2017–2018 Activities and Accomplishments

**Committee leaders:**
Dr. Norman Stockbridge  
US Food and Drug Administration  
Dr. Brian Berridge  
National Institutes of Health/National Toxicology Program

**HESI managers:**
Ms. Alexandra Feitel

**HESI associate:**
Ms. Jennifer B. Pierson, MPH

**Key accomplishments:**
- **Proarrhythmia.** The first phase of the HESI-FDA database assessing concordance between nonclinical repolarization assays and clinical measures of cardiac repolarization (QT, proarrhythmia) was drafted. The High-Throughput Systems (HTS) Subteam completed the second phase of the automated patch clamp ion study and submitted data to the FDA. Data from the Phase I HTS is being included in a draft manuscript. A new subteam exploring use of the J-Tpeak biomarker to understand proarrhythmic potential was initiated; a retrospective study as proof of concept was completed and a manuscript was submitted for publication.
- **Cardiac Contractility.** Two additional documents highlighting additional endpoints and alternative statistical strategies were published using the data generated from the earlier study assessing contractility in dogs. A poster with results from the combined echocardiography-telemetry study was presented at the 2017 Safety Pharmacology Society Annual Meeting and a manuscript is in progress. A new partnership was launched with the University of Surrey and Imperial College London to explore using mathematical modeling to assess contractility. A manuscript was written outlining a framework of criteria for using non-animal cellular systems to assess contractility.
- **Stem Cell-Derived Cardiomyocytes.** The pilot study text exploring use of human induced pluripotent stem cells (hPSCs) on the microelectrode array (MEA) platform was accepted for publication. The Myocyte Subteam completed the core validation study with the assistance of funds received through an FDA Broad Agency Announcement (BAA) and submitted a manuscript with the results, which included the development and use of a novel statistical model. They presented the body of work related to the Comprehensive In Vitro Proarrhythmia Assay (CiPA) Initiative to the ICH S7B/E14 Working Group in April 2018 in preparation for further discussions around the guidance. A CiPA Update meeting was co-sponsored by HESI in May 2018 and the Myocyte Subteam, along with other groups, presented the latest findings.
- **Biomarkers.** The second proof-of-concept study, modeling prothrombotic states associated with metabolic syndrome in the Zucker diabetic fatty rat fed high-fat diets, was completed and a manuscript with the results is in progress. A poster with preliminary results of the second proof-of-concept study was presented at the 2017 Safety Pharmacology Society Annual Meeting. Approval was received for a third proof-of-concept study and planning began.
- **Mechanism, Human-Based Assay Evaluation.** A workshop was convened in May 2018 to focus the committee’s mission on identifying and evaluating human-relevant, mechanism-based testing. At this meeting, cardiovascular failure modes were identified, and possible solutions as well as challenges and opportunities with moving in this direction were discussed.

**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 mechanism-based paradigm utilizing assessment of human cardiac ion channel effects and in silico reconstruction of the human ventricular action potential and in vitro confirmation of drug effects in human stem cell–derived cardiomyocytes (hSC-CMs).
- Assisting in the discovery of translatable cardiovascular biomarkers in early preclinical studies of blood coagulation and thrombosis in healthy and diseased rats and rodent models of human disease.
- Developing better analytic methods to explore an existing in vivo dataset developed to assess sensitivity and reproducibility of inotrophic effects.
- Assessing hSC-CM preparations and applications for cardiovascular risk assessment, including functional and structural toxicities.
- Evaluating high-throughput methods for cardiac ion channel screening for early drug discovery processes.
- **New for 2018!** Identifying cardiovascular failure modes that would benefit from a human-relevant, mechanistically informed approach and evaluating assays to assess these.

**Why get involved?**
The HESI Cardiac Safety Committee is the leader in the field, with multi-disciplinary scientific experts positively impacting future drug development and regulatory perspectives. No other group is working internationally to bridge structural, functional, nonclinical, and clinical approaches to cardiovascular safety.

**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, prediction, and elimination of cardiac risk as well as improved understanding of cardiovascular toxicology and pathobiology.
- Bringing together experts across a broad range of cardiovascular 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.
- Working toward better understanding and characterizing mechanistic assays using human components that may eventually reduce, replace, or refine some of the animal models used for cardiovascular risk assessment in drug development.

**HESI Technical Committee**

**Cardiac Safety**

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The Committee’s focus for May 2018–May 2019:

- **Proarrhythmia.** The manuscripts in progress for both the Database Phase II and HTS Phase I work will be completed and submitted. The J-Tpeak Subteam will execute a larger prospective study in collaboration with the FDA to ensure that alignment with their clinical study is in place.

- **Cardiac Contractility.** The combined echocardiography-telemetry text will be submitted for publication, as will the cellular systems document. A study to quantify the framework to understand challenges and opportunities when using in vitro methods to evaluate contractility methods will also be planned. The partnership with the University of Surrey and Imperial College London will continue with milestone checkpoints on project progress.

- **Stem Cell-Derived Cardiomyocytes.** The validation study results will be published, and results will be shared with the broader scientific community. The group will also facilitate further interactions and discussions with the ICH S7B/E14 Working Group. This team will also have a large role in scoping future projects focused on mechanism-based assays.

- **Biomarkers.** The results from the second proof-of-concept study will be published, which highlight not only the effects of diet on the Zucker diabetic fatty rat model but also the effects of doxorubicin on various biomarkers associated with hypercoagulability and prothrombosis. In addition, the protocol for the third proof-of-concept study will be discussed, finalized, and launched.

- **Mechanism, Human-Based Assay Evaluation.** Discussions within the committee will continue around this topic and projects identified during the May 2018 workshop will be pursued, with cellular systems being one example.

Recent publications:


2017–2018 Participating organizations

AbbVie

ACEA Biosciences, Inc.

Amgen Inc.

Axion Biosystems

Axol Biosciences

Bayer Healthcare Pharmaceuticals

Biogen Idec MA Inc.

Boehringer Ingelheim GmbH

Bristol-Myers Squibb Company

Bristol University

Celgene Corporation

Cellular Dynamics International, A Fuji Film Company

ChanTest, A Charles River Company

CitiToxLAB

Columbia University

Cornell University

Covance

Coyne Scientific

Cyprotex

Data Sciences International

Eli Lilly and Company

European Medicines Agency

Genentech

George Washington University

GlaxoSmithKline

Harvard University

Health Canada

InvivoSciences, Inc.

Ipsyte

Jagellonian University Medical College

Janssen Pharmaceuticals

Johns Hopkins University

Karolinska Institute

Lifespan Hospitals

Medicines and Healthcare Products Regulatory Agency (UK)

Merck & Co., Inc.

Miami University

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

National Toxicology Program

Ncardia

Northwestern University

Novartis Pharmaceuticals

Ohio State University

Pfizer Inc.

Pharmaceuticals and Medical Devices Agency (Japan)

Pharmacological Evaluation Institute of Japan

Purdue Pharma

Q-State Biosciences

Quintiles

Roche

Sanofi

Scintillon Institute

Sony

Stanford University

Stony Brook University

SUNY Buffalo

Takara Bio Europe AB

Takeda Pharmaceutical Company Limited

TARA Biosystems

Toho University Medical School

UCB-Biopharma

University of California, Davis School of Medicine

University of California, San Francisco

University of Hambourg

University of Miami

University of Michigan

University of Minnesota

University of Nottingham

University of Oxford

University of Tokyo

University of Tübingen, Natural and Medical Sciences Institute

University of Washington

University of Wisconsin

US Environmental Protection Agency

US Food and Drug Administration

Vala Sciences, Inc.

Vanderbilt University

VistaGen Therapeutics, Inc.

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