



DILIsym Services

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

What's New in DILIsym Version 7A?

January 30, 2018

Brett A. Howell, President

DILIsym Services, Research Triangle Park, NC

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



2012	Stage 1	2015	Stage 2
<u>Mechanisms</u> <ul style="list-style-type: none">• Reactive metabolites• Oxidative stress• Mitochondrial toxicity• Bile acid toxicity		<u>Mechanisms</u> <ul style="list-style-type: none">• Lipotoxicity• Innate immunity	
<u>Patients and animals</u> <ul style="list-style-type: none">• Rats, mice, dogs• Healthy volunteers		<u>Patients and animals</u> <ul style="list-style-type: none">• Healthy volunteers• Disease area patients	
<u>Compounds</u> <ul style="list-style-type: none">• Exemplars for optimization		<u>Compounds</u> <ul style="list-style-type: none">• 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



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2012	Stage 1	2015	Stage 2	2018	Stage 3
<u><i>Mechanisms</i></u> <ul style="list-style-type: none">• Reactive metabolites• Oxidative stress• Mitochondrial toxicity• Bile acid toxicity <u><i>Patients and animals</i></u> <ul style="list-style-type: none">• Rats, mice, dogs• Healthy volunteers <u><i>Compounds</i></u> <ul style="list-style-type: none">• Exemplars for optimization		<u><i>Mechanisms</i></u> <ul style="list-style-type: none">• Lipotoxicity• Innate immunity <u><i>Patients and animals</i></u> <ul style="list-style-type: none">• Healthy volunteers• Disease area patients <u><i>Compounds</i></u> <ul style="list-style-type: none">• Exemplars for optimization• Exemplars for validation		<u><i>Mechanisms</i></u> <ul style="list-style-type: none">• Adaptive immunity• Cholestasis• Improve <i>in vitro</i> assay systems <u><i>Patients and animals</i></u> <ul style="list-style-type: none">• Larger more robust SimPops and biomarkers• Disease area patients <u><i>Compounds</i></u> <ul style="list-style-type: none">• Exemplars for optimization• Exemplars for validation	



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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

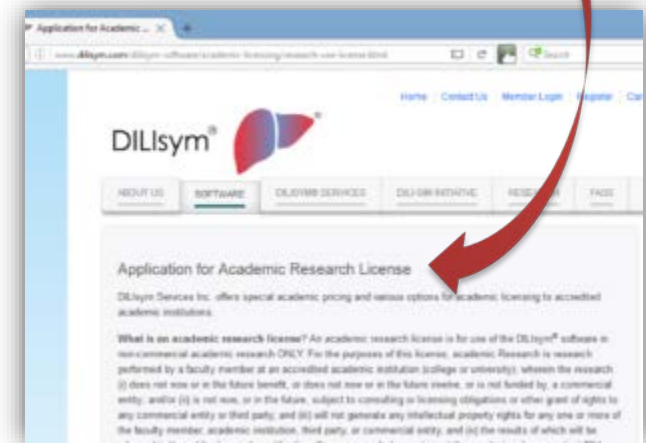
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Academic Licensing Program for DILIsym and MITOsym

- 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



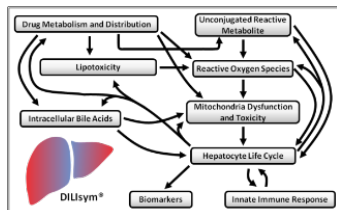
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Highlights of DILIsym v7A

- Several NEW Validation Compounds included with varying clinical presentations
 - 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

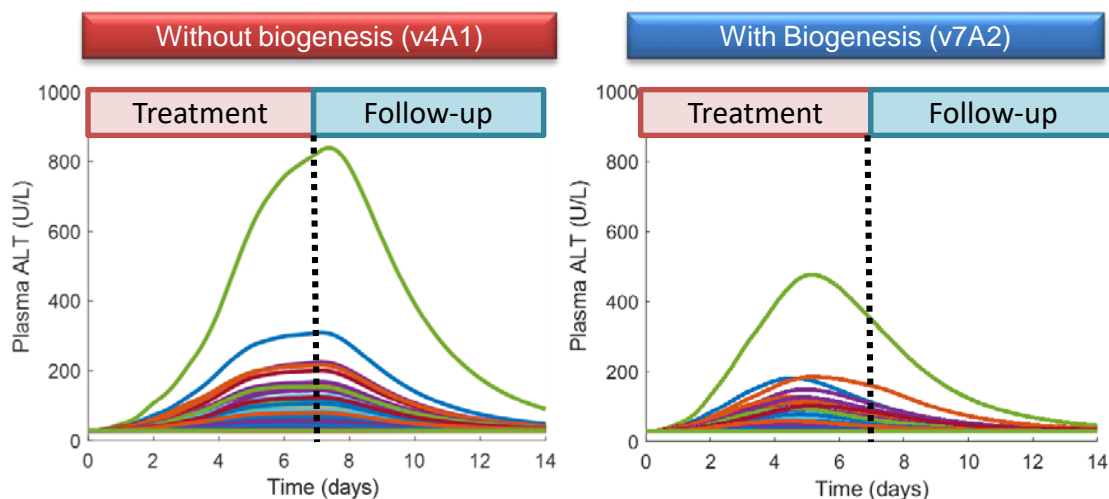
- Five macrolide antibiotics: solithromycin, erythromycin, clarithromycin, azithromycin, telithromycin
 - Originally represented as part of a project for Cempra
 - Simulation results presented to FDA and at several conferences, including ACoP 2017
 - Publication on macrolide antibiotics in DILIsym forthcoming
- 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



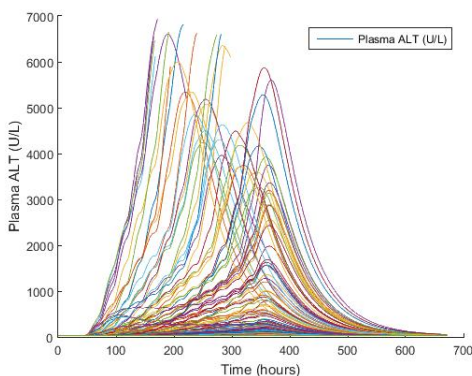


SimPops Including Variability in ALT Parameters Included in DILIsym v7A

- 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)

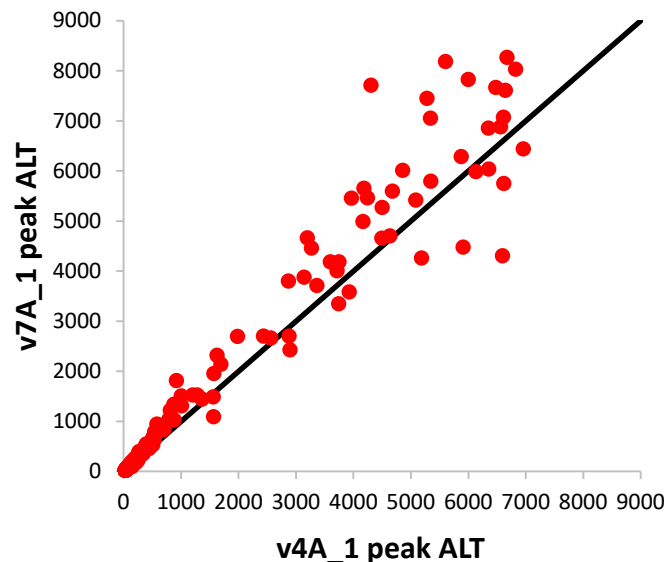
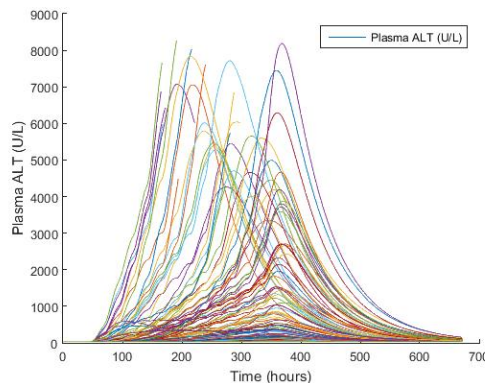
v4A_1 SimPops

114/285 with ALT >3x ULN



v7A_1 SimPops

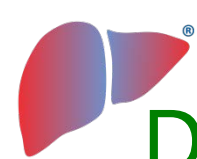
121/285 with ALT >3x ULN



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

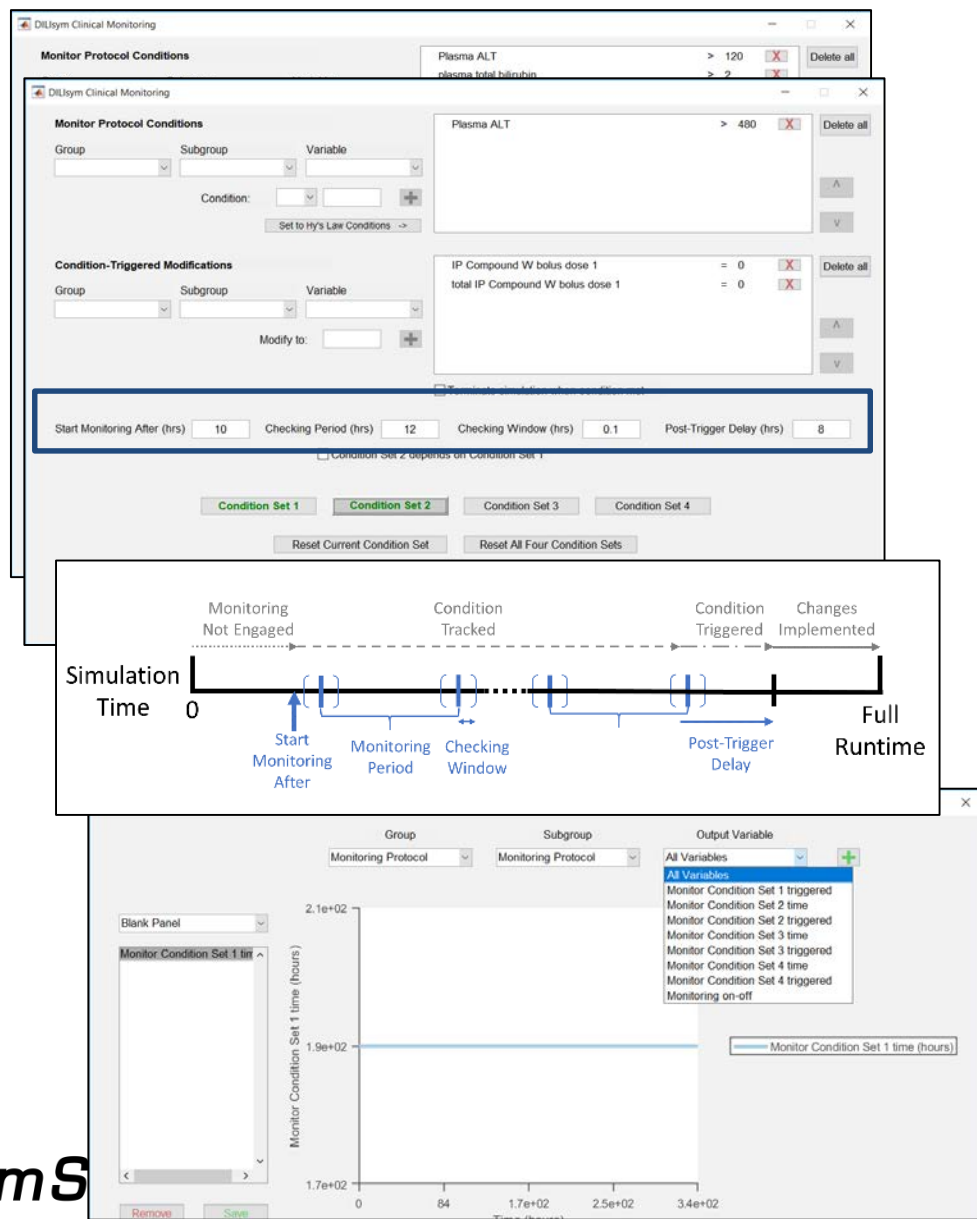
The screenshot shows the 'DILIsym Optimization' window. It contains several sections for configuring an optimization:

- Optimization Parameters:** Includes dropdowns for 'Group', 'Subgroup', and 'Variable'. Below these are input fields for 'Lower Bound' and 'Upper Bound', and a '+' button. A button labeled 'Add Distribution Type' is also present.
- Parameter Constraints (Covariates):** Includes dropdowns for 'Variable1' and 'Variable2', a 'Relation' dropdown, and a 'Multiplier' input field. A '+' button is next to the multiplier.
- SimSingle(s):** Includes a 'SimSingle Selection' dropdown and a '+' button.
- Comparison Data:** Includes a 'Weight' input field (set to 1) with a '+' button, a 'SimSingle Reference' dropdown, and a 'Comparison Method' dropdown. A button labeled 'Add Comparison Data' is at the bottom of this section.
- Simulation Settings:** Includes 'Population #' (set to 200) and 'Generation' (set to 10) input fields.
- Probability:** A checkbox labeled 'Probability' with a note '(penalty for unlikely occurrence based on distribution)'.
- Buttons:** 'Run', 'Save Setup', 'Load Setup', and 'Cancel' buttons are at the bottom.



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



DILIsymS



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

Create Custom SimCohorts



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

The screenshot shows the 'DILIsym Parameter Customization' window. The 'Group' is set to 'CompWDosing'. The 'Subgroup' dropdown menu is open, showing options: 'All Subgroups', 'Compound W IP', 'Compound W IP weight adj', 'Compound W IV bolus', 'Compound W IV bolus weight adj', 'Compound W IV infus weight adj', 'Compound W IV infusion', 'Compound W oral', and 'Compound W oral weight adj'. The 'Variable' dropdown is set to 'Parameter Not Selected'.

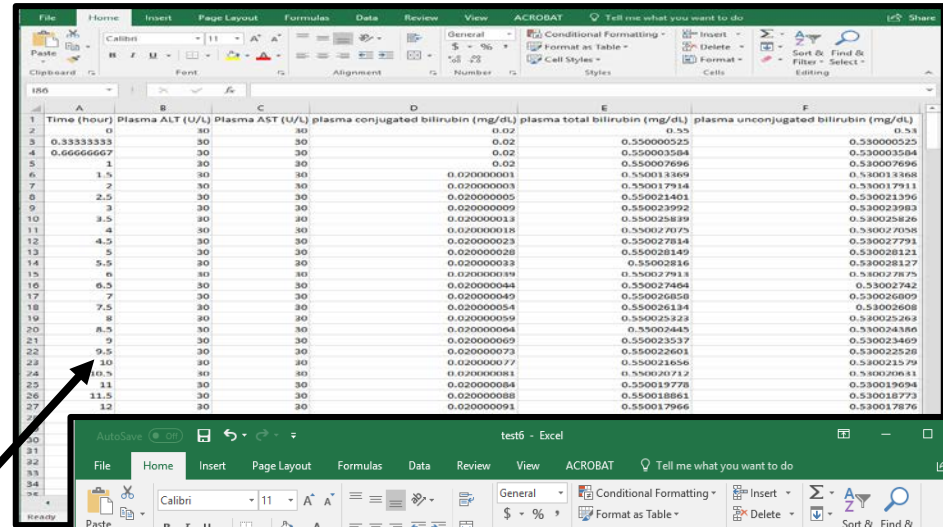
The screenshot shows the 'DILIsym Parameter Customization' window with a list of parameters. A yellow highlight indicates that weight-adjusted parameters override non-weight-adjusted parameters. A red box highlights the weight-adjusted parameters for 'Compound W IV bolus weight adj'.

Group	Subgroup	Variable	Value	Unit	Override
CompWDosing	Compound W IV bolus...	start time IV Compoun...	0	hour	
Weight adjusted parameters override non-weight adjusted parameters					
CompWDosing	Compound W IV bolus	IV Compound W bolus dose 1	100	mg	X
CompWDosing	Compound W IV bolus	total IV Compound W bolus dose 1	1	dimensionless	X
CompWDosing	Compound W IV bolus	IV Compound W bolus dose 2	10	mg	X
CompWDosing	Compound W IV bolus	total IV Compound W bolus dose 2	1	dimensionless	X
CompWDosing	Compound W IV bolus weight adj	IV Compound W bolus dose 1 weight adjusted	10	mg/kg	X
CompWDosing	Compound W IV bolus weight adj	total IV Compound W bolus dose 1 weight adjusted	1	dimensionless	X

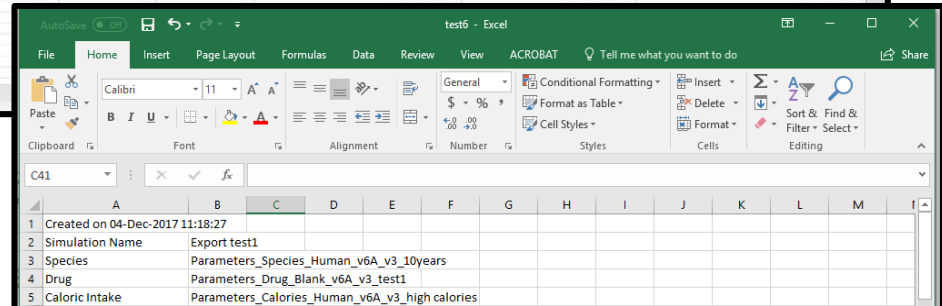
These values will override the standard dose 1 parameters above, but the standard dose 2 parameters will be non-weight adjusted

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

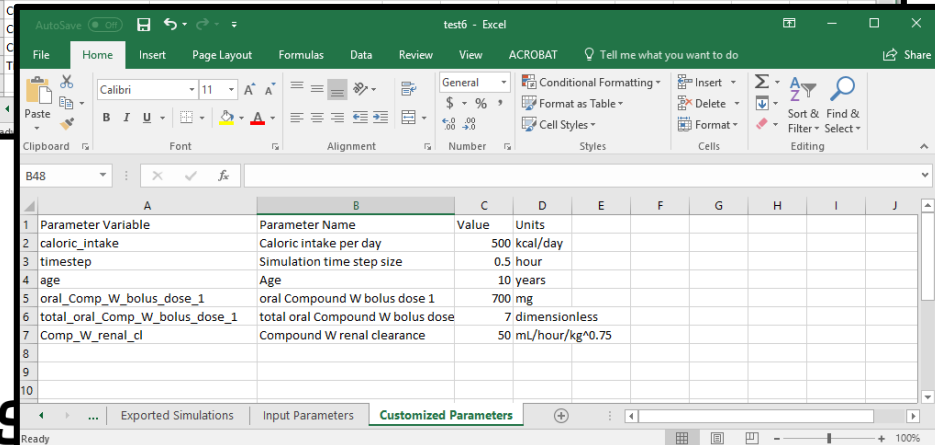
- Export to Excel option exists for results and can be accessed after a simulation from the main screen
- Excel file will now contain further information about the simulation that generated those results
 - Date and time
 - Simulation setup
 - Parameters listed as customized
- Better audit trail



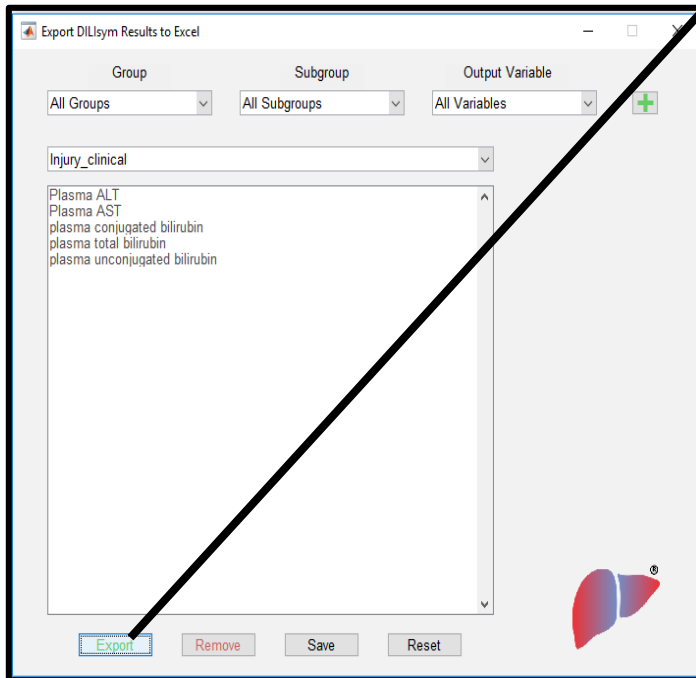
Time (hour)	Plasma ALT (U/L)	Plasma AST (U/L)	plasma conjugated bilirubin (mg/dL)	plasma total bilirubin (mg/dL)	plasma unconjugated bilirubin (mg/dL)
1	0.33333333	30	0.02	0.550000525	0.530000525
2	0.66666667	30	0.02	0.550003584	0.530003584
3	1	30	0.02	0.550007696	0.530007696
4	1.5	30	0.020000001	0.550013369	0.530013368
5	2	30	0.020000001	0.550017914	0.530017911
6	2.5	30	0.020000001	0.550021401	0.530021396
7	3	30	0.020000001	0.550023992	0.530023983
8	3.5	30	0.020000013	0.550025839	0.530025826
9	4	30	0.020000018	0.550027075	0.530027058
10	4.5	30	0.020000023	0.550027814	0.530027793
11	5	30	0.020000028	0.550028149	0.530028121
12	5.5	30	0.020000033	0.55002816	0.530028127
13	6	30	0.020000039	0.550027913	0.530027875
14	6.5	30	0.020000044	0.550027464	0.53002742
15	7	30	0.020000049	0.550026858	0.530026809
16	7.5	30	0.020000054	0.550026134	0.530026068
17	8	30	0.020000059	0.550025323	0.530025263
18	8.5	30	0.020000064	0.550024445	0.530024386
19	9	30	0.020000069	0.550023537	0.530023469
20	9.5	30	0.020000073	0.550022601	0.530022528
21	10	30	0.020000077	0.550021656	0.530021579
22	10.5	30	0.020000081	0.550020712	0.530020631
23	11	30	0.020000084	0.550019778	0.530019694
24	11.5	30	0.020000088	0.550018861	0.530018773
25	12	30	0.020000091	0.550017966	0.530017876



Created on	Simulation Name	Species	Drug	Caloric Intake
04-Dec-2017 11:18:27	Export test1	Parameters_Species_Human_v6A_v3_10years	Parameters_Drug_Blank_v6A_v3_test1	Parameters_Calories_Human_v6A_v3_high calories



Parameter Variable	Parameter Name	Value	Units
caloric_intake	Caloric intake per day	500	kcal/day
timestep	Simulation time step size	0.5	hour
age	Age	10	years
oral_Comp_W_bolus_dose_1	oral Compound W bolus dose 1	700	mg
total_oral_Comp_W_bolus_dose_1	total oral Compound W bolus dose	7	dimensionless
Comp_W_renal_cl	Compound W renal clearance	50	mL/hour/kg*0.75



Export DILysm Results to Excel

Group: All Groups Subgroup: All Subgroups Output Variable: All Variables

Injury_clinical

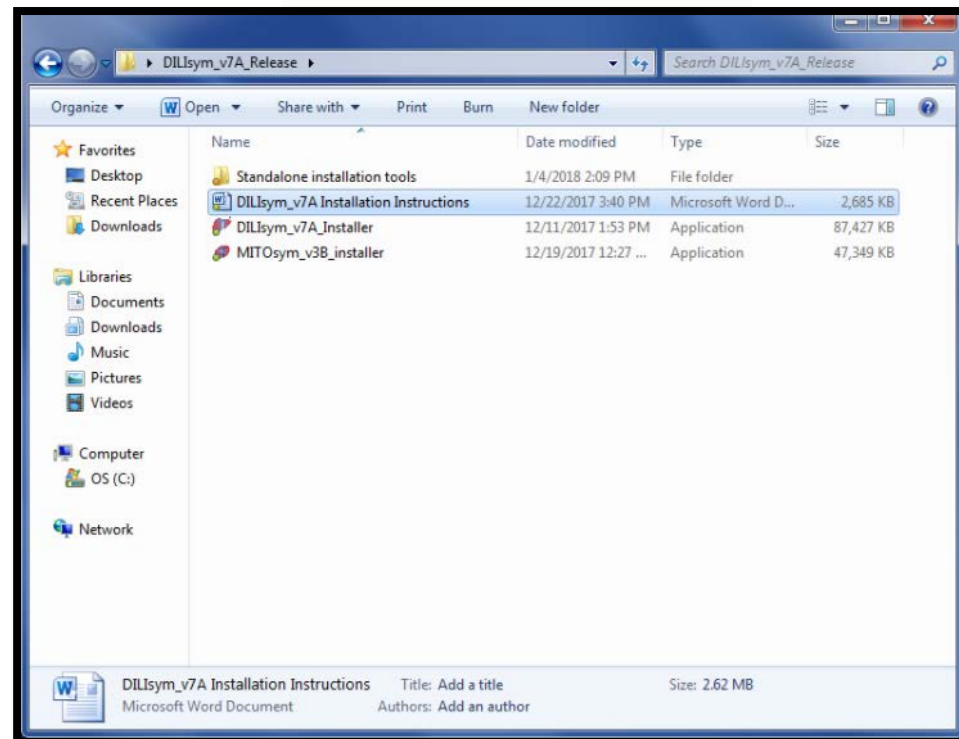
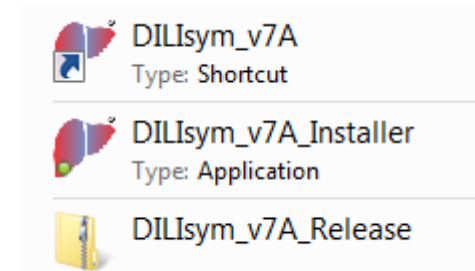
Plasma ALT
Plasma AST
plasma conjugated bilirubin
plasma total bilirubin
plasma unconjugated bilirubin

Export Remove Save Reset



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

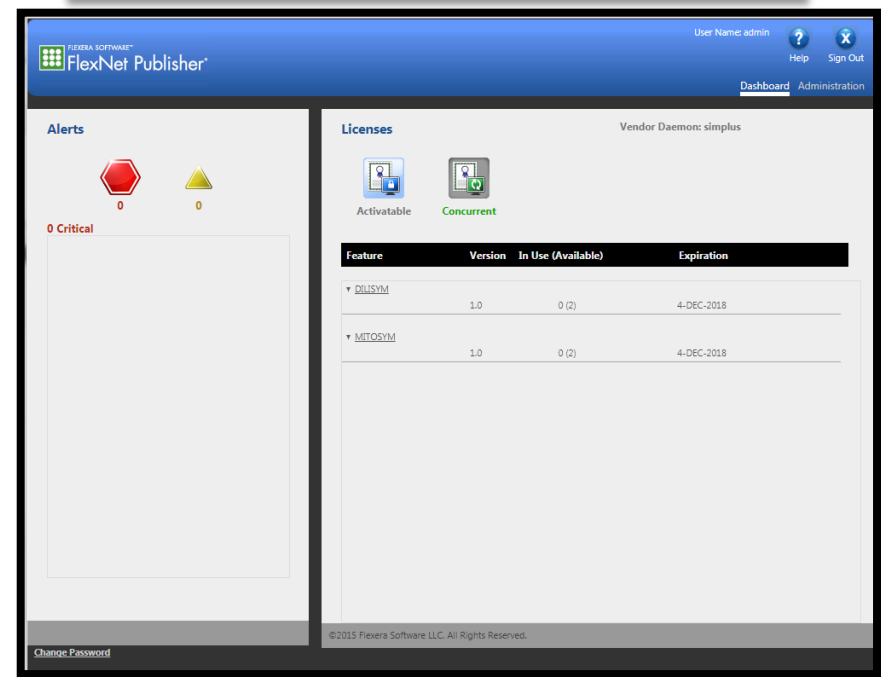
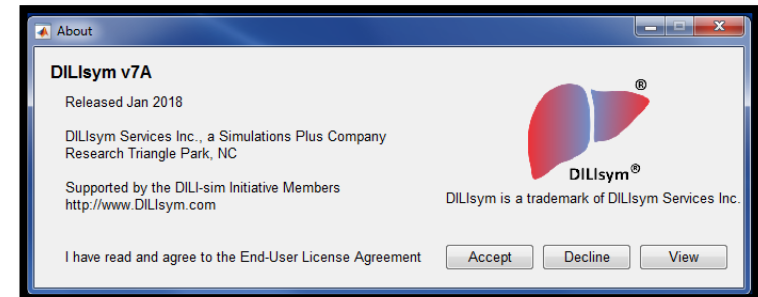


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DILIsym and MITOsym Licenses Will Be Managed Using Flexera

- 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

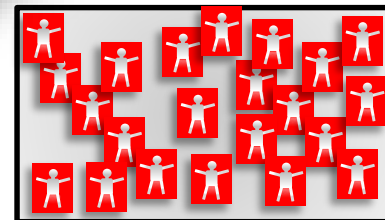
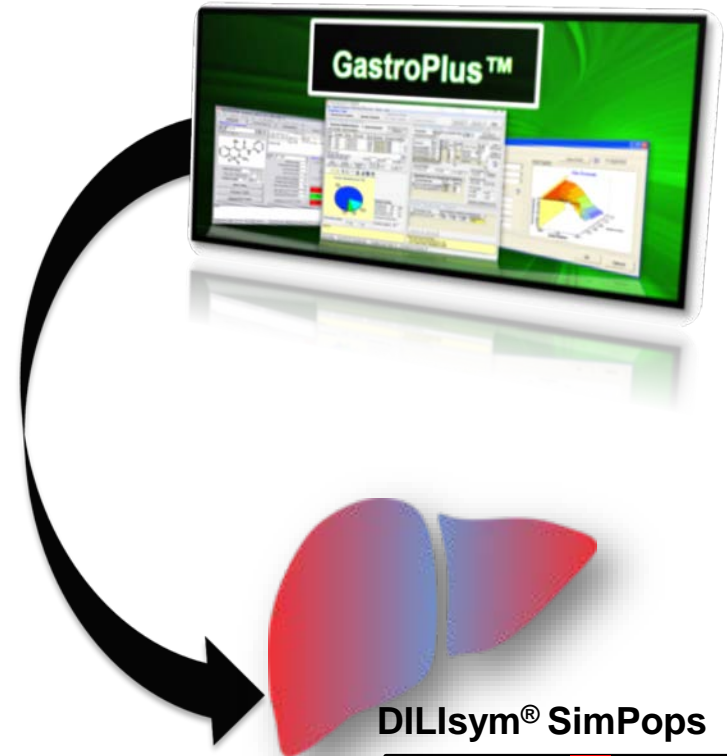


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Next Release of GastroPlus™ Will Allow for Efficient Use of GastroPlus PBPK Models Combined with DILIsym SimPops

- 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

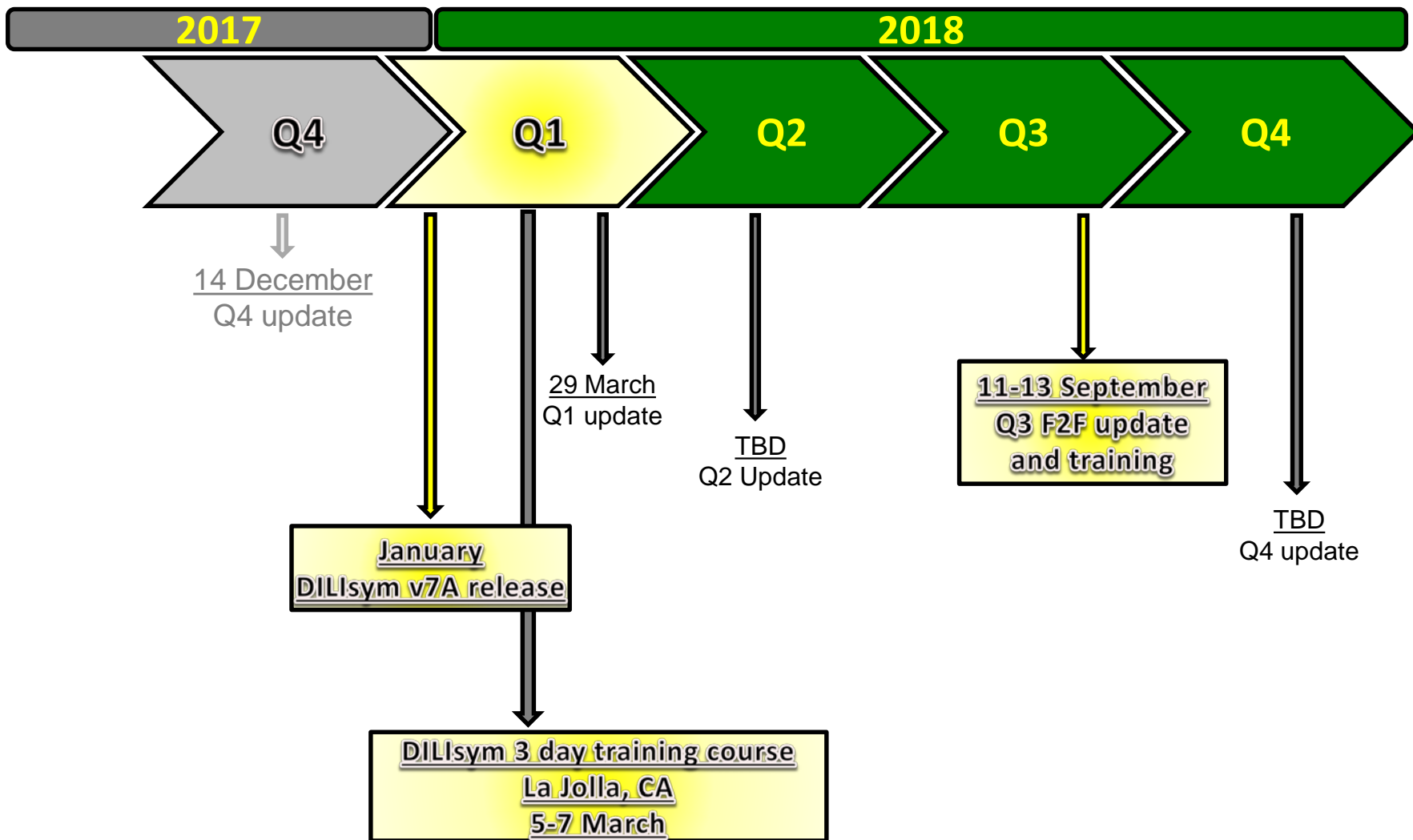


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2018 DILI-sim Initiative Key Dates



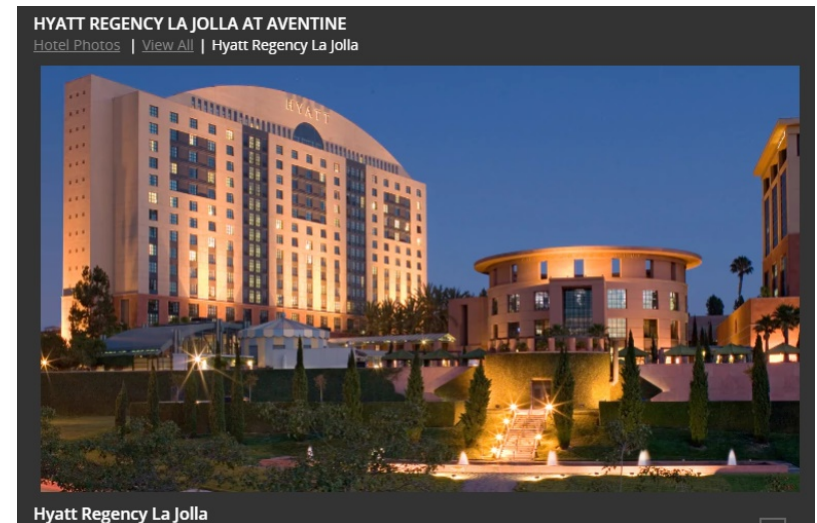
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First DILIsym Workshop Will be Offered in La Jolla Alongside GastroPlus Workshop

- 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



***DILI-sim Members, Non-members,
Academics, and Government Personnel
Welcome to Attend!***

***Existing or Prospective Users
Welcome to Attend!***

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