HESI Technical Committee

2015–2016 Activities and Accomplishments

Committee leaders:
Dr. Norman Stockbridge
US Food and Drug Administration
Dr. Brian Berridge
GlaxoSmithKline

HESI managers:
Dr. Stan Parish
Ms. Jennifer Pierson, MPH

HESI associate:
Ms. Melissa Gilden

This scientific program is committed to:

- Improving public health by reducing unanticipated cardiovascular-related adverse effects from drugs or chemicals and developing innovative approaches to support early detection and prediction as well as improved understanding of cardiovascular toxicology and pathobiology. The committee brings together nonclinical safety assessment scientists and technical disciplines within the international community of public, private, and government sectors to develop best practices for translation of in vitro and nonclinical cardiovascular data.

Areas of scientific focus:

- Facilitating the development, refinement, and adoption of a more comprehensive and efficient nonclinical paradigm for assessment of proarrhythmic risk of evolving drug candidates, including a paradigm based on assessment of ion channel effects and in silico reconstruction of the action potential.
- Determination of translatable cardiac biomarkers during the assessment of hemostasis in both healthy and thrombo-occlusive disease preclinical animal models.
- Assessing the sensitivity of canine and rat in vivo models for detection of inotropic effects resulting from exposures to drugs with known clinical effects, and whether that sensitivity is due to study design or environmental conditions.
- Compiling information on comparative physiology of non-traditional animal models for use in predictive cardiovascular safety assessment.
- Facilitating opportunities for improved nonclinical safety testing approaches for cancer drug–related cardiotoxicity.
- Evaluating high-throughput methods for cardiac ion channel screening for early drug discovery processes.

Why get involved?
As a member of the HESI Cardiac Safety Committee, you will join a multi-disciplinary team of scientific experts developing translational solutions to contemporary cardiovascular public and environmental health concerns. No other group is working internationally to bridge structural, functional, nonclinical, and clinical approaches to cardiovascular safety.

Key accomplishments:

- **Proarrhythmia.** The manuscript detailing the results of the HESI-FDA database assessing concordance between nonclinical repolarization assays and clinical measures of cardiac repolarization (QT, proarrhythmia) was completed and submitted. The Phase II Subteam continues to identify mechanisms of discordance found in the HESI-FDA database by further exploring pharmacokinetics/pharmacodynamics and additional nonclinical data. A new subteam formed to assess high-throughput automated patch clamp systems.
- **Contractility.** After completing multi-site experimental studies to evaluate the sensitivity and reproducibility of canine and rodent cardiac contractility assays in 2013, a series of manuscripts are in final preparation. Additionally, a new symposium proposal was recently accepted for the 2016 American College of Toxicology Meeting titled “Drug-Induced Changes in Vascular Hemodynamics: Clinical and Drug Development Implications.”
- **Predictive Strategies.** HESI was recently awarded funds from the Pardee Foundation for the THRIVE initiative, which focuses on translational and collaborative cardiovascular research to enhance cancer survivor quality of life. The THRIVE initiative provides seed funding in the form of grants for innovative research.
- **Stem Cell–Derived Cardiomyocytes.** The Cardiac Stem Cell Working Group initiated monthly educational webinars to share some of the latest research in the area. The Myocyte Subteam was awarded funds through an FDA Broad Agency Announcement (BAA) competitive grant program for the proposal titled “Validating Human Stem Cell Cardiomyocyte Technology for Better Predictive Assessment of Drug-Induced Cardiac Toxicity.” The subteam met regularly to plan the protocol and data analysis for the Phase II validation study.
- **Biomarkers.** With the completion of a proof-of-concept study to investigate new technologies for detection of incipient procoagulant and prothrombotic states, a manuscript has been submitted that highlights the findings from that study. In addition, a second proof-of-concept study recently concluded its in-life portion that utilized the Zucker Diabetic Fatty rodent model to investigate how those cardiac biomarkers identified in the first study are affected when treated with doxorubicin.
The Committee’s focus for May 2016–May 2017:

- **Proarrhythmia.** Members will continue active participation in the Comprehensive In Vitro Proarrhythmia Assay (CiPA) work streams. CiPA aims to eliminate the need for a clinical TQT study for compounds entering clinical development based on the newly proposed in vitro paradigm (along with existing, robust preclinical cardiovascular studies). The new subteam will execute a study on high-throughput systems and provide data to the CiPA initiative.

- **Biomarkers.** A manuscript will be completed to report the findings of the second proof-of-concept study that compares markers of homeostasis in the Zucker Diabetic Fatty rodent model with treatment with doxorubicin. Additionally, a third proof of concept will be under consideration that will take into account the results from the first two proof-of-concept studies.

- **Contractility.** The remaining manuscripts based on the data generated during the contractility study will be completed and submitted for publication. New proposals will also be discussed and further developed as the group looks toward next steps and opportunities to address.

- **Predictive Strategies.** Committee members will develop a manuscript reviewing the comparative physiology of multiple preclinical species and their clinical predictability. The committee will seek proposals to award seed funds through the THRIVE initiative.

- **Stem Cell–Derived Cardiomyocytes.** The BAA award will help fund the Phase II validation study using microelectrode array (MEA) and voltage-sensitive dye/optical technologies. The data will be used to help complete a draft CiPA package that will be presented to the ICH E14 Working Group. Collaboration with the Japan iPS Cardiac Safety Assessment group will continue to quantitate and standardize results seen in the hSC-CMs for CiPA purposes.

Recent publications:


**2015–2016 Participating organizations:**

- AbbVie
- ACEA Biosciences, Inc.
- Amgen Inc.
- AstraZeneca AB
- Auburn University
- Axion Biosystems
- Bayer HealthCare Pharmaceuticals
- Biogen Idec MA Inc.
- Boehringer Ingelheim GmbH
- Bristol-Myers Squibb Company
- Brown University Medical School
- Celgene Corporation
- Cellular Dynamics International, Inc.
- ChanTest, A Charles River Company
- CiToxLAB
- Cornell University
- Covance
- Cytotex
- Daiichi Sankyo Co. Ltd.
- Data Sciences International
- Eli Lilly and Company
- European Medicines Agency
- GE Healthcare
- George Washington University
- GlaxoSmithKline
- Health Canada
- IBM T.J. Watson Research Center
- InvivoSciences, Inc.
- iPSyte, Inc.
- Jagiellonian University Medical College
- Janssen Pharmaceuticals
- Johns Hopkins University
- Karolinska Institute, Department of Medicine
- Lifespan Hospitals
- Medicines and Healthcare Products Regulatory Agency (UK)
- Merck & Co., Inc.
- Michigan State University
- MultiChannel Systems
- Nanion Technologies
- National Center for Safety Evaluation of Drugs (China)
- National Institute of Environmental Health Sciences
- National Institute of Health Sciences (Japan)
- National Institutes of Health
- New York Stem Cell Foundation
- Northwestern University
- Novartis Pharmaceuticals
- Ohio State University
- Pfizer Inc.
- Pharmaceuticals and Medical Devices Agency (Japan)
- Purdue Pharma

For more information, contact the Committee’s managers, Dr. Stan Parish, sparish@hesiglobal.org, or Ms. Jennifer B. Pierson, jpierson@hesiglobal.org.