The Potential Role of CiPA on Drug Discovery, Development, and Regulatory Pathways

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This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies
Drug Development

- 10,000 Compounds
- 250 Compounds
- 5 Compounds
- 1 FDA Review
- 1 Approved Drug

Comprehensive in vitro Proarrhythmia Assay (CiPA)
Problem Statement

• 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

• QT prolongation has good sensitivity for drugs that cause proarrhythmia (torsade de pointes), but its specificity is poor
Result of 2005 International Council on Harmonization (ICH) Guidelines

• Guidelines resulted in no new drugs with unrecognized torsade risk

• However, there are drugs with hERG block or QT prolongation that do not cause torsade

• Thus there has been a significant cost
  – Premature discontinuation of drugs from development due to hERG block or QT prolongation
  – Many potentially good drugs never get evaluated in humans
  – Drugs with QT prolongation require intensive ECG monitoring
  – Many drugs with FDA labels that warn about QT prolongation are unlikely to cause torsade de pointes
The Scale of the Problem

• hERG is “promiscuous”

Up to 70% of compounds block hERG*

• Many of these compounds are dropped from development – which is not always justified!

That Can Cause Problems …

Drug Development

- 10,000 Compounds
- 250 Compounds
- 5 Compounds
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Are we selecting the best compounds to move forward?
How Can We Improve?

• We have a deep mechanistic understanding of the factors that cause arrhythmias that can support a new approach

• We need to:
  • Focus on arrhythmia mechanisms
  • Evaluate drug effects on multiple cardiac ion channels
  • Integrate effects in relevant laboratory and computer models
  • Use high-throughput approaches that can be applied early in drug development so we do not lose promising new drugs
Where Can CiPA Be Implemented?

1. Drug discovery?
2. Nonclinical-regulatory?
3. Clinical-regulatory?
4. Postmarket (currently marketed drugs)?
1. Drug Discovery

**Drug Development**

Mechanistic studies early in drug development

- High-throughput patch clamp with hERG, calcium and late sodium and/or iPSC-cardiomyocyte assays
- Select better compounds to move forward from large compound libraries (large pharma)
- De-risk limited number of compounds early in development (small pharma)
Optional CiPA Application in Drug Discovery / Early Drug Development
(Each Company Can Implement However They Want)

- hERG block?
  Automated high-throughput with standardized CiPA IC50 protocol
  Consider hERG IC50 to target concentration ratio

- Low risk hERG blocker?
  Consider dynamic hERG protocol to refine Torsade Metric Score if borderline low risk

  - Yes
  - No

  - Yes
  - No

  - Select a different compound or consider risk (intermediate/high risk) vs. benefit
2. Nonclinical Regulatory and 3. Clinical Regulatory

Drug Development

Mechanistic studies early in drug development

hERG/IKr blockers and QT prolongers with low torsade risk could advance

Can CiPA Be Implemented within the ICH S7B & E14 Framework?
ICH S7B Non-Clinical Testing Strategy
CiPA in ICH S7B

• **Background** (Sec. 1.2) – plateau of action potential reflects balance between inward (e.g. L-type calcium) and outward (e.g. hERG potassium) currents

• **Follow-up Studies** (Sec. 2.3.5) – provide greater depth of understanding of risk and can be a significant component of an integrated risk assessment
  – Relevant non-clinical and clinical information
  – Including ventricular repolarization assays and inhibition of other channels not previously evaluated
Current ICH S7B Non-Clinical Testing Strategy

(with CiPA)

Non-clinical Testing Strategy

CiPA Assessment

In Vitro $I_{Kr}$ Assay

In Vivo QT Assay

IFr or QT positive?

Follow-up Studies

Integrated Risk Assessment

Evidence of Risk

Chemical/Pharmacological Class

Relevant Non-clinical and Clinical Information
Integrated Risk Assessment (ICH S7B Sec 2.3.6)

• Evaluation of non-clinical study results including the results from follow-up studies and other relevant information

• Should be scientifically based and individualized for the test substance

• Can contribute to the design of clinical investigations and interpretation of their results

• When available, should be included in the Investigator’s Brochure and the Non-clinical Overview
CiPA in ICH S7B

- **Simulated Pathological Conditions and Arrhythmias** (Sec. 3.1.4) – precise relationship between delay of ventricular repolarization and proarrhythmia is not known
  - Directly assessing proarrhythmic risk of pharmaceuticals that prolong the QT interval would be a logical undertaking
  - Interested parties are encouraged to develop these models and test their usefulness in predicting risk in humans
CiPA in ICH E14

- **Regulatory Implications, Labeling and Risk Management Strategies** (Sec. 5) – is inconclusive as to whether drugs that prolong QT by 5-20 ms are proarrhythmic.

- Factors proposed to modify the risk of QT prolongation
  - Drugs might prolong QT up to a “plateau” value, above which there is no dose-dependent increase.
  - Proarrhythmic risk might be influenced by other pharmacologic effects (e.g., other channel effects).

- The approach for ECG monitoring in late stage clinical trials is currently described in the ICH E14 Q&A (sec 7.1)
  - This could be updated to be informed by a CiPA assessment.
Current ICH E14 Q&A
(with CiPA)

QTc upper bound $\geq 10$ ms

Mean $\Delta\Delta QTc$ at Therapeutic Concentrations

- $< 10$ ms
  - If large exposure margin, routine ECGs
- 10-20 ms
  - Targeted ECG monitoring in specific populations
- $> 20$ ms
  - Intensive ECGs

Use CiPA to inform the need for ECG monitoring

Phase 3 trials

QT Study
Integrated Nonclinical Risk Assessment
Confirm No Unanticipated Effects Clinically

**IKr or QT positive?**

**Nonclinical Assessment**

- In Vitro IKr Assay
- In Vivo QT Assay
- Chemical/Pharmacological Class
- Relevant Nonclinical and Clinical Information

**Integrated Risk Assessment**

**Clinical Assessment**

- QTc upper bound >= 10 ms
- Mean ΔQTc at Therapeutic Concentrations
  - < 10 ms
  - 10-20 ms
  - >20 ms

- If large exposure margin, routine ECGs
- Targeted ECG monitoring in specific populations
- Intensive ECGs
- Intensive ECGs + Risk Mitigation Strategies
**Current ICH S7B/E14 Practice with Proposed CiPA Option**

**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

- **No**
  - E14: Clinical QTc prolongation?
    - No
      - Low Torsade de Pointes (TdP) Risk
        - Current ICH S7B/E14 Practice with Proposed CiPA Option
    - Yes
      - Current E14 recommendations for QTc prolonging drug

- **Yes**
  - CiPA integrated risk assessment as follow-up studies (see next slide for pathway)
Potential CiPA Details Integrated into S7B/E14

**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

- **No**
- **Yes**

**E14: clinical QTc prolongation?**

- **No**
- **Yes**

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

- **Yes**
- **No**

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

- **Yes**
- **No**

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

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

- **Yes**
- **No**

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

- **Perform CiPA calcium IC50, late sodium IC50 & hERG kinetic data to generate in silico Torsade Metric Score**
- **iPSC-myocyte assays and/or additional follow-up studies optional**

**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

**Low TdP risk**
(Reduces need for intensive QT monitoring in Phase 3 and informs labeling; to be discussed in subsequent presentations)

- **Yes**
- **No**

**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

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

- **Yes**
- **No**

**Current E14 recommendations for QTc prolonging drug**
(Follow-up studies may inform decision making)
Potential Questions to Address through the ICH Q&A Process

- **S7B** states that directly assessing the proarrhythmic risk of pharmaceuticals that prolong the QT interval would be a logical undertaking
  
  - **Question**: Is there now a reasonable approach to assess proarrhythmia risk for compounds that block hERG and/or prolong QT and to apply this to the Integrated Risk Assessment?

- **E14** states that it is inconclusive as to whether some QT prolonging drugs are proarrhythmic and that risk might be influenced by other pharmacologic factors (e.g., other channel effects)
  
  - **Question**: Has more data emerged to inform which drugs that prolong QT are likely to be proarrhythmic and which are not? If so, how would this affect ECG monitoring in phase 3 trials and drug labeling?
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?

Committee voted in favor of all questions

https://www.fda.gov/AdvisoryCommittees/Calendar/ucm535513.htm
Additional Opportunities

• Permit an alternative risk assessment for drugs with significant heart rate increases or other factors that confound QT assessment
  – Already recommended to multiple sponsors with drugs in development

• May be able to reduce the exposure margins in Phase 1 QT assessments

• Permit an earlier assessment in Phase 1 oncology drugs regarding the lack of a concerning proarrhythmic risk
CiPA Summary & Expected Impact

Drug Development

Mechanistic studies early in drug development

QT prolongers with low torsade risk could advance

Update drug labels for marketed drugs

Low Risk

QT
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, Yasunari Kanda, Yuko Sekino, Zhihua Li

**FDA Contributors**
- Norman Stockbridge
- Christine Garnett
- John Koerner
- Issam Zineh

**Ion channel**
- Wendy Wu
- Phu Tran
- Jiansong Sheng
- Min Wu
- Aaron Randolph

**In silico**
- Zhihua Li
- Sara Dutta
- Kelly Chang
- Kylie Beattie
- Xiaomei Han
- Bradley Ridder

**Cardiomyocyte**
- Ksenia Blinova
- Derek Schocken
- Li Pang

**Phase 1 ECG biomarker**
- Jose Vicente
- Lars Johannesen
- Meisam Hosseini
- Robbert Zusterzeel
- Murali Matta
- Roberto Ochoa-Jimenez

**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!)**
- HESI, SPS, CSRC
- FDA, EMA, PMDA, NIHS, Health Canada
- Many pharmaceutical and laboratory device companies
- Academic collaborators
What’s Coming!

• In Silico Modeling and Ion Channel Approaches
  – In Silico modeling- state of the art
  – Summary of In Silico model approach and validation study; In Silico Results
  – Ion Channel Assays and Data – lessons learned and data quality criteria

• iPS-Cardiomyocytes and Phase 1 ECG
  – iPS Cells: Summary of approach, Detailed results and implications
  – New ECG biomarkers and their potential role in CiPA; Results and implications
  – Implementation of ECG biomarkers

• Regulatory Evaluation and Potential Implementation
  – Data summary overview
  – How CiPA might impact pre-clinical safety testing and S7B
  – How CiPA might be implemented in clinical development and regulatory decision making
  – Regulatory considerations and next steps