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What's New in DILIsym Version 7A?

January 30, 2018

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DILIsym Services, Research Triangle Park, NC

The DILI-sim Initiative is a Consortium Style Collaboration Between DILIsym Services and Pharmaceutical Companies to Minimize DILI

2012 Stage 1	2015 Stage 2
Mechanisms	*Mechanisms*
• Reactive metabolites	• Lipotoxicity
• Oxidative stress	• Innate immunity
• Mitochondrial toxicity	
• Bile acid toxicity	
Patients and animals	*Patients and animals*
• Rats, mice, dogs	• Healthy volunteers
• Healthy volunteers	• Disease area patients
Compounds	*Compounds*
• Exemplars for optimization	• Exemplars for optimization
	• Exemplars for validation

Application of DILIsym in Drug Development

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Stage 3 Will Include Key Components Necessary for Predicting Idiosyncratic Liver Injury

2012 Stage 1	2015 Stage 2	2018 Stage 3
Mechanisms	*Mechanisms*	*Mechanisms*
• Reactive metabolites	• Lipotoxicity	• Adaptive immunity
• Oxidative stress	• Innate immunity	• Cholestasis
• Mitochondrial toxicity		• Improve *in vitro* assay systems
• Bile acid toxicity		
Patients and animals	*Patients and animals*	*Patients and animals*
• Rats, mice, dogs	• Healthy volunteers	• Larger more robust SimPops and biomarkers
• Healthy volunteers	• Disease area patients	• Disease area patients
Compounds	*Compounds*	*Compounds*
• Exemplars for optimization	• Exemplars for optimization	• Exemplars for optimization
	• Exemplars for validation	• Exemplars for validation

SLP Software Advances

Application of DILIsym in Drug Development

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DILI-sim Membership Benefits – Stage 3

Access to DILIsym software, equations, and support
- DILI-sim members receive access to the DILIsym software during their active membership term
- DILI-sim members receive an electronic copy of all equations included in each version of the DILIsym software released during their active membership term
- DILI-sim members have exclusive access to DILIsym training materials and support, including 10 hours of one-on-one support, free training once per year at annual meeting, and reduced rates on off-site workshops
- Tier 1 (3 year) members receive a 31% discount on consulting; Tier 2 (annual) members receive a 17% discount (compared to non-member pricing)
- DILI-sim members have exclusive access to the DILIsym Discovery Support Program (DDSP); not available to non-members or academics

Influence over DILIsym development
- Member companies guide DILIsym development
- DILI-sim members have option to donate data from current or failed compounds to serve as exemplars for DILIsym

Participation in regular meetings with colleagues
- Representatives from member companies attend quarterly DILI-sim update meetings to monitor progress and provide feedback, along with model design review sessions
- Members gather in person once per year for a more comprehensive overview during the annual DILI-sim Face to Face Meeting
- Attendance, voting, and data generation are optional benefits of membership and are not required

Membership Inquiries:
www.DILIsym.com
bhowell@DILIsym.com
919-558-1323

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Academic Licensing Program for DILIsym and MITOsym

- Applicants apply via www.DILIsym.com

- Licenses are available for teaching use (in classroom with students) and for non-commercial academic research use

- Academic members of DILI-sim will receive password protected, subscription-based versions of DILIsym and MITOsym in the compiled formats

- Goal of the academic licensing program is to increase broad use, testing, and validation of DILIsym and MITOsym software
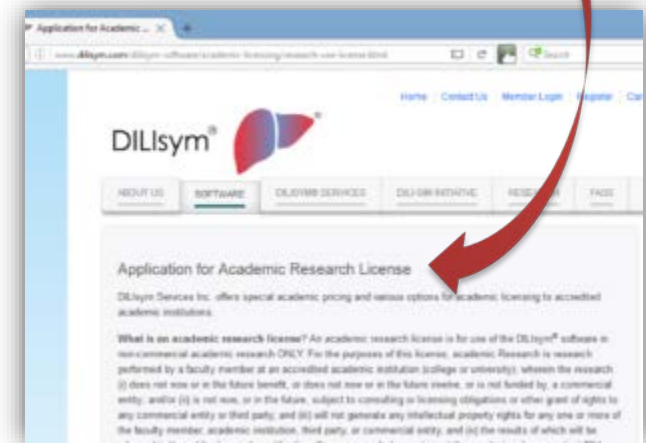

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Highlights of DILIsym v7A

- 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

- 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
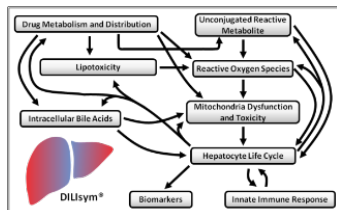
- 2 NEW SimPops

  - 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

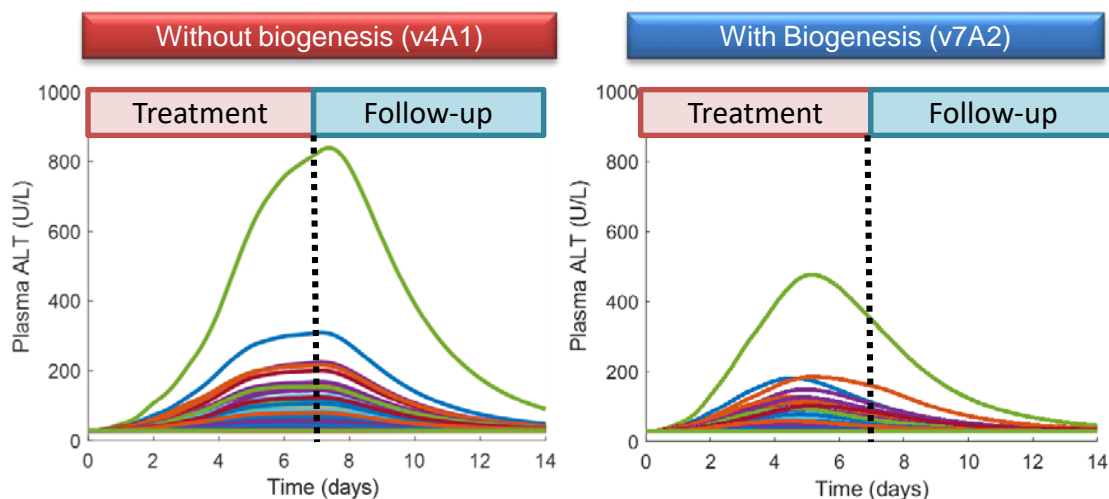# 8 New Compounds Included in DILIsym v7A

- 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
  - <u>Default human parameter values set to have 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_v7A_2 (n=285); <u>for exploration only</u>
  - 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

HUMAN

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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)

v4A_1 SimPops
114/285 with ALT >3x ULN
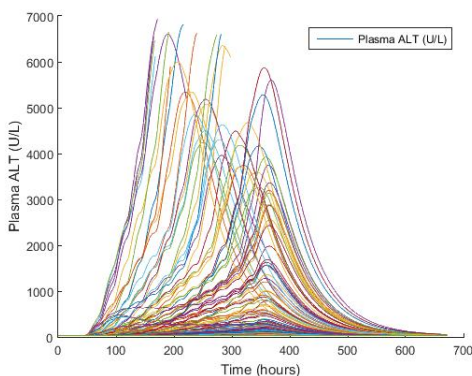
v7A_1 SimPops
121/285 with ALT >3x ULN
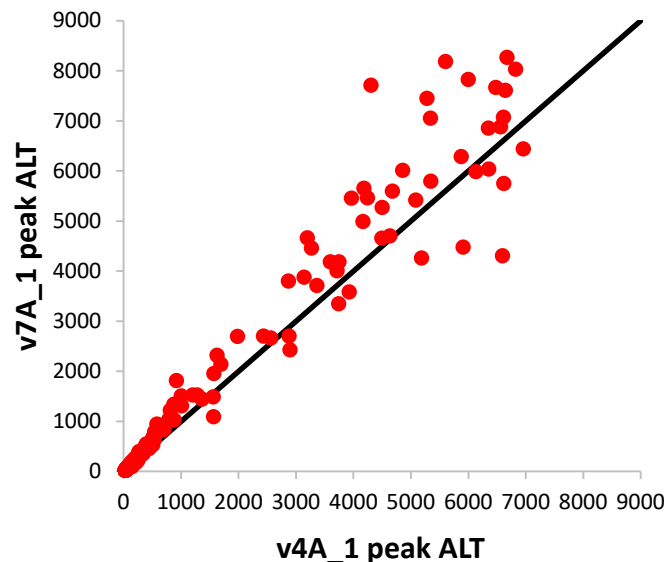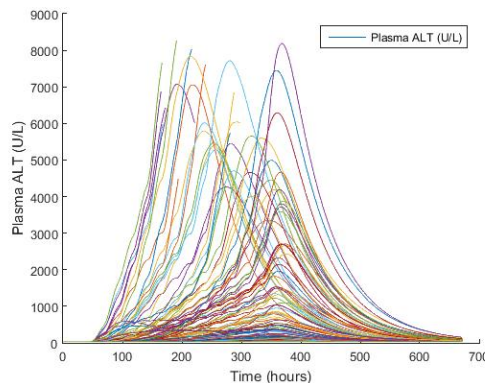
Simulation Results

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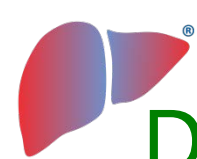
DILIsym v7A Includes Optimization Feature

- 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

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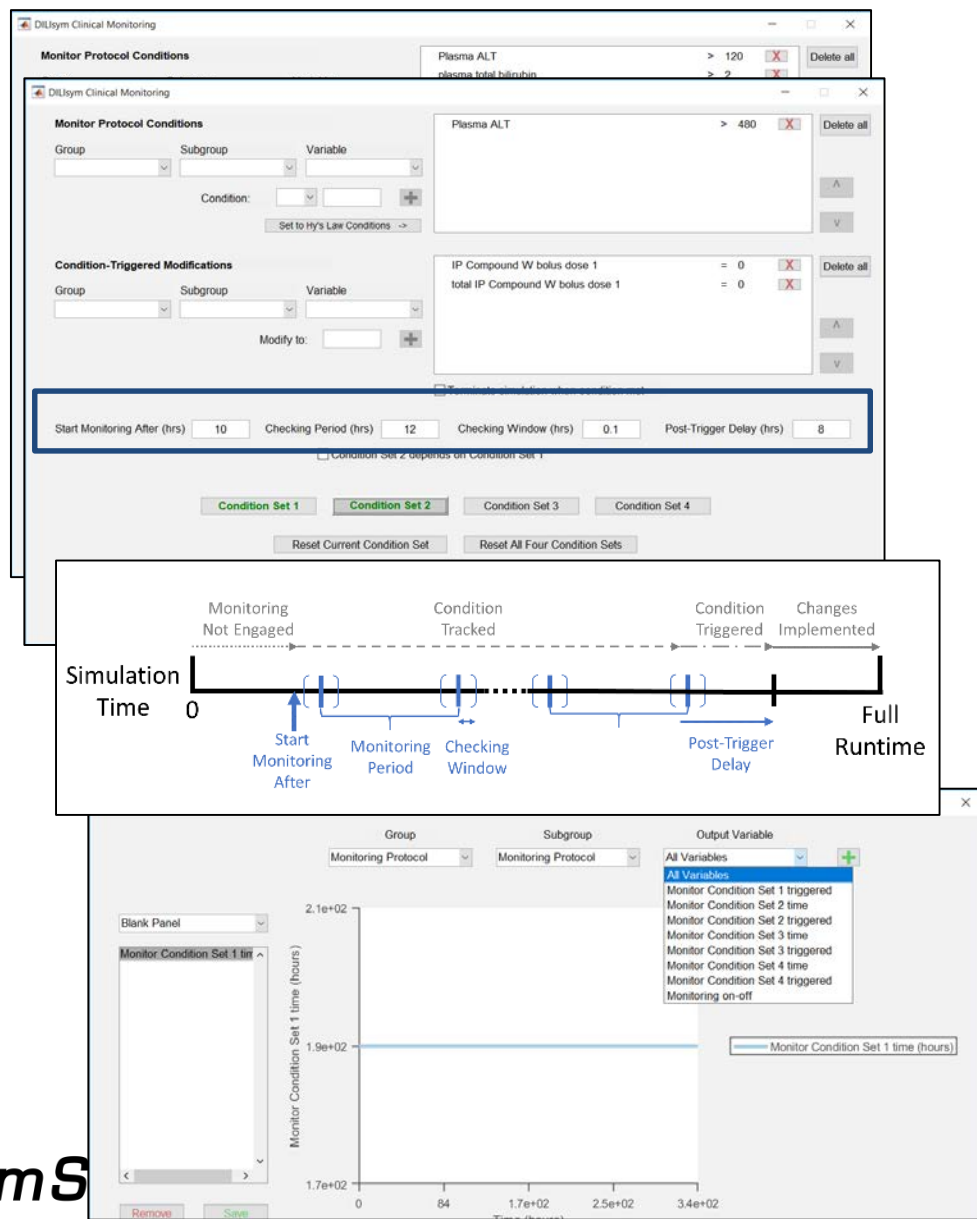
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DILIsym v7A Includes Ability to Create Custom SimCohorts from Any Existing SimPops or SimCohorts

- 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

Create Custom SimCohorts

Use Selected Individuals ☐

Input Individual Indexes [   ] *(Enter sequential indexes using a colon and non-sequential indexes separated by a comma, e.g. 1,5,8,9,30:38)*

Choose Source SimPops [Dog_ROS_apop_mito_v3B_3 ▼]

[Create Custom SimCohorts]

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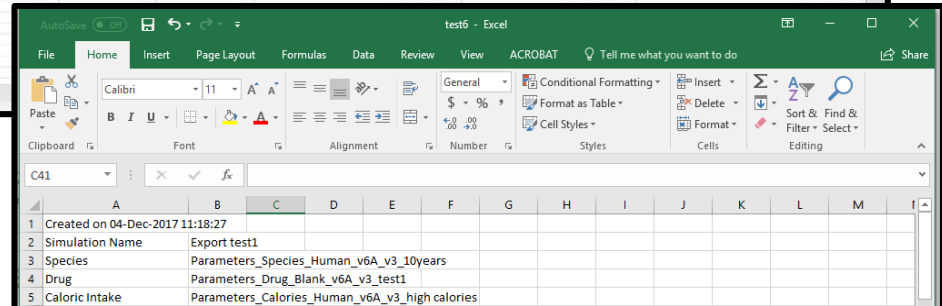
These values will override the standard dose 1 parameters above, but the standard dose 2 parameters will be non-weight adjusted

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Information on Simulation Setup Added to Results Exported to Excel for v7A
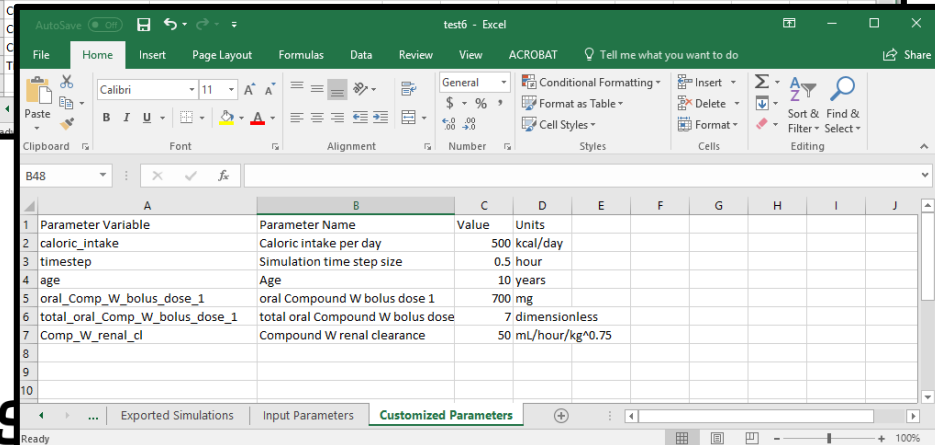
- Export to Excel option exists for results and can be accessed after a simulation from the main screen
- Excel file will now contain further information about the simulation that generated those results
  - Date and time
  - Simulation setup
  - Parameters listed as customized
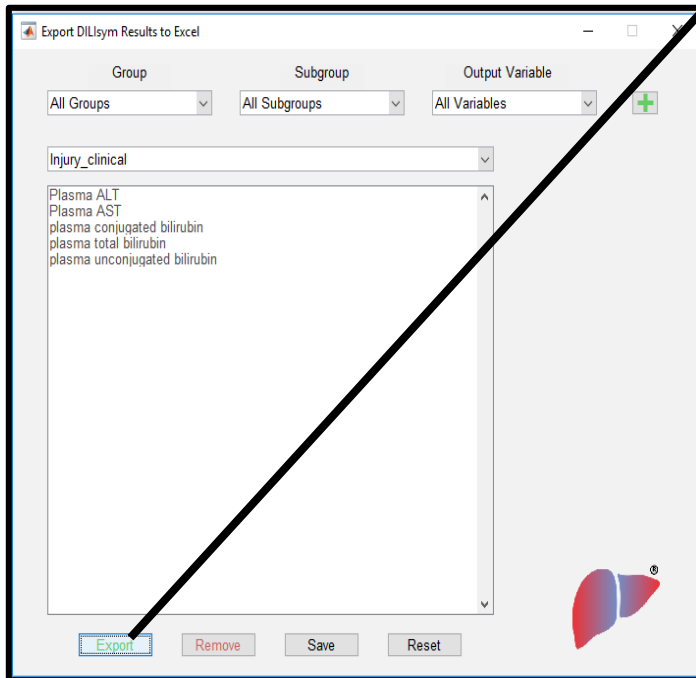- Better audit trail

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

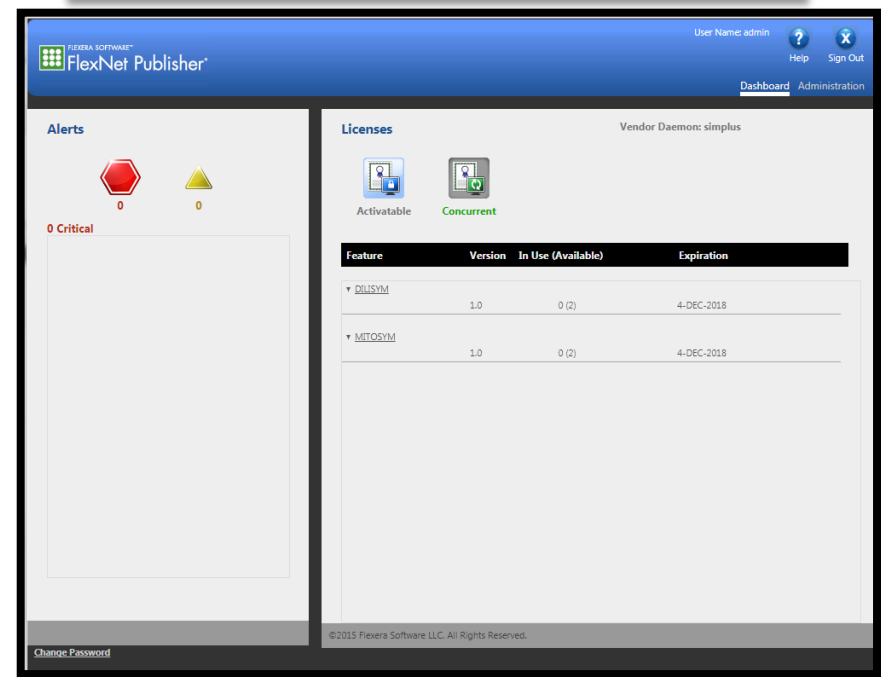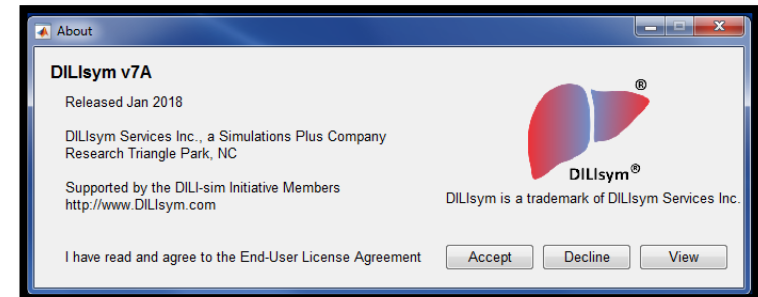**DILIsym Services**

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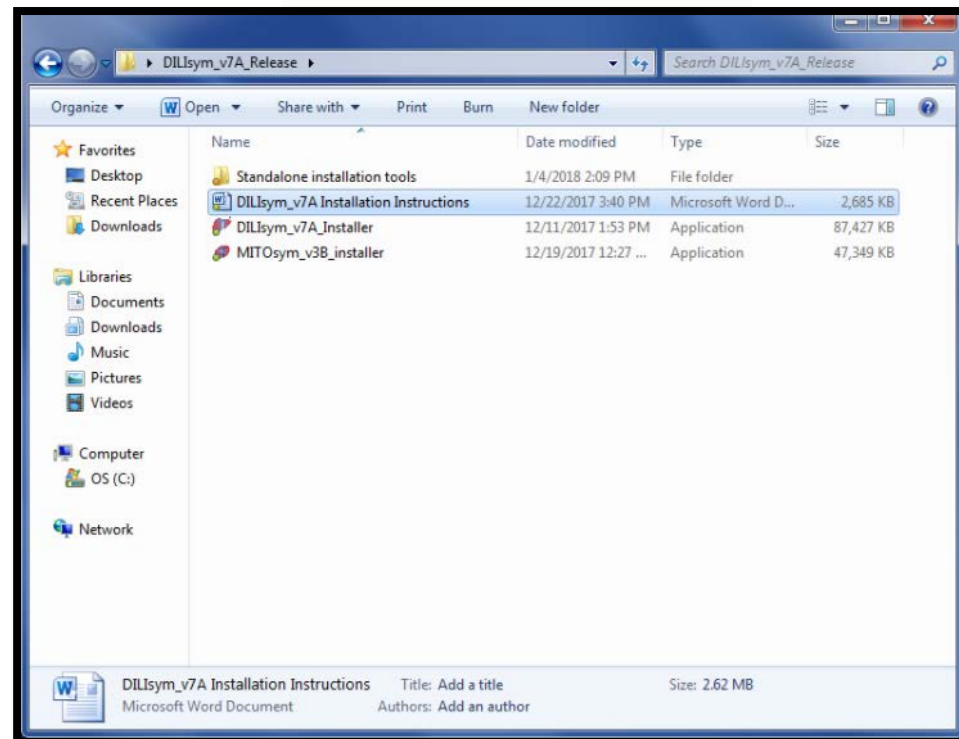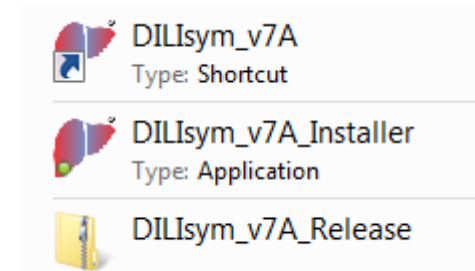
DILIsym and MITOsym Licenses Will Be Managed Using Flexera

- 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
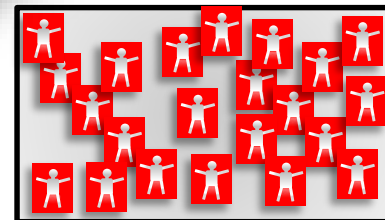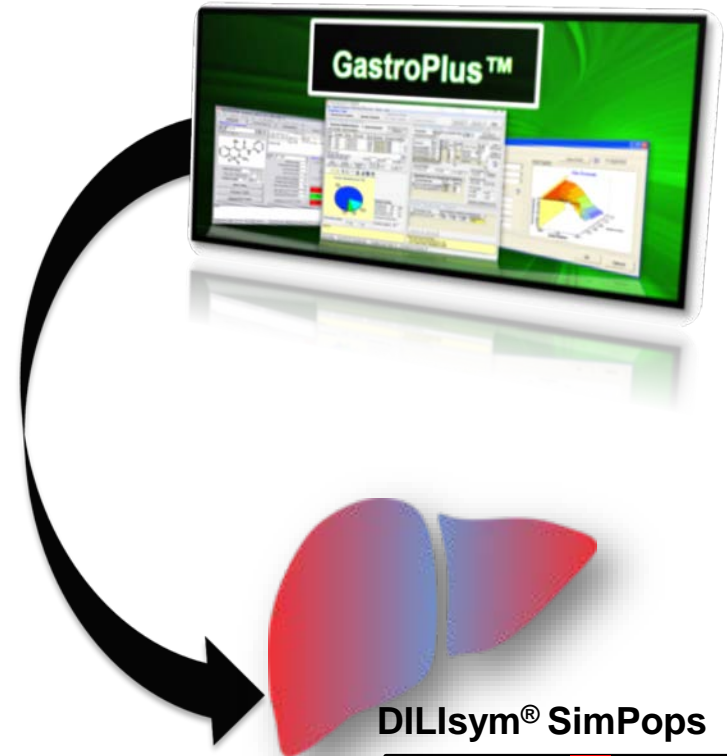 - Additional DILIsym licenses available at significantly reduced rates

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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 **the right number of body-weight matched** rats, dogs, mice or humans

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2018 DILI-sim Initiative Key Dates

2017

2018

Q4 | Q1 | Q2 | Q3 | Q4

14 December
Q4 update

29 March
Q1 update

TBD
Q2 Update

11-13 September
Q3 F2F update
and training

TBD
Q4 update

January
DILIsym v7A release

DILIsym 3 day training course
La Jolla, CA
5-7 March
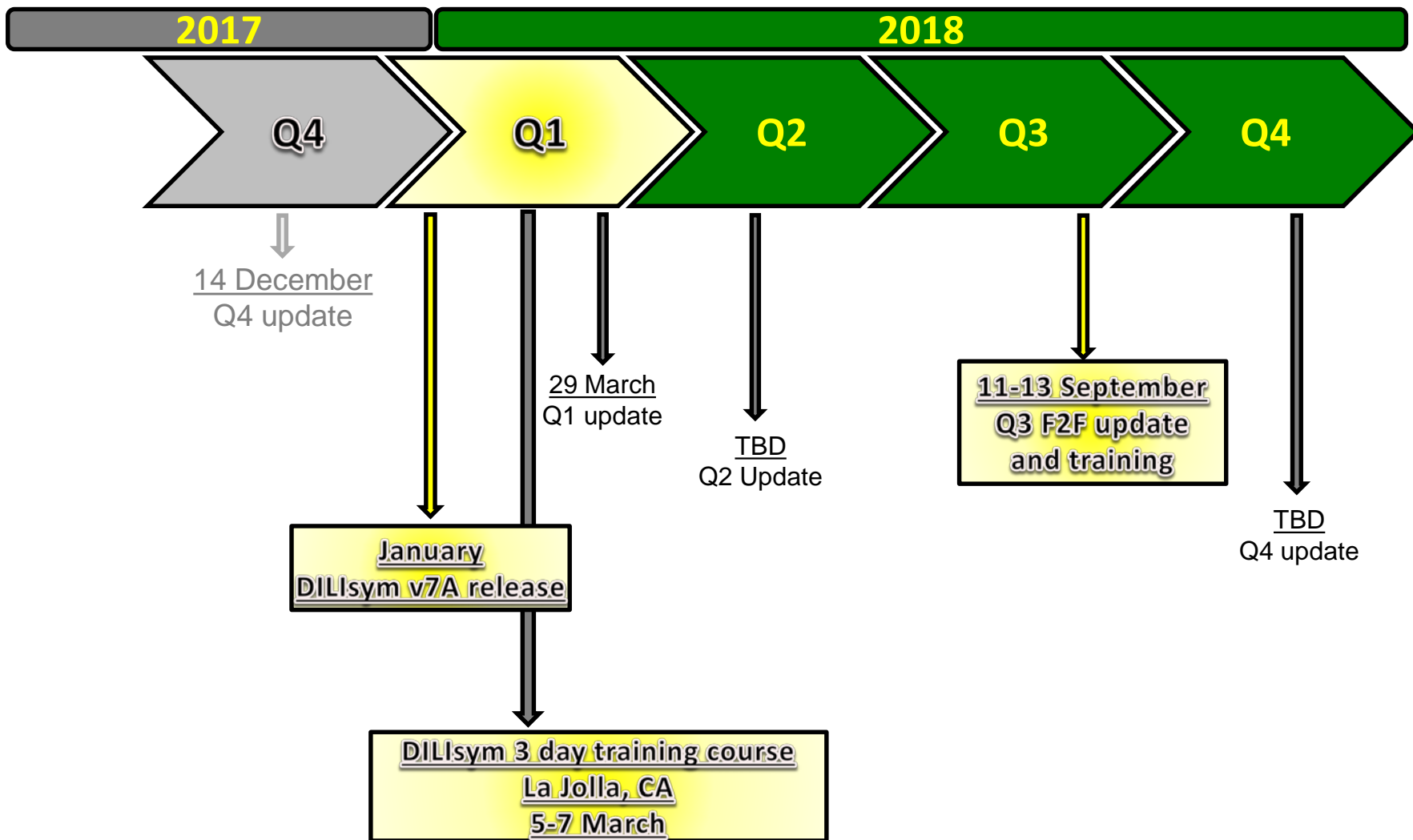
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First DILIsym Workshop Will be Offered in La Jolla Alongside GastroPlus Workshop

- When: March 5-7th, 2018 (3 day workshop in parallel with basic GastroPlus workshop)
- Where: Hyatt Regency La Jolla at Aventine, CA
- What: 3 day DILIsym workshop to include training on:
  – background information on DILI
  – data collection for DILIsym use
  – parameterization of DILIsym from *in vitro* data
  – typical workflow for DILIsym use
  – various features available in DILIsym v7A
    • SimPops
    • Clinical monitoring
    • Optimization
    • Analysis of results
    • Sensitivity analysis
  – Hands-on examples with DILIsym and MITOsym
- Who: beginning and advanced users of DILIsym
- Pricing per attendee
  – $1200 – Industry non-members of DILI-sim
  – $996 – DILI-sim Tier 2 members
  – $828 – DILI-sim Tier 1 members
  – $600 – government or academic

HYATT REGENCY LA JOLLA AT AVENTINE
Hotel Photos | View All | Hyatt Regency La Jolla

Hyatt Regency La Jolla
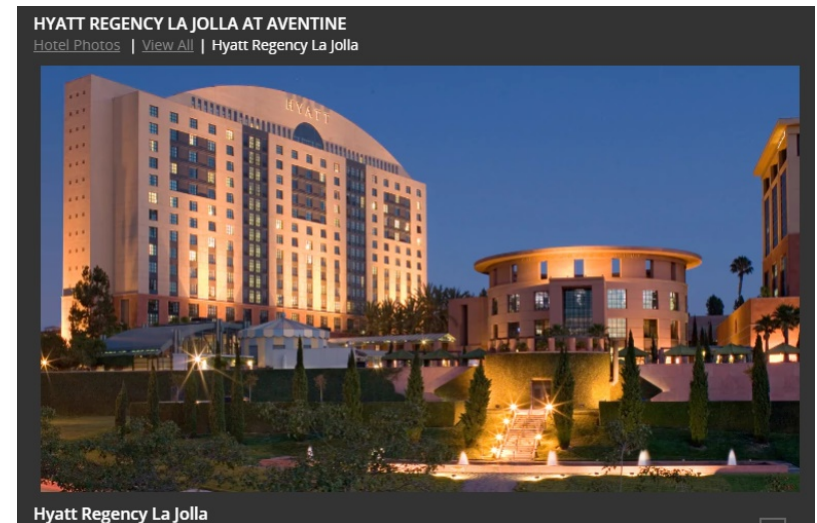
DILI-sim Members, Non-members, Academics, and Government Personnel Welcome to Attend!

Existing or Prospective Users Welcome to Attend!

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