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

# DILIsym User Training – DILIsym v7A Updates Overview

## January 2018

## Research Triangle Park, NC

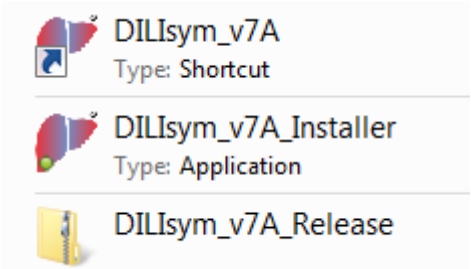
# Goal for This Training Session

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

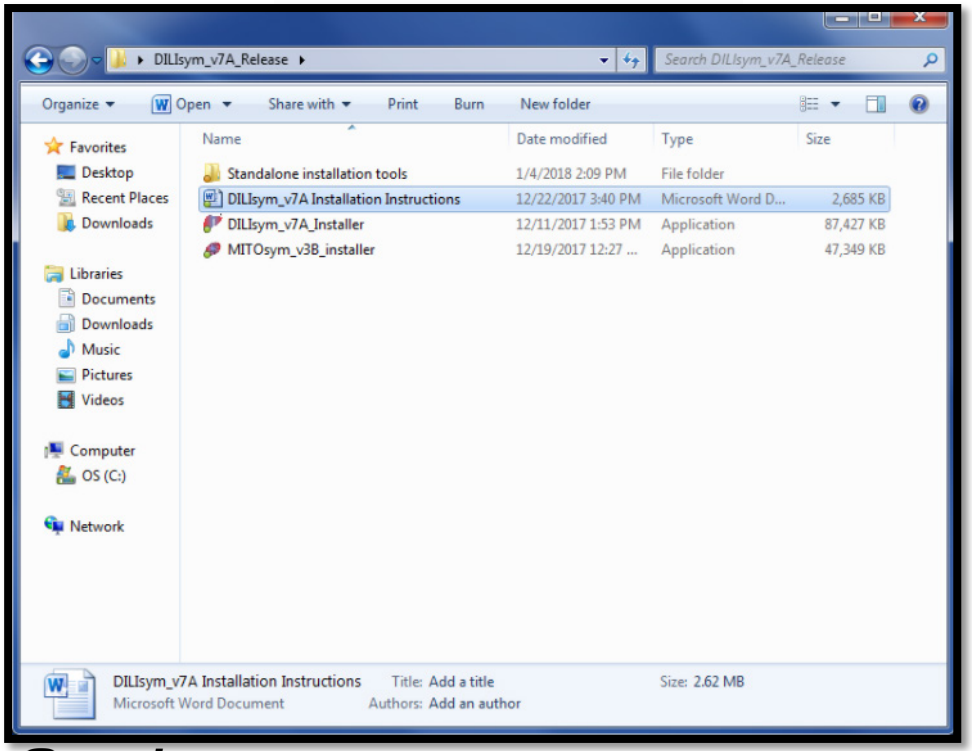
- The most notable updates included in DILIsym v7A as compared to v6A
- Some practical considerations for utilizing DILIsym v7A as compared to v6A

# DILIsym Installation Has Changed with Version 7A

- Moving forward from version 7A, DILIsym will be released as an executable application which will not require a MATLAB license
  - A required (free) MATLAB 2017b Runtime library will be downloaded during installation




- DILIsym v7A will be released as a zipped archive containing installation instructions and installers for both DILIsym and the Flexera licensing software
  - Future versions likely to be delivered as a single bundled installer




- MITOsym v3B is included in the same installation package

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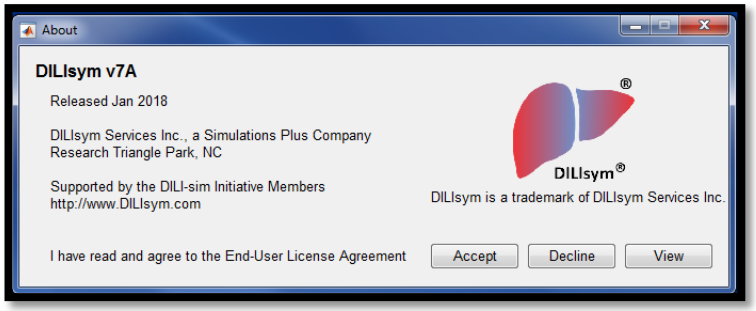
# DILIsym and MITOsym Licenses Will Be Managed Using Flexera

- Flexera license management software will be included in the DILIsym v7A and MITOsym v3B releases
- Installation instructions will detail how to receive licenses
  - Instructions on DILIsym/MITOsym installation, as well as the licensing process, will also be detailed on the online documentation site
- Base membership fee will guarantee at least 2 simultaneous users per company during active membership period, although sharing licenses is permitted
  - Consistent with Simulations Plus policies – never a “named user” requirement
  - Additional DILIsym licenses available at significantly reduced rates
- **Each member company will need to decide between standalone installations or a network based, centrally managed license server**





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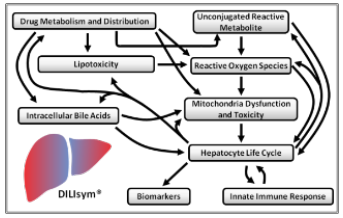
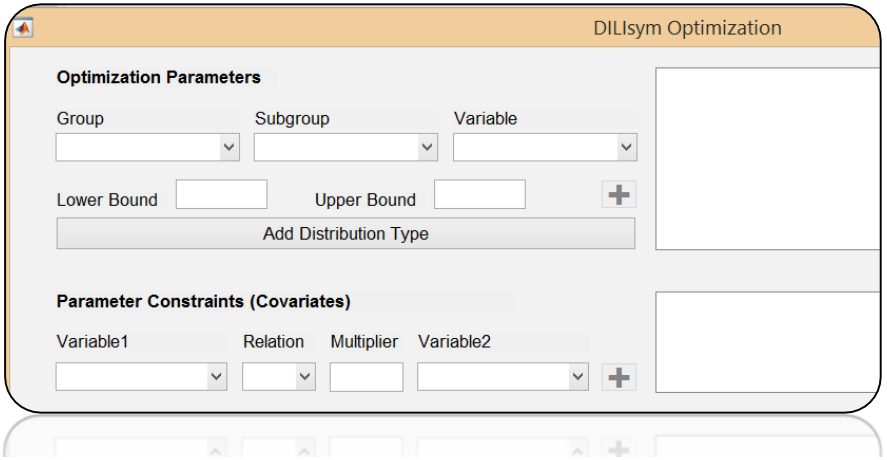
# Highlights of DILIsym v7A

- Several NEW Validation Compounds included with varying clinical presentations
  - Tolvaptan and lixivaptan - vasopressin receptor 2 antagonists
  - 5 Macrolides
    - Erythromycin
    - Clarithromycin
    - Azithromycin
    - Solithromycin
    - Telithromycin




  - BMS-932481
    - compound donated by BMS to consortium
    - 2 compound parameter sets included in DILIsym v7A: toxicity parameters determined independently by DSS team and BMS
- NEW Optimization interface added allowing complex fitting from GUI using genetic algorithm
- NEW Clinical Monitoring feature allowing dynamic clinical trials with dose alterations based on specified thresholds
- NEW Weight Adjusted Dosing option
- NEW Export enhancements providing better information on simulation setup within exported Excel file
- MATLAB 2017b friendly – faster simulations




- 2 NEW SimPops
  - Combined ALT biomarker parameter variability with toxicity pathway parameters
  - Mitochondrial biogenesis parameter variability added to an existing SimPops with toxicity pathway parameters
- NEW feature allowing for creation of Custom SimCohorts from existing SimPops and SimCohorts
- UPDATED Initial Conditions infrastructure allowing for importing of custom SimPops within compiled version
- UPDATED Output Table with more clinically important metrics built in
- DILIsym documentation resources updated for new features

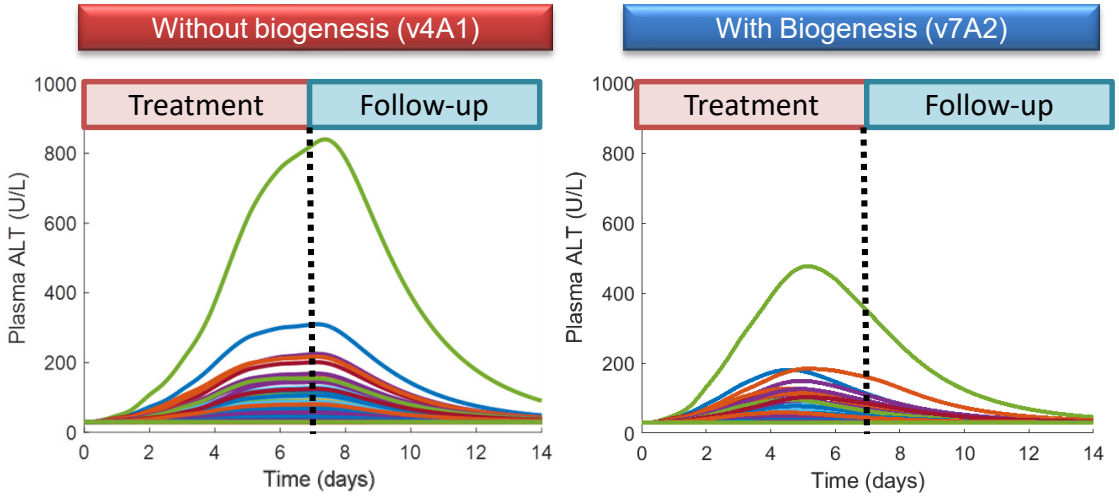
# 8 New Compounds Included in DILIsym v7A

- Five macrolide antibiotics: solithromycin, erythromycin, clarithromycin, azithromycin, telithromycin
  - Originally represented as part of a project for Cempra
  - Simulation results presented to FDA and at several conferences, including ACoP 2017
  - Publication on macrolide antibiotics in DILIsym forthcoming
- Two vasopressin V2 receptor antagonists: tolvaptan and lixivaptan
  - Compounds for the treatment of autosomal-dominant polycystic kidney disease (ADPKD)
  - Tolvaptan originally represented as part of a joint project with the IDSS sponsored by Otsuka
    - Results in DILIsym v4B published in 2016
  - Lixivaptan originally represented as part of a project sponsored by Palladio
    - Results presented at F2F meeting in 2017 as well as at ACoP 2017
    - Publication forthcoming
- BMS-932481
  - Represented by both BMS and DSS in parallel using BMS-derived PBPK model
  - Both BMS version and DSS version (of toxicity parameters) included in v7A
  - Results presented at DILI-sim Face to Face meeting in September of 2017

# SimPops Including Variability in Mitochondrial Biogenesis Included in DILIsym v7A

- Mitochondrial biogenesis equations are included in DILIsym
  - Enables exploration of hypothesis that mitochondrial adaptations can mitigate DILI
  - Biogenesis parameters optimized to represent clinically observed adaptation of solithromycin
  - Default human parameter values set to have NO effect
  - For more information about mitochondrial biogenesis, please refer to *DILIsym review Session 21* on the website
- Human mitochondrial biogenesis SimPops will be added to DILIsym v7A
  - Human_ROS_apop_mito_BA_Biogenesis_v7A_2 (n=285); for exploration only
  - Generated using general toxicity parameters from the SimPops v4A_1 combined with mitochondrial biogenesis parameters
  - Variability added to "Mitochondria protein proliferation Vmax" assuming 30% CV
- Solithromycin simulations with biogenesis SimPops recapitulate clinically observed ALT normalization during treatment

| Parameter | Unit | Baseline Value | SimPops value |
|---|---|---|---|
| Mitochondria protein proliferation Vmax | mmol/hour | 4e-14 | 1e-14 – 7e-14 |
| Mitochondria protein proliferation Km | dimensionless | 0.8 | 0.8 |
| Mitochondria protein proliferation Hill | dimensionless | 1.5 | 1.5 |
| ATP decrement delay constant for mitochondria | hr | 96 | 96 |




Simulation Results

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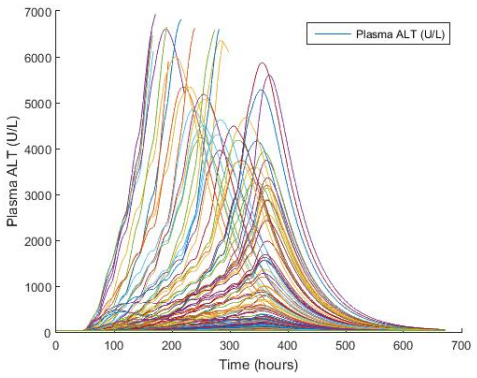
HUMAN

# SimPops Including Variability in ALT Parameters Included in DILIsym v7A

- ALT Mechanistic SimPops (Human_ROS_apop_mito_BA_ALT_v7A_1) includes variability in mechanistic DILI parameters (i.e. RNS-ROS generation, mitochondrial function, and bile acid transport) and parameters related to ALT levels occurring for a given level of injury
- 40 parameters included; 285 simulated individuals
- v7A_1 SimPops generated by superimposing variability in ALT responses onto biochemical variability in v4A_1 SimPops
  - Simulated peak ALT responses for exemplar compounds comparable between the new v7A_1 SimPops and the v4A_1 SimPops (example shown for 100 mg BID AMG009 4 week simulations)

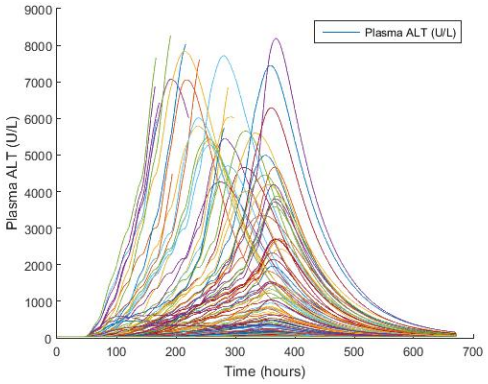
**v4A_1 SimPops**

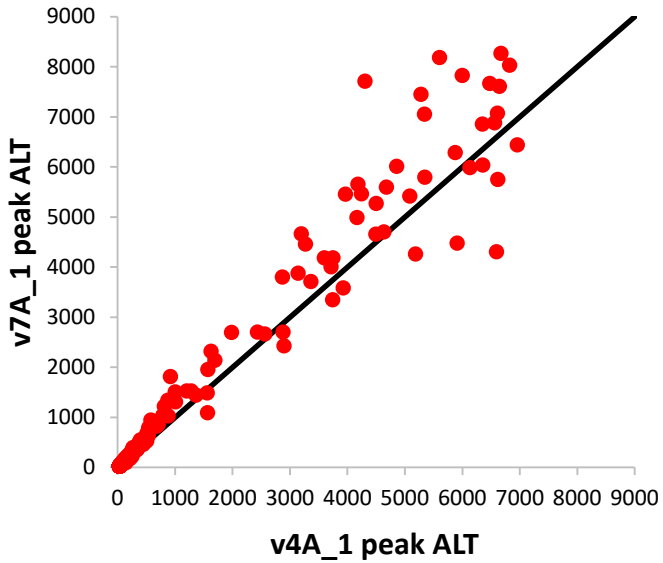
**114/285 with ALT >3x ULN**




**v7A_1 SimPops**

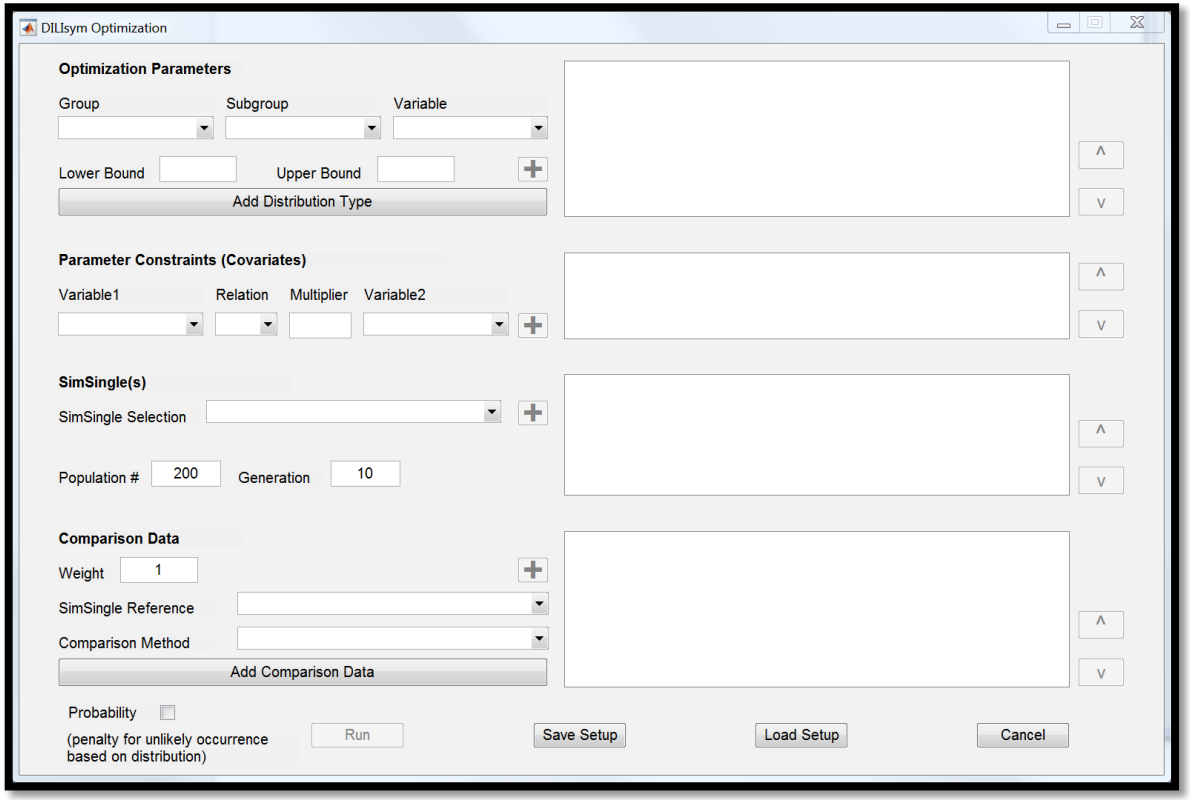
**121/285 with ALT >3x ULN**



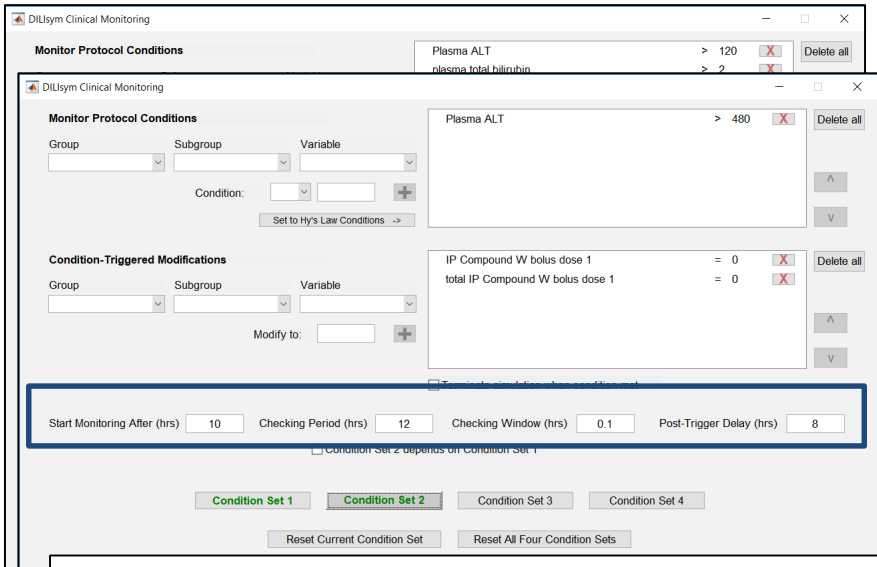
# DILIsym v7A Includes Optimization Feature

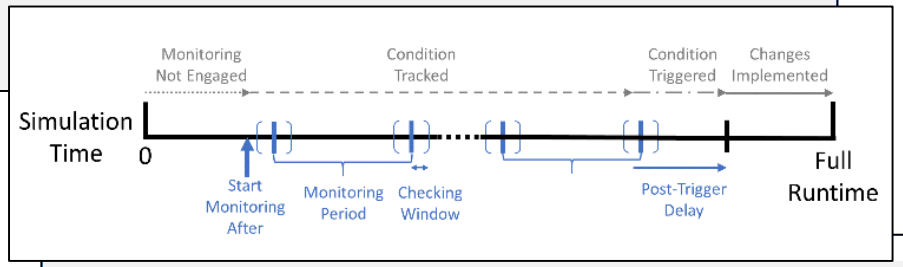
- Tool constructed within DILIsym to allow the user to optimize parameters to user-supplied data
- Utilizes genetic algorithm-based optimization
- Several elements necessary to define for an optimization
  - Parameter ranges and distributions
  - Parameter constraints (e.g. if two parameters are covariates)
  - Simulations to run
  - Data sets to compare to simulation results
    - Can include plasma $C_{max}$ and AUC for PBPK optimization
  - Comparison method for simulation results
- More comprehensive training on optimization forthcoming

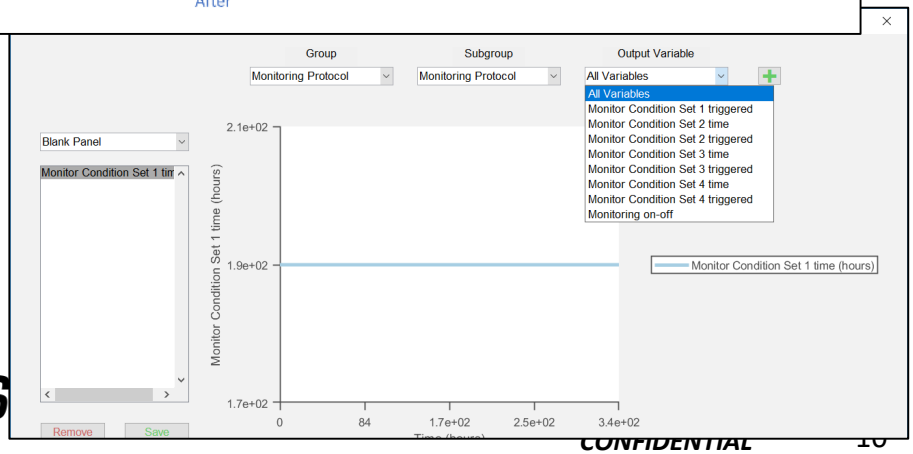


# DILIsym v7A Includes New Monitoring Tool

- DILIsym v7A includes a clinical monitoring tool to modify simulation behavior during simulations
  - Designed to replicate clinical protocol employed when liver signals are detected
- Specify up to four “Condition Sets”
  - Variables to monitor, relative to a specified condition and value
  - Modifications to make when conditions met
  - Monitoring protocol parameters
  - Dependency on prior condition set
- Clinical monitoring timeline based on
  - Time when monitoring should start
  - The period with which a condition is monitored, and corresponding measurement checking window
  - Any delay in implementing the modifications (e.g., time it takes between blood draw and corresponding results)
- Outputs now include monitoring status and time any Condition Set was triggered, if applicable

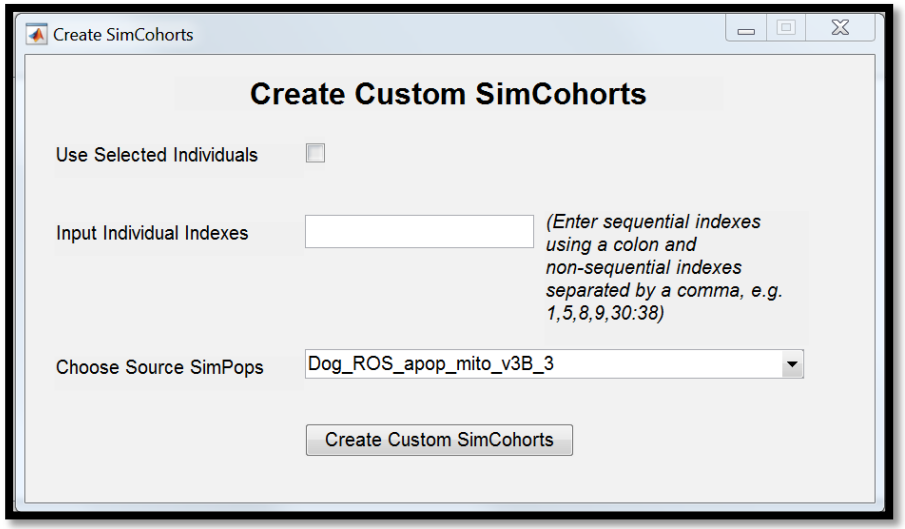


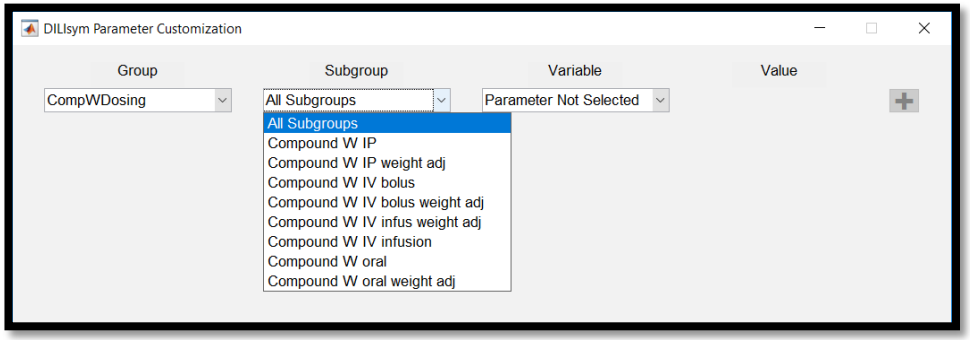
# DILIsym v7A Includes Ability to Create Custom SimCohorts from Any Existing SimPops or SimCohorts

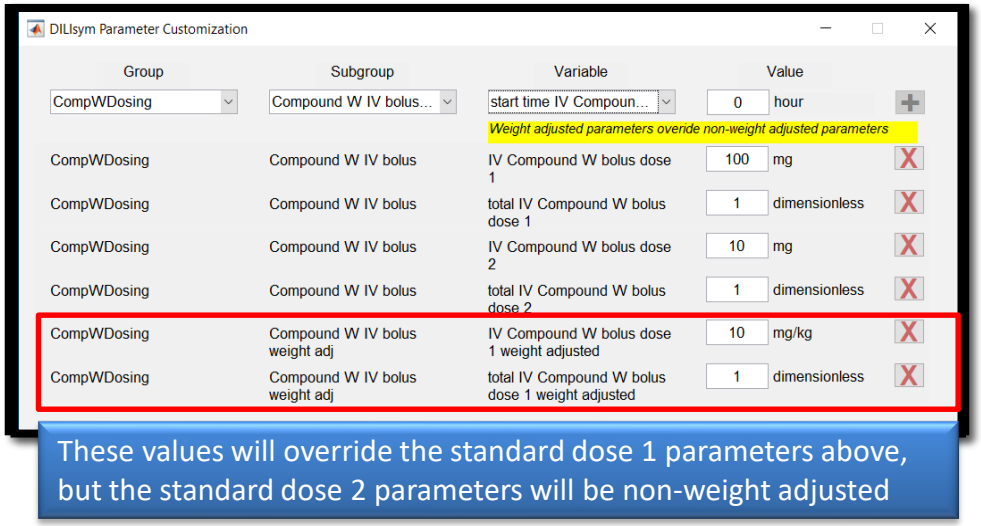
- DILIsym now allows the user to create a SimCohorts out of certain individuals within a SimPops
  - Accessible from Plot -> Show Individuals or from main screen
- Individuals for SimCohorts creation can be selected two different ways
  - Highlighted individuals from a plot
    - Option only available when used from the Plotting screen
  - Individuals selected by the user
- Initial conditions automatically created
  - Running initial condition equilibration with custom SimCohorts is not necessary
- Functionality allowing creation of SimCohorts based on a certain result criteria (*e.g.* individuals with ALT > 3x ULN) under development for future versions



# New Weight-Adjusted Dosing Option Included in DILIsym v7A

- DILIsym v7A includes set of weight-adjusted parameters added to all dosing scaffolds
  - Mirror of “standard” dosing options
- User may mix and match between prior “standard” dosing and new weight-adjusted dosing
- Implements weight-adjusted dosing by overriding “standard” dose values with corresponding weight-adjusted values
  - Nonzero “total IV Compound W bolus dose 1 weight adjusted” field turns on a specific weight-adjusted dose
  - GUI features a warning box indicating override when using weight-adjusted parameters
- Example on right shows mix of “standard” and weight-adjusted dosing

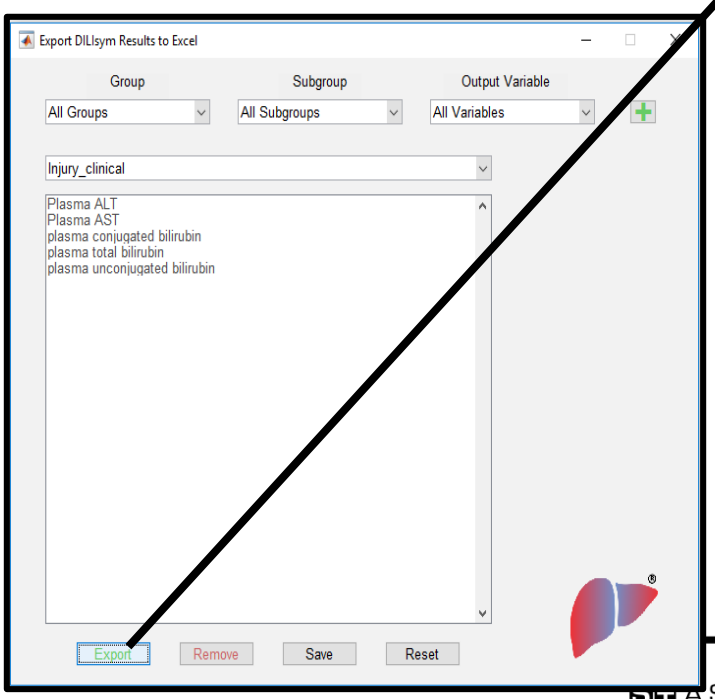


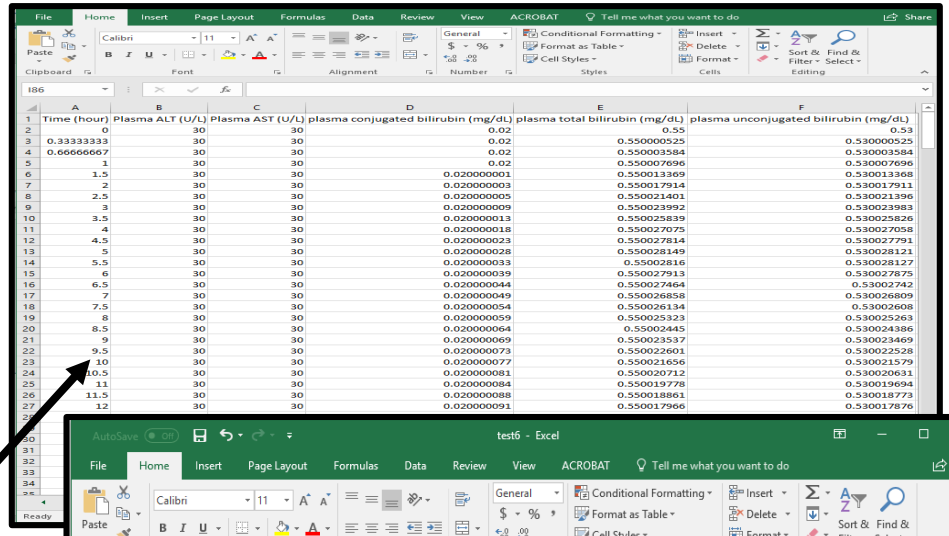



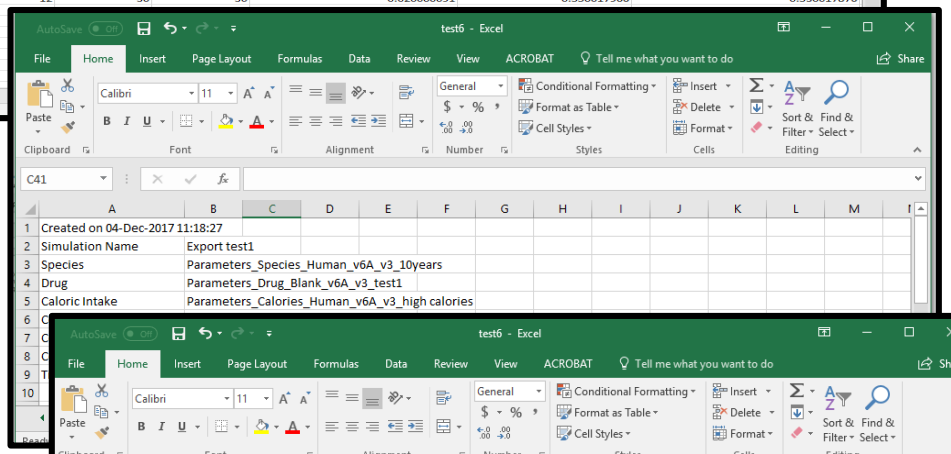

These values will override the standard dose 1 parameters above, but the standard dose 2 parameters will be non-weight adjusted

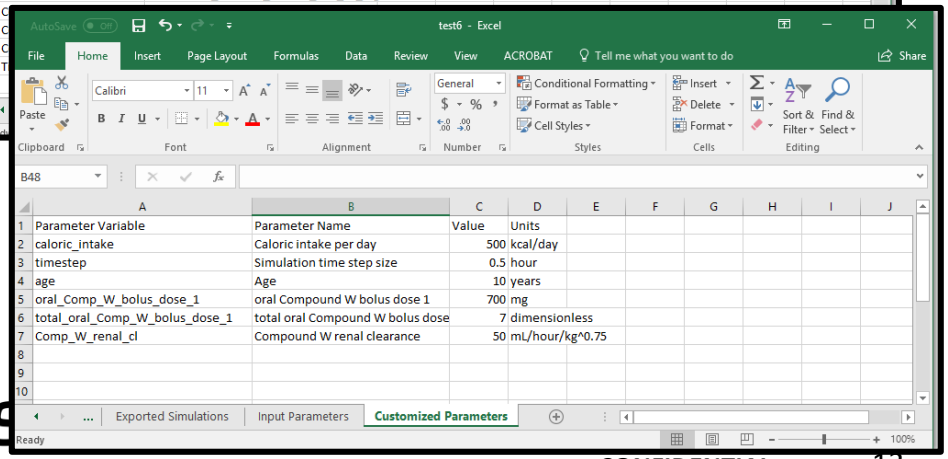
# Information on Simulation Setup Added to Results Exported to Excel for v7A

- Export to Excel option exists for results and can be accessed after a simulation from the main screen
- Excel file will now contain further information about the simulation that generated those results
  - Date and time
  - Simulation setup
  - Parameters listed as customized
- Better audit trail



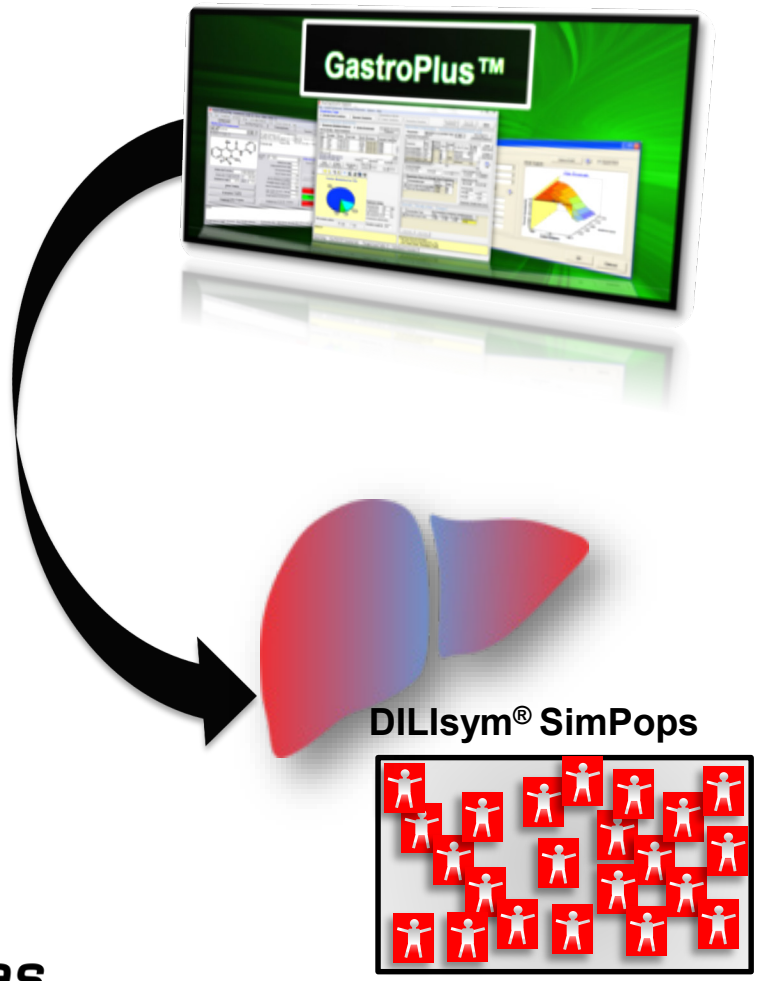



# Next Release of GastroPlus™ Will Allow for Efficient Use of GastroPlus PBPK Models Combined with DILIsym SimPops

- GastroPlus users build PBPK models within GastroPlus
- The "DILIsym" simulation mode will allow users to select a mapping of GastroPlus outputs to DILIsym PK inputs
- All DILIsym SimPops and SimCohorts will be 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

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