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DILIsym User Training – Using GastroPlus™ PBPK to Drive DILIsym Simulations

DILIsym Development Team

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Goal for This Training Session on Using GastroPlus to Drive DILIsym Simulations

Participants should understand the following general concepts:

- How to use GastroPlus 9.6 and the 'Specified Data' feature within DILIsym to run simulations with loaded PK results (*note: review of the general DILIsym Specified Data training segment is a recommended prerequisite to this training segment*)

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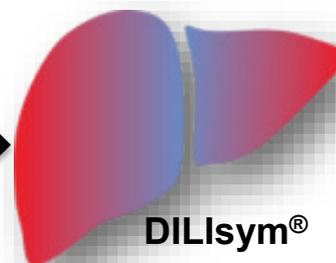
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GastroPlus 9.6 Allows for Efficient Use of GastroPlus PBPK Models in Combination with DILIsym SimPops

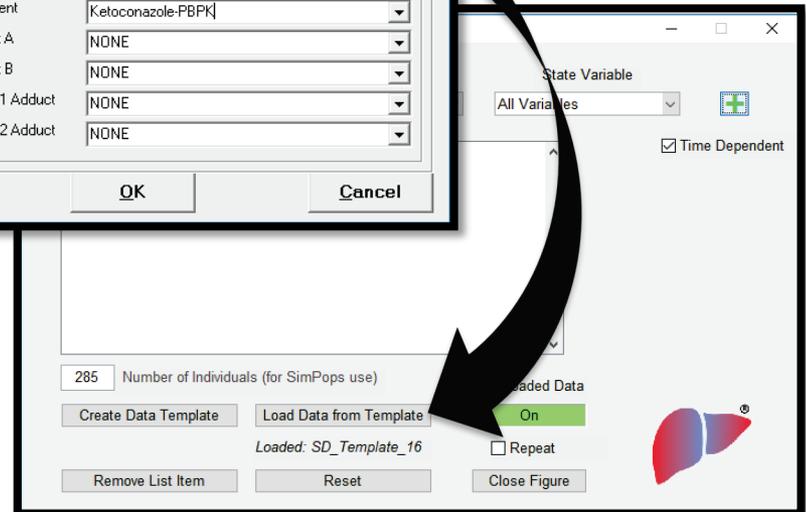
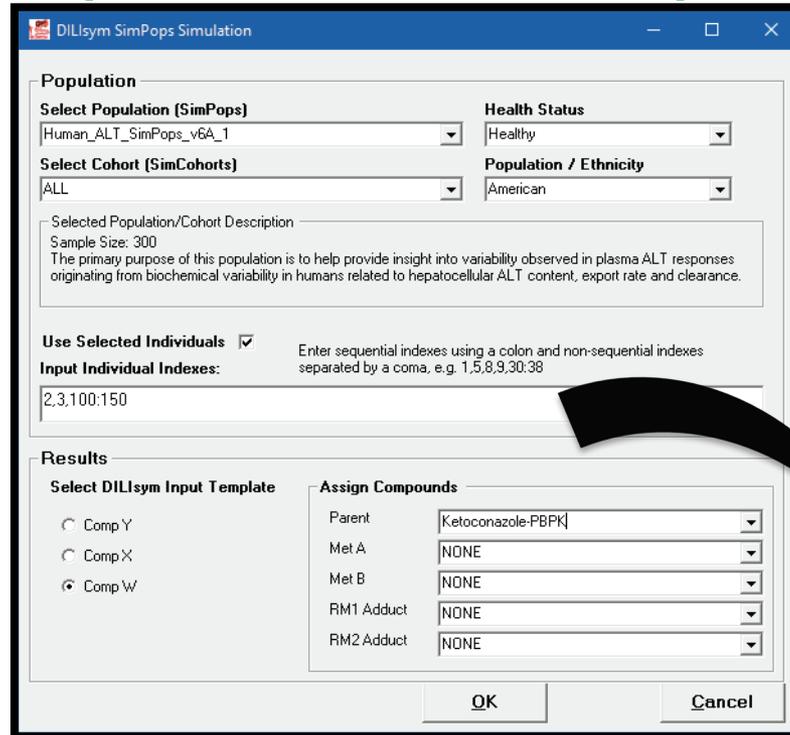
- GastroPlus users build PBPK models within GastroPlus
- The “DILIsym” simulation mode in v9.6 will allow users to select a mapping of GastroPlus outputs to DILIsym PK inputs
- All DILIsym SimPops and SimCohorts are embedded within GastroPlus so user can select option of their choice
- Exported DILIsym Specified Data Excel template will be 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***





GastroPlus 9.6 Includes a DILIsym Simulation Mode to Bridge with the DILIsym Specified Data Option

- GastroPlus users with an existing PBPK model can select the DILIsym simulation mode
- An interface will allow for specific compound mapping choices between GastroPlus outputs and DILIsym PK and the specific SimPops or SimCohorts desired
- A Specified Data template for DILIsym will be generated
- The DILIsym Specified Data feature will allow for direct import of the template to drive simulations with the GastroPlus PK outputs
- No manual pasting required





Important Details on the DILIsym Simulation Mode Within GastroPlus (Page 1 of 3)

- The DILIsym Simulation mode only works with the PBPK module of GastroPlus
- American, Japanese, and Chinese ethnicities available within DILIsym mode
 - Only affect exported PK information, not toxicity pathway variability in DILIsym SimPops
- Healthy, liver impaired (Cirrhosis: CP=A, CP=B, and CP=C), and renally impaired (Mild, Moderate, Severe, End-stage) options available (for humans)
 - Only affect exported PK information, not toxicity pathway variability in DILIsym SimPops
- DILIsym Specified Data templates (Excel worksheets) can be exported from the following GastroPlus simulation modes:
 - “Single Sim” for SimSingle use (N of 1)
 - “DILIsym” mode for SimPops use (N > 1)
 - “Drug-Drug Interaction” for SimSingle or SimPops use

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Important Details on the DILIsym Simulation Mode Within GastroPlus (Page 2 of 3)

- Only existing SimPops and SimCohorts can be selected, but specific simulated subjects within an existing SimPops or SimCohorts can be selected, effectively allowing for some alternative SimCohorts options
 - The body weights for each individual have been imported into GastroPlus behind the scenes so that the body weight related parameters will match reasonably well with the corresponding simulated individual in DILIsym
 - This avoids awkward mismatches where a subject's PK is predicted in GastroPlus based on a fairly high or low body weight but the DILIsym SimPops individual is on the opposite end of the body weight spectrum
- This initial compatibility feature does not allow for PK-toxicity-PK feedback (PKPD loop)



Important Details on the DILIsym Simulation Mode Within GastroPlus (Page 3 of 3)

- Users should pick the compound scaffold (Compound X, W or Y) that matches their desired scaffold in DILIsym
- A parent molecule and up to four metabolites are possible
 - Met A, Met B, RM1 Adduct, and RM2 Adduct should all be considered stable metabolites for this purpose
 - To use RM1 Adducts and RM2 Adducts as stable metabolites in DILIsym, some unique parameterization is required to rapidly conjugate these to proteins so that they can be transported into the blood
- Be sure to extend the GastroPlus PBPK module simulation time to match the desired time in DILIsym, unless the “repeat” option can be used
- The resulting Specified Data Excel template should not be altered by the user once created within GastroPlus
 - In some cases, manual extension of the simulation time is necessary within the template
- The SimPops selected and the molecule name(s) from GastroPlus will be included in the exported template
- ***Be sure to include the molecular weight of the compound(s) in the DILIsym PBPK parameter set***



GastroPlus Drug/Metabolite Concentration Mapping to DILIsym Concentrations *(Done Automatically for User)*

GastroPlus Concentration Compartment	DILIsym Concentration Compartment
Hepatic junction blood	Sinusoidal blood
Total liver	Liver (all zones same)
Arterial blood	Blood
Blood coming out of ACAT gut compartment	Gut (applicable for stable metabolites only)



Hands-on Specified Data Example 2 – Step 1 – Generate Exported Specified Data Excel File for Caffeine from GastroPlus

- Generate Specified Data template labeled:
 - **Caffeine-PBPK-16Subjects**
- Note location of SimPops / SimCohorts and compound names
- Note various tabs
- Ethnicity and health status from GastroPlus are reported in cells A1 and A2

The screenshot shows a Windows File Explorer window with the path: Example_Files > Specify_Data > SDTemplates. A file named 'Caffeine-PBPK-16Subjects' is selected, with a date of 1/23/2011. Below the file explorer is a Microsoft Excel spreadsheet. The spreadsheet has a formula bar showing '4.4' and a grid of data. The data is organized into columns for Ethnicity, Health status, Specified Data, and Time (hour). The data is organized into individual subject columns (Individual 1 to Individual 6) and rows for time points from 0 to 0.6 hours.

	A	B	C	D	E	F	G	H
1	Ethnicity: A	Human_RO	Human_RO	Human_RO	Human_RO	Human_RO	Human_RO	Human
2	Health statu	Caffeine-PB	Caffeine-PB	Caffeine-PB	Caffeine-PB	Caffeine-PB	Caffeine-PB	Caffein
3	Specified D	Specifi						
4		Individual 1	Individual 2	Individual 3	Individual 4	Individual 5	Individual 6	Individ
5	time	blood_com	blood_com	blood_com	blood_com	blood_com	blood_com	blood_
6	Time (hour)	Blood Comp	Blood C					
7	0	0	0	0	0	0	0	0
8	0.1	0.40343	0.40353	0.38231	0.40353	0.40353	0.3479	0.2
9	0.2	1.29097	1.29128	1.22617	1.29128	1.29128	1.12049	0.8
10	0.3	2.005	2.00548	1.90486	2.00548	2.00548	1.74166	1.3
11	0.4	2.47288	2.47347	2.34911	2.47347	2.47347	2.14769	1.6
12	0.5	2.74814	2.7488	2.61006	2.7488	2.7488	2.38578	1.8
13	0.6	2.89347	2.89417	2.7474	2.89417	2.89417	2.51073	1.9