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# **DILIsym User Training – Physiologically-based Pharmacokinetic (PBPK) Modeling in DILIsym**

## **DILIsym Development Team**

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# Goal for The DILIsym PBPK Sub-model Session

***Participants should understand the following general concepts:***

- How to use the DILIsym PBPK sub-model, including the most recent updates

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# DILIsym Training on PBPK Structure

- Overview of the PBPK sub-model changes in DILIsym v6A
- Parameterizing the PBPK sub-model for DILIsym v6A



# v6A PBPK Update Summary

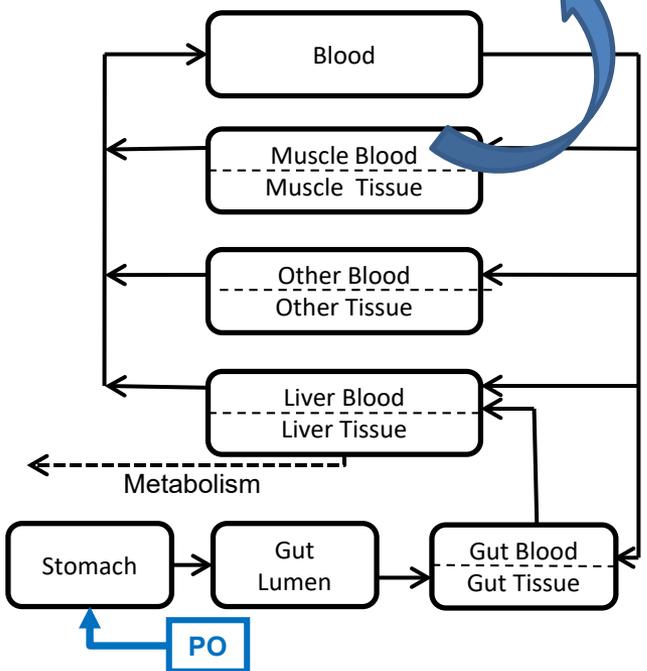
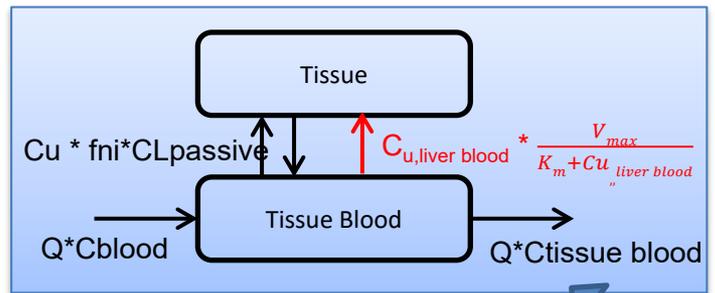
Pathway	v5A	v6A
<b>Passive diffusion</b>	Only unbound compound undergoes passive diffusion	Unbound, unionized compound undergoes passive diffusion
<b>Hepatic uptake transport</b>	Hepatic uptake only represented for Comp W and X	Transporter-mediated hepatic uptake added for stable metabolites and Compound Y
<b>Hepatic efflux transport</b>	No basolateral hepatic efflux	Transporter-mediated basolateral efflux added for parent compounds, stable metabolites and Compound Y
<b>Tissue permeability</b>	Permeability-limited distribution represented only for the liver	Permeability-limited models added for all extra-hepatic tissues



# Perfusion- and Permeability-limited Distribution Represented for All Tissues Using a Two-compartment Tissue Model

fni: fraction non-ionized

Active uptake transporter represented only in the liver



- Perfusion-limited distribution if  $CL_{passive} \gg Q$  (default)
  - Instant mixing of tissue and tissue blood; reach equilibrium quickly
  - Extent of tissue distribution will be determined by  $f_{u\_P}$  and  $f_{u\_T}$  (calculated using tissue: blood ratio), pKa, compound type (acid/base)
  - User input:  $f_{u\_P}$ , B:P, Tissue:Blood partition coefficients, compound type (acid/base), pKa
- For permeability-limited distribution,  $CL_{passive}$  of each compound can be optimized or calculated from *in vitro* permeability data
  - Only unbound, non-ionized drugs can undergo passive diffusion; frac non-ionized calculated by DILIsym using compound type (acid/base) and pKa values
  - $CL_{passive}$  calculated by DILIsym using *in vitro* permeability and the tissue surface area
  - User input: compound type (acid/base), pKa, *in vitro* permeability, transporter Km/Vmax if a substrate of hepatic uptake transporters

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# Switched Added for Tissue Distribution Model

[Red box]

1: perfusion-limited  
(tissue passive CL set to 1E10)  
2: permeability-limited  
(tissue passive CL calculated using  
liver\_CLpd or Papp)

[Red box]

Used when permeability-limited model is selected:  
1: liver\_CLpd is used to calculate tissue passive CL  
2: Papp is used to calculate tissue passive CL

Default values :

Liver\_CL\_pd: 1 mL/hr/kg<sup>0.75</sup>  
Perm\_app: 1E-06 cm/sec

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# Passive Diffusion CL Calculated by DILIsym from *In Vitro* Permeability or Liver Passive Diffusion CL

Variable	Name	Unit	Default Value
Comp_X_liver_CL_pd	Compound X liver passive clearance	mL/hr/kg <sup>0.75</sup>	1
Comp_X_perm_app	Compound X apparent passive permeability	cm/sec	1e-6

- Perm\_app: obtained from distributional permeability assays
- Default: 1e-06 cm/sec

- Liver\_CL\_pd: obtained from mechanistic modeling using SCH data, parameter optimization, or HC uptake study
- Easier to compare contribution of passive vs. active hepatic CL

Perm\_app: input parameter  
(cm/sec)

$P_{neutral} = 2 * Perm\_app / frac\_nonionized$   
(cm/sec)

$CL_{passive\_L} = P_{neutral} * liver\ SA * 3600$   
(mL/hr/kg<sup>0.75</sup>)

$CL_{passive\_M} = P_{neutral} * muscle\ SA * 3600$   
(mL/hr/kg<sup>0.75</sup>)

Liver\_CL\_pd: input parameter  
(mL/hr/kg<sup>0.75</sup>)

$CL_{passive\_L} = CL_{passive\_L\_app} / frac\_nonionized$   
(mL/hr/kg<sup>0.75</sup>)

$CL_{passive\_M} = CL_{passive\_L} * muscle\ SA / liver\ SA$   
(mL/hr/kg<sup>0.75</sup>)



# Compound Ionization is Determined by Compound pKa and System pH

- The default assay pH for in vitro permeability is 7.4 - can be changed if in vitro experiment is run under different assay conditions
- The pKa of Comp W/X/Y and stable metabolites now need to be entered as parameters

DILIsym Parameter Customization

Group: Species | Subgroup: Biological specifications

Variable	Value	Units	
Other tissue surface area	4.4607e+05	cm <sup>2</sup> /kg*0.75	This parameter represents the other
Plasma pH	7.4000	dimensionless	This parameter represents the plas
Gut tissue pH	7	dimensionless	This parameter represents the intra
Liver tissue pH	7	dimensionless	This parameter represents the intra
Muscle tissue pH	7	dimensionless	This parameter represents the intra
Other tissue pH	7	dimensionless	This parameter represents the intra
In vitro permeability assay pH	7.4000	dimensionless	This parameter represents the pH i
Hepatocyte membrane potential	-0.0350	V	This parameter represents the mer
Universal gas constant	8.3145	J/K/mol	This parameter represents the univ
Abscu temperature	310.1500	K	This parameter represents the tem

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DILIsym Parameter Customization

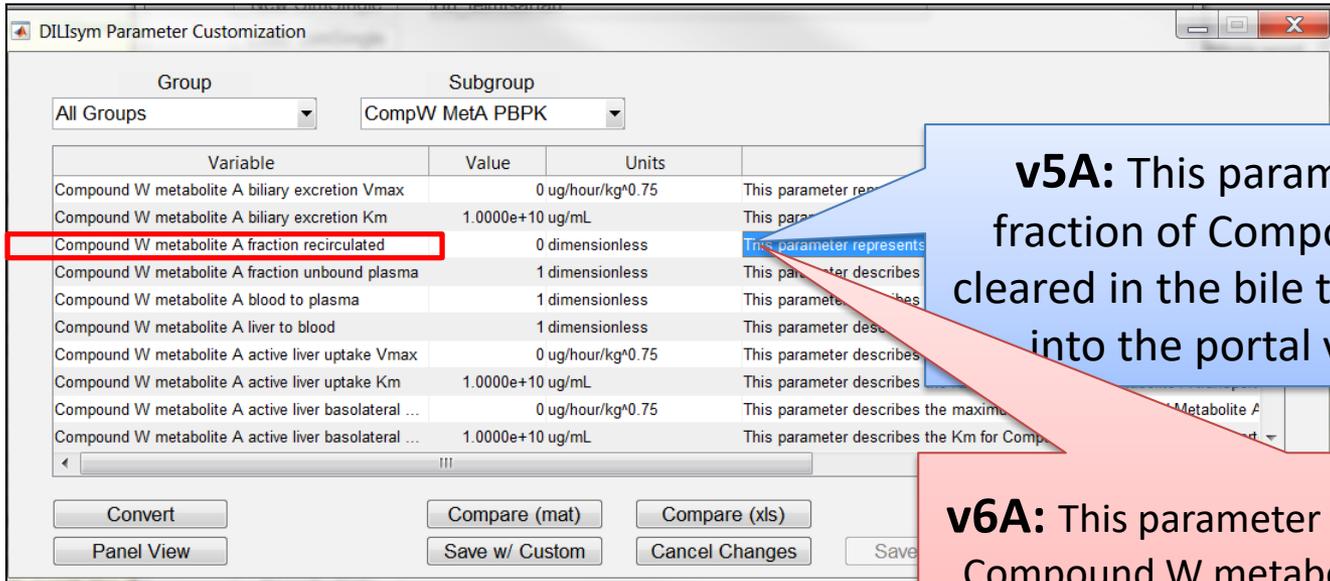
Group: Drug | Subgroup: Compound W PBPK

Variable	Value	Units	
Compound W fu liver correlation constant	0	dimensionless	This parameter is the cons
Compound W fu liver switch	0	dimensionless	This parameter is the switc
Compound W fu liver defined by the user	0	dimensionless	This parameter represent t
Compound W molecular weight	1.0000e-03	g/mol	This parameter represents
Compound W acid base switch	1	switch	This parameter describes t
Compound W pKa 1 or pKa base (for zwitter ion)	0	dimensionless	This parameter describes t
Compound W pKa 2 or pKa acid (for zwitter ion)	0	dimensionless	This parameter describes t
Compound W renal clearance	0	mL/hour/kg*0.75	This parameter represents
k(diss) - Compound W	12	1/hour	This parameter describes t
k(ge) - Compound W	12	1/hour	This parameter describes t
k(kt) - Compound W	7.4000	1/hour	This parameter describes t

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# Clarify Parameter Names and Descriptions for Recirculation



DILIsym Parameter Customization

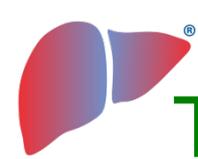
Group: All Groups      Subgroup: CompW Meta PBPK

Variable	Value	Units	Description
Compound W metabolite A biliary excretion Vmax	0 ug/hour/kg <sup>0.75</sup>		This parameter represents the maximum biliary excretion rate of Compound W metabolite A.
Compound W metabolite A biliary excretion Km	1.0000e+10 ug/mL		This parameter describes the concentration of Compound W metabolite A at which the biliary excretion rate is half of Vmax.
Compound W metabolite A fraction recirculated	0 dimensionless		This parameter represents the fraction of Compound W metabolite A cleared in the bile that is recirculated back into the portal vein.
Compound W metabolite A fraction unbound plasma	1 dimensionless		This parameter describes the fraction of Compound W metabolite A that is unbound in plasma.
Compound W metabolite A blood to plasma	1 dimensionless		This parameter describes the ratio of the concentration of Compound W metabolite A in blood to its concentration in plasma.
Compound W metabolite A liver to blood	1 dimensionless		This parameter describes the ratio of the concentration of Compound W metabolite A in the liver to its concentration in blood.
Compound W metabolite A active liver uptake Vmax	0 ug/hour/kg <sup>0.75</sup>		This parameter describes the maximum active liver uptake rate of Compound W metabolite A.
Compound W metabolite A active liver uptake Km	1.0000e+10 ug/mL		This parameter describes the concentration of Compound W metabolite A at which the active liver uptake rate is half of Vmax.
Compound W metabolite A active liver basolateral ...	0 ug/hour/kg <sup>0.75</sup>		This parameter describes the maximum active liver basolateral uptake rate of Compound W metabolite A.
Compound W metabolite A active liver basolateral ...	1.0000e+10 ug/mL		This parameter describes the Km for Compound W metabolite A active liver basolateral uptake.

Buttons: Convert, Panel View, Compare (mat), Save w/ Custom, Compare (xls), Cancel Changes, Save

**v5A:** This parameter represents the fraction of Compound W metabolite A cleared in the bile that is recirculated back into the portal vein (Min:0, Max:1)

**v6A:** This parameter represents the fraction of Compound W metabolite A cleared in the bile that is converted to Compound W in the gut lumen and recirculated back into the portal vein as Compound W (Min:0, Max:1)



# Transporter-Mediated Hepatic Basolateral Efflux Added for Comp W, X, Y





# New Outputs Added for QWBA Comparison

CompW_all_liver_to_blood	Compound W liver to blood ratio including parent and metabolites	dimensionless
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- Calculates liver:blood ratio for the sum of all species (parent+metabolites) in the simulation
- In the QWBA study, radioactivity is measured and reported as “ug equivalent of parent/g tissue”
  - Stable metabolite concentrations corrected for M.W. differences
  - RM and RM-adducts in molar unit converted to ug using the m.w. of the parent
  - Plasma RM-adduct concentrations converted to blood RM-adduct concentrations



# DILIsym Training on PBPK Structure

- Overview of the PBPK sub-model changes in DILIsym v6A
- Parameterizing the PBPK sub-model for DILIsym v6A



# The PBPK Representation in DILIsym Depends Heavily on the Development Stage of the Compound being Simulated

## Early candidate screening

- Metabolic clearance of parent compound and coincidental appearance of specific metabolites *in vitro*
- Potential for active transport in the liver *in vitro* (rate of hepatocyte uptake); transport kinetic information if possible
- Basic molecular properties
  - Acid or base?
  - Monoprotic or diprotic
  - pKa(s)
  - log P (oil:water and octanol:water)
  - Fraction bound to plasma or serum proteins
  - Fraction partitioned into red blood cells

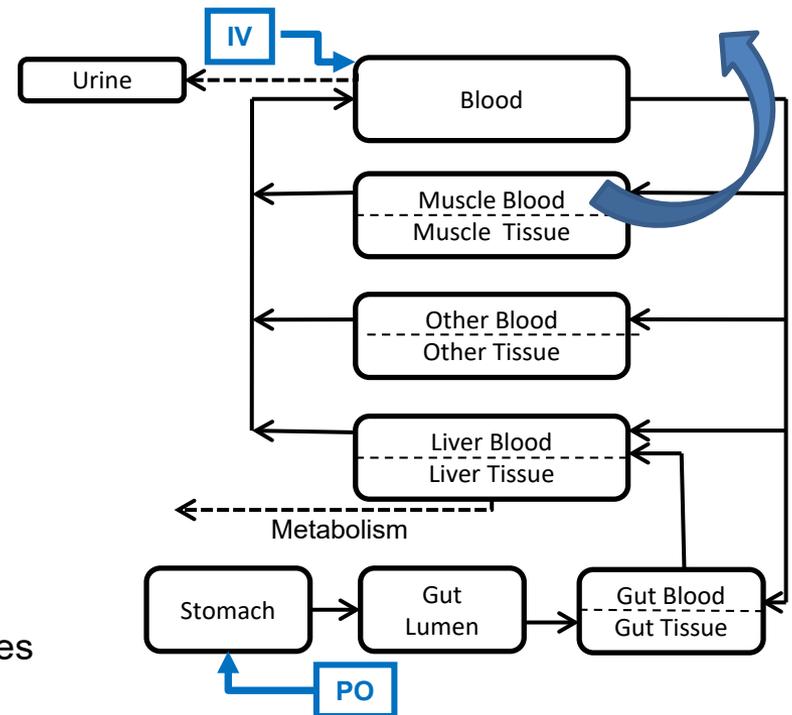
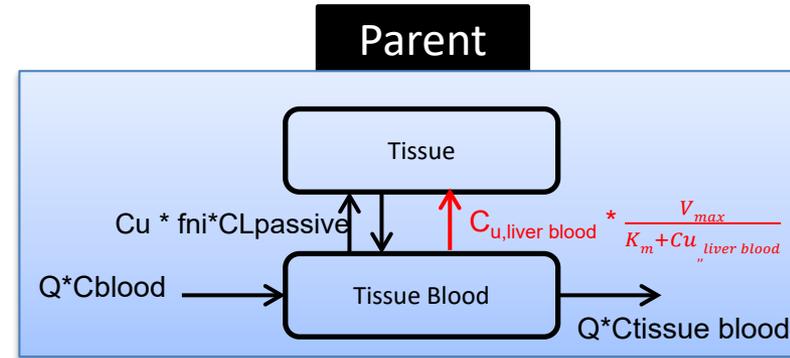
## Late-stage development / OTM

- *In vivo* PK time-course and dose-response
- Mass balance tissue distribution studies in animals (*in vitro* accumulation as well)
- *In vitro* drug metabolism assays identifying the appropriate metabolizing enzymes for the drug
- Metabolic clearance of parent compound and coincidental appearance of specific metabolites
- Potential for active transport in the liver (rate of hepatocyte uptake); transport kinetic information if possible
- Basic molecular properties



# DILIsym PBPK Overview – Compounds W and X

- Compound W, X, and Y PBPK models for drug combinations
- Compound W and X PBPK models feature five main compartments
  - Gut, liver, blood, muscle, other
- Parent metabolized to metabolite A or B, or reactive metabolites A or B in the liver
  - Michaelis-Menten kinetics
  - Primary metabolite models include three main compartments (liver, blood, other)
  - As of v5A, stable metabolites A and B can be generated by intestinal metabolism
- Oral and IV dosing available
  - IP dosing also included; not generally used for human
- Liver is divided into periportal (PP), midlobular (ML), and centrilobular (CL) zones to allow for zonal distribution of drug and injury
  - 5:3:1 volume distribution
  - Blood flow goes from PP → ML → CL
  - Metabolic activity can be adjusted among the zones



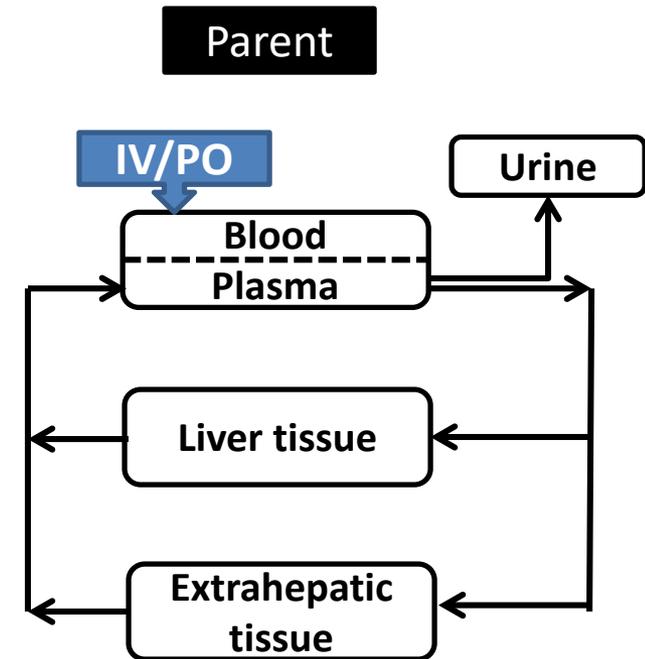
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# DILIsym PBPK Overview – Compound Y

- Compound Y is a simpler two compartment model
- Minimal PBPK sub-model:
  - Consists of blood, liver, and extrahepatic compartments
  - Metabolite disposition is not tracked
  - Clearance options include renal, non-renal from plasma compartment, and hepatic clearance from liver compartment
- Oral and IV dosing available
  - IP dosing also included; not generally used for human
- Liver is represented with a single, well-mixed compartment
- Extrahepatic distribution is determined by volume of distribution

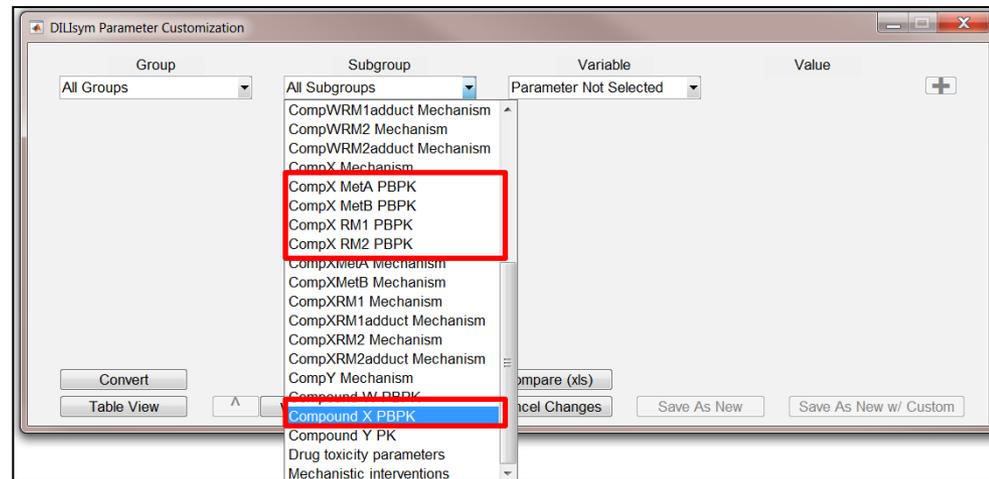




# Selecting Proper PBPK Parameters Is Necessary to Get Maximum Value from DILIsym Simulations

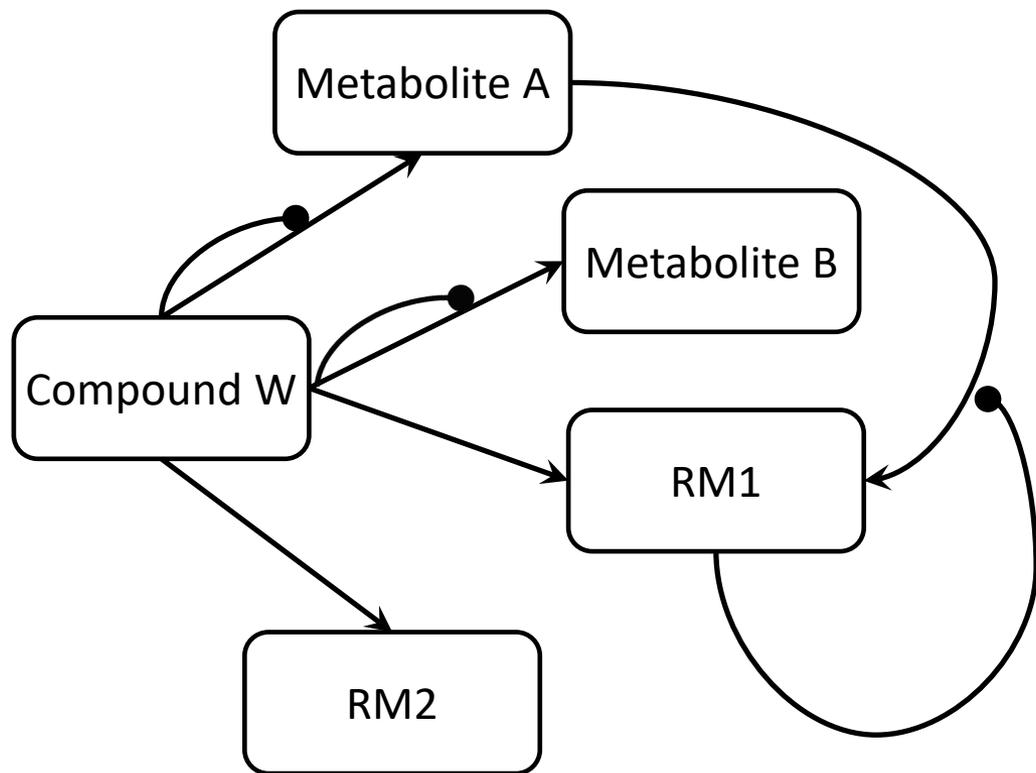
- Liver concentration dynamics are important for the accurate prediction of toxicity
- DILIsym contains many PBPK parameters for the Compound W and X models
- PBPK model parameterization requires two main steps

- Selecting appropriate metabolic scaffold
- Parameterizing model





# DILIsym Can Represent Up To Four Metabolites In Addition to Parent Compound

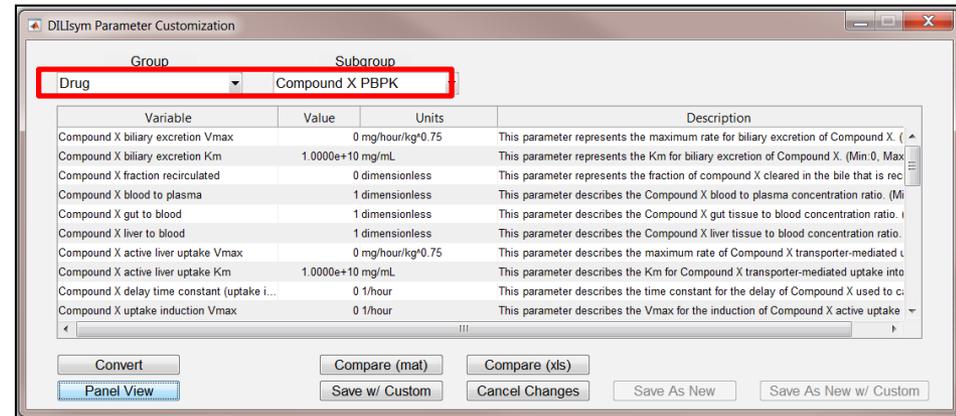


- Selecting the proper metabolism scaffold requires:
  - Knowing what data are available for each metabolite
  - Knowing what chemical species are likely to be involved in toxic mechanisms
- Example: bosentan
  - Two main metabolites, neither reactive
  - Minor metabolite involved in toxicity
  - Parent compound induces metabolism



# Selecting Proper PBPK Parameters Is Necessary to Get Maximum Value from DILIsym Simulations

- Liver concentration dynamics are important for the accurate prediction of toxicity
- DILIsym contains many PBPK parameters for the Compound W and X models
- PBPK model parameterization requires two main steps
  - Selecting appropriate metabolic scaffold
  - Parameterizing model





# DILIsym PBPK Input Parameters Fall Into Several Main Categories

- Absorption
  - Saturable and linear models

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

Variable	Value	Units	
Compound X renal clearance	0	mL/hour/kg <sup>0.75</sup>	This parameter r
k(diss) - compound X	12	1/hour	This parameter d
k(ge) - compound X	12	1/hour	This parameter d
k(ab) - compound X	5	1/hour	This parameter d
Compound X absorption from gut Vmax	0	1/hour	This parameter d
Compound X absorption from gut Km	1.0000e+10	mg	This parameter d
Compound X rate of elimination in feces	0	1/hour	This parameter d
k(ab) conjugates - compound X	0	1/hour	This parameter d
k(ab,IP dose) - compound X	12	1/hour	This parameter d
k(IV) - compound X	60	1/hour	This parameter d



# DILIsym PBPK Input Parameters Fall Into Several Main Categories

- Absorption
  - Saturable and linear models
- Distribution
  - Linear and non-linear plasma protein binding
  - Blood to plasma partition coefficient
  - Tissue partition coefficients
  - Transporter-mediated uptake model for liver
  - Liver partition coefficient and volume of distribution for metabolites

Variable	Value	Units	
Compound X blood to plasma	1	dimensionless	This parameter de
Compound X gut to blood	1	dimensionless	This parameter de
Compound X liver to blood	1	dimensionless	This parameter de
Compound X active liver uptake Vmax	0	mg/hour/kg <sup>0.75</sup>	This parameter de
Compound X active liver uptake Km	1.0000e+10	mg/mL	This parameter de
Compound X delay time constant (uptake i...	0	1/hour	This parameter de
Compound X uptake induction Vmax	0	1/hour	This parameter de
Compound X uptake induction Km	1.0000e+10	mg/mL	This parameter de
Compound X uptake induction Hill	0	dimensionless	This parameter de
Compound X membrane permeability	0	mL/hour/kg <sup>0.75</sup>	This parameter de



# DILIsym PBPK Input Parameters Fall Into Several Main Categories

- Absorption
  - Saturable and linear models
- Distribution
  - Linear and non-linear plasma protein binding
  - Blood to plasma partition coefficient
  - Tissue partition coefficients
  - 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

Variable	Value	Units	
Km(Compound X metabolite A)		1 mol/mL	This parameter desc
Vmax(Compound X metabolite A)		0 mol/hour/kg <sup>0.75</sup>	This parameter desc
Compound X delay time constant (metabol...		0 1/hour	This parameter desc
Compound X metabolite A induction Vmax		0 1/hour	This parameter desc
Compound X metabolite A induction Km	1.0000e+10	mg/mL	This parameter desc
Compound X metabolite A induction Hill		0 dimensionless	This parameter desc
CL to PP activity Compound X metabolite A		1 dimensionless	This parameter desc
ML to PP activity Compound X metabolite A		1 dimensionless	This parameter desc
PP to PP activity Compound X metabolite A		1 dimensionless	This parameter desc
Vmax for intestinal formation of Compound		0 mol/hour/kg <sup>0.75</sup>	This parameter desc



# DILIsym PBPK Input Parameters Fall into Several Main Categories

- Absorption
  - Saturable and linear models
- Distribution
  - Linear and non-linear plasma protein binding
  - Blood to plasma partition coefficient
  - Tissue partition coefficients
  - 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
- Excretion
  - Biliary excretion ( $K_m$  and  $V_{max}$ ) and renal clearance of parent and main metabolites
  - Intestinal efflux
  - Clearance of protein adducts

Group	Subgroup	Variable	Value	Units	
Drug	Compound X PBPK	Compound X biliary excretion Vmax	0	mg/hour/kg <sup>0.75</sup>	This parameter repre
		Compound X biliary excretion Km	1.0000e+10	mg/mL	This parameter repre
		Compound X fraction recirculated	0	dimensionless	This parameter repre
		Compound X blood to plasma	1	dimensionless	This parameter desc
		Compound X gut to blood	1	dimensionless	This parameter desc
		Compound X liver to blood	1	dimensionless	This parameter desc
		Compound X active liver uptake Vmax	0	mg/hour/kg <sup>0.75</sup>	This parameter desc
		Compound X active liver uptake Km	1.0000e+10	mg/mL	This parameter desc
		Compound X delay time constant (uptake i...	0	1/hour	This parameter desc
		Compound X uptake induction Vmax	0	1/hour	This parameter desc

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# Fraction Unbound in Tissue Is Calculated by DILIsym or Can Be Defined by the User

- As of DILIsym v5A, drug disposition in the PBPK sub-model is based on the unbound concentration
  - Hepatic/intestinal metabolism and transport
  - Renal and biliary excretion
- DILIsym calculates tissue fraction unbound for liver, gut, muscle, and other tissue in the static calculation (default)
  - Calculated by the user prior to v5A
- Alternatively, the user can define the unbound fraction in the liver using the “Compound (X) fu liver switch”
  - If the switch is set to 1, “Compound (X) fu liver defined by the user” will be used in the PBPK sub-model
  - This option is available from v5A

Make sure to select relevant chemical entity (e.g., Compound W/X/Y, metabolite A/B...)

Variable	Value	Units	
Compound X fraction unbound plasma	1	dimensionless	This
Compound X fraction unbound correlation ...	0	dimensionless	This
Compound X fu correlation 2nd-order coeffi...	0	dimensionless	This
Compound X fu correlation 1st-order coeffi...	0	dimensionless	This
Compound X fu correlation constant	0	dimensionless	This
Compound X fu liver switch	0	dimensionless	This
Compound X fu liver defined by the user	0	dimensionless	This
Compound X molecular weight	1.0000e-03	g/mol	This
Compound X renal clearance	0	mL/hour/kg <sup>0.75</sup>	This
k(diss) - compound X	12	1/hour	This



# Fraction Unbound in Tissue Calculated by DILIsym v6A

- Unless the user turns on the “Compound (X) fu liver switch”, DILIsym calculates tissue fraction unbound for liver, gut, muscle, and other tissue in the static calculation
- In case of passive diffusion, the unbound, non-ionized tissue concentration is equal to the unbound, non-ionized plasma concentration

- $f_{u,tissue}$  is calculated from partition coefficients and the blood:plasma ratio

$$f_{u,tissue} = \frac{f_{u,plasma} \times f_{nonionized,plasma}}{\left(\frac{C_{tissue}}{C_{blood}}\right) \times B : P \times f_{nonionized,tissue}}$$

- In case of transporter-mediated liver uptake, the unbound liver concentration is not in equilibrium with the unbound plasma concentration

- An empirical equation used to estimate  $f_{u,liver}$  (Poulin and Theil 2000)

$$f_{u,cell} = \frac{1}{1 + \left(\frac{1 - f_{u,p}}{f_{u,p}} \cdot C_{m,tissue}\right)}$$

$C_{m,tissue}$ : relative albumin conc in the liver compared to plasma  
(often assumed to be 0.5)

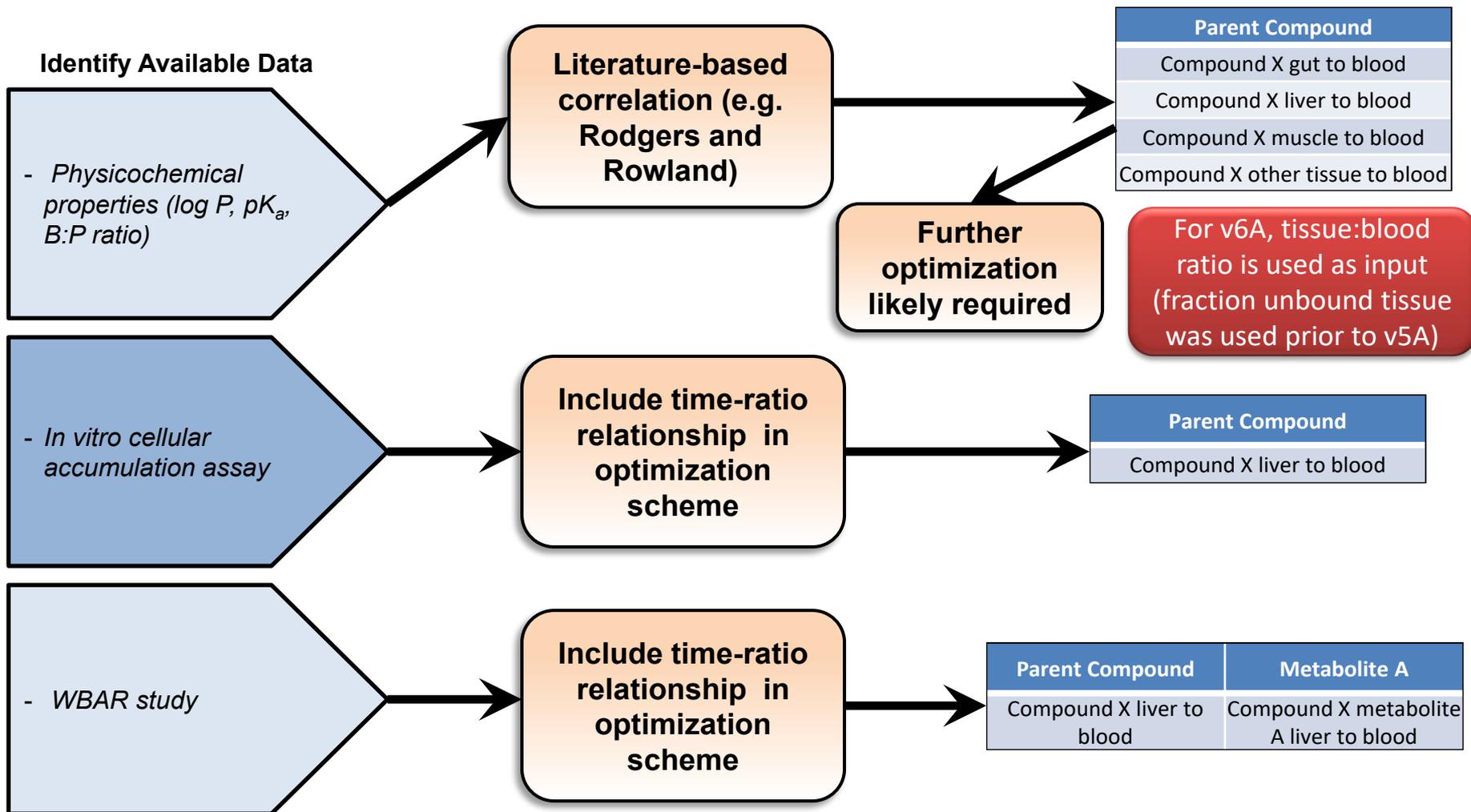


# Method for Determining Distribution Parameters Depends on Data Available

- Distribution parameters can be determined from either *in vivo* or *in vitro* data
  - Physicochemical properties
  - *In vitro* cellular uptake assays
  - Animal WBAR studies
- Input panel document provides some insight into most useful assays for best DILIsym inputs

Variable	Value	Units	
Compound X blood to plasma	1	dimensionless	This parameter de
Compound X gut to blood	1	dimensionless	This parameter de
Compound X liver to blood	1	dimensionless	This parameter de
Compound X active liver uptake Vmax	0	mg/hour/kg <sup>0.75</sup>	This parameter de
Compound X active liver uptake Km	1.0000e+10	mg/mL	This parameter de
Compound X delay time constant (uptake i...	0	1/hour	This parameter de
Compound X uptake induction Vmax	0	1/hour	This parameter de
Compound X uptake induction Km	1.0000e+10	mg/mL	This parameter de
Compound X uptake induction Hill	0	dimensionless	This parameter de
Compound X membrane permeability	0	mL/hour/kg <sup>0.75</sup>	This parameter de

# Predicting Partition Coefficients for Use in DILIsym

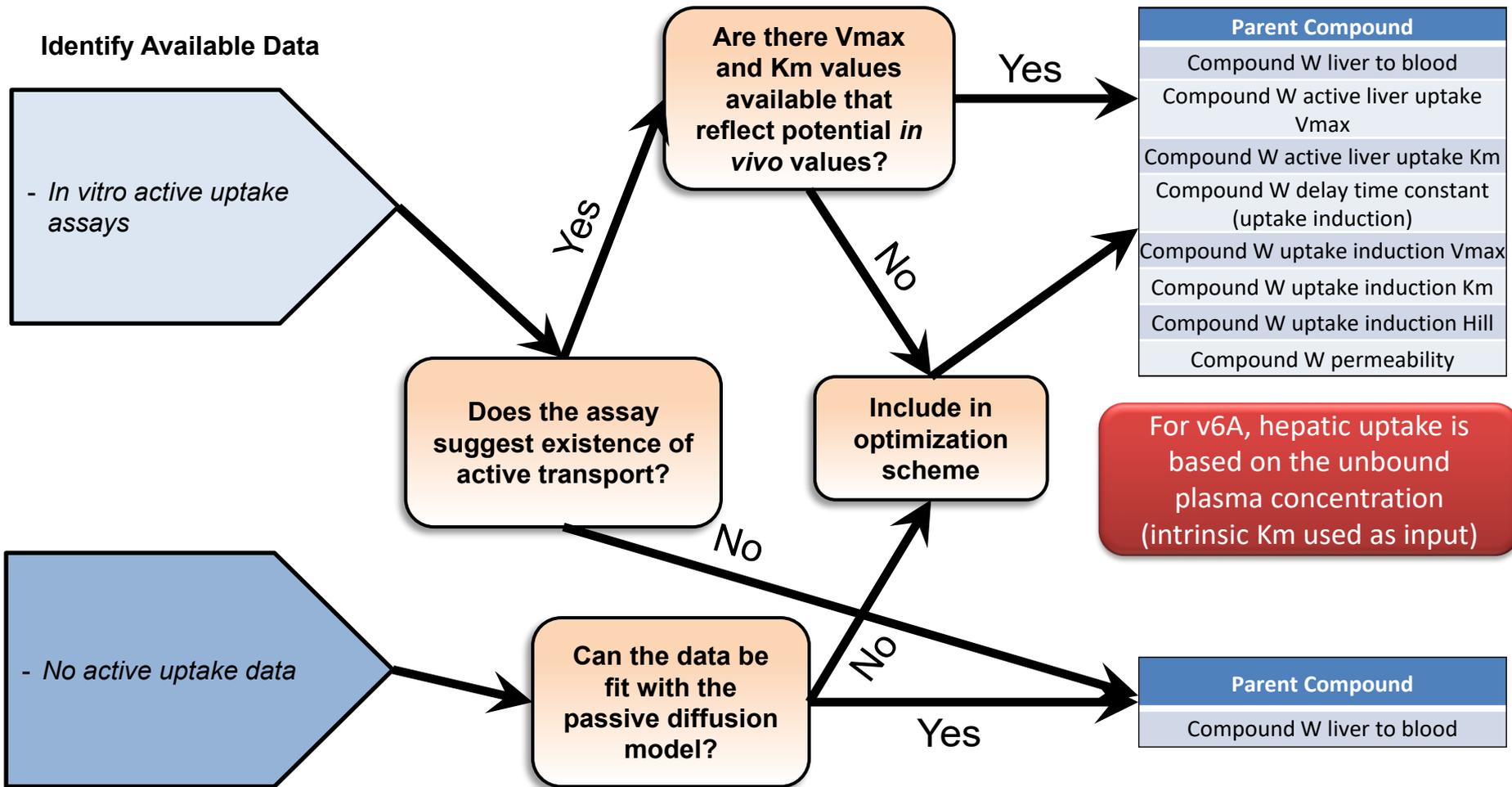


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# Selecting the DILIsym Parameters to Use for Active Liver Uptake



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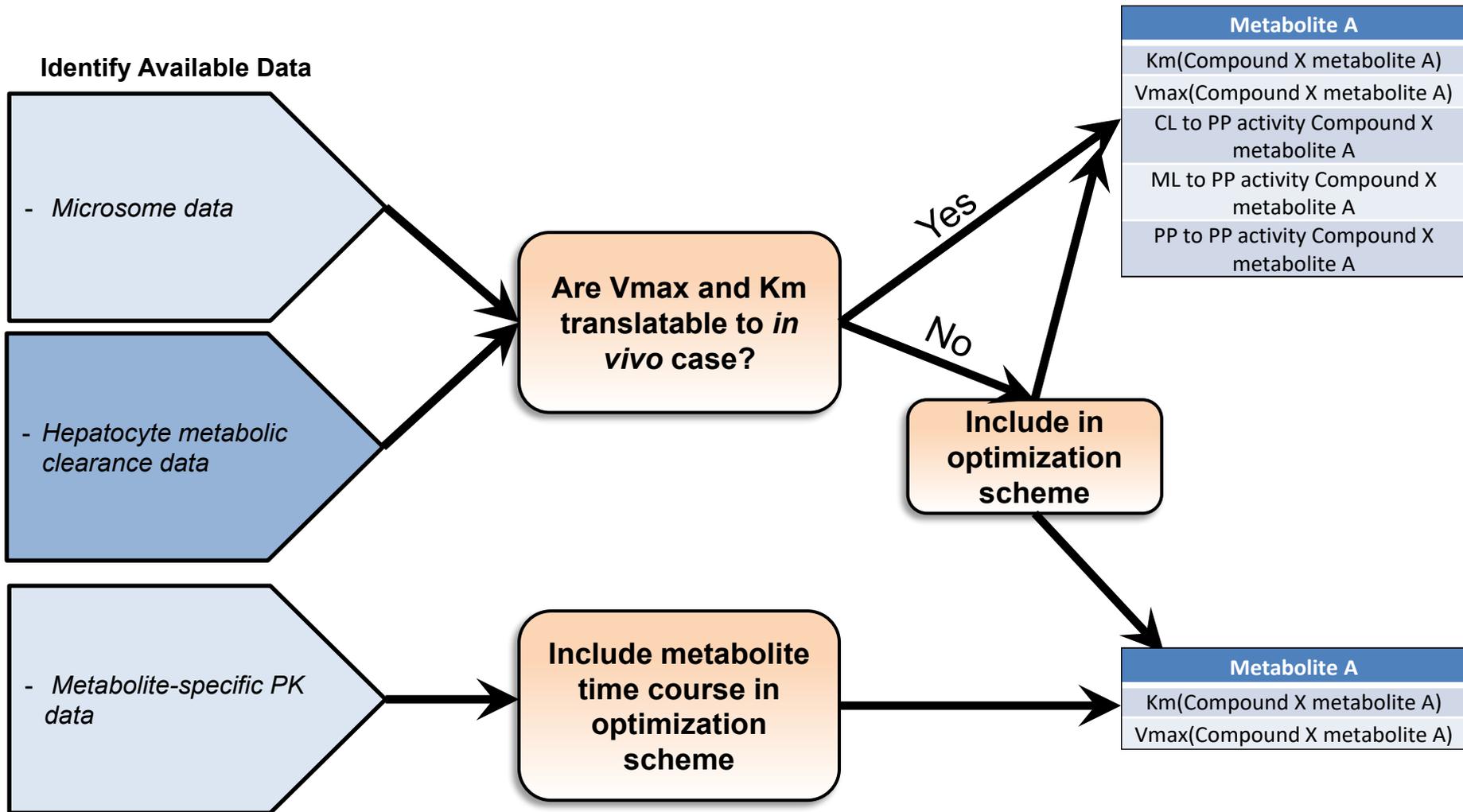
# Method for Determining Metabolism Parameters Depends on Data Available

- Metabolism parameters can be determined from *in vitro* data or by fitting to PK data
  - *In vitro* microsome data
  - Hepatocyte metabolic clearance data
  - PK data **including complete metabolite time course in plasma**
- Input panel document provides some insight into most useful assays for best DILIsym inputs

Group	Subgroup	Variable	Value	Units	
Drug	CompX MetA PBPK	Km(Compound X metabolite A)	1	mol/mL	This parameter desc
		Vmax(Compound X metabolite A)	0	mol/hour/kg <sup>0.75</sup>	This parameter desc
		Compound X delay time constant (metabol...)	0	1/hour	This parameter desc
		Compound X metabolite A induction Vmax	0	1/hour	This parameter desc
		Compound X metabolite A induction Km	1.0000e+10	mg/mL	This parameter desc
		Compound X metabolite A induction Hill	0	dimensionless	This parameter desc
		CL to PP activity Compound X metabolite A	1	dimensionless	This parameter desc
		ML to PP activity Compound X metabolite A	1	dimensionless	This parameter desc
		PP to PP activity Compound X metabolite A	1	dimensionless	This parameter desc
		Vmax for intestinal formation of Compound	0	mol/hour/kg <sup>0.75</sup>	This parameter desc



# Determining Metabolism Parameters for Use in DILIsym



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# Intestinal Metabolism and Transport Represented in DILIsym v6A

- As of v5A, intestinal metabolism and transport available for Compound X and W
  - Based on the unbound gut concentration
  - The user can define “Compound X fraction unbound in enterocyte”
- Stable metabolites (metabolite A and B) can be generated by gut metabolism
  - Saturable process ( $K_m$  and  $V_{max}$ )
  - Generated metabolites enter into liver tissue and are combined with liver-generated metabolites
- Efflux of parent compounds from gut tissue to intestinal lumen represented
  - Saturable process ( $K_m$  and  $V_{max}$ )

Variable	Value	Units
Compound X absorption from gut $V_{max}$	0	1/hour
Compound X absorption from gut $K_m$	1.0000e+10	mg
Compound X rate of elimination in feces	0	1/hour
$k(ab)$ conjugates - compound X	0	1/hour
$k(ab,IP)$ dose - compound X	12	1/hour
$k(lV)$ - compound X	60	1/hour
Compound X fraction unbound in enterocyt...	1	Dimensionless
Compound X gut efflux $V_{max}$	0	mg/hour/kg*0.75
Compound X gut efflux $K_m$	1.0000e+10	mg/mL
Compound X conversion factor to perfusion...	1	Dimensionless

Metabolism parameters are in the “metabolite” subgroup

Variable	Value	Units
Compound X delay time constant (metabol...	0	1/hour
Compound X metabolite A induction $V_{max}$	0	1/hour
Compound X metabolite A induction $K_m$	1.0000e+10	mg/mL
Compound X metabolite A induction Hill	0	dimensionless
CL to PP activity Compound X metabolite A	1	dimensionless
ML to PP activity Compound X metabolite A	1	dimensionless
PP to PP activity Compound X metabolite A	1	dimensionless
$V_{max}$ for intestinal formation of Compound...	0	mol/hour/kg*0.75
$K_m$ for intestinal formation of Compound X...	1.0000e+10	mol/mL
Compound X metabolite A conversion fact...	1	Dimensionless



# Determining DILIsym Parameter Values for Biliary Excretion

## Data Available for Compound

- Log P  
- pKa  
- Fraction unbound (blood)  
- B:P ratio



- Absorption – IV dosing  
- Organ partition coefficients and fractions unbound  
- Renal clearance  
- Biliary excretion

- Prior to v5A, biliary excretion was represented as a linear biliary clearance
  - Based on the total liver concentration
- As of v5A, biliary excretion is represented as a saturable process
  - Michaelis Menten kinetics employed ( $K_m$  and  $V_{max}$ )
  - Based on the unbound liver concentration
  - Kinetic parameters can be obtained by translating *in vitro* transport data or optimized to *in vivo* data (e.g., biliary recovery)

Parent Compound
Comp_W_bil_cl



Parent Compound
Comp_W_bil_Vmax
Comp_W_bil_Km

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