Overview of the ICH E14 Guideline and its Implementation within FDA

Christine Garnett, Pharm.D.
Division of Cardiovascular and Renal Products, U.S. FDA

Pharmaceutical Science and Clinical Pharmacology Advisory Committee
March 15, 2017
CiPA Presentations

12:10 p.m. **Presentation #1**  
Overview of the ICH E14 Guideline and its Implementation within FDA  
Christine Garnett, PharmD  
Clinical Analyst and QT Lead  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I, Office of New Drugs, CDER, FDA

12:30 p.m. **Presentation #2**  
Goals of CiPA: the Comprehensive In Vitro Proarrhythmia Assay  
Gary Gintant, PhD  
Senior Research Fellow  
Department of Integrative Pharmacology  
Abbvie

12:50 p.m. **Presentation #3**  
Background and Rationale for Mechanistic Cardiac Electrophysiology Models  
Gary Mirams, PhD  
Sir Henry Dale Fellow  
Centre for Mathematical Medicine and Biology  
University of Nottingham, United Kingdom

1:05 p.m. **Presentation #4**  
CiPA In Silico Modeling Development Strategy and Results  
Zhihua Li, PhD  
Staff Fellow  
Division of Applied Regulatory Science  
OCP, OTS, CDER, FDA

1:20 p.m. **Presentation #5**  
Phase 1 ECG Analysis under CiPA, Integration of All CiPA Components, and Potential Implementation Strategy  
David Strauss, MD, PhD  
Division Director  
Division of Applied Regulatory Science  
OCP, OTS, CDER, FDA
# Drugs Withdrawn from Market Due to QTc Prolongation or Torsade de Pointes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
Regulatory Guidelines

• ICH S7B: The nonclinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals

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

ICH E14 Guideline

• Design, conduct, analysis and interpretation of clinical studies to assess a drug’s ability to delay cardiac repolarization

• Thorough QT study – Randomized, placebo- and positive-controlled study in healthy volunteers to evaluate QT/QTc interval at supratherapeutic dose levels
ICH E14 Regulatory Threshold

ΔΔQTc (ms)

10 ms

5 ms

"Positive Study"

Mean and one-sided 95% CI

ΔΔQTc, change from baseline QTc placebo corrected; CI, confidence interval; ms, milliseconds
Concentration-QTc Analysis Pivotal for TQT Study Results

<table>
<thead>
<tr>
<th>Condition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic dose</td>
<td>4 (UCL=8) ms</td>
</tr>
<tr>
<td>Supra-therapeutic dose</td>
<td>15 (UCL=18) ms</td>
</tr>
</tbody>
</table>


\( \Delta \Delta \text{QTc} \), change from baseline QTc placebo corrected; \( C_{\text{max}} \), maximum concentration; DDI, drug-drug interaction; SS, steady state; UCL, upper one-sided 95% confidence limit.
Evolution of Concentration-QTc Analysis as the Primary Analysis

ICH E14: C-QTc use is “under active investigation”

FDA publication on role of C-QTc in regulatory decision-making

ICH E14 (R2): Role of C-QTc analysis

ICH E14 (R3): Use of C-QTc analysis as primary analysis

2005

FDA IRT: C-QTc analysis conducted for all TQT studies

2006

2008

FDA agreement of the design of IQ/CSRC Study and impact of positive results

2012

2014

Results of the IQ/CSRC Study to evaluate C-QTc in Phase 1 study

2015
QTc Evaluation in Drug Development

- In vitro and in vivo assays per ICH S7b
- High quality ECGs in SAD/MAD studies
- TQT study
- ECG monitoring in patients for QT prolonging drugs
- Labeling and risk mitigation strategies for QT prolonging drugs

ECG, electrocardiogram; SAD/MAD, single/multiple ascending dose study; TQT, thorough QT

Replace TQT with Phase 1 Study
Phase 3 Monitoring Considerations For QTc Prolonging Drugs

Mean $\Delta\Delta$QTc at Therapeutic Exposures

- **<10 ms**
  - If large exposure margin, routine ECGs

- **10-20 ms**
  - Targeted ECG monitoring in specific populations

- **>20 ms**
  - Intensive ECGs + Risk Mitigation Strategies

*Intensity of ECG monitoring depend PK characteristics, patient characteristics, and AEs that increase proarrhythmic risk*
QTc Prolongation and Concern for Torsade de Pointes Risk

Regulatory decisions based on benefit-risk of drug

- Low Concern
  \(\Delta\Delta QTc < 10\ ms\)

- Increasing Concern
  \(\Delta\Delta QTc 10–20\ ms\)
  +QTc Outliers
  ±Clinical AEs

- Definite Concern
  \(\Delta\Delta QTc > 20\ ms\)
  +QTc Outliers
  ±Clinical AEs

QTc Outliers: individual-level QTc >500ms and/or \(\Delta QTc > 60\)ms
Clinical AEs: TdP, sudden death, ventricular tachycardia, ventricular fibrillation or flutter, syncope, seizure

\(\Delta\Delta QTc\), change from baseline QTc placebo corrected; AE, adverse event; TdP, torsade de pointes
# Communicating Risk: Product Label

**Caprelsa (vadetanib)**

\[\Delta\Delta QTc \geq 20\text{ ms plus TdP and sudden death in clinical trials}\]

<table>
<thead>
<tr>
<th>Label</th>
<th>Risk Mitigation (REMS program)</th>
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<tr>
<td>- Box Warning</td>
<td>- Do not use in high risk patients</td>
</tr>
<tr>
<td>- Contraindications</td>
<td>- Monitor ECGs and serum electrolytes</td>
</tr>
<tr>
<td>- Warnings &amp; Precautions</td>
<td>- Avoid use with other QT meds</td>
</tr>
<tr>
<td>- Adverse Reactions</td>
<td>- Dose reductions in specific populations</td>
</tr>
<tr>
<td>- Drugs Interactions</td>
<td>- Treatment discontinuation criteria</td>
</tr>
<tr>
<td>- Overdosage</td>
<td>- Restricted distribution program</td>
</tr>
<tr>
<td>- Pharmacodynamics</td>
<td></td>
</tr>
<tr>
<td>- Patient Counseling</td>
<td></td>
</tr>
</tbody>
</table>

\[\Delta\Delta QTc,\ \text{change from baseline QTc placebo corrected; REMS, Risk Evaluation and Mitigation Strategies; TdP, torsade de pointes}\]
Communicating Risk: Product Label

Invega (paliperidone)
ΔΔQTc: 10–19 ms
No clinical AEs

- Warnings & Precautions
- Adverse Reactions
- Overdosage

Xenazine (tetrabenazine)
ΔΔQTc: 5–10 ms
No clinical AEs

- Warnings & Precautions
- Drug Interactions
- Pharmacodynamics

ΔΔQTc, change from baseline QTc placebo corrected
QT Interdisciplinary Review Team

- Provides expert review advice to sponsors and review divisions on TQT studies
- Monitors the FDA ECG Warehouse
- Contributes to the evolution of the science
FDA Model for QTc Assessment

- Identify Need
- Identify Resource
- Develop Science
- Manage Technology
- Share

- TQT Study Design and Analysis
- QT Interdisciplinary Review Team
- Working Groups, Research Consortiums
- Meetings, Publications
- Standards, Databases, Templates, Tools
Summary

• All new drugs undergo clinical evaluation to assess the effects on QTc interval
  – TQT study, or dose-ranging Phase 1 study with concentration-QTc analysis

• Magnitude of QT prolongation at therapeutic exposures will influence the intensity of ECG monitoring in late-phase trials

• Labeling of drugs that prolong QTc interval is based on concern for TdP—extent of QTc prolongation, presence of clinical AEs and factors that modify the risk of TdP

• Centralized team implementing ICH E14 has facilitated and managed innovation and organizational learning
ICH E14 is Working—No Increase in Number of Torsade Events with Approval of New Drugs

Need for Better Understanding of Proarrhythmic Potential of Drugs

- 8 drugs with Known TdP Risk**
- 22 Labeled with Warning and Precautions
- 39 drugs approved with positive TQT study

*Excludes oncology drugs because these products do not have TQT studies
**https://crediblemeds.org. All 8 drugs were approved prior to implementation of ICH E14 guideline.
TdP, torsade de pointes; TQT, thorough QT
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CiPA In Silico Modeling Development Strategy and Results

Zhihua Li, Ph.D.

Division of Applied Regulatory Science
Office of Clinical Pharmacology, Office of Translational Sciences, U.S. FDA

Pharmaceutical Science and Clinical Pharmacology Advisory Committee
March 15, 2017
CiPA \textit{in silico} Model Development Strategy

- **Model selection**: O’Hara-Rudy (ORd) human ventricular cardiomyocyte model was chosen as the consensus base model for CiPA.

- **Model calibration (training)/validation**: A set of 12 \textit{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 \textit{independent} validation.

- **Goal**: identify a \textit{mechanistic} metric that’s related to early after depolarization (EAD, the cellular basis for TdP), rather than action potential prolongation (APD, cellular basis for QT prolongation).
## 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>Methadone</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>
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</tbody>
</table>

Clinical Translational Working Group
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.
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 allows drug to be trapped within closed channel (red arrows), a feature important for many high TdP risk drugs.

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 preparation)
Experimental data were taken from O’Hara et al. PloS Computational Biology. 2011
Key Mechanism of TdP: Imbalance of Inward and Outward Currents

Major currents modulating plateau duration

<table>
<thead>
<tr>
<th>Inward</th>
<th>Outward</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICaL (L type calcium)</td>
<td>IKr (potassium)</td>
</tr>
<tr>
<td>INaL (late sodium)</td>
<td>IKs (potassium)</td>
</tr>
<tr>
<td></td>
<td>IK1 (potassium)</td>
</tr>
<tr>
<td></td>
<td>Ito (potassium)</td>
</tr>
</tbody>
</table>

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

\[ \text{Inet} = ICaL + INaL + IKr + IKs + IK1 + Ito \]
Performance of qlnet on 12 CiPA Training Compounds

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

★: EAD induced

**Change of qlnet**: % change of integral of Inet between drug and control

All drugs are separated into three categories along all concentrations from 1x to 25x Cmax

Simulation with 2000 ms cycle length

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

★: EAD induced

**Change of qlnet**: % change of integral of Inet between drug and control

Simulation with 2000 ms cycle length

- **All drugs are separated into three categories along all concentrations from 1x to 25x Cmax**
Another Candidate Metric: Change of $q_{\text{Inward}}$

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

$\star$: EAD induced

**Change of $q_{\text{Inward}}$:**
% change of integral of inward currents (late sodium and L type calcium) currents

- Quinidine
- Bepridil
- Dofetilide
- Sotalol
- Cisapride
- Ondansetron
- Chlorpromazine
- Terfenadine
- Verapamil
- Ranolazine
- Diltiazem
- Mexiletine

- All drugs are separated into three categories at high concentrations.
- Due to the interaction between inward and outward currents, the change of inward currents carries the information of outward currents too and reflects the shifted balance between inward and outward currents.


Simulation with 2000 ms cycle length
Comparison of the Best Two Metrics with All Other Tested Markers

- Change of qInward and qInet are the only two metrics achieving 0 training error
- Metrics based on action potential duration (APD), the cellular basis for QT interval, failed to classify all training drugs
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 Inet) values due to experimental uncertainty.

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

• The consensus cardiac model (ORd) is further enhanced with temperature-dependent dynamic drug-hERG interaction, and optimized model parameters based on human cardiomyocyte data
• Two promising metrics identified using training drugs; their 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.
Acknowledgements

**FDA In Silico Working Group Members**
David Strauss  
Sara Dutta  
Kelly Chang  
Kylie Beattie  
Thembi Mdluli (now Perdue)  
Wendy Wu (patch clamp)  
Phu Tran (patch clamp)  
Jiansong Sheng (patch clamp)

**ICWG / Rapid Response Team**
Bernard Fermini (Pfizer)  
Najah Abi-Gerges (AnaBios)  
Adam Hill (Victor Chang CRI)  
Jamie Vandenberq (Victor Chang CRI)  
Jules Hancox (Bristol)  
William Crumb (Zenas)

**FDA Research Colleagues**
Norman Stockbridge  
Rick Gray  
Pras Pathmanathan  
Ksenia Blinova  
Jose Vicente  
Lars Johannesen  
Maria Iacono

**External Research Colleagues**
Alfonso Bueno (Oxford)  
Gary Mirams (U Nottingham)  
Blanca Rodriguez (Oxford)  
Tom O’Hara (LLNL)  
Thomas Colatsky
The Next Presentation

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David Strauss, MD, PhD
Director, 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

Pharmaceutical Science and Clinical Pharmacology Advisory Committee
March 15, 2017
Comprehensive *in vitro* Proarrhythmia Assay: Four Components

1. **High Throughput Assessment of Effects on Multiple Ionic Currents**
   - $I_{Na}$, $I_{NaL}$, $I_{Ca,L}$, $I_{to1}$, $I_{Kr}$, $I_{Ks}$, $I_{K1}$
   - 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**
   - Image of cardiomyocytes

4. **Evaluation of Unanticipated Effects in Clinical Phase 1 Studies**
   - ECG data

**Goal:** Use human phase 1 ECG data to determine if there are unexpected ion channel effects compared to preclinical ion channel data
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
Analysis of 34 Clinical Thorough QT (TQT) Studies

• Analysis of 500,000 digital ECGs from 34 TQT studies with comparison to nonclinical ion channel data

• Identified an ECG biomarker (J-Tpeak) that could differentiate drugs that selectively block hERG (torsade risk) from drugs that block hERG + late sodium or calcium currents (low torsade risk)
ECG Biomarkers to Differentiate Multichannel Block

Prospective Clinical Trials

Differentiating Drug-Induced Multichannel Block on the Electrocardiogram: Randomized Study of Dofetilide, Quinidine, Ranolazine, and Verapamil

L Johannesen\textsuperscript{1,2}, J Vicente\textsuperscript{1,3}, JW Mason\textsuperscript{4}, C Sanabria\textsuperscript{4}, K Waite-Labott\textsuperscript{4}, M Hong\textsuperscript{5}, P Guo\textsuperscript{5}, J Lin\textsuperscript{5}, JS Sørensen\textsuperscript{6}, L Galeotti\textsuperscript{1}, J Florian\textsuperscript{6}, M Ugander\textsuperscript{1,2}, N Stockbridge\textsuperscript{7} and DG Strauss\textsuperscript{1,2}


Late Sodium Current Block for Drug-Induced Long QT Syndrome: Results From a Prospective Clinical Trial

L Johannesen\textsuperscript{1,2}, J Vicente\textsuperscript{1,3,4}, JW Mason\textsuperscript{5,6}, C Erato\textsuperscript{5}, C Sanabria\textsuperscript{5}, K Waite-Labott\textsuperscript{5}, M Hong\textsuperscript{7}, J Lin\textsuperscript{7}, P Guo\textsuperscript{7}, A Mutlib\textsuperscript{7}, J Wang\textsuperscript{7}, WJ Crumb\textsuperscript{8}, K Blinova\textsuperscript{1}, D Chan\textsuperscript{1}, J Stohlman\textsuperscript{1}, J Florian\textsuperscript{3}, M Ugander\textsuperscript{1,2}, N Stockbridge\textsuperscript{3} and DG Strauss\textsuperscript{1,2}

Both dofetilide (selective hERG block) and ranolazine (hERG + late sodium block) prolong QTc.
- Dofetilide prolongs QTc by prolonging J-Tpeakc and Tpeak-Tend.
- Ranolazine prolongs QTc by prolonging Tpeak-Tend with no effect on J-Tpeakc.

Late Sodium Current Block Shortens J-Tpeakc, Not Tpeak-Tend

- Late sodium current block shortens J-Tpeakc.
- Late sodium current block has no effect on Tpeak-Tend.

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;
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
How Do the Components Fit Together?

1. High Throughput Assessment of Effects on Multiple Ionic Currents

2. \textit{In silico} Reconstruction of Human Ventricular Cardiomyocyte Electrophysiology

3. \textit{In vitro} Effects on Human Stem-Cell Derived Ventricular Cardiomyocytes

4. Evaluation of Unanticipated Effects in Clinical Phase 1 Studies

\begin{equation}
I_{\text{stim}} = C \frac{dV_m}{dt} + I_m
\end{equation}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{diagram.png}
\caption{Diagram showing different ionic currents.}
\label{fig:ionic-curves}
\end{figure}

modified from Hoekstra et al., 2012
Potential CiPA Assessment

Output in silico proarrhythmia risk

- Low TdP Risk Prediction
  - Low Risk (no ion channel effects)
    - iPSC-CM repolarization effects?
      - No: CiPA Low Risk
      - Yes: Discrepancy
        - QTc prolongation?
          - No: Low TdP Risk
          - Yes: Discrepancy; Investigate mechanism

- Intermediate TdP Risk Prediction
  - Low Risk (balanced ion channel effects)
    - iPSC-CM repolarization effects? (exact role pending validation data)
      - No: Low TdP Risk
      - Yes: Discrepancy; Investigate mechanism

- High TdP Risk Prediction
  - No Yes
    - CiPA Low Risk
    - Discrepancy; Integrated risk assessment; assess J-Tpeakc/Tpeak-Tend; effect due to minor potassium channel? Effect due to metabolite? Effect due to hERG trafficking, non-acute effect?

Legend
- Red = in silico / ion channel
- Green = iPSC-cardiomyocytes
- Blue = Phase 1 ECG

iPSC-CM = induced pluripotent stem cell – cardiomyocytes
TdP = torsade de pointes
CiPA Summary

• CiPA is intended to be 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
Question 1

• For a QT prolonging drug, will this mechanistic, model-based approach will be fit for the following 2 applications:
  a. Determining whether ECGs need to be collected in Phase 3?
  b. Informing proarrhythmic risk language in drug labeling?
Question 1 Background: Current Effect of QT Prolongation on Drug Development

• Currently, a positive TQT study often results in further ECG follow-up in late phase studies
  – Extent of the ECG follow up influenced by magnitude of QTc prolongation
  – If QTc prolongation is substantial, the goal of ECG monitoring is to protect patients in later trials and obtain further information on the frequency of substantial QTc prolongation to understand the potential proarrhythmic risk of the drug

• QTc prolongation at therapeutic exposures results (at a minimum) in labeling in the Warnings & Precautions and advising to avoid use with other QTc prolonging drugs or in high risk patients
Question 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?
  – If not, what else should be done?
Question 2 Background: CiPA Validation Strategy Summary

• A set of 28 compounds with well-defined electrophysiology and known clinical characteristics was identified by a team of expert clinicians, safety pharmacologists, and cardiac electrophysiologists from regulatory agencies, industry and academia.

• Compounds were categorized into high, intermediate and low risk of TdP based on published reports, analysis of the FDA adverse event reporting system (AERS) database, other data sources and expert opinion.

• The set of 28 drugs was divided into 12 drugs for CiPA training and calibration, with the remaining 16 used for CiPA validation.

• CiPA validation will include assessing the 28 CiPA compounds in ion channel/in silico and iPSC-cardiomyocyte assays.

• For the CiPA phase 1 ECG approach, analysis has included an assessment of a large number of TQT studies, two prior FDA-sponsored clinical trials including 8 drugs and a confirmatory prospective study involving 6 drugs to be completed in 2017.
Question 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?
Question 3 Background: Continuing to Improve Over Time

• As occurred with implementation of QT Interdisciplinary Review Team and digital ECG warehouse, FDA intends to
  – Expand to a Proarrhythmia Interdisciplinary Review Team
  – Collect digital waveform data from in vitro experiments to collect the world’s experience and further refine the paradigm over time

• FDA anticipates that this will inform enhanced in vitro laboratory protocols and improve the computational model over time
  – Similar to the evolution of QT studies to implement exposure-response analysis and design more efficient studies
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
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

• CiPA Steering Committee is also optimistic that the work outlined here can be completed by the end of 2017

• After 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

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• Sara Dutta
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• Jiangsong Sheng
• Kelly Chang
• Kylie Beattie
• Min Wu
• Richard Gray

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

Cardiomyocyte
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• Li Pang

Phase 1 ECG biomarker
• Jose Vicente
• Lars Johannesen
• Meisam Hosseini
• Alexander Wong
• Dustin McAfee
• Robbert Zusterzeel
• Krystal Lansdowne
Data and Algorithms Made Publicly Available

- ECG signals and clinical data from 2 FDA-sponsored clinical trials
  - **FDA Study 1** (NCT01873950) data are available at PhysioNet's PhysioBank
    https://physionet.org/physiobank/database/ecgrdvq/
    (doi:10.13026/C2HP45)

  - **FDA Study 2** (NCT02308748) data are available at PhysioNet's PhysioBank
    https://physionet.org/physiobank/database/ecgdmmld/
    (doi:10.13026/C2D016)
    - Vicente et al. *PLOS ONE* 2016. doi:10.1371/journal.pone.0163619

- Automated algorithm for J-Tpeak and Tpeak-Tend
  - **Open source code** available at: https://github.com/FDA/ecglib
CLOSING COMMENTS

• THANK YOU
  – Advisory Committee members
  – Presenters
  – Audience and participants
  – Organizers
  – ASCPT
MIDD

Value proposition for New & Generic Drug Development

• Incredible opportunities to:
  – Streamline and optimize drug development
  – Implications across the entire drug lifecycle
  – Impact on study design
  – Impact on regulatory decision making
    • Improve accuracy and efficiency
    • Make better and faster decisions
    • Decrease regulatory burden
  – Future expansion beyond PBPK & safety areas discussed today
Selfishly I want to spend more time on this area.
DRUG DEVELOPMENT

• DRUG in the context of today
  – New innovator brand name drug
  – Generic drug

• In the context of Clinical Pharmacology
  – Drug “substance”
  – Drug “product”
DRUG “PRODUCT”

- Active ingredient (drug substance)
- Microcrystalline cellulose (filler)
- Lactose monohydrate (filler)
- Povidone (binder)
- Sodium starch glycolate (disintegrant)
- Purified water (solvent)
- Kollicoat (coating polymer)
- Triethyl citrate (plasticizer)
- Talc (anti-tacking agent)
- Magnesium stearate (lubricant)
- Gelatin
DRUG LIFECYCLE

Industry concept vs. CDER concept

IND

NDA

Generic Drugs/ANDA

Postmarket
<table>
<thead>
<tr>
<th>NEW DRUGS</th>
<th>GENERIC DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• PK-PD modeling</td>
<td>• Same – core of BE assessment</td>
</tr>
<tr>
<td>• Exposure-response analysis</td>
<td>• Narrow Therapeutic Index</td>
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<tr>
<td>• Clinical trial simulation</td>
<td>• Virtual BE study</td>
</tr>
<tr>
<td>• Population PK</td>
<td>• Model-based BE assessment for drugs with sparse PK</td>
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</tbody>
</table>
PBPK UTILITIES

Predicting untested clinical situations

New Drugs
1. Drug-drug Interactions (DDI) – most experienced area
2. Dosing recommendations in labeling
3. Dose extrapolation (peds or other populations)
4. Dose determination for patients with organ dysfunction
5. Justification for prioritizing studies (“when”)
6. Supporting a particular study design (“how”)

Generic Drugs
1. Formulation strategies
2. Food effect predictions
3. BE risk assessment
4. Dissolution specifications
5. Identification of critical quality attributes for BE assessment for locally acting product
6. Regulatory standard development, e.g., product-specific guidance
Increasing trend whereby modeling & simulation, including PBPK models, are being used to support generic drug product development and regulatory decision making.

BE: bioequivalence; PPI: proton pump inhibitor; GI: gastrointestinal; DDI: drug-drug interaction
# PBPK UTILITY

**Backgrounder & Internal Documents**

<table>
<thead>
<tr>
<th>Year</th>
<th>New Drugs</th>
<th>Generic Drugs</th>
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<tbody>
<tr>
<td>2009</td>
<td>(1)</td>
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<tr>
<td>2016</td>
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<td>(14++)</td>
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</table>
VALUE & IMPACT OF GENERIC DRUGS

• ~90% of drugs dispensed in the US are generics
• Only ~27% of drug spending
• Generic drugs saved the US healthcare system $1.46 Trillion in last 10 years
SCOPE of FDA’s GENERIC DRUG PROGRAM

- ~1,000 Abbreviated New Drug Applications (ANDA’s) submitted annually
- 813 ANDAs approved CY2016
  - 630 Full Approvals; 183 Tentative Approvals
- ~10,000 currently approved ANDAs
- ~25% of all currently approved generic drugs were approved in last 4 years (since GDUFA implementation)
GDUFA II and “PRE-ANDA”

To Infinity and Beyond....

• Intended to decrease number of review cycles and increase chances for first cycle ANDA approval

• Complex products (defined in GDUFA II):
  – Complex active ingredients, complex formulations, routes of delivery or dosage forms, complex drug-device combinations, and others

• Most approved generic drugs are for oral drugs

• Translates into LOTS of opportunities for generics:
  – Dermal, inhalants, ophthalmics, nasal, transdermal
“DDRU” PARADIGM

1. A Molecular Basis for Innovation in Drug Excipients
   (Irwin, Pottel, Zou, Zuk, Sterling, Shoichet, Lionberger, and Giacomini)

2. Between-Batch Pharmacokinetic Variability Inflates Type I Error Rate in Conventional Bioequivalence Trials: A Randomized Advair Diskus Clinical Trial
   (Getz, Carroll, Mielke, Benet, Jones)

March 2017
PBPK REGULATORY SIGNIFICANCE

• Opportunity for **NEW and GENERIC** drug industries to submit more PBPK data/analyses

• Innovation and modernization of **NEW and GENERIC** drug development and regulatory review
  – Mechanism-based modeling based on knowledge of: 1) drug substance property 2) formulation characteristics 3) in-vitro release profiles 4) physiological variables

• Enhance NDA review quality and efficiency

• Enhance Pre-ANDA process for complex products

• Enhance ANDA review program
  - Improve first cycle approval rate
  - Reduce cost and time
  - Facilitate patient access to high quality, affordable generic drug products

- Opportunity for FDA to highlight appropriate submission standards
  - Submission of valid Modeling & Simulation (M&S) components can support approval and reduce regulatory uncertainty and burden
  - Critical to have the “right” submission, e.g., high quality

TRANSFORMATIVE POTENTIAL FOR GENERICS

• For generic drug development
• For generic drug regulatory decision making
  – Move beyond the oral absorption model
  – Apply to other locally acting drugs and complex drug products
• For GDUFA II

• Abundant Opportunities