Drug-Induced Injury of Liver, Heart, Kidney, and Skin: Employing Recent Advances to Improve Patient Safety and Speed Up the Pipeline

May 7-9 | North Bethesda, MD
Bethesda North Marriott Hotel and Conference Center

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Senior Director
Safety and Risk Management
Worldwide Research and Development
Pfizer Inc.

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Professor of Medicine
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OVERVIEW:

Establishing safety of new drug candidates remains a major challenge at every stage of the development process. This conference will explore the current state of the art as well as how our evolving understanding of underlying mechanisms is leading to new strategies for risk assessment and mitigation. This includes the application of novel translational biomarkers and other personalized medicine approaches.

The focus will be on drug injury to the liver, heart, kidney, and skin. Within each organ system, what is worth doing? ...what evaluations add value? What is possible to predict about organ injury... before a compound is synthesized? ...in nonclinical assessments? ...in high-throughput assays? Having identified an important risk, should development be abandoned or can it proceed? Can personalized medicine be applied to risk management? Can patients be protected by monitoring organ function or by assaying new translational biomarkers? Benefit must outweigh risk to patients across the entire product life cycle. Do the strategies used in clinical development translate to the postmarketing setting?

This is the one conference that should be attended by all those with responsibilities that span the entire life cycle of a drug, whether those responsibilities are directly in drug safety or are in related departments. In just two and a half days your team will receive the latest updates on drug-induced organ injury from the US, Europe, and Japan.

Learning Objectives:

At the conclusion of this conference, participants should be able to:

• Recognize how to better handle cases of suspected drug-induced liver injury, including causality assessment and use of new biomarkers
• Describe the importance of prioritizing drug-induced heart injury
• Discuss drug-induced kidney injury and the use of novel biomarkers for early detection
• Recognize the essential features of drug-induced kidney injury
• Discuss population differences and genetic biomarkers of risk for severe drug-induced skin injury and how benefit-risk profiles may differ by population for a given compound
• Discuss essential requirements for assessment of drug-induced organ injuries from a regulatory reviewer’s perspective
• Identify common pitfalls and potential approaches to causality assessment for drug-induced organ injury
• Apply a strategy early in the product life cycle for handling possible drug-induced organ injury

This program is developed with the DIA Clinical Safety and Pharmacovigilance Community in collaboration with academia, regulators, and industry experts.

Register at

diahome.org/DILO
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This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and the Drug Information Association. PIM is accredited by the ACCME to provide continuing medical education for physicians.

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**WEDNESDAY, MAY 7**

**7:30–8:20AM**  REGISTRATION AND CONTINENTAL BREAKFAST

**8:20–8:30AM**  WELCOME AND OPENING REMARKS

**William W. Gregory, PhD**  
Senior Director  
Safety and Risk Management  
Worldwide Research and Development  
Pfizer Inc.

**Susan Cantrell**  
Senior Vice President and Managing Director  
DIA Americas

**8:30–10:00AM**  SESSION 1

**Impact on Drug Development of Novel Translational Safety Biomarkers for Improved Detection of Drug-Induced Acute Kidney Injury**

**Session Chair:**  
**Aliza M. Thompson, MD**  
Clinical Team Leader  
Division of Cardiovascular and Renal Products  
Office of New Drugs (OND), CDER, FDA

The first speaker will describe the scientific and business benefits being realized from qualifying improved translational kidney safety biomarkers for drug development, focusing on animal study data that have been developed to support the claims that several novel biomarkers can outperform conventional biomarkers for monitoring potential drug effects on renal function. The second speaker will discuss initial experiences of using novel renal biomarkers in early clinical studies, highlighting some of the challenges and presenting options for optimizing early clinical study designs. The third speaker will discuss how kidney safety biomarkers are being used in drug development programs and share her perspective on interpreting biomarker findings in clinical studies.

**Speakers:**

**Preclinical Evidence for the Value of New Translational Biomarkers to Monitor Renal Safety in Early Drug Development**  
**Yi-Zhong Eddie Gu, PhD**  
Principal Scientist  
Cellular Toxicology Safety Assessment  
Merck Research Labs

**Optimizing the Design of Early Clinical Trials Using Novel Biomarkers to Monitor for Tubular Toxicity**  
**Stefan Sultana, MD, FRCS** (Presenting Via Telecommunications)  
Senior Medical Director  
Companion Diagnostics  
Novartis

**A Regulatory Perspective on the Role of Translational Renal Safety Biomarkers in Drug Development**  
**Aliza M. Thompson, MD**  
Clinical Team Leader  
Division of Cardiovascular and Renal Products  
Office of New Drugs (OND), CDER, FDA

**10:00–10:30AM**  REFRESHMENT BREAK

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**The Promise of Improved Longitudinal Assessment of Kidney Health Status Using New Kidney Safety Biomarkers**

**Session Chair:**

**Gary S. Friedman, MD**  
Director, Clinical Affairs, Specialty Care Medicines Development Group  
Pfizer Inc.

The first speaker will describe how volume depletion, altered renal hemodynamics and the inhibition of specific renal transporters can impact serum creatinine levels. Whether or not changes in serum creatinine caused by these physiologic responses are associated with renal injury, and whether drugs with pharmacologic activity on kidney function are associated with renal injury. Data from animal toxicology studies of drugs with pharmacodynamic activity on renal blood flow and glomerular filtration and the association of translational kidney safety biomarkers with renal histopathology will be presented.

The second speaker will describe the promise of new translational renal biomarkers for detecting drug induced kidney injury that occurs (1) after chronic exposure and is slow to develop but is progressive with continued exposure (e.g. lithium toxicity) and (2) in patients with underlying chronic kidney disease. In both of these clinical scenarios, recognition that specific injury is occurring would permit dose adjustments or modifications to the drug regimen. Further understanding how biomarker thresholds might track with severity and course of injury might be helpful in determining appropriate therapeutic interventions and/or predict the prognosis for the kidney injury.

The third timeslot in this session will be used to introduce a panel and audience discussion on the opportunities with novel kidney safety biomarkers to improve detection of drug induced kidney injury. This panel will include members of academia, industry and a regulatory authority. They will take questions from the audience and further discuss the application of translational kidney safety biomarkers to drug-induced kidney injury and the drug development process. The expertise on the panel will be able to discuss a broad range of topics ranging from the practical use of biomarkers in preclinical and clinical drug development through to the qualification of preclinical and clinical biomarkers for use in regulatory decision making.

**Speakers:**

**Drugs Can Affect Renal Hemodynamics and Serum Creatinine, but Is the Kidney Injured?**

**Jonathan Barasch, MD, PhD**  
Associate Professor of Medicine and Anatomy & Cell Biology  
University of California, San Diego

**Role of Kidney Biomarkers for the Detection of Drug-Induced Kidney Injury**

**Ravindra L. Mehta, MD, FACP, FASN, FRCP**  
Professor of Clinical Medicine,  
Associate Chair for Clinical Research Department of Medicine  
University of California, San Diego

**Panelists:**

**Yi-Zhong Eddie Gu, PhD**  
Principal Scientist  
Cellular Toxicology Safety Assessment  
Merck Research Labs

**Stefan Sultana, MD, FRCS** (Presenting Via Telecommunications)  
Senior Medical Director  
Companion Diagnostics  
Novartis

**Jonathan Barasch, MD, PhD**  
Associate Professor of Medicine and Anatomy & Cell Biology  
University of California, San Diego

**Ravindra L. Mehta, MD**  
Professor of Clinical Medicine  
Associate Chair for Clinical Research Department of Medicine  
University of California, San Diego

**Aliza M. Thompson, MD**  
Clinical Team Leader  
Division of Cardiovascular and Renal Products  
Office of New Drugs (OND), CDER  
FDA

**Melanie Blank, MD**  
Medical Officer  
Division of Cardiovascular and Renal Products  
Office of New Drugs (OND), CDER  
FDA
Prediction and Prevention of Serious Drug-Induced Skin Injury

**Session Chair:**

**Stewart Geary, MD**  
Vice President, Chief Medical Officer, Director  
Corporate Medical Affairs HQ  
Eisai Co., Ltd.  
Japan

Serious skin reactions are rare but can be life-threatening and leave patients with lasting disabilities. Reports of these reactions tend to cluster around certain drugs or drug classes. Biomarkers of risk for Stevens Johnson Syndrome or Toxic Epidermal Necrolysis (SJS/TEN) based on HLA subtype have shown some usefulness in identifying patients at risk of these reactions but the utility of the biomarker tested varies by ethnic group. This session will discuss what is currently known about biomarkers for risk of serious skin reactions, identification of patients or drugs at greatest risk for these reactions and what can be imputed about the mechanisms of these reactions.

**Speakers:**

**What Do We Know About Serious Skin Reactions and Causality?**

**Manfred Hauben, MD, MPH**  
Senior Director, Safety Risk Research  
Pfizer Inc.

**Biomarkers for Risk of SJS/TEN in Japanese Compared to Other Populations**

**Ryosuke Nakamura, PhD**  
Chief, Division of Medicinal Safety Science  
National Institute of Health Sciences  
Japan

**Practical Issues in Applying Biomarkers for Significant Skin Reactions During Clinical Development and Post-Marketing**

**Stewart Geary, MD**  
Vice President, Chief Medical Officer, Director  
Corporate Medical Affairs HQ  
Eisai Co., Ltd.  
Japan

3:00–3:20pm  REFRESHMENT BREAK

3:20–3:30pm  DRUG-INDUCED HEART INJURY

**Speaker:**

**Norman Stockbridge, MD, PhD**  
Director  
Division of Cardiovascular and Renal Products  
Office of New Drugs (OND), CDER, FDA

3:30–5:00pm  SESSION 4

Models and Biomarkers of Drug-Induced Cardiac Injury

**Session Chair:**

**Brian R. Berridge, DVM, PhD**  
Director  
World Wide Animal Research Strategy  
GlaxoSmithKline R&D

This session will explore bench to bedside approaches to identifying and monitoring drug-induced cardiac injury. Novel approaches to in vitro modeling will be explored as well as assessing changes in cardiac structure and function in nonclinical studies. Translational approaches to non-invasive detection and monitoring injury and dysfunction will be discussed as will clinical strategies for detecting and managing cardiac liabilities.

**Speakers:**

**Cardiotoxicity of Oncology Drugs; High Content Screening of Bioenergetic Modulation of Kinase Inhibitor Mitochondrial Toxicity in hESC Derived Cardiomyocytes**

**Nick Thomas, PhD**  
Principal Scientist  
GE Healthcare

**Integrated Approaches to in Vivo Nonclinical Modeling of Cardiovascular Liabilities**

**Jim Turk, DVM, PhD, DACVP**  
Pathologist Director  
Amgen Inc.

**Advances in Translational Biomarkers of Cardiac Injury and Dysfunction**

**Dana B. Walker, DVM, MS, PhD, DACVP**  
Director  
Translational Safety Biomarkers  
Discovery and Investigative Pathology  
Novartis Institutes for BioMedical Research, Inc.

**Nonclinical Modeling of Patient Susceptibility to Drug-Induced Cardiotoxicity**

**Brian R. Berridge, DVM, PhD**  
Director  
World Wide Animal Research Strategy  
GlaxoSmithKline R&D

5:00–6:00pm  NETWORKING RECEPTION
THURSDAY, MAY 8

7:30–8:30AM  REGISTRATION AND CONTINENTAL BREAKFAST

8:30–10:00AM  SESSION 5

Proarrhythmia

SESSION CHAIR:

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of New Drugs (OND), CDER
FDA

This session introduces two very different concepts for non-clinical assessment of proarrhythmic risk, one highly integrative, the other highly mechanistic. Then, two very different approaches to clinical assessment of risk are presented—both very different from the “Thorough QT Study”—one obtaining QT information from early phase studies conducted for other purposes, the other seeking to get mechanistic insight from a more detailed analysis of the ECG than just the QT interval.

SPEAKERS:

Assessment of Dysrhythmic Potential in Isolated Cardiac Myocytes

Blake D. Anson, PhD
Product Manager
iCell Cardiomyocytes
Cellular Dynamics International, Inc

Comprehensive Mechanistic Assessment of Proarrhythmic Potential of Drugs

Gary Gintant, PhD, MA
Research Fellow
AbbVie

Early QT Assessment - “Thorough QT”- Like Assessment in Phase 1 Clinical Studies

Borje Darpo, MD, PhD
Associate Professor of Cardiology
Department of Clinical Sciences, Danderyd’s Hospital, Division of Cardiovascular Medicine, Stockholm, Sweden
Global Medical Director
iCardiac

Going Beyond QT to Improve the ECG Assessment of Proarrhythmic Risk

David G. Strauss, MD, PhD
Medical Officer
Center for Devices and Radiological Health, FDA

10:00–10:30AM  REFRESHMENT BREAK

10:30AM–12:00PM  SESSION 6

Drug-Induced Liver Injury (DILI) in Clinical Trials and Post Marketing

SESSION CHAIR:

Paul B. Watkins, MD
Director
Hamner - UNC Institute For Drug Safety Sciences
Professor of Medicine, Pharmacy and Public Health
University of North Carolina - Chapel Hill

DILI remains one of the most frequent injuries that result in termination of clinical development programs, and regulatory actions on drugs post-approval. The costs and other consequences of discovering significant liver safety concerns rises exponentially at each successive stage in clinical development. It is therefore essential to detect and interpret liver safety signals as early as possible during clinical development. This session will cover current approaches to collecting, managing and interpreting liver safety data at each stage in the clinical life of a new drug candidate. This session will end with a panel discussion.

SPEAKERS:

Using Data from Controlled Clinical Trials to Evaluate the Risk of Serious Liver Injury and Dysfunction

John R. Senior, MD
Associate Director for Science
Office of Surveillance and Epidemiology, CDER, FDA

Detecting, Assessing, and Reporting DILI for Approved and Marketed Drugs

Mark I. Avigan, MD
Associate Director for Critical Path Initiatives
Office of Surveillance and Epidemiology, CDER, FDA

The Future

Paul B. Watkins, MD
Director
Hamner - UNC Institute For Drug Safety Sciences
Professor of Medicine, Pharmacy and Public Health
University of North Carolina - Chapel Hill

12:00–1:30PM  LUNCHEON
Causality Assessment for Suspected Drug-Induced Liver Injury (DILI)

Session Chair:

Arie Regev, MD
Head, Safety Advisory Hub
Chair Liver and GI Safety Committee
Global Patient Safety Eli Lilly & Co.
Adjunct Associate Professor of Medicine Division of Gastroenterology and Hepatology
Indiana University School of Medicine

Causality assessment for suspected DILI is a major challenge in clinical practice and during drug development. In contrast to many other liver disorders, there is currently no specific biomarker or a combination of tests that will establish the diagnosis of DILI and differentiate it from other causes of liver injury. DILI may resemble almost any type of liver disease, and the clinicopathologic spectrum may range from nonspecific injury, to acute and chronic hepatitis, granulomatous liver disease, cholestasis, fatty infiltration, vascular lesions, and hepatic tumors.

The diagnosis of DILI is therefore virtually always presumptive, as it is based on clinical assessment and exclusion of other possible causes rather than on absolute criteria and specific diagnostic tests. Abnormal liver tests may be caused by numerous liver disorders as well as extra-hepatic disorders, many of which are considerably more common than typical DILI. It is therefore critical to exclude other liver diseases before attributing a liver injury to a drug. Exclusion of other causes requires detailed information pertaining to the patient’s clinical course and laboratory data. Failure to test for other causes may result in assigning guilt by association which may often be erroneous.

This session will address three topics pertaining to causality assessment during drug development. The first session will focus on common pitfalls and potential solutions, the second session will address causality assessment in patients with underlying hepatitis B and C, and the third session will address the use of the Roussel Uclaf Causality Assessment Method (RUCAM) versus expert opinion for causality assessment during drug development.

Speakers:

Causality Assessment for Suspected DILI During Drug Development: Common Pitfalls and Potential Solutions

Arie Regev, MD
Head, Safety Advisory Hub
Chair Liver and GI Safety Committee
Global Patient Safety Eli Lilly & Co.
Adjunct Associate Professor of Medicine Division of Gastroenterology and Hepatology
Indiana University School of Medicine

Causality Assessment in Patients with Hepatitis B and C

James H. Lewis, MD, FACP, FACC, AGAF
Professor of Medicine, Georgetown University School of Medicine
Director of Hepatology, Division of Gastroenterology,
Georgetown University Hospital

RUCAM versus Expert Opinion for Causality Assessment

Leonard B. Seeff, MD
Consultant in Hepatology
Former VA, FDA and Hill Group

Risk Factors for Idiosyncratic DILI

Session Chair:

John R. Senior, MD
Associate Director for Science
Office of Surveillance and Epidemiology, CDER FDA

A great unknown challenge is how to identify the patient who is especially susceptible to drug-induced injury, or who may not be able to adapt to the drug after an initial mild injury and thenceforth be able to tolerate the drug, before giving the drug, or in time to stop it before irreversible damage occurs. Serious DILI is usually rare, but we have no biomarker, genetic test, or other way to know who will get it in advance. We rely on observation of the patient’s response to the new (for them) drug. Whether early symptoms, such as nausea, fatigue, right upper abdominal discomfort, or some other symptom may come first, or whether slight elevations of serum transaminase activity (or gammaglutamyl transpeptidase, or other) activity comes first, we don’t yet know. For now, either symptoms or serum enzyme elevations should be reported very promptly and rechecked within a few days to find out whether they are worsening or improving, and what can be learned by additional tests, questions, or other ways to diagnose the most likely or probable cause of the abnormalities. In this Session, we shall explore the question of whether underlying liver diseases of various types (fatty liver-steatohepatitis, alcoholic liver disease, or viral hepatitis C, B, or other) can be distinguished from drug-induced injury, i.e., acute-on-chronic injury, and if the diseases may either enhance or diminish drug-effects. These difficult distinctions will be discussed by master clinicians whose work it is to make such diagnoses in practice, or in evaluation of new drugs.

Speakers:

Nonalcoholic Fatty Liver Disease/Non-Alcoholic Steatohepatitis (NAFLD/NASH) and the Risk of Idiosyncratic DILI

Raj K. Vuppalanchi, MD
Associate Professor of Clinical Medicine
Indiana University School of Medicine

Alcohol/Concomitant Drugs and the Risk of Idiosyncratic DILI

James W. Freston, MD, PhD
Emeritus Professor of Medicine and Clinical Pharmacology
University of Connecticut Health Center

The Risk of Idiosyncratic DILI in Patients with Viral Hepatitis B and C

Kendall Marcus, MD
Deputy Division Director Antiviral Products, CDER FDA

Utility of Data Standards: Learning from Hepatitis C

Jefry Florian, PhD
Reviewer, Division of Pharmacometrics, CDER FDA
Drug-Induced Liver Injury: Models and Biomarkers

**Session Chair:**

Mark I. Avigan, MD
Associate Director, Office of Surveillance and Epidemiology
CDER, FDA

One of the key challenges for prediction and assessment of idiosyncratic DILI in drug development is the lack of suitable models and safety biomarkers. This session will present examples on recent advances in both areas based on collaborative research. The first talk will focus on a mechanistic simulation platform being developed at the Hamner Institute, supporting decision-making at transition from preclinical to clinical development. The second talk will present an overview on current work surrounding the development of in vitro models using induced pluripotent stem cells to investigate human diversity as a basis of idiosyncratic DILI. It is hoped that such cell systems will be eventually applied as screening tools for new drugs in development regarding their potential to induce DILI. The third speaker will provide background information on and discuss initial results of the work of the Predictive Safety Testing Consortium (PSTC) in the US and the IMI SAFE-T consortium in Europe, both precompetitive consortia collaborating closely on preclinical and clinical qualification of new safety biomarkers for DILI.

**Speakers:**

**In Silico Models: Where are we Today?**

Brett A. Howell, PhD
Lead Scientist and Manager, DILI-sim
The Hamner-UNC Institute for Drug Safety Sciences

**Advanced In Vitro Models: Induced Pluripotent Stem Cells as a Model of Human Diversity in DILI**

Edward L. LeCluyse, PhD
Associate Investigator
Institute for Chemical Safety Sciences
The Hamner Institutes for Health Sciences

**New Translational DILI Biomarkers: The Predictive Safety Testing Consortium (PSTC) and the IMI Safer and Faster Evidence-based Translation (SAFE-T) Collaboration**

Jeffrey W. Lawrence, PhD
Director, Biochemical Toxicology
Amgen Inc.

Herbal (including Dietary Supplement)-Induced Liver Injury [HILI] and Other Organ Injuries: How that May Impact Rx Benefit-Risk?

**Session Chair:**

Pradip Paul, MD, MS
Consultant, Strategic Pharmacovigilance & Risk Management

Recent DILI data indicates about 25% of the DILI are due to herbs. If the natural health products (NHP) or herbals are natural - why one should expect liver injury? However, the US Drug Induced Liver Injury Network (DILIN) findings are factual data. This session will discuss in depth “Herbal-Induced Liver Injury (HILI)”. The first speaker will discuss the historical perspective, prevalence of use and regulation of herbals and dietary supplements in liver injury to set the platform for the second speaker who will describe the experience of the Drug Induced Liver Injury network study with liver injury from herbals and dietary supplements. The third speaker will discuss the possible impact of the HILI on the benefit-risk in Rx products.

**Speakers:**

**Historical Perspective, Prevalence of Use and Regulation of Herbals and Dietary Supplements**

Leonard B. Seeff, MD
Consultant in Hepatology
Former VA, FDA and Hill Group

**Herbal (including Dietary Supplement) Induced Liver Injury: Challenges and Diagnosis**

Victor J. Navarro, MD
Chair, Hepatology
Einstein Medical Center

**Can Rx Benefit-Risk Be Impacted by HILI?**

Pradip Paul, MD, MS
Consultant, Strategic Pharmacovigilance & Risk Management
Emerging Cross-cutting Approaches to Assessment of Drug Safety

**Session Chair:**
**Robert J. Temple, MD**  
Deputy Center Director for Clinical Science  
CDER, FDA

This session will present ideas for novel approaches to assessment of drug safety: One relevant to the earliest stages of development—selecting lead compounds on the basis of the activity of structurally related compounds—and the other relevant to post-marketing surveillance—based on systematic data mining of electronic medical history data. This session will end with a panel discussion on how innovations get incorporated into standard practice.

**Speakers:**
**Quantitative Structure-Activity Relationships (QSAR)**  
Naomi L. Kruhlak, PhD  
Senior Staff Fellow, CDER  
FDA

**Future Role of Electronic Medical Records (EMR) Data in Postmarketing Safety Surveillance**  
Sandra S. Garrett, PhD  
Executive Chair  
Global Record Services, LLC

**Panelists:**
**John R. Senior, MD**  
Associate Director for Science  
Office of Surveillance and Epidemiology  
CDER, FDA

**Paul B. Watkins, MD**  
Director, Hamner - UNC Institute For Drug Safety Sciences  
Professor of Medicine, Pharmacy and Public Health  
University of North Carolina - Chapel Hill

**Norman Stockbridge, MD, PhD**  
Director, Division of Cardiovascular and Renal Products  
Office of New Drugs (OND), CDER  
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**Stewart Geary, MD**  
Vice President  
Chief Medical Officer, Director Corporate Medical Affairs HQ  
Eisai Co., Ltd., Japan

**Aliza M. Thompson, MD**  
Clinical Team Leader, Division of Cardiovascular and Renal Products  
Office of New Drugs (OND), CDER, FDA

1:00–1:15 pm  
Closing Remarks

William W. Gregory, PhD  
Senior Director  
Safety and Risk Management  
Worldwide Research and Development  
Pfizer Inc.

1:15 pm  
Conference Adjourned

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