An Update on CiPA Activities from an FDA Perspective

Zhihua Li, Ph.D.

Division of Applied Regulatory Science
Office of Clinical Pharmacology, Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

SPS Webinar 2017
June 22, 2017
Disclaimer

This presentation is not an official US Food and Drug Administration guidance or policy statement. No official support or endorsement by the US FDA is intended or should be inferred.
Outline of the Talk

• A brief description of the regulatory issue, the mechanistic background, and the current international guideline
• Overall picture of CiPA, and a brief introduction of the goals and progresses of the four components
• Detailed explanation of the In Silico work and current TdP risk assessment metric
• Expected outcomes of CiPA as a new regulatory paradigm
# Drugs Withdrawn from Market Due to QTc Prolongation or Torsade de Pointes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Class</th>
<th>Year of Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenylamine</td>
<td>Antianginal</td>
<td>1988 (EU, not marketed in US)</td>
</tr>
<tr>
<td>Terodiline</td>
<td>Antianginal/urinary incontinence</td>
<td>1991 (EU, not marketed in US)</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>Antihistamine</td>
<td>1998</td>
</tr>
<tr>
<td>Sertindole</td>
<td>Antipsychotic</td>
<td>1998 (not marketed in US, EU reintroduction in 2002)</td>
</tr>
<tr>
<td>Astemizole</td>
<td>Antihistamine</td>
<td>1999</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>Antibiotic</td>
<td>2001</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Gastric prokinetic</td>
<td>2000</td>
</tr>
<tr>
<td>Droperidol</td>
<td>Tranquilizer/analgesic</td>
<td>2001</td>
</tr>
<tr>
<td>Levacetylmethadol</td>
<td>Methadone substitution</td>
<td>2003</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Antipsychotic</td>
<td>2005 (ex-US)</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>Opioid analgesic</td>
<td>2010</td>
</tr>
</tbody>
</table>

Adapted from Table 1 in Stockbridge et al. Drug Safety (2013) 36:167-82

EU, European Union; US, United States
Cellular Mechanism of Torsade de Pointes: Early After Depolarization

- Early after depolarization (EAD)
- Torsade de pointes (TdP)
- Plateau
- Action potential (AP)
- Delayed repolarization (AP prolongation)
- QT prolongation

Delayed repolarization/QT prolongation usually happens before EAD/TdP and could be used as a surrogate marker.
Ionic Currents Underlying Repolarization

- Balance between depolarizing (inward) currents and repolarizing (outward) currents determines the rate of repolarization (AP duration/QT interval)

- IKr (hERG channel) is the most prominent repolarizing current
Regulatory Guidelines

• ICH S7B: The nonclinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals, with the focus on IKr/hERG

• ICH E14: The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs
  – Revisions made through Questions and Answers

Consequences of ICH S7B and E14

• Successful: No drugs that went through the ICH S7B and E14 assessment removed from market due to TdP

• However:
  – Both guidelines assess the surrogate marker (delayed repolarization/QT prolongation), not the clinical end point TdP (cellular mechanism = early afterdepolarization [EAD])
  – S7B focuses on IKr/hERG, sensitive but not specific
  – Triggers additional costly synthetic efforts to remove hERG liability
  – Some drugs that came to market before S7B/E14 may not be available today
Outline of the Talk

• A brief description of the regulatory issue, the mechanistic background, and the current international guideline

• Overall picture of CiPA, and a brief introduction of the goals and progresses of the four components

• Detailed explanation of the In Silico work and current TdP risk assessment metric

• Expected outcomes of CiPA as a new regulatory paradigm
Comprehensive *in vitro* Proarrhythmia Assay (CiPA)

1. **In Vitro** Assessment of Effects on Multiple Ionic Currents
   - Na, Na,L, Ca,L, Ito1, Kr, Ks, I1.
   - Modified from Hoekstra et al., 2012

2. **In silico** Reconstruction of Human Ventricular Cardiomyocyte Electrophysiology
   - \[ I_{stim} = C \frac{dV_m}{dt} + I_m \]

3. **In vitro** Effects on Human Stem-Cell Derived Ventricular Cardiomyocytes
   - Characterize and assess relative TdP risk levels

4. Evaluation of Unanticipated Effects in Clinical Phase 1 Studies
   - Check for missed or unanticipated effects

McEvoy Ctr for Regen Med., Toronto
1. Ion Channel Working Group

Goals: characterize effects of drugs on prominent ionic currents that define ventricular repolarization

- Reliably characterize block of human cardiac ionic currents in heterologous expression systems

- Design standard protocols and quality metrics to ensure reproducibility of in vitro drug block experiments

- Explore the impact of different experimental conditions (temperature, platform, etc.) on the quality and variability of in vitro data

- Seven cardiac currents initially selected to be measured in CiPA assays (IKr, IKs, IK1, Ito, INa, INaL, ICaL)

  - IKr, ICaL, INa/INaL found to be most critical
Ion Channel Progress

• Decided on the dynamic protocol to be used for studying drug-hERG dynamic interactions (Milnes et al., 2010)

• hERG data has been generated using manual voltage clamp technique at physiologic temperature (Wendy Wu lab, FDA) and room temperature (Adam Hill, Victor Chang Research Institute)

• Percent block (IC50) data are being generated using manual system for all remaining, non-hERG, channels

• Automated High Throughput Patch Clamp Systems (HTS) are being used to generate data for all channels
An evaluation of 30 clinical drugs against the comprehensive *in vitro* proarrhythmia assay (CiPA) proposed ion channel panel

William J. Crumb Jr. a,*, Jose Vicente b, Lars Johannesen b, David G. Strauss b

**Key findings:**

- Most commonly blocked ion channel currents at clinically relevant concentrations are hERG, late sodium and calcium
- Drugs with low torsade risk had equal or greater late sodium or L-type calcium block compared to hERG block
Ongoing High Throughput System Study

Goals: assess variability and reproducibility of automated high throughput patch clamp systems (HTS) for defining drug effects on cardiac ionic currents across different platforms & sites using standardized protocols

- Generate steady state drug block data (IC50s) for all CiPA compounds
- Generate drug binding kinetic data for hERG (selected platforms/sites)
- Data across platforms/sites are being analyzed by In Silico Working Group (ISWG) to assess variability and compatibility with the model
- Phase 1 (12 drugs) completed; Phase 2 (16 drugs) to be started
2. In Silico Working Group

Goals: Integrate in vitro data into a computational model of human ventricular myocyte and identify a mechanistic metric that can quantify the relative risk of inducing EAD/TdP

- O’Hara-Rudy (ORd) human ventricular cardiomyocyte model was chosen as the consensus base model for CiPA
- The base model to be further optimized based on new and published data of drug effects on selected human cardiac currents
- A set of 12 training drugs classified into 3 torsade de pointes (TdP) risk categories (high, intermediate and low) is used to calibrate the model; Another set of 16 drugs for independent validation
## CiPA Drugs Selected for Model Development

<table>
<thead>
<tr>
<th>High TdP Risk</th>
<th>Intermediate TdP Risk</th>
<th>Low TdP Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Training:</strong></td>
<td><strong>Training:</strong></td>
<td><strong>Training:</strong></td>
</tr>
<tr>
<td>Bepridil</td>
<td>Chlorpromazine</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Cisapride</td>
<td>Mexiletine</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Terfenadine</td>
<td>Ranolazine</td>
</tr>
<tr>
<td>D,L Sotalol</td>
<td>Ondansetron</td>
<td>Verapamil</td>
</tr>
<tr>
<td><strong>Validation:</strong></td>
<td><strong>Validation:</strong></td>
<td><strong>Validation:</strong></td>
</tr>
<tr>
<td>Azimilide</td>
<td>Astemizole</td>
<td>Loratadine</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>Clarithromycin</td>
<td>Metoprolol</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>Clozapine</td>
<td>Nifedipine</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Domperidone</td>
<td>Nitrendipine</td>
</tr>
<tr>
<td></td>
<td>Droperidol</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td></td>
<td>Pimozide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risperidone</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Translational Working Group
3. Cardiomyocyte Working Group

Goals: To identify potential gaps in cellular electrophysiological effects (not detected from in vitro/in silico studies) that may impact TdP risk assessment

- Relies on ability of myocytes to recapitulate integrated effects of critical systems that influence electrophysiology found in human myocytes
- Report drug-induced repolarization abnormalities using induced pluripotent stem cell derived cardiomyocytes
- Approaches: microelectrode arrays and voltage-sensing dyes

*In Vitro Effects Human Stem-Cell Derived Ventricular Myocytes*
Cardiomyocyte Measurements

Key measurements:

• Action potential duration (APD)
• Early after depolarizations (EAD) and other arrhythmias

Optical Imaging – Voltage Sensitive Dyes

Microelectrode Arrays

FPD: Field Potential Duration
Cardiomyocyte Progress

• Pilot study evaluated reproducibility and variability of electrophysiologic responses across multiple cells, platforms and volunteer study sites for 8 compounds
  • Additional published FDA study (next slide) with voltage sensitive dye and microelectrode arrays with multiple cell vendors

• Phase II validation study with all 28 CiPA drugs – study completed, data analysis ongoing

• Results will be compared with prospective in silico reconstructions and categories of high-, intermediate- and low-risk of torsade de pointes
FDA iPSC-cardiomyocyte Study

Methods:

• Voltage sensitive dyes (VSD) and microelectrode arrays (MEA)
• 2 different commercially available cell lines
• 26 drugs + 3 drug combinations
4. Phase 1 ECG Biomarker Working Group

- **Goal**: Use human phase 1 ECG data to determine if there are unexpected ion channel effects compared to preclinical ion channel data
  - Human specific metabolite, protein binding
- New ECG biomarker(s) would need to add additional information beyond QTc
  - Differentiate multi-ion channel effects during repolarization
  - Can be corrected for heart rate (if needed)
  - Sufficient power to detect changes in small sample sizes with exposure-response analysis
  - Available for wide-spread use
ECG Biomarker Analysis Summary

• Examined 12 potential ECG biomarkers and compared to ion channel data
  – 2 prospective FDA-sponsored clinical trials including 8 drugs and 3 drug combinations, some additional drugs
• Multiple ECG biomarkers can be applied in exposure-response analysis
• Receiver operating characteristic – area under the curve analysis showed that J-Tpeakc is the strongest predictor of late sodium block in the presence of hERG block
• J-Tpeak has similar inter/intra-subject variability and heart rate relationship as QT; other ECG biomarkers have variable heart rate relationship
• J-Tpeak & Tpeak-Tend FDA algorithms released as open-source software

Vicente et al. J Am Heart Assoc 2015 pii: e001615;
Ongoing Prospective Clinical Validation Study

• Prospective small sample size early Phase 1-type clinical study to verify that a combined assessment of QTc and J-Tpeakc can differentiate between drugs that
  • Are selective hERG blockers versus
  • Have balanced block of hERG and late sodium and/or calcium

• Will include 6 drugs
  – selective hERG block (dofetilide, chloroquine)
  – hERG + late sodium block (ranolazine)
  – hERG + calcium block (verapamil, dofetilide + diltiazem)
  – hERG + late sodium + calcium block (lopinavir/ritonavir)

• To be completed in 2017
  • See details at: https://clinicaltrials.gov/ct2/show/NCT03070470
Outline of the Talk

• A brief description of the regulatory issue, the mechanistic background, and the current international guideline
• Overall picture of CiPA, and a brief introduction of the goals and progresses of the four components
• Detailed explanation of the In Silico work and current TdP risk assessment metric
• Expected outcomes of CiPA as a new regulatory paradigm
O’Hara-Rudy (ORd) Cardiomyocyte Model

Improving the ORd Model for CiPA

• Making the IKr/hERG component temperature dependent
• Modeling dynamic drug-hERG interactions rather than using simple IC50s
• Optimizing model parameters based on experimentally recorded drug effects on human ventricular myocytes
Development of a Temperature Sensitive hERG Model

Because O’Hara-Rudy model operates at physiological temperature, while industry-generated hERG data are often obtained at room temperature, a dynamic, temperature-sensitive hERG model is required.

We developed a modified hERG model that can reproduce temperature-induced changes in major channel gating processes.
Modeling Dynamic drug-hERG Interactions

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


• Because the same drug may show different block potency under different conditions (i.e. heart rate), a novel model was developed to capture this dynamic drug-hERG interaction

• This model can distinguish between hERG blockers with similar IC50s but different TdP liabilities because of some drugs’ ability to induce reverse use-dependent AP prolongation
Optimizing Model Parameters Based on Human Cardiomyocyte Data

- Human cardiomyocyte action potential duration (APD) was recorded under L-type calcium current (ICaL) blocker (1 µM nisoldipine)
- The optimized model was able to reproduce the experimental data better than the original model
- Similar improvement seen for other major potassium currents (IKr/hERG, IKs, IK1) and also late sodium current INaL.

Dutta S et al. Optimization of an In Silico Cardiac Cell Model for Proarrhythmia Risk. (In revision)
Experimental data were taken from O’Hara et al. PloS Computational Biology. 2011
Key Mechanism of TdP: imbalance of Inward and Outward Currents

- **Inward Currents**:
  - ICaL (L type calcium)
  - INaL (late sodium)

- **Outward Currents**:IKr (potassium), IKs (potassium), IK1 (potassium), Ito (potassium)

**Action potential**

*Early after depolarization (EAD)*

*Increased ratio between inward and outward currents*

The net current between inward and outward currents reflect their balance.

\[ \text{Inet} = \text{ICaL} + \text{INaL} + \text{IKr} + \text{IKs} + \text{IK1} + \text{Ito} \]

qNet: Amount of electronic charge carried by Inet
Performance of qNet on 12 CiPA Training Compounds

- **Red**: CiPA TdP High Risk
- **Blue**: CiPA TdP Intermediate Risk
- **Green**: CiPA TdP Low/No Risk

🌟: EAD induced

**qNet**: Net amount of electronic charges passing through the membrane carried by selected currents

Simulation with 2000 ms cycle length

- **Drug separation is good along all concentrations from 1x to 25x Cmax**
Comparison of the New Metric(s) with All Other Tested Markers

- qNet is the only metric with 0 training error across all concentrations.
- Metrics based on action potential duration (APD), the cellular basis for QT interval, failed to classify all training drugs.
qNet vs APD: A Case Study

Q: Which cell is in a more dangerous status (closer to EAD generation)?
- APD: The cell with ranolazine (black)
- qNet: The cell with cisapride (grey)

- Applying the same pro-EAD “push”
- Added 91.6% IKr conductance reduction

- qNet, but not APD, correctly predicts the distance from EAD
- qNet, but not APD, independently supports the rank order of the two drugs in CiPA categories
What About Experimental Uncertainty?

• Experimental data have intrinsic (i.e. inherent randomness) and extrinsic (i.e. cell-to-cell variability) uncertainty.
• This will lead to uncertainty in metric calculation and TdP risk assessment.
• Thus each drug at a specific concentration should have a range of possible metric values.
A method was developed to translate experimental uncertainty (i.e. variability of IC50s) to uncertainty in metric calculation.

Each drug has a distribution of possible metric (change of qNet) values due to experimental uncertainty.

The distribution peaks (most probable metric values for each drug) are completely separated for the three categories.
Summary of In Silico Work

- The consensus cardiac model (ORd) is further enhanced with temperature-dependent dynamic drug-hERG interaction, and optimized model parameters based on human cardiomyocyte data
- A promising metric identified using training drugs; its performance to be assessed using independent validation drugs
- Method to incorporate experimental uncertainty established; Method to capture inter-subject variability also being considered
- The experimental quality criteria, data format standard, and efficient route for sponsor data submission are being developed in collaboration with industry collaborators.
Outline of the Talk

• A brief description of the regulatory issue, the mechanistic background, and the current international guideline
• Overall picture of CiPA, and a brief introduction of the goals and progresses of the four components
• Detailed explanation of the In Silico work and current TdP risk assessment metric
• Expected outcomes of CiPA as a new regulatory paradigm
CiPA Summary

• CiPA is a fit-for-purpose assay
• Will utilize an in silico mechanistic model to serve as the prediction of proarrhythmic risk of a drug in comparison to known clinical comparators
• An additional preclinical check with iPSC-cardiomyocytes to ensure that drug effects on repolarization are not missed
• ECGs will still be assessed in Phase 1 clinical studies with exposure-response modeling
CiPA Expected Outcomes

• Standardized, nonclinical mechanistic-based studies to determine proarrhythmic risk that can be applied early in drug development to aid in compound selection

• Proarrhythmic risk calibrated against consensus clinical comparators ranked according to clinical experience

• Compounds with hERG block/QTc prolongation that might be dropped from development under current paradigm could have a clearer path to advance if they are shown to not be proarrhythmic

• QTc prolonging drugs on the market that are not proarrhythmic could have labeling updated to reflect this

• Model for comprehensive, model-informed, mechanistic-based approaches to be applied to other drug safety areas
2017 FDA Advisory Committee Meeting

• On March 15th 2017, FDA held a Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting on the topic of “Model Informed Drug Development”, where CiPA was presented as a potential new regulatory paradigm to seek external expert opinions

• The Committee was asked to vote on three questions:
  1. For a QT prolonging drug, does the committee think that this mechanistic, model-based approach will be fit for determining whether ECGs need to be collected in Phase 3, and informing proarrhythmic risk language in drug labeling?
  2. Does the committee agree with the proposed approach for validating the new paradigm that involves assessing 28 drugs classified into low, intermediate and high risk by an expert panel?
  3. As this new mechanistic, model-based approach is implemented, should FDA collect the world’s experience (i.e. digital waveform data from in vitro experiments) to facilitate future enhancements as was done by the FDA with the ECG warehouse for QT studies?

• The Committee voted in favor of all these three questions
CiPA Progress from the Steering Committee

- CiPA teams have presented multiple times to the ICH S7B/E14 Discussion Group the rationale and approach being taken in the CiPA project.

- CiPA Steering Committee is optimistic that this interaction will speed acceptance of this alternative pathway for assessment of proarrhythmic potential for regulatory purposes.

- After the planned implementation, we are interested in carefully evaluating approved drugs that show evidence of being QTc prolongers without TdP risk, with the expectation that application of CiPA will result in drugs having their current labeling changed to more benign language if appropriate.

Acknowledgements

CiPA Steering Committee
Ayako Takei, Bernard Fermini, Colette Strnadova, David Strauss, Derek Leishman, Gary Gintant, Jean-Pierre Valentin, Jennifer Pierson, Kaori Shinagawa, Krishna Prasad, Kyle Kolaja, Natalia Trayanova, Norman Stockbridge, Philip Sager, Tom Colatsky, Yuko Sekino, Zhihua Li, Gary Mirams

All CiPA Working groups
• Ion Channel working group
• In silico working group
• Cardiomyocyte working group
• Phase 1 ECG working group

ALL contributors to CiPA (there are a lot!)
• Public-private partnerships: HESI, SPS, CSRC
• Regulatory Agencies: FDA, EMA, PMDA/NIHS, Health Canada
• Many pharmaceutical, CRO, and laboratory device companies
• Academic collaborators

FDA Contributors
• Norman Stockbridge
• Christine Garnett
• John Koerner

In silico / ion channel
• Zhihua Li
• Wendy Wu
• Sara Dutta
• Phu Tran
• Jiangsong Sheng
• Kelly Chang
• Kylie Beattie
• Min Wu
• Richard Gray

Cardiomyocyte
• Ksenia Blinova
• Derek Schocken
• Li Pang

Phase 1 ECG biomarker
• Jose Vicente
• Lars Johannesen
• Meisam Hosseini
• Alexander Wong
• Dustin McAfee
• Robbert Zusterzeel
• Krystal Lansdowne