





THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

### DILIsym<sup>®</sup> User Training -Defining RNS/ROS Toxicity Parameter Values in DILIsym<sup>®</sup>

#### **DILI-sim** Team

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### **Goal for This Training Session**

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

 Methods used to parameterize and to simulate disturbances in the reactive oxygen species balance in DILIsym<sup>®</sup>





# Modeling Compounds that Disturb the Reactive Oxygen Species Balance

- Outline of method used to translate *in vitro* ROS/RNS data to DILIsym<sup>®</sup> parameters
  - Establish a dose response to use for the optimization
    - Dose response comparing RNS/ROS to producer concentration
    - Intracellular concentration preferred
  - Implement an '*in vitro*' like environment within DILIsym<sup>®</sup> using Compound Y
    - *'in vitro*' Compound Y drug parameters available in DILIsym<sup>®</sup> v4B
      - "Parameters\_Drug\_Human\_ROS\_invitro\_CompY\_SteadyState"
  - Optimize the simulations to match the in vitro data
    - Use Parameter Sweep tool to find value of RNS\_ROS\_prod\_const that produces appropriate amount of RNS/ROS at most concentrations
    - Requires some iteration in order to match all concentrations





### Example of Determining ROS Production Toxicity Parameter Value in DILIsym<sup>®</sup>

Objective: determine ROS production toxicity parameter value for the following mock RNS/ROS data







### Setup an "in vitro-like" Simulation within DILIsym<sup>®</sup> Using Compound Y

DILIsym v4B			• Set u	up SimSingle with Compound Y in
File Results View Help			vitro	drug parameters
u 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2				
SimSingle Setup			- ;	Set compound molecular weight
New SimSingle	in_vitro_ROS_parameter_ID			
Load SimSingle				<ul> <li>MW = 400 g/mol for this example</li> </ul>
Input Parameters				
Species	Parameters_Species_Human_v4B	▼ <mark>ize</mark>		
Drug	Parameters_Drug_Human_ROS_invitro_Comp	oY_St ▼ Customized		
		Mechanism		
		DILIsym Parameter Customization		
Caloric Intake	Parameters_Calories_Blank_v4B	Group	Subaroup	
Comp W Dosing	Parameters_CompWDosing_Blank_v4B	Drug	Compound Y PK	
Comp X Dosing	Parameters_CompXDosing_Blank_v4B			
Comp Y Dosing	Compound_Y_24hr_IV_infusion	Variable	Value Units	Description
		k(ab,IP) -Compound Y	15 1/hour	This parameter describes the rate of Compound Y absorption (ab) into the blood aft
Time	Parameters_Time_24hr_Default_v4B	k(ab,IV) - Compound Y	1000 <mark>1/hour</mark>	This parameter describes the rate of Compound Y absorption (ab) into the b
Solver	Parameters_Solver_Default_v4B	k(ab,oral) - Compound Y	5 1/hour	This parameter describes the rate of Compound Y absorption (ab) into the blood aft
		Compound Y mg to mol	2.5000e-06 mol/mg	This parameter represents the conversion factor from mg to moles tor Comr
Input Panel	Panel_Blank	Compound Y non-renal clearance	0 mL/hour/ka^0.75	This parameter represents the non- renal clearance rate of Compound Y. (Min:0. M
		Compound Y hepatic clearance	1000 mL/hour/kg^0.75	This parameter represents the hepatic clearance rate of Compound Y. (Min:
Simulate	Run in Parallel SimPops Pa	Compound Y oral bioavailability	1 dimensionless	This parameter represents the fraction of an oral dose of Compound Y that reaches
Specify Data		Compound Y renal clearance	0 mL/hour/kg^0.75	This parameter represents the renal clearance rate of Compound Y. (Min:0, Max:Int
Opecity Data		Compound Y transport Km	1 mol/mL	This parameter describes the Michaelis-Menten constant (Km) for the influx of Cor
Plot	Table Export Sa	•	m	4
		Panel View	Save w/ Custom	Cancel Changes Save As New Save As New w/ Custom





### Setup an "in vitro-like" Simulation within DILIsym<sup>®</sup> Using Compound Y

DILIsym v4B				•	Set up 24 h	nour IV infusio	n dosina	
File Results View Help								
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SimSingle Setup								
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Load SimSingle								
Input Parameters								
Species	Parameters_Species_Human_v4B	customiz	ze					
Drug	Parameters_Drug_Human_ROS_invitro_CompY_St	Customiz	zed				_	
		Mecha	DILIsym Parameter Customi	zation				
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Comp X Dosing	Parameters_CompXDosing_Blank_v4B	Custor	CompYDosing		Compound Y IV infusion	Compound Y IV infusion rate	1000	
Comp Y Dosing	Compound_Y_24hr_IV_infusion	Custom	j				1000 mg/nour	
Time	Parameters Time 24hr Default v4B	Custon						
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Contra								
Input Panel	Panel_Blank •	View						
Simulate	Run in Parallel         SimPops         Param Sweep	Data Com	Toble View		V Sava w/ Custom	Consol Changes		ow w/ Custom
Specify Data			Table View		V Save w/ Custom	Cancer Changes Save As N	Save As IN	ew w/ Cusion
Plot	Table         Export         Save Results	SimSing	le					





#### Constant Liver Exposure Achieved with "in vitro-like" Setup

DILIsym v4B				
File Results View Help				Constant liver exposure mimics
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SimSingle Setup				the <i>in vitro</i> environment
New SimSingle	in_vitro_ROS_pa	arameter_ID		
Load SimSingle				
Input Parameters				
Species	Parameters_Spe	ecies_Human_v4B	Customize	
Drug	Parameters_Dr	RUS_INNS	Customized	
		Plot DILIsym Results		
Caloric Intake	arameters_Cal		Group	Subgroup Output Variable
Comp W Dosi	Parameters_Cor		Pharmacokinetics	✓ Compound Y ✓ All Variables ✓
Comp X D	Parameters_Cor		0.041 -	
Comp Y	Compound_Y_2	Blank Panel	0.041	
Time	Parameters_Tim	Liver Compound Y	ur)	
Sol	Parameters_Sol			
Inn	Panel Blank	-	) × P	
		-	й 0.021 —	Liver Compound Y (mg/mL)
	Run in Parallel		dwo	
Specify Data			ර කු 0.01 –	
Plot	Table		Ľ.	
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				Time (hours)
		Standard		
		Time	Table View	Export Plot eDISH Reset

Simulation Results





### Tune Compound Y Infusion Rate to Approximate Liver Exposure

- Pick an exposure level: 0.5 mg/mL
- Tune the Compound Y infusion rate to get exposures in the liver in the range of the *in vitro* exposure estimates
  - 12000 mg/hour in our example



\Lambda DILIsym I	Parameter Sweep				
	Group	Subgroup	)	Vari	iable
Com	oYDosing -	Compound Y I	/ inf ▼	All Variable	es
Lowe	r limit of sweep	1000	Number of sv	veep steps	8
Base	value (from SimSinale)	1000	Type of swee	ae	Linear
Uppe	r limit of sweep	15000	Add to table		
	7000 9000 11000				
Step Selec Save Sav	13000 15000 through bles simu et DIV uts Pr Sweep results Load Setu	Itaneousiv New output to data file p Reset	panel	All	Cancel
Step Selec Save Sav	13000 15000 through ples simu et DIV uts Pr Sweep results Load Setu Parameters_Solver_	Itaneously New output to data file P Reset Default_v4B	panel		Cancel
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Step Selec Save Sav Diver put Panel Simulate Specify Dat	13000 15000 through Des simu th DIV Uts Pr Sweep results Load Setu Parameters_Solver Panel_Blank R	Itaneousiv New output s to data file p Reset Default_v4B	panel Run	All	Cancel Customize Viewer Comparison

Theoretical Preclinical Data and Simulation Results



Institute for Drug Safety Sciences



## Using the Parameter Sweep Tool for RNS/ROS Production Rate Constant 1

- For the selected exposure level (.5 mg/mL concentration), use the parameter sweep tool within DILIsym<sup>®</sup> to find a Liver RNS/ROS production rate constant 1 value that gives a reasonable level of ROS (i.e. ~2.5x) at the corresponding time point (24 hrs)
  - Make sure to update Compound Y infusion rate to 12000 mg/hr
  - Output to use for ROS is 'Liver average RNS/ROS'
  - For our case, value is roughly 80,000



Group	Subgroup		Variable
Drug 💌	Drug toxicity par	ram… ▼ All Var	iables -
Lower limit of sweep	10000	Number of sweep s	teps 8
Base value (from SimSinale)	0	Type of sweep	Log10 -
Upper limit of sweep	100000	Add to table	E E
Liver RNS/ROS production rat	te constant 1		
	10000		
	1.3895e+04		
	1.9307e+04		
	2.6827e+04		
	3.7276e+04		
	5.1795e+04		
	7.1969e+04		
	100000		
Step through all variables simu	Iltaneously		
Select DILIsvm Outputs	New output p	All	•
Save Parameter Sweep results	s to data file		<b>v</b>





## Setup SimSingle<sup>™</sup> with New RNS/ROS Production Rate Constant 1

ILLISYM v4B		
File Results View Help		
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SimSingle Setup		
New SimSingle	in_vitro_ROS_parameter_ID	
Load SimSingle		
Input Parameters		
Species	Parameters_Species_Human_v4B	С
Drug	Parameters_Drug_Human_ROS_invitro_CompY_St 🔽	Cu
		Mechanism
Caloric Intake	Parameters Calories Blank v4B	Customize
Comp W Dosing	Parameters CompWDosing Blank v4B	Customize
Comp X Dosing	Parameters_CompXDosing_Blank_v4B	Customize
Comp Y Dosing	Compound_Y_24hr_IV_infusion	Customized
Time	Description Time Other Default utD	Customizo
Time	Parameters_1ime_24nr_Detault_v4B	Customize
Solver	Parameters_Solver_Default_v4B	Customize
Input Panel	Panel_Blank	Viewer
Simulate	Run in Parallel SimPops Param Sweep	Data Comparison
Specify Data		
Plot	Table Export Save Results	SimSingle

DILIsym Parameter Custo	mization		
Molecule All Molecules	-	Mechanisms All Mechanisms	
CompY		incRNSROSproduction1	Liver RNS/ROS production 80000 mL/mol/hour 2

- Return to SimSingle<sup>™</sup> setup
- Change RNS/ROS Production Rate Constant 1
   to new value in drug parameters
- Save drug parameter set





#### Parameter Sweep on In Vitro Dose

- Run dose sweep over entire exposure range measured in *in vitro* experiments
  - Dose scales with in vitro intracellular concentration
- Compare simulated results with experimental results
- Iterate if necessary using different ROS production rate constants
  - Not necessary here

