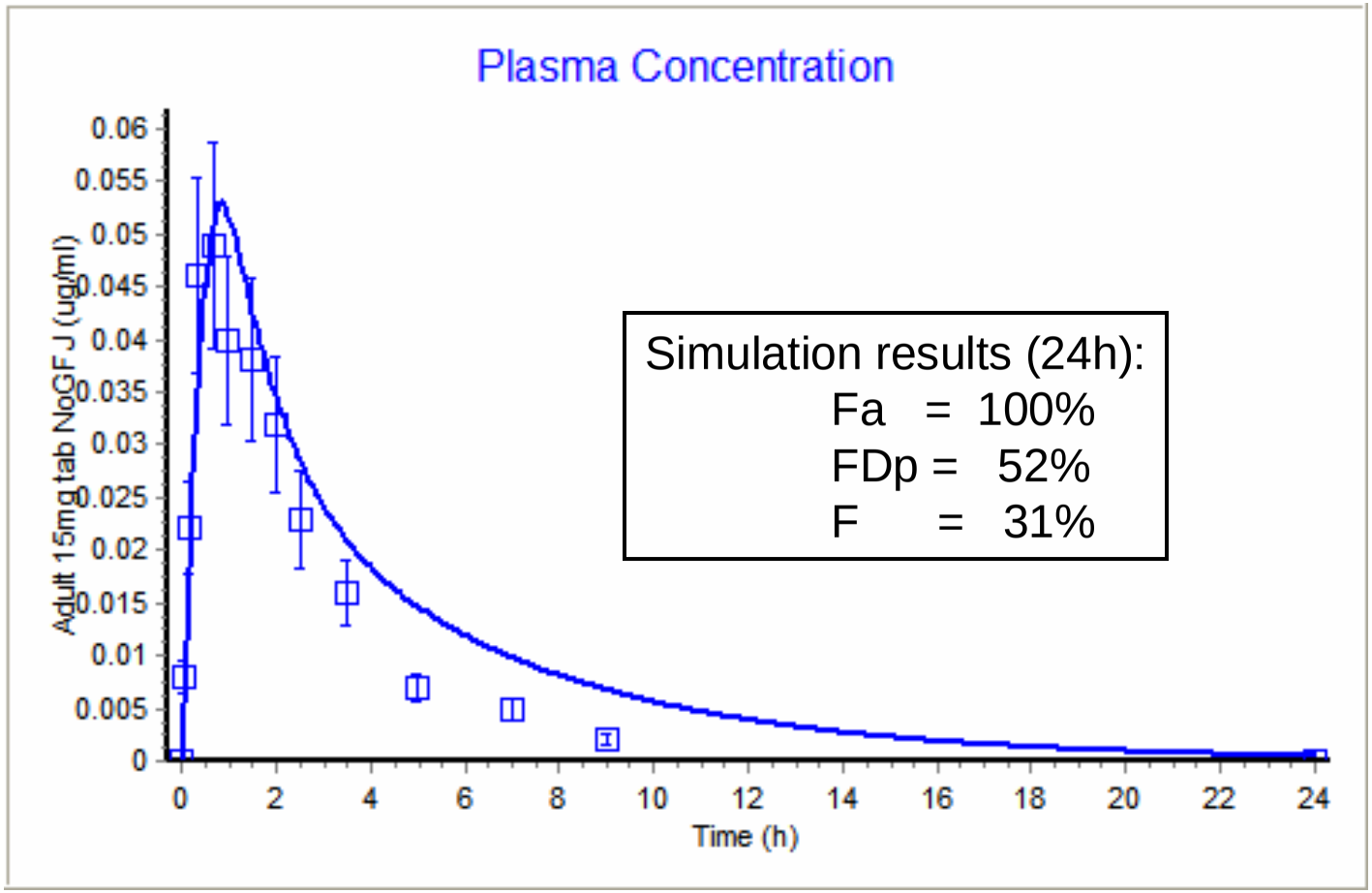
In vitro Vmax and Km, *in silico* Kps, American male 18 yo physiology, default ACAT

Results: Midazolam Adult 15 mg Oral Solution – *in silico* Peff (12 E-4 cm/s)



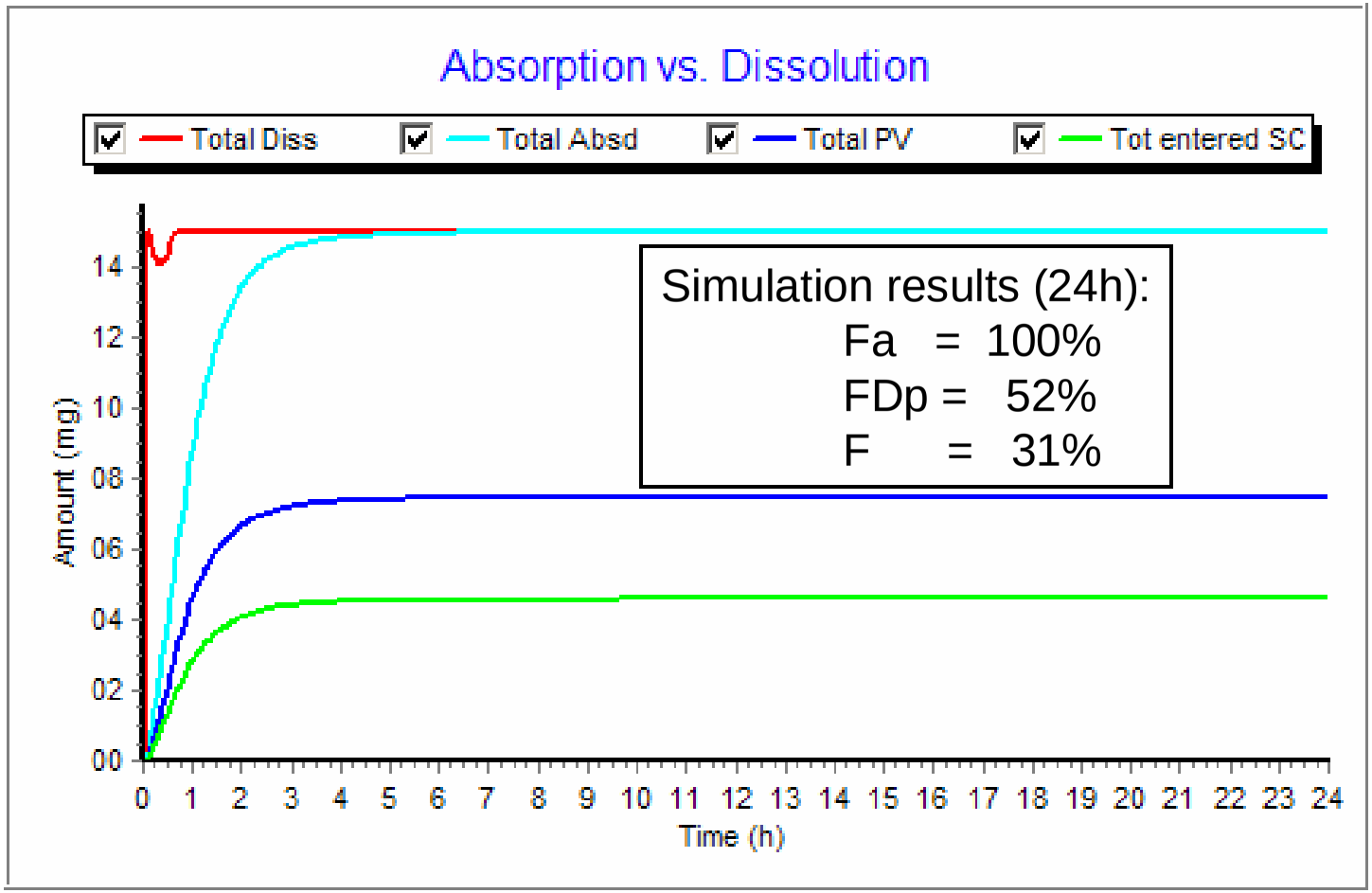
In vitro Vmax and Km, *in silico* Kps, *in silico* Peff (12 E-4 cm/s), American male 18 yo physiology

Results: Midazolam Adult 15 mg Oral Solution – with Fitted Peff (3.5 E-4 cm/s)



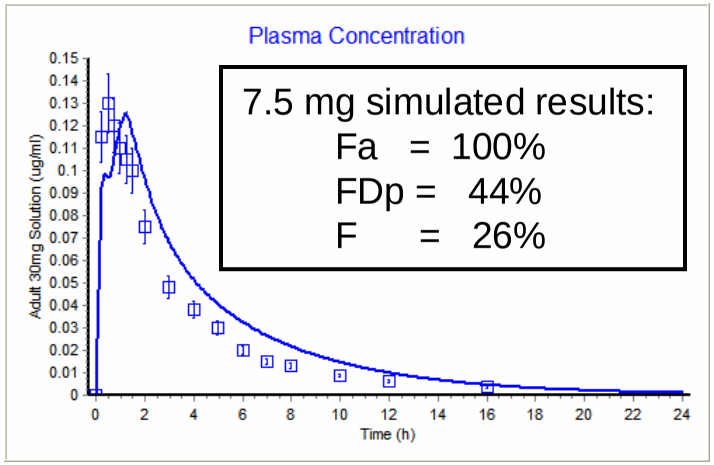
In vitro Vmax and Km, *in silico* Kps, fitted Peff (3.5 E-4 cm/s), American male 18 yo physiology

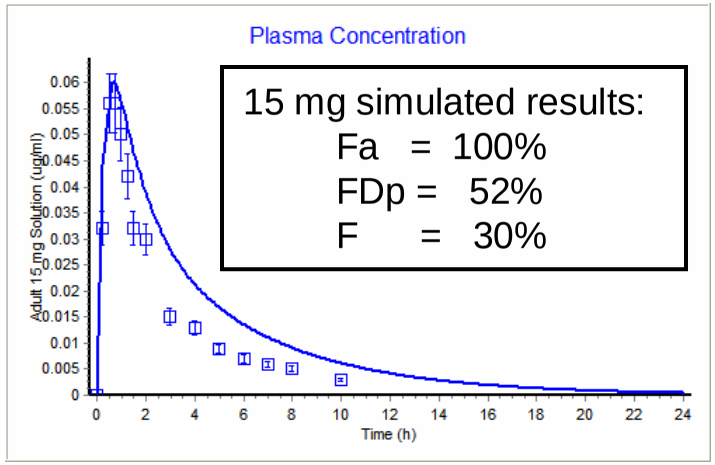
Results: Midazolam Adult 15 mg Oral Solution – with Fitted Peff (3.5 E-4 cm/s)

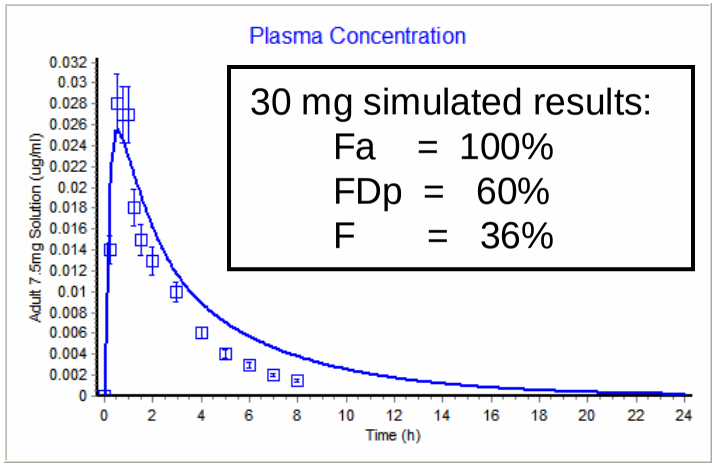


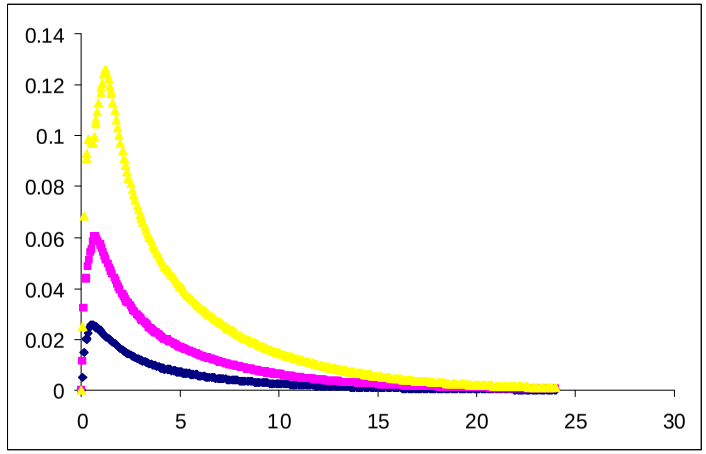
In vitro Vmax and Km, *in silico* Kps, fitted Peff (3.5 E-4 cm/s), American male 18 yo physiology

Comparison of 7.5, 15, and 30 mg po Doses with Same Nonlinear Model

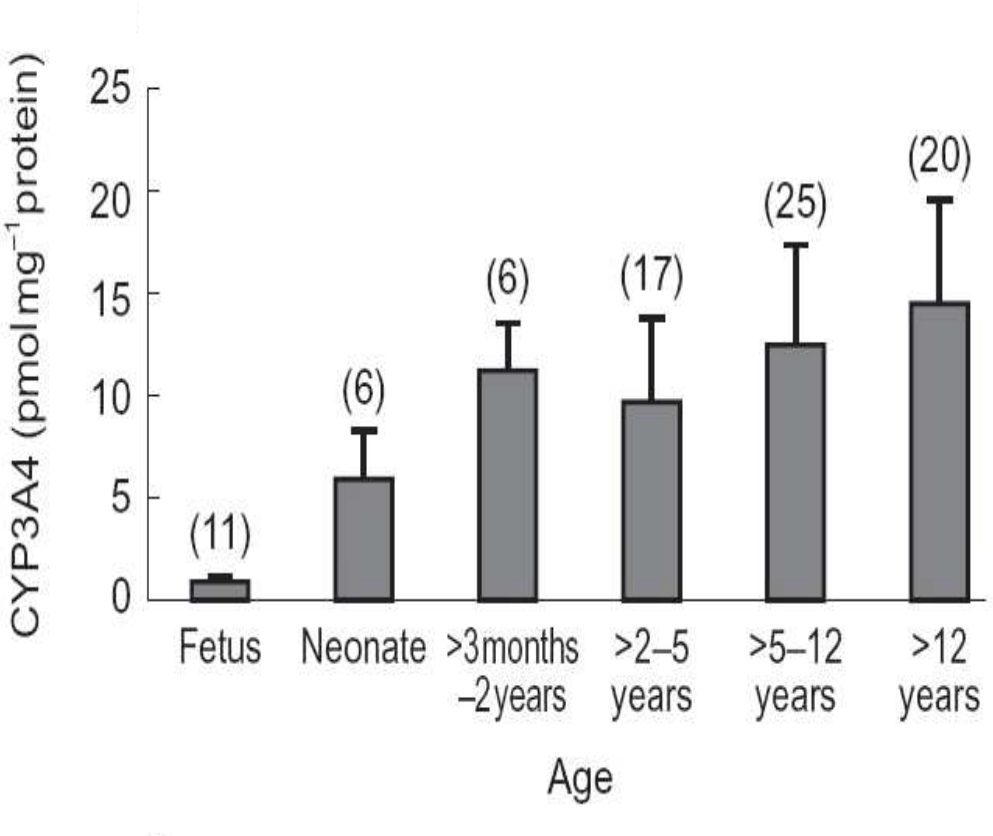






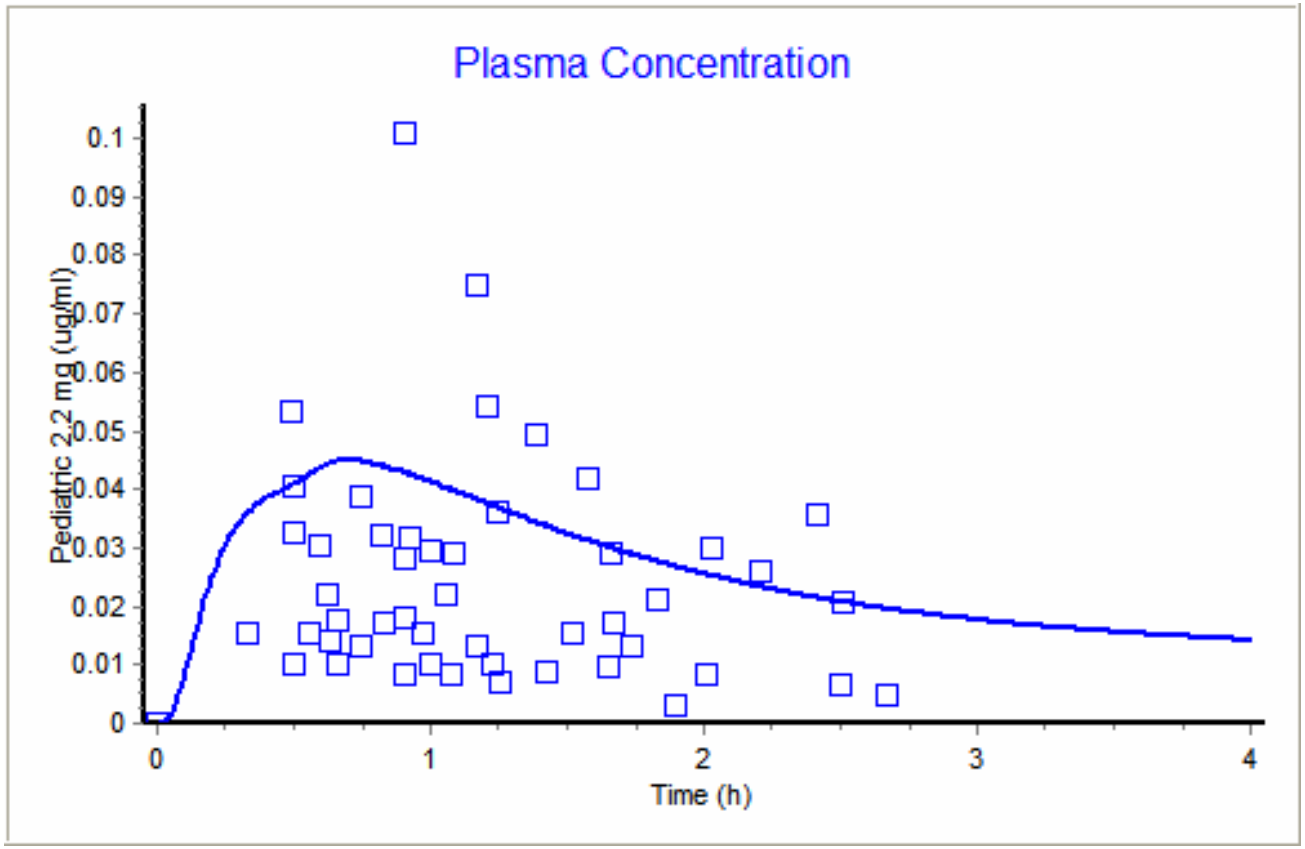


Changes in CYP 3A4 Expression in Duodenum of Pediatric Subjects (1 – 12 yo)



Johnson, T.N., Br. J. Clin. Pharm. 51(5):451 (2001)

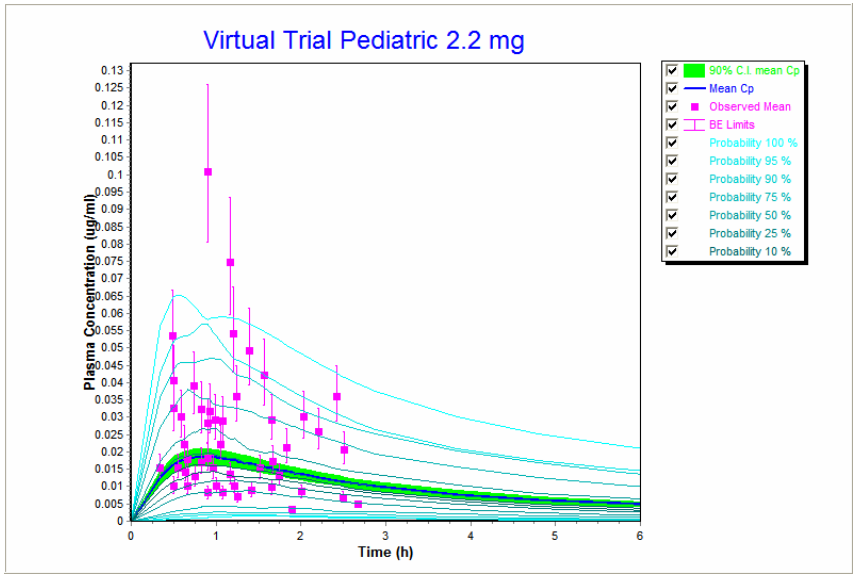
Results: Midazolam Pediatric 2.2 mg Oral Solution – Vmax Reduced 30%

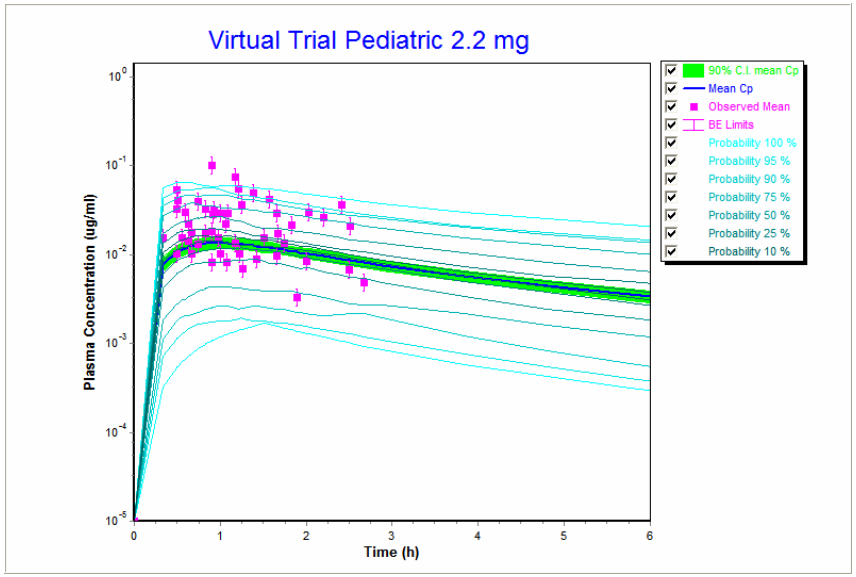


In vitro Vmax and Km, *in silico* Kps, fitted Peff (3.5 E-4 cm/s), American male 5 yo physiology

Pediatric PBPK Virtual Trial Results

Virtual Trial sampled variables: all ACAT physiological variables, all PK parameters, subject age and gender within constraints, body weight and height around baseline physiology for sampled age and gender, all PBPK tissue volumes and perfusion rates



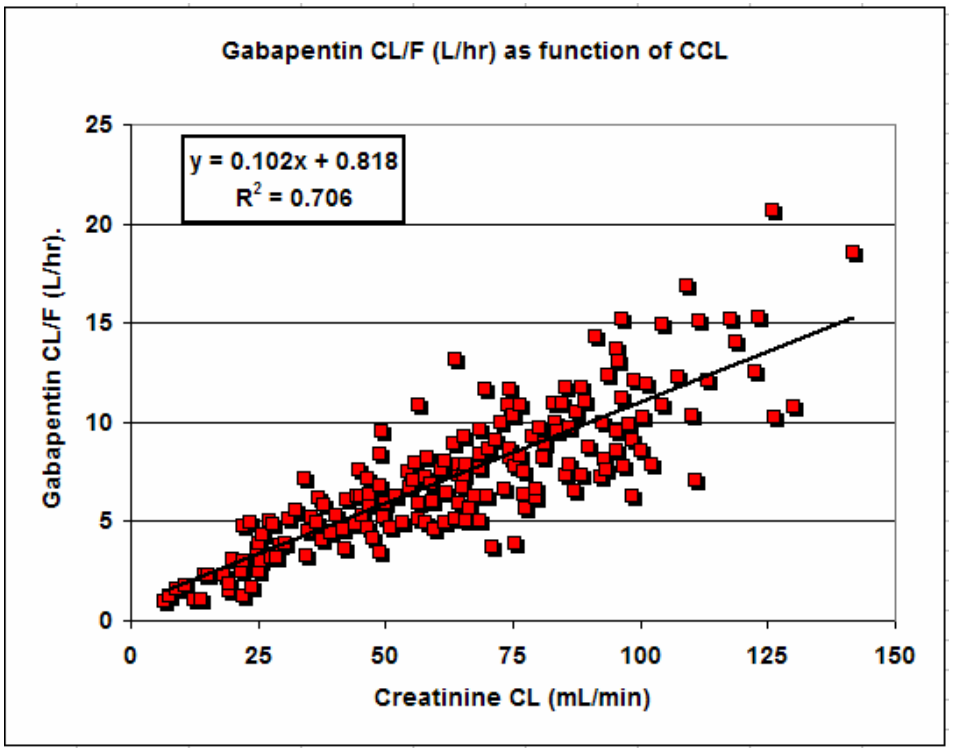


Methods – Gabapentin PK

- Obtain literature data for gabapentin PK in adults and children
- Build absorption and PBPK model based on adult data
- Conduct Virtual Trial for pediatric population and compare results with observed pediatric population data

[1]Ouellet D., Epilepsy Research 47:229 (2001)
[2]Gildal B.E., Epilepsy Res. 40:123 (2000)
[3]Gidal B.E., Epilepsy Res. 31:91 (1998)

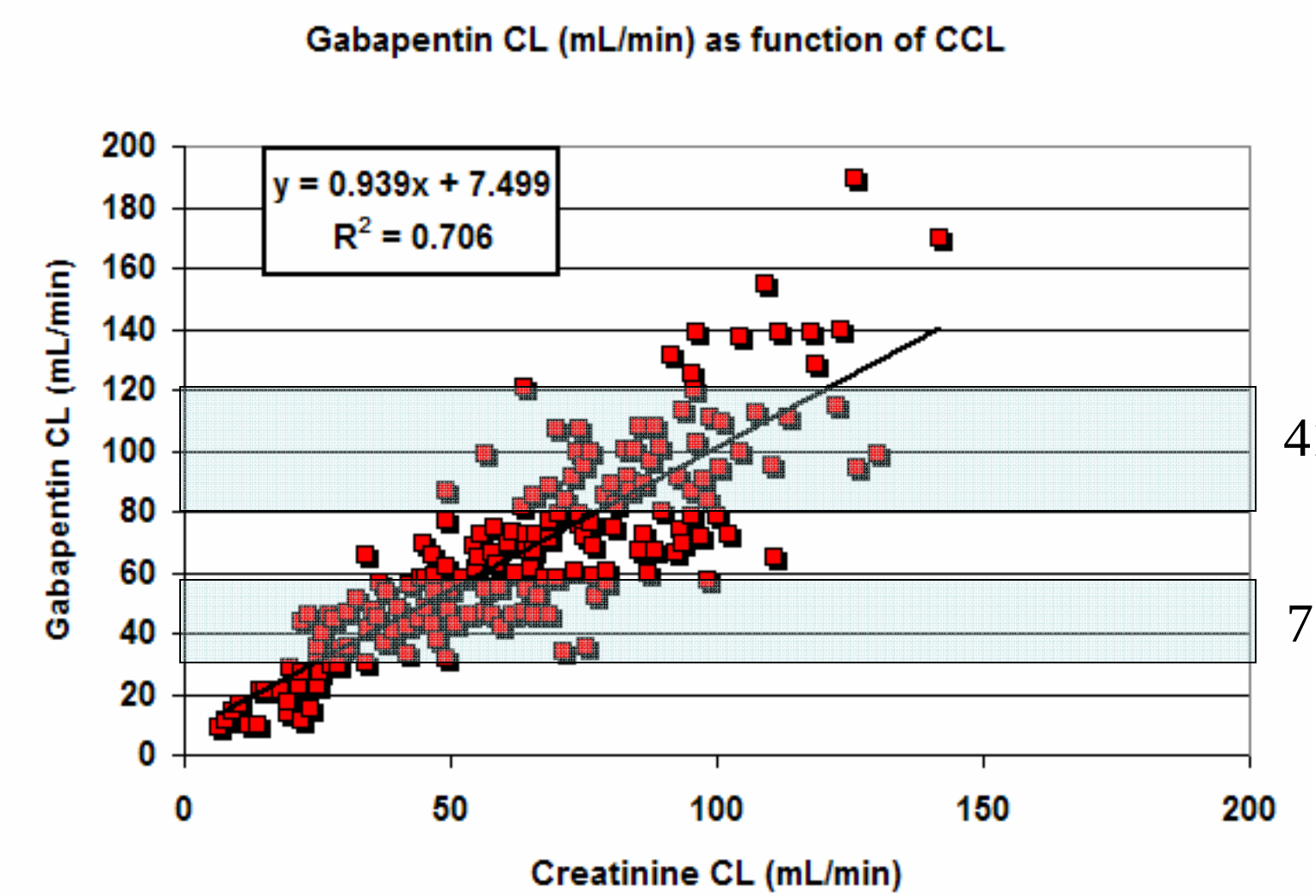
Gabapentin CL Modeled as Function of Creatinine Clearance



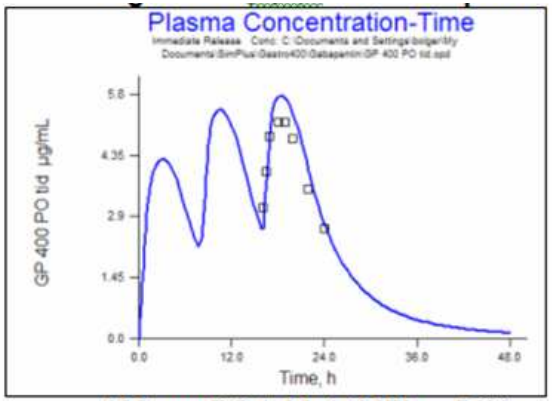
- Renal Clearance of Gabapentin estimated from Creatinine CL (CCL):
- Creatinine CL estimated from serum creatinine vs. age.[2]
- Adult and Child Gabapentin CL (GCL in L/h) = 0.102 x CCL(mL/min) + 0.818
- Adult GCL average of Schwartz and Cockroft-Gault = 10.3 L/hr
- 7 yo Child GCL = 5.21 L/hr.

[1]Ouellet D., Epilepsy Research 47:229 (2001)
[2] Tiao-Cardiovasc. Surg. 10(5):445 (2002)

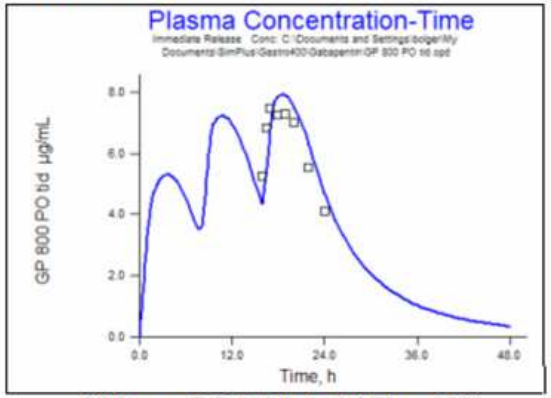
Gabapentin Renal CL vs. CrCL



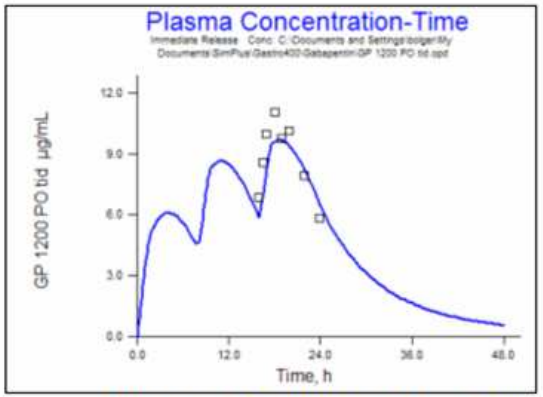
Results: Gabapentin Nonlinear Dose Dependence in Adults



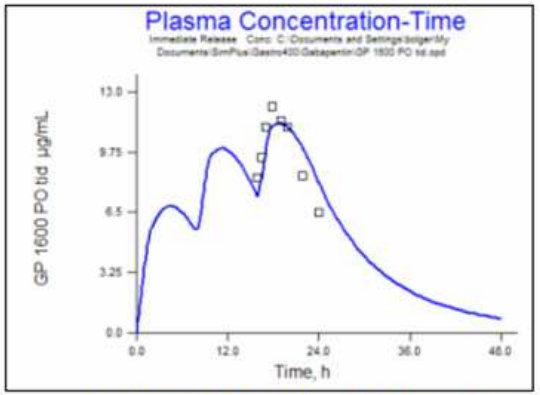
400 mg PO tablet *tid* Fb = 54%



800 mg PO tablet *tid* Fb= 42%

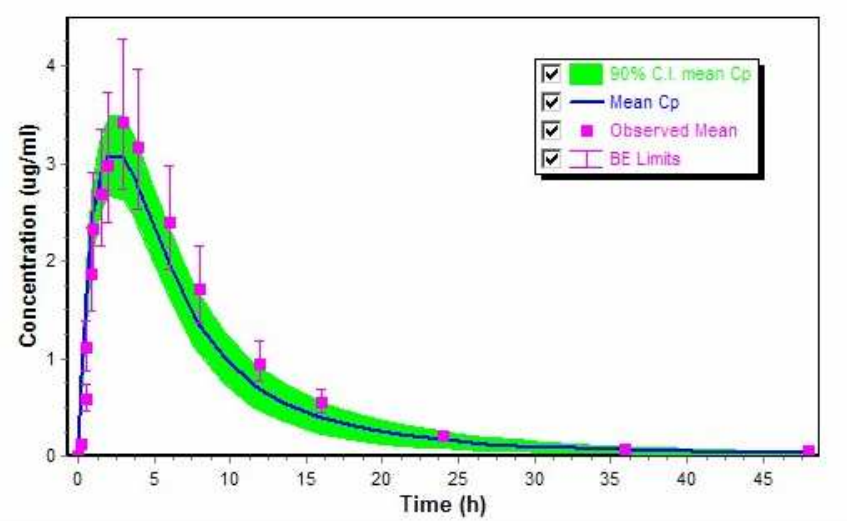


1200 mg PO tablet *tid* Fb = 37%

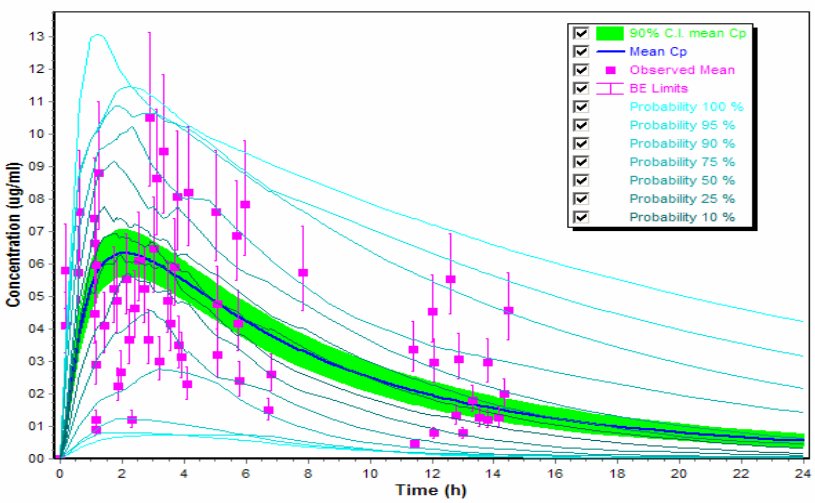


1600 mg PO tablets *tid* Fb = 35%

Results: Adult and Pediatric Population Simulations



400 mg solution: 41 yo adult female



400 mg tablet, 7 yo children

Conclusions

- State-of-the-art PBPK modeling methods are appropriate for nonlinear metabolism and transport
- Bioavailability and plasma concentration-time can be predicted with reasonable accuracy from *in vitro* data and *in silico* predictions when the *in vitro* measures of metabolism/clearance are representative of *in vivo* processes
- State-of-the-art PBPK modeling can predict pediatric PK from adult and *in vitro* data when such data are available
- Population studies with PBPK models allow the selection of focused populations with specified ethnicity, age ranges, and gender percentages
- PBPK/PD modeling may provides a new approach for the modeling and prediction of pharmacodynamic effects based on simulated tissue concentrations

Acknowledgements

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Thomas Gilman
John Rose (Lilly)
Boyd Steere (Lilly)