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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

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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



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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
 - <u>Tolvaptan</u> and <u>lixivaptan</u> vasopressin receptor 2 antagonists
 - <u>5 Macrolides</u>
 - Erythromycin
 - Clarithromycin
 - Azithromycin
 - Solithromycin
 - Telithromycin
 - <u>BMS-932481</u>
 - compound donated by BMS to consortium
 - 2 compound parameter sets included in DILIsym v7A: toxicity parameters determined independently by DSS team and BMS

Intracellular Bile Acids

patocyte Life Cycle

- 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

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- 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 <u>NO effect</u>
 - 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_v7
 A_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



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Simulation Results

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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)



DILIsym v7A Includes Optimization Feature

- Tool constructed within DILIsym to allow the user to optimize parameters to usersupplied data
- Utilizes genetic algorithmbased 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

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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

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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

Create SimCohorts			
Cre	ate Custom Sim	Cohorts	
Use Selected Individuals			
Input Individual Indexes		(Enter sequential indexe using a colon and non-sequential indexes separated by a comma, 1,5,8,9,30:38)	s e.g.
Choose Source SimPops	Dog_ROS_apop_mito_v3B_	_3	•
	Create Custom SimCohor	ts	



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New Weight-Adjusted Dosing Option Included in DILIsym v7A

- DILIsym v7A includes set of weightadjusted parameters added to all dosing scaffolds
 - Mirror of "standard" dosing options
- User may mix and match between prior "standard" dosing and new weightadjusted 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



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

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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 <u>the right number of body-weight</u> <u>matched</u> rats, dogs, mice or humans



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