
# What's New in GastroPlus® v9.7?



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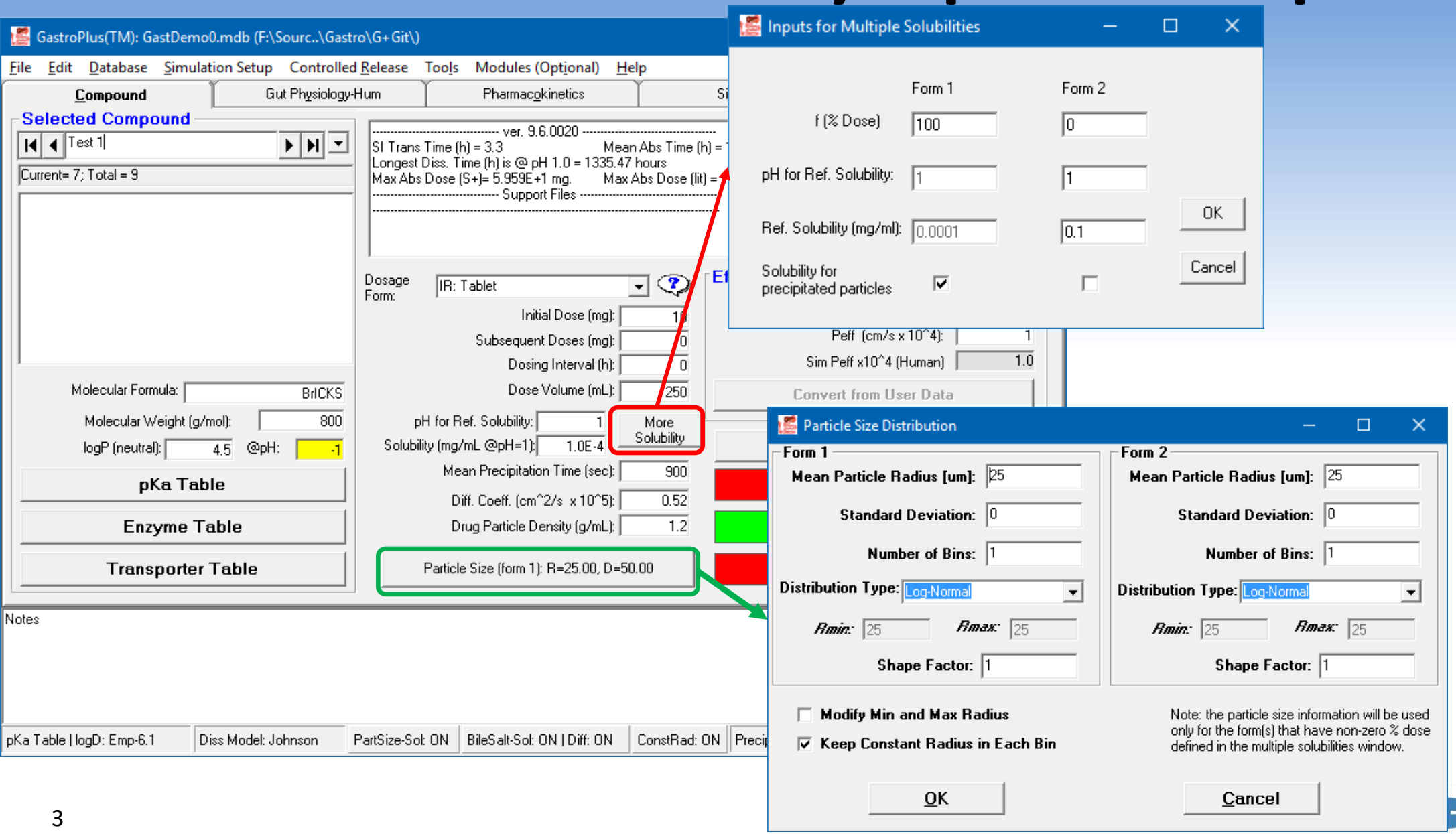
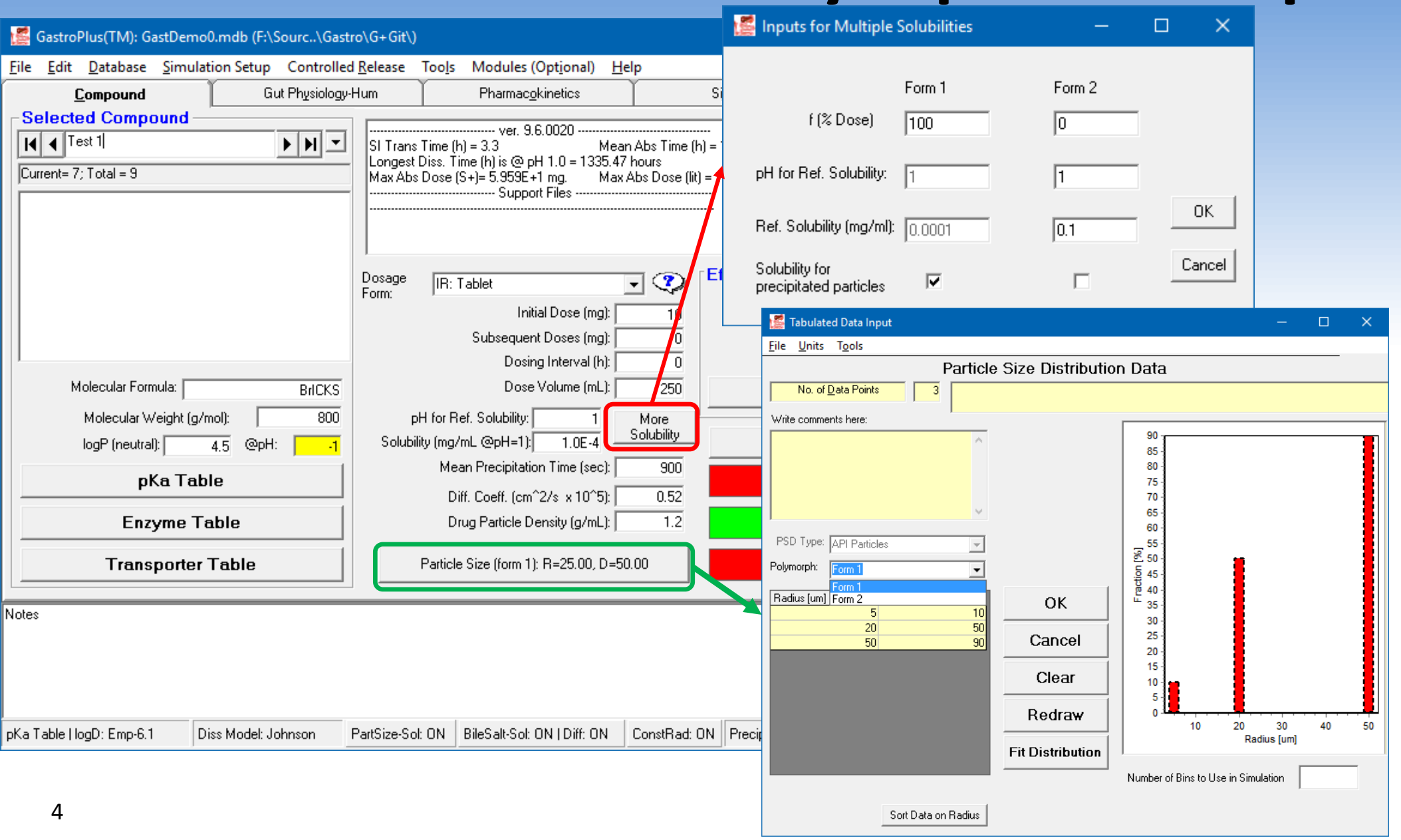
# GastroPlus® v9.7

- **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



# Two Solubility Inputs - Setup



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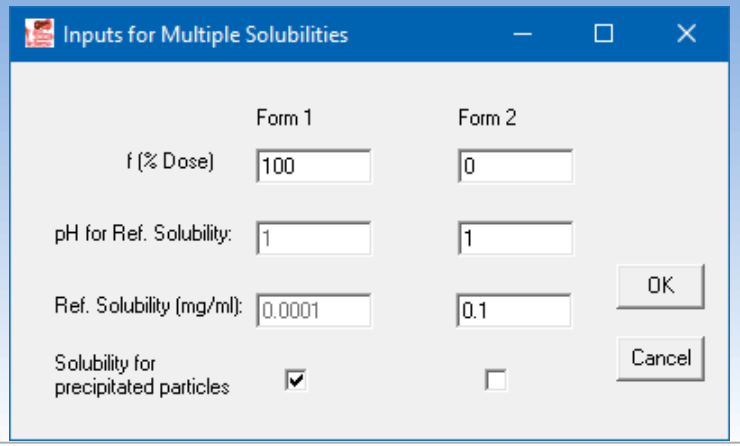
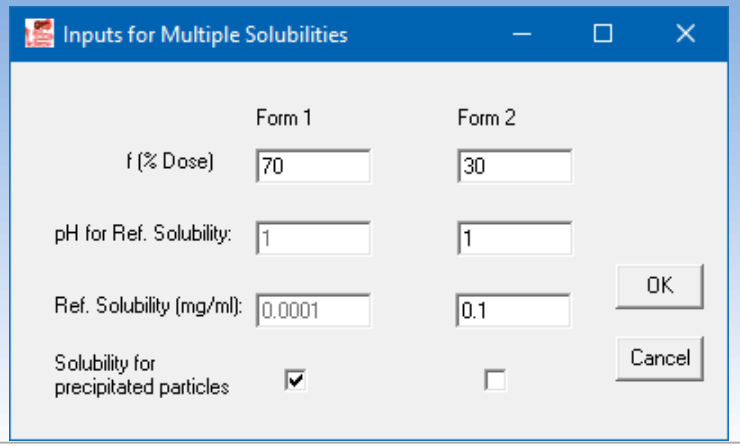
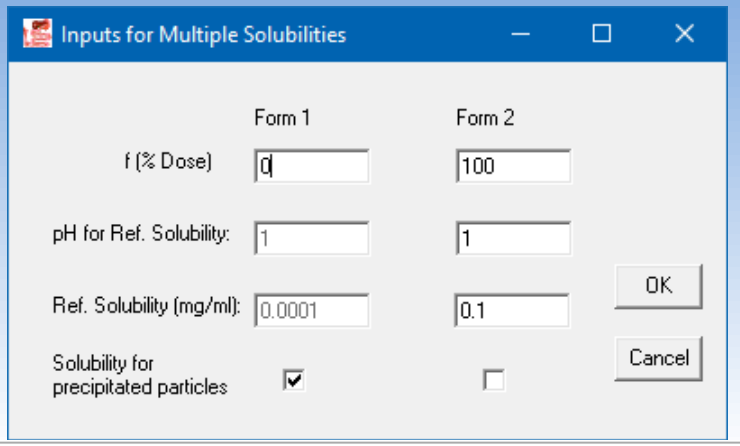
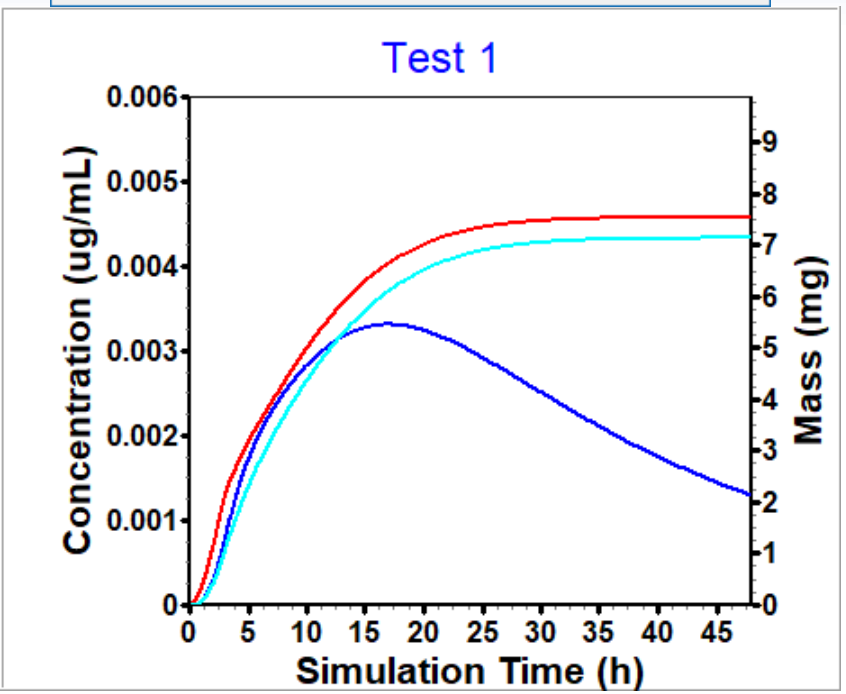
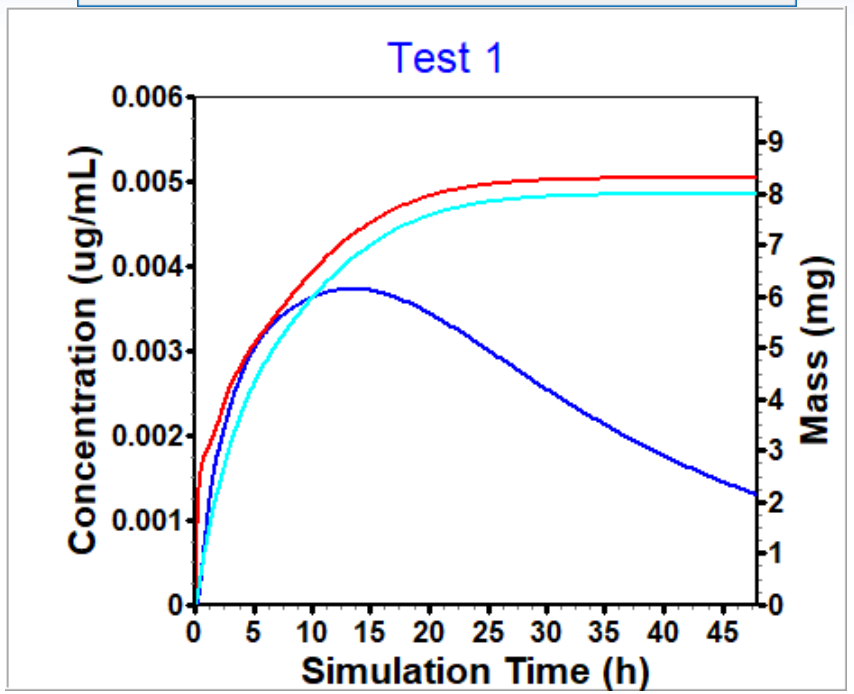
# Simulation Results: Example 1

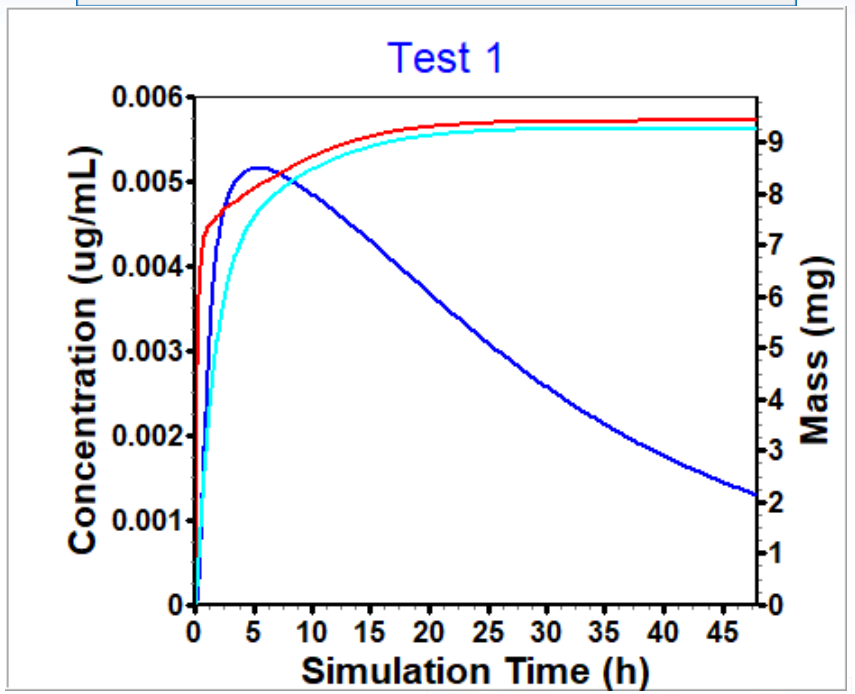


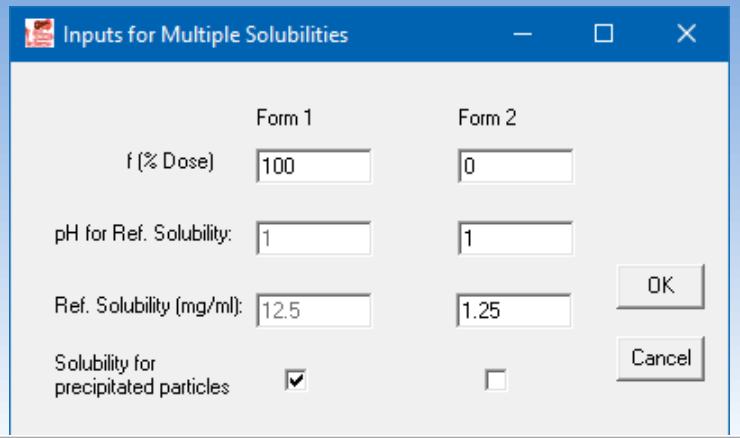



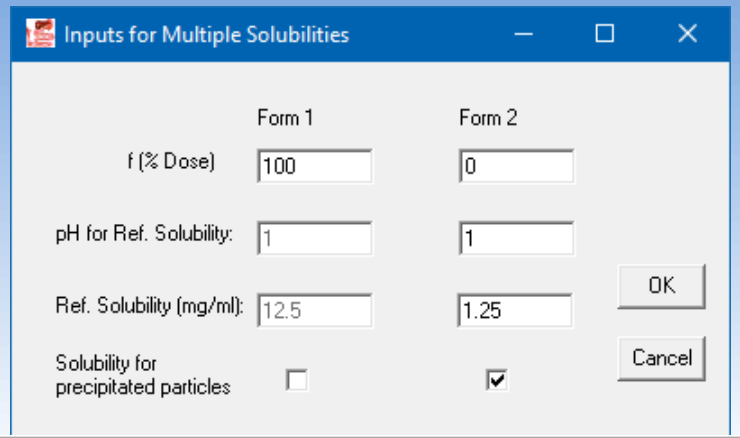



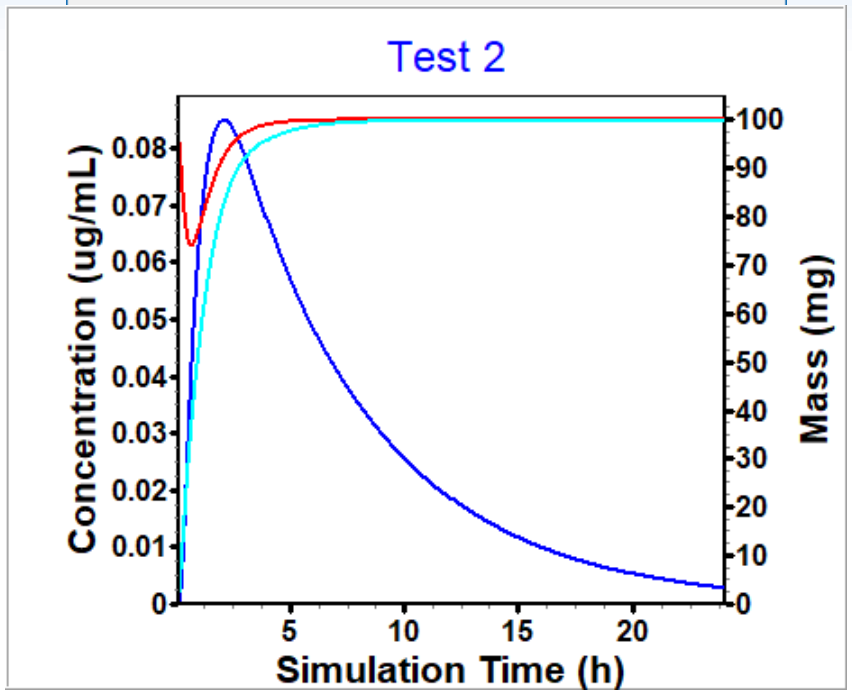


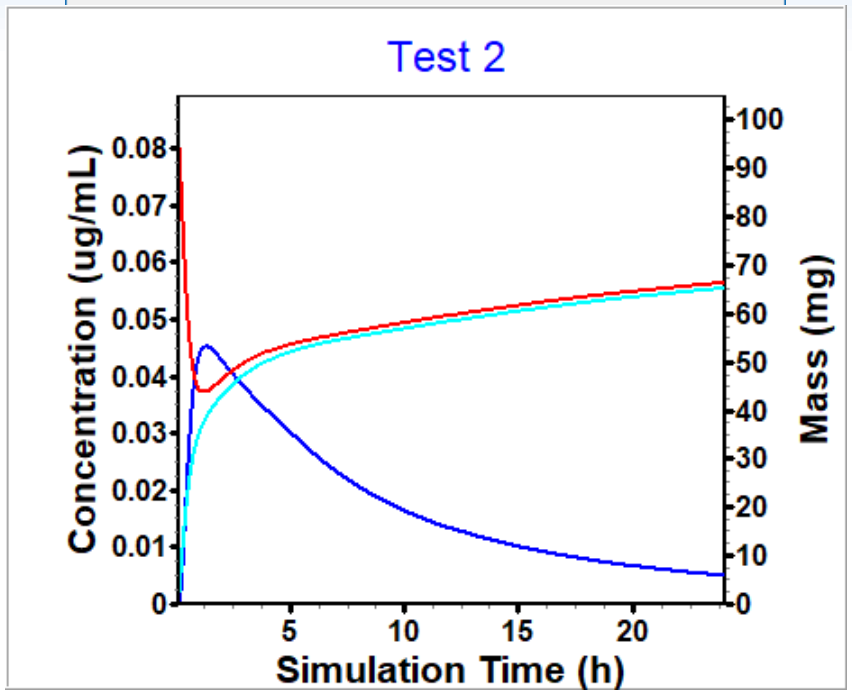

blue – plasma concentration, red – amount dissolved, cyan – amount absorbed

# Simulation Results: Example 2

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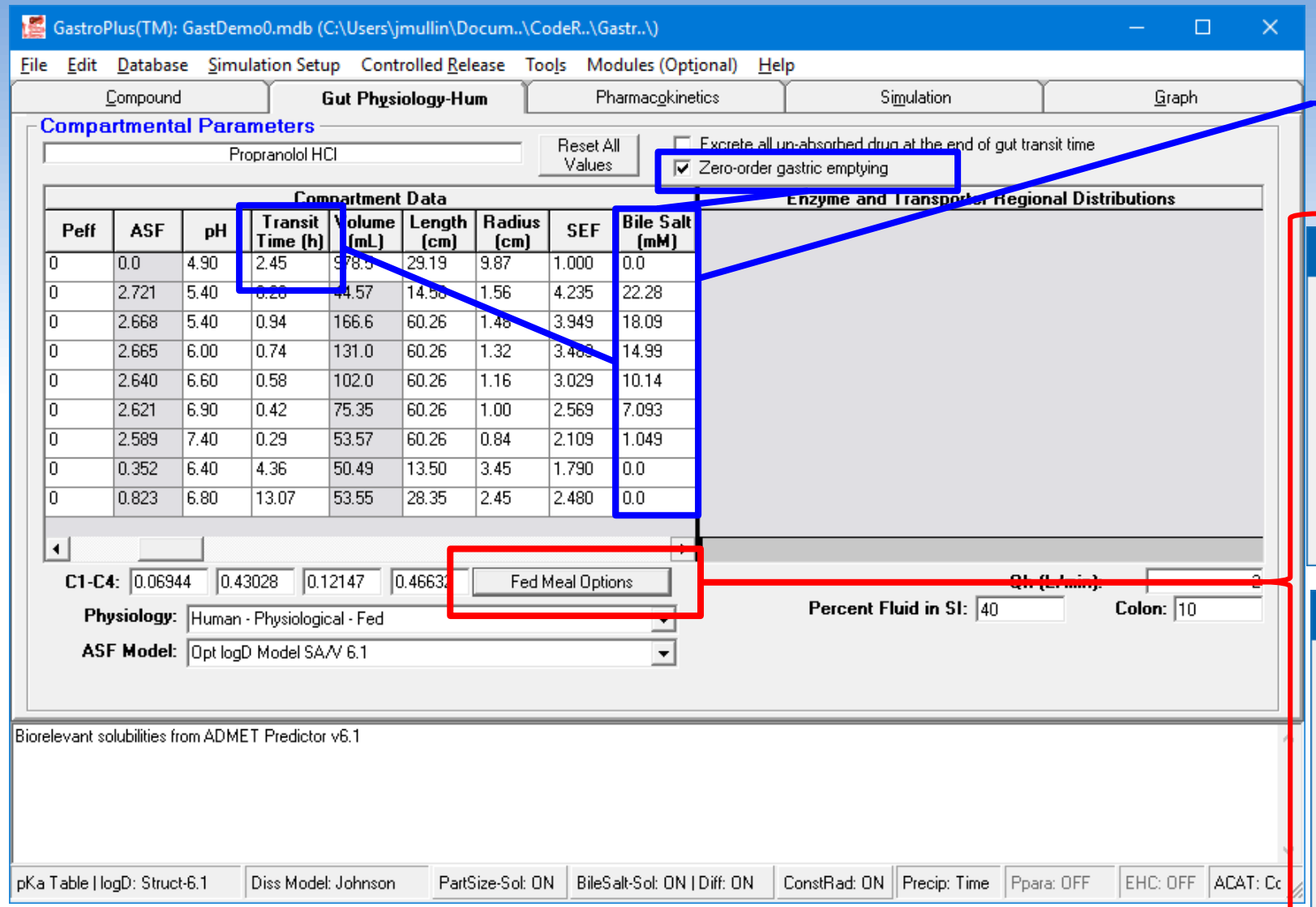
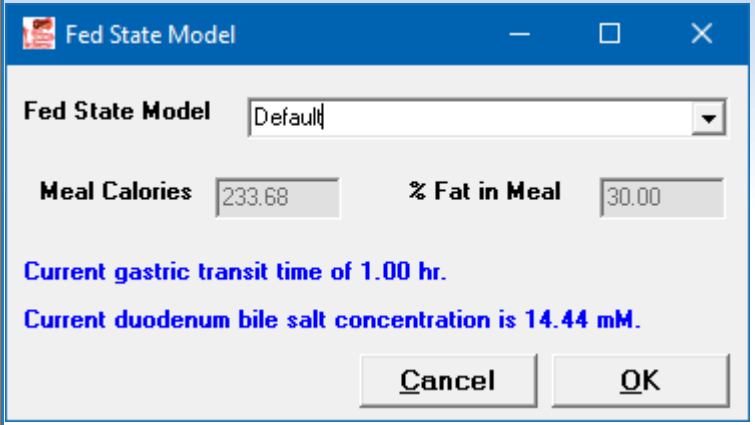
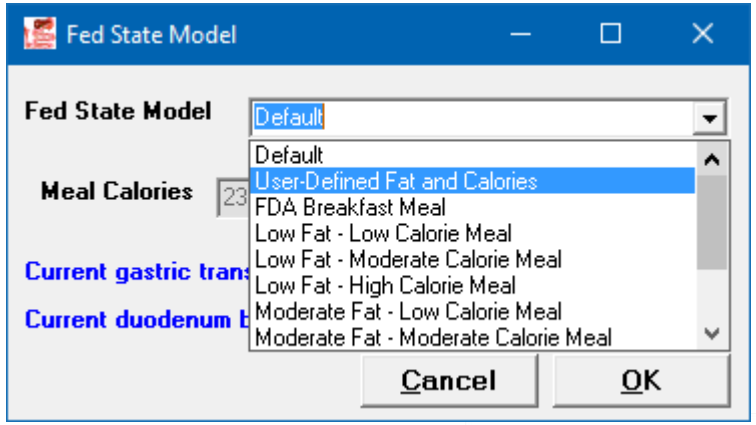
# Built-in Fed Physiologies for Different Meal Types




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



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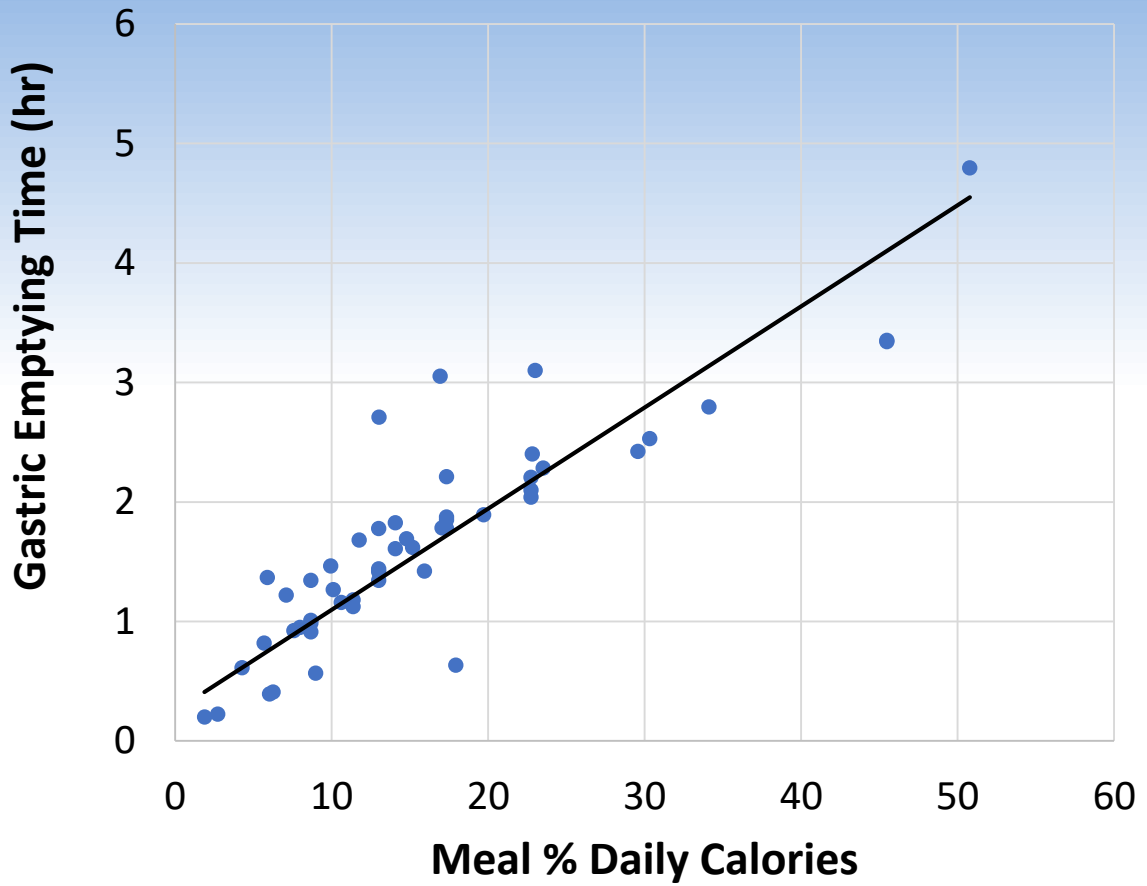
# Gastric Emptying Time vs. Calories

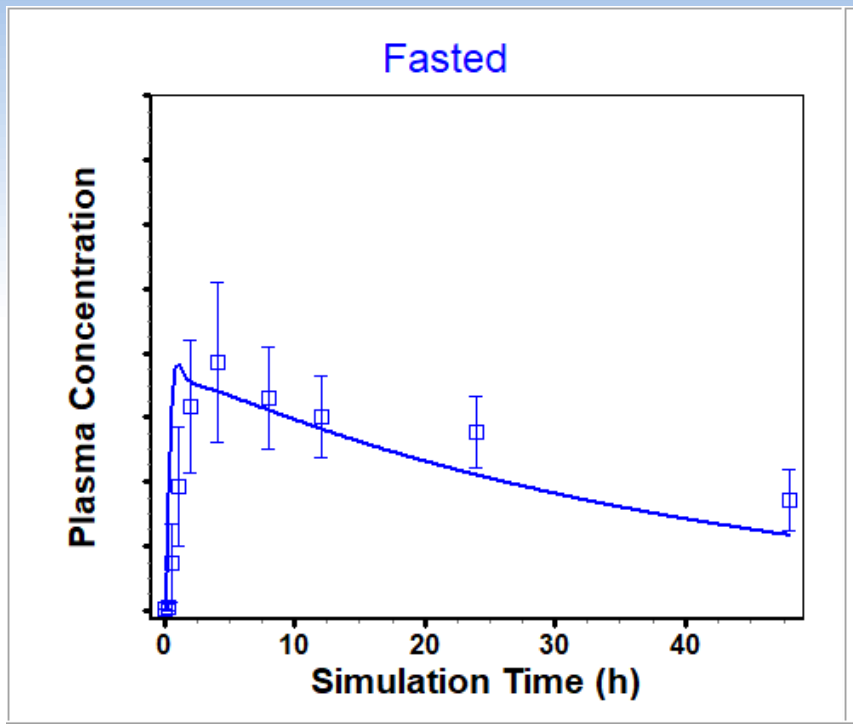


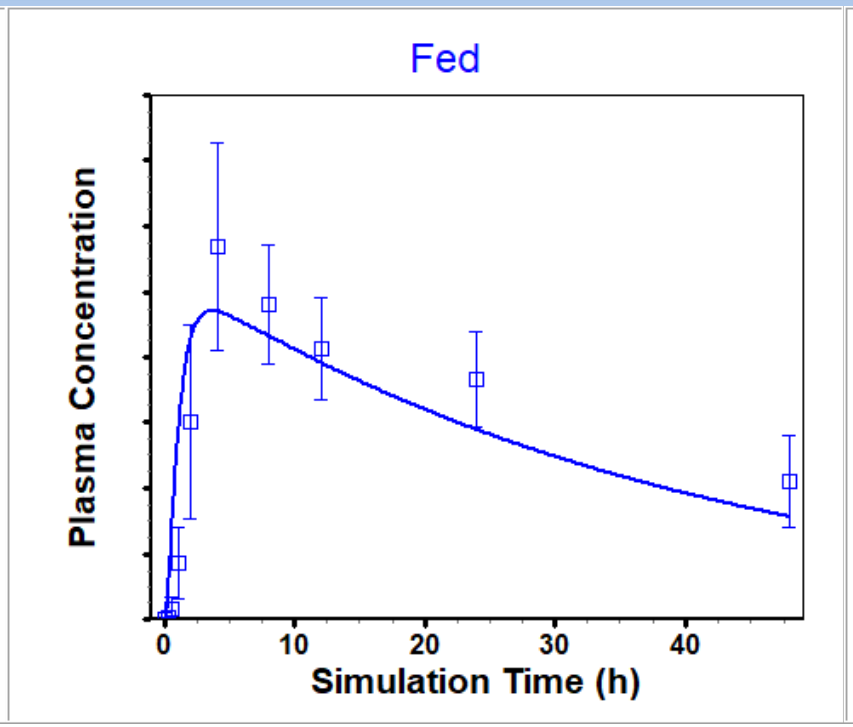

- Based on meal size (calories) the gastric emptying rate will change
- Correlation based on 12 literature papers and 51 measured gastric emptying time curves from ~45-1200 calories

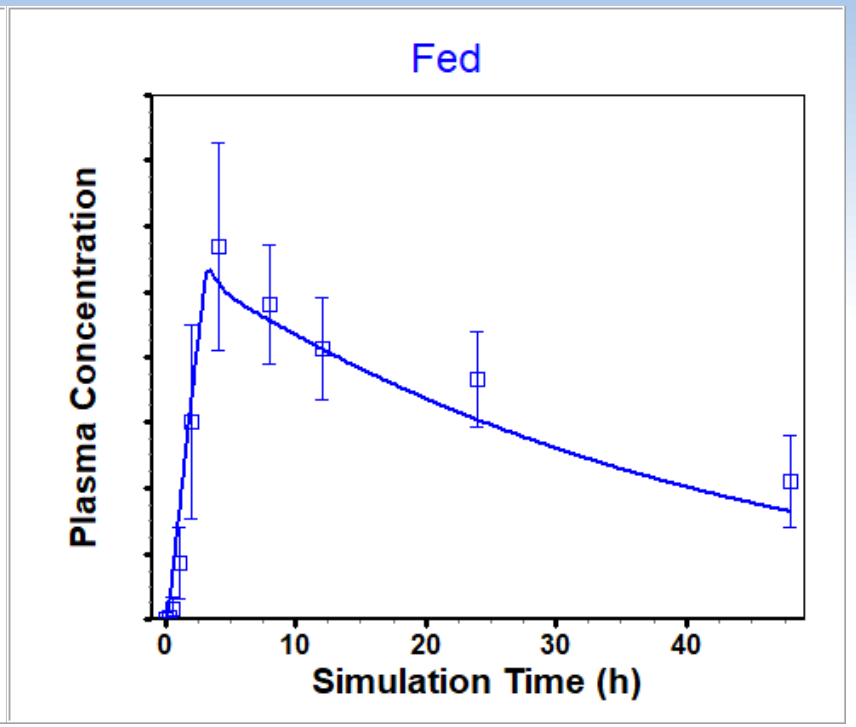
# High Fat Meal: Prediction

Default Fed in GP9.6

Default for FDA standard breakfast



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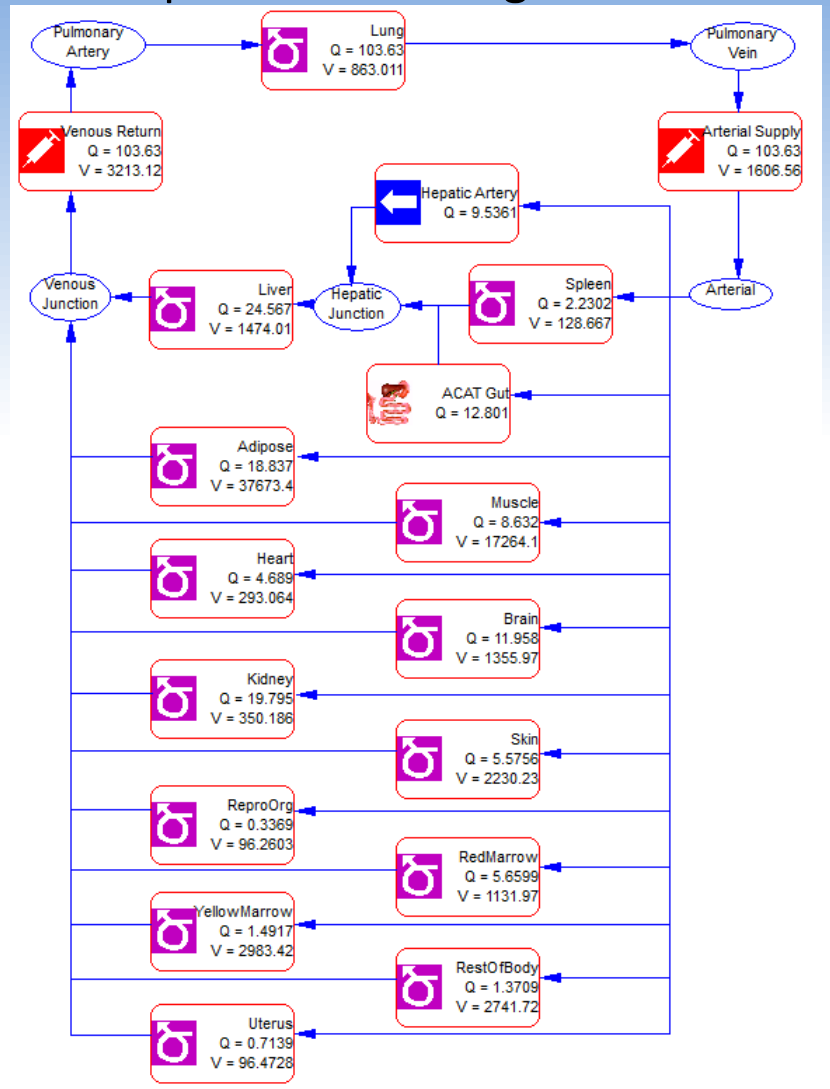
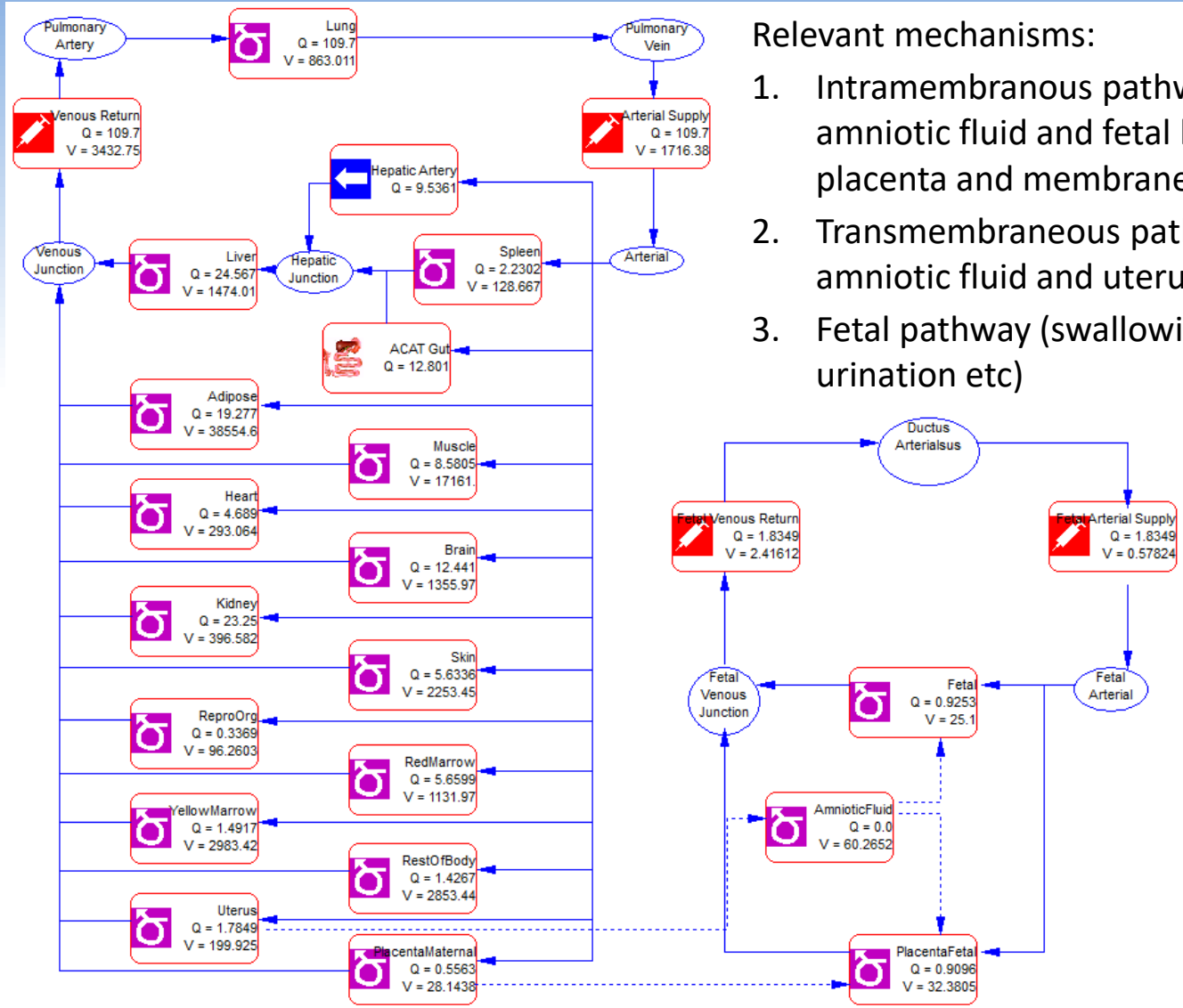
# Pregnancy PBPK Model Structure

up to 6 weeks of gestation




> 6 weeks

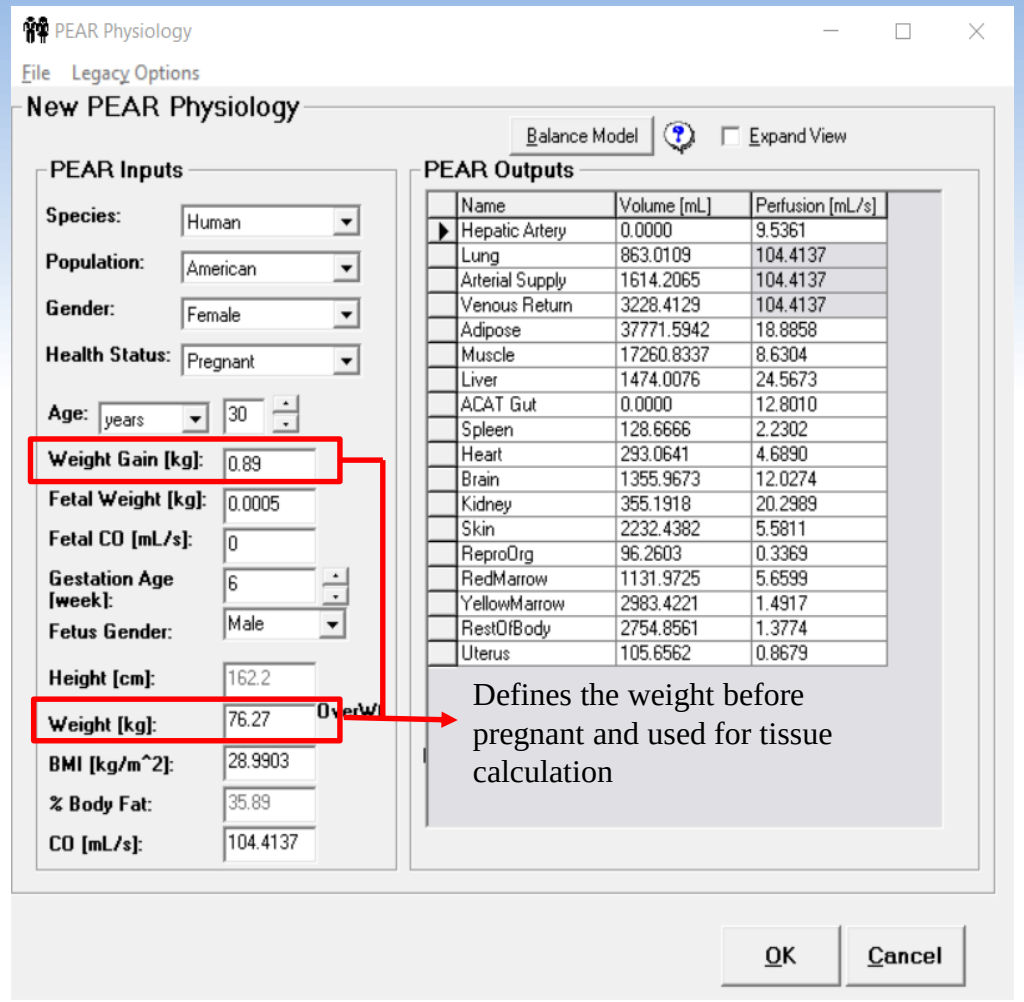



Relevant mechanisms:

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)

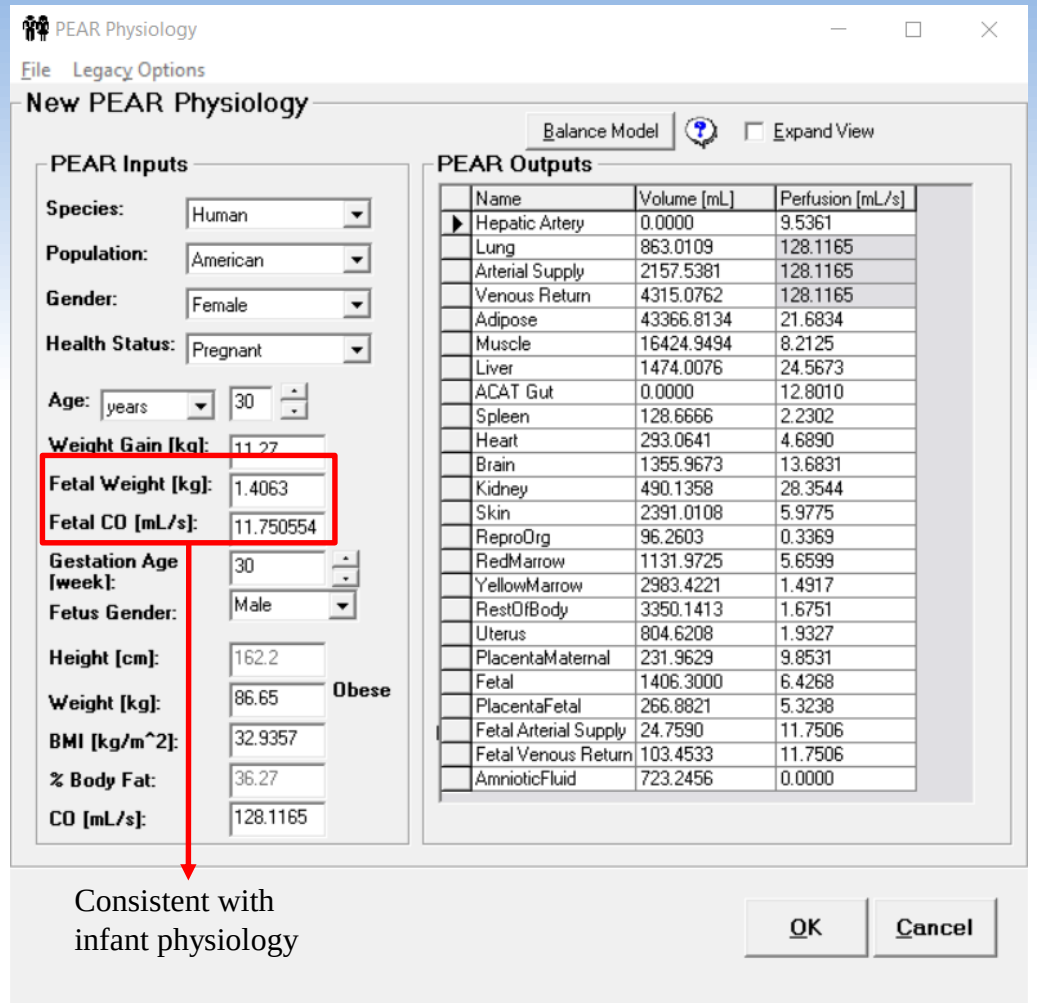
# Creating Physiology for Pregnancy PBPK

up to 6 weeks of gestation




Defines the weight before pregnant and used for tissue calculation

> 6 weeks




Consistent with infant physiology

**User input:**

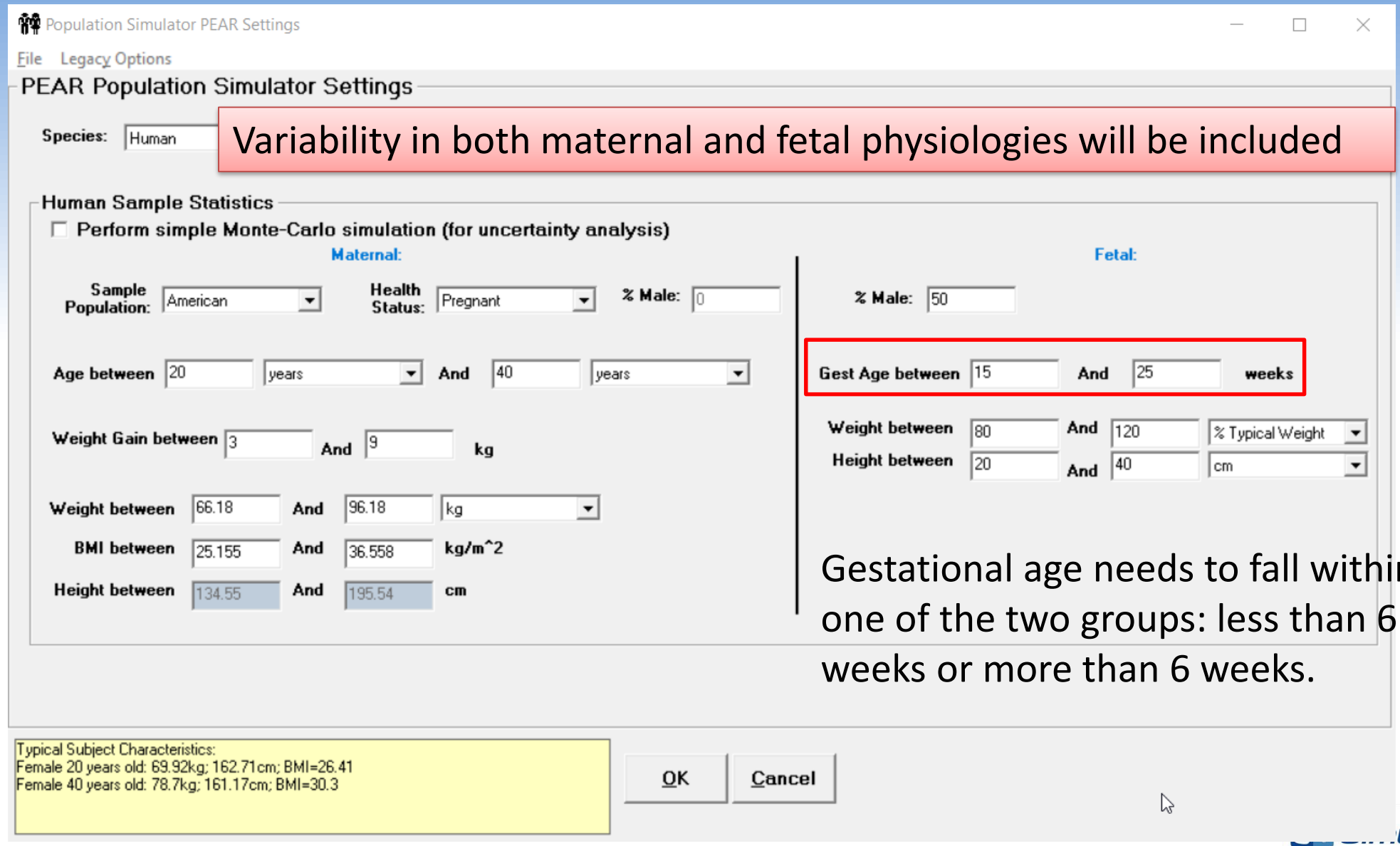
- Age
- Gender
- Gestational age

**Program creates** (can be modified by user):

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

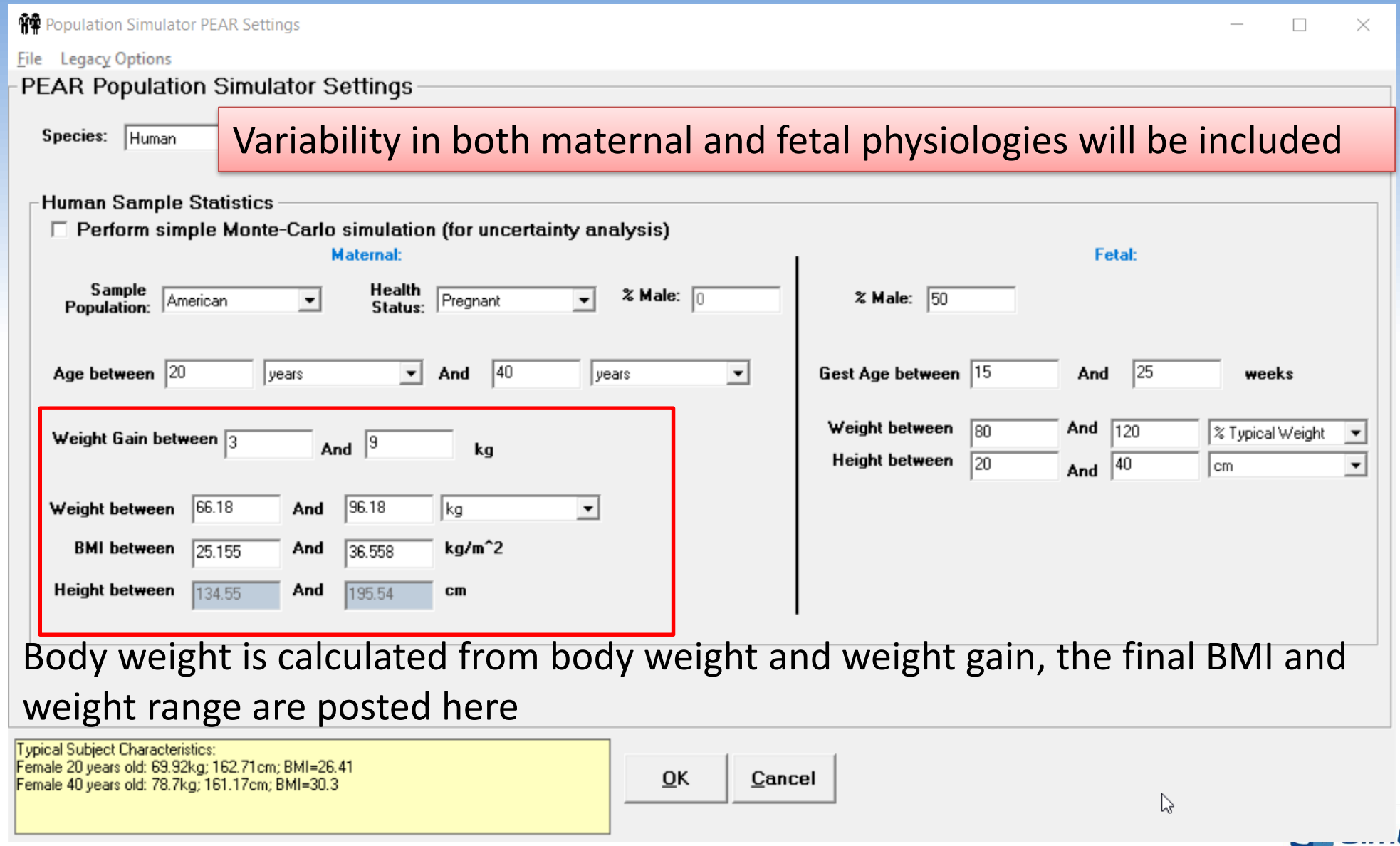
Gestation week = 6 - fetus starts to have heartbeat.

# Population Simulator: Pregnancy




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

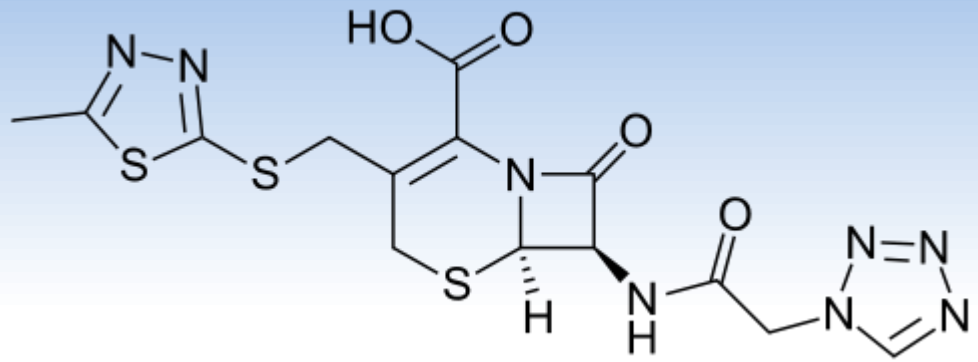
# Population Simulator: Pregnancy




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

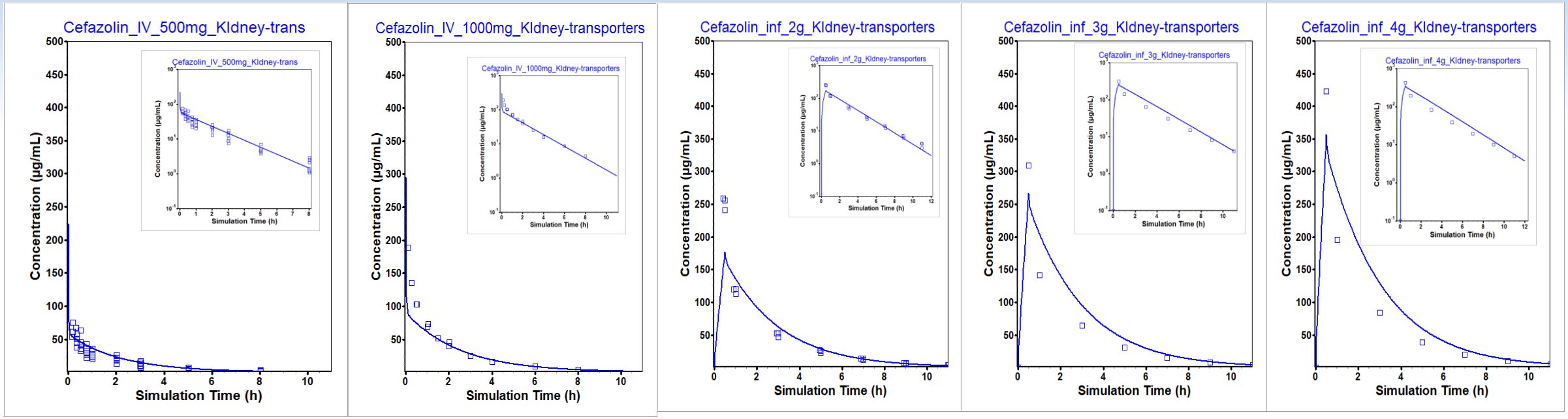
# Example: Cefazolin

- 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 fup*GFR is used.



# Example: Cefazolin

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



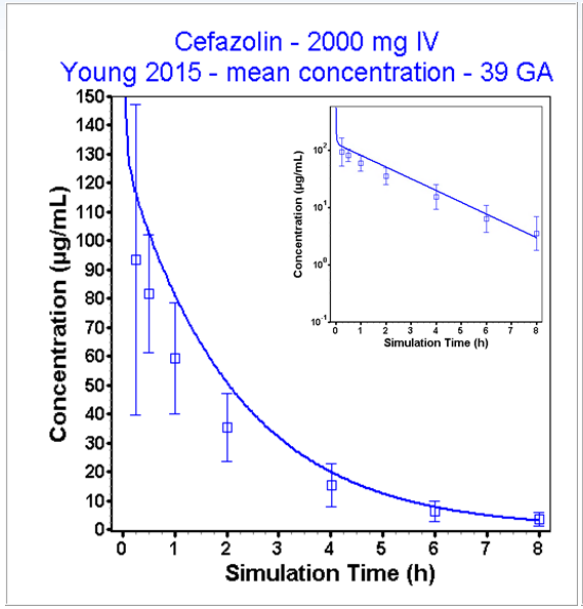

Observed Data: Philipson 1987 → 0.5 g IV; Rattie 1974→ 1 g IV; Smyth 1979→ 2; 3; 4 g IV

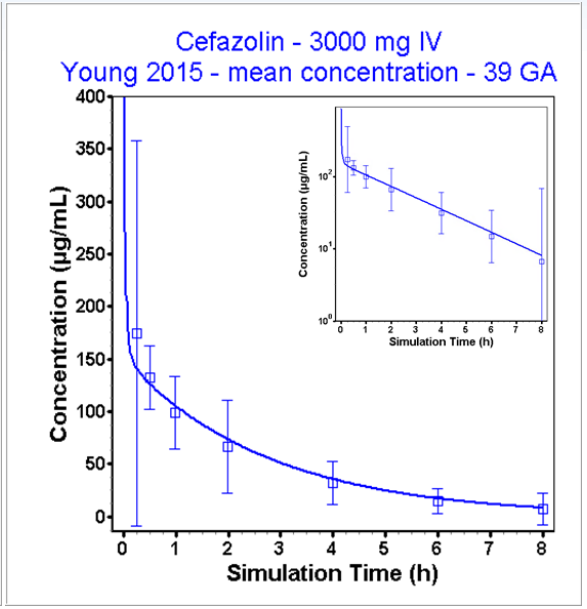
# Example: Cefazolin

Validated model was then used to predict maternal and fetal PK

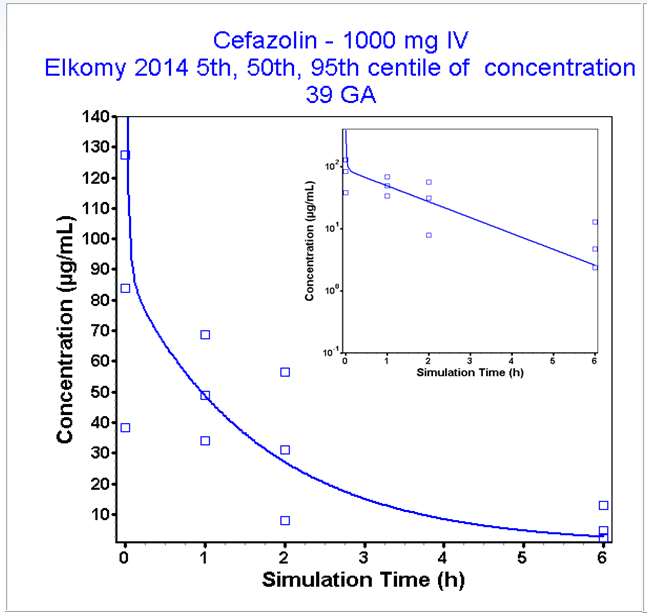
Cefazolin was administered to pregnant women before undergoing cesarean delivery

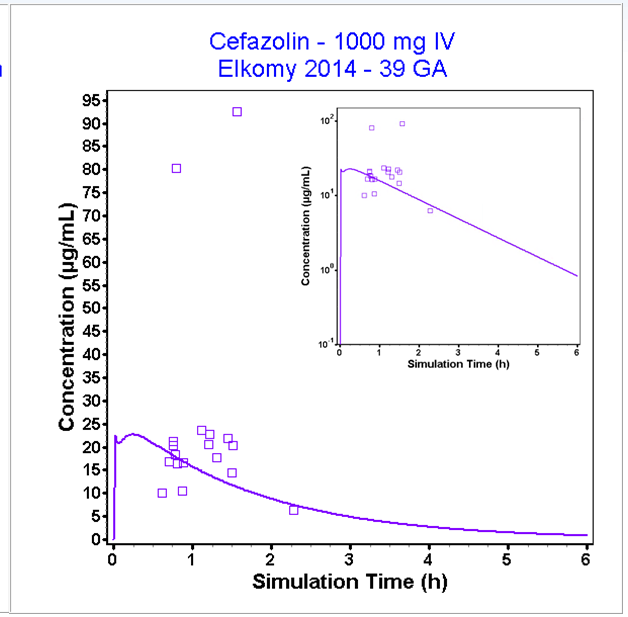
## Maternal plasma




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



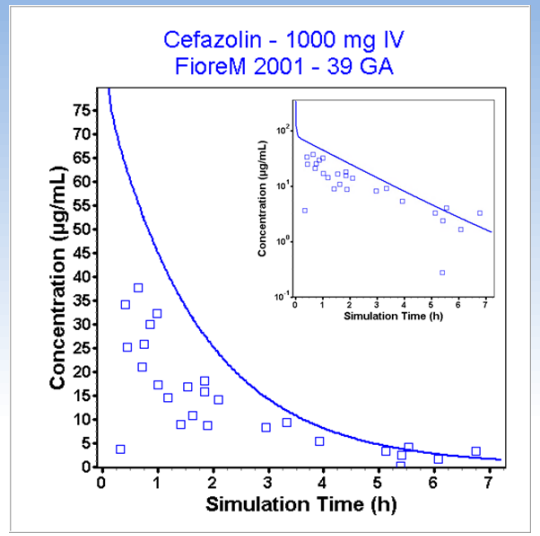



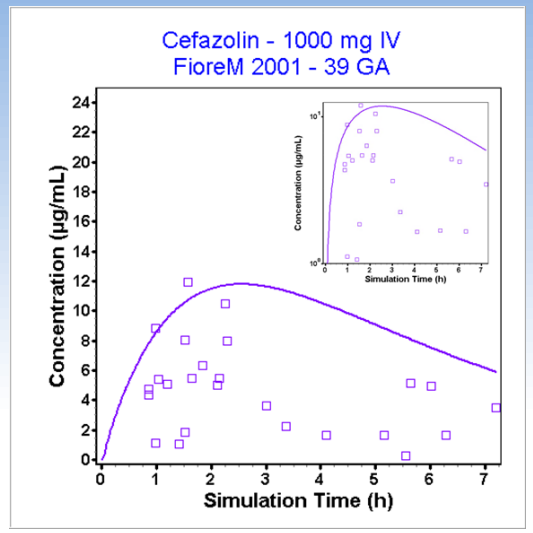

Observed Data: Young 2015; Elkomy 2014

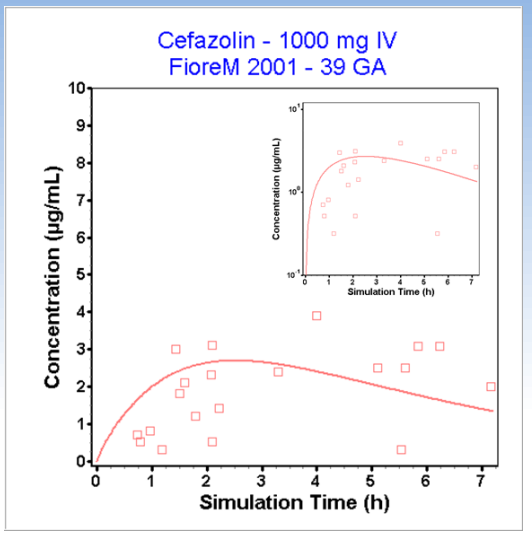
# Example: Cefazolin

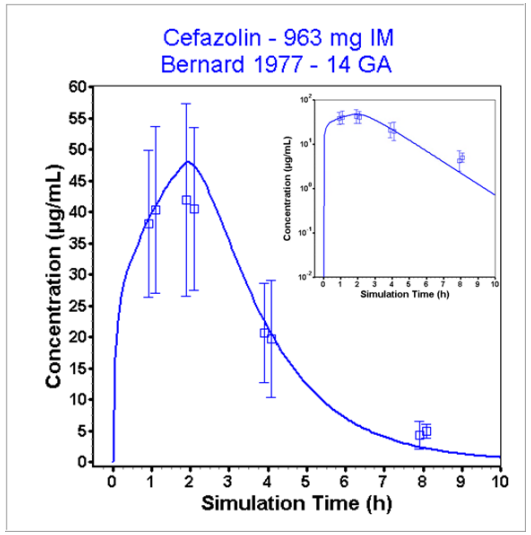
Maternal plasma (left), neonatal plasma (middle), amniotic fluid (right)

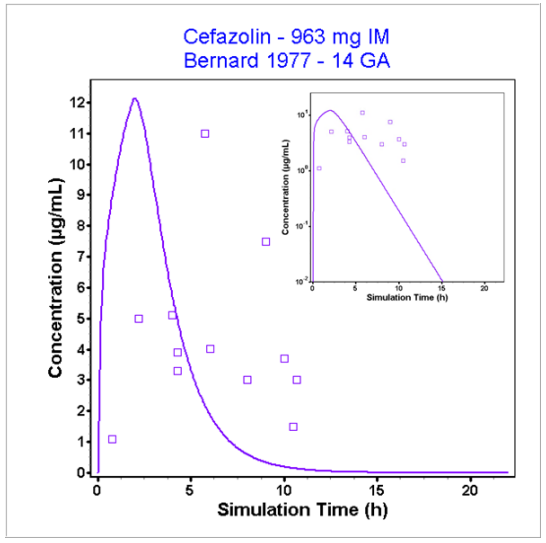
- Validated model was then used to predict maternal and fetal PK
- Cefazolin was administered to pregnant women (IV or IM) before undergoing elective cesarean delivery or hysterectomy

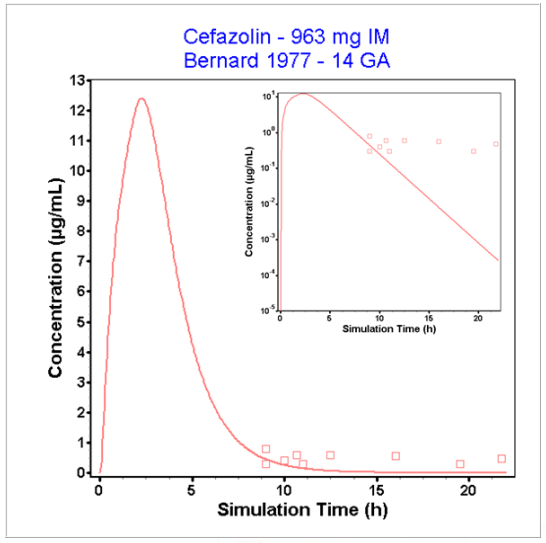



Observed Data: Fiore Mitchell 2001; Bernard 1977

# Lysosomal Trapping: Equation

Lukacova Kp method was extended to include lysosomal compartment

Accumulation in lysosomal water compartment

$$Kpu = V_{ew} + \frac{1/X_{[D],iw}}{1/X_{[D],p}} V_{iw} + \frac{1/X_{[D],Lys}}{1/X_{[D],p}} V_{Lys} + \left( \frac{P \cdot V_{nlt} + (0.3 \cdot P + 0.7) \cdot V_{pht} \cdot}{1/X_{[D],p}} \right) +$$

$$(Fn + Fa) \cdot \left[ \frac{1}{fup} - 1 - \left( \frac{P \cdot V_{nlp} + (0.3 \cdot P + 0.7) \cdot V_{php} \cdot}{1/X_{[D],p}} \right) \right] \cdot RAtp +$$

$$(Fc) \cdot \frac{Ka \cdot [AP]_T}{(1/X_{[D],P})} \cdot \left[ (1 - V_{Lys}) \cdot \frac{X_{[D^+],iw}}{X_{[D],iw}} + V_{Lys} \cdot \frac{X_{[D^+],Lys}}{X_{[D],Lys}} \right]$$

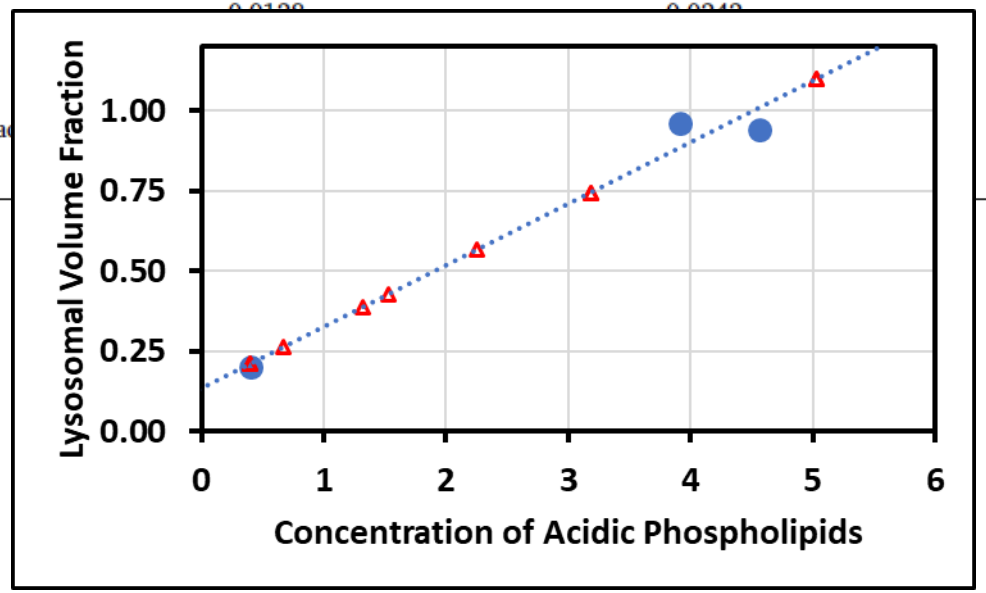
Binding to acidic phospholipids in lysosomes

# Lysosomal Trapping: Parameters

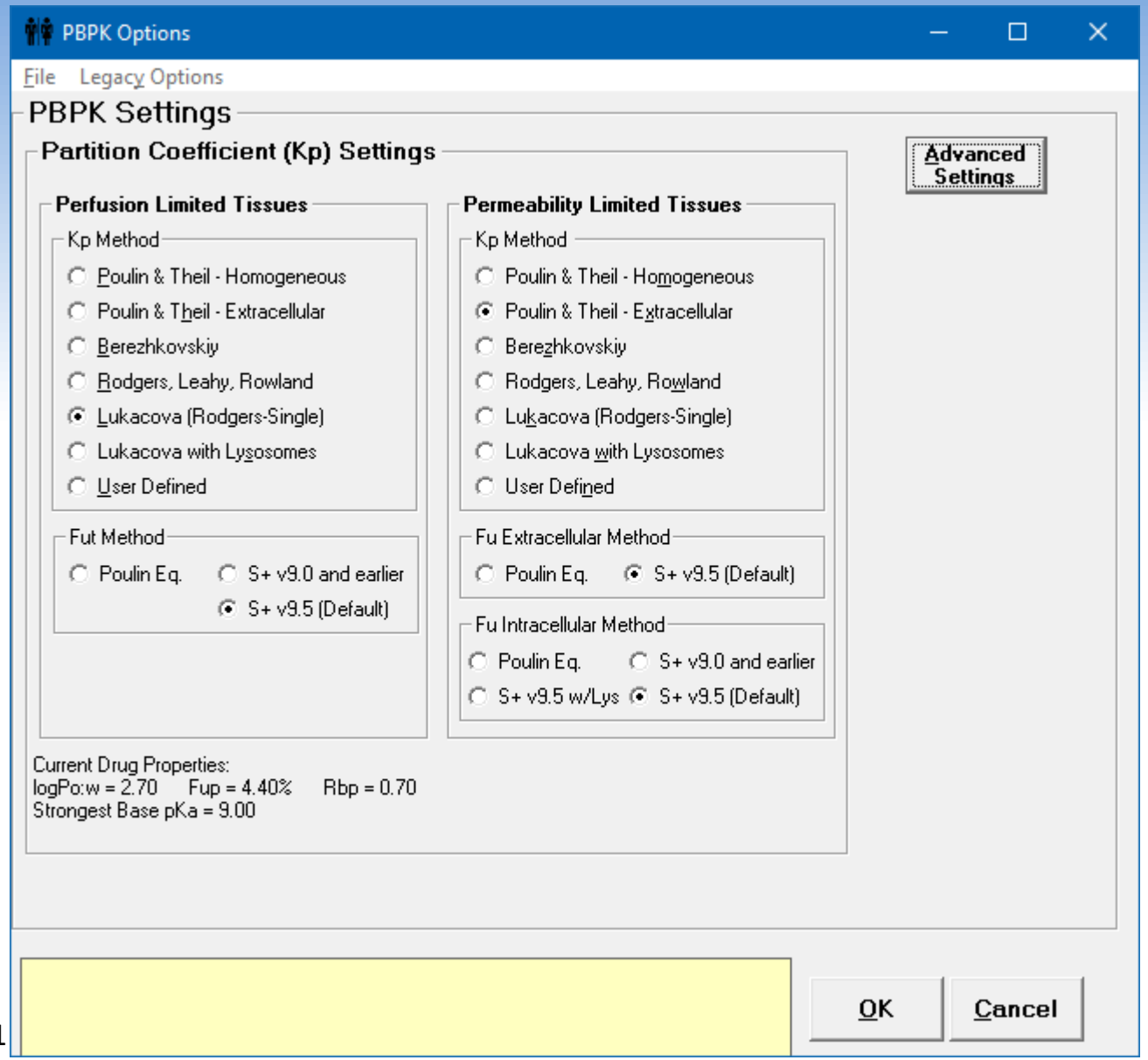
Assmus (Eur J Pharm Sci 2017, 109:419-430) summarized measured properties for lysosomal compartment in lung and liver and that information was used as basis to parameterize lysosomal compartments in all tissues

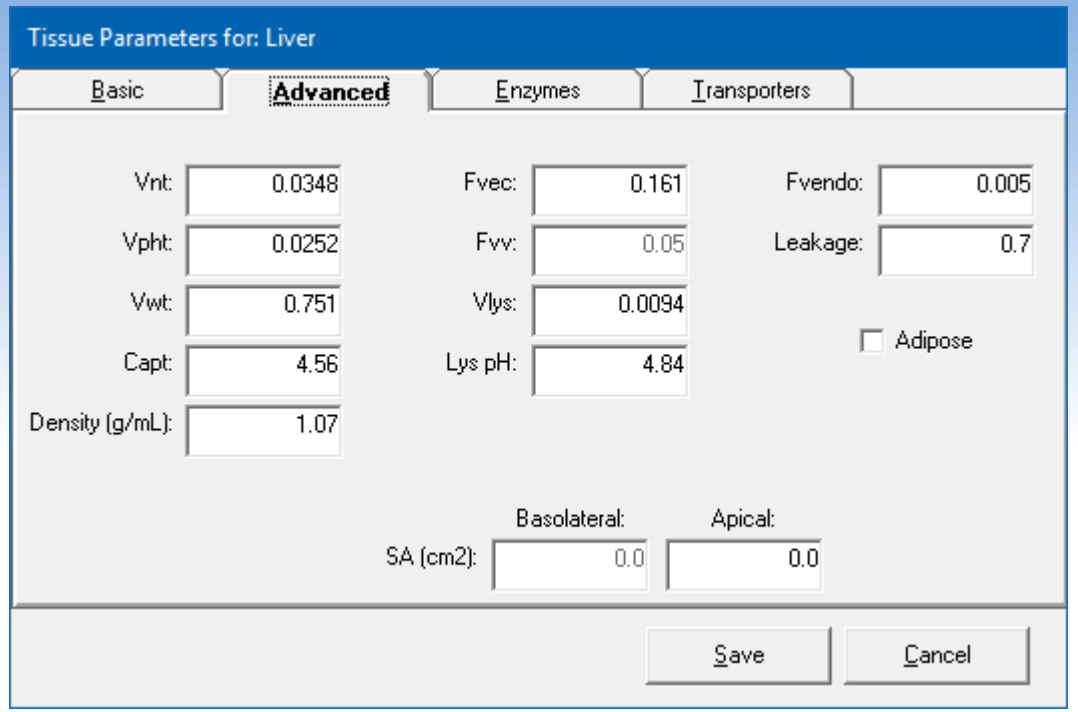
Table 1
Tissue-specific input parameters for the extended Rodgers model used to predict *Kpu* values in lung, kidney and liver in rat.

| | 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[a] | 8.3[a] | 87.6[a] | 100 | 77.8[b] | 2.1[b] | 2.8[b] | 1.4[b] |
| $f_{lys}$ [%] | 7.8[c] | 3 | 1 | 1.2[d] | 0.82[e] | 13.57[e] | 6.86[e] | 0.23[e] |
| $pH_{lys}$ | 4.75[f] | 5.1[g] | 5.1 | 5.1[h] | 4.72[i] | 4.94[j] | 5.1 | 5.1 |
| Fractional tissue volume (total tissue)[k] | | | | | | | | |
| $f_{NL}$ | | 0.022 | | 0.012 | | | 0.014 | |
| $f_{NP}$ | | | | | | | 0.0240 | |
| $f_{EW}$ | | | | | | | 0.161 | |
| $f_{IW}$ | | | | | | | 0.573 | |
| Tissue concentration of ac | | | | | | | | |
| $AP^-$ [mg/g] | | | | | | | 4.56 | |



# Lysosomal Trapping: Implementation



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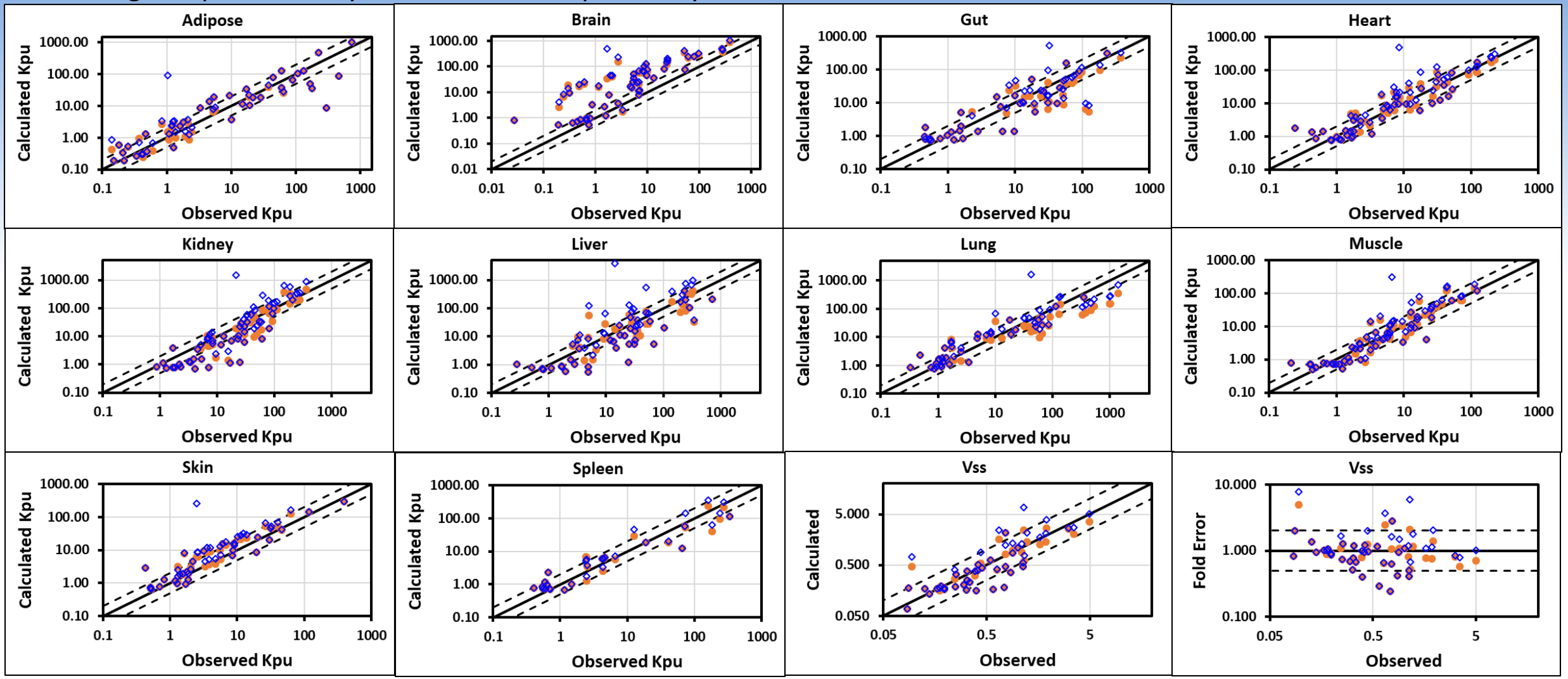
# Lysosomal Trapping: Validation

Orange – Kps without lysosomes; blue – Kps with Lysosomes




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



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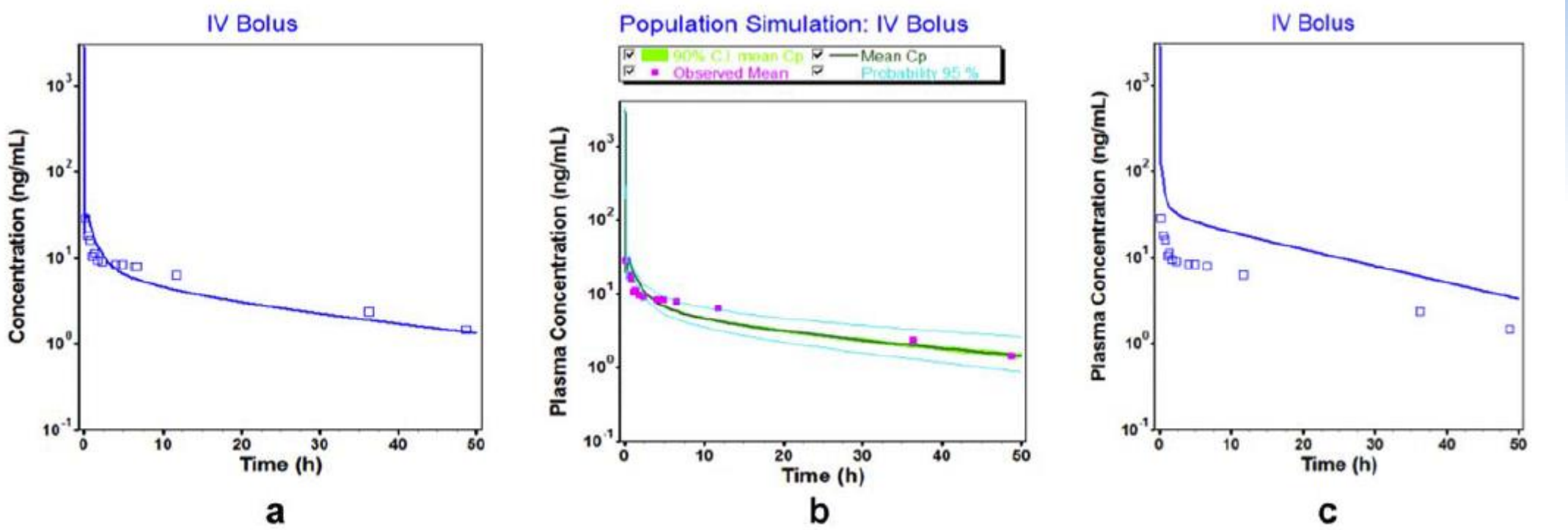
# Lysosomal Trapping: Validation

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

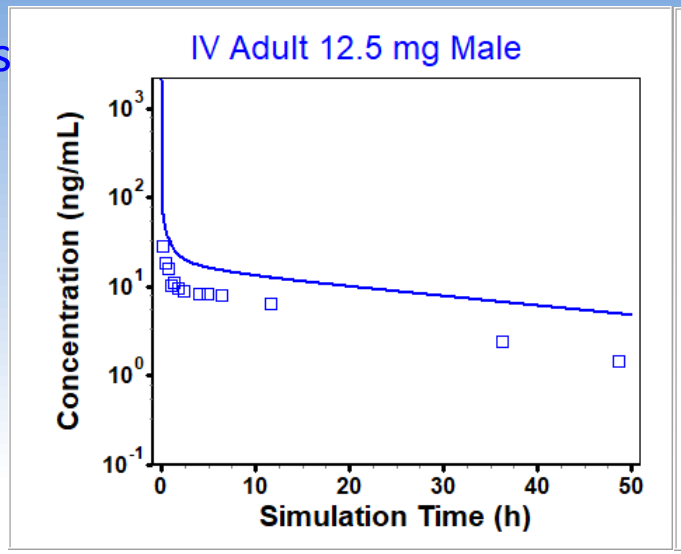


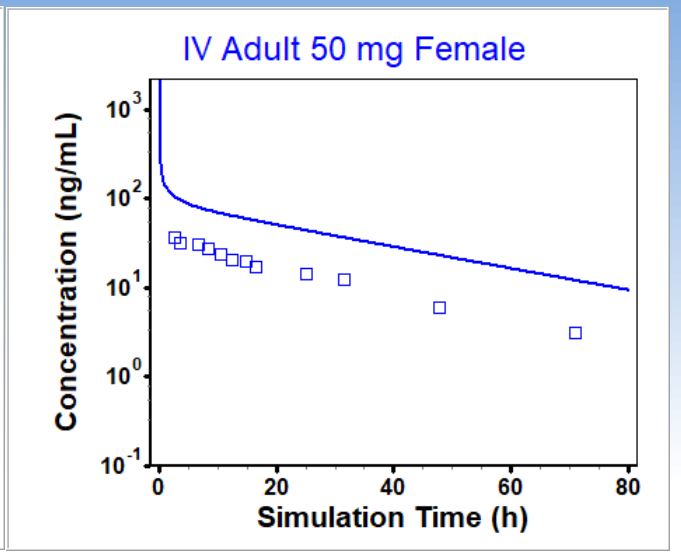

Samant – CPT: PSP 2017, 6, 315-321

# Lysosomal Trapping: Validation

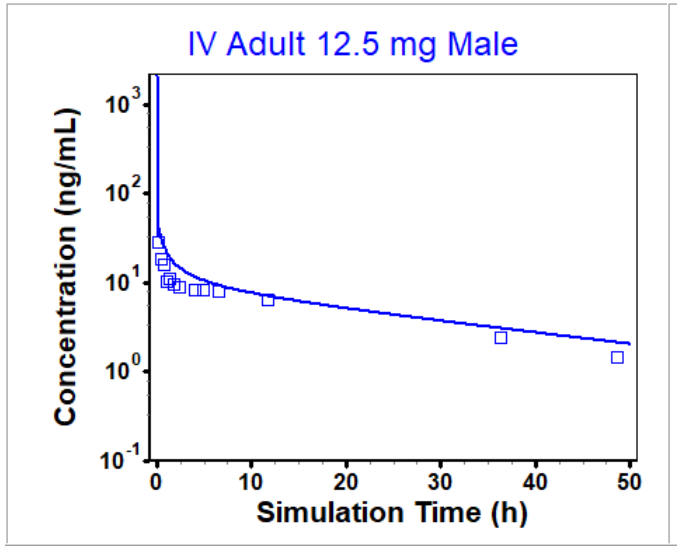
- Updated B/P ratio to experimental values (Bogema, 1974, PhD dissertation, Virginia Commonwealth University
- Calculated Kps with default Kp method without lysosomal trapping (top) and new method with lysosomes (bottom).

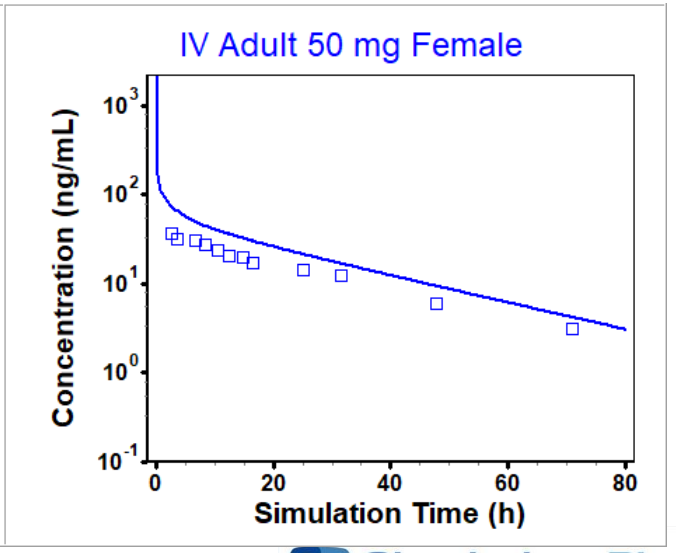
Without Lysosomes



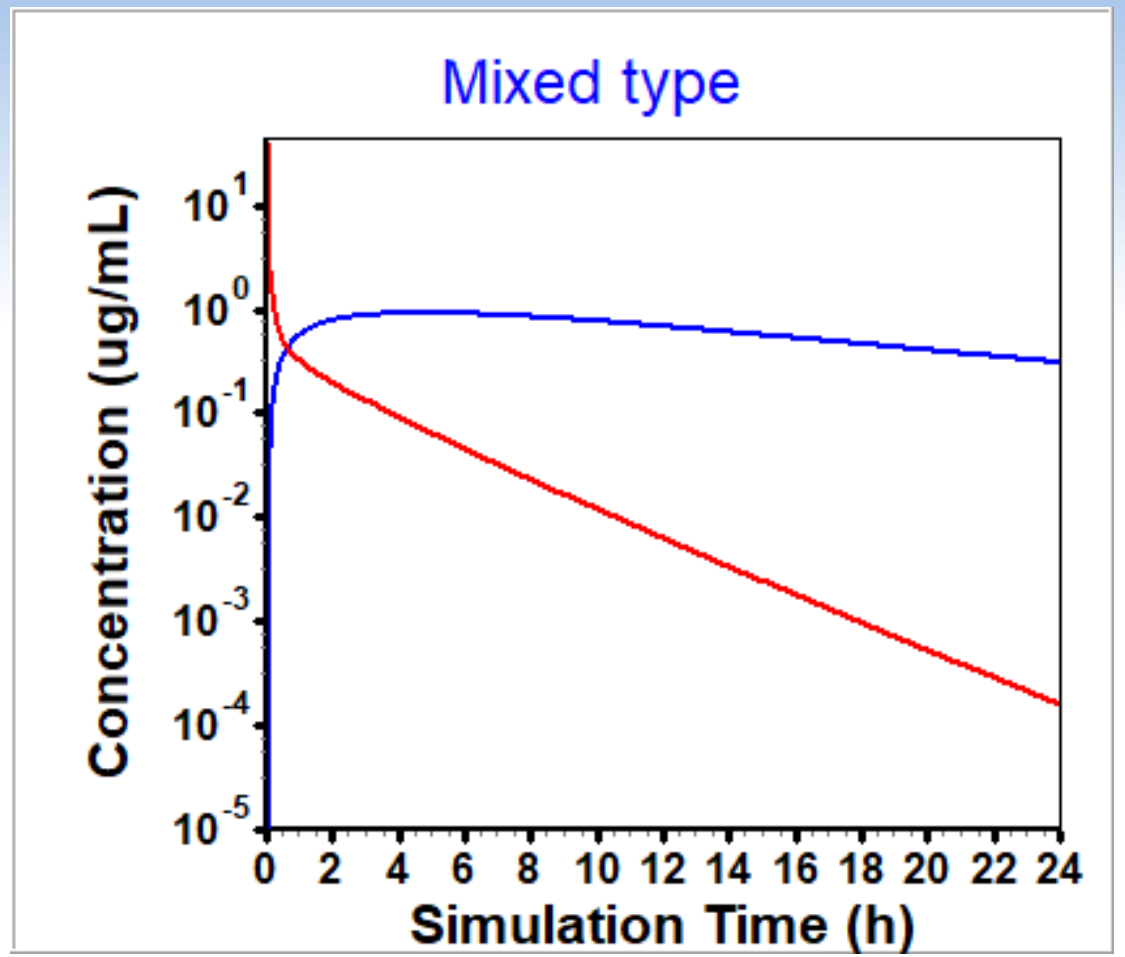

With Lysosomes

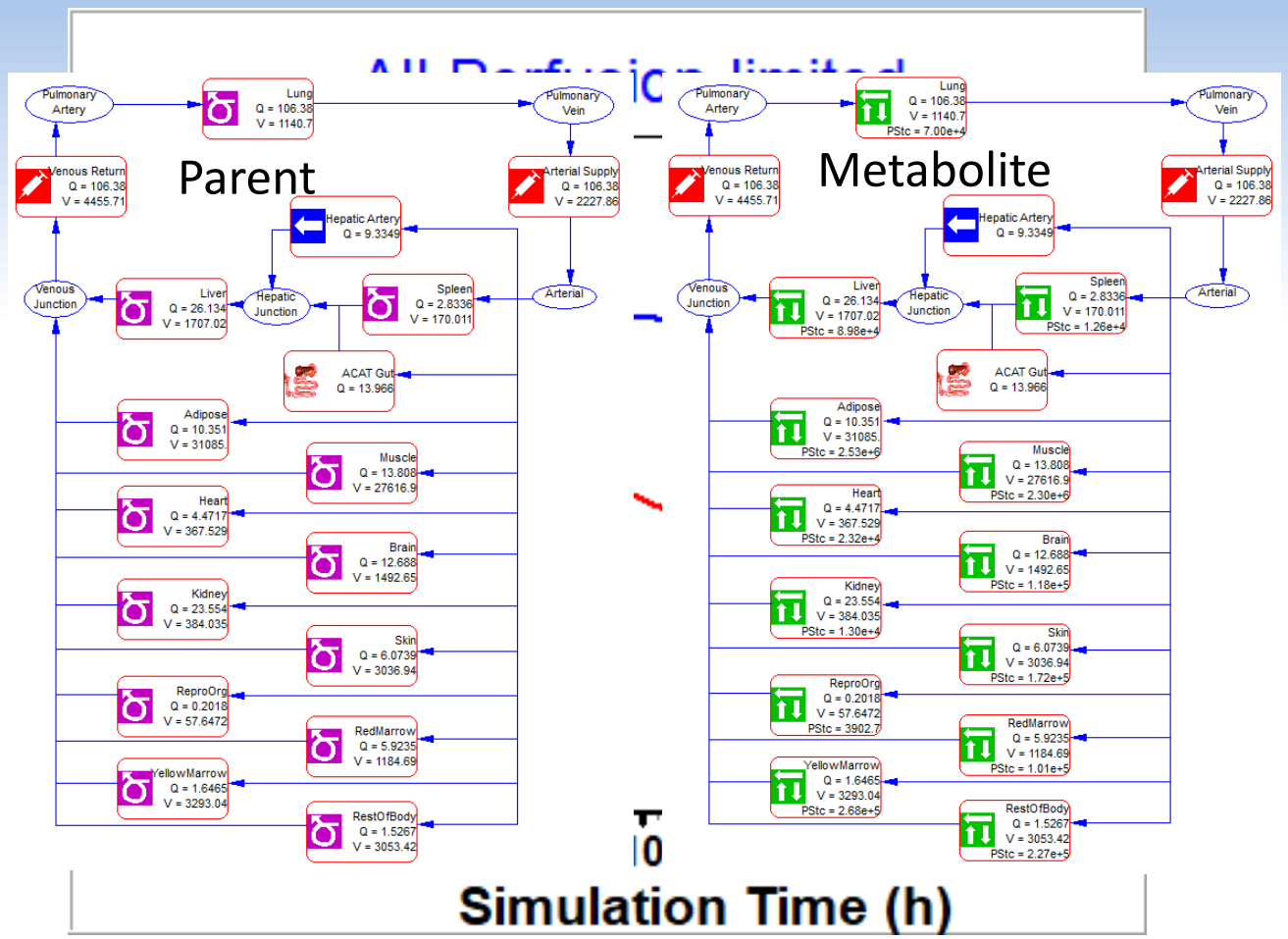


# Mixing Tissue Types

Parent compound – good tissue distribution
Metabolite – polar molecule with slow diffusion through membranes






blue – metabolite, red – parent

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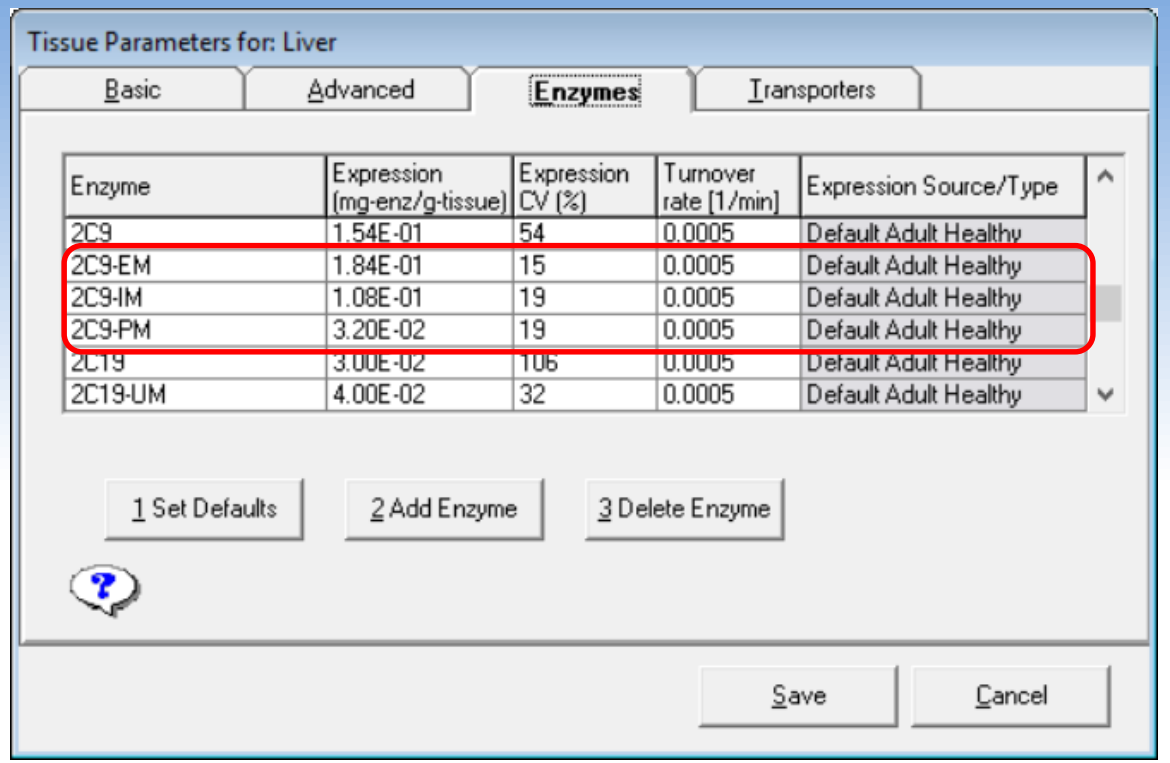
- ADRM Module:
  - API evaporation with transdermal administration
  - Effect of immune response with intramuscular injection
- Others:
  - Flexibility in solubility vs. pH model fitting
  - Updates in Peff converter

# 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

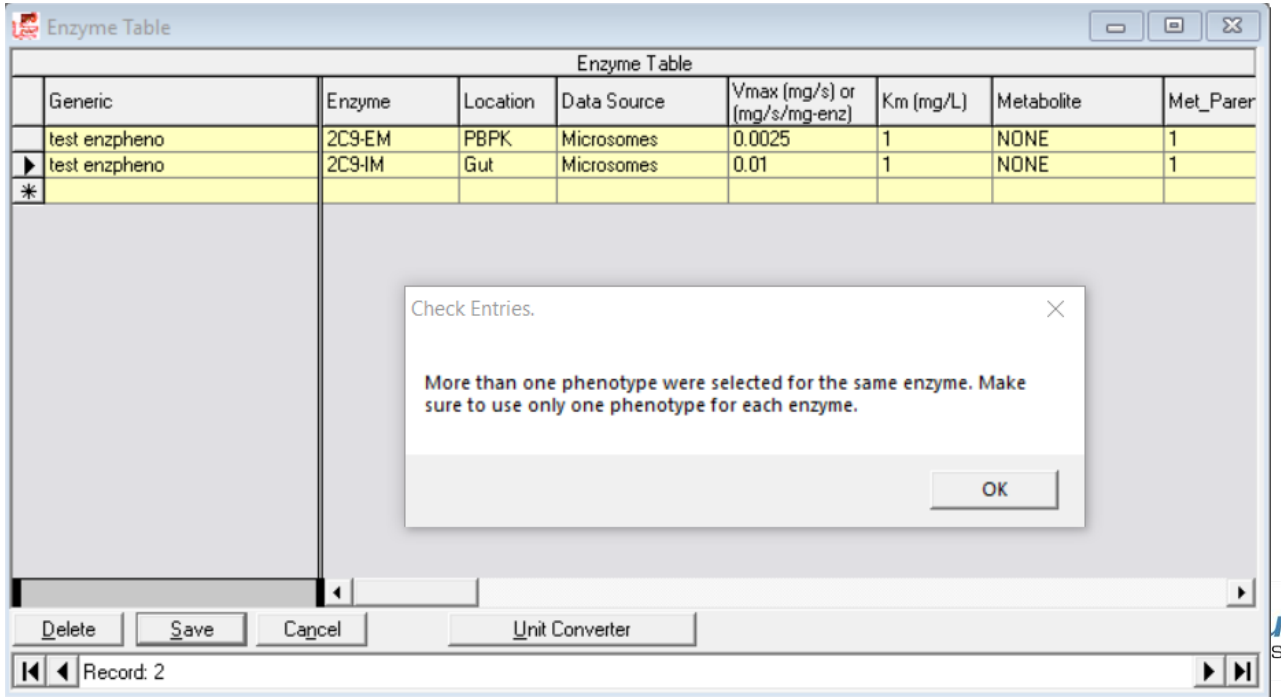
# Create Subject with Different Enzyme Phenotypes




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

Benefit:

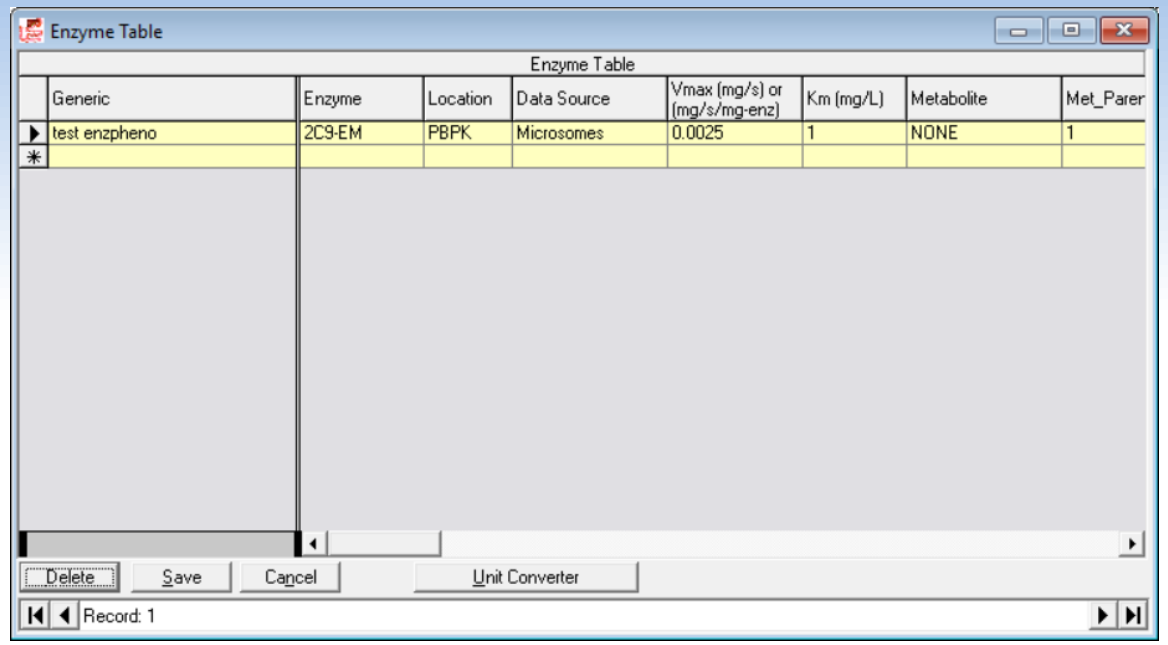
1) Users do not need to pre-select the phenotype of each enzyme for the subject (too many combinations).
2) User could add phenotypes to any enzyme.



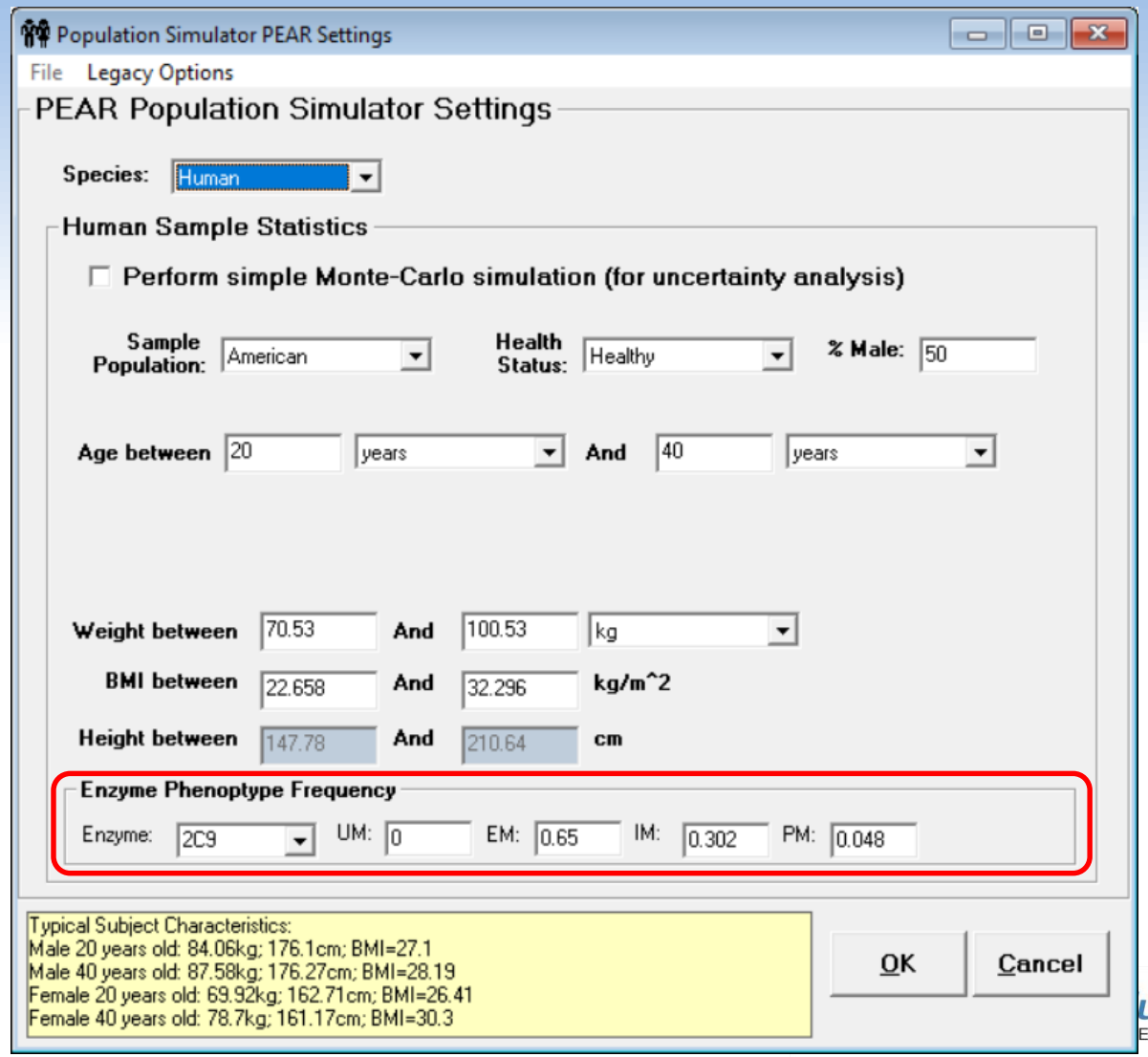

Only one phenotype can be selected for a specific enzyme in given record.

# Population Simulation: Enzyme Phenotypes

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




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 Simulation Results: Enzyme Phenotypes

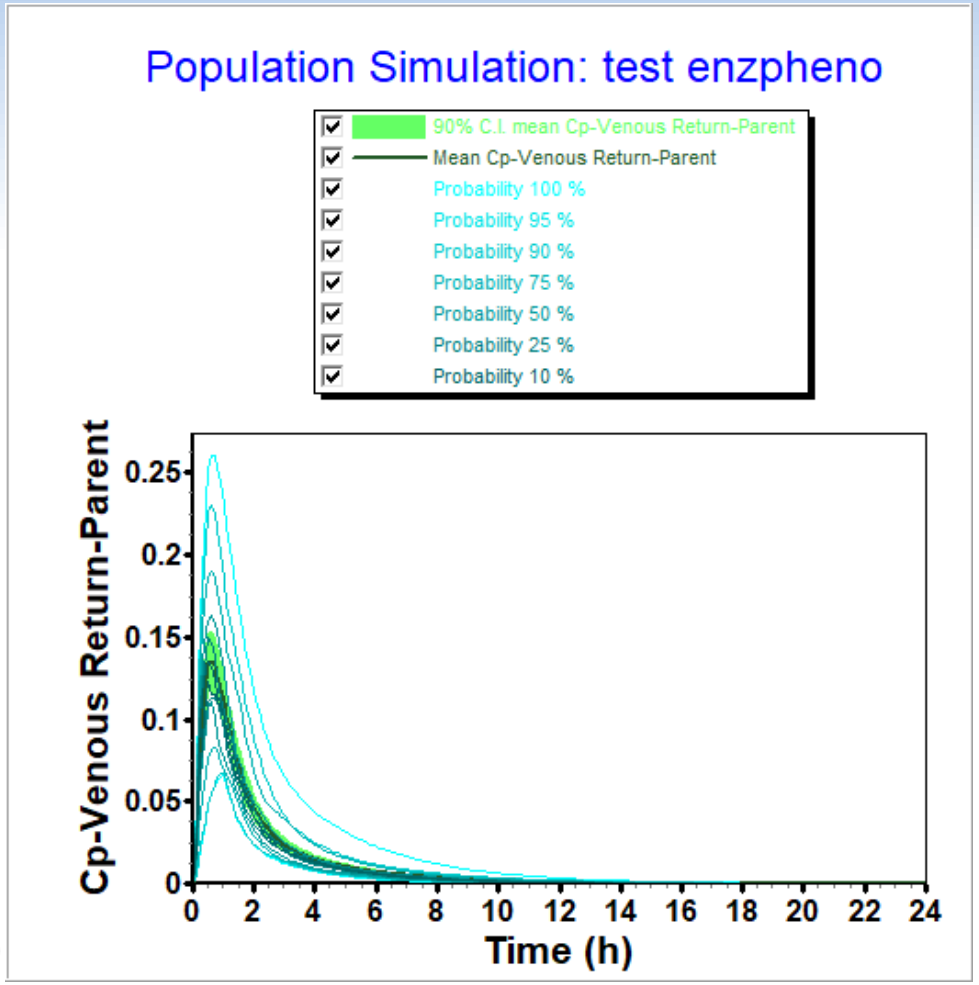
Scenario 1:

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 Phenoptype Frequency**

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




Subject parameters and results

| Subject Nu | Subject Ag | Subject We | 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

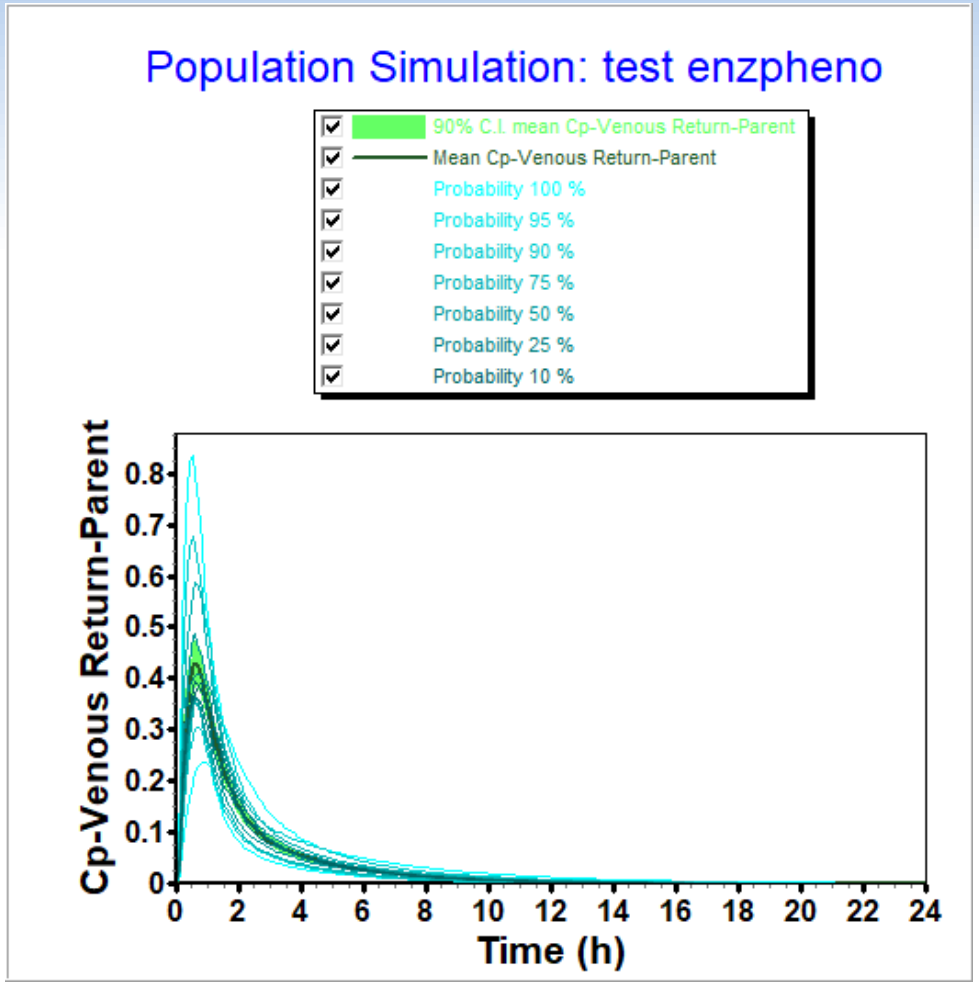
Scenario 2:

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 Phenoptype Frequency**

Enzyme: 2C9 UM: 0 EM: 0 IM: 0 PM: 1




Subject parameters and results

| Subject Nu | Subject Ag | Subject We | 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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  - 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
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  - API evaporation with transdermal administration
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- 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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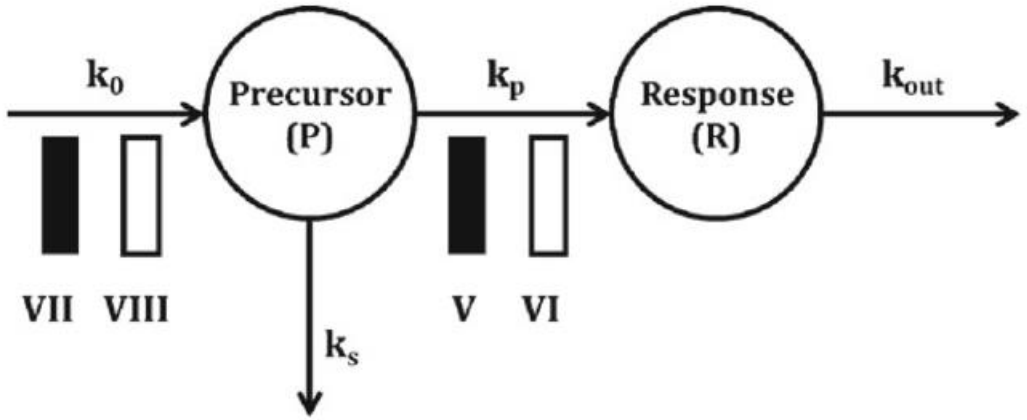
# New PD Model
# (Precursor – dependent Indirect Model)




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

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

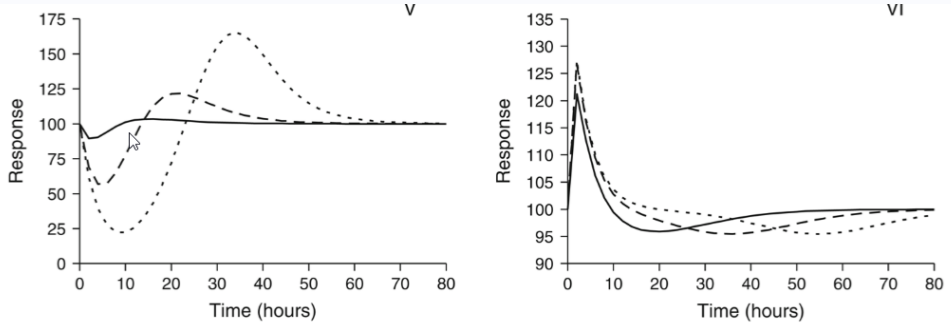
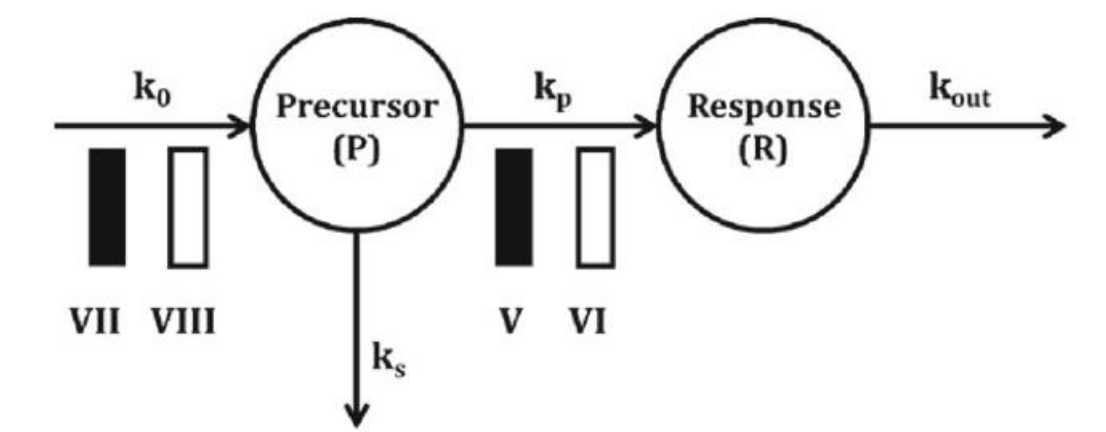



**Fig. 6.**
Multiple compartment indirect response models (*top panel*) and signature profiles for Models V and VI (*bottom panel*). Response curves were simulated using Eqs. 11 and 12 driven by drug concentrations following monoexponential disposition: $C_p = C^o e^{(-kt)}$. $C^o$ was set to 10, 100, 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, $k_o = 25$ 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.

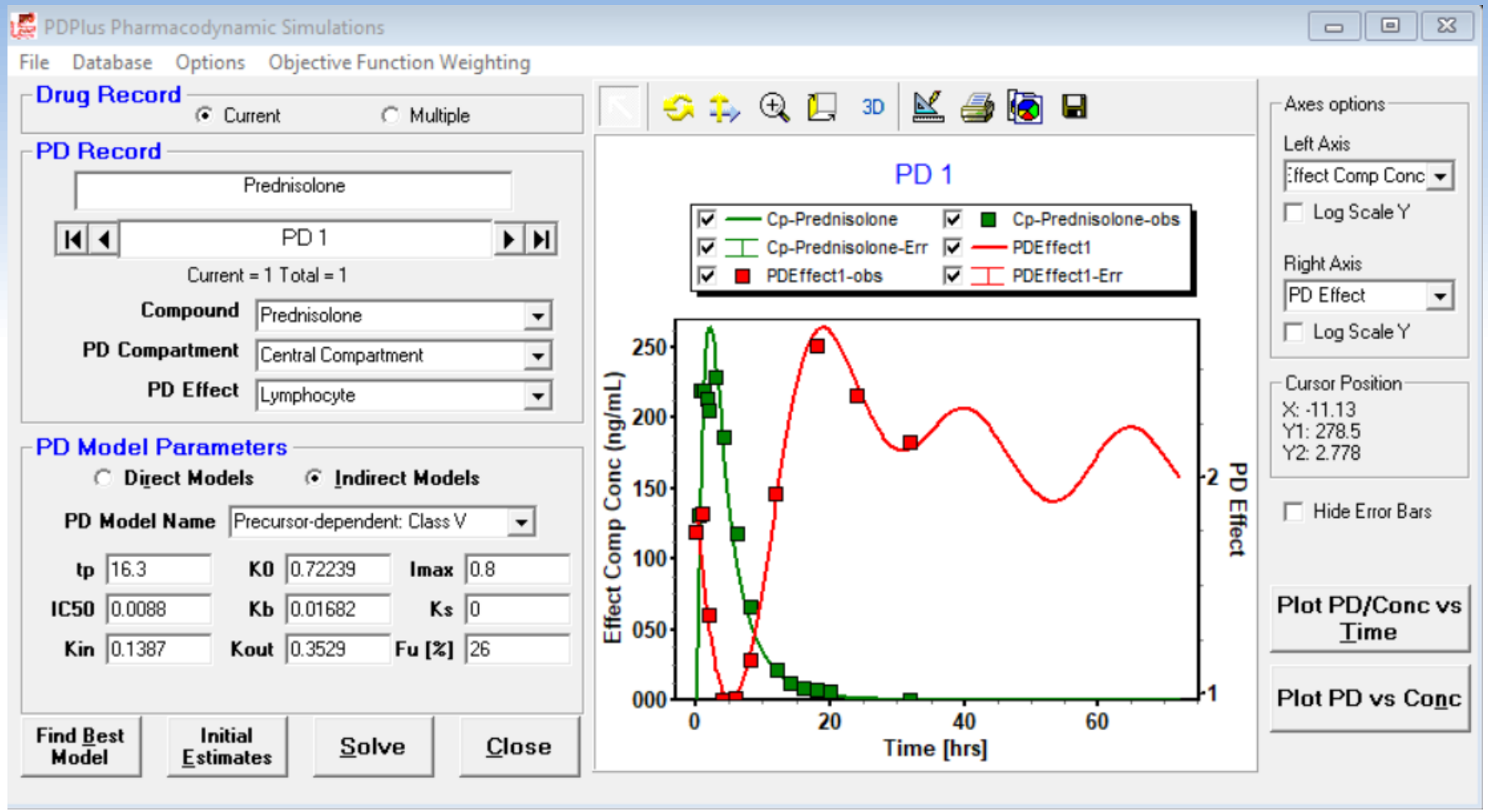
From Felmlee et al. (2012)

# 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




Experimental data from Magee et al. (2002)

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  - Allow different tissue model types (perfusion- or permeability-limited) for different compounds in simulation
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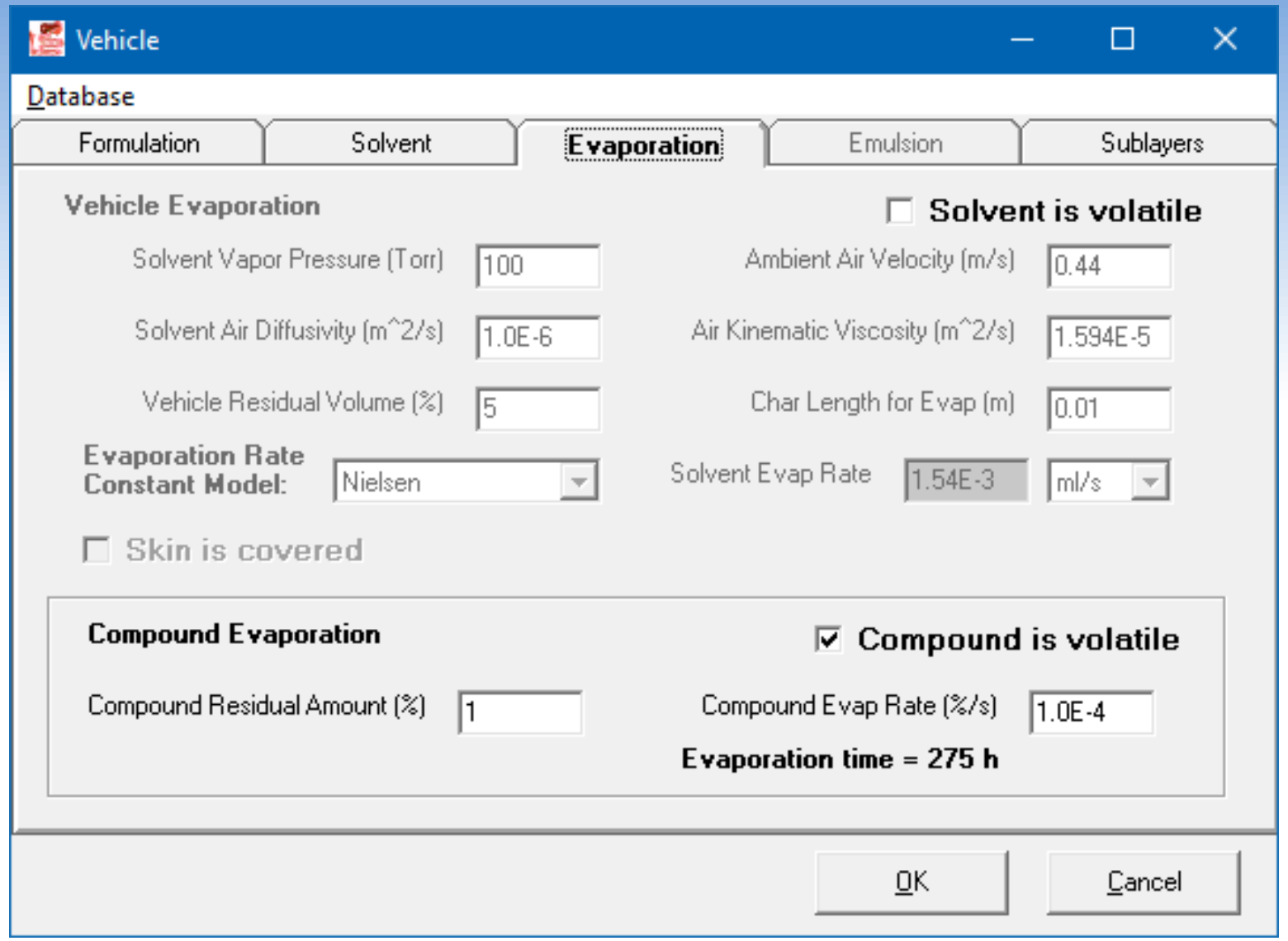
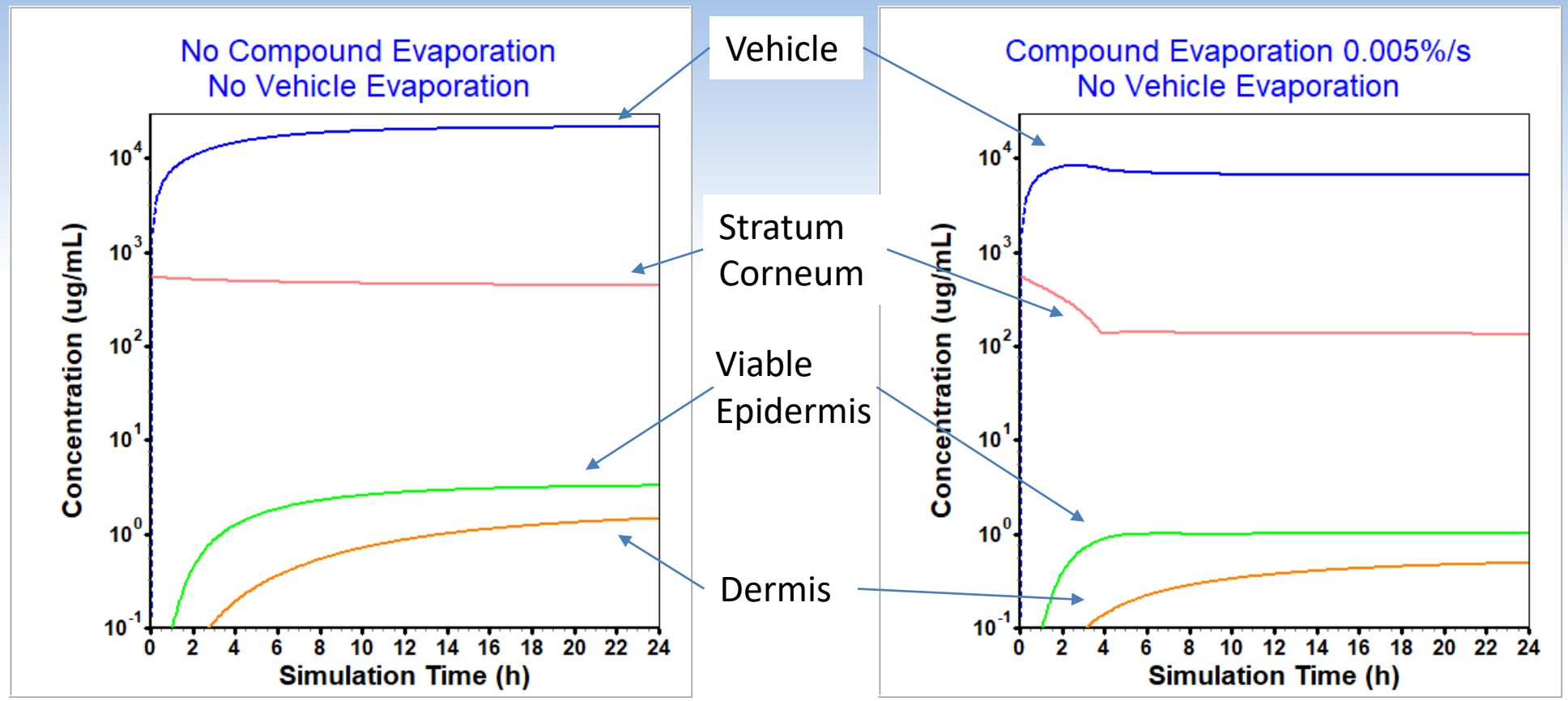
  - Effect of immune response with intramuscular injection
- Others:
  - Flexibility in solubility vs. pH model fitting
  - Updates in Peff converter

# Transdermal: API Evaporation



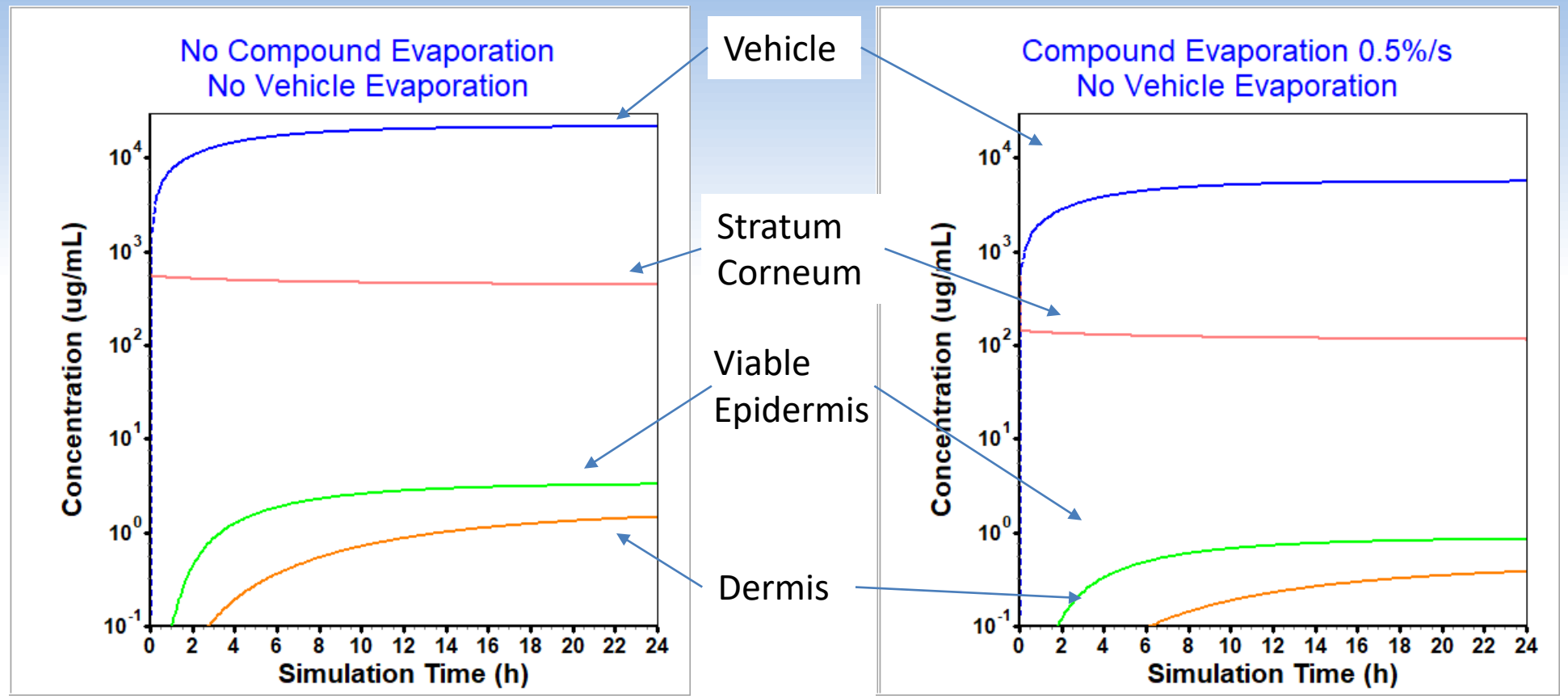
# Compound Evaporation

Dissolved drug concentration in:



# Compound Evaporation

Dissolved drug concentration in:



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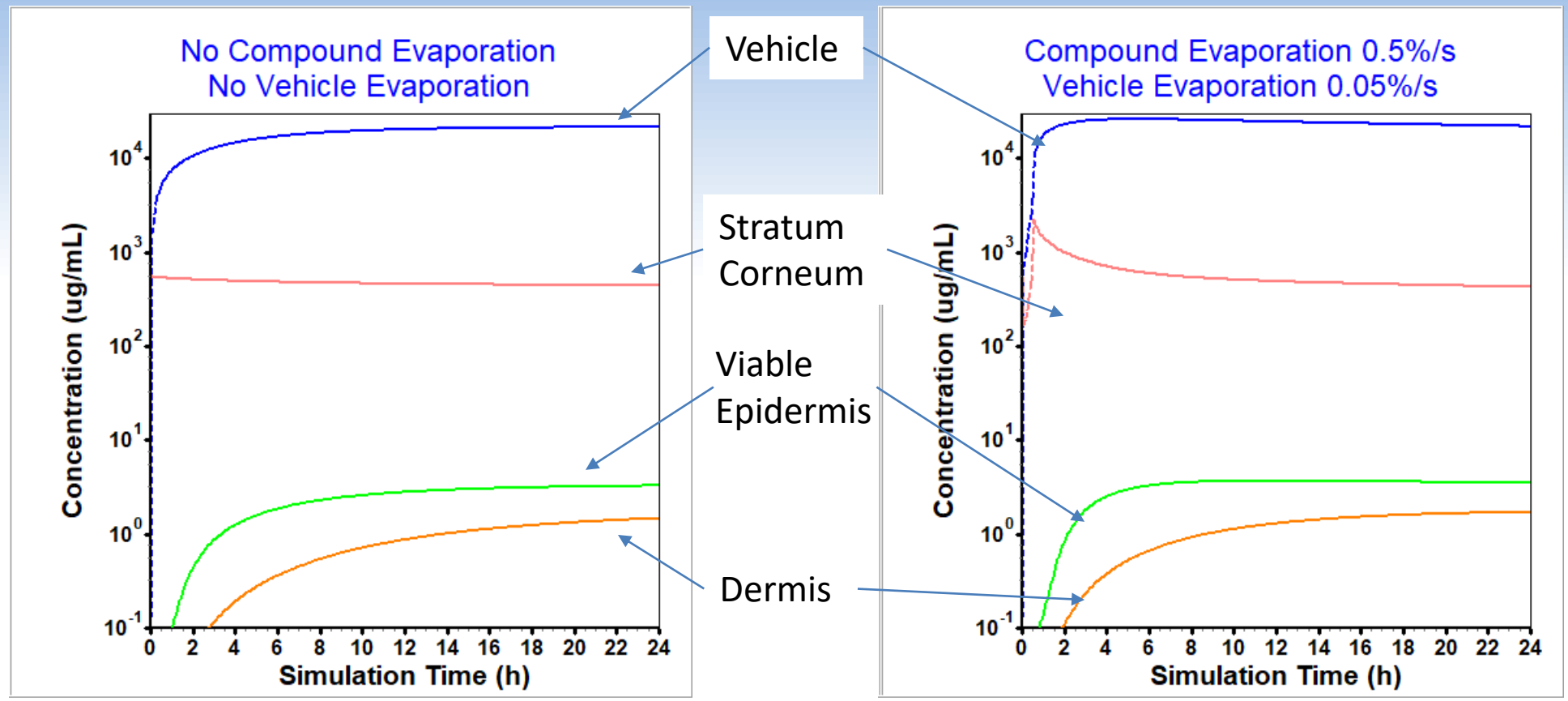
# Compound Evaporation

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

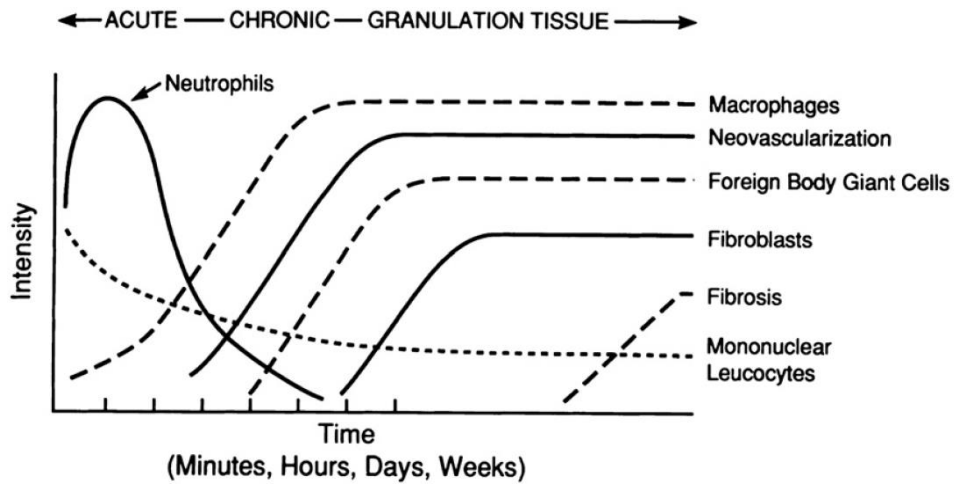
Occurs within one week following administration and is characterized by the presence of neutrophils in the area of the injection or implant.

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

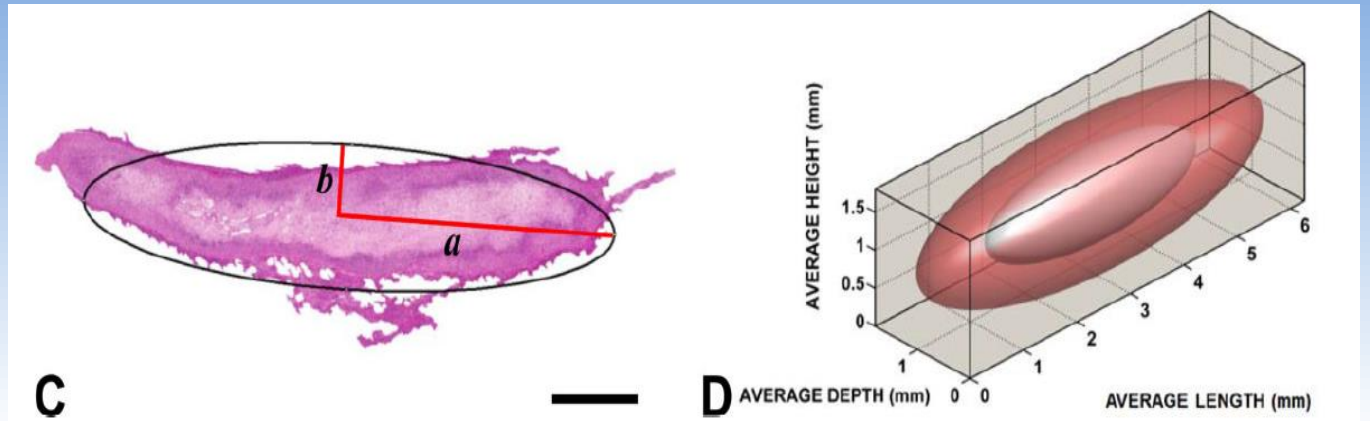
Fibroblasts infiltrate the site and collagen deposition is initiated to form a fibrous capsule. Neo-angiogenesis is also observed during this period



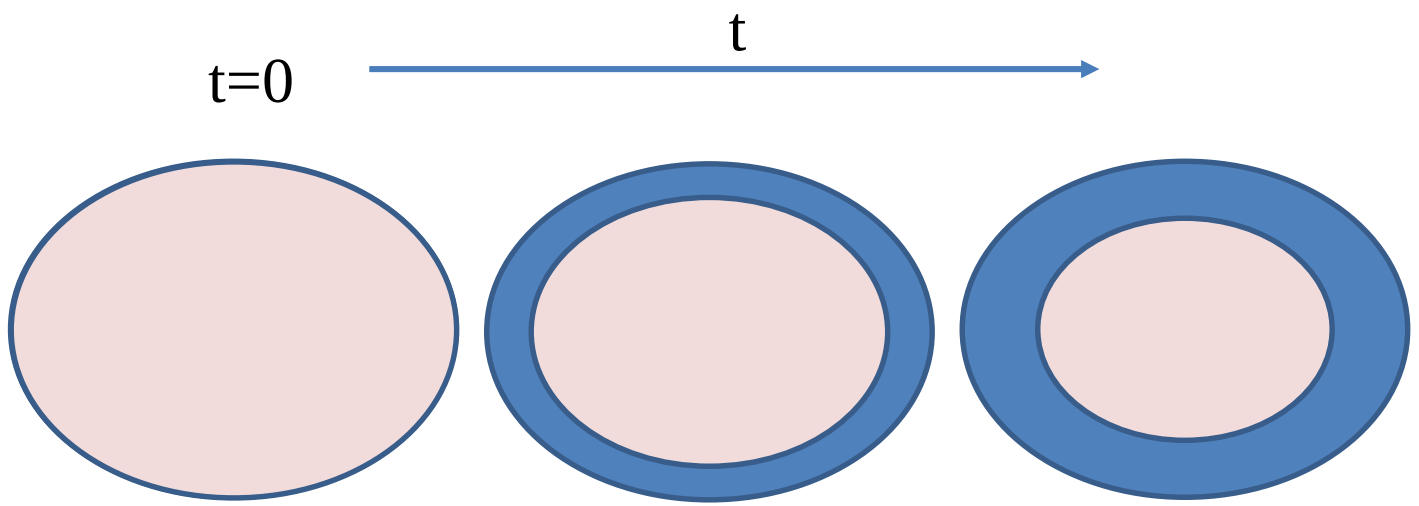

*The temporal variation in the three phases of inflammatory response resulting from administration of biodegradable microspheres*

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

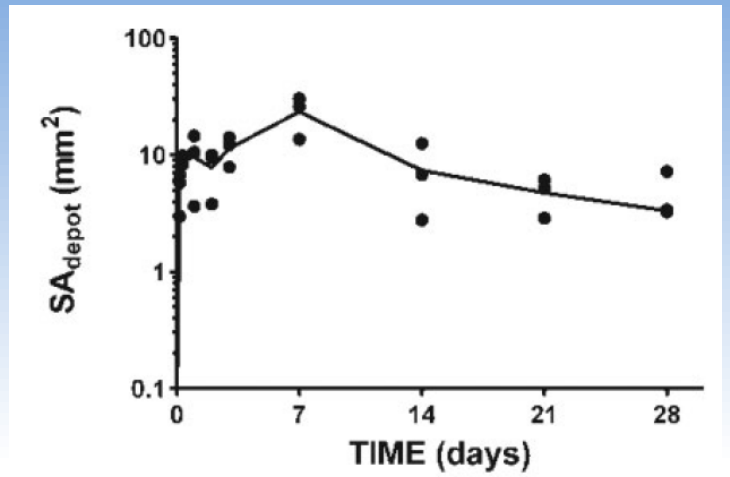
# Intramuscular: Immune Cell Layer



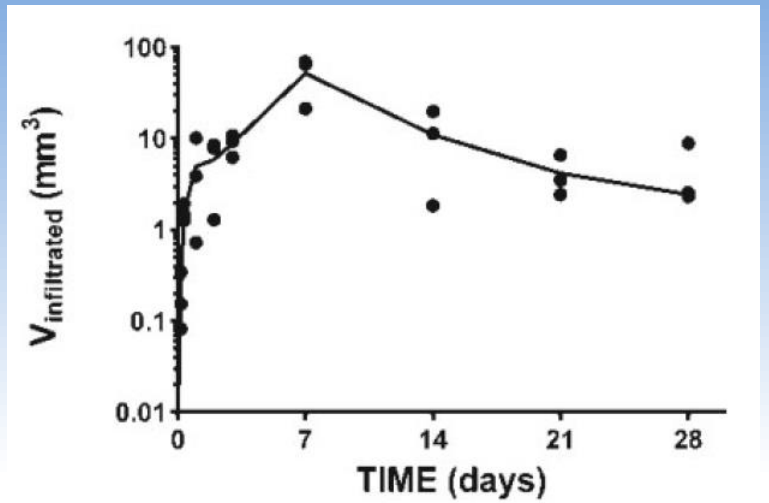

Darville et al, Toxicologic Pathology, 2016, Vol. 44(2) 189-210



# Intramuscular: Immune Cell Layer

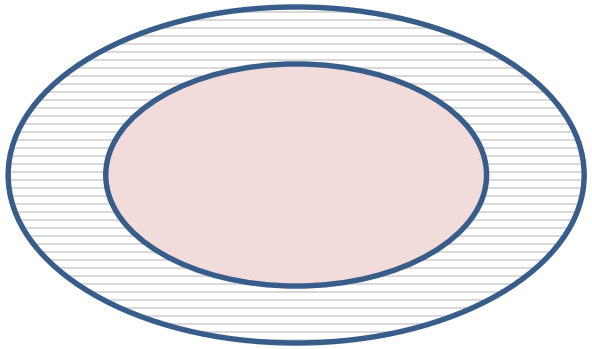


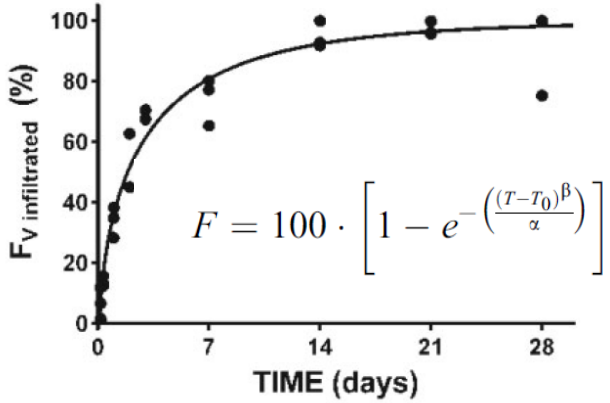

The temporal evolution of $V_{infiltr.}$ was analogous to that of $S_{depot}$




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

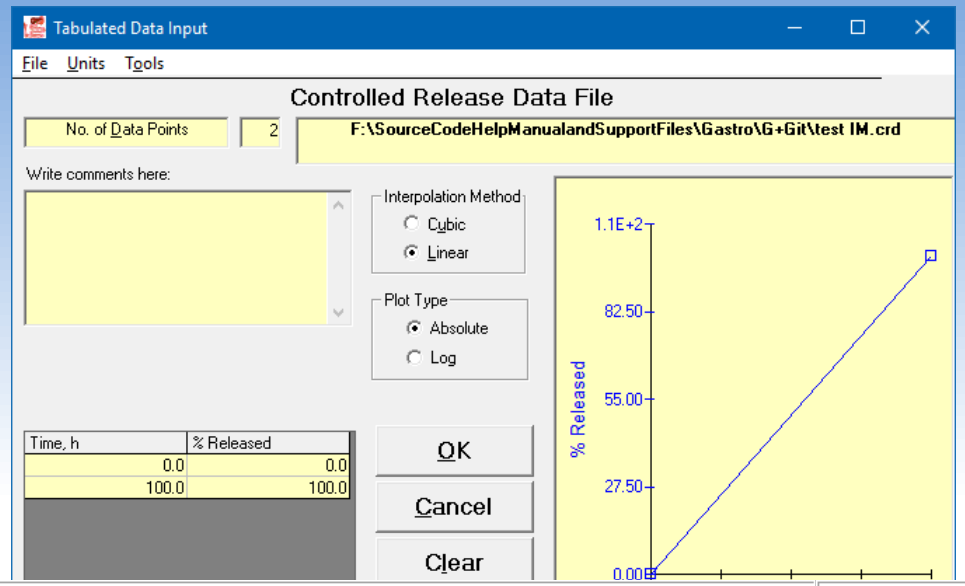
The calculated net volumes of the PP-LAI and PS formulation depots that were infiltrated by inflammatory cells ($V_{infiltr.}$)

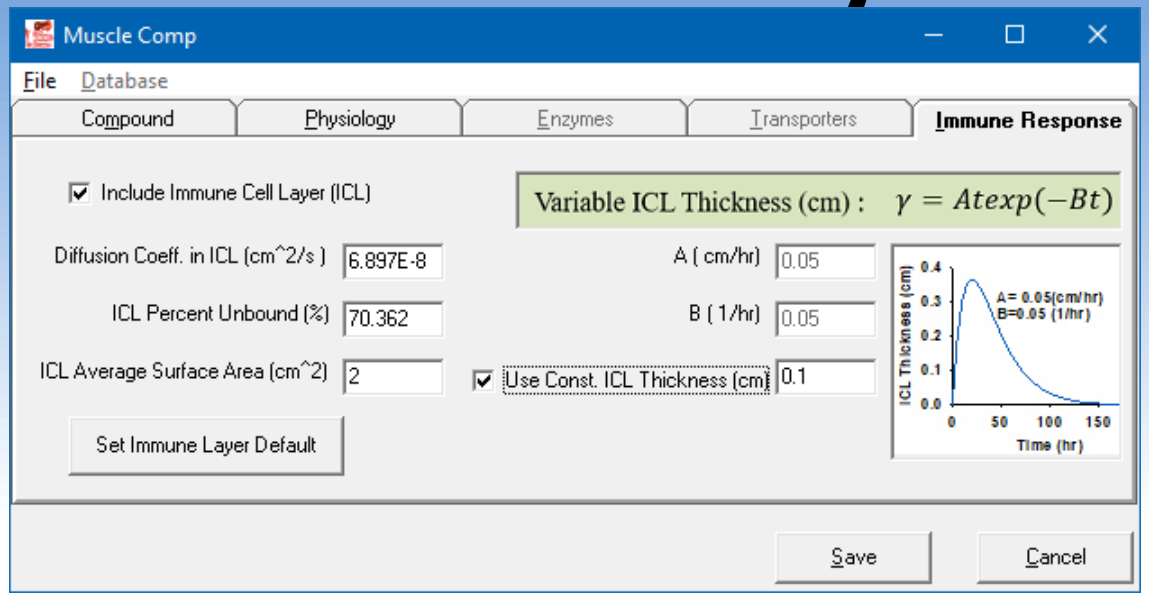


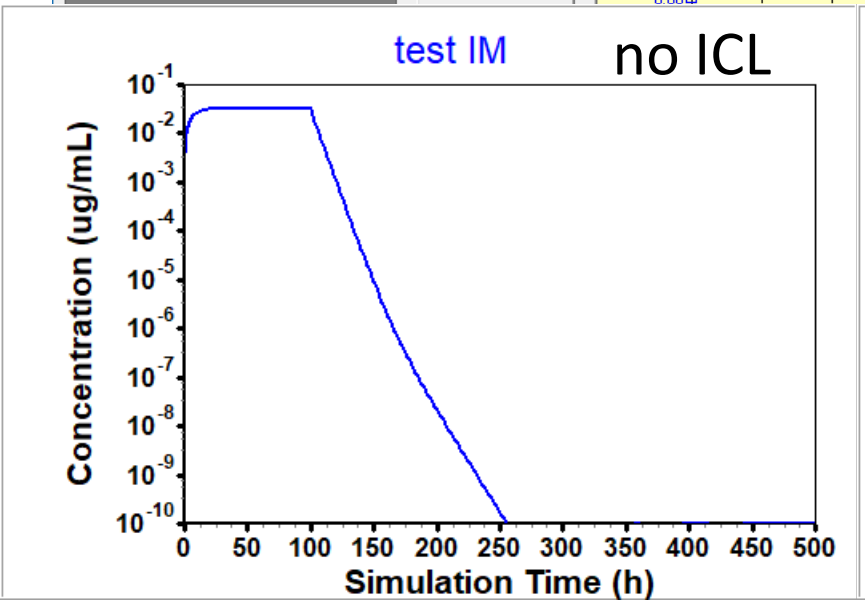


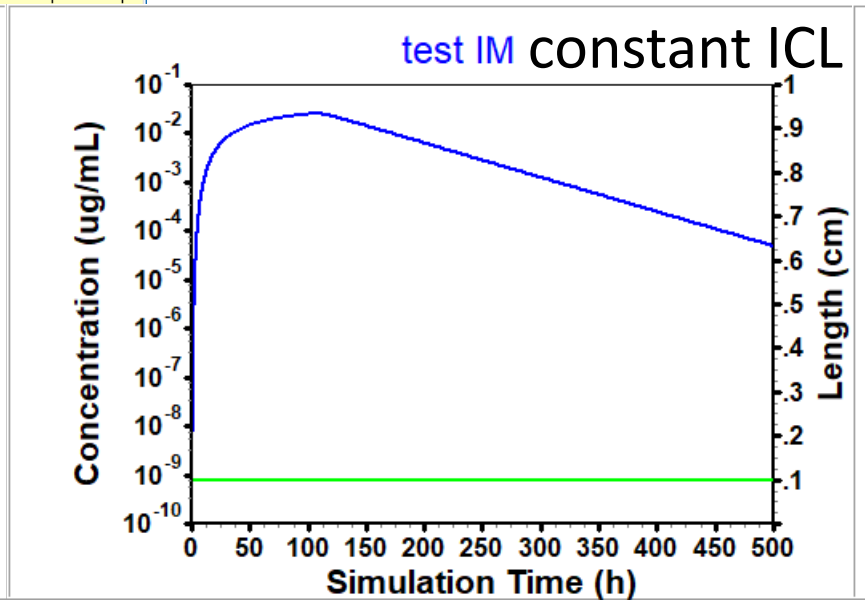

$F_{v,infiltr}$= the ratio of $V_{infiltr.}$ over $V_{depot}$;

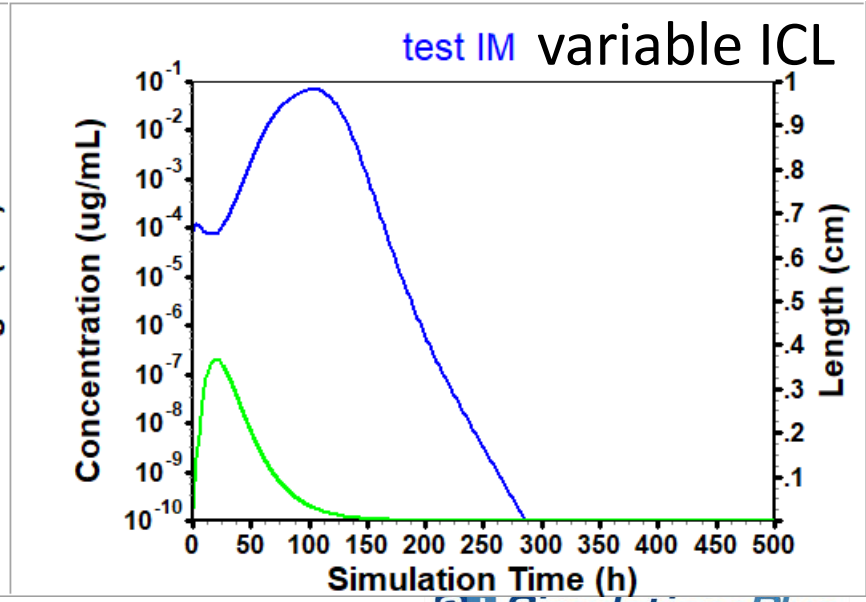
# Intramuscular: Immune Cell Layer



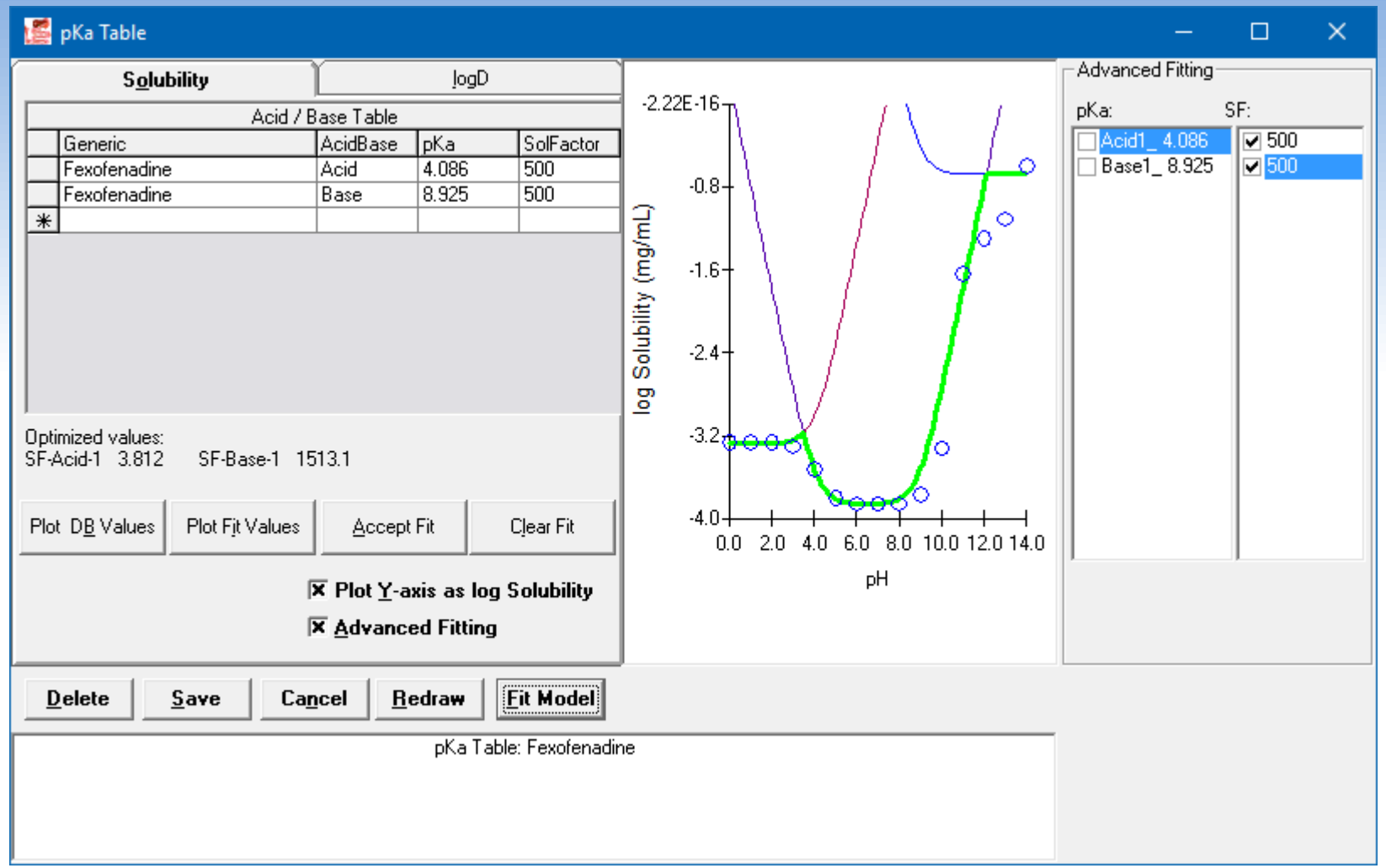



blue – plasma concentration, green – ICL thickness

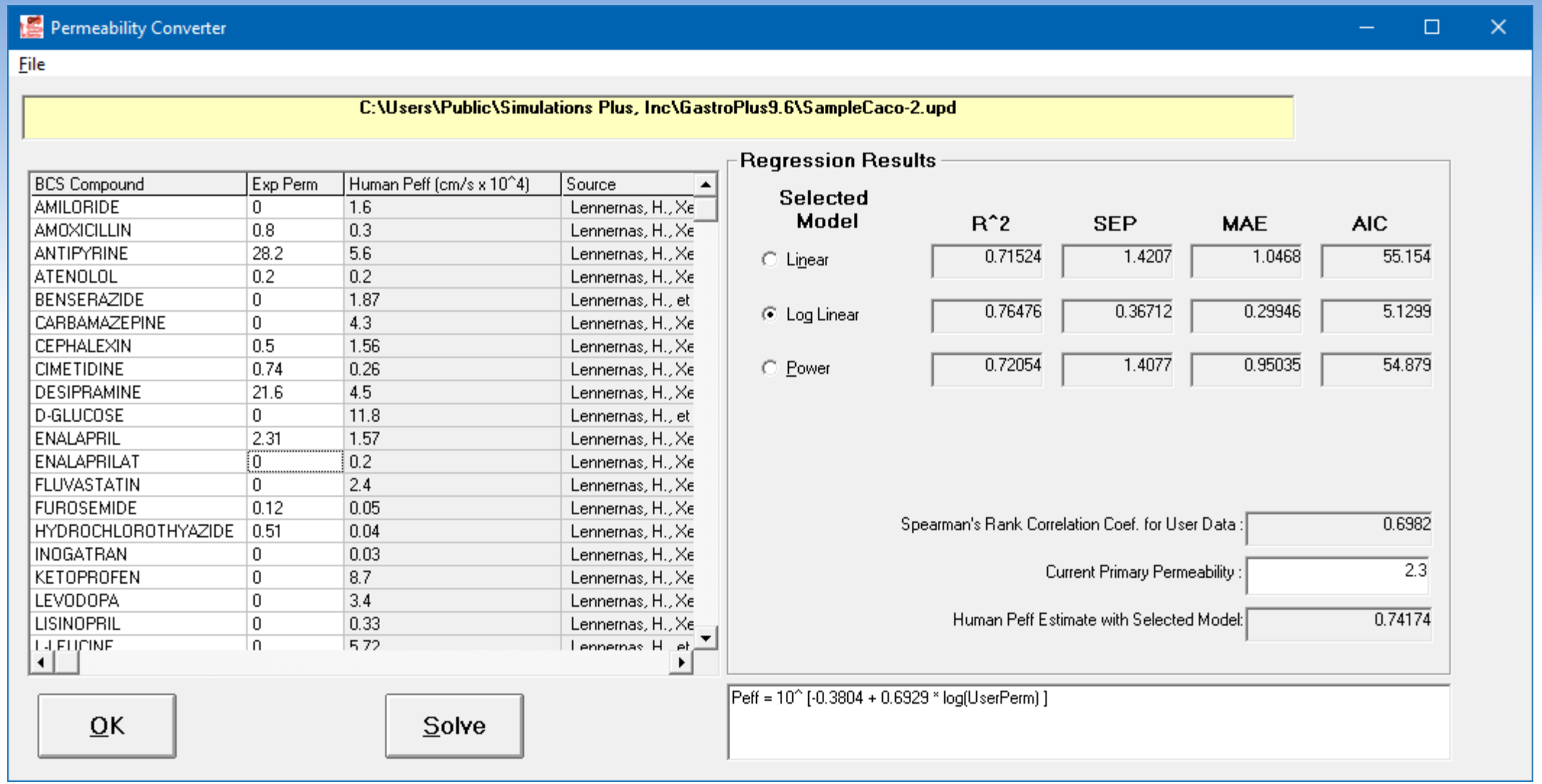
# GastroPlus® v9.7

- 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






SimulationsPlus
SCIENCE + SOFTWARE = SUCCESS

# Acknowledgements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**With support from:**

Michael Bolger, Ph.D. (Chief Scientist)

**and other teams at Simulations Plus:**

Computational Technologies

Consulting Studies

ADMET Cheminformatics

Discovery Cheminformatics