WebEx Tools for Interacting with Presenters Will Be in Use During this Meeting

- <u>Recording meeting for</u> <u>future reference</u>
- Large number of meeting participants requires system for orderly interaction
 - Will use WebEx tools
- To make a comment and/or ask a question during the presentation period:
 - Submit in text by using the Chat window (purple outline) and addressing message to 'Questions Here'
- More in-depth Q&A period planned for end of meeting











THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

DILIsym[™] v2A Model User Training

April 25, 2013

Speakers: Brett A. Howell

Please note: this presentation, including questions from the audience, is being recorded Please send questions to the DILIsym[™] team through the individual listed as "Questions Here" (chat) so we can read them aloud and answer them, time permitting

The DILI-sim Team and the SAB





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The DILIsym.com Website

www.DILlsym.com:

- Stand-alone webpage, linked to the Hamner Institutes webpage, that provides information and file access
- Online forum for virtual discussions through threads and post between member companies, the modeling team, and the SAB
 - Password protected
 - · Allows for model access via the web
 - General scientific discussions
 - DILI-sim Initiative related discussions (operations)
 - DILlsym[™] model design discussions
 - DILIsym[™] technical/practical discussions related to use
 - Additional means for tech support for model users
- DILIsym[™] model files and documentation are available via a password protected site
- DILI-sim members register for an account to access files and forum discussions







DILIsym[™] Model v2A Overview

- Multiple species: human, rat, mouse, and dog
 - Population variability
- The three primary acinar zones of liver represented
- Essential cellular processes represented to multiple scales in interacting sub-models
 - Pharmacokinetics
 - Dosing (IP, IV, Oral)
 - Transporter Inhibition
 - Drug metabolism
 - GSH depletion
 - Injury progression
 - Mitochondrial dysfunction, toxicity
 - Bile acid mediated toxicity
 - Cellular energy balance
 - Hepatocyte life cycle
 - Macrophage, LSEC life cycles
 - Immune mediators
 - Caloric intake
 - Biomarkers





- Hepatotoxicity exemplars
 - Reactive metabolite mediated
 - Acetaminophen
 - Methapyrilene
 - Furosemide
 - Aflatoxin B1
 - Mitochondrial dysfunction
 - Etomoxir
 - Buprenorphine
 - Bile acid transporter inhibition
 - Glibenclamide
 - CP-724714
 - Single, multiple dose protocols
 - Single, combination drug protocols
- Compartment-based modeling
 - >480 state variables
 - 'Form to function' connection
 - Ordinary differential equations
 - Alternative mathematical approaches are possible
 - Simulations can be run using code or GUI developed in house



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Highlights of DILIsym[™] v2A



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- Added direct mitochondria toxicitymediated hepatocellular necrosis
- Added bile acid-mediated toxicity hepatocellular necrosis
- Expanded representation of innate immune contributions to injury and recovery
- Expanded number of represented biomarkers of hepatocellular injury
 - Circulating (e.g., mir-122)
 - Hepatocellular (e.g., triglyceride)



Buprenorphine
CP-724714

Etomoxir

Introduced additional exemplar

 Additional SimPops[™], capturing impact of variability in key pathways

compounds for exposure-related toxicity

• Expanded capabilities of GUI interface



Expanded Capabilities and Features of DILIsym[™] v2A

- New capability to dose up to 3 compounds at once
 - W, X, and Y; v1A included APAP, X, and NAC
 - NAC representation still available
- New Compound Y option includes a simple, two compartment PK model representation
- Drug and Species parameters are now split into two separate value sets
 - Easier cross-species predictions
 - Improved clarity on what parameters apply to the biology versus the intersection of the drug and the biology
- New Output Table feature allows for easy calculation of Max, Min, AUC, Mean, and other metrics
- New Parameter Sweep option allows GUI users to sweep across a range of values for a given model parameter
 - Includes all model parameters; dose sweeps and sensitivity analyses possible
- New 2-Parameter Sweep option (MATLAB code version only)
- New Load/Save options for GUI results
- *New* Override protection for standard drug and species parameter sets (GUI version only)
- Data Comparisons include many more data sets and new plot options
- Caloric intake is now included for mitochondria toxicity and bile acid homeostasis; the role of caloric intake will continue to expand
- New 'events' feature avoids skipping discrete events, regardless of maximum step size
 - Compound W, X, and Y doses, caloric intake (meals), and mechanistic interventions included
- Added dog optimizations and capabilities
- Streamlined code base
 - No separate algebraics file
 - ODE file and many Excel and GUI files are now automatically called
- Expanded Zotero reference database (contact us for real-time access)



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DILIsym[™] v2A Training Session Goals

- This training session will provide users with knowledge of updates and additions to DILIsym[™] as of the v2A release
- This training session should be a supplement to previously recorded training sessions
 - DILlsym[™] v1A user training January 2012
 - In-depth DILIsym[™] v1A user training September 2012
 - Both sessions accessible at www.DILlsym.com
- This training session is not an in-depth exploration of the application of the model
 - This will be done during the annual DILI-sim on-site meeting in RTP on September 26th, 2013





DILIsym[™] v2A User Training Agenda

The Items Below will be Discussed During the Live MATLAB Demo

- Overview of DILIsym[™] v2A and MATLAB directory structure
 - Installation changes
 - Directory structure review
 - File content changes/updates
- Running simulations using the Graphical User Interface
 - Updates to the DILIsym 'Home' screen
 - Updates to the 'Data Comparison' window
 - Updates to the 'Run in Parallel' window
 - New Output Table feature
- Running simulations using the MATLAB code files
 - 'Run_DILIsym' file changes
 - Solver updates and changes
 - SimPops[™] and parameter sweeps
- New DILIsym[™] model results formats
- Troubleshooting
- Questions
- Bonus Material (if time permits)
 - Exploring SimPops[™] parameters
 - Setting up an example DILI case Compound Y





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2013 DILI-sim Initiative Key Dates





