Cardiac Safety

OUR MISSION
The committee’s mission is to improve public health by reducing unanticipated cardiovascular-related adverse effects from drugs or chemicals and develop innovative approaches to support early detection and prediction as well as improved understanding of cardiovascular toxicology and pathobiology.

CHAIRS
Public Chairs
Dr. Norman Stockbridge (US Food and Drug Administration)
Dr. Brian Berridge (National Toxicology Program)

Steering Team Members
Dr. Norman Stockbridge (US Food and Drug Administration)
Dr. Eugene Herman (National Institutes of Health)
Dr. Gary Gintant (AbbVie)
Dr. Eric Schultze (Eli Lilly and Company)
Dr. Jean-Pierre Valentim (UCB)
Dr. Michael Pugsley (Cytokinetics)
Dr. John Koerner (US Food and Drug Administration)
Dr. Marjory Brooks (Cornell University)
Dr. Frank Selke (Lifespan Heart Center)
Dr. Brian Berridge (National Toxicology Program)

HESI STAFF
Ms. Jennifer B. Pierson, MPH (jpierson@hesiglobal.org)
Dr. Stan Parish (sparish@hesiglobal.org)

2019 COMMITTEE HIGHLIGHTS

Participating Organizations
11 government/regulatory agencies, 31 academic/research institutes, 2 other, 40 industry

Publications
2 accepted/published, 1 submitted, 4 in progress

Scientific Meetings and Trainings
2 advisory/other meetings: Cardiac Failure Modes Advisory Group (Washington, DC) and Workshop on Cardiomyocytes for Mechanistic CV Safety Liabilities (March 2019 in Silver Spring, Maryland)

Outreach
2 posters, 2 presentations
• Cardiac Failure Modes Advisory Group (Washington, DC)
• Workshop on Cardiomyocytes for Mechanistic CV Safety Liabilities (March 2019 in Silver Spring, Maryland)

Collaborations
3 external
• University of Surrey and Imperial College London, European Bioinformatics Institute
• Safety Pharmacology Society
• CiPA Steering Team

Geographic Representation
Australia, Belgium, Canada, China, Denmark, France, Germany, Japan, Netherlands, Poland, Singapore, Sweden, Switzerland, United Kingdom, United States

WORKING GROUPS
• ProArrhythmia Working Group. This working group is dedicated to investigating mechanisms of proarrhythmic risk. The most recent projects have focused on concordance/discordance between nonclinical assays (hERG, APD, QTc in vivo) and clinical TQT studies. Additional work focused around CiPA has also been initiated, including two subteams: high-throughput systems (HTS) ion channel work and JT peak ECG work in nonclinical species. This group is engaged in cross-collaborations with the Stem Cell Working Group and Myocyte Subteam and Integrative Strategies with the Implanted Telemetry Subteam.
• Stem Cell Working Group. This group is working to understand and characterize use of stem cell–derived cardiomyocytes in cardiac safety assessments. The Myocyte Subteam is working to support data collection for CiPA.
• Cardiac Biomarkers. This working group is dedicated to investigating preclinical cardiac biomarkers of hypercoagulability induced under a thrombotic state, in both normal and diseased states.
• Integrative Strategies. This working group has examined the sensitivity within a preclinical species to assess the function of contractility. Additionally, it has provided guidance on what parameters need to be met within an in vitro system to have confidence in that assay to assess contractility.
AREAS OF FOCUS FOR 2020
• Alignment to mechanistic, human relevant approaches
• Working toward implementation of the 3Rs and human relevant work
• Supporting the goals of the CiPA program through publication and data development

STRATEGIC IMPACT AREAS

**Enhanced Efficiency and Accuracy in Safety Assessment Practice**
The committee works to increase efficiency and accuracy of the current paradigm as well as impacting 3Rs. Working to implement in vitro technologies, such as stem cells, in cardiac safety assessment will allow for improved decision-making at earlier phases in drug development. Within both the biomarkers and integrative working groups, having a better understanding of in vivo pathways and useful application of preclinical species increases efficiencies and accuracy in results derived through in vivo studies.

**Catalysis of New Science**
Stem cells and related assay platforms are still new technology in drug safety and development. HESI is working to test and validate these technologies.

**Increasing the Audiences for Collaborative Safety Science**
HESI was asked to manage several projects under CiPA and continues to see additional projects come to this group. The Blinova paper was made possible through an FDA Broad Agency Announcement that was awarded to HESI based partly on our reputation for rigorous science.

**2019 AWARDS AND GRANTS**
The HESI Cardiac Safety Committee was awarded two publicly funded grants in 2019. The first is a multi-year U01 grant from the US Food and Drug Administration (FDA) on the Evaluation of Integrated Human-Relevant Approaches to Identify Drug Induced Cardiovascular Liabilities. This grant will support HESI in procuring and managing novel, in vitro experimental studies to develop targeted mechanistic data to inform drug safety assessment for key cardiac ‘failure modes’. This program of work is expected to provide a robust complement to the committee’s existing efforts in this space. The second award is an 18-month Broad Agency Announcement grant from the US FDA on assessing variability and reproducibility of manual and automated patch clamp platforms. HESI will organize and manage a multi-site study with manual and automated patch clamp platforms and the 28 CiPA compounds to help set expectations, limitations, and confidence in the ion channel platforms. Results will provide objective data and confidence in the risk assessment approach proposed as part of CiPA, including further testing and validation of the in silico model.

In 2019, HESI partnered with the FDA Center for Drug Evaluation and Research and the National Toxicology Program (NTP) in a new Memorandum of Understanding (MOU) to support improved cardiovascular safety and reduce the use of animals for testing. This first of its kind MOU across the three organizations will allow HESI to work with experts in the cardiotoxicology space to identify and evaluate innovative efforts focused on human-relevant assays, and will expand existing work by the Cardiac Safety Committee and formalize the partnership between HESI, NTP, and FDA.

**PUBLICATIONS**


Valentin et al. Why is it so difficult to predict drug effects on repolarization in humans? Submitted.


Pugsley et al. A high fat diet induces hypercoagulability and dyslipidemia and exacerbates renal insufficiency progressing to mortality in male ZDF rats. Final draft in progress.

## Participating Organizations

### Government/Regulatory Agencies
- European Medicines Agency
- Health Canada
- Medicines and Healthcare Products Regulatory Agency (UK)
- National Institute of Health Sciences (Japan)
- National Institutes of Health
- National Toxicology Program
- Pharmaceuticals and Medical Devices Agency (Japan)
- Pharmacological Evaluation Institute of Japan
- UK National Institute for Biological Standards and Control
- US Environmental Protection Agency
- US Food and Drug Administration

### Academic/Research Institutes
- Boston University
- Bristol University
- Columbia University
- Cornell University
- George Washington University
- Hamburg University
- Harvard University
- Jagiellonian University Medical College
- Johns Hopkins University
- Michigan State University
- Natural and Medicines Institute, University of Tubingen
- National Shanghai Center for New Drug Safety Evaluation and Research
- Northwestern University
- Ohio State University
- Scintillon Institute
- Stanford University
- SUNY Buffalo
- Toho University Medical School
- University of Alberta
- University at Buffalo
- University of Calgary
- University of California, Davis
- University of Glasgow
- University of Hamburg
- University of Miami
- University of Michigan
- University of Nottingham
- University of Tokyo
- University of Washington
- University of Wisconsin
- Victor Chang Institute

### Other
- Lifespan Hospitals
- Marshview Life Science Advisors

### Industry
- ABBVie
- ACEA Biosciences, Inc.
- Amgen Inc.
- Axion Biosystems
- Bayer
- Biogen Idec MA Inc.
- Boehringer Ingelheim GmbH
- Bristol-Myers Squibb Company
- Celgene Corporation
- Cellular Dynamics International, A Fujifilm Company
- ChanTest, A Charles River Company
- Charles River Laboratories
- CIToxLAB
- Covance
- Cyprotex
- Dana Solutions
- Data Sciences International
- Eli Lilly and Company
- Genentech
- GlaxoSmithKline
- InvivoSciences, Inc.
- IPSyte
- Janssen Pharmaceuticals
- LSI Medience
- Merck & Co., Inc.
- Metriion Biosciences Ltd.
- MyoKardia
- Nanion Technologies
- Nanosurface
- Ncardia
- Novoheart
- Pfizer Inc.
- Roche
- Sanofi
- Sony
- Stemonix
- Takeda Pharmaceutical Company Limited
- TARA Biosystems
- UCB-Biopharma
- Vistagen