



***DILIsym Services***

**S+** A SIMULATIONS PLUS COMPANY

# **DILIsym User Training – Using the Specified Data Feature within DILIsym**

## **DILIsym Development Team**

*\* DILIsym®, NAFLDsym®, and MITOsym® are registered trademarks and SimPops™ and SimCohorts™ are trademarks of DILIsym® Services Inc. for computer modeling software and for consulting services.*

**CONFIDENTIAL**



# Goal for The Specified Data Training Session

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

- The behind-the-scenes structure of the Specified Data feature
- The basics of using the 'Specified Data' feature within DILIsym
- How to use the 'Specified Data' feature within DILIsym to run simulations with loaded PK results, which may be derived from direct measurements or other simulation engines such as GastroPlus, etc.

***DILIsym Services***



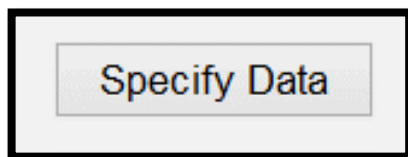
A SIMULATIONS PLUS COMPANY

**CONFIDENTIAL**



# DILIsym Specified Data Feature – General Introduction

- The 'Specify Data' tool allows users to specify values for one or more state variables
- The tool allows a user to overwrite the differential equations in DILIsym with user-defined values
- Values for any state variable in DILIsym can be specified using this tool
  - ONLY state variables can be specified, e.g., drug concentration in plasma over time cannot be specified, but blood concentrations can be
- The 'Specify Data' tool can be used with SimSingle simulations or with Run in Parallel, Parameter Sweep, or SimPops simulations



***DILIsymServices***

**S+** A SIMULATIONS PLUS COMPANY

CONFIDENTIAL



# Some Applications of Specified Data

1. Drug concentration time course profiles from data or predicted using another PK simulation program can be used as inputs into DILIsym
  - Allows for compatibility with other PK simulation programs (GastroPlus, PK Sim, Berkeley Madonna, Simcyp, etc.)
  - As of GastroPlus 9.6, Specify Data allows for direct importation of drug concentration time course profiles from Gastroplus into DILIsym (when using the 'DILIsym mode' for export within GastroPlus)
  - ***Avoids the need to build PBPK representation in DILIsym***
2. Drug concentrations can be specified in a manner that mimics *in vitro* exposure for toxicity parameter identification
3. Values for other DILIsym state variables can be specified for exploration of hypothesized or published scenarios
  - e.g., ATP levels in the liver could be specified
  - e.g., bile acid concentration profiles could be specified
  - These types of applications require an advanced expertise level with DILIsym
  - Often used for model development or hypothesis testing



# The Infrastructure Required for the DILIsym Specified Data Feature

- Specified state variables are overwritten going into and coming out of the differential equations file
- All other equations are solved as usual
  - *Other DILIsym outputs will use the specified value in their equations if the specified state appears*
  - *Important to input parameters for other needed calculations using the specified state variable*
- The process of overriding states at a particular time within the simulation requires interpolation (if time dependent)
  - MATLAB interp1 function used
  - Linear interpolation between 2 points
  - Very sparse input data will not work as well as granular data – true shape of curve could be missed
    - e.g. AUC would be over predicted with only peak and final values provided

Specified state variables are overwritten prior to the equation solving process so the specified values are used during the process; practically, the value of the differential equation does not matter



*DILIsym Differential Equations and Algebraic Expressions*  
Mathematics behind the simulations; all equations solved as usual except overwritten state variables



Specified state variables are overwritten after the equation solving process so the specified values are exported for reporting purposes



# Important Considerations When Using Specified Data

- ***Only state variables can be specified (note the absence of some outputs when building the template because they are not states)***
- ***Parameters determining the relationship between specified and non-specified state variables must be put in by the user***
  - e.g. specifying blood concentration does not automatically determine liver concentration; specifying blood concentration does not lead to correct plasma concentration value unless B:P is entered
  - **Must put in molecular weight of compound and metabolites if concentrations specified**
  - **Must put in toxicity mechanism parameters for compounds if concentrations specified for them to have an effect**
- Accumulation is conserved when repeating a specified data set (i.e. if a cycle does not return to starting value, the state variable will accumulate over time)
- Feedback between liver injury and PK is lost when using specified data for PK inputs
- Specified data is primarily designed for PK inputs
  - **Recommendation: always specify blood concentrations when liver is specified**



# DILIsym Specify Data Tool – Critical Components

1. SimSingle (simulation setup) within DILIsym via the home screen
  - Parameter selections (dosing, species, time, etc.) are made from the primary DILIsym home screen
  - A simulation needs to be set up, during which the overwriting will occur
2. Selection of options for template generation
  - State variables
  - Time dependent or constant for each one
  - Number of simulated individuals included in template
3. Populate Excel template with required information and save
4. Load data in from template and select other options

***DILIsymServices***

**S+** A SIMULATIONS PLUS COMPANY

CONFIDENTIAL



# DILIsym Specify Data Tool – Step By Step Instructions

1. SimSingle (simulation setup) within DILIsym via the home screen
  - Parameter selections (dosing, species, time, etc.) are made from the primary DILIsym home screen
  - A simulation needs to be set up, during which the overwriting will occur
2. Selection of options for template generation
  - State variables
  - Time dependent or constant for each one
  - Number of simulated individuals included in template
3. Populate Excel template with required information and save
4. Load data in from template and select other options

***DILIsymServices***

**S+** A SIMULATIONS PLUS COMPANY

CONFIDENTIAL





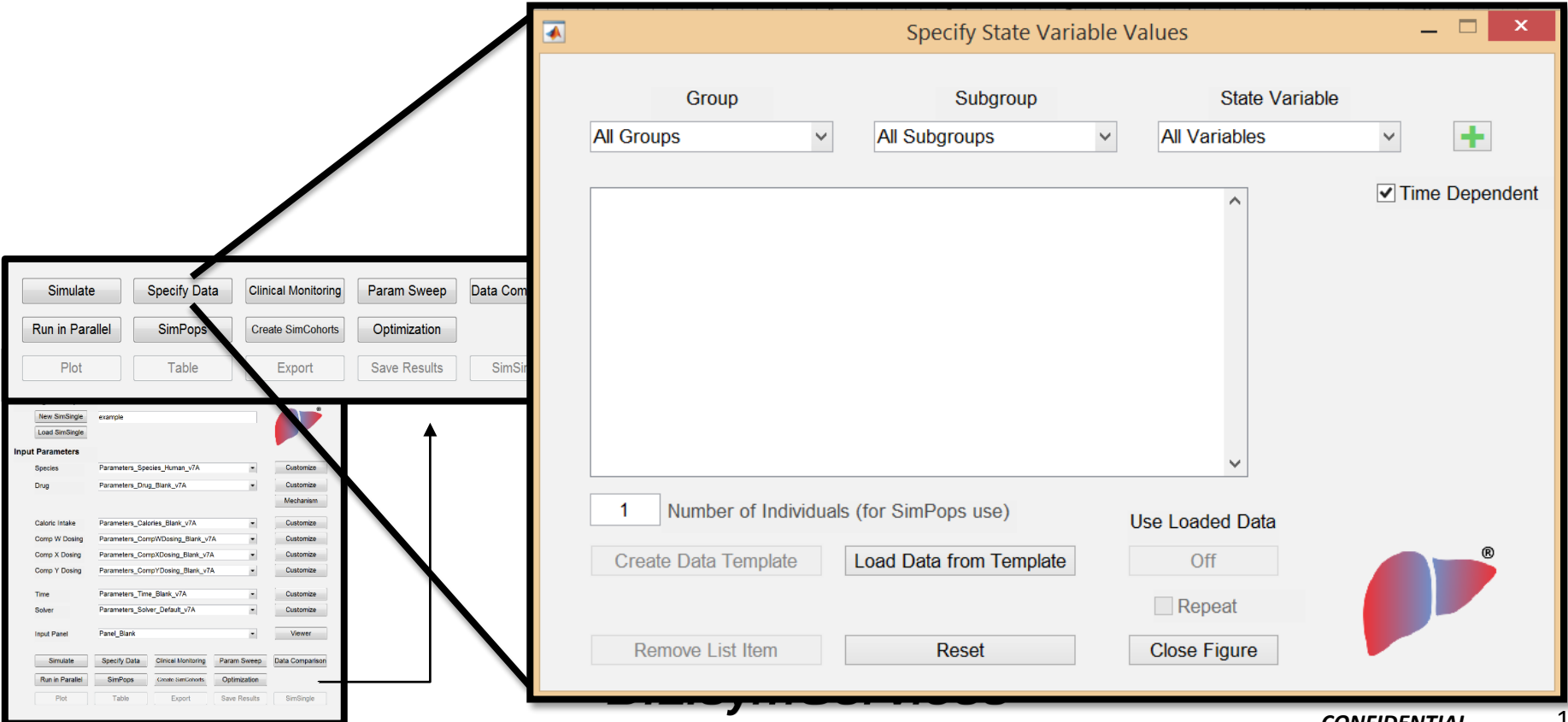
# DILIsym Specify Data Tool – Step By Step Instructions

1. SimSingle (simulation setup) within DILIsym via the home screen
  - Parameter selections (dosing, species, time, etc.) are made from the primary DILIsym home screen
  - A simulation needs to be set up, during which the overwriting will occur
2. Selection of options for template generation
  - State variables
  - Time dependent or constant for each one
  - Number of simulated individuals included in template
3. Populate Excel template with required information and save
4. Load data in from template and select other options



# The DILIsym Specify Data Feature is Accessed from the DILIsym Home Screen

- The Specify Data window has two main sections:
  - Template setup options
  - Template loading and simulation options





# Add the Specified State Variables for Overwriting and Choose Your Time Dependency Option

- The DILIsym state variable is selected from the drop-down menus marked “Group”, “Subgroup”, and “State Variable”
- Option of time dependent versus constant variable allows user to deselect “Time Dependent” when possible and greatly improve efficiency
  - *Constant option is much more efficient, as it avoids the need for interpolation between data points to match simulation time steps*
- **Click “Create Data Template”**

- Users can input **1 to 1000** specified data profiles
  - *If number of data profiles put in is greater than SimPops size (N), first N profiles are used and rest are ignored*
  - *If number of data profiles put in is less than SimPops size (N), data profiles are repeated until full SimPops is done*

**DILIsymServices**

**S+** A SIMULATIONS PLUS COMPANY

CONFIDENTIAL

11



# DILIsym Specify Data Tool – Step By Step Instructions

1. SimSingle (simulation setup) within DILIsym via the home screen
  - Parameter selections (dosing, species, time, etc.) are made from the primary DILIsym home screen
  - A simulation needs to be set up, during which the overwriting will occur
2. Selection of options for template generation
  - State variables
  - Time dependent or constant for each one
  - Number of simulated individuals included in template
3. Populate Excel template with required information and save
4. Load data in from template and select other options



# A “Time Dependent” Tab Will Exist for Specified Data Templates with 1 Individual, If Applicable

- If time dependent state variables were selected for 1 individual, one tab will contain all of them together
  - Time vector in left column
  - State variable columns to the right
  - Be sure all columns have equal number of data points
  - Time must start at zero and be monotonic
  - Do not alter text in other areas of worksheet

DELETE\_Nof1.xlsx - Microsoft Excel

	A	B	C	D
1	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW	
2	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW	
3	Specified Data - TD	Specified Data - TD	Specified Data - TD	
4		Individual 1	Individual 1	
5	time	blood_compound_x_met_a	cl_compound_x_met_a_to_rm1_enzyme_status	
6	Time (hour)	Blood Compound X Met A (ug/ml)	CL Compound X Met A to RM1 enzyme status (dimensionless)	
7	0	0		3
8	1	0.7		2.5
9	2	2.5		2
10	4	1.2		1.5
11	8	0.36		1
12				
13				
14				
15				
16				

Sheet1 Time Dependent Constant



# A “Constant” Tab Will Exist for Specified Data Templates with 1 Individual, If Applicable

- If constant state variables were selected for 1 individual, one tab will contain all of them together
  - State variables start on row 4 and progress down
  - State variable values entered into Column D
  - No negative values
  - Do not alter text in other areas of worksheet

DELETED\_Nof1.xlsx - Microsoft Excel

	A	B	C	D	E	F	G
1	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW			
2	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW			
3	Specified Data - C	Specified Data - C	Specified Data - C	Specified Data - C			
4	Individual 1	blood_compound_x	Blood compound X (ug/mL)	2			
5	Individual 1	cl_compound_x_rm2	CL Compound X RM2 (umol/L)	0.03			
6	Individual 1	cl_liver_compound_x	CL liver compound X (ug/mL)	1.8			
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							

Sheet1 | Time Dependent | **Constant**



# Each State Variable Will Contain Its Own Tab If Number of Individuals is Greater than 1

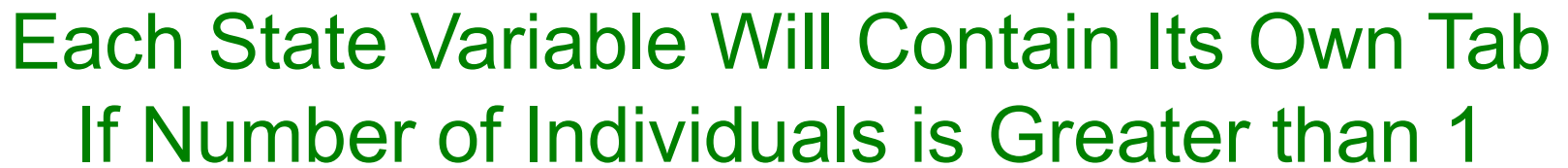
- For templates with multiple simulated individuals, tabs correspond to state variables
- Time dependent example shown at right
  - Time vector in left column
  - Individual's columns to the right (all for same state variable)
  - Be sure all columns have equal number of data points
  - Time must start at zero and be monotonic
  - Do not alter text in other areas of worksheet

DELETE\_Nof10.xlsx - Microsoft Excel

	A	B	C	D	E	F
1	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW
2	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW
3	Specified Data - TD	Specified Data - TD	Specified Data - TD	Specified Data - TD	Specified Data - TD	Specified Data - TD
4	Individual 1	Individual 2	Individual 3	Individual 4	Individual 5	
5	time	blood_compound_y	blood_compound_y	blood_compound_y	blood_compound_y	blood_compound_y
6	Time (hours)	Blood Compound Y (ug/mL)	Blood Compound Y (ug/mL)	Blood Compound Y (ug/mL)	Blood Compound Y (ug/mL)	Blood Compound Y (ug/mL)
7	0	0	0	0	0	
8	1	0.7	0.6	0.5	0.9	
9	2	2.5	2.9	3.3	2.6	
10	4	1.2	1.1	0.8	1	
11	8	0.36	0.3	0.25	0.4	
12						
13						
14						
15						
16						

Sheet1: Blood Compound Y, Compound W absorbed oral, Compound Y renal clearance, Liver Compound Y





- 
- DELETE\_Nof10.xlsx - Microsoft Excel
- File Home Insert Page Layout Formulas Data Review View
- Calibri 11 A<sup>+</sup> A<sup>-</sup>
- Paste
- Clipboard
- Font
- Alignment
- Number
- General
- Conditional Formatting
- Format as Table
- Cell Styles
- Insert
- Delete
- Format
- Cells
- Editing
- Sort & Find & Filter & Select
- D14
- |    | A                  | B                          | C                               | D                  | E | F |
|----|--------------------|----------------------------|---------------------------------|--------------------|---|---|
| 1  | DO NOT DELETE ROW  | DO NOT DELETE ROW          | DO NOT DELETE ROW               | DO NOT DELETE ROW  |   |   |
| 2  | DO NOT DELETE ROW  | DO NOT DELETE ROW          | DO NOT DELETE ROW               | DO NOT DELETE ROW  |   |   |
| 3  | Specified Data - C | Specified Data - C         | Specified Data - C              | Specified Data - C |   |   |
| 4  | Individual 1       | compound_y_renal_clearance | Compound Y renal clearance (ug) | 30                 |   |   |
| 5  | Individual 2       | compound_y_renal_clearance | Compound Y renal clearance (ug) | 28                 |   |   |
| 6  | Individual 3       | compound_y_renal_clearance | Compound Y renal clearance (ug) | 33                 |   |   |
| 7  | Individual 4       | compound_y_renal_clearance | Compound Y renal clearance (ug) | 32                 |   |   |
| 8  | Individual 5       | compound_y_renal_clearance | Compound Y renal clearance (ug) | 28                 |   |   |
| 9  | Individual 6       | compound_y_renal_clearance | Compound Y renal clearance (ug) | 30                 |   |   |
| 10 | Individual 7       | compound_y_renal_clearance | Compound Y renal clearance (ug) | 27                 |   |   |
| 11 | Individual 8       | compound_y_renal_clearance | Compound Y renal clearance (ug) | 26                 |   |   |
| 12 | Individual 9       | compound_y_renal_clearance | Compound Y renal clearance (ug) | 35                 |   |   |
| 13 | Individual 10      | compound_y_renal_clearance | Compound Y renal clearance (ug) | 33                 |   |   |
| 14 |                    |                            |                                 |                    |   |   |
| 15 |                    |                            |                                 |                    |   |   |
| 16 |                    |                            |                                 |                    |   |   |
- Ready
- Sheet1 Blood Compound Y Compound W absorbed oral Compound Y renal clearance Liver Compound Y
- 100%





# DILIsym Specify Data Tool – Step By Step Instructions

1. SimSingle (simulation setup) within DILIsym via the home screen
  - Parameter selections (dosing, species, time, etc.) are made from the primary DILIsym home screen
  - A simulation needs to be set up, during which the overwriting will occur
2. Selection of options for template generation
  - State variables
  - Time dependent or constant for each one
  - Number of simulated individuals included in template
3. Populate Excel template with required information and save
4. Load data in from template and select other options



# Load the Desired Specified Data Template and Activate the Use of the Feature

- Save Specified Data Excel template
- Click “Load Data from Template” button and load desired file
  - Should see “*Loaded: Template\_Name*” beneath button
- Click “Use Loaded Data” button
  - Should turn **green**
- Consider “Repeat” option
  - Check box if you desire this feature on
  - Leave unchecked if not
- Close Figure
- “Specify Data” Button should now appear green on DILIsym home screen
- Save SimSingle

**DILIsymServices**

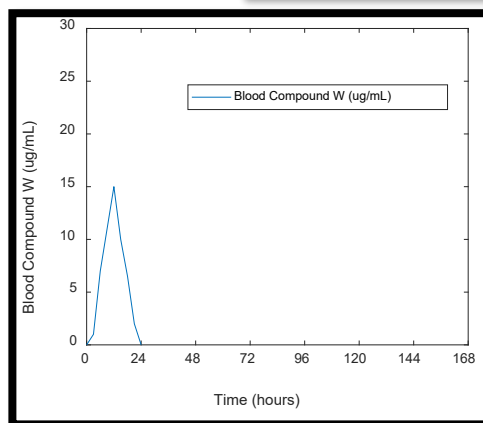
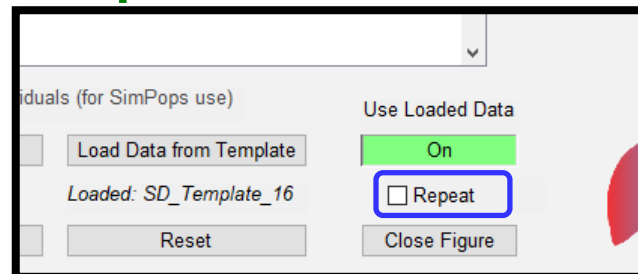
**S+** A SIMULATIONS PLUS COMPANY

CONFIDENTIAL

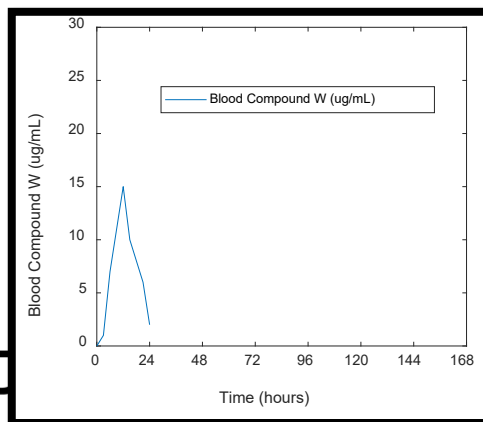
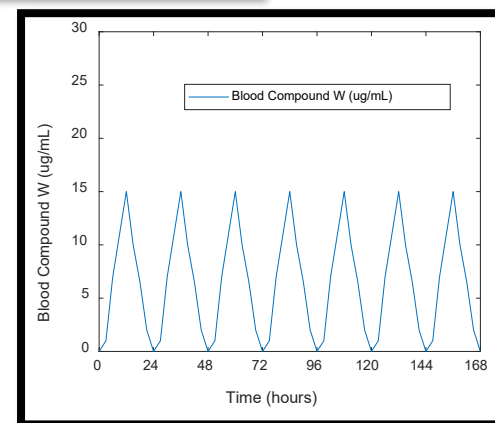


# Understanding the Implications of the Repeat Option for Specified Data

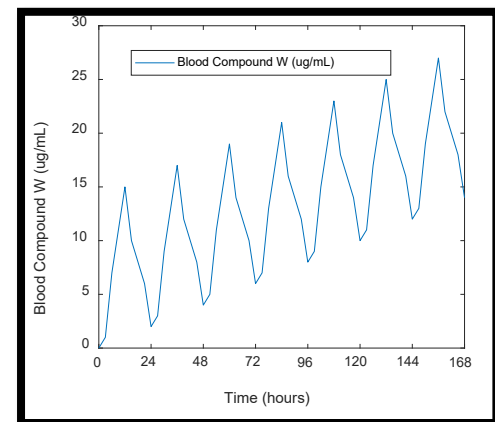
- If specified data contains time vector less than simulation time:
  - Simulation will stop prematurely if “Repeat” option is OFF
  - Simulation will continue until simulation time complete if “Repeat” option is ON
  - *Not applicable for constant specified states*
- “Repeat” option leads to superposition of specified data set
  - If specified (time course) data set does not return to zero, accumulation will occur



Repeat



Repeat

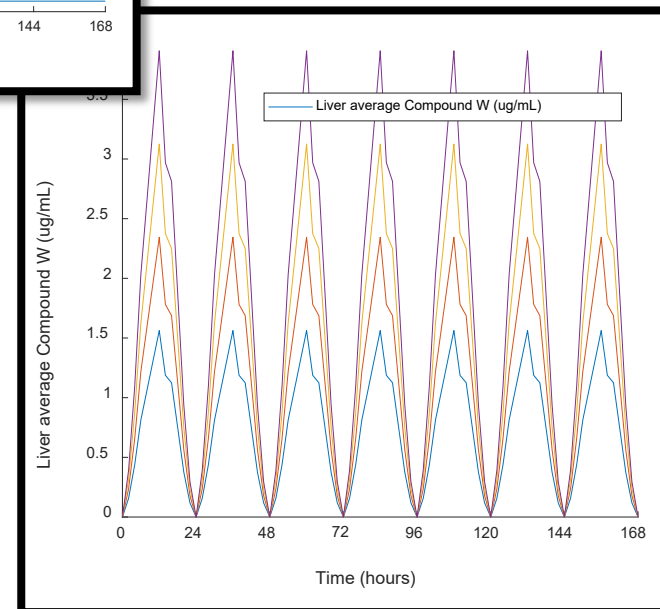
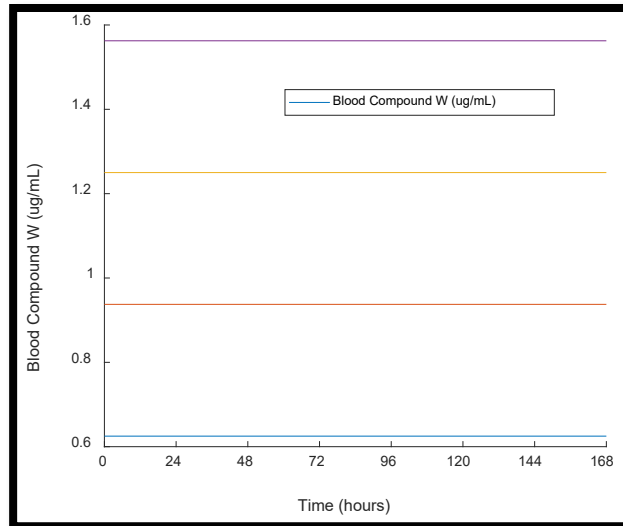


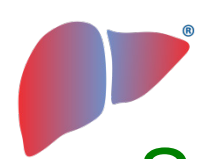
Simulation Results



# Hands-on Specified Data Example – Specifying Blood and Liver Concentrations

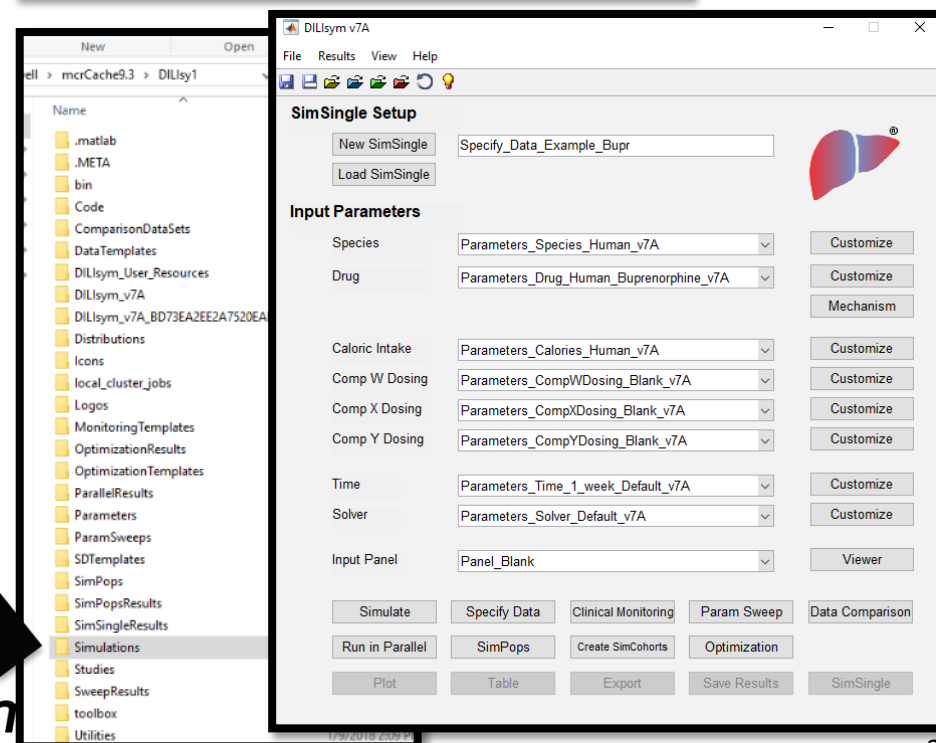
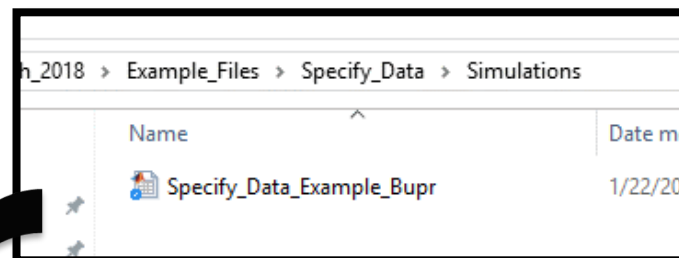
- Goal is to simulate buprenorphine treatment for 1 week in humans using Specified Data to drive exposure (PK)
- Specifying blood and liver concentrations
  - Blood: constant
  - Liver: time dependent
- SimCohorts of 4 used:
  - v4A\_1\_SensMito
- Example is simplified for the purposes of illustration
  - Blood and liver concentrations typically both time dependent or both constant





# Hands-on Specified Data Example – *Step 1 – Place Provided SimSingle Setup in Simulations Folder and Review SimSingle*

- Find Simulations directory by clicking any load option within DILIsym and copying location from Windows Explorer
- Copy one provided SimSingle into your Simulations directory
- Explore SimSingle
  - Human species selected
  - Human Buprenorphine Drug parameter file selected
  - Human caloric intake
  - No drug dosing
    - Specified Data will be used for drug exposure
  - 1 week simulation time



Llsyn



# Hands-on Specified Data Example – *Step 2 - Add State Variables for Overwriting*

- Add 4 State Variables
  1. **Blood Compound W**  
– constant
  2. **CL liver Compound W**  
– time dependent
  3. **ML liver Compound W**  
– time dependent
  4. **PP liver Compound W**  
– time dependent
- 4 Individuals
- **Click “Create Data Template”**
- Excel file will be generated and should open
  - If not, navigate to local DILIsym directory and open “SDTemplates” directory and open file



# Hands-on Specified Data Example – Step 3 – *Paste Provided Data Into Created Specified Data Template*

- Open provided Excel data file in Example\_Files -> Specify\_Data -> Data\_For\_Pasting\_Comp\_W\_Bupr
- **Paste highlighted data into corresponding tabs in template file**
- Note 4 total tabs for pasting
- Paste same data into last 3 tabs – 3 zones of the liver
  - Assumption in example is same drug exposure across zones
- Save template after pasting data in

	A	B	C	D	E
1	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW	
2	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW	
3	Specified Data - C	Specified Data - C	Specified Data - C	Specified Data - C	
4	Individual 1	blood_compound_w	Blood Compound W (ug/mL)	0.625	
5	Individual 2	blood_compound_w	Blood Compound W (ug/mL)	0.9375	
6	Individual 3	blood_compound_w	Blood Compound W (ug/mL)	1.25	
7	Individual 4	blood_compound_w	Blood Compound W (ug/mL)	1.5625	

	A	B	C	D	E	F	G
1	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW		
2	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW	DO NOT DELETE ROW		
3	Specified	Specified	Specified	Specified	Specified Data - TD		
4	Individual	Individual	Individual	Individual	Individual 4		
5	time	cl_liver_ccl_liver_ccl_liver_ccl_liver_compound_w					
6	Time (hou)	CL liver CcCL liver CcCL liver CcCL liver Compound W (ug/mL)					
7	0	0	0	0	0		
8	2	0.15625	0.234375	0.3125	0.390625		
9	4	0.4375	0.65625	0.875	1.09375		
10	6	0.8125	1.21875	1.625	2.03125		
11	8	1.0625	1.59375	2.125	2.65625		
12	10	1.3125	1.96875	2.625	3.28125		
13	12	1.5625	2.34375	3.125	3.90625		
14	14	1.1875	1.78125	2.375	2.96875		
15	16	1.125	1.6875	2.25	2.8125		
16	18	0.75	1.125	1.5	1.875		
17	20	0.375	0.5625	0.75	0.9375		
18	22	0.11875	0.178125	0.2375	0.296875		
19	24	0	0	0	0		
20							
21							
22							
23							
24							
25							
26							
27							



# Hands-on Specified Data Example – Step 4 – Load the Template with Pasted Data and Activate the Use of the Feature

- Click “Load Data from Template” button and load file with pasted data
  - Should see “Loaded: Template\_Name” beneath button
- Click “Use Loaded Data” button
  - Should turn **green**
- Turn “Repeat” option ON
  - Data in template only spans 24 hours
  - Simulation is for 1 week
- Close Figure
- “Specify Data” Button should now appear green on DILysm home screen
- Save SimSingle

**DILysmServices**

**S+** A SIMULATIONS PLUS COMPANY

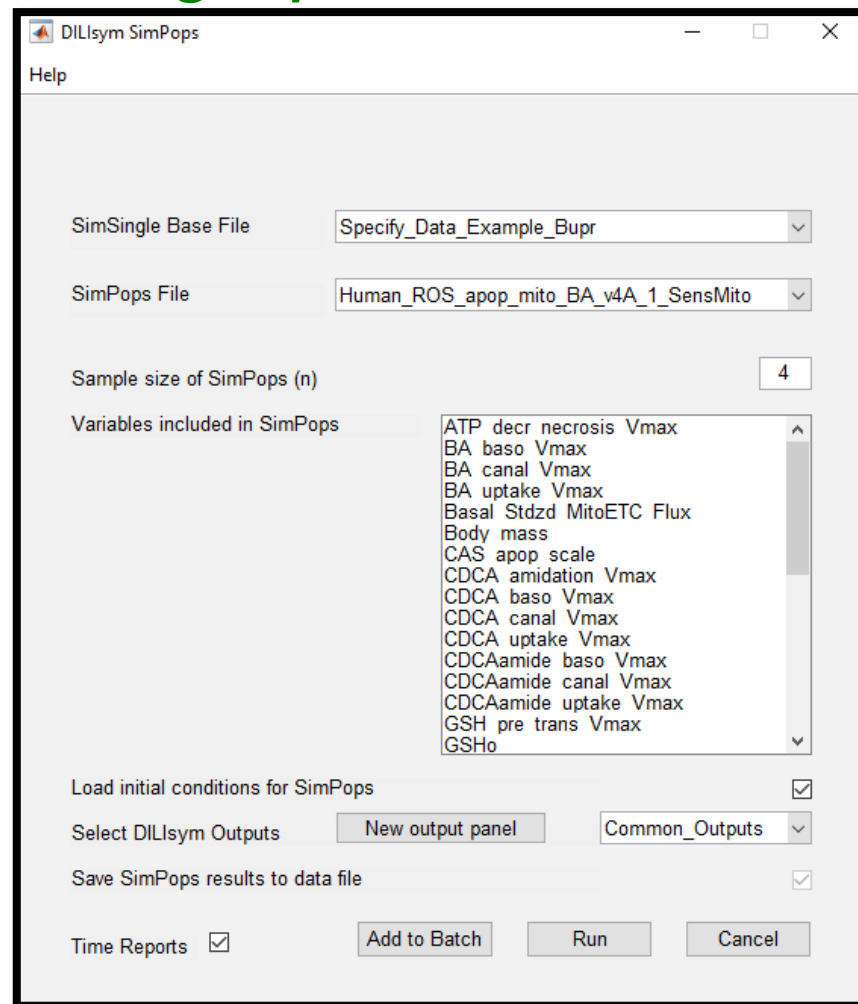
CONFIDENTIAL





# Hands-on Specified Data Example – *Step 5 – Run v4A\_1\_SensMito SimCohorts with Updated SimSingle Including Specified Data*

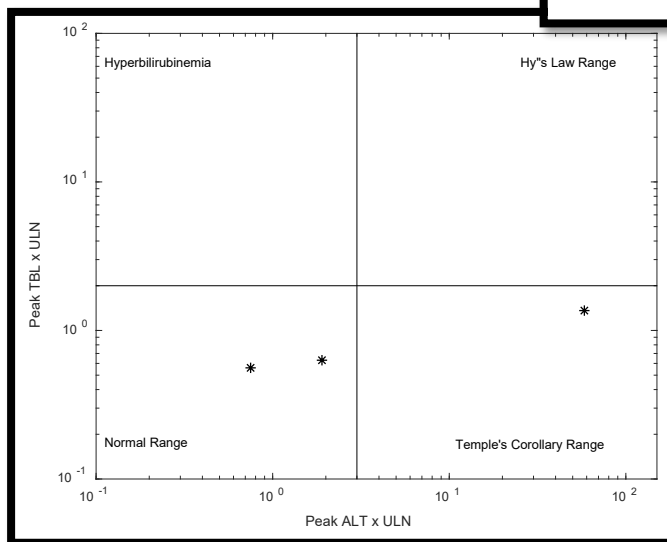
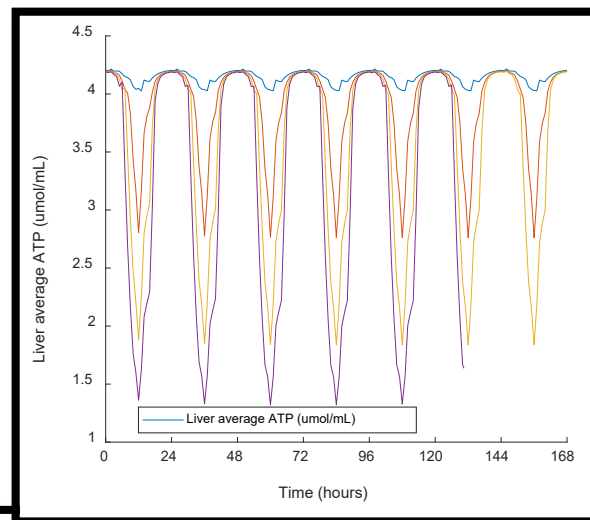
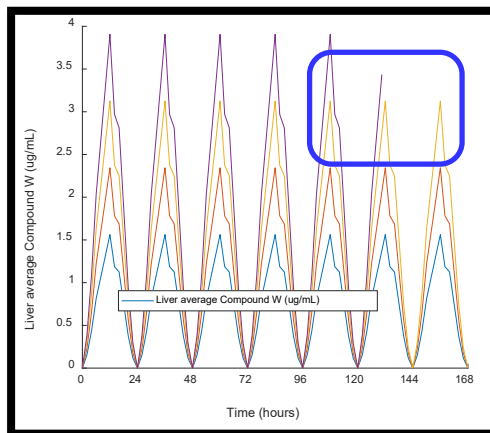
- Push “SimPops” button from DILIsym home screen
- Select provided SimSingle, but version with Specified Data added
  - Note that if you customized the name of the SimSingle (Save As), you will need to select the newly named SimSingle
- SimPops to select:
  - **Human\_ROS\_apop\_mito\_BA\_v4A\_1\_SensMito**
- Change DILIsym outputs to “Common\_Outputs” panel
- Click “Run”
- Expect several minutes to complete simulation





# Hands-on Specified Data Example – Step 6 – Analyze Simulation Results from Buprenorphine Simulation with Specified Data

- Note that individual with highest exposure died prior to 168 hours
  - Pharmacokinetics -> Compound W -> **Liver average Compound W**
- Note variability in liver ATP levels
  - Mitochondria -> Bioenergetics -> **Liver average ATP**
- Note range of liver injury by opening eDISH plot



Simulation Results