Examples of the Value of Partnering with the US FDA in Toxicology

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Office of New Drugs
Center for Drug Evaluation and Research
FDA
This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.
Evolution of this presentation:

Began with the idea of talking about the FDA participation in the NCATS/DARPA microphysiological system program as *an* example of a successful partnership.

Why not talk about *multiple* examples?

Problem: I went from one example to MANY examples!

Solution: I will try to summarize several, using a fairly broad definition of “partnership”.
FDA’s Predictive Toxicology Roadmap

1. Organizing Committee – Toxicology Working Group
2. Training
3. Continued Communication
4. Collaborations
5. Research
6. Oversight
Training of FDA regulators and researchers

• Continuing ongoing education in new predictive toxicology methods is essential for FDA regulators.

• Established an Agency-wide education calendar of events and a Toxicology Seminar Series to introduce concepts of new toxicology methodologies and updates in toxicology-related topics.
Training

Who needs training and about what?

Who?
• FDA Reviewers
• Industry toxicologists/regulatory
• General public
• Legislators

What?
• New science
  – Basic and applied
  – Opportunities and limitations
• Rules, regulations and guidances
FDA attends and provides toxicology training both inside and outside the Agency

• Continuing education and other presentations at scientific meetings
  – Society of Toxicology
  – American College of Toxicology
  – Toxicology Forum
  – World Congress on Alternatives and Animal Use in the Life Sciences
  – Teratology Society
  – ...

• Toxicology Working Group – across centers
• Scientific Rounds, Seminars, Visiting Speakers
• **Purpose:** The goal of the workshop is to provide an educational forum to discuss current challenges and opportunities for nonclinical models for immuno-oncology, a priority topic for oncology with a growing number of compounds that are approved or in clinical development.
Colloquium Series

• Partnering US FDA’s Center for Food Safety and Applied Nutrition (CFSAN) and the Society of Toxicology (SOT)

• Based on MOU from FDA Office of the Chief Scientist

• Stimulates a dialogue among leading toxicology experts on future-oriented toxicological science relevant to food and food ingredient safety assessment

• Includes, so far, 15 wide-ranging topics related to toxicology and food safety

• Offered quarterly since November 2014
Broad Participation in Each of 15 Colloquium

Scheduled as half-day session with 4-5 speakers and panel discussion

- Onsite audience ~60, Webcast ~300
- Participants
  - FDA employees
  - Other agencies (DOD, USDA)
  - Academic
  - Industry
  - Global reach
- Recordings and slides accessed frequently at no charge from SOT website
  [www.toxicology.org](http://www.toxicology.org)

24 Countries

October 2016, December 2016, and March 2017 Colloquia
2018-2019 Colloquia

- October  Food Tolerance Allergenicity
- December  Bio-Printing as a Tool for Testing
- February  Foods and Flavor Modifiers
- April/May  Has the Time Passed for Separate Cancer and Non-Cancer Risk Assessment?

Betty J. Eidemiller, PhD,
Education Director
Society of Toxicology
Continued Communication

• Reaffirm FDA’s commitment to incorporate data from newly qualified toxicology methods into regulatory missions.

• Encourage discussions with stakeholders as part of the regulatory submission process.

• Encourage sponsors to submit a scientifically valid approach for using a new method early in the regulatory process.
Critical Path Innovation Meetings (CPIM)

The Critical Path Innovation Meeting (CPIM) was developed by CDER to address issues in drug development identified in the 2004 FDA publication, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products Report*. The report identified several areas of product development in need of improvement, including “technical methods such as animal or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques,” and cited a need “to create better tools for developing medical technologies and a knowledge base built not just on ideas from biomedical research, but on reliable insights into the pathway to patients.”

The CPIM is a means by which the Center for Drug Evaluation and Research (CDER) and investigators from industry, academia, patient advocacy groups, and government can communicate to improve efficiency and success in drug development. The goals of the CPIM are to discuss a methodology or technology proposed by the meeting requester and for CDER to provide general advice on how this methodology or technology might enhance drug development. CDER will identify some of the larger gaps in existing knowledge that requesters might consider addressing in the course of their work. CDER expects to become more familiar with prospective innovations in drug development, broadening its regulatory perspective. The discussions and background information submitted through the CPIM are drug product-independent and nonbinding on both FDA and CPIM requesters. The meeting does not substitute for formal pre-IND, IND, NDA, or BLA meetings.

New! Change in Process for Qualification of Drug Development Tools

Get updates and details.
Critical Path Innovation Meetings

• 65 meetings in past five years
• Mostly clinical but some nonclinical or toxicology topics
  – Use of in vitro Testing to Predict Drug Sensitization Potential
  – Digital Pathology Software System
  – Bile Salt Export Pump Inhibition as a Biomarker
  – Biomarkers to Identify Drug Induced Pancreatic Injury
  – 3D Bioprinted Human Tissue Models
Collaborations with Stakeholders

• Foster collaborations across sectors and disciplines nationally and internationally.

• Pivotal to identifying the needs, maintaining momentum, and establishing a community to support delivery of new predictive toxicology methods.
ICH

INTERNATIONAL COUNCIL FOR HARMONISATION
of
Technical Requirements
for Pharmaceuticals for Human Use

- Unique harmonisation initiative for regulators and pharmaceutical industry
- Originally founded in 1990
- Reformed as a non-profit legal entity under Swiss Law on October 23, 2015
ICH Members

Members:

- **Founding Regulatory**: EC, Europe; MHLW/PMDA, Japan; FDA, US
- **Founding Industry**: EFPIA, Europe; JPMA, Japan; PhRMA, US
- **Standing Regulatory**: Swissmedic, Switzerland; Health Canada, Canada
- **Industry**: IGBA, WSMI, BIO
- **Regulatory**: ANVISA, Brazil; CFDA, China; HAS, Singapore; MFDS, Republic of Korea; TFDA, Chinese Taipei

See http://www.ich.org/about/members-observers.html for details
Purpose of ICH

Promotion of public health through international harmonisation that contributes to:

• Prevention of unnecessary duplication of clinical trials and post market clinical evaluations
• Development and manufacturing of new medicines
• Registration and supervision of new medicines
• Reduction of unnecessary animal testing without compromising safety and effectiveness

Accomplished through Technical Guidelines that are implemented by the regulatory authorities.
VICH = International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VMPs)

Full Members

Observers

EU
UEMOA
Morocco
Ukraine
Saudi Arabia
India
China
ASEAN
Taiwan
Thailand
Malaysia
Russia
Japan
USA
Canada
Mexico
Brazil
CAMEVET
Argentina

OIE : Associate Member, HealthforAnimals : Secretariat
CDRH Medical Device Development Tool Program

FDA Center of Devices and Radiologic Health program to foster qualification of device development tools.

See Peter Goering’s talk for more information about this program.
Centers of Excellence in Regulatory Science and Innovation (CERSI)

FDA’s Centers of Excellence in Regulatory Science and Innovation (CERSIs) are collaborations between FDA and academic institutions to advance regulatory science through innovative research, education, and scientific exchanges. Evolving areas of science are prompting new approaches to improving our health while demanding new ways to evaluate the safety and effectiveness of the products FDA regulates. FDA’s Strategic Plan for Advancing Regulatory Science describes how FDA is harnessing these new technologies in collaboration with academia, industry, and other governmental agencies to develop the tools, standards, and approaches required to assess the safety, efficacy, quality, and performance of innovative products.

FDA CERSI: University of Maryland, Georgetown University, UCSF-Stanford, Johns Hopkins University, and Yale-Mayo Clinic

FDA CERSI at the University of Maryland, Georgetown University, University of California at San Francisco (UCSF) in a joint effort with Stanford University (UCSF-Stanford)@, Johns Hopkins University@, and Yale University@. In joint effort with Mayo Clinic the are part of FDA efforts to foster a robust, collaborative, regulatory science culture to address the scientific challenges presented by revolutions in medical product development and to improve food safety and quality.

Research, Scientific Exchanges, and Professional Development

A strong in-house contingent of scientific and technical experts proficient in cutting-edge science together with a network of collaborations is key to FDA’s capacity to evaluate increasingly complex products and promote innovation that addresses unmet public health needs.
Priority areas for the CERSI program

- **High-priority topics, with needs across product lifecycle and relevant subpopulations (sex, gender, age, race/ethnicity):**
  - Tobacco, including, but not limited to toxicity, addiction, health effects:
    - See link on CTP research priorities for more information.
  - Reducing healthcare-associated infection:
    - Developing better understanding of the effectiveness of sterilization and reprocessing of medical devices
    - Further developing pathogen-reduction technologies for whole blood and blood components
    - Promoting development of innovative antimicrobial approaches
  - Issues related to opioid use, misuse, and dependence
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- **Develop and evaluate methods to improve quality and safety of FDA-regulated products for use by patients and consumers, including methods to improve predictive value of nonclinical evaluation:**
  - Biocompatibility and biological risk evaluation of medical devices and their component materials
  - Evaluation of innovative methods such as:
    - Microphysiological systems (MPS) (organs on a chip)
    - Computer modeling and simulation (e.g., in silico clinical trials and biocompatibility modeling)
    - Discovery and validation of minimally invasive biomarkers, particularly for diseases and medical states, where few markers exist (such as traumatic brain injury), including predictive microbiome biomarkers and use of current methods such as EEG and bio-imaging.
  - Developing better understanding of the effectiveness of sterilization and reprocessing of medical devices
  - Further developing pathogen-reduction technologies for whole blood and blood components
  - Promoting development of innovative antimicrobial approaches
  - Issues related to opioid use, misuse, and dependence
Office of Regulatory Science and Innovation
Regulatory Science Extramural Research and Development Projects

• Broad Agency Announcements (BAA)
  – proposals solicited from industry, academia, and other government agencies
  – FDA Scientific Priority areas
    • Includes: Modernize Toxicology to Enhance Product Safety
      – Extramural Research Funded through the BAA related to this priority
        » The Impact of Graphene-Based Nanomaterials (Phases 1 and 2)
        » The Musculoskeletal Atlas Project
        » A Systems Approach to Measuring and Modeling Toxic Response
        » The Diversity Outbred: A Tool to Improve Preclinical Safety Testing and Pharmacogenomic Analysis
        » Validating Human Stem Cell Cardiomyocyte Technology for Better Predictive Assessment of Drug-Induced Cardiac Toxicity
        » Scientific and Methodological Advancements in Liquid Biopsies to Further the Development of Lung Cancer-Based Precision Medicine
CDER Office of Translation Science

- Promote networking/collaborations on specific projects within CDER, more broadly throughout FDA, NIH (including NCI and NCATS (National Center for Advancing Translational Sciences))

- Explore existing and novel areas for collaboration with other Centers and Agencies

- Facilitate scientific, training and partnership (including data sharing) interactions with NCTR, NIH, and CTSAs (Clinical and Translational Science Awards Program-NCATS)

Contact: Shashi Amur, Ph.D.
Scientific Advisor, Science and Research Team, Office of Translational Sciences, Center for Drug Evaluation and Research, FDA
Publications with NIH and FDA coauthors -

pubmed keyword search results

N=583

Note: Does not include other NIH Centers (e.g., NCI) and Institutes (NCATS)
NLM-Generated information

Number of NIH-and FDA- coauthored publications

WoS N=3796
Scopus N=3392

Note: Includes other NIH Centers (e.g., NCI) and Institutes (NCATS)
FDA-NIH COAUTHORED PUBLICATIONS (1991-2018)
Web Of Science (WoS) Search Results

Visualization: Treemap
Number of results: 10

- Immunology: 533 publications
- Biochemistry Molecular Biology: 358 publications
- Infectious Diseases: 233 publications
- Cell Biology: 207 publications
- Medicine Research Experimental: 268 publications
- Virology: 203 publications
- Toxicology: 175 publications
- Pharmacology Pharmacy: 243 publications
- Microbiology: 194 publications
- Oncology: 407 publications
Scientific Public Private Partnerships and Consortia

Back to Science & Research (Drugs)

- The Role of Scientific Consortia in Drug Development
- Critical Path Initiative: The Role of Consortia
- Engagement with PPPs and Consortia

The Importance of Partnerships and Consortia

The Role of Scientific Consortia in Drug Development

Background Information

The Critical Path Initiative (CPI), and the Strategic Plan for Advancing Regulatory Science Initiative seek to help identify scientific gaps in drug development. Find out how these relationships improve FDA's ability to advance public health.
IQ-DILI Initiative
Drug induced liver injury – including use of nonclinical toxicology in predicting DILI and development of new biomarkers

The Predictive Safety Testing Consortium
Efforts to explore biomarkers for vascular injury, DILI, kidney injury, skeletal muscle injury

Product Quality Research Institute
Efforts at characterizing impurity toxicity and establishing thresholds
Advancing Regulatory Science Program
NIH – FDA Joint Leadership Council

- Started in 2010 through the NIH Common Fund
- RFA-RM-10-006 “Advancing Regulatory Science through Novel Research and Science-Based Technologies (U01)”
- MOU between NIH and FDA; $7M over 3 years
- 4 awards were made that address four distinct, high priority areas of regulatory science which include:
  - Accelerating Drug and Device Evaluation through Innovative Clinical Trial Design
  - Replacement Ocular Battery
  - Heart-Lung Micromachine for Safety and Efficacy Testing
  - Characterization/Bioinformatics-modeling of Nanoparticle: Complement Interactions
Tissues-on-Chips: What are they?

- **Scaffold**
  - Microfluidic cell culture devices
- **Cells**
  - Created with microchip manufacturing methods
- **Structure**
  - Contains continuously perfused chambers
- **Spatial and Temporal Patterning**
  - Seeded by human-derived cells
- **Perfusion**
  - Cytoarchitecture mimics tissue- and organ-level physiology
- **Bioreactor**
- **Innervation**
- **Host Response**
- **Functional Readout**
  - High-resolution, real-time imaging and in vitro analysis of biochemical, genetic and metabolic activities
- **Computational Design**
Microphysiological Systems Program “Tissue Chips for Drug Screening” 2012-2017

Platform and cell resources development

Functional Validation, training set of compounds, multi-organ integration


$75 M over 5 years – cell source, platform development, validation and integration (NCATS, CF, NIBIB, NIEHS, NICHD, ORWH, NCI)

$75 M over 5 years - development of 10-organ platform

**FDA provides insight and expertise throughout the program

Publications: (cited over 5600 times)
A total of 506 original and review articles published in top tier journals, including Nature Medicine, Nature Communications, Nature Materials, PNAS, Science, Science Translational Medicine, etc.
The Tissue Chip Program

Overall goal: Develop an *in vitro* platform that uses human tissues to evaluate the efficacy, safety and toxicity of promising therapies.

**Specific Goals:**
- Integration
- Compound testing
- Validation
- Partnerships
- Adoptions of the tech to the community

**Tissue Chip Testing Centers (TCTC)**
- TEX-VAL: Texas A&M Tissue Chip Validation Center
- MIT: Translational Center of Tissue Chip Technologies for Quantitative Characterization of Microphysiological Systems
- University of Pittsburgh Microphysiological Systems Testing Database Center
Tissue Chip Testing Centers: Validating Microphysiological Systems

- RFA-TR-16-006
- Resource Centers (U24)
- **GOAL:** Independent validation of tissue chip platforms
- Partnerships between NCATS, FDA and IQ Consortium
- NCATS support: $12 M over two years; **awarded 9/28/16**
- FDA and IQ provides expert guidance on reference set of validation compounds, assays, biomarkers

- **Testing Centers:**
  - MIT (Murat Cirit and Alan Grudzinsky)
  - TAMU (Ivan Rusyn)

- **MPS Database:**
  - U Pittsburgh (Mark Schurdak)
Tissue-on-chips Disease Models for Efficacy Testing

• RFA-TR-16-017
• **GOAL:** Develop models for a wide range of human diseases for efficacy testing, assessment of candidate therapies and establishing the pre-clinical foundation that will inform clinical trial design
  – NCATS joined by NCI, NEI, NHLBI, NIAMS, NIBIB, NICHD, NIDCR, NIDDK, NIEHS, NINDS, ORWH
  – NIH support: approximately $ 80 M over five years
  – Bi-phasic:
    • Develop and characterize models of diseases
    • Testing for efficacy of candidate therapeutics
FDA and MPS

- CFSAN working with Emulate (spin-off from Wyss Institute)
- CDER working with CN Bio (spin-off from MIT) and Kevin Healy at UC Berkeley
- What are challenges of setting up such systems?
- Quality Control – cells, chips, measuring devices
- Reproducibility
- “validation” – what to test?
- Can we write some “standards” or “best practices” for how to use such systems if results from such systems are to be included in a regulatory submission?
Leveraging Research

FDA’s research programs will identify data gaps and support intramural and extramural research to ensure that the most promising technologies are identified, developed, validated, and integrated into the product pipeline.
National Toxicology Program (NTP)

Goals include:

• Coordinate toxicological testing programs within HHS
• Develop and validate improved testing methods that reduce, refine, or replace the use of animals
• Develop approaches and generate data to strengthen scientific knowledge about potentially hazardous substances
• Communicate information about potentially hazardous substances to health regulatory and research agencies, scientific and medical communities and the public

Established in 1978

http://ntp.niehs.nih.gov
Interagency agreement between the NIEHS/NTP and the FDA/NCTR

- Established in 1992
- Conduct of toxicological assessments at NCTR on FDA priority chemicals/agents nominated to the NTP
- Overseen by the Toxicology Study Selection and Review Committee (TSSRC), composed by NCTR, NTP, and FDA center representatives
- Examples of comprehensive toxicological studies conducted in recent years: BPA, furan, acrylamide, glycidamide, melamine and cyanuric acid, triclosan, aloe vera
- Resulted in the publication of over 275 peer-reviewed manuscripts and 22 NTP technical and toxicity reports
Toxicity Testing in the 21st Century (Tox21)
HESI Mission
Create science-based solutions for a sustainable, healthier world.

- Accurate and Efficient Chemical Risk Assessment
- Safe and Effective Medicines
- Environmental Quality and Sustainability
- Food Safety
From 14 Countries
90 University & Research Centers

From 12 Countries
47 Government Agencies

Across multiple sectors
66 Corporate Sponsors

Impact via Quality Science

> Genetic toxicology
> Immunotoxicology
> Protein allergenicity
> Risk assessment in the 21st century (RISK21)
> Sustainable chemical alternatives
> Translational biomarkers of neurotoxicity
> Use of imaging for translational safety assessment

Emerging Issues Subcommittee
> Framework for intelligent non-animal methods for risk assessment
CONSORTIUM

Subcommittee on Translational Biomarkers of Neurotoxicity
Health and Environmental Sciences Institute (HESI)
International Life Sciences Institute (ILSI)

Co-Chairs:
- Ruth Roberts, PhD, ApConix, UK
- William Slikker Jr, PhD, FDA
- David Calligaro, PhD, Lilly

Study Lead:
- Syed Z. Imam, MS. PhD, FDA

HESI Staff:
- Ms. Jennifer Pierson, Program Manager
- Ms. Alexandra Feitel, Program Associate

Work Sites:
- Pre/Post TMT MRI - Serguei Liachenko - NCTR
- Pre/Post TMT Behavior - Sherry Ferguson - NCTR
- Proteomics – Joseph Hanig – CDER/US FDA
- Histopathology - Christopher Somps – Pfizer
- Oxidative Biology - Susan Lantz/Syed Imam – NCTR
- Bioplex Assays - Susan Lantz/Syed Imam – NCTR
- Neuropathology – Syed Imam/Sumit Sarkar – NCTR
- GFAP ELISA - Jim O’Callaghan/Diane Miller - CDC-NIOSH
- Biocrates Metabolome - David Herr/Ginger Moser - US EPA
- Lipidomics – Andrea Armirrotti – Institute of Technology, Italy
- miRNA analyses - David Calligaro/Aaron Smith - Eli Lilly/Covance
A search for biomarkers of neurotoxicity: Trimethyltin as a prototypic neurotoxicant

Identify biomarkers in bodily fluids and in tissue that are associated with the expression of neurotoxicity.

- Young adult male Sprague-Dawley rats (12 weeks) were given a single 7 mg/kg intra-peritoneal injection of the known neurotoxicant Trimethyltin (TMT)
- Animals sacrificed at 2, 6, 10 and 14 days post treatment

Biological Fluids – CSF, PLASMA, SERUM, URINE

Tissue Samples – BRAIN, LIVER, THYMUS, ADRENAL, KIDNEY, SPINAL CORD, SCIATIC NERVE

- “Changes in the metabolome and microRNA levels in biological fluids might represent biomarkers of neurotoxicity: A trimethyltin study” Imam et al., Experimental Biology and Medicine 2018; 243: 228–236. DOI: 10.1177/1535370217739859
HESI Technical Committee

DEVELOPMENTAL AND REPRODUCTIVE TOXICOLOGY (DART)

2016–2017 Activities and Accomplishments

Committee leaders:
Ms. Susan Makris
US Environmental Protection Agency

Dr. Graeme Moffat
Amgen Inc.

HESI manager:
Dr. Connie Chen

HESI associate:
Mr. Oscar Bermudez

This scientific program is committed to:
• Providing a forum in which scientists from industry, government, and academia can exchange information and ideas;
• Initiating activities to advance science related to DART; and
• Developing consensus in the scientific community on the appropriate use of experimental toxicity data for human health risk assessment.
Technical Objective:
Compare Rat and Rabbit Embryo Fetal Developmental (EFD) toxicity data for pharmaceuticals:
- Strength of developmental toxicity signal in each species
- Putative safety margin against human therapeutic dose/exposure in each species
- Pharmacologic relevance of each species

Questions:
• Which species is, in retrospect, the most sensitive for detecting developmental toxicity potential of a compound?
• Are there situations in which testing in a single species would suffice?
• Can we designate one of the two species as a default first choice, and might the first study inform sufficiently about the need for a second species study?
• When developmental toxicity data are available in a pharmacologically relevant species at adequate exposures and clinical trials can maintain effective contraception, what impact would delaying the second species developmental toxicity study have on risk assessment and informed consent for the Phase III trials?
ILSI-HESI-DART 2nd species workgroup

Public:
Belgium FAGG
CBG-MEB
EMA
RIVM
US-FDA
US-EPA

Private:
AbbVie
AstraZeneca
BMS
Celgene
Charles River
Covance
Dow Chemical
Eli Lilly
Exxon Mobil
GSK
J&J
Merck
Pfizer
Roche
Sanofi
Takeda

Workgroup Chairs:
Gregg Cappon (Pfizer)
Alan Hoberman (CRL)
Aldert Piersma (RIVM)

ILSI-HESI Staff
Connie Chen
Megan Harries
James Kim

This research is funded by:
ILSI-HESI DART Technical Committee
SLIM (Synergy in Life Science, Innovation and Marketing)
Comparison of rat and rabbit embryo-fetal developmental toxicity data for 379 pharmaceuticals: on the nature and severity of developmental effects


Comparing rat and rabbit embryo-fetal developmental toxicity data for 379 pharmaceuticals: on systemic dose and developmental effects

Results

• 31% of compounds (118/379) produced embryofetal developmental toxicity in only one of the two species
  – 18% induced an effect in rat and not rabbit
  – 13% induced an effect in rabbit and not rat

• 74% of compounds produced embryofetal developmental toxicity in at least one species when two species were tested

• The rat and rabbit show similar sensitivity to embryofetal developmental toxicity with approximately 80% of the compounds
Why does this matter?

• ICH S5(R2): For embryofetal development: “Usually, two species: one rodent, preferably rats; one non-rodent, preferably rabbits. Justification should be provided when using one species.”

• ICH S5 is currently under revision. Concept paper February 2015. Draft was published in 2017. Comments being addressed.

• Topics include:
  – Potential delay of studies to later in development
  – Potential use of alternative assays in some circumstances

• HESI results suggest
  – No particular reason to pick one species as initial default
  – Elimination of one species entirely could miss some embryofetal developmental toxicity
Computational Toxicology at FDA/CDER

• Long-time history of collaboration with software vendors in development of QSAR models through formal agreements
• QSAR now accepted to assess mutagenic potential of impurities in human pharmaceuticals
  • Described in ICH M7 guidance
Principles and procedures for implementation of ICH M7 recommended (Q)SAR analyses

Alexander Amberg a, Lisa Beilke b, Joel Bercu c, Dave Bower d, Alessandro Brigo e, Kevin P. Cross d, Laura Custer f, Krista Dobo g, Eric Dowdy c, Kevin A. Ford h, Susanne Glowienke i, Jacky Van Gompel j, James Harvey k, Catrin Hasselgren d, Masamitsu Honma l, Robert Jolly m, Raymond Kemper n, Michelle Kenyon o, Naomi Kruhlak p, Penny Leavitt q, Scott Miller d, Wolfgang Muster c, John Nicolette p, Andreja Plaper q, Mark Powley v, Donald P. Quigley d, M. Vijayaraj Reddy t, Hans-Peter Spirk l, Lidiya Stavitskaya o, Andrew Teasdale s, Sandy Weiner t, Dennie S. Welch p, Angela White k, Joerg Wichard u, Glenn J. Myatt d, *
The Potential Role of CiPA on Drug Discovery, Development, and Regulatory Pathways

David Strauss, MD, PhD
Director, Division of Applied Regulatory Science
Office of Clinical Pharmacology, Office of Translational Sciences
Center for Drug Evaluation and Research
Comprehensive in vitro Proarrhythmia Assay (CiPA)

• Current paradigm for assessing proarrhythmic risk is largely based on assessing one cardiac ion channel and whether a drug prolongs the QT interval on the ECG (ICH S7B and ICH E14)

• Some limitations to this approach – may be too conservative

• CiPA initiative is an FDA, Cardiac Safety Research Consortium and HESI collaboration with participation from EMA, Health Canada, PMDA and industry from all the regions
Components of CiPA

- In vitro Assessment of Drug Effects in Multiple Ionic Currents
  - Sodium
  - Calcium
  - hERG
  - Potassium

- In silico Computer Modeling to Predict Risk
  \[ I_{\text{clin}} = C \frac{dV_m}{dt} + I_m \]

- In vivo ECG Biomarker in Phase 1 Clinical Trials
  - Torsade Metric Score (qNET)

- In vitro effects on Human Stem Cell Derived Ventricular Cardiomyocytes

**I_{Ks} and I_{Na} Peak in specific situations**

**Torsade Metric Score (qNET)**

**Check for unanticipated human effects, confirm mixed channel effects using JT_{peakc}**

**Can be considered for unanticipated nonclinical effects, or if human ECG data is insufficient**

Modified from Jose Vicente
Model Development and Validation Strategy

Select a Base Cardiomyocyte Model

Model Optimization

CiPA Training Drugs (12)

Model Training

Metric Development

Evaluate the Training Results; Freeze Model for Validation

CiPA Validation Drugs (16)

Model Validation

Predict Validation Drugs

Compare Prediction Accuracy to Pre-defined Performance Measures
Optimized Arrhythmia Risk Prediction & Defining Experimental Uncertainty

Original Article

Improving the In Silico Assessment of Proarrhythmia Risk by Combining hERG (Human Ether-à-go-go-Related Gene) Channel–Drug Binding Kinetics and Multichannel Pharmacology

Zhihua Li, PhD; Sara Dutta, PhD; Jiansong Sheng, PhD; Phu N. Tran, PhD; Wendy Wu, PhD; Kelly Chang, PhD; Thembi Mdluli, PhD; David G. Strauss, PhD; Thomas Colatsky, PhD

Circulation: Arrhythmia & Electrophysiology 2017;10:e004628

Optimization of an In silico Cardiac Cell Model for Proarrhythmia Risk Assessment

Sara Dutta, Kelly C. Chang, Kylie A. Beattie, Jiansong Sheng, Phu N. Tran, Wendy W. Wu, Min Wu, David G. Strauss, Thomas Colatsky* and Zhihua Li*


Uncertainty Quantification Reveals the Importance of Data Variability and Experimental Design Considerations for in Silico Proarrhythmia Risk Assessment

Kelly C. Chang†, Sara Dutta†, Gary R. Mirams‡, Kylie A. Beattie†, Jiansong Sheng†, Phu N. Tran†, Min Wu†, Wendy W. Wu†, Thomas Colatsky†, David G. Strauss† and Zhihua Li†

ipSC-Cardiomyocytes Initial Studies

Title: Cross-Site Reliability of Human Induced Pluripotent Stem-Cell Derived Cardiomyocyte Based Safety Assays using Microelectrode Arrays: Results from a Blinded CiPA Pilot Study

Authors: Daniel Millard*, Qianyu Dang†, Hong Shi†, Xiaou Zhang§, Chris Strock¶, Udo Kraushaar∥, Haoyu Zeng||, Paul Levesque¶, Hua-Rong Lu|||, Jean-Michel Guillou|||, Joseph C. Wu**, Yingxin Li**, Greg Tuerman††, Blake Anson¶, Liang Guo‡‡, Mike Clements*, Yama A. Abassii, James Ross*, Jennifer Pierson†, Gary Gintant‡

Toxicological Sciences 2018; doi: 10.1093/toxsci/kfy110

Comprehensive Translational Assessment of Human-Induced Pluripotent Stem Cell Derived Cardiomyocytes for Evaluating Drug-Induced Arrhythmias

Ksenia Blinova,*† Jayna Stohlman,* Jose Vicente,*‡ Dulciana Chan,* Lars Johannesen,* Maria P. Hortigón-Vinagre,§§ Victor Zamora,§§ Godfrey Smith,§§ William J. Crumb,∥ Li Pang,∥ Beverly Lyn-Cook,∥ James Ross,∥ Mathew Brock,∥ Stacie Chvatal,∥ Daniel Millard,∥ Loriano Galeotti,∥ Norman Stockbridge,‡ and David G. Strauss‡,*

Toxicological Sciences 2017;155:234-47.

Toxicological Sciences 2018; doi: 10.1093/toxsci/kfy110


Research article
A new paradigm for drug-induced torsadogenic risk assessment using human iPSC cell-derived cardiomyocytes

Clinical Studies

Improving the Assessment of Heart Toxicity for All New Drugs Through Translational Regulatory Science
L. Johannesen1,2,3, J. Vicente2,4, RA Gray5, I. Galeotti5, Z. Loring2, CE Garnett1,2, J. Florian1, M. Ugander1,2, N. Stockbridge6 and DG Strauss2


Differentiating Drug-Induced Multichannel Block on the Electrocardiogram: Randomized Study of Dofetilide, Quinidine, Ranolazine, and Verapamil
L. Johannesen1,2, J. Vicente1,3, JW Mason4, C. Sanabria5, K. Waite-Labott6, M. Hong7, P. Guo5, J. Lin5, JS Sorensen6, I. Galeotti5, J. Florian6, M. Ugander1,2, N. Stockbridge7 and DG Strauss1,2


Late Sodium Current Block for Drug-Induced Long QT Syndrome: Results From a Prospective Clinical Trial
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Automated Algorithm for $J-T_{\text{peak}}$ and $T_{\text{peak}}-T_{\text{end}}$ Assessment of Drug-Induced Proarrhythmia Risk

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Comprehensive T wave Morphology Assessment in a Randomized Clinical Study of Dofetilide, Quinidine, Ranolazine, and Verapamil
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Mechanistic Model-Informed Proarrhythmic Risk Assessment of Drugs: Review of the “CiPA” Initiative and Design of a Prospective Clinical Validation Study
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**Potential CiPA Details Integrated into S7B/E14**

- **Low TdP risk**
  - (Current E14 Recommendations for drug that does not prolong QT)

- **Intermediate/high TdP risk**
  - (Integrated risk assessment to decide path forward)

- **Current E14 recommendations for QTc prolonging drug**
  - (Follow-up studies may inform decision making)

**S7B: hERG block and/or nonclinical QTc prolongation?**
(CiPA hERG IC50/Cmax) < safety margin (e.g. 100 or 200) and/or observed nonclinical in vivo QTc prolongation

**E14: clinical QTc prolongation?**

**In silico Torsade Metric Score low risk & human QTc <20 ms?**

**ECG consistent with balanced ion channel blocker?**
(No J-Tpeakc prolongation)

- Yes
  - Low TdP risk
  - (Current E14 Recommendations for drug that does not prolong QT)

- No
  - Intermediate/high TdP risk
  - (Integrated risk assessment to decide path forward)

- Consider CiPA iPSC-myocyte assays +/- other follow-up studies (e.g. metabolites, protein binding, other ion channels to investigate discrepancies)

- **No**

  - Yes
    - Intermediate/high TdP risk
    - (Integrated risk assessment to decide path forward)

- Yes
  - Low TdP risk
  - (Current E14 Recommendations for drug that does not prolong QT)

- No
  - Intermediate/high TdP risk
  - (Integrated risk assessment to decide path forward)

- Consider CiPA iPSC-myocyte assays +/- other follow-up studies (e.g. metabolites, protein binding, other ion channels to investigate discrepancies)
Conclusion

• FDA has a responsibility to engage with diverse stakeholders.
• FDA toxicologists recognize the value in partnerships as a means to enhance the development and understanding of new methods.
• FDA involvement can help bring a regulatory perspective that may facilitate eventual incorporation of new methods into regulatory use.