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Please note: this presentation, including questions from the audience, is being recorded

DILIsym Review Session 27:

IVIVE in DILIsym Using GastroPlus/ADMET Predictor

November 8, 2018

Kyunghee Yang, Christina Battista

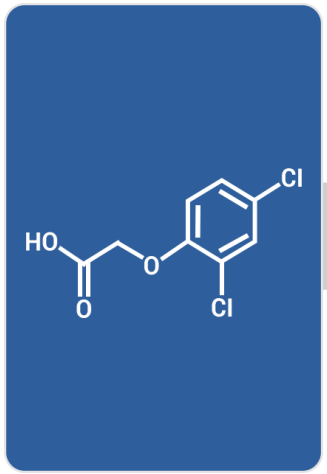
DILIsym Review Session Agenda

- Introduction
- IVIVE in DILIsym using ADMET Predictor
- IVIVE in DILIsym using GastroPlus
- A case study: IVIVE using GastroPlus & DILIsym to predict liver safety of investigational drugs

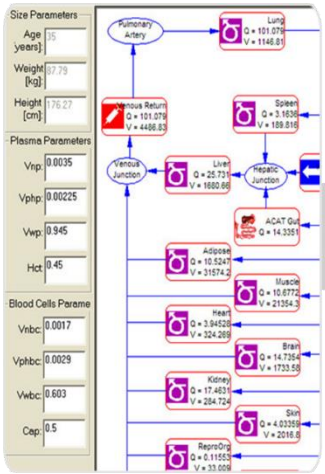
DILIsym is a Quantitative Systems Toxicology Platform That Predicts *In Vivo* Liver Safety Using *In Vitro*/Preclinical Data

- What is IVIVE?
  - Represents “In Vitro-In Vivo Extrapolation”
  - Method of applying the results from *in vitro* experiments to predict *in vivo* outcomes
  - Reduces animal studies and improve predictivity of human outcomes
  - IVIVE can range from very simple, static equations, all the way to sophisticated dynamic models that combine PBPK and systems pharmacology/toxicology models
- IVIVE in DILIsym
  - PBPK sub-model predicts *in vivo* systemic/hepatic exposure of drugs/metabolites using *in vitro* data
  - Integrates predicted exposure and *in vitro* mechanistic toxicity data to predict *in vivo* liver safety of drugs/metabolites
    - Training videos available at www.DILIsymHelp.com to outline IVIVE process for toxicity data

Saying “I do” to the QSAR / PBPK / QST marriage…



Permeability, solubility vs. pH, pKa(s), logD vs. pH, Fup, blood:plasma ratio, tissue Kps, CLint, CLfilt



Local & systemic exposure, drug distribution, parent and metabolite levels, patient variability

Quantitative Structure Activity Relationships (QSAR)

ADMET Predictor™

Physiologically-Based Pharmacokinetics (PBPK)

GastroPlus™

Quantitative Systems Pharmacology/Toxicology (QSP/QST)

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DILIsym Utilizes Various Data Types to Inform Decisions

Exposure Data

PBPK Modeling

- **Compound Properties**
  - Tissue partition coefficients
- **Tissue penetration studies**
  - *Liver to blood ratio*
- **Pharmacokinetic data**
  - *Absorption, extra-hepatic clearance, metabolites*
- ***in vitro* data**
  - *Metabolite synthesis, active uptake*

Modeling & Simulation

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Simulations and Assays inform:

- **Prediction of DILI risk**
- **Participating DILI mechanisms**
- **Characteristics of patients at risk for DILI**
- **Drug dosing paradigms**
- **DILI monitoring strategies**

In vitro Mechanistic DILI Data

Assays performed to determine quantitative aspects of DILI mechanisms

- **Oxidative stress**
  - *Direct and reactive metabolite-mediated*
- **Mitochondrial toxicity**
  - *ETC inhibition*
  - *Uncoupling*
- **Bile acid transporter inhibition**
  - *BSEP, MRP3 and 4, NTCP*
- **Bilirubin transport/metabolism**
  - *OATP1B1, OATP1B3, UGT1A1, MRP2, MRP3*

Clinical Data

- **Dosing Protocols, fasting/fed state, meal times**
- **Anthropometric data**
  - **Body weight, age, ethnicity**
- **Pharmacokinetic data**
  - **Absorption, extra-hepatic clearance, metabolites**

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DILIsym Utilizes Various Data Types to Inform Decisions

Exposure Data

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ADMET Predictor, GastroPlus

Modeling & Simulation

Simulations and Assays inform:

- **Prediction of DILI risk**
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In vitro Mechanistic DILI Data

Assays performed to determine quantitative aspects of DILI mechanisms

- **Oxidative stress**
  - *Reactive metabolite-mediated*
- **Mitochondrial toxicity**
  - *Efflux*
  - *Uncoupling*
- **Bile acid transporter inhibition**
  - *BSEP, MRP3 and 4, NTCP*
- **Bilirubin transport/metabolism**
  - *OATP1B1, OATP1B3, UGT1A1, MRP2, MRP3*

ADMET Predictor, MembranePlus

ADMET Predictor

Clinical Data

- **Dosing Protocols, fasting/fed state, meal times**
- **Anthropometric data**
  - **Body weight, age, ethnicity**
- **Pharmacokinetic data**
  - **Absorption, extra-hepatic clearance, metabolites**

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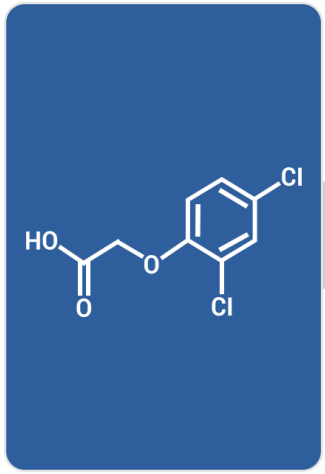
ADMET Predictor Can Predict Input Parameters for DILIsym PBPK Sub-Model From Structure



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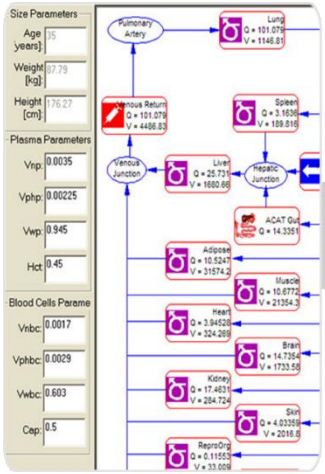

Local & systemic exposure, drug distribution, parent and metabolite levels, patient variability

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Quantitative Systems Pharmacology/Toxicology (QSP/QST)

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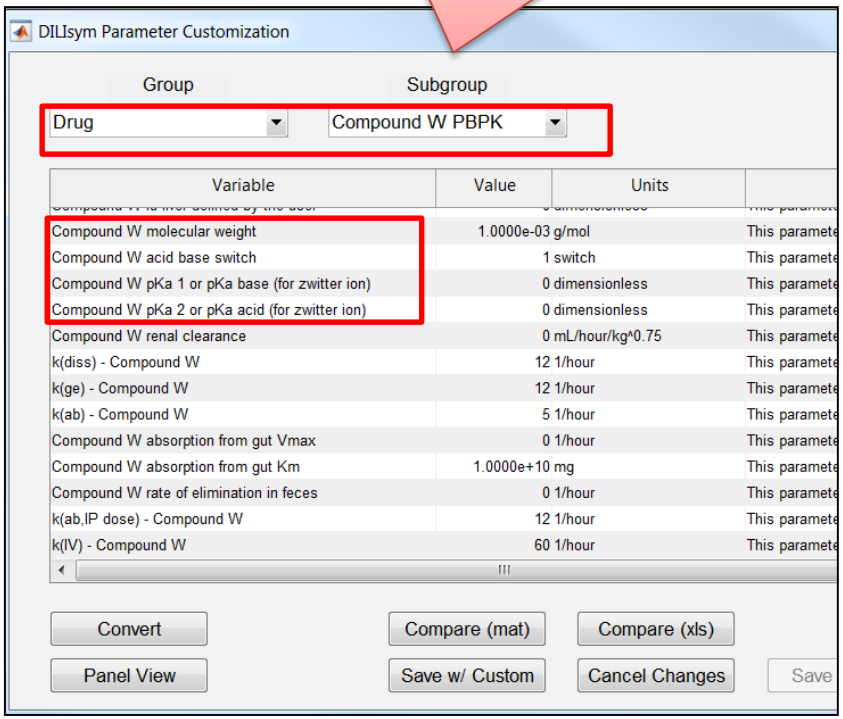
DILIsym PBPK Sub-Model Input Parameters Fall into Several Main Categories

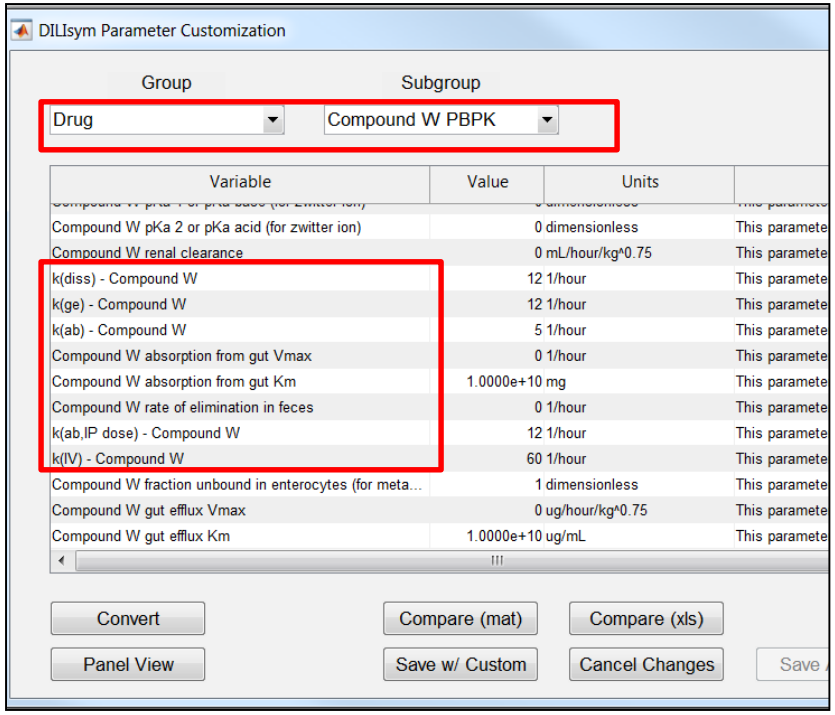
- Physicochemical properties
  - Acidic/basic pKa

Make sure to select relevant subgroup (e.g., Compound W, X, Y…)



DILIsym PBPK Sub-Model Input Parameters Fall into Several Main Categories

- Physicochemical properties
  - Acidic/basic pKa
- Absorption
  - Saturable and linear models



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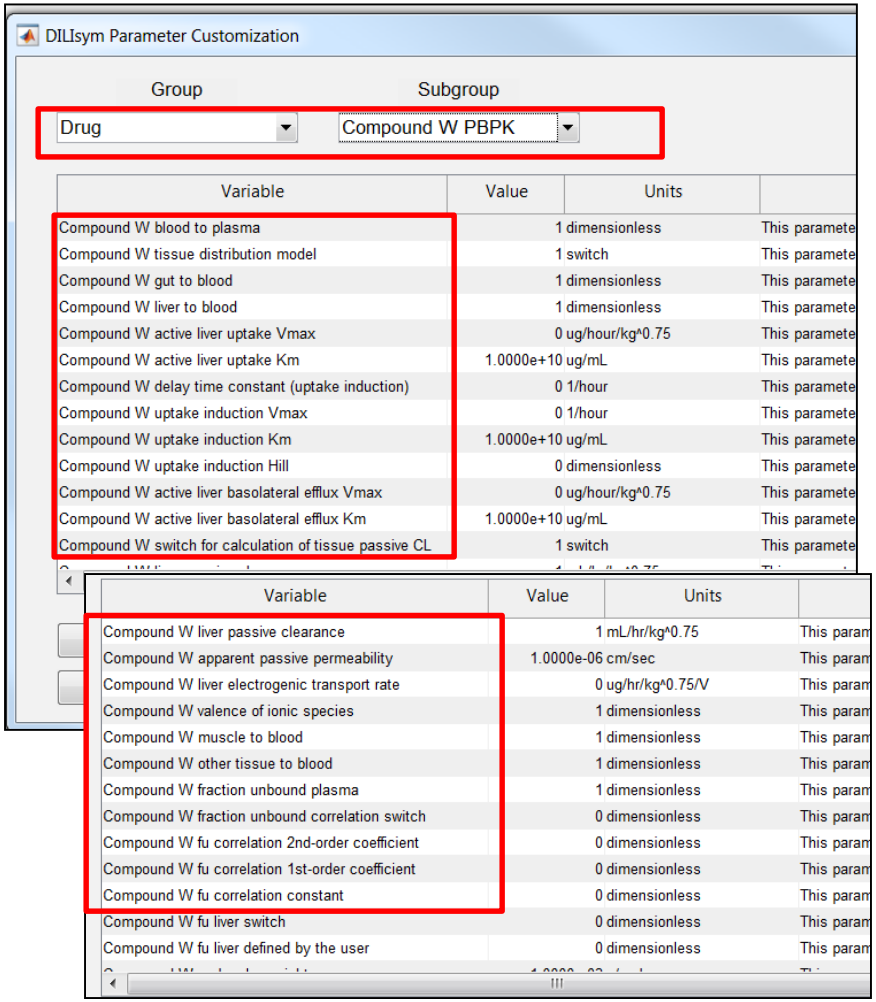
DILIsym PBPK Sub-Model Input Parameters Fall into Several Main Categories

- Physicochemical properties
  - Acidic/basic pKa
- Absorption
  - Saturable and linear models
- Distribution
  - Linear and non-linear plasma protein binding
  - Blood to plasma partition coefficient
  - Permeability (if permeability-limited model is selected)
  - Tissue partition coefficients
  - Transporter-mediated uptake model for liver
  - Liver partition coefficient and volume of distribution for metabolites



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DILIsym PBPK Sub-Model Input Parameters Fall into Several Main Categories

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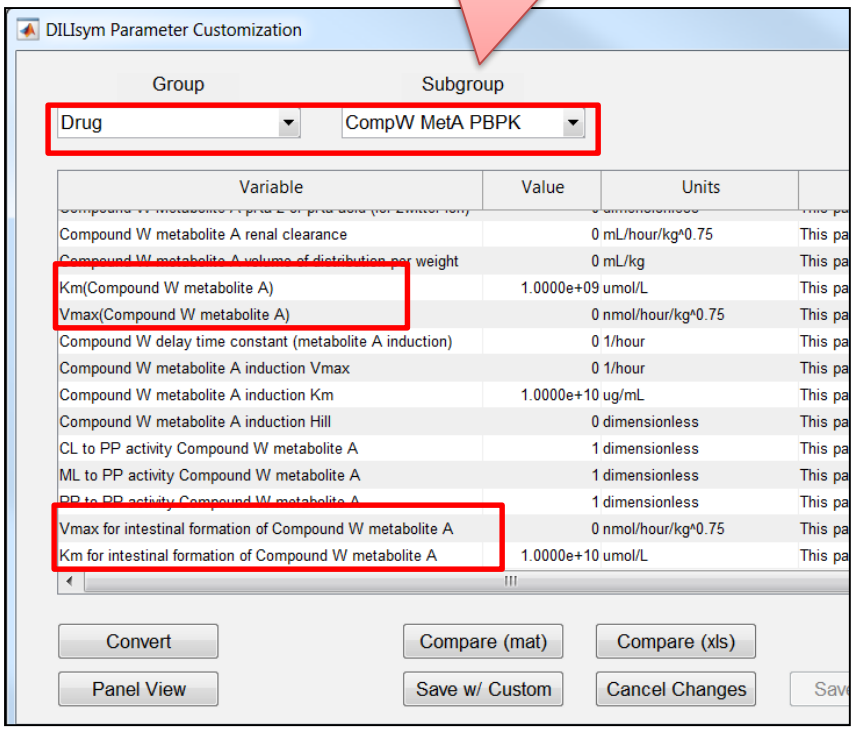
  - Transporter-mediated uptake model for liver
  - Liver partition coefficient and volume of distribution for metabolites
- Metabolism
  - Michaelis-Menten kinetics from parent to stable metabolites in liver and gut
  - RM reactions with GSH and protein in liver

Metabolism parameters are in the "metabolite" subgroup



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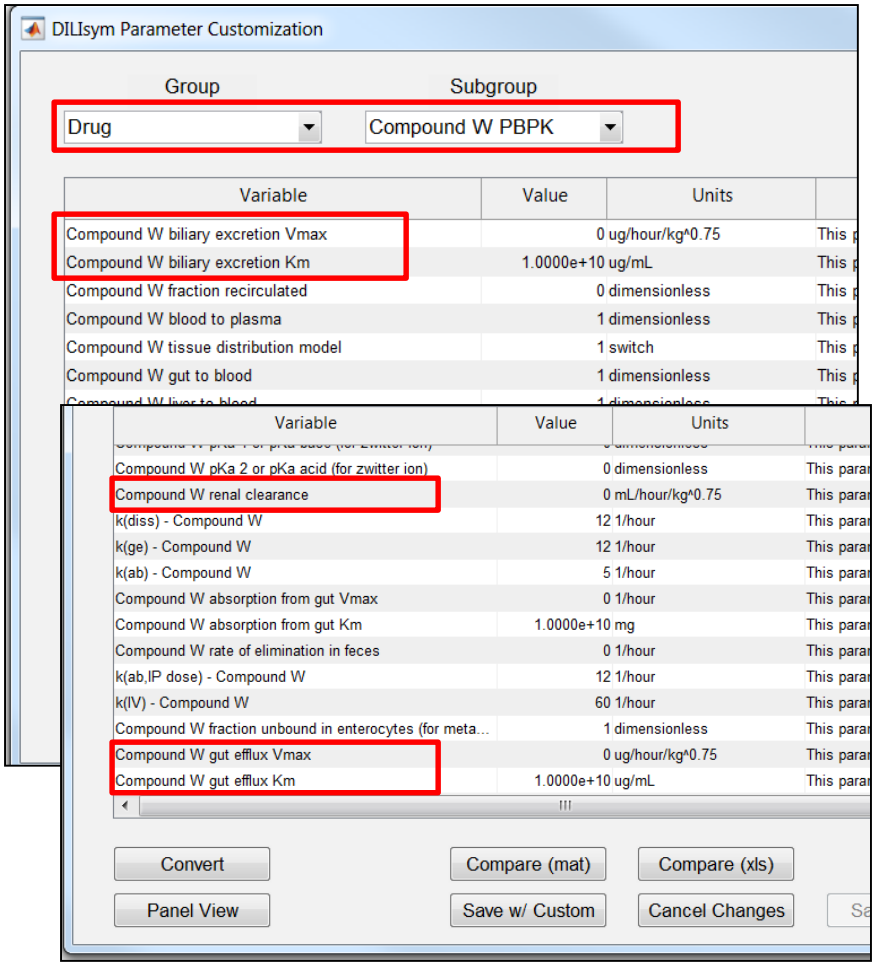
  - Biliary excretion (K_m and V_{max}) and renal clearance of parent and main metabolites
  - Intestinal efflux
  - Clearance of protein adducts



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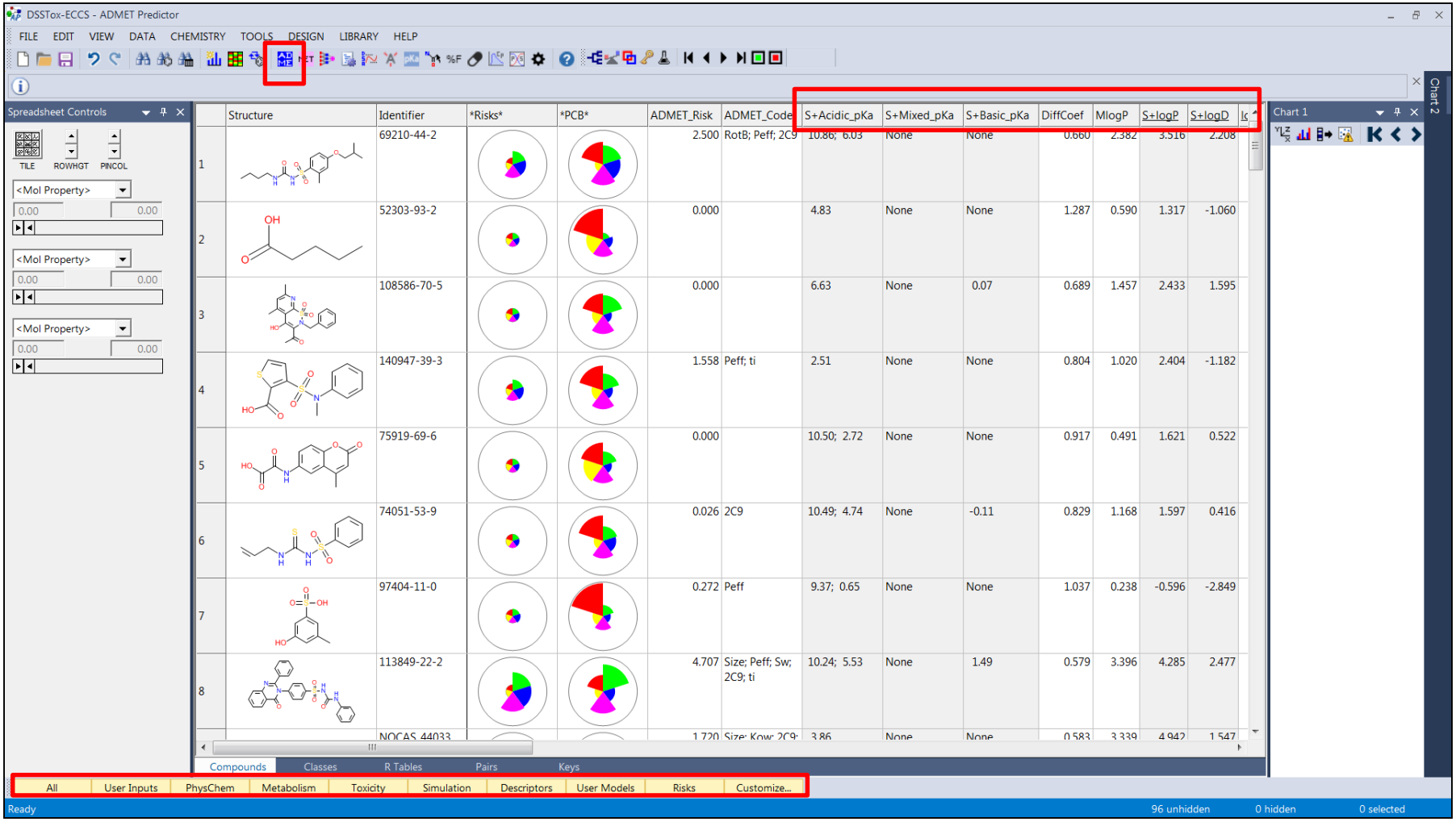
ADMET Predictor Predicts ADME-Tox Properties from Structure



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ADMET Predictor Can Predict Input Parameters for DILIsym PBPK Sub-Model From Structure

- Physicochemical properties
  - Acidic/basic pKa ← S_Acidic/Mixed/Basic_pKa
- Absorption
  - Saturable and linear models
- Distribution
  - Linear and non-linear plasma protein binding ← Hum fup%
  - Blood to plasma partition coefficient ← RBP
  - Permeability (if permeability-limited model is selected) ← S+MDCK
  - Tissue partition coefficients ← G+ Prediction
  - Transporter-mediated uptake model for liver
  - Liver partition coefficient and volume of distribution for metabolites ← G+ Prediction
- Metabolism
  - Michaelis-Menten kinetics from parent to stable metabolites in liver and gut ← CYP1A2/2C9/2C19/2D6/3A4_ Km/Vmax; CYP HLM CLint
  - RM reactions with GSH and protein in liver
- Excretion
  - Biliary excretion (K_m and V_{max}) and renal clearance of parent and main metabolites
  - Intestinal efflux
  - Clearance of protein adducts

ADMET Predictor may be used to predict DILIsym toxicity inputs in the future

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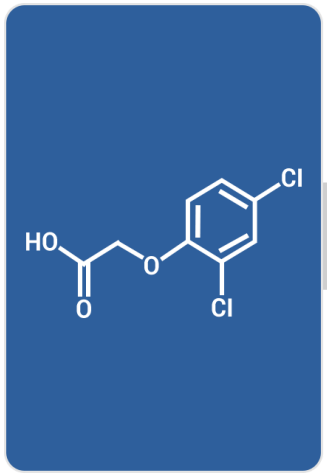
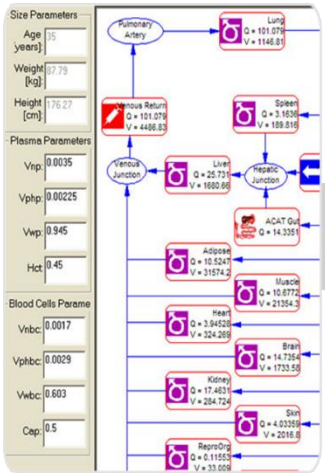
Exposure Profiles Generated From GastroPlus Can Be Directly Used in DILIsym



Permeability, solubility vs. pH, pKa(s), logD vs. pH, Fup, blood:plasma ratio, tissue Kps, CLint, CLfilt



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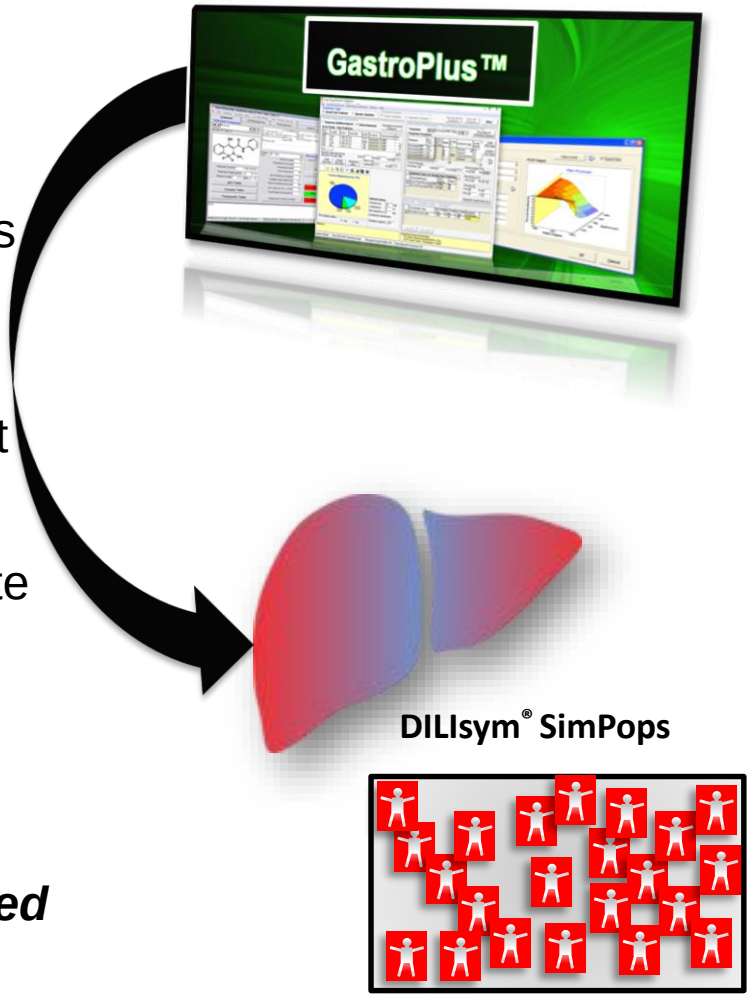
GastroPlus 9.6 Allows for Efficient Use of GastroPlus PBPK Models in Combination with DILIsym SimPops

- GastroPlus users build PBPK models within GastroPlus
- The “DILIsym” simulation mode in v9.6 allows users to select a mapping of GastroPlus outputs to DILIsym PK inputs
- All DILIsym SimPops and SimCohorts are embedded within GastroPlus so user can select option of their choice
- Exported DILIsym Specified Data Excel template is seamlessly compatible with DILIsym and contain PK outputs for **the right number of body-weight matched** rats, dogs, mice or humans
- ***This makes the manual creation of a Specified Data template unnecessary***



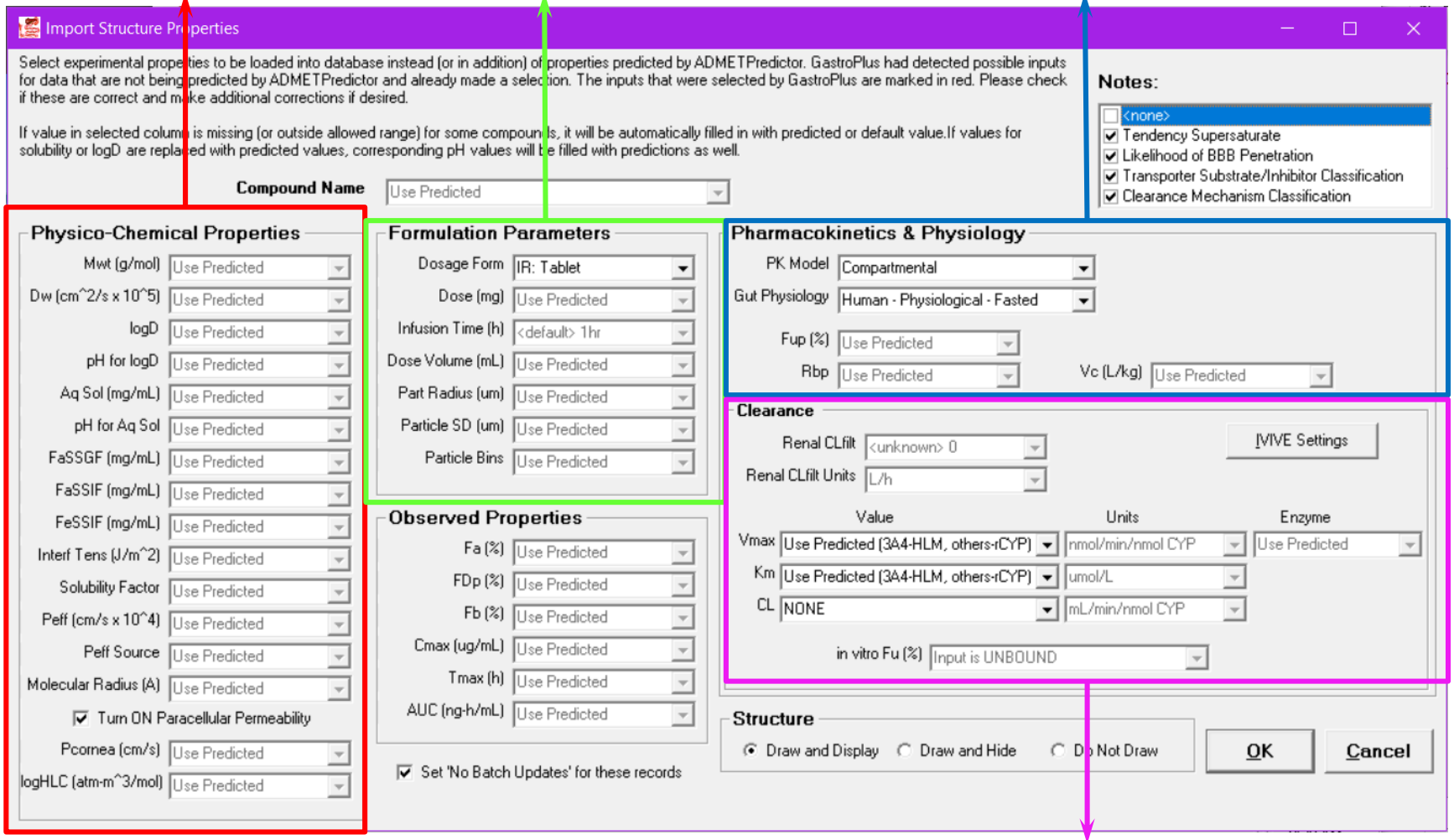
ADMET Predictor Can Predict Many Inputs in GastroPlus Drug Database

- With the ADMET Predictor Module, a user can automatically create a new GastroPlus drug database that contains estimates for:
  - pKa(s)
  - Human effective permeability
  - Diffusion coefficient in water
  - Human (or rat) plasma protein binding
  - Human volume of distribution
  - Human (or rat) blood:plasma concentration ratio
  - CYP metabolism kinetics
  - Log D vs. pH profile
  - Aqueous/biorelevant solubility vs. pH profile

Define physiochemical properties for compounds

Define the initial formulation conditions for compounds

Define the pharmacokinetic model for compounds, along with the fu,p and B:P concentration ratio



Define how clearance will be estimated for compounds. Include renal clearance? Use Vmax and Km for CYP enzymes of Clint?

Slide adapted from Simulations Plus GastroPlus training

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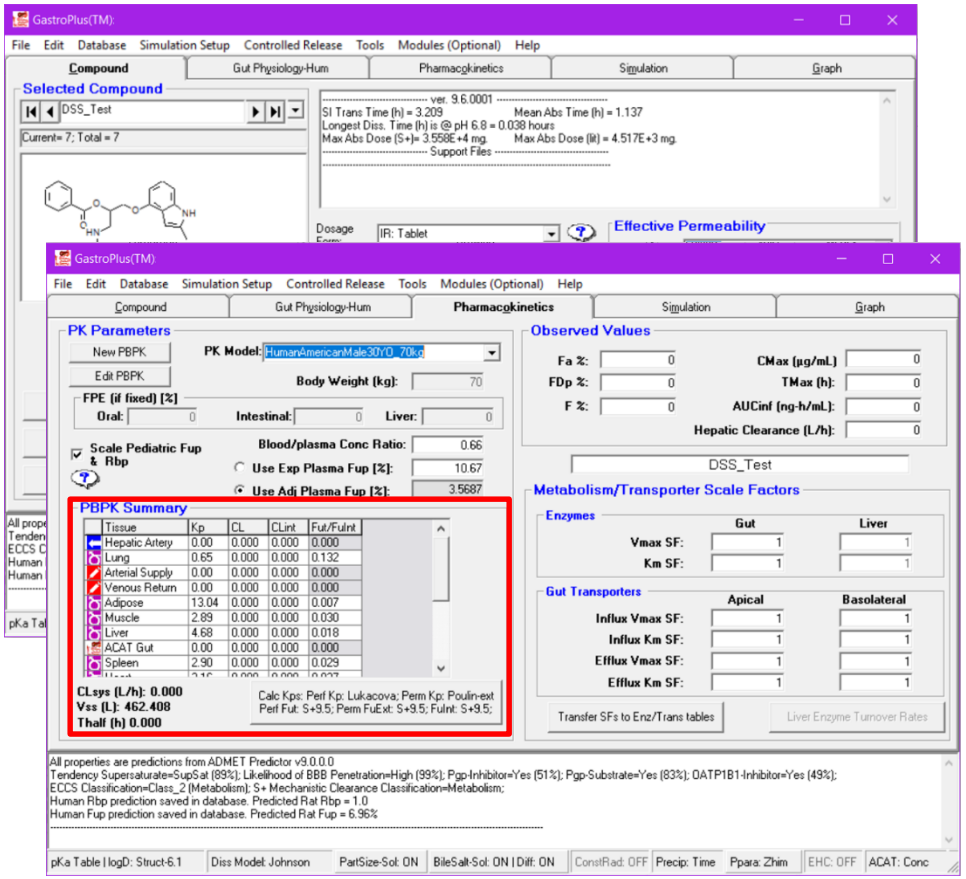
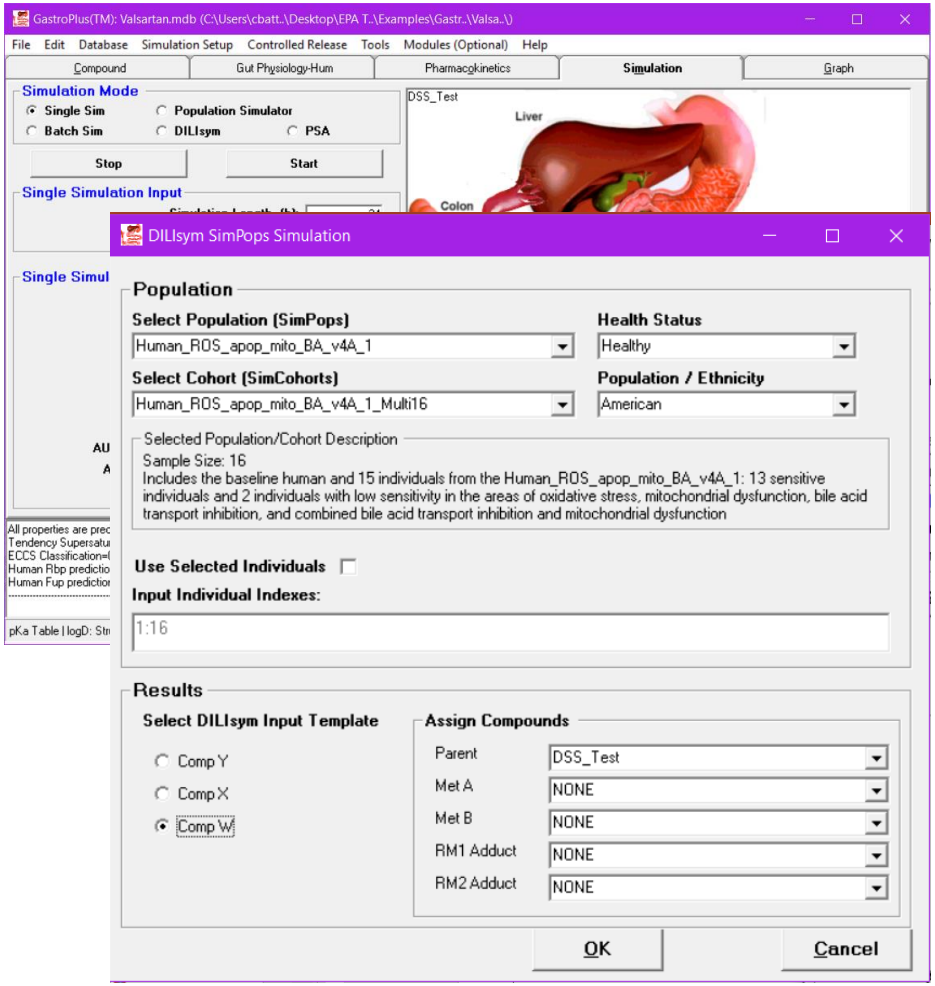
User Can Refine Inputs or Use Pure Prediction to Determine Partition Coefficients

- Using the import structure with the ADMET Predictor Module will auto-populate many of the input parameters
  - If user has any further measurements for physiochemical properties (pKa, B:P, fu,p, etc), they can adjust them manually
  - No adjustments are necessary for an initial simulation
- Switching to the PK tab and selecting the PBPK model, the user can predict tissue partition coefficients
  - Number of different models available to calculate; Lukacova is generally the most trusted



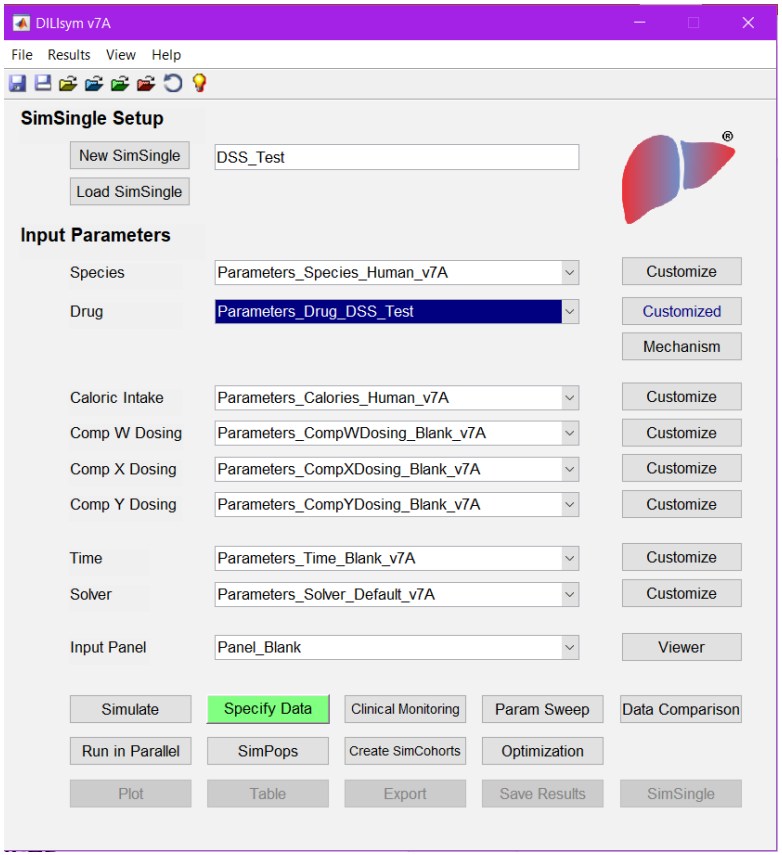
GastroPlus Includes Ability to Export Excel File to be Directly Read into DILIsym

- Simulation can be run to generate necessary concentrations to be used in DILIsym
  - Selecting DILIsym allows users to choose the corresponding SimPops or SimCohorts within DILIsym GUI
- User can select which compound scaffold to use
  - Metabolites can also be specified
- Generates Excel file with relevant concentrations:
  - Blood concentration
  - Zonal liver concentration
  - Zonal sinusoidal blood concentration
  - Gut blood concentration



Compound Can Be Set Up Quickly and Easily within DILIsym

- User only needs to specify data (Excel generated by GastroPlus) and input a few additional drug parameters for toxicity predictions in DILIsym:
  - Molecular weight
  - Toxicity mechanism parameters (see Training Videos at www.DILIsymHelp.com)



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Example Project Goal – Assess Compound X and Compound Y

- The primary goal of this simulation work within the DILIsym software was to:
  - quantitatively and mechanistically assess the liver toxicity potential of Compound X and Compound Y combining clinical and mechanistic *in vitro* data with DILIsym and GastroPlus software simulations of previous or prospective clinical dosing paradigms.

Mitochondrial Toxicity Parameters Determined for Compound Y and Compound X

- Parameter values were fit to mitochondrial data for Compound Y and Compound X
  - Electron transport chain inhibition for Compound Y
  - Both electron transport chain inhibition and uncoupling for Compound X
  - 24 hour data used
- MITOsym and DILIsym used to parameterize both compounds

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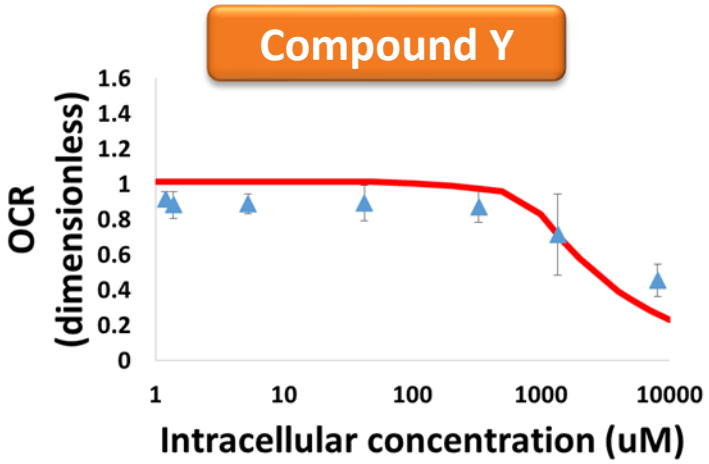
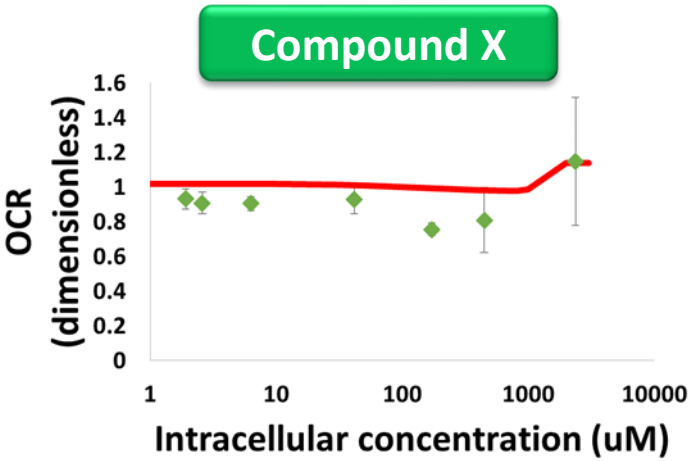
DILIsym Parameter	Compound Y Value	Compound X Value	Units
Coefficient for ETC inhibition 1	38,000	Not used	µM
Coefficient for ETC Inhibition 3	0.1	4,200	µM
Max inhibitory effect for ETC inhibition 3	0.2	0.4 (max effect)	dimensionless
Uncoupler 1 effect Km	No effect	15,000	µM
Uncoupler 1 effect Vmax	No effect	22	dimensionless
Uncoupler 1 effect Hill	No effect	4	dimensionless





Preclinical Data and Simulation Results

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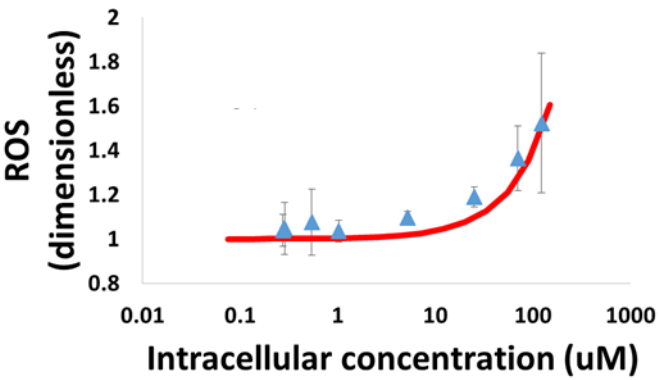
Oxidative Stress Parameters Determined for Compound Y and Compound X

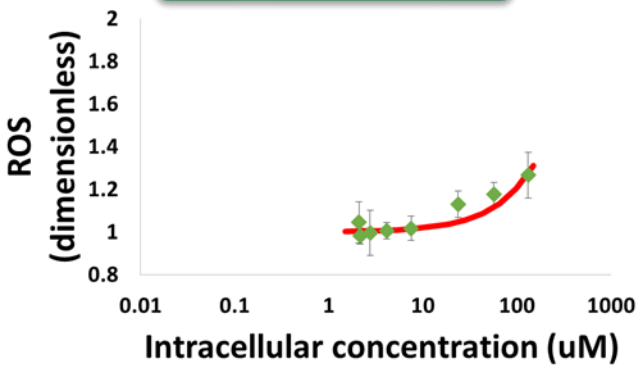
- Parameter values were fit to 24-hour ROS data for Compound Y and Compound X
- DILIsym representation of *in vitro* environment used to parameterize both compounds
- Saturable model explored but did not lead to better fit

DILIsym Parameter	Compound Y Value	Compound X Value	Units
RNS/ROS production rate constant 1	3.4×10^{-4}	1.7×10^{-4}	mL/nmol/hr

Compound Y



Compound X



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Preclinical Data and Simulation Results

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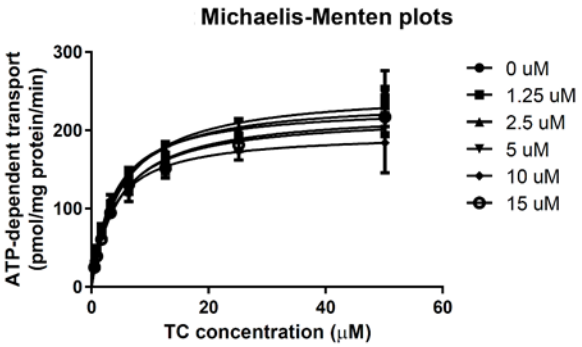
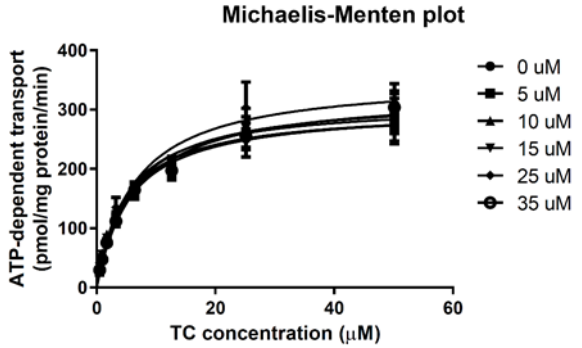
Compound Y Weakly Inhibits BSEP; Compound X Does Not

- Compound Y is a weak but noncompetitive/uncompetitive inhibitor of BSEP
- Compound X does not inhibit BSEP
  - No changes to V_{max} or K_m of transporters observed over course of assay

Compound Y; K_i = 140 μM, α = 0.6



Compound X; no inhibition



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Preclinical Data

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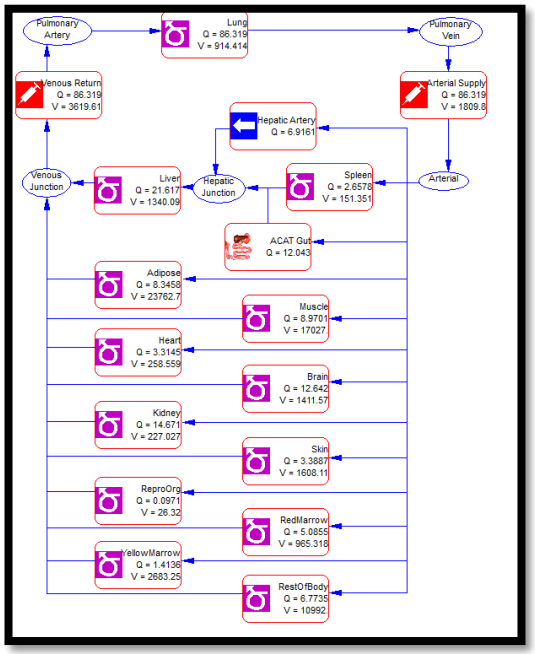
DILIsym Toxicity Parameters for Compound Y and X

Mechanism	Parameter	Unit	DILIsym Parameter Value*	
			Compound Y	Compound X
Mitochondrial Dysfunction	Coefficient for ETC inhibition 1	µM	38,000	Not used
	Coefficient for ETC Inhibition 3	µM	0.1	4,200
	Max inhibitory effect for ETC inhibition 3	dimensionless	0.2	0.4
	Uncoupler 1 effect Km	µM	No effect	15,000
	Uncoupler 1 effect Vmax	dimensionless	No effect	22
	Uncoupler 1 effect Hill	dimensionless	No effect	4
Oxidative Stress	RNS/ROS production rate constant 1	mL/nmol/hr	3.4×10^{-4}	1.7×10^{-4}
Bile Acid Transporter Inhibition	BSEP inhibition constant	µM	140	No inhibition
	BSEP inhibition alpha value	dimensionless	0.6	No inhibition
	NTCP inhibition constant	µM	No inhibition	No inhibition
	MRP4 inhibition constant	µM	40	75

*Values shown in the table for DILIsym input parameters should not be interpreted in isolation with respect to clinical implications, but rather, should be combined with exposure in DILIsym to produce simulations that have predictive and insightful value

GastroPlus PBPK Model Used to Predict Liver Exposure of Compound Y and Compound X

- Data on Compound Y and Compound X pharmacokinetics not available in the literature
  - No plasma time courses available; no *in vitro* or animal studies available either
  - Data on T_{max}, Compound Y $f_{u,plasma}$ available
  - *In vitro* data on liver distribution available from intracellular data collected for this project
- Structure of each compound available online
  - QSAR modeling using ADMET Predictor and GastroPlus provided the best possible estimate of Compound Y and Compound X distribution and pharmacokinetics



- Plasma time course was estimated in GastroPlus and translated into DILIsym using "specified data" option
  - Liver:plasma partition coefficient was calculated from the cell:media ratio in the *in vitro* data and used as input into GastroPlus; the remainder of the parameters were calculated by ADMET Predictor
- Both compounds distribute significantly into the liver
  - Compound Y average cell:media was 18; Compound X average cell:media was 9

Compound Y | Compound X

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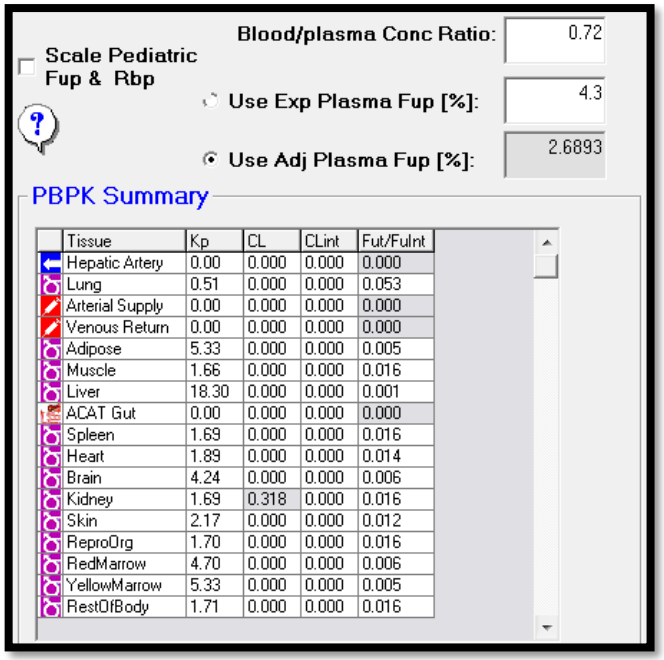
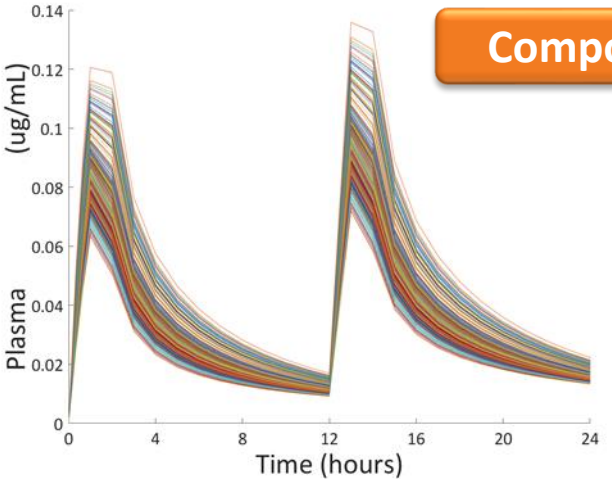
Compound Y PBPK Representation Calculated at Clinical Dose

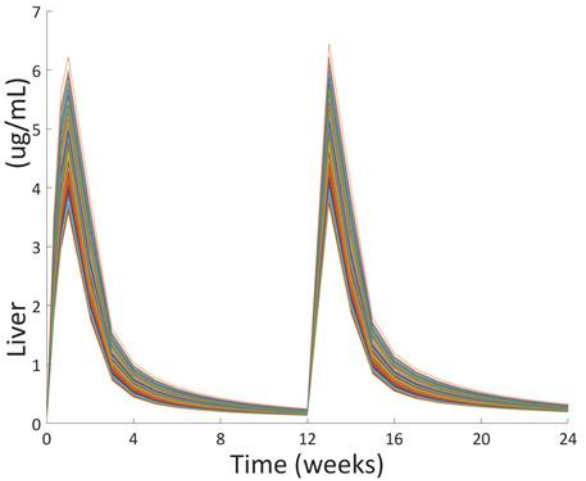
- GastroPlus predictions for liver and plasma at clinical dose shown at right
  - PBPK model specific predictions shown below
  - Dose escalation was simulated



Tissue	Kp	CL	CLint	Fut/FuInt
Hepatic Artery	0.00	0.000	0.000	0.000
Lung	0.51	0.000	0.000	0.053
Arterial Supply	0.00	0.000	0.000	0.000
Venous Return	0.00	0.000	0.000	0.000
Adipose	5.33	0.000	0.000	0.005
Muscle	1.66	0.000	0.000	0.016
Liver	18.30	0.000	0.000	0.001
ACAT Gut	0.00	0.000	0.000	0.000
Spleen	1.69	0.000	0.000	0.016
Heart	1.89	0.000	0.000	0.014
Brain	4.24	0.000	0.000	0.006
Kidney	1.69	0.318	0.000	0.016
Skin	2.17	0.000	0.000	0.012
ReproOrg	1.70	0.000	0.000	0.016
RedMarrow	4.70	0.000	0.000	0.006
YellowMarrow	5.33	0.000	0.000	0.005
RestOfBody	1.71	0.000	0.000	0.016

Compound Y





Simulation Results

DILIsym Services

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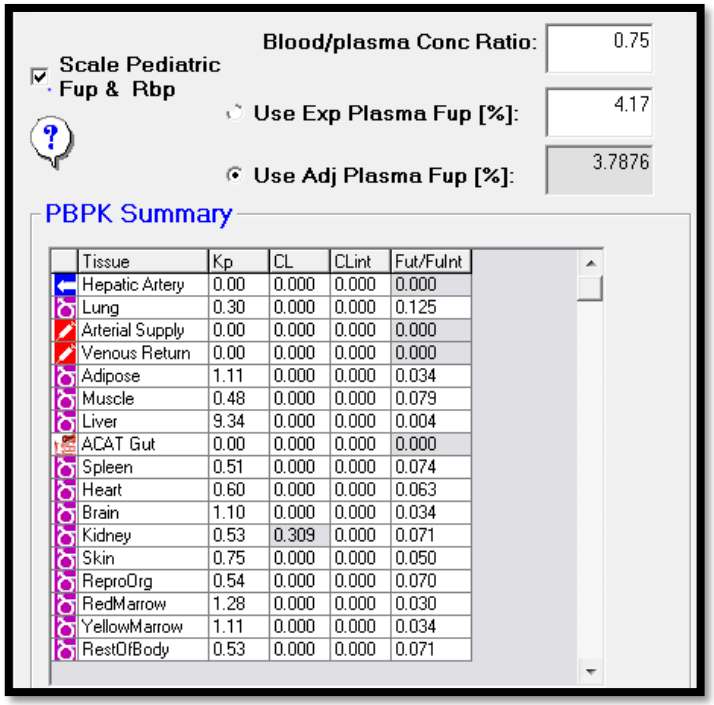
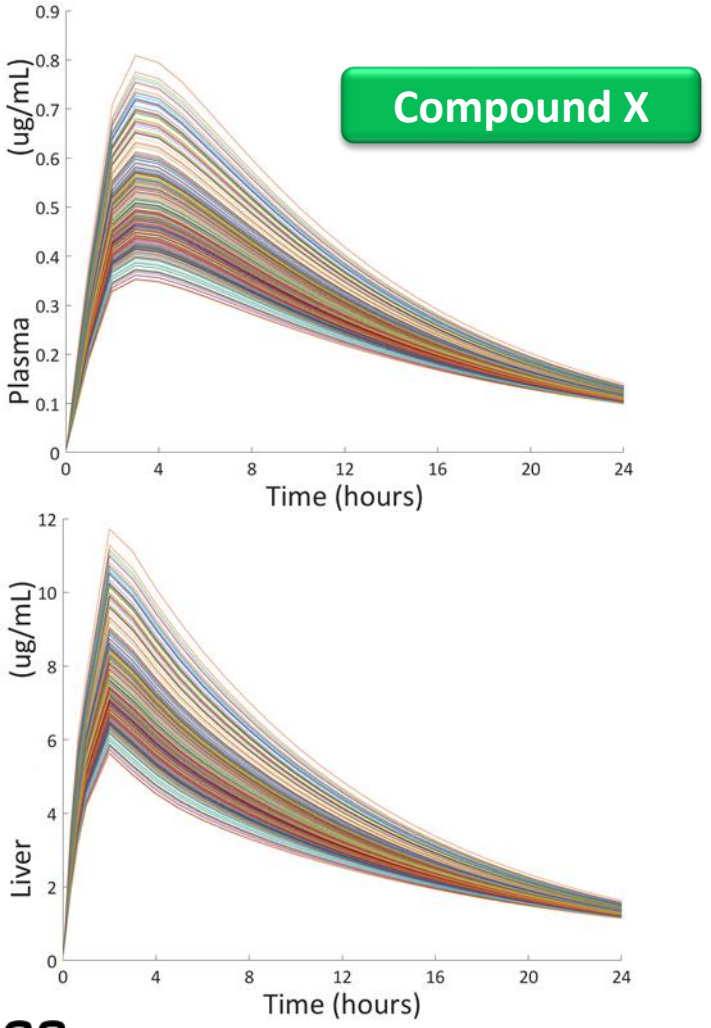
Compound X PBPK Representation Calculated at Clinical Dose

- GastroPlus predictions for liver and plasma at clinical dose for 25 days shown at right
  - PBPK model specific predictions below
  - Dose escalation and alternate protocols were also simulated



Tissue	Kp	CL	CLint	Fut/Fulnt
Hepatic Artery	0.00	0.000	0.000	0.000
Lung	0.30	0.000	0.000	0.125
Arterial Supply	0.00	0.000	0.000	0.000
Venous Return	0.00	0.000	0.000	0.000
Adipose	1.11	0.000	0.000	0.034
Muscle	0.48	0.000	0.000	0.079
Liver	9.34	0.000	0.000	0.004
ACAT Gut	0.00	0.000	0.000	0.000
Spleen	0.51	0.000	0.000	0.074
Heart	0.60	0.000	0.000	0.063
Brain	1.10	0.000	0.000	0.034
Kidney	0.53	0.309	0.000	0.071
Skin	0.75	0.000	0.000	0.050
ReproOrg	0.54	0.000	0.000	0.070
RedMarrow	1.28	0.000	0.000	0.030
YellowMarrow	1.11	0.000	0.000	0.034
RestOfBody	0.53	0.000	0.000	0.071



Simulation Results

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SimPops Results Show Compound X and Compound Y to be Safe at Clinical Doses; ALT Elevations Occur at Higher Doses for Both Compounds

Compound Y **Compound X**

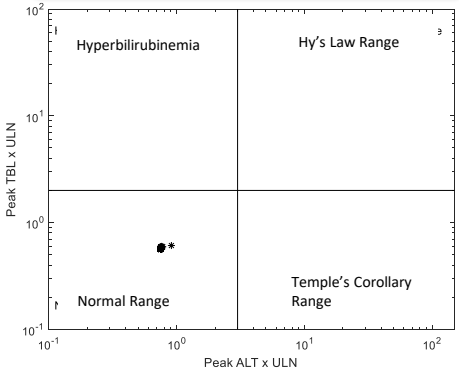
- Neither Compound Y nor Compound X are predicted to cause toxicity at the highest clinical dose
  - Some exposure variability included in these predictions due to GastroPlus population generation
- Both Compound Y and Compound X are predicted to cause mild ALT elevations at supratherapeutic doses
  - No bilirubin elevations or Hy's Law cases occurred in simulations with Compound X
  - 2 Hy's Law cases occurred at 10x clinical dose simulations with Compound Y

	Compound	Dosing Protocol	Simulated* ALT > 3X ULN**
Compound Y	Compound Y	1X Dose, 12 weeks	0% (0/285)
		2X Dose, 12 weeks	0% (0/285)
		5X Dose, 12 weeks	0.3% (1/285)
		10X Dose, 12 weeks	10.2% (29/285)
Compound X	Compound X	1X Dose, 15 days	0% (0/285)
		2X Dose, 15 days	0% (0/285)
		5X Dose, 15 days	1.1% (3/285)
		10X Dose, 15 days	11.6% (33/285)

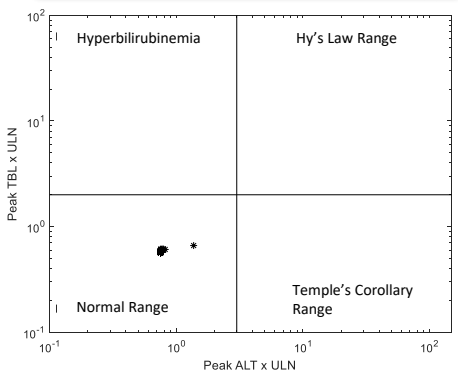
*The full v4A-1 SimPops (n=285) of normal healthy volunteers was used
**Upper limit of normal (ULN) in DILIsym is 40 U/L

SimPops Results Show Lack of Severe Liver Injury for Both Compound Y and Compound X at Clinical Doses

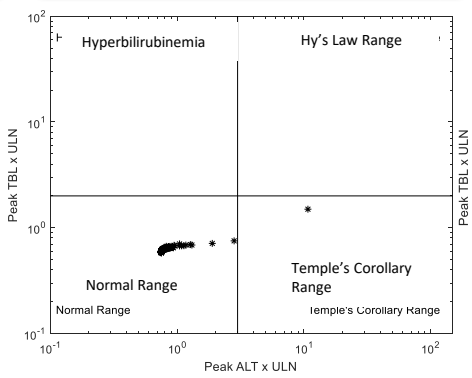
Compound Y; 1X Dose, 12 weeks



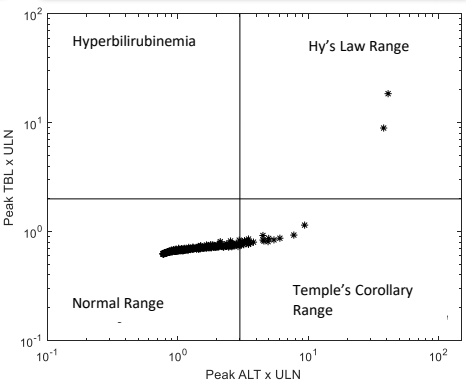
Compound Y; 2X Dose, 12 weeks



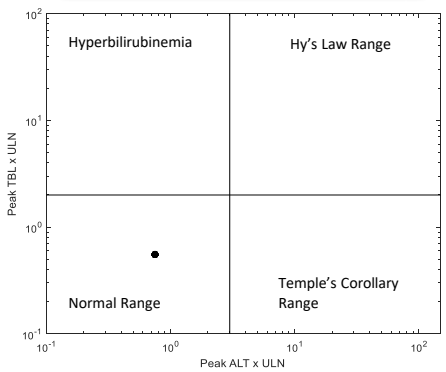
Compound Y; 5X Dose, 12 weeks



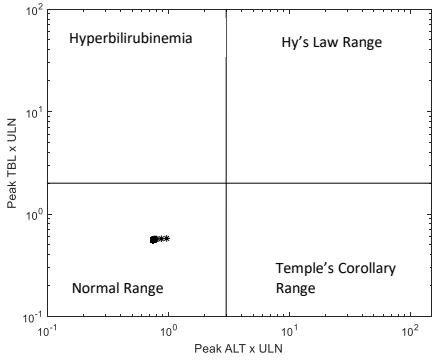
Compound Y; 10X Dose, 12 weeks



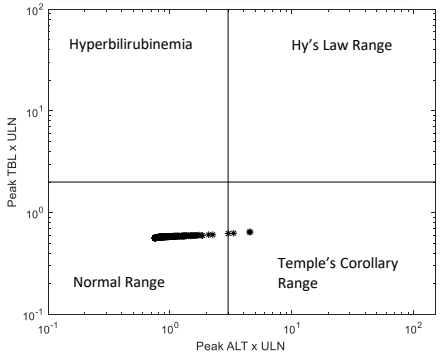
Compound X; 1X Dose



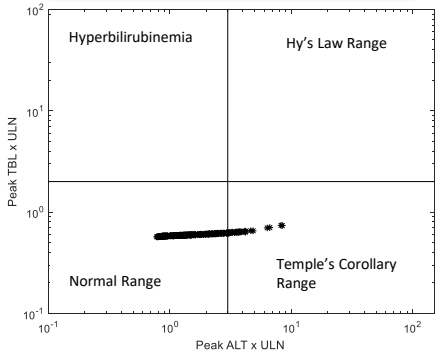
Compound X; 2X Dose



Compound X; 5X Dose



Compound X; 10X Dose



*The full v4A-1 SimPops (n=285) of normal healthy volunteers was used
**Upper limit of normal (ULN) in DILIsym is 40 U/L

Simulation Results

DILIsym S

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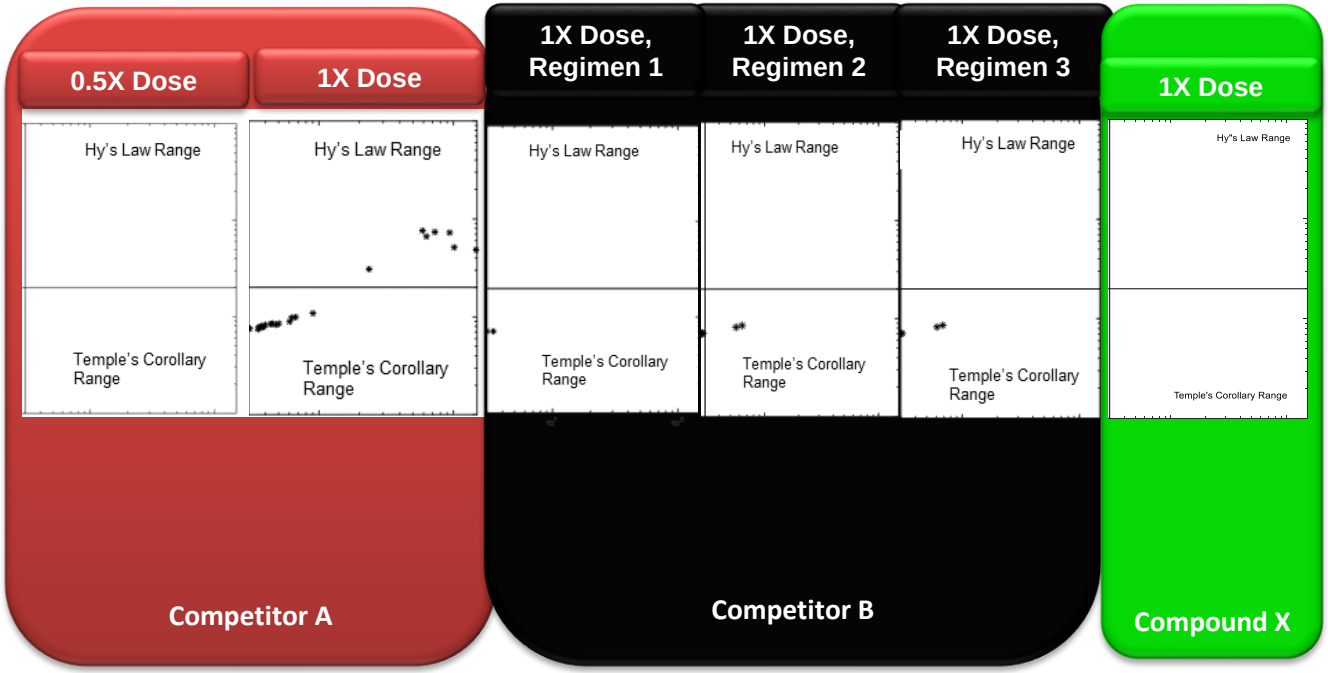
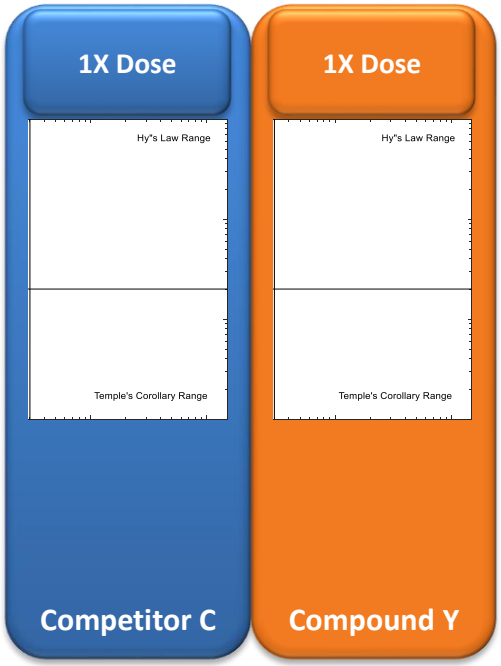
Focus on Hy's Law Side of eDISH Plot – Comparison of Competitors and Compound X at Clinical Doses (285 Simulated Individuals in All Cases)



Focus on Hy's Law Side of eDISH Plot – Comparison of Competitor and Compound Y at Predicted Clinical Doses (285 Simulated Individuals in All Cases)



Clinical trial results recently confirmed Compound Y Predictions

Example Project Summary

- GastroPlus™ software, along with *in vitro* data, was used to construct PBPK representations to predict liver exposures for both compounds
- DILIsym parameters were successfully calculated from *in vitro* data for both compounds
- SimPops results show Compound X and Compound Y to be safe at projected clinical doses
- ALT elevations predicted within DILIsym at higher doses for both compounds
- SimPops results suggest that neither compound is likely to cause severe liver injury
- ***Phase IIb / III clinical trial results have subsequently confirmed the predictions for Compound Y***

Summary

- DILIsym can utilize the capabilities of ADMET Predictor and GastroPlus to move its place further ahead in the drug development pipeline
  - Can predict exposure in humans at early discovery/development stage
- ADMET Predictor uses QSAR to predict physiochemical and ADME properties which can be input into GastroPlus to predict tissue partition coefficients
- GastroPlus PBPK models easily compatible with DILIsym SimPops and SimCohorts
  - Applies to all species: human, rat, mouse, dog

Upcoming DILIsym Review Sessions

Join us for:

- **Review Session 28: “Cholangiocyte toxicity and MDR3 inhibition.” January, 2019**