



# What's New in GastroPlus® v9.7?

# GastroPlus® v9.7

## – ACAT™ model:

- Allow two solubility inputs for different drug forms (crystalline, amorphous)
- Fed state conditions based on meal type

## – PBPKPlus™ Module:

- Mechanistic pregnancy PBPK model
- Lysosomal trapping
- Allow different tissue model types (perfusion- or permeability-limited) for different compounds in simulation

## – Metabolism and Transporter Module:

- New enzyme/transporter distribution information
- Provide default population for extensive, intermediate, and poor metabolizers based on specific genotypes

## – DDI Module:

- Additional compound model files for substrates & inhibitors

## – PDPlus™ Module:

- Precursor-dependent indirect models

## – ADRM Module:

- API evaporation with transdermal administration
- Effect of immune response with intramuscular injection

## – Others:

- Flexibility in solubility vs. pH model fitting
- Updates in Peff converter

# Two Solubility Inputs - Setup

**Inputs for Multiple Solubilities**

	Form 1	Form 2
f (% Dose)	100	0
pH for Ref. Solubility:	1	1
Ref. Solubility (mg/ml):	0.0001	0.1
Solubility for precipitated particles	<input checked="" type="checkbox"/>	<input type="checkbox"/>

**Particle Size Distribution**

Form 1	Form 2	
Mean Particle Radius [um]:	25	25
Standard Deviation:	0	0
Number of Bins:	1	1
Distribution Type:	Log-Normal	Log-Normal
Rmin:	25	25
Rmax:	25	25
Shape Factor:	1	1

# Two Solubility Inputs - Setup

GastroPlus(TM): GastDemo0.mdb (F:\Sourc...\Gastro\G+Git\)

File Edit Database Simulation Setup Controlled Release Tools Modules (Optional) Help

Compound: Gut Physiology-Hum Pharmacokinetics

**Selected Compound**

Test 1 | Current= 7; Total = 9

SI Trans Time (h) = 3.3 | Mean Abs Time (h) =  
 Longest Diss. Time (h) is @ pH 1.0 = 1335.47 hours | Max Abs Dose (S+)= 5.959E+1 mg. | Max Abs Dose (lit) =  
 Support Files

Ver. 9.6.0020

Dosage Form: IR: Tablet

Initial Dose (mg): 10  
 Subsequent Doses (mg): 0  
 Dosing Interval (h): 0  
 Dose Volume (mL): 250

pH for Ref. Solubility: 1 | **More Solubility**

Solubility (mg/mL @pH=1): 1.0E-4

Mean Precipitation Time (sec): 900  
 Diff. Coeff. (cm<sup>2</sup>/s x 10<sup>-5</sup>): 0.52  
 Drug Particle Density (g/mL): 1.2

Particle Size (form 1): R=25.00, D=50.00

Notes

pKa Table | logD: Emp-6.1 | Diss Model: Johnson | PartSize-Sol: ON | BileSalt-Sol: ON | Diff: ON | ConstRad: ON | Precip

**Inputs for Multiple Solubilities**

	Form 1	Form 2
f (% Dose)	100	0
pH for Ref. Solubility:	1	1
Ref. Solubility (mg/ml):	0.0001	0.1
Solubility for precipitated particles	<input checked="" type="checkbox"/>	<input type="checkbox"/>

OK | Cancel

**Tabulated Data Input**

File Units Tools

Particle Size Distribution Data

No. of Data Points: 3

Write comments here:

PSD Type: API Particles

Polymorph: Form 1

Radius (um)	Form 1	Form 2
5	10	
20	50	
50	90	

OK | Cancel | Clear | Redraw | Fit Distribution

Number of Bins to Use in Simulation:

Sort Data on Radius

# Simulation Results: Example 1

Inputs for Multiple Solubilities

	Form 1	Form 2
f (% Dose)	100	0
pH for Ref. Solubility:	1	1
Ref. Solubility (mg/ml):	0.0001	0.1
Solubility for precipitated particles	<input checked="" type="checkbox"/>	<input type="checkbox"/>

OK Cancel

Inputs for Multiple Solubilities

	Form 1	Form 2
f (% Dose)	70	30
pH for Ref. Solubility:	1	1
Ref. Solubility (mg/ml):	0.0001	0.1
Solubility for precipitated particles	<input checked="" type="checkbox"/>	<input type="checkbox"/>

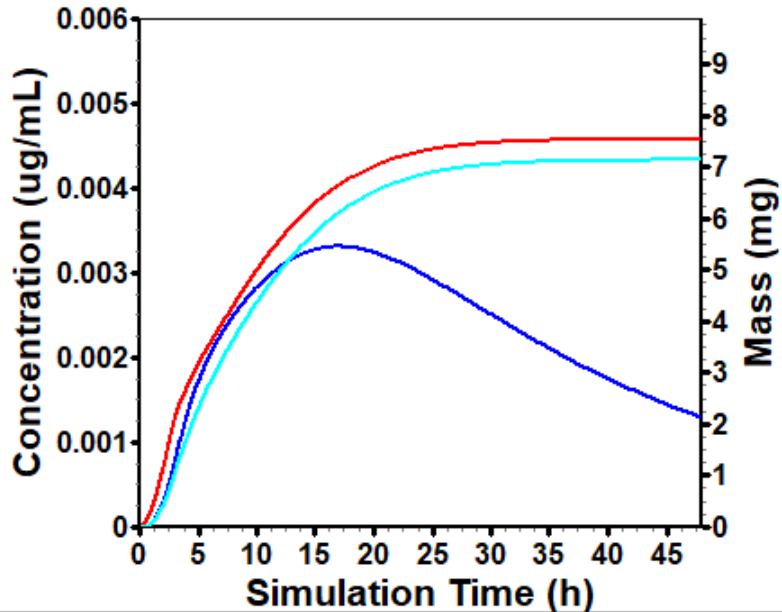
OK Cancel

Inputs for Multiple Solubilities

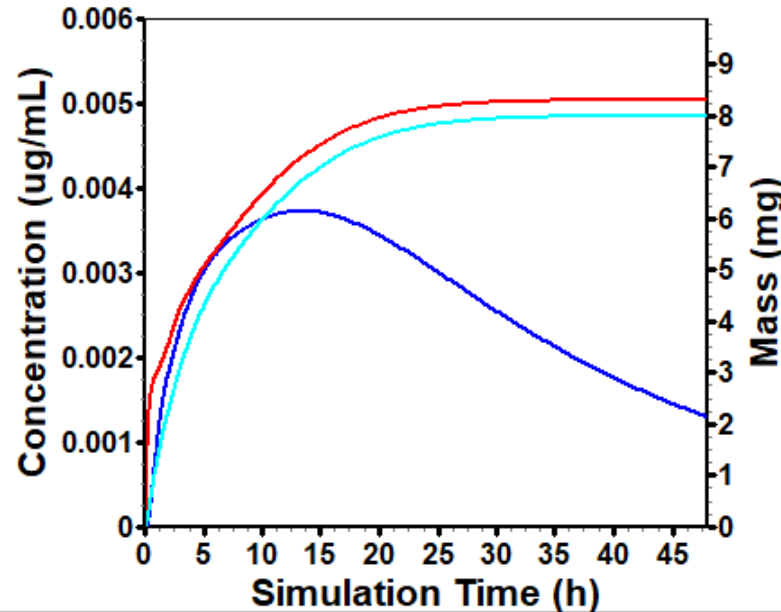
	Form 1	Form 2
f (% Dose)	0	100
pH for Ref. Solubility:	1	1
Ref. Solubility (mg/ml):	0.0001	0.1
Solubility for precipitated particles	<input checked="" type="checkbox"/>	<input type="checkbox"/>

OK Cancel

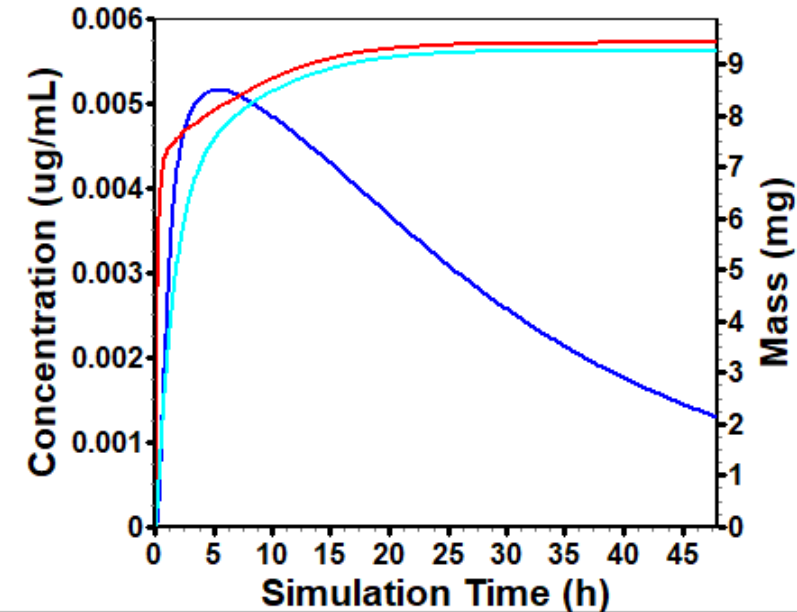
Test 1



Test 1



Test 1



# Simulation Results: Example 2

Inputs for Multiple Solubilities

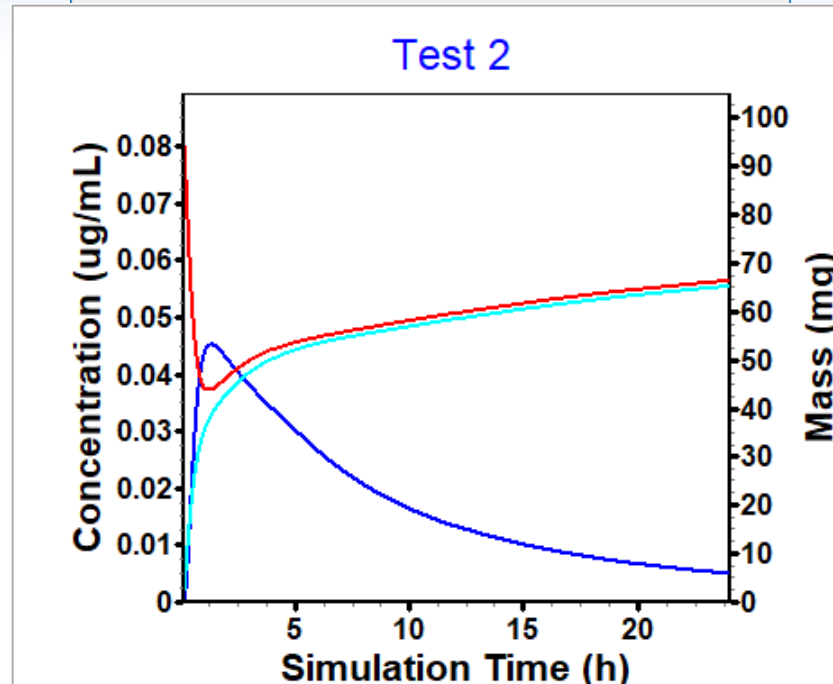
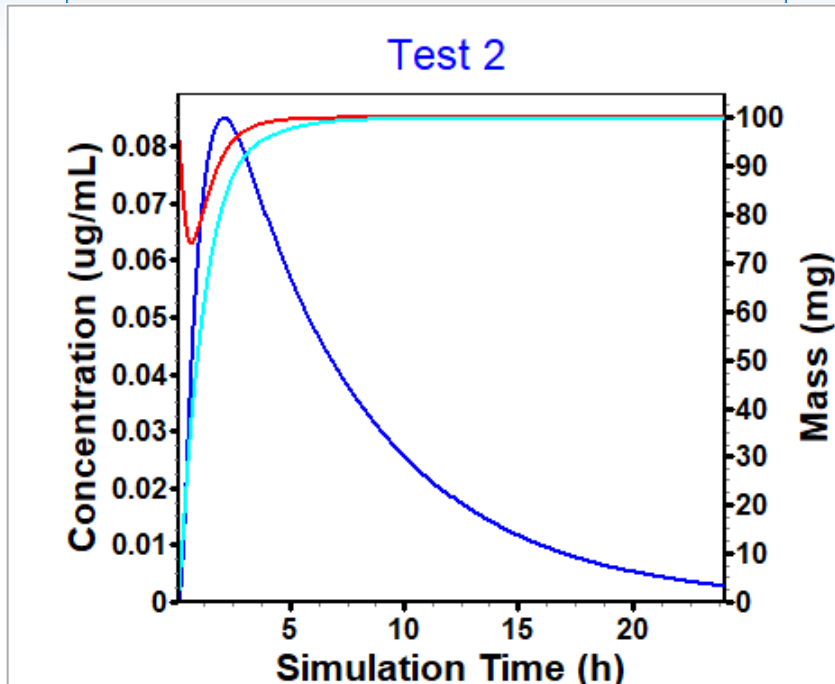
	Form 1	Form 2
f (% Dose)	100	0
pH for Ref. Solubility:	1	1
Ref. Solubility (mg/ml):	12.5	1.25
Solubility for precipitated particles	<input checked="" type="checkbox"/>	<input type="checkbox"/>

OK Cancel

Inputs for Multiple Solubilities

	Form 1	Form 2
f (% Dose)	100	0
pH for Ref. Solubility:	1	1
Ref. Solubility (mg/ml):	12.5	1.25
Solubility for precipitated particles	<input type="checkbox"/>	<input checked="" type="checkbox"/>

OK Cancel



# Built-in Fed Physiologies for Different Meal Types

GastroPlus(TM): GastDemo0.mdb (C:\Users\jmullin\Docum...\CodeR...\Gastr..)

File Edit Database Simulation Setup Controlled Release Tools Modules (Optional) Help

Compound: Propranolol HCl

Gut Physiology-Hum Pharmacokinetics Simulation Graph

Compartmental Parameters

Reset All Values  Excrete all un-absorbed drug at the end of gut transit time  Zero-order gastric emptying

Peff	ASF	pH	Transit Time (h)	Volume (mL)	Length (cm)	Radius (cm)	SEF	Bile Salt (mM)
0	0.0	4.90	2.45	978.5	29.19	9.87	1.000	0.0
0	2.721	5.40	0.28	44.57	14.56	1.56	4.235	22.28
0	2.668	5.40	0.94	166.6	60.26	1.48	3.949	18.09
0	2.665	6.00	0.74	131.0	60.26	1.32	3.488	14.99
0	2.640	6.60	0.58	102.0	60.26	1.16	3.029	10.14
0	2.621	6.90	0.42	75.35	60.26	1.00	2.569	7.093
0	2.589	7.40	0.29	53.57	60.26	0.84	2.109	1.049
0	0.352	6.40	4.36	50.49	13.50	3.45	1.790	0.0
0	0.823	6.80	13.07	53.55	28.35	2.45	2.480	0.0

Enzyme and Transporter Regional Distributions

C1-C4: 0.06944 0.43028 0.12147 0.4663

Physiology: Human - Physiological - Fed

ASF Model: Opt logD Model SA/V 6.1

Fed Meal Options

Percent Fluid in SI: 40 Colon: 10

Biorelevant solubilities from ADMET Predictor v6.1

pKa Table | logD: Struct-6.1 Diss Model: Johnson PartSize-Sol: ON BileSalt-Sol: ON | Diff: ON ConstRad: ON Precip: Time Ppara: OFF EHC: OFF ACAT: Co

- Link gastric emptying time to meal calories
- Account for effect of fat content on bile salt concentration

Fed State Model

Fed State Model: Default

Meal Calories: 233.68 % Fat in Meal: 30.00

Current gastric transit time of 1.00 hr.

Current duodenum bile salt concentration is 14.44 mM.

Cancel OK

Fed State Model

Fed State Model: Default

Meal Calories: 233.68

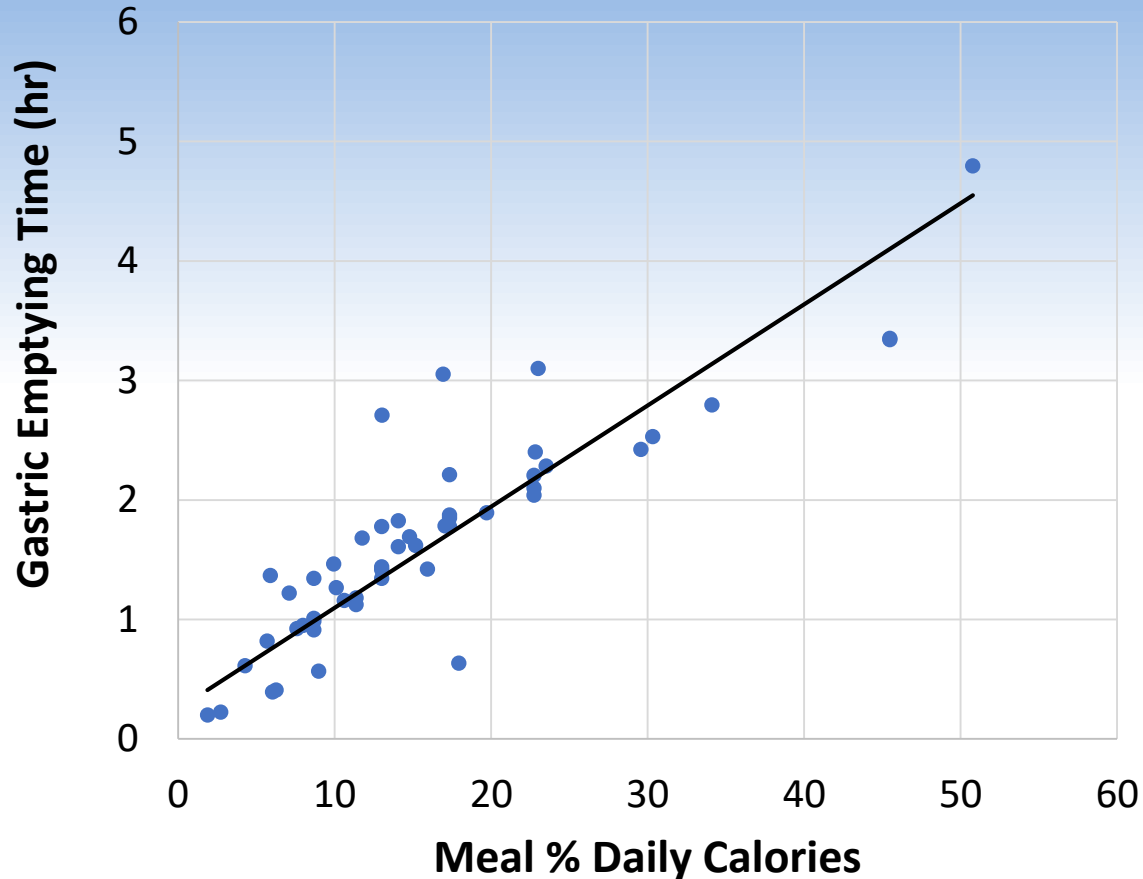
Current gastric transit time of 1.00 hr.

Current duodenum bile salt concentration is 14.44 mM.

Default  
User-Defined Fat and Calories  
FDA Breakfast Meal  
Low Fat - Low Calorie Meal  
Low Fat - Moderate Calorie Meal  
Low Fat - High Calorie Meal  
Moderate Fat - Low Calorie Meal  
Moderate Fat - Moderate Calorie Meal

Cancel OK

# Gastric Emptying Time vs. Calories



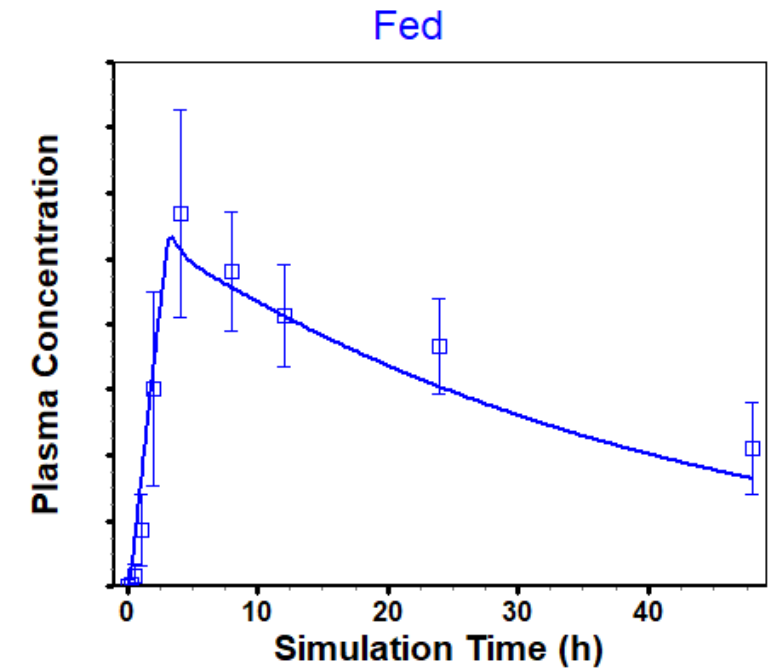
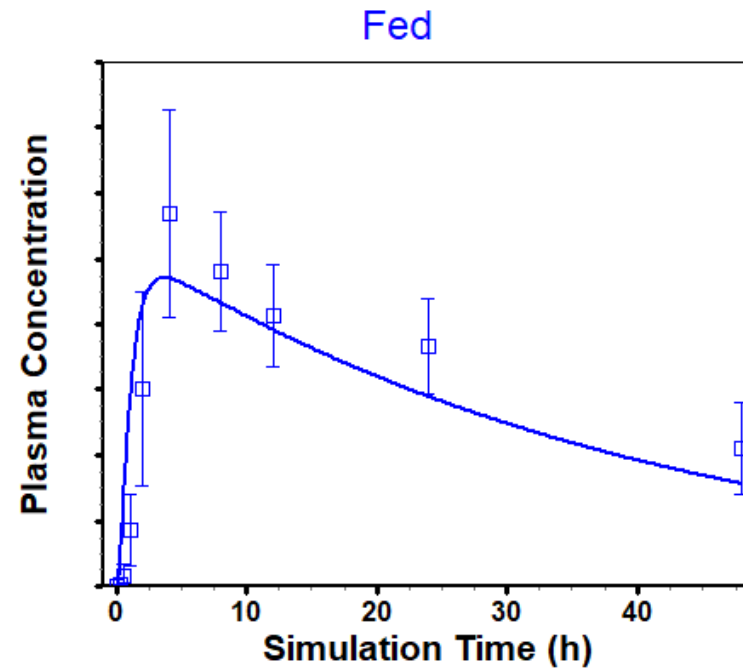
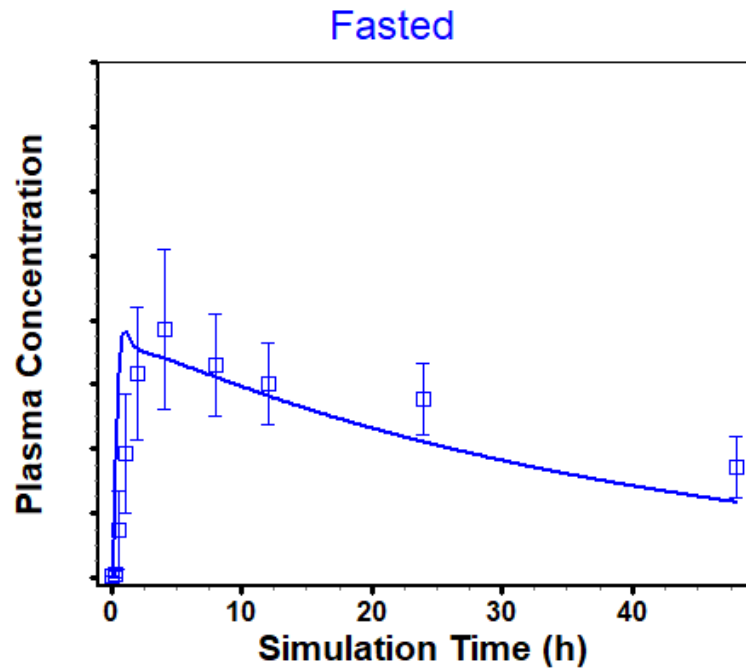
- Based on meal size (calories) the gastric emptying rate will change
- Correlation based on 12 literature papers and 51 measured gastric emptying time curves from ~45-1200 calories



# High Fat Meal: Prediction

Default Fed in GP9.6

Default for FDA standard breakfast



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- Precursor-dependent indirect models

## – ADRM Module:

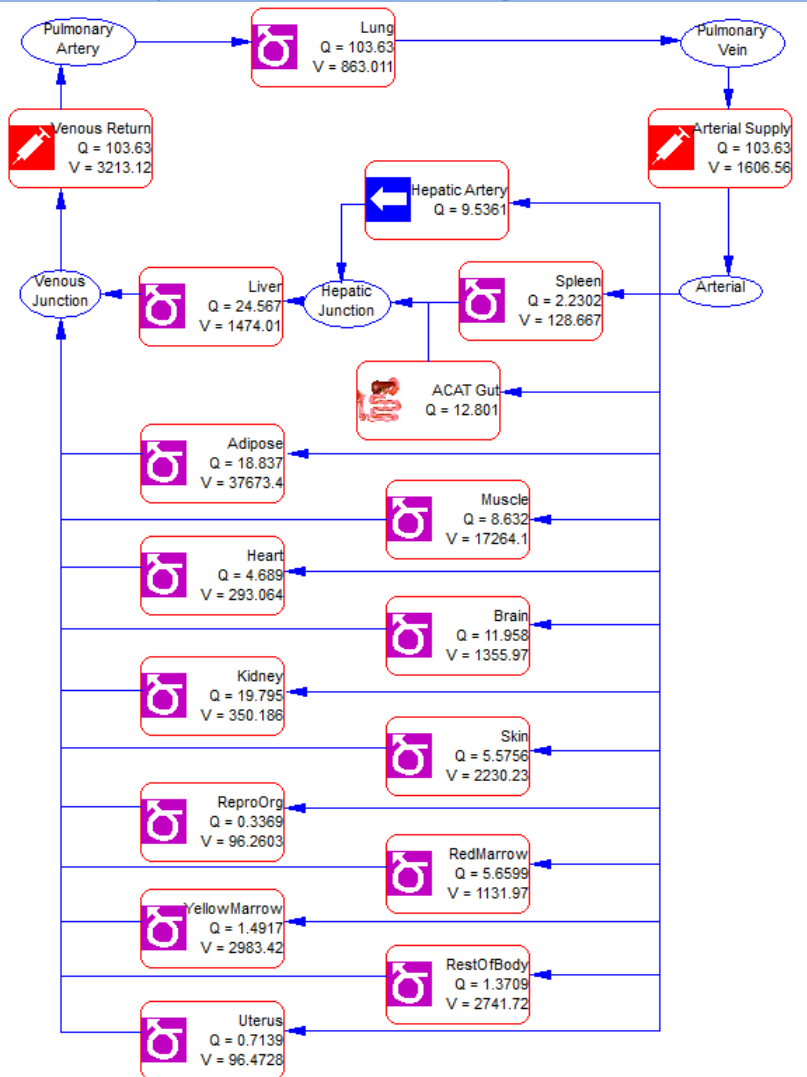
- API evaporation with transdermal administration
- Effect of immune response with intramuscular injection

## – Others:

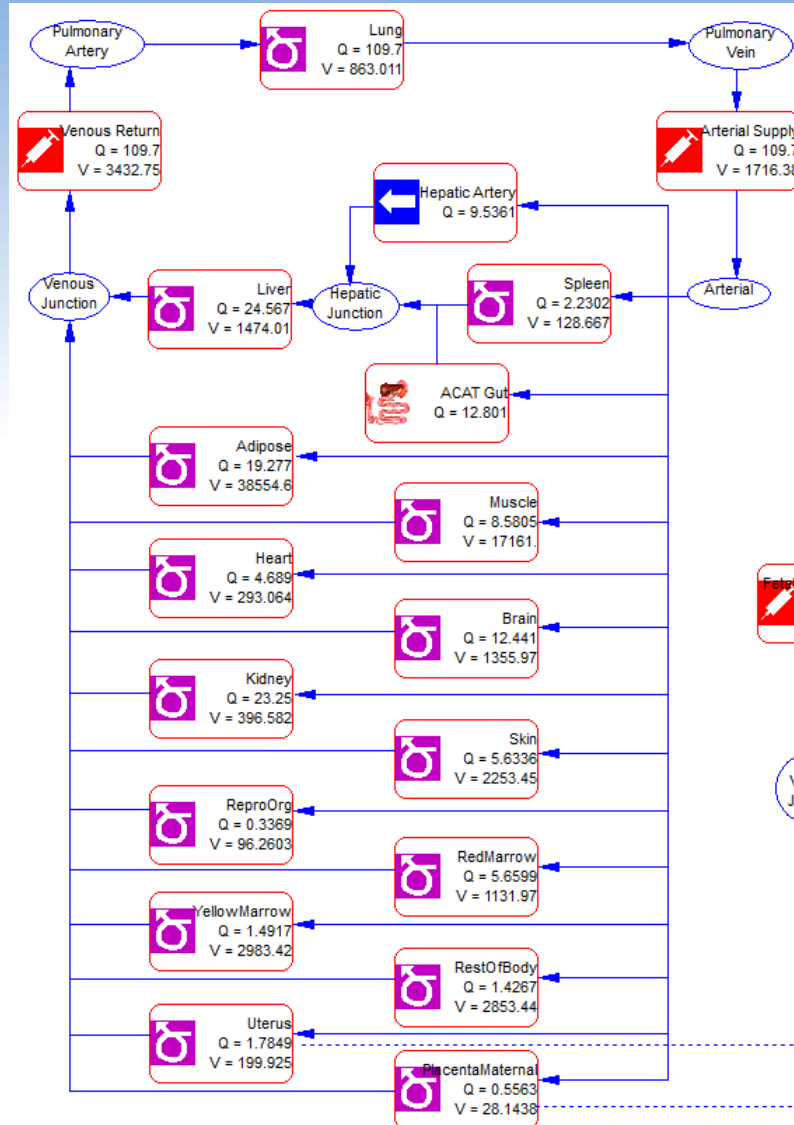
- Flexibility in solubility vs. pH model fitting
- Updates in Peff converter

# Pregnancy PBPK Model Structure

up to 6 weeks of gestation

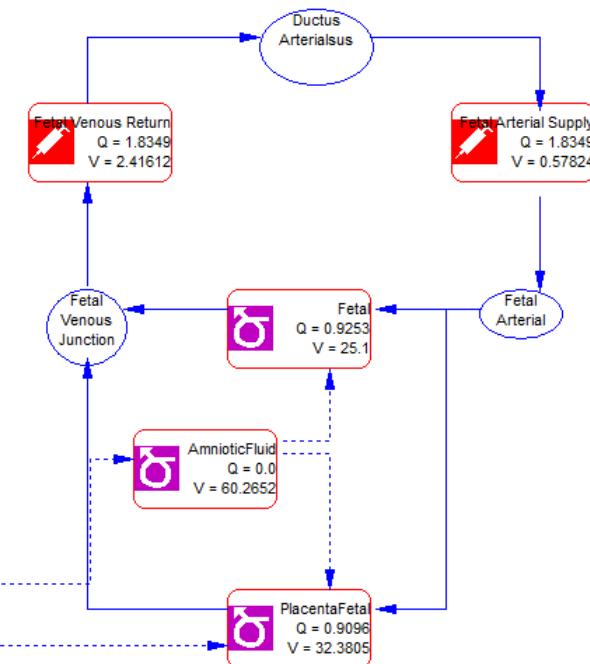


> 6 weeks



Relevant mechanisms:

1. Intramembranous pathway (between amniotic fluid and fetal blood within the placenta and membranes)
2. Transmembraneous pathway (between amniotic fluid and uterus)
3. Fetal pathway (swallowing, secretion, urination etc)



# Creating Physiology for Pregnancy PBPK

up to 6 weeks of gestation

> 6 weeks

PEAR Physiology

File Legacy Options

New PEAR Physiology

Balance Model  Expand View

**PEAR Inputs**

Species: Human

Population: American

Gender: Female

Health Status: Pregnant

Age: years 30

**Weight Gain [kg]: 0.89**

Fetal Weight [kg]: 0.0005

Fetal CO [mL/s]: 0

Gestation Age [week]: 6

Fetus Gender: Male

Height [cm]: 162.2

**Weight [kg]: 76.27** OverW

BMI [kg/m<sup>2</sup>]: 28.9903

% Body Fat: 35.89

CO [mL/s]: 104.4137

**PEAR Outputs**

Name	Volume [mL]	Perfusion [mL/s]
Hepatic Artery	0.0000	9.5361
Lung	863.0109	104.4137
Arterial Supply	1614.2065	104.4137
Venous Return	3228.4129	104.4137
Adipose	37771.5942	18.8858
Muscle	17260.8337	8.6304
Liver	1474.0076	24.5673
ACAT Gut	0.0000	12.8010
Spleen	128.6666	2.2302
Heart	293.0641	4.6890
Brain	1355.9673	12.0274
Kidney	355.1918	20.2989
Skin	2232.4382	5.5811
ReproOrg	96.2603	0.3369
RedMarrow	1131.9725	5.6599
YellowMarrow	2983.4221	1.4917
RestOfBody	2754.8561	1.3774
Uterus	105.6562	0.8679

Defines the weight before pregnant and used for tissue calculation

OK Cancel

PEAR Physiology

File Legacy Options

New PEAR Physiology

Balance Model  Expand View

**PEAR Inputs**

Species: Human

Population: American

Gender: Female

Health Status: Pregnant

Age: years 30

**Weight Gain [kg]: 11.27**

**Fetal Weight [kg]: 1.4063**

**Fetal CO [mL/s]: 11.750554**

Gestation Age [week]: 30

Fetus Gender: Male

Height [cm]: 162.2

Weight [kg]: 86.65 **Obese**

BMI [kg/m<sup>2</sup>]: 32.9357

% Body Fat: 36.27

CO [mL/s]: 128.1165

**PEAR Outputs**

Name	Volume [mL]	Perfusion [mL/s]
Hepatic Artery	0.0000	9.5361
Lung	863.0109	128.1165
Arterial Supply	2157.5381	128.1165
Venous Return	4315.0762	128.1165
Adipose	43366.8134	21.6834
Muscle	16424.9494	8.2125
Liver	1474.0076	24.5673
ACAT Gut	0.0000	12.8010
Spleen	128.6666	2.2302
Heart	293.0641	4.6890
Brain	1355.9673	13.6831
Kidney	490.1358	28.3544
Skin	2391.0108	5.9775
ReproOrg	96.2603	0.3369
RedMarrow	1131.9725	5.6599
YellowMarrow	2983.4221	1.4917
RestOfBody	3350.1413	1.6751
Uterus	804.6208	1.9327
PlacentaMaternal	231.9629	9.8531
Fetal	1406.3000	6.4268
PlacentaFetal	266.8821	5.3238
Fetal Arterial Supply	24.7590	11.7506
Fetal Venous Return	103.4533	11.7506
AmnioticFluid	723.2456	0.0000

Consistent with infant physiology

OK Cancel

User input:

- Age
- Gender
- Gestational age

Program creates (can be modified by user):

- Pre-pregnancy weight
- Current weight
- Fetal info (weight, height, cardiac output, etc.)

# Population Simulator: Pregnancy

Population Simulator PEAR Settings

File Legacy Options

PEAR Population Simulator Settings

Species: Human

Variability in both maternal and fetal physiologies will be included

Human Sample Statistics

Perform simple Monte-Carlo simulation (for uncertainty analysis)

**Maternal:**

Sample Population: American Health Status: Pregnant % Male: 0

Age between 20 years And 40 years

Weight Gain between 3 And 9 kg

Weight between 66.18 And 96.18 kg

BMI between 25.155 And 36.558 kg/m<sup>2</sup>

Height between 134.55 And 195.54 cm

**Fetal:**

% Male: 50

Gest Age between 15 And 25 weeks

Weight between 80 And 120 % Typical Weight

Height between 20 And 40 cm

Gestational age needs to fall within one of the two groups: less than 6 weeks or more than 6 weeks.

Typical Subject Characteristics:  
Female 20 years old: 69.92kg; 162.71cm; BMI=26.41  
Female 40 years old: 78.7kg; 161.17cm; BMI=30.3

OK Cancel

# Population Simulator: Pregnancy

Population Simulator PEAR Settings

File Legacy Options

PEAR Population Simulator Settings

Species: Human

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Age between 20 years And 40 years

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Height between 134.55 And 195.54 cm

**Fetal:**

% Male: 50

Gest Age between 15 And 25 weeks

Weight between 80 And 120 % Typical Weight

Height between 20 And 40 cm

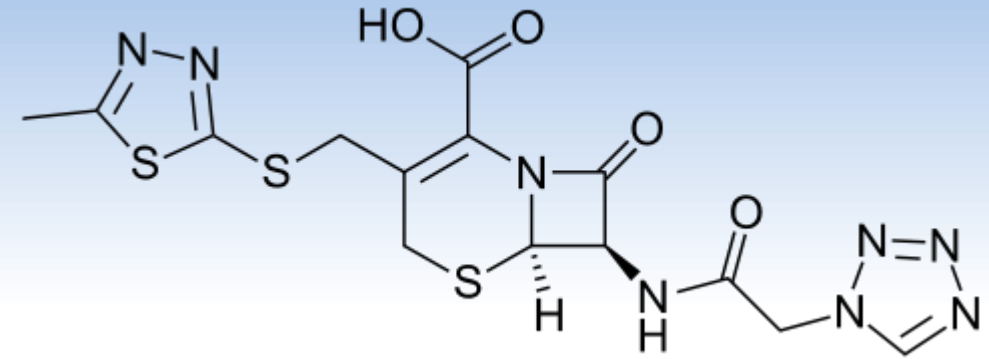
Typical Subject Characteristics:  
Female 20 years old: 69.92kg; 162.71cm; BMI=26.41  
Female 40 years old: 78.7kg; 161.17cm; BMI=30.3

OK Cancel

Body weight is calculated from body weight and weight gain, the final BMI and weight range are posted here

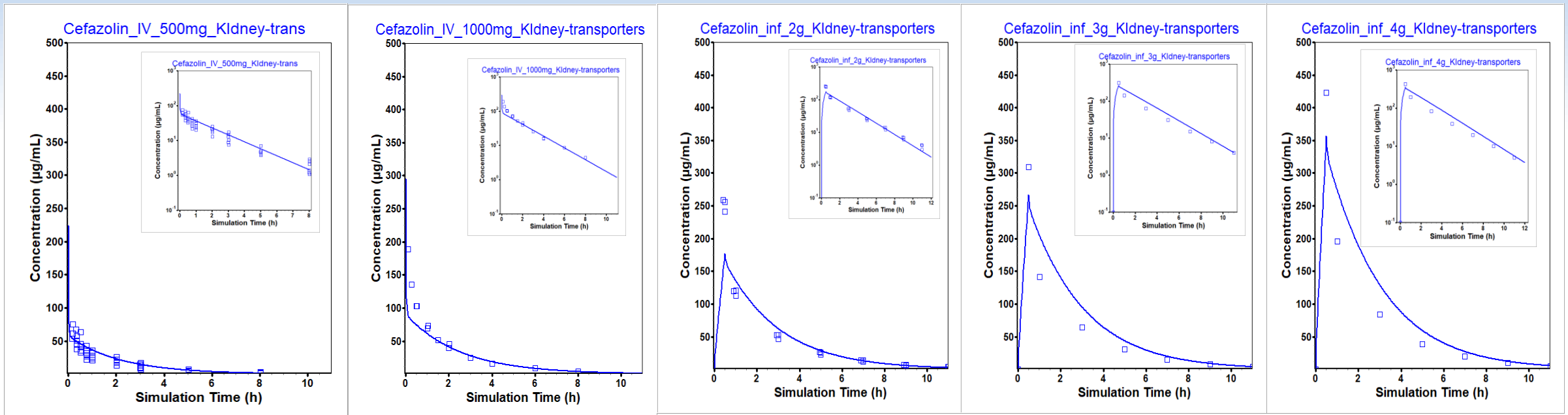
# Example: Cefazolin

- Widely used for antibacterial prophylaxis during several surgical procedures in pregnant women
- Urinary recovery of unchanged cefazolin constitutes 100% of the administered dose
- Renal elimination of cefazolin involves glomerular filtration and tubular secretion mediated by influx OATs 1/3 and efflux transporter MRP 4 (Km and Vmax values were fitted for healthy subjects). For Kidney filtration, the default  $f_{up} \cdot GFR$  is used.



# Example: Cefazolin

Baseline model was calibrated/validated against in vivo data from literature (healthy males)



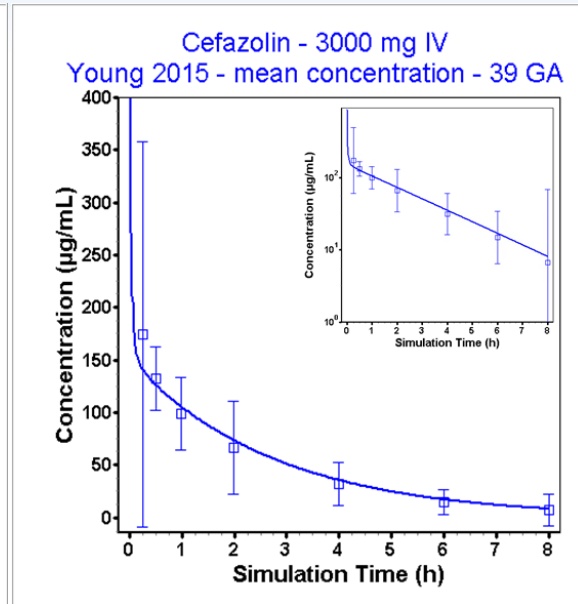
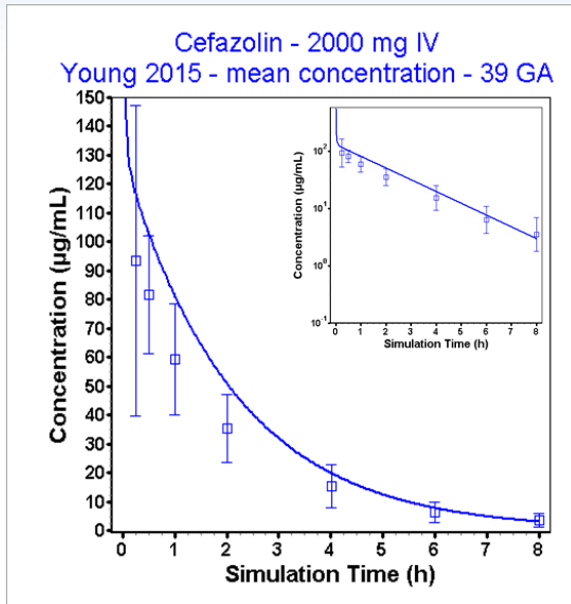


# Example: Cefazolin

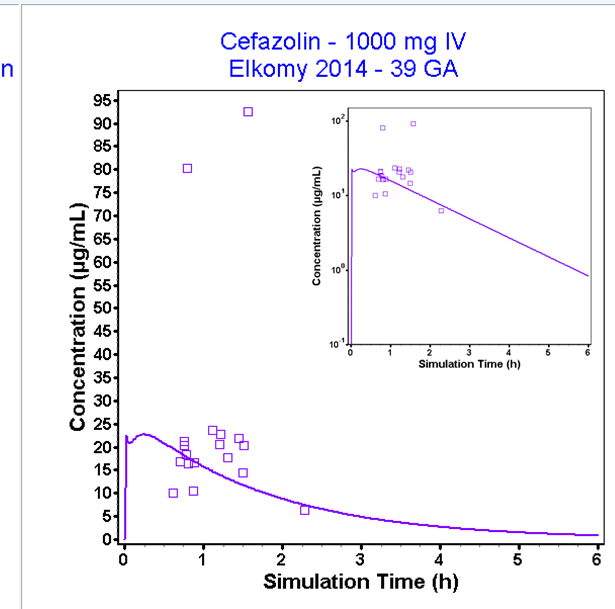
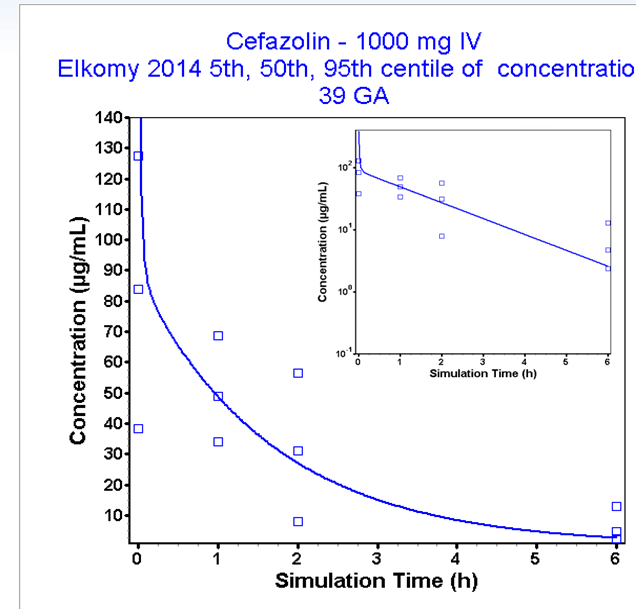
Validated model was then used to predict maternal and fetal PK

Cefazolin was administered to pregnant women before undergoing cesarean delivery

## Maternal plasma



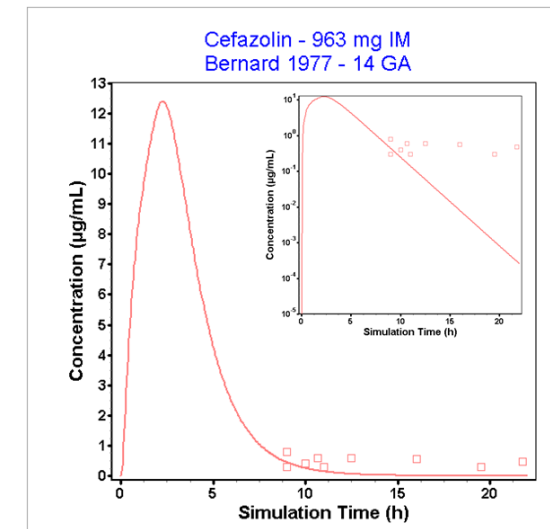
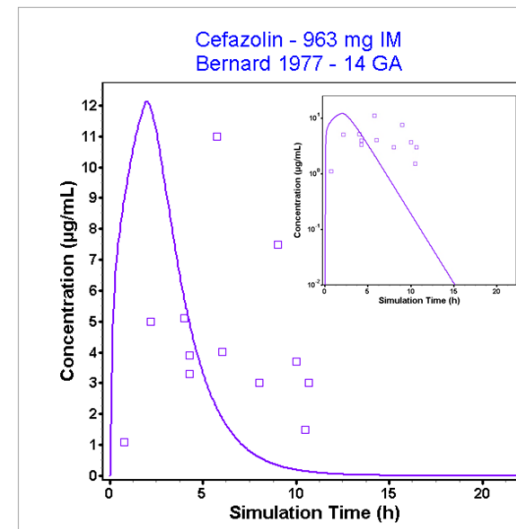
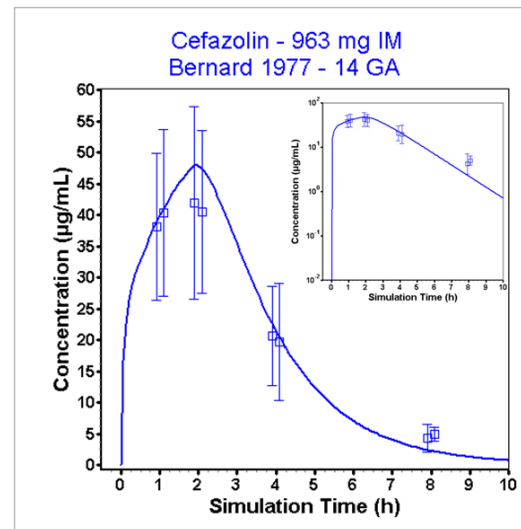
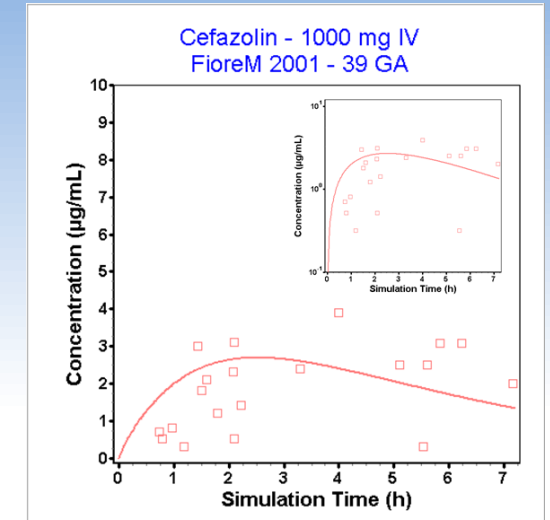
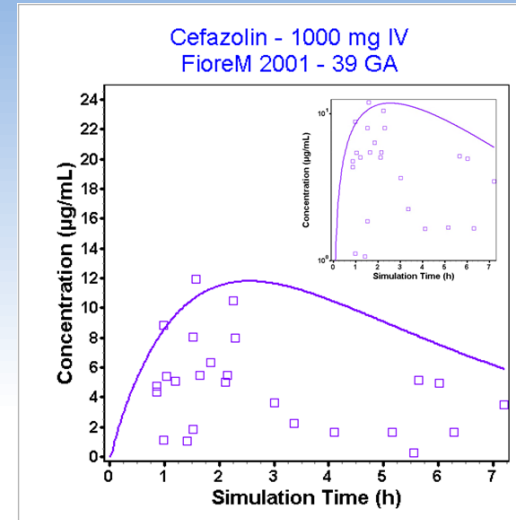
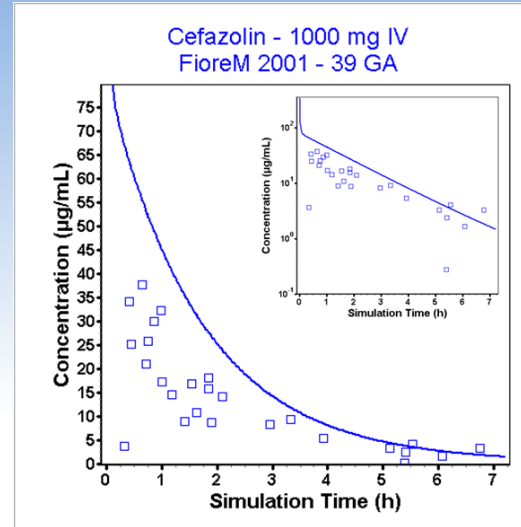
## Maternal (left) and neonatal (right) plasma



# Example: Cefazolin

Maternal plasma (left), neonatal plasma (middle), amniotic fluid (right)

- Validated model was then used to predict maternal and fetal PK
- Cefazolin was administered to pregnant women (IV or IM) before undergoing elective cesarean delivery or hysterectomy



# Lysosomal Trapping: Equation

Lukacova Kp method was extended to include lysosomal compartment

Accumulation in lysosomal water compartment

$$\begin{aligned}
 Kpu = & V_{ew} + \frac{1/X_{[D],iw}}{1/X_{[D],p}} V_{iw} + \frac{1/X_{[D],Lys} V_{Lys}}{1/X_{[D],p}} + \left( \frac{P \cdot V_{nlt} + (0.3 \cdot P + 0.7) \cdot V_{pht}}{1/X_{[D],p}} \right) + \\
 & (Fn + Fa) \cdot \left[ \frac{1}{fup} - 1 - \left( \frac{P \cdot V_{nlp} + (0.3 \cdot P + 0.7) \cdot V_{php}}{1/X_{[D],p}} \right) \right] \cdot RAtp + \\
 & (Fc) \cdot \frac{Ka \cdot [AP]_T}{(1/X_{[D],p})} \cdot \left[ (1 - V_{Lys}) \cdot \frac{X_{[D^+],iw}}{X_{[D],iw}} + V_{Lys} \cdot \frac{X_{[D^+],Lys}}{X_{[D],Lys}} \right]
 \end{aligned}$$

Binding to acidic phospholipids in lysosomes

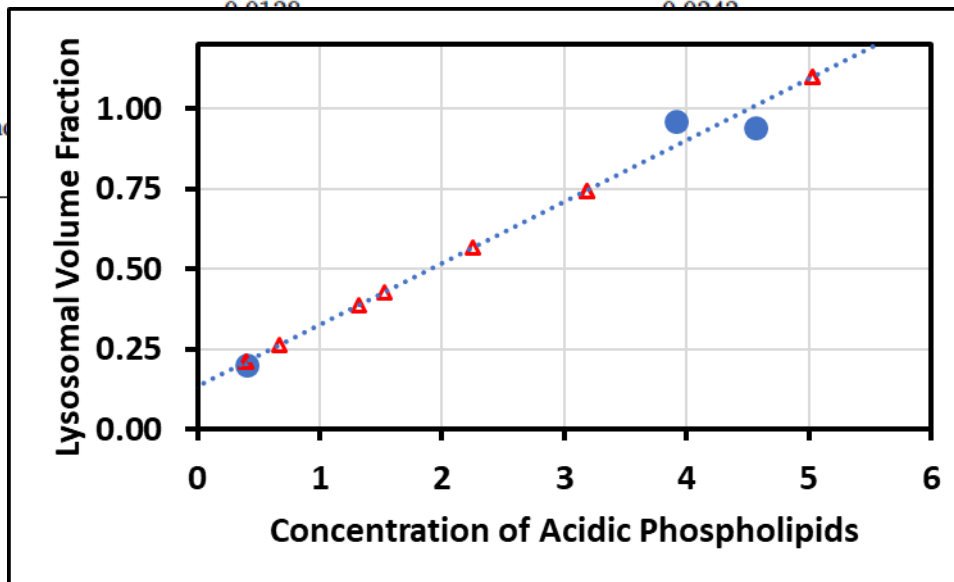
# Lysosomal Trapping: Parameters

Assmus (Eur J Pharm Sci 2017, 109:419-430) summarized measured properties for lysosomal compartment in lung and liver and that information was used as basis to parameterize lysosomal compartments in all tissues

Table 1

Tissue-specific input parameters for the extended Rodgers model used to predict  $K_{pu}$  values in lung, kidney and liver in rat.

	Lung			Kidney	Liver			
	Alveolar macrophages	Type II cells	Residual cells	Total kidney	Hepatocytes	Kupffer cells	Endothelial cells	Fat-storing cells
$f_{cell\ type}$ [%]	4.1 <sup>a</sup>	8.3 <sup>a</sup>	87.6 <sup>a</sup>	100	77.8 <sup>b</sup>	2.1 <sup>b</sup>	2.8 <sup>b</sup>	1.4 <sup>b</sup>
$f_{lys}$ [%]	7.8 <sup>c</sup>	3	1	1.2 <sup>d</sup>	0.82 <sup>e</sup>	13.57 <sup>e</sup>	6.86 <sup>e</sup>	0.23 <sup>e</sup>
$pH_{lys}$	4.75 <sup>f</sup>	5.1 <sup>g</sup>	5.1	5.1 <sup>h</sup>	4.72 <sup>i</sup>	4.94 <sup>j</sup>	5.1	5.1
Fractional tissue volume (total tissue) <sup>k</sup>								
$f_{NL}$		0.022		0.012			0.014	
$f_{NP}$		0.0199		0.0049			0.0240	
$f_{EW}$							0.161	
$f_{TW}$							0.573	
Tissue concentration of acidic phospholipids $AP^-$ [mg/g]							4.56	



# Lysosomal Trapping: Implementation

PBPK Options

File Legacy Options

### PBPK Settings

#### Partition Coefficient (Kp) Settings

##### Perfusion Limited Tissues

Kp Method

- Poulin & Theil - Homogeneous
- Poulin & Theil - Extracellular
- Berezhkovskiy
- Rodgers, Leahy, Rowland
- Lukacova (Rodgers-Single)
- Lukacova with Lysosomes
- User Defined

Fut Method

- Poulin Eq.
- S+ v9.0 and earlier
- S+ v9.5 (Default)

##### Permeability Limited Tissues

Kp Method

- Poulin & Theil - Homogeneous
- Poulin & Theil - Extracellular
- Berezhkovskiy
- Rodgers, Leahy, Rowland
- Lukacova (Rodgers-Single)
- Lukacova with Lysosomes
- User Defined

Fu Extracellular Method

- Poulin Eq.
- S+ v9.5 (Default)

Fu Intracellular Method

- Poulin Eq.
- S+ v9.0 and earlier
- S+ v9.5 w/Lys
- S+ v9.5 (Default)

Current Drug Properties:  
logPo:w = 2.70    Fup = 4.40%    Rbp = 0.70  
Strongest Base pKa = 9.00

OK    Cancel

### Tissue Parameters for: Liver

Basic    **Advanced**    Enzymes    Transporters

Vnt:	0.0348	Fvec:	0.161	Fvendo:	0.005
Vpht:	0.0252	Fvv:	0.05	Leakage:	0.7
Vwt:	0.751	Vlys:	0.0094	<input type="checkbox"/> Adipose	
Capt:	4.56	Lys pH:	4.84		
Density (g/mL):	1.07				

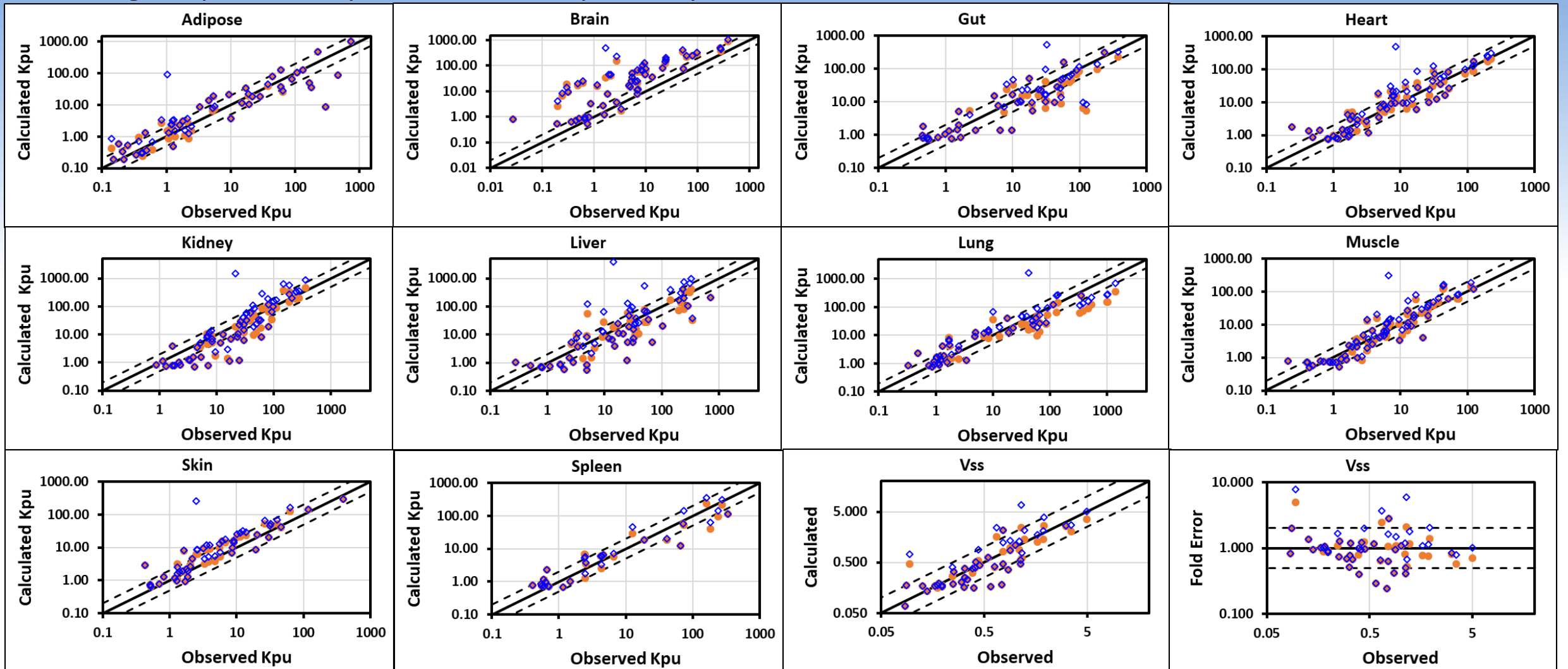
Basolateral:    Apical:

SA (cm2):    0.0    0.0

Save    Cancel

# Lysosomal Trapping: Validation

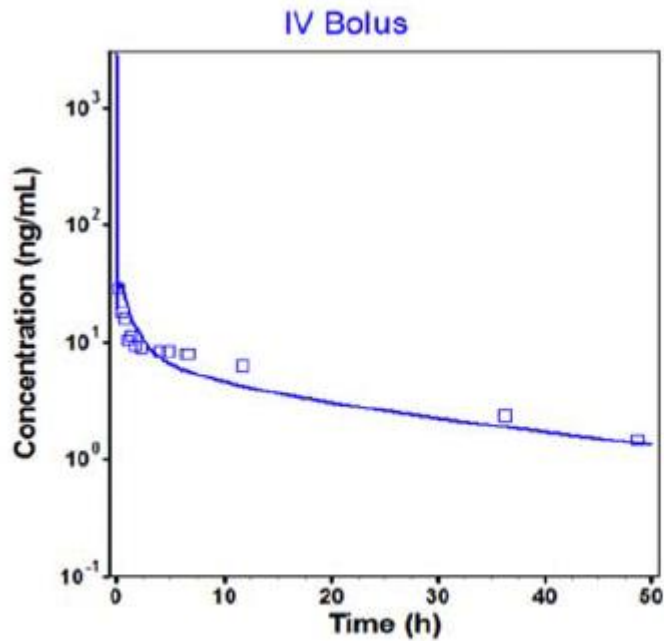
Orange – Kps without lysosomes; blue – Kps with Lysosomes



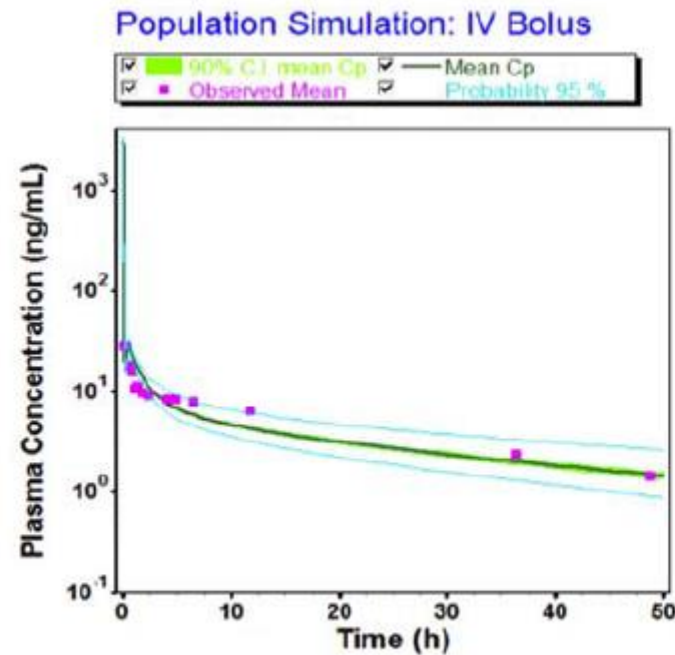
Observed data from Rodgers 2005, 2006 (Kps) and Poulin 2002 (Vss) – different sets of compounds

# Lysosomal Trapping: Validation

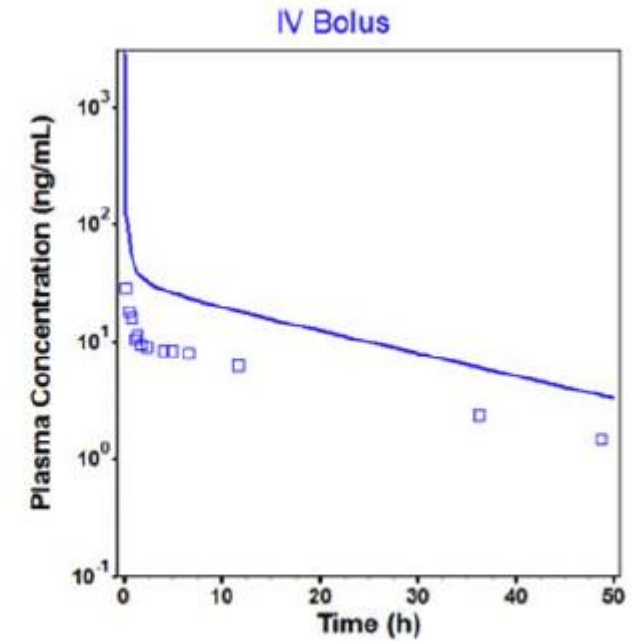
Previously approximated the effect of lysosomal trapping by increasing B/P ratio for  $K_p$  calculation



a



b



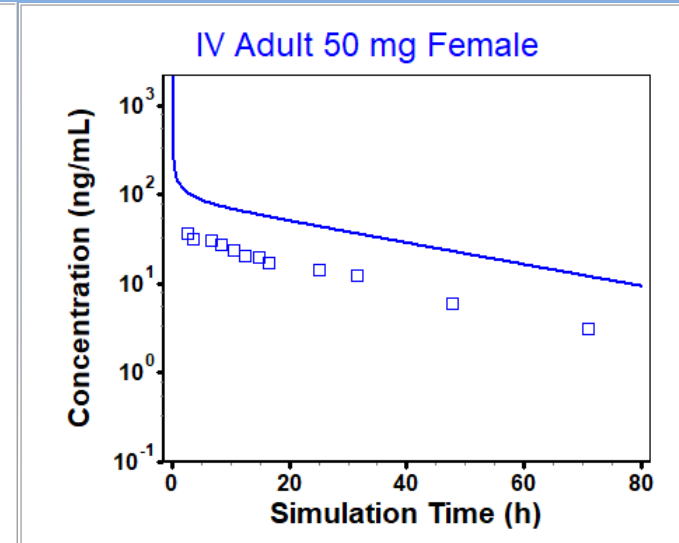
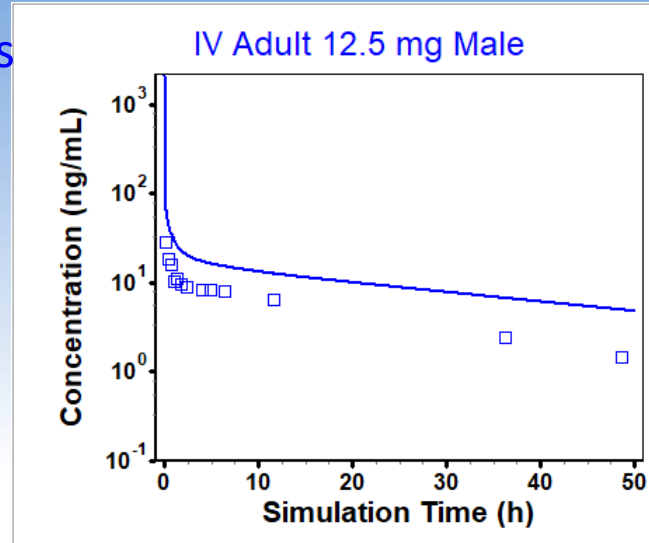
c

Samant – CPT: PSP 2017, 6, 315-321

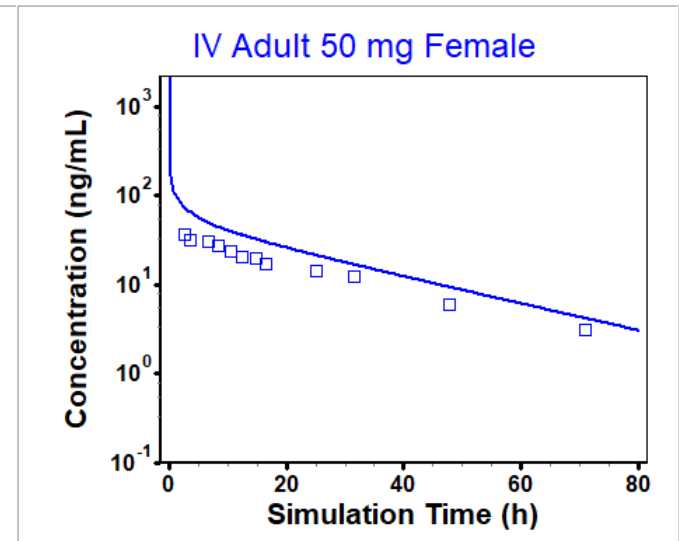
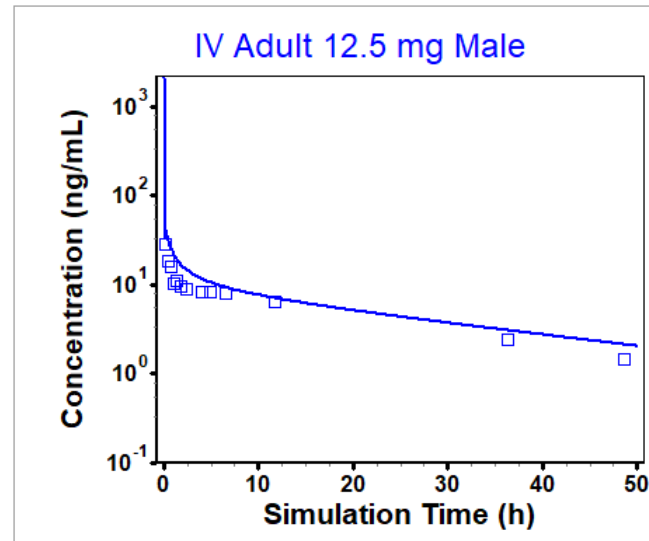
# Lysosomal Trapping: Validation

## Without Lysosomes

- Updated B/P ratio to experimental values (Bogema, 1974, PhD dissertation, Virginia Commonwealth University)
- Calculated Kps with default Kp method without lysosomal trapping (top) and new method with lysosomes (bottom).



## With Lysosomes

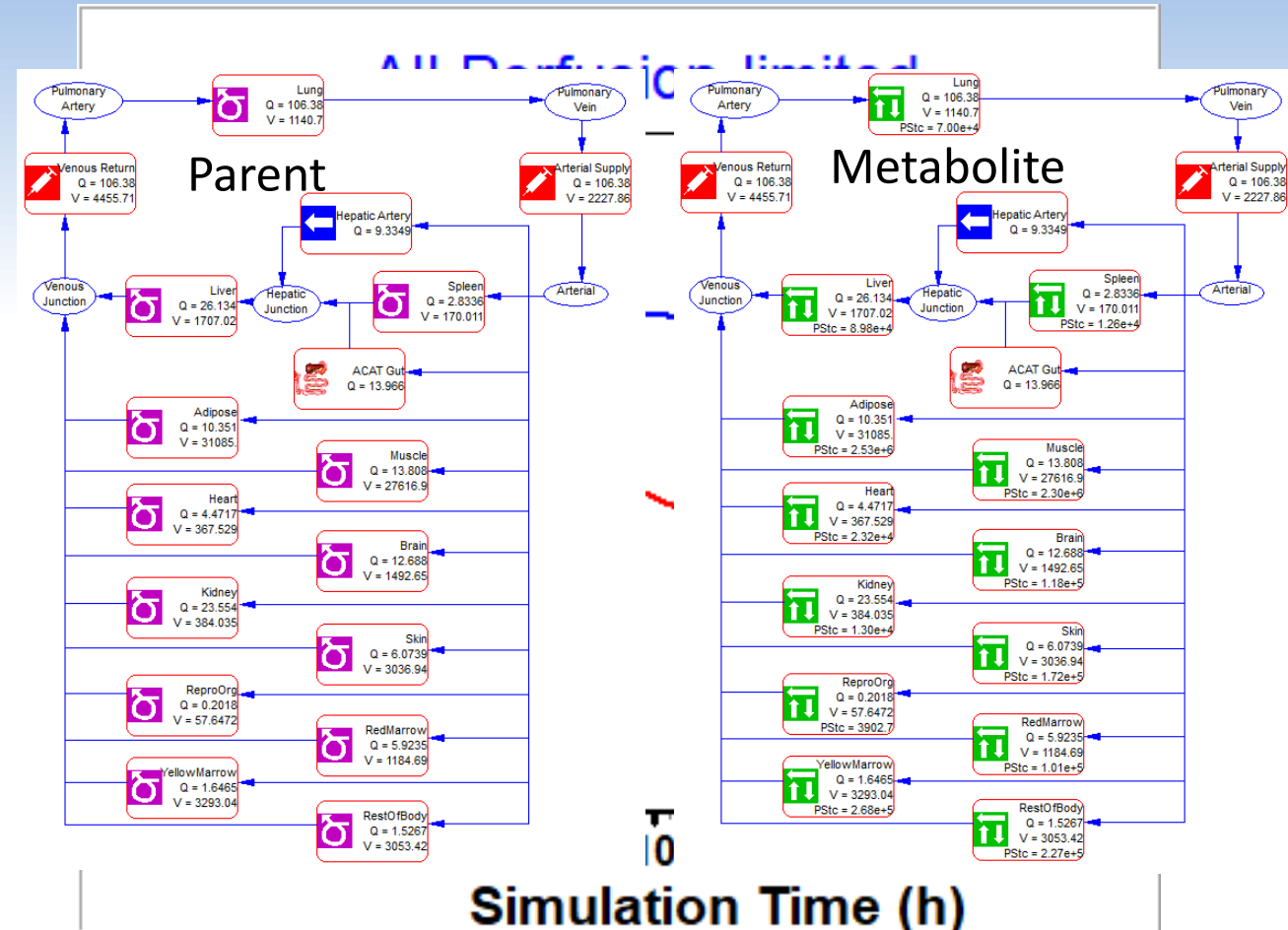
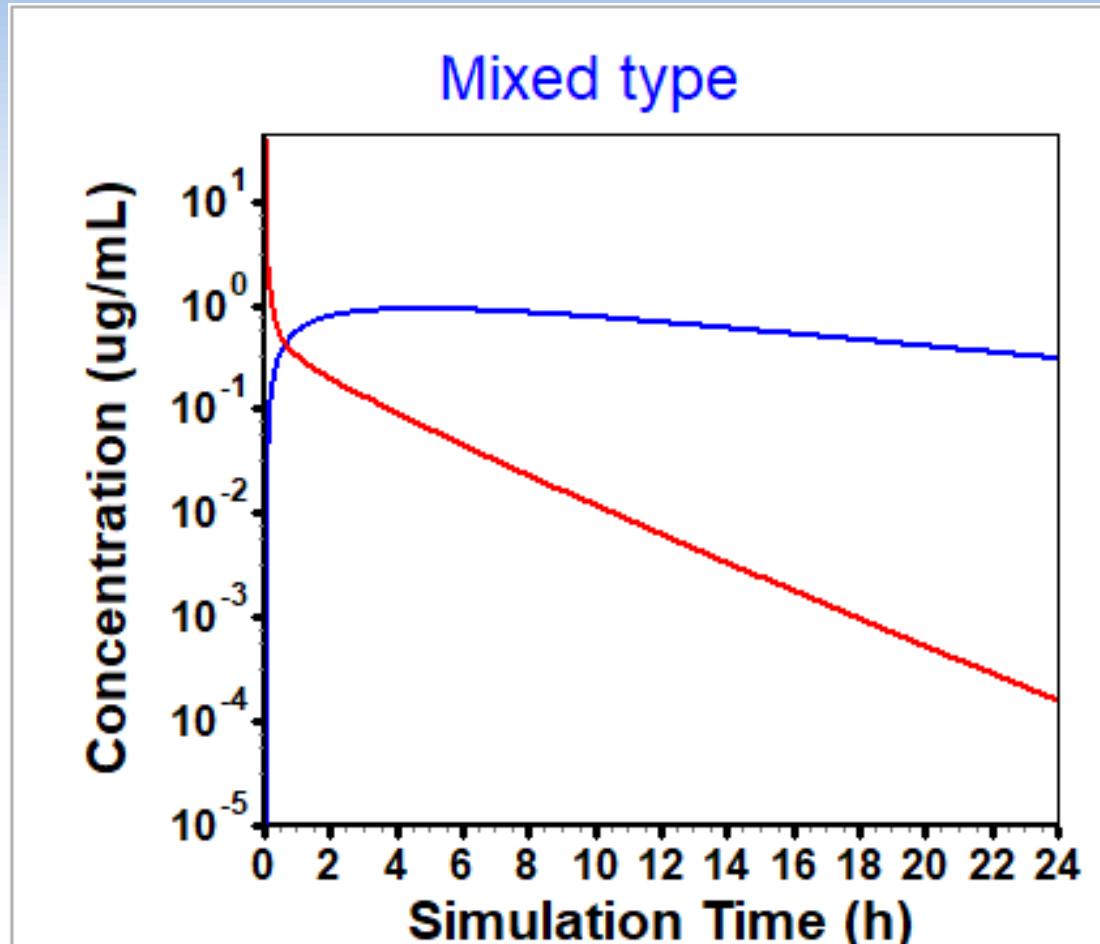




# Mixing Tissue Types

Parent compound – good tissue distribution

Metabolite – polar molecule with slow diffusion through membranes



# GastroPlus® v9.7

## – ACAT™ model:

- Allow two solubility inputs for different drug forms (crystalline, amorphous)
- Fed state conditions based on meal type

## – PBPKPlus™ Module:

- Mechanistic pregnancy PBPK model
- Lysosomal trapping
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## – **Metabolism and Transporter Module:**

- New enzyme/transporter distribution information
- Provide default population for extensive, intermediate, and poor metabolizers based on specific genotypes

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- Additional compound model files for substrates & inhibitors

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## – ADRM Module:

- API evaporation with transdermal administration
- Effect of immune response with intramuscular injection

## – Others:

- Flexibility in solubility vs. pH model fitting
- Updates in Peff converter

# Provide Default Enzyme Genotype

Enzyme	Phenotype	Genotype
2C9	EM	*1/*1
	IM	*1/*2; *1/*3
	PM	*2/*2; *2/*3; *3/*3
2C19	UM	*1/*17; *17/*17
	EM	*1/*1
	IM	*1/*2; *1/*3; *1/*5; *1/*8; *2/*17
	PM	*2/*2; *2/*3; *2/*5; *2/*6; *3/*3
2D6	UM	Duplicate EM alleles
	EM	*1; *2; *2A; *35
	IM	*9; *10; *17; *29; *41
	PM	*3; *4; *5; *6; *7; *8; *14; *36; *71
2B6	EM	*1/*1; *1/*4; *1/*6
	PM	*5/*5; *5/*6; *6/*6

UM: ultra-rapid metabolizer; EM: extensive metabolizer; IM: intermediate metabolizer; PM: poor metabolizer

# Create Subject with Different Enzyme Phenotypes

Tissue Parameters for: Liver

Basic   Advanced   **Enzymes**   Transporters

Enzyme	Expression (mg-enz/g-tissue)	Expression CV (%)	Turnover rate [1/min]	Expression Source/Type
2C9	1.54E-01	54	0.0005	Default Adult Healthy
2C9-EM	1.84E-01	15	0.0005	Default Adult Healthy
2C9-IM	1.08E-01	19	0.0005	Default Adult Healthy
2C9-PM	3.20E-02	19	0.0005	Default Adult Healthy
2C19	3.00E-02	106	0.0005	Default Adult Healthy
2C19-UM	4.00E-02	32	0.0005	Default Adult Healthy

1 Set Defaults   2 Add Enzyme   3 Delete Enzyme

Save   Cancel

Only one phenotype can be selected for a specific enzyme in given record.

The expression levels of different phenotypes are saved in the same .pbk file.

Benefit:

- 1) Users do not need to pre-select the phenotype of each enzyme for the subject (too many combinations).
- 2) User could add phenotypes to any enzyme.

Enzyme Table

Generic	Enzyme	Location	Data Source	Vmax (mg/s) or (mg/s/mg-enz)	Km (mg/L)	Metabolite	Met_Parer
test enzpheno	2C9-EM	PBPK	Microsomes	0.0025	1	NONE	1
test enzpheno	2C9-IM	Gut	Microsomes	0.01	1	NONE	1
*							

Check Entries.

More than one phenotype were selected for the same enzyme. Make sure to use only one phenotype for each enzyme.

OK

Delete   Save   Cancel   Unit Converter

Record: 2

# Population Simulation: Enzyme Phenotypes

If the user selects one specific phenotype, the population simulator will provide the selection of different phenotypes for that enzyme.

Generic	Enzyme	Location	Data Source	Vmax (mg/s) or (mg/s/mg-enz)	Km (mg/L)	Metabolite	Met_Parar
test enzpheno	2C9-EM	PBPK	Microsomes	0.0025	1	NONE	1

Users can modify the frequency of each phenotype (e.g. the population simulator will select only EM subjects if the frequency of EM is set to 1)

Population Simulator PEAR Settings

File Legacy Options

PEAR Population Simulator Settings

Species: Human

Human Sample Statistics

Perform simple Monte-Carlo simulation (for uncertainty analysis)

Sample Population: American Health Status: Healthy % Male: 50

Age between 20 years And 40 years

Weight between 70.53 And 100.53 kg

BMI between 22.658 And 32.296 kg/m<sup>2</sup>

Height between 147.78 And 210.64 cm

**Enzyme Phenotype Frequency**

Enzyme: 2C9 UM: 0 EM: 0.65 IM: 0.302 PM: 0.048

Typical Subject Characteristics:  
Male 20 years old: 84.06kg; 176.1cm; BMI=27.1  
Male 40 years old: 87.58kg; 176.27cm; BMI=28.19  
Female 20 years old: 69.92kg; 162.71cm; BMI=26.41  
Female 40 years old: 78.7kg; 161.17cm; BMI=30.3

OK Cancel

# Population Simulation Results: Enzyme Phenotypes

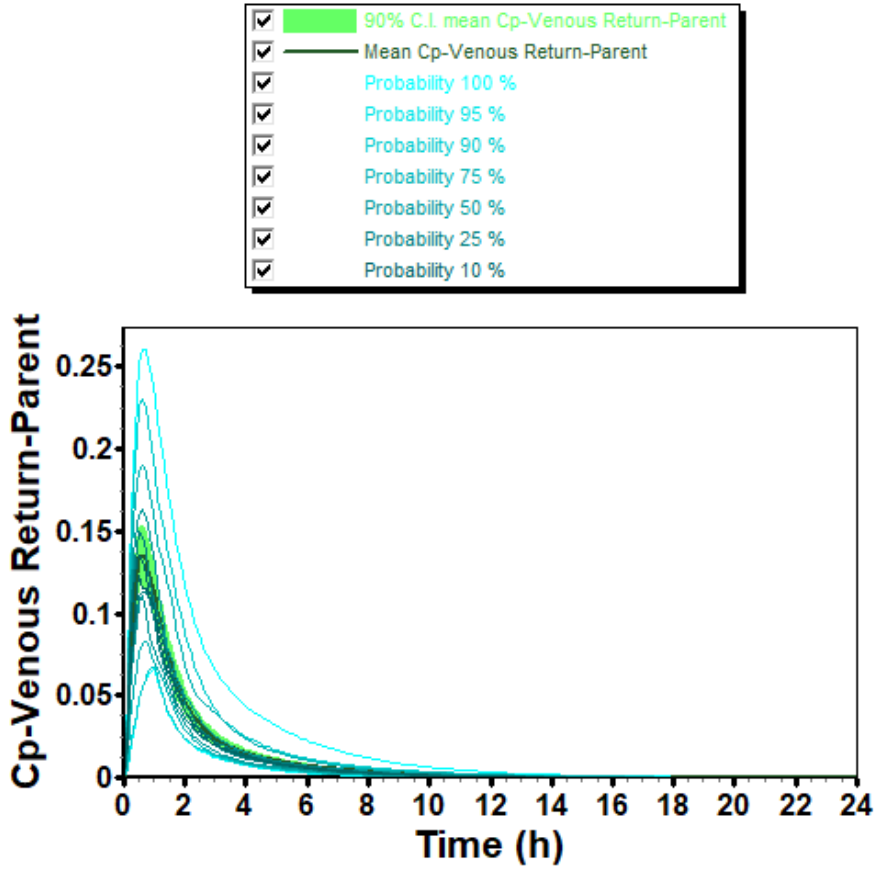
Scenario 1:

Enzyme Table							
Generic	Enzyme	Location	Data Source	Vmax (mg/s) or (mg/s/mg-enz)	Km (mg/L)	Metabolite	Met_Parer
test enzpheno	2C9-EM	PBPK	Microsomes	0.0025	1	NONE	1

**Enzyme Phenotype Frequency**

Enzyme:  UM:  EM:  IM:  PM:

Population Simulation: test enzpheno



Subject Nu	Subject Ag	Subject Wt	Subject He	Subject BS	Subject Ge	Subject Po	Subject He	Infant Age	Birth Wk	2C9 Phenotype
1	34	77.6734	178.82	1.96216	Male	American	Healthy	N/A	N/A	EM
2	29	76.2129	179.43	1.9512	Male	American	Healthy	N/A	N/A	EM
3	32	77.9915	161.18	1.823	Female	American	Obese	N/A	N/A	IM
4	27	72.2791	156.77	1.72987	Female	American	Healthy	N/A	N/A	EM
5	32	76.2215	168.15	1.86157	Female	American	Healthy	N/A	N/A	IM
6	39	77.7514	161.04	1.81947	Female	American	Healthy	N/A	N/A	IM
7	23	78.2012	156.39	1.7856	Female	American	Obese	N/A	N/A	EM
8	27	87.1356	170.63	1.99154	Female	American	Healthy	N/A	N/A	EM
9	25	78.5424	168.53	1.88854	Female	American	Healthy	N/A	N/A	EM
10	32	73.8821	179.33	1.92484	Male	American	Healthy	N/A	N/A	EM
11	31	76.4011	162.84	1.82058	Female	American	Healthy	N/A	N/A	EM
12	31	87.1662	172.56	2.00815	Male	American	Healthy	N/A	N/A	EM
13	35	85.7451	170.34	1.97554	Female	American	Healthy	N/A	N/A	IM
14	29	71.0286	156.38	1.71398	Female	American	Healthy	N/A	N/A	EM
15	35	92.7883	174.16	2.07605	Male	American	Obese	N/A	N/A	PM
16	40	82.2229	160.2	1.85617	Female	American	Obese	N/A	N/A	EM
17	34	85.4754	170.71	1.976	Male	American	Healthy	N/A	N/A	EM
18	32	72.5206	168.26	1.82347	Male	American	Healthy	N/A	N/A	EM
19	32	89.7869	169.69	2.00901	Male	American	Obese	N/A	N/A	EM
20	36	84.7552	175.74	2.0108	Female	American	Healthy	N/A	N/A	EM
21	36	86.4055	172.48	2.00001	Female	American	Healthy	N/A	N/A	IM
22	37	81.4844	175.53	1.97573	Male	American	Healthy	N/A	N/A	IM
23	25	80.8528	163.9	1.87373	Female	American	Obese	N/A	N/A	IM
24	31	85.5945	166.51	1.94178	Female	American	Obese	N/A	N/A	EM
25	33	74.6525	180.85	1.94521	Male	American	Healthy	N/A	N/A	EM

# Population Simulation Results: Enzyme Phenotypes

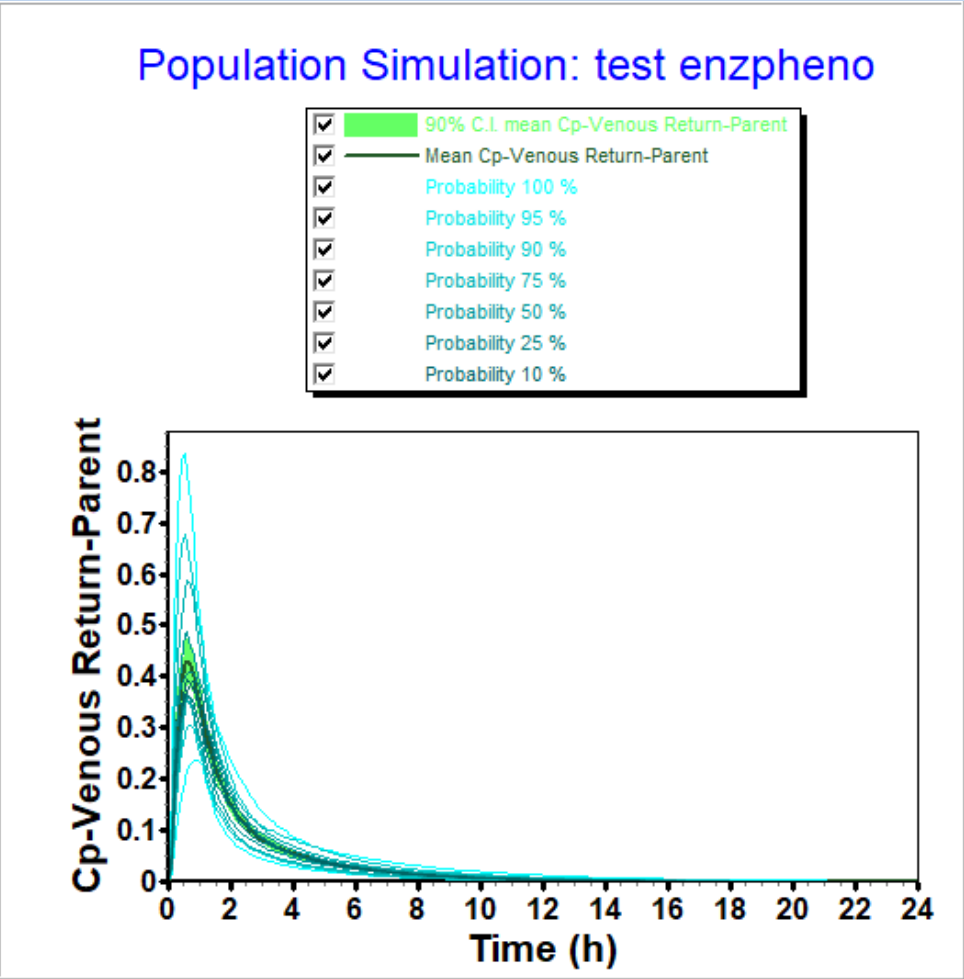
Scenario 2:

Enzyme Table							
Generic	Enzyme	Location	Data Source	Vmax (mg/s) or (mg/s/mg-enz)	Km (mg/L)	Metabolite	Met_Parer
test enzpheno	2C9-EM	PBPK	Microsomes	0.0025	1	NONE	1

**Enzyme Phenotype Frequency**

Enzyme:  UM:  EM:  IM:  PM:



Subject Nu	Subject Ag	Subject Wt	Subject He	Subject BS	Subject Ge	Subject Po	Subject He	Infant Age	Birth Wk	2C9 Phenotype
1	30	71.6793	160.96	1.75703	Female	American	Healthy	N/A	N/A	PM
2	31	80.0239	175.14	1.95744	Male	American	Healthy	N/A	N/A	PM
3	23	89.3789	193.29	2.20365	Male	American	Healthy	N/A	N/A	PM
4	37	86.4166	180.03	2.06322	Male	American	Healthy	N/A	N/A	PM
5	29	79.593	166.45	1.88221	Male	American	Healthy	N/A	N/A	PM
6	30	87.8761	173.06	2.01931	Female	American	Healthy	N/A	N/A	PM
7	32	91.5686	182.15	2.13265	Male	American	Healthy	N/A	N/A	PM
8	30	98.3295	178.53	2.16644	Male	American	Obese	N/A	N/A	PM
9	34	85.7651	170.5	1.97708	Female	American	Healthy	N/A	N/A	PM
10	23	85.185	166.66	1.93909	Male	American	Obese	N/A	N/A	PM
11	24	72.1392	158.38	1.74129	Female	American	Healthy	N/A	N/A	PM
12	37	96.7692	174.49	2.11635	Male	American	Obese	N/A	N/A	PM
13	35	73.5218	177.06	1.90318	Male	American	Healthy	N/A	N/A	PM
14	32	76.3609	160.59	1.80191	Female	American	Healthy	N/A	N/A	PM
15	28	86.1443	164.68	1.93153	Female	American	Obese	N/A	N/A	PM
16	35	99.5256	178.65	2.17867	Female	American	Obese	N/A	N/A	PM
17	31	94.7591	175.49	2.10627	Male	American	Obese	N/A	N/A	PM
18	31	87.6359	167.1	1.96636	Male	American	Obese	N/A	N/A	PM
19	39	97.7394	177.3	2.15011	Male	American	Obese	N/A	N/A	PM
20	36	72.1387	152.75	1.69619	Female	American	Obese	N/A	N/A	PM
21	35	98.3794	176.64	2.15026	Male	American	Obese	N/A	N/A	PM
22	28	100.19	181.12	2.20669	Male	American	Obese	N/A	N/A	PM
23	22	80.8824	159.72	1.83925	Female	American	Obese	N/A	N/A	PM
24	27	79.5737	174.97	1.95138	Male	American	Healthy	N/A	N/A	PM
25	24	96.4991	174.21	2.11138	Male	American	Obese	N/A	N/A	PM



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## – ACAT™ model:

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- Fed state conditions based on meal type

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- Lysosomal trapping
- Allow different tissue model types (perfusion- or permeability-limited) for different compounds in simulation

## – Metabolism and Transporter Module:

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- Provide default population for extensive, intermediate, and poor metabolizers based on specific genotypes

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- Precursor-dependent indirect models

## – ADRM Module:

- API evaporation with transdermal administration
- Effect of immune response with intramuscular injection

## – Others:

- Flexibility in solubility vs. pH model fitting
- Updates in Peff converter



# DDI: New Built-in Models

Alfentanil – CYP3A4 substrate

Efavirenz – moderate CYP3A4 inducer

Voriconazole – CYP3A inhibitor

Digoxin – Pgp substrate

Erythromycin – Pgp inhibitor

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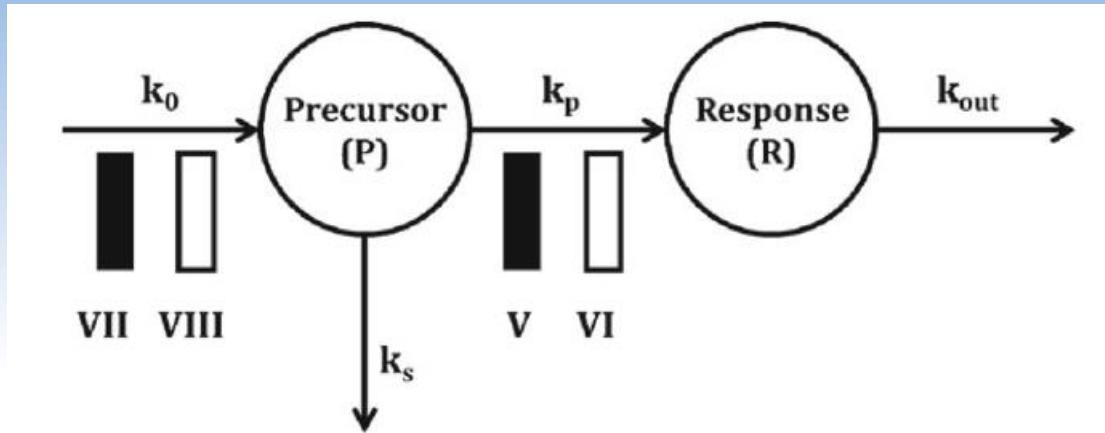
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- Effect of immune response with intramuscular injection

## – Others:

- Flexibility in solubility vs. pH model fitting
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# New PD Model (Precursor – dependent Indirect Model)



$$\frac{dP}{dt} = k_0 \{1 \pm H_1(C_p)\} - (k_s + k_p \{1 \pm H_2(C_p)\})P, \quad (11)$$

$$\frac{dR}{dt} = k_p \{1 \pm H_2(C_p)\} \times P - k_{out} \times R, \quad (12)$$

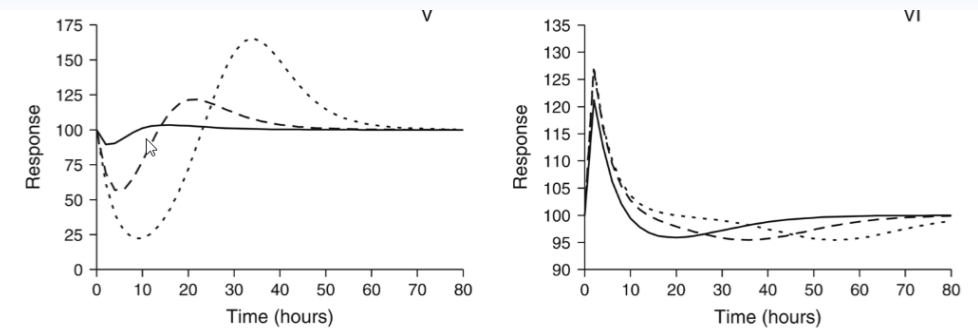


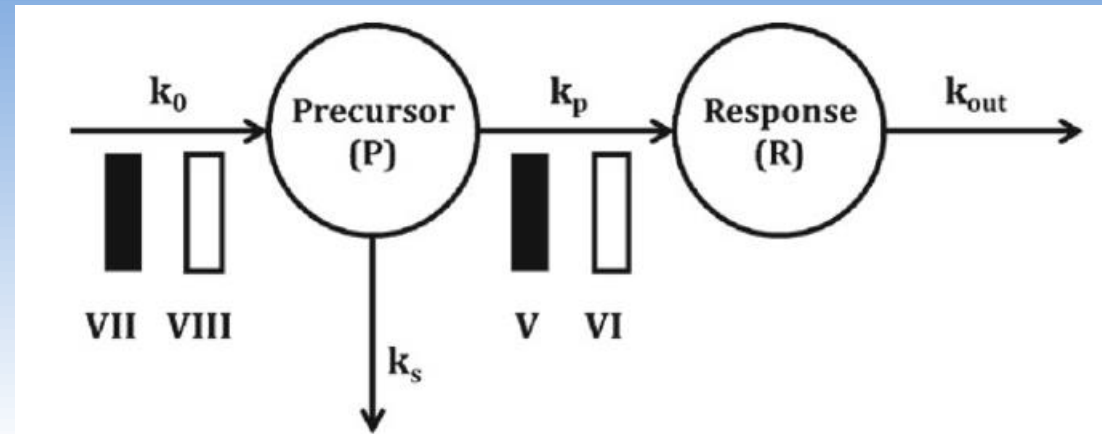
Fig. 6.

Multiple compartment indirect response models (*top panel*) and signature profiles for Models V and VI (*bottom panel*). Response curves were simulated using Eqs. 11 and 12 driven by drug concentrations following monoexponential disposition:  $C_p = C^0 e^{-kt}$ .  $C^0$  was set to 10, 100, or 1,000 units to achieve increasing doses. Parameter values were  $k = 0.12/h$ ,  $I_{max} = 1$  unit,  $S_{max} = 10$  units,  $EC_{50} = 15$  units,  $k_0 = 25$  unit/h,  $k_p = 0.5/h$ , and  $k_{out} = 0.25/h$ .

$k_0$ : the zero-order rate constant for precursor production  
 $k_p$ : the first-order rate constant for production of the response variable  
 $k_s$  and  $k_{out}$ : first-order rate constants for loss of the precursor or response  
 $H_1$ : the inhibition or stimulation of precursor production  
 $H_2$ : the inhibition or stimulation of response production

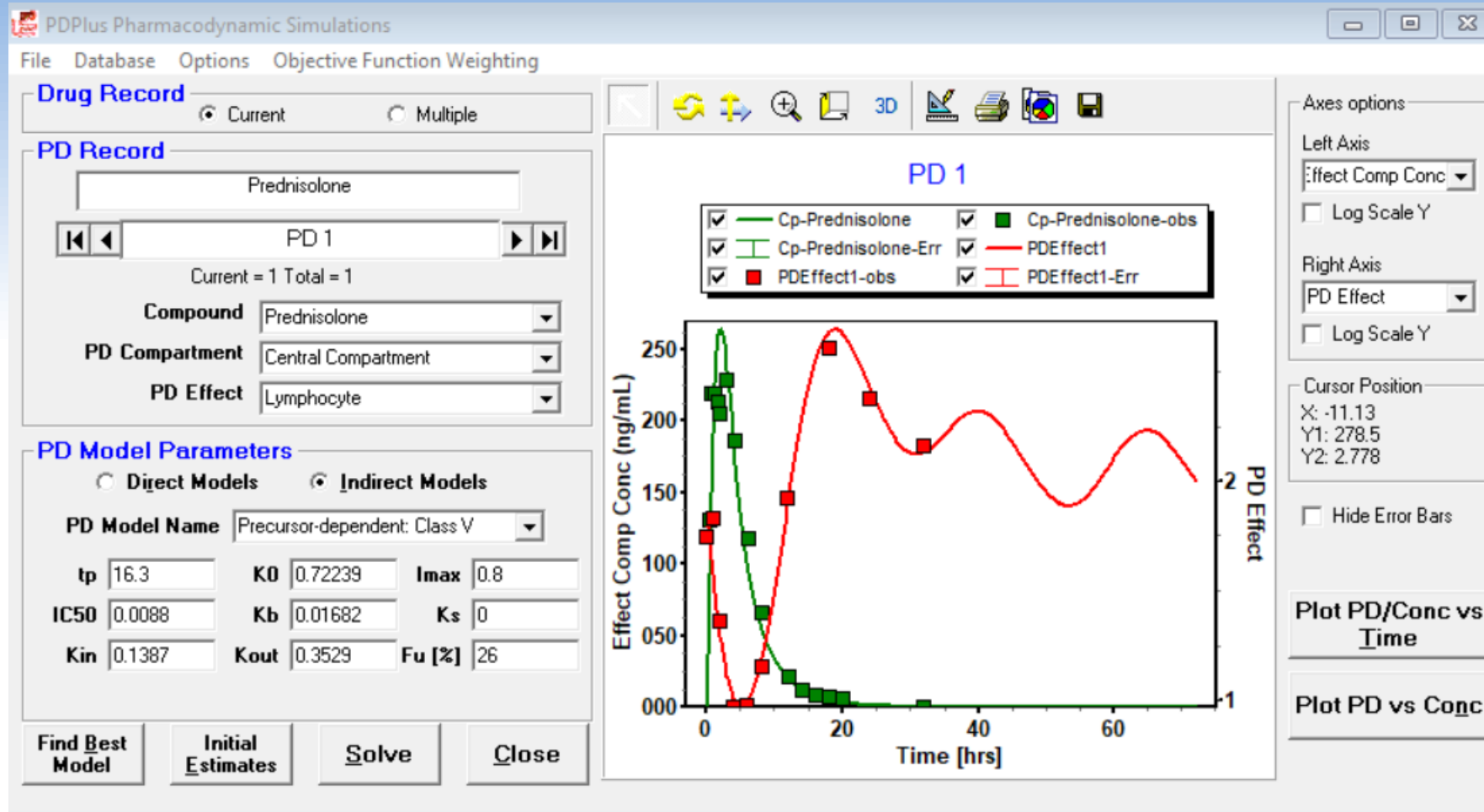
Stimulation or inhibition of  $k_p$  is more commonly observed than alterations in the production of precursor.

# Models Added to v9.7



1. Precursor-dependent: Class V (Inhibition of response production)
2. Precursor-dependent: Class VI (Stimulation of response production)
3. Precursor-dependent: Class VII (Inhibition of precursor production)
4. Precursor-dependent: Class VIII (Stimulation of precursor production)

# Simulated T-lymphocyte Cell Counts ( $10^6$ cells/ml) after Prednisolone administration



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- Effect of immune response with intramuscular injection

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# Transdermal: API Evaporation

Vehicle

Database

Formulation Solvent **Evaporation** Emulsion Sublayers

**Vehicle Evaporation**  **Solvent is volatile**

Solvent Vapor Pressure (Torr)  Ambient Air Velocity (m/s)

Solvent Air Diffusivity (m<sup>2</sup>/s)  Air Kinematic Viscosity (m<sup>2</sup>/s)

Vehicle Residual Volume (%)  Char Length for Evap (m)

**Evaporation Rate Constant Model:**  Solvent Evap Rate

**Skin is covered**

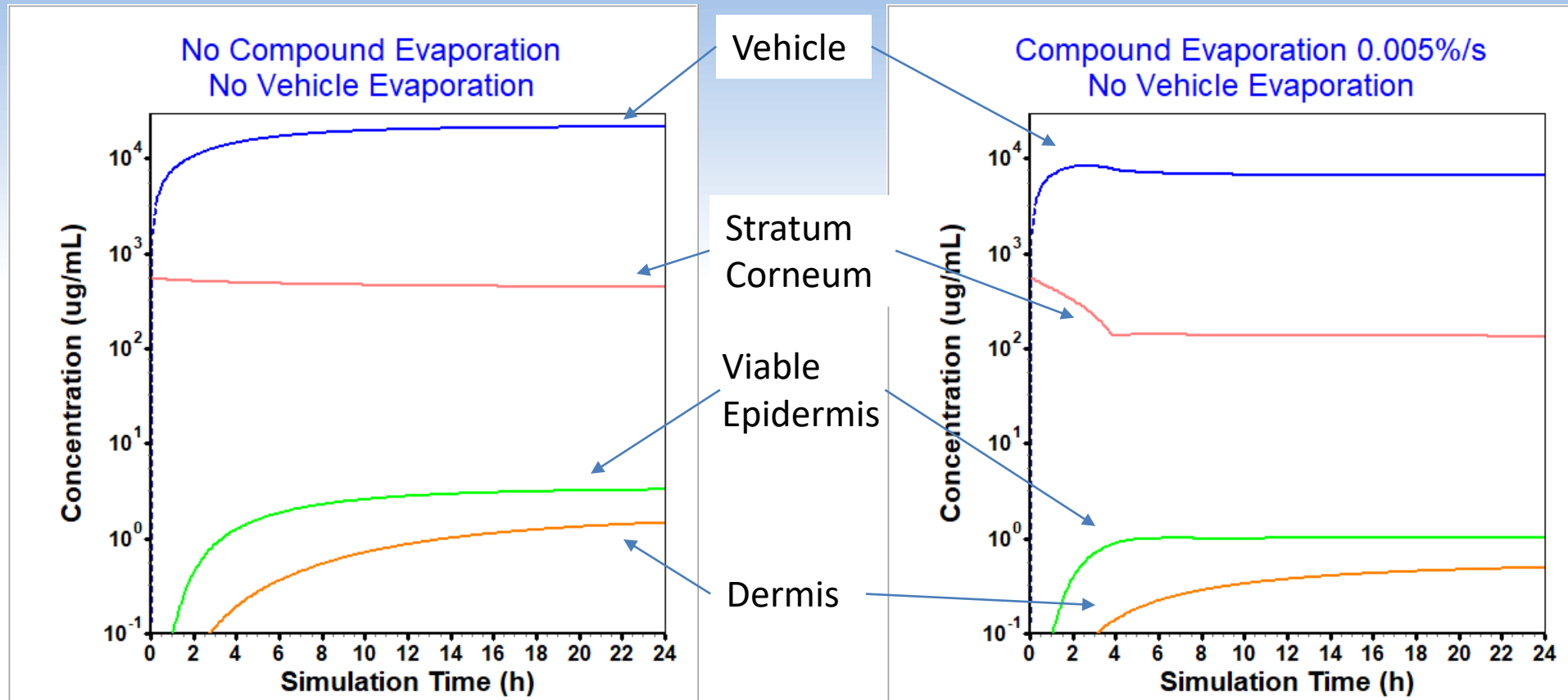
**Compound Evaporation**  **Compound is volatile**

Compound Residual Amount (%)  Compound Evap Rate (%/s)

**Evaporation time = 275 h**

# Compound Evaporation

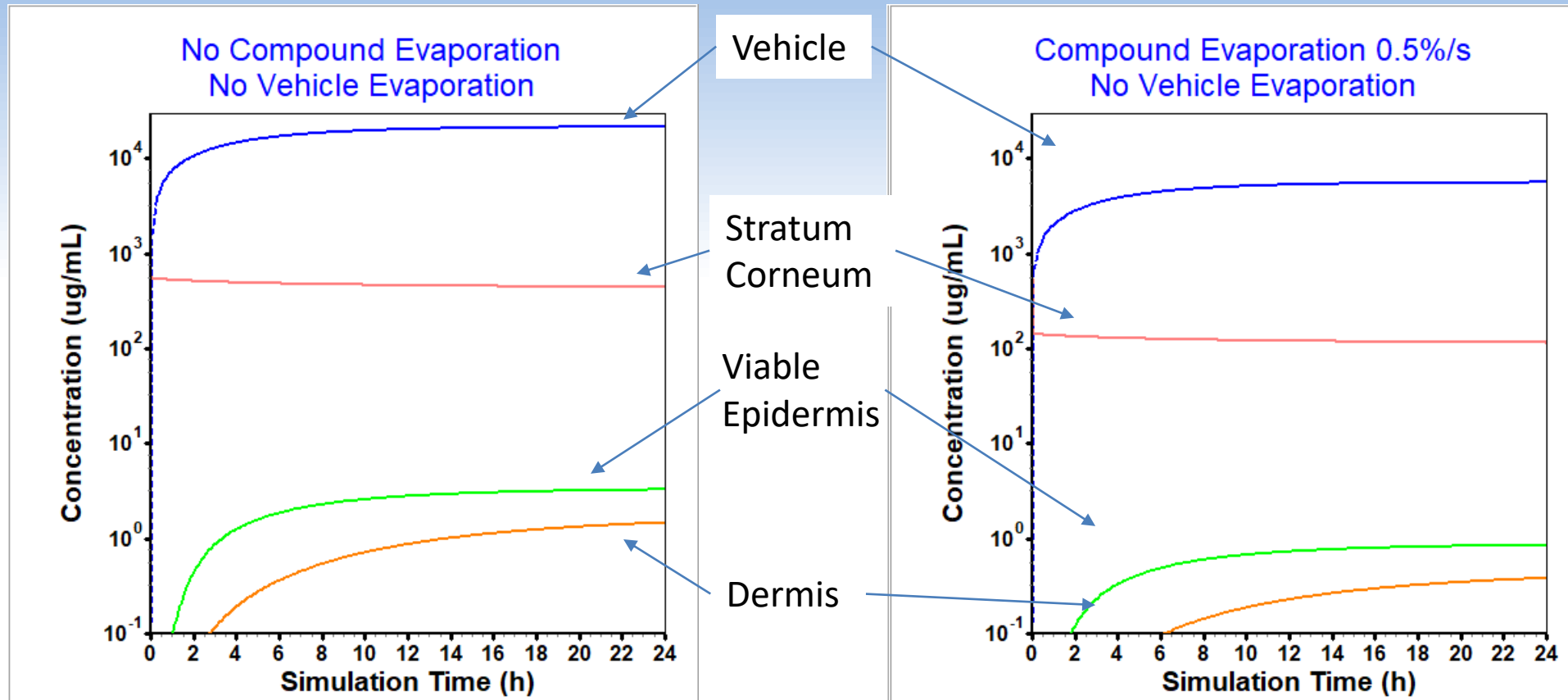
Dissolved drug concentration in:





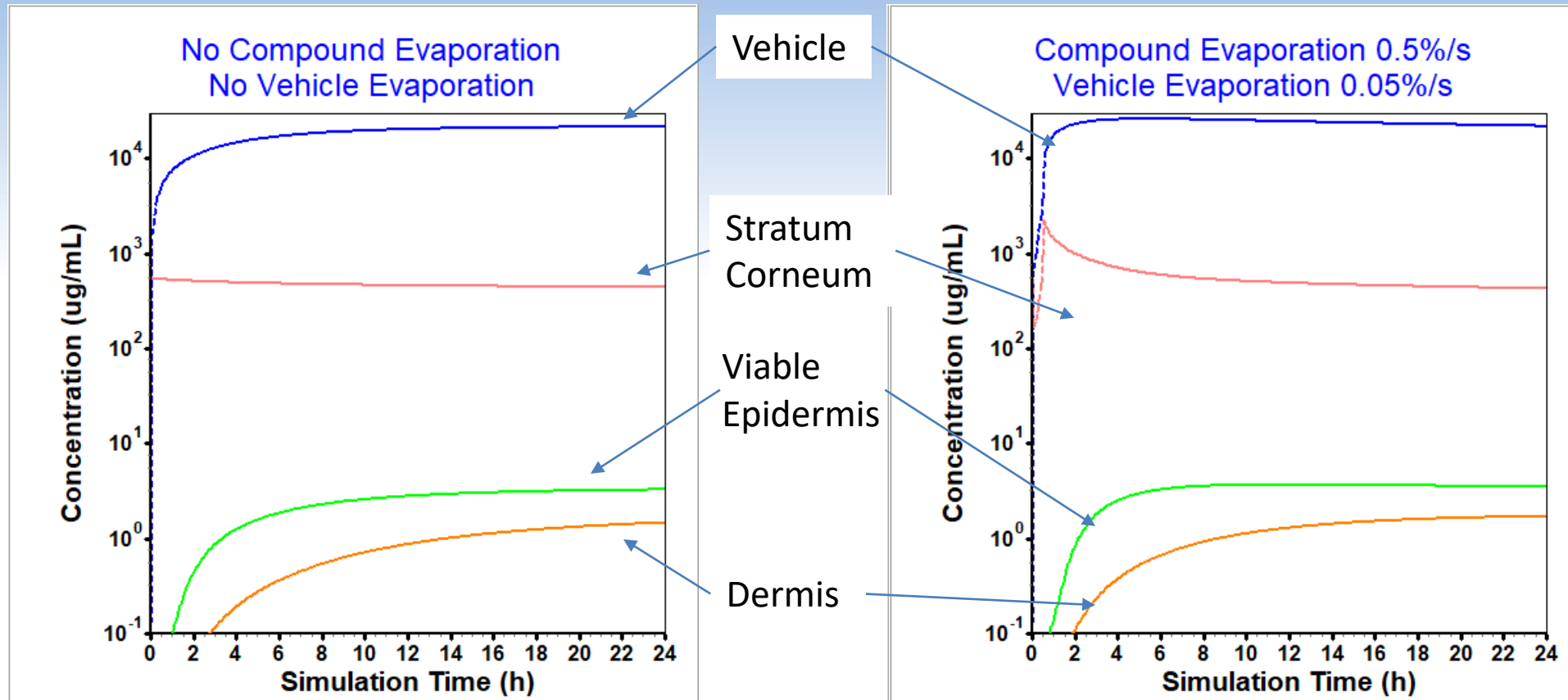
# Compound Evaporation

Dissolved drug concentration in:



# Compound Evaporation

Dissolved drug concentration in:



# Intramuscular: Immune Cell Layer

The tissue response to PLGA microsphere administration can be divided into three phases:

## I. Acute phase of the inflammatory response

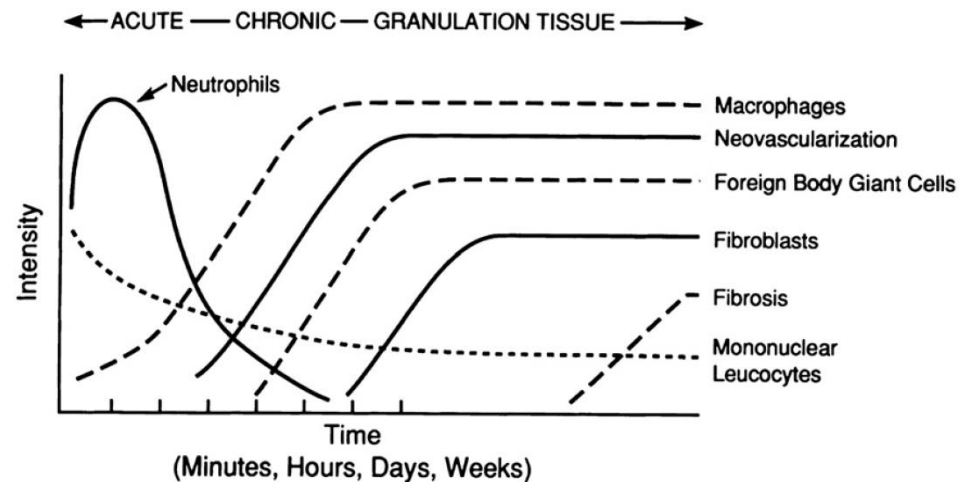
Occurs within one week following administration and is characterized by the presence of neutrophils in the area of the injection or implant.

## II. Onset of the chronic phase of inflammation

Onset of the chronic phase of inflammation, is characterized by the appearance of monocytes and macrophages

## III. Fibroblasts infiltration and collagen deposition

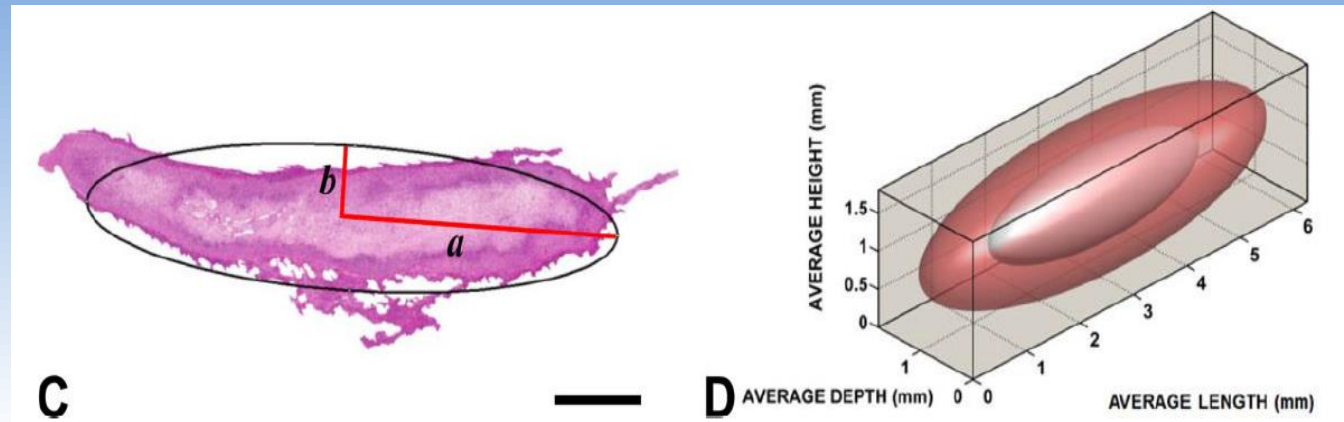
Fibroblasts infiltrate the site and collagen deposition is initiated to form a fibrous capsule. Neo-angiogenesis is also observed during this period



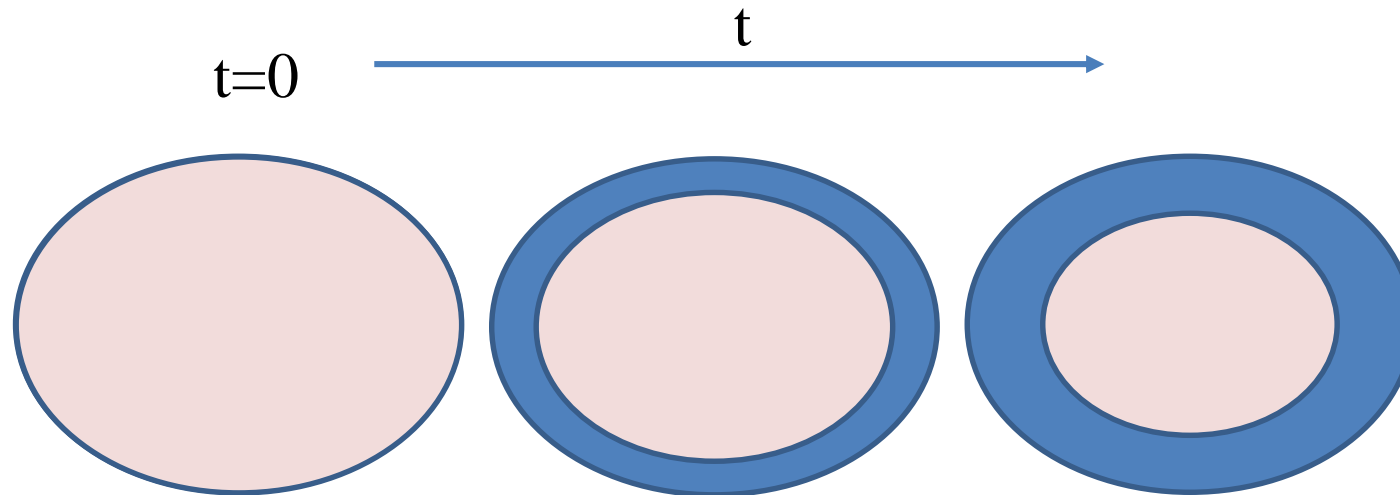
*The temporal variation in the three phases of inflammatory response resulting from administration of biodegradable microspheres*

Anderson et. al., Advanced Drug Delivery Reviews 64 (2012), 2012

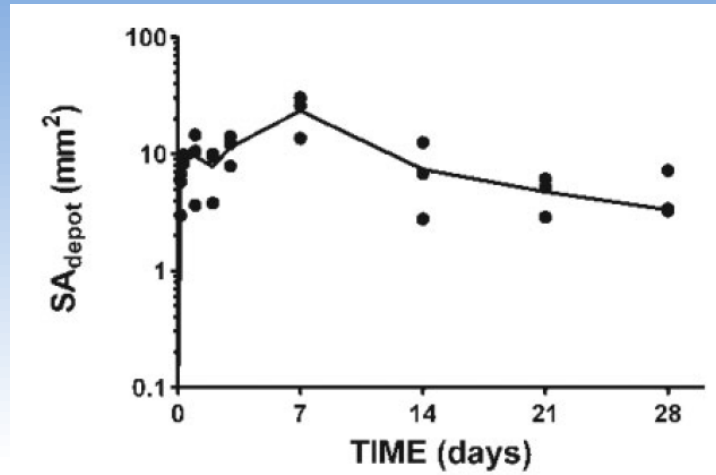
# Intramuscular: Immune Cell Layer



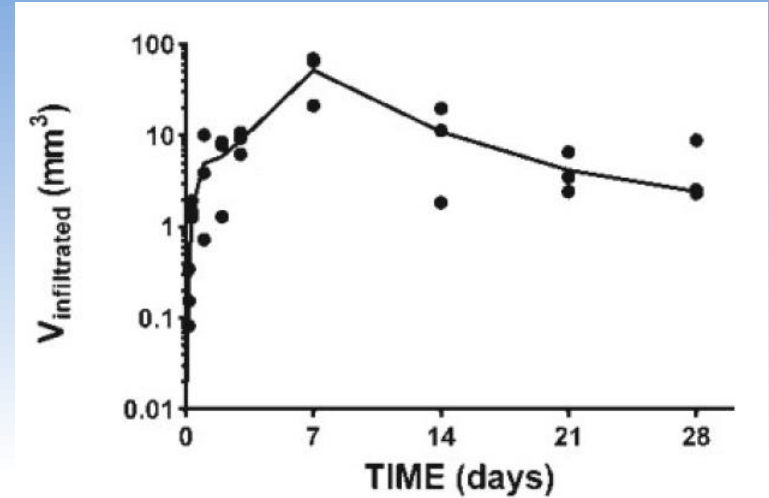
Darville et al, Toxicologic Pathology, 2016, Vol. 44(2) 189-210



# Intramuscular: Immune Cell Layer

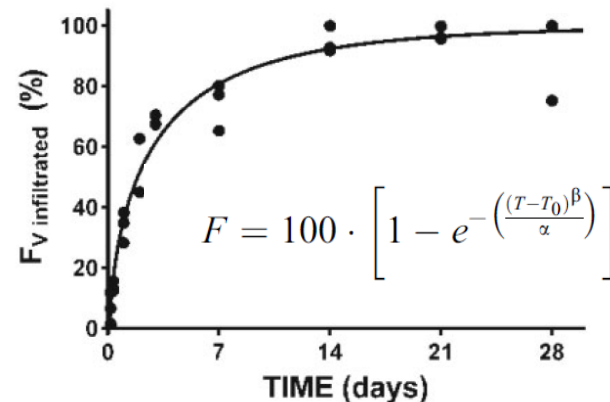
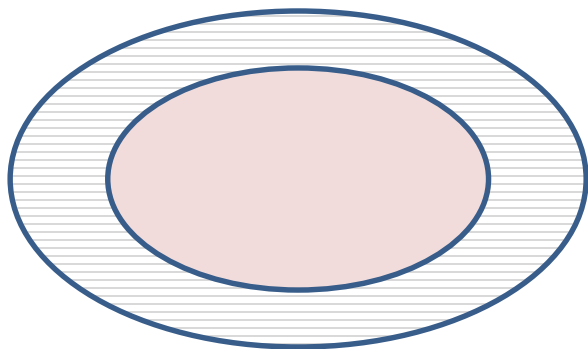


The temporal evolution of  $V_{infiltr.}$  was analogous to that of  $S_{depot}$



Total cross-sectional area of the formulation depots (i.e., including cellular infiltration;  $S_{depot}$ ).

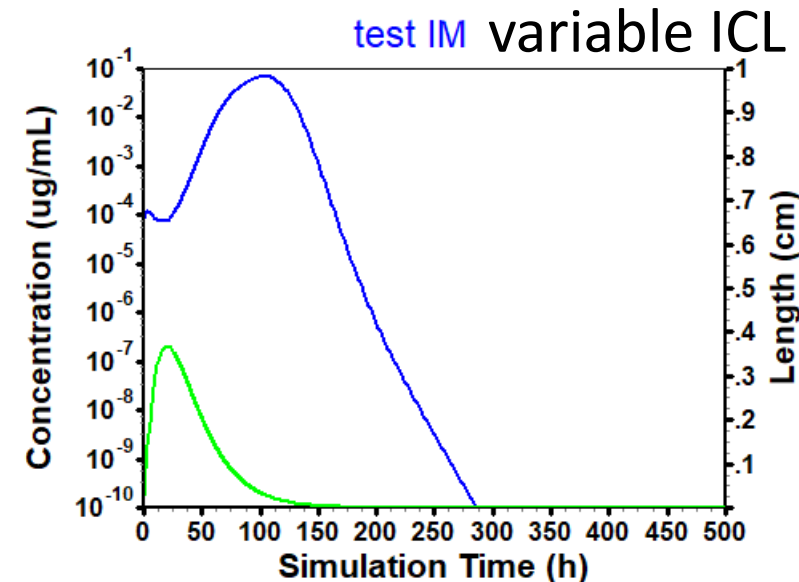
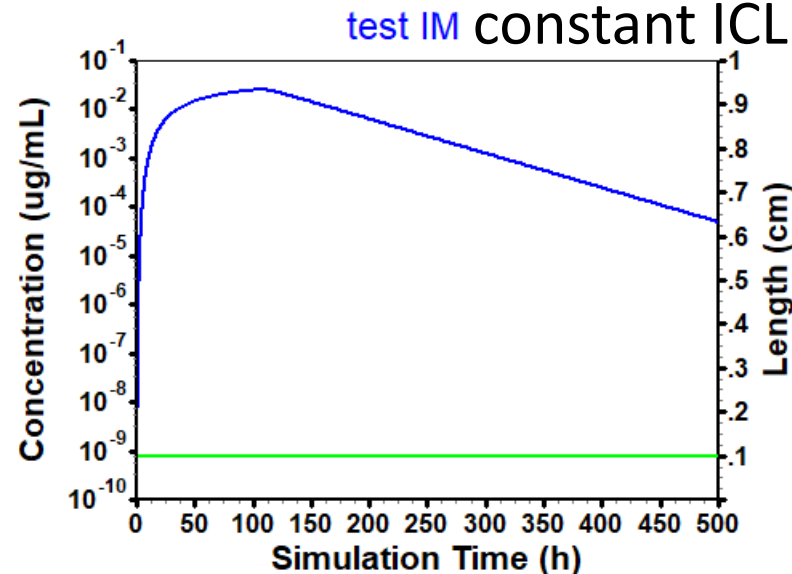
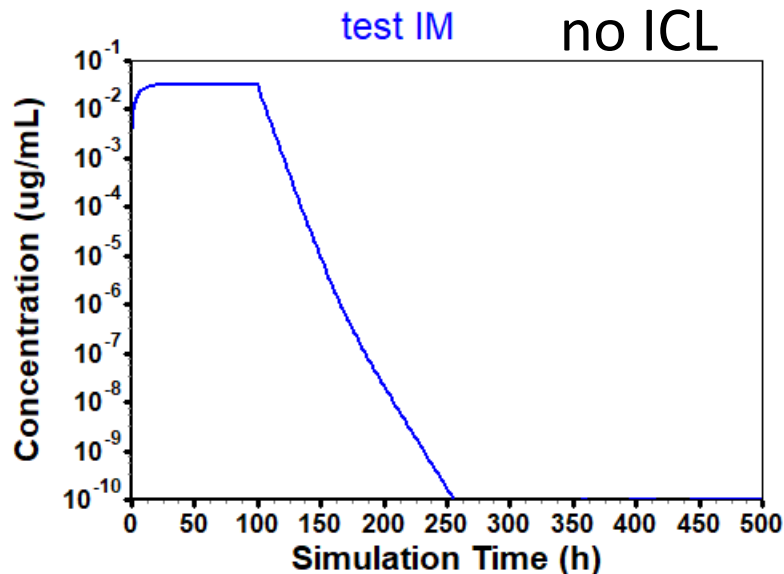
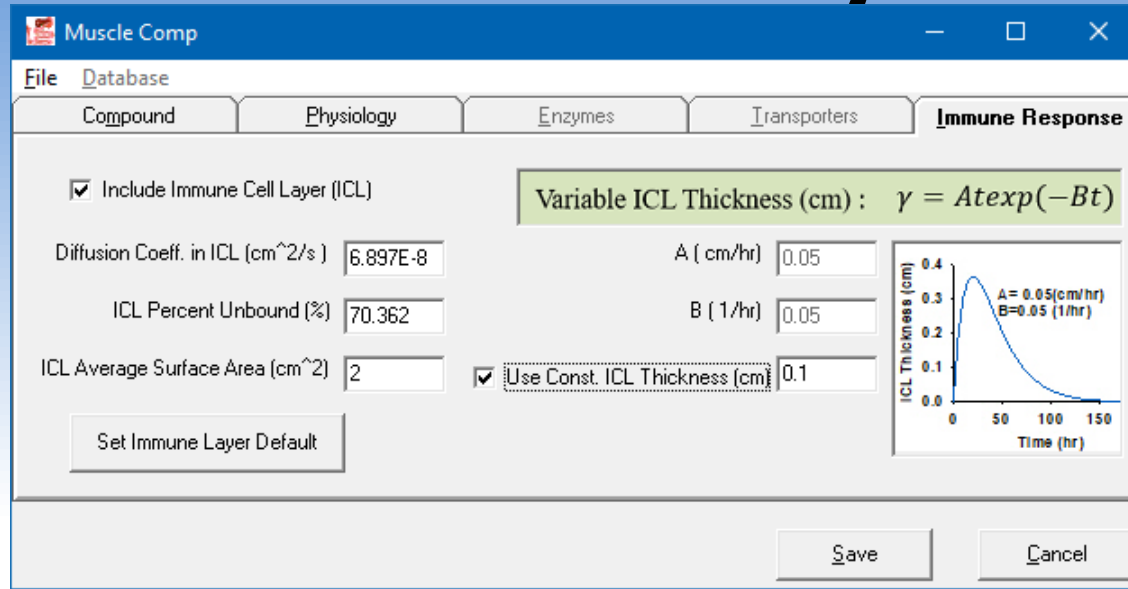
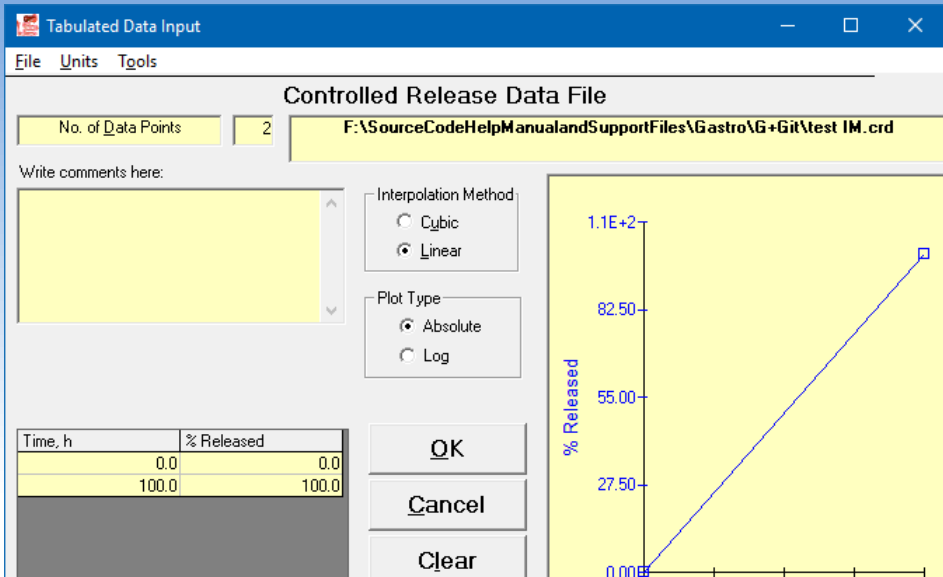
The calculated net volumes of the PP-LAI and PS formulation depots that were infiltrated by inflammatory cells ( $V_{infiltr.}$ )



$$F = 100 \cdot \left[ 1 - e^{-\left(\frac{(t-T_0)^\beta}{\alpha}\right)} \right]$$

$F_{v,infiltr}$  = the ratio of  $V_{infiltr.}$  over  $V_{depot}$ ;

# Intramuscular: Immune Cell Layer



# GastroPlus® v9.7

## – ACAT™ model:

- Allow two solubility inputs for different drug forms (crystalline, amorphous)
- Fed state conditions based on meal type

## – PBPKPlus™ Module:

- Mechanistic pregnancy PBPK model
- Lysosomal trapping
- Allow different tissue model types (perfusion- or permeability-limited) for different compounds in simulation

## – Metabolism and Transporter Module:

- New enzyme/transporter distribution information
- Provide default population for extensive, intermediate, and poor metabolizers based on specific genotypes

## – DDI Module:

- Additional compound model files for substrates & inhibitors

## – PDPlus™ Module:

- Precursor-dependent indirect models

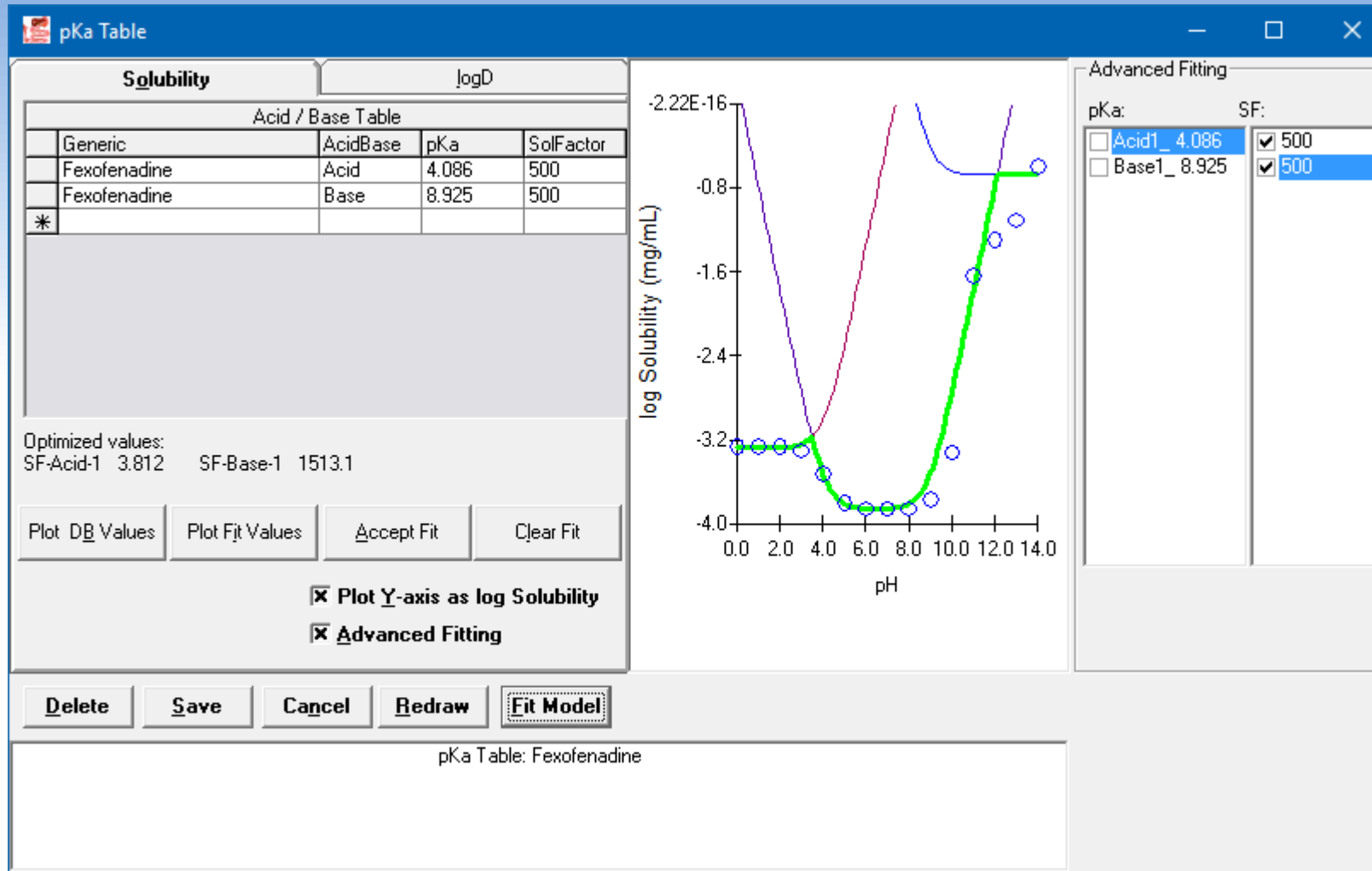
## – ADRM Module:

- API evaporation with transdermal administration
- Effect of immune response with intramuscular injection

## – Others:

- Flexibility in solubility vs. pH model fitting
- Updates in Peff converter

# Flexibility in Solubility vs. pH Model Fitting





# Peff Converter Update

Permeability Converter

C:\Users\Public\Simulations Plus, Inc\GastroPlus9.6\SampleCaco-2.upd

BCS Compound	Exp Perm	Human Peff (cm/s x 10 <sup>4</sup> )	Source
AMILORIDE	0	1.6	Lennernas, H., Xe
AMOXICILLIN	0.8	0.3	Lennernas, H., Xe
ANTIPYRINE	28.2	5.6	Lennernas, H., Xe
ATENOLOL	0.2	0.2	Lennernas, H., Xe
BENSERAZIDE	0	1.87	Lennernas, H., et
CARBAMAZEPINE	0	4.3	Lennernas, H., Xe
CEPHALEXIN	0.5	1.56	Lennernas, H., Xe
CIMETIDINE	0.74	0.26	Lennernas, H., Xe
DESIPRAMINE	21.6	4.5	Lennernas, H., Xe
D-GLUCOSE	0	11.8	Lennernas, H., et
ENALAPRIL	2.31	1.57	Lennernas, H., Xe
ENALAPRILAT	0	0.2	Lennernas, H., Xe
FLUVASTATIN	0	2.4	Lennernas, H., Xe
FUROSEMIDE	0.12	0.05	Lennernas, H., Xe
HYDROCHLOROTHYAZIDE	0.51	0.04	Lennernas, H., Xe
INOATRAN	0	0.03	Lennernas, H., Xe
KETOPROFEN	0	8.7	Lennernas, H., Xe
LEVODOPA	0	3.4	Lennernas, H., Xe
LISINOPRIL	0	0.33	Lennernas, H., Xe
L-FENICINE	0	5.72	Lennernas, H., et

**Regression Results**

Selected Model	R <sup>2</sup>	SEP	MAE	AIC
<input type="radio"/> Linear	0.71524	1.4207	1.0468	55.154
<input checked="" type="radio"/> Log Linear	0.76476	0.36712	0.29946	5.1299
<input type="radio"/> Power	0.72054	1.4077	0.95035	54.879

Spearman's Rank Correlation Coef. for User Data : 0.6982

Current Primary Permeability : 2.3

Human Peff Estimate with Selected Model: 0.74174

Peff = 10<sup>^</sup> [-0.3804 + 0.6929 \* log(UserPerm) ]

OK Solve

# Acknowledgements

## Simulation Technologies Team

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Maxime Le Merdy

Manas Shah

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