Beyond QT—
The Comprehensive in Vitro Proarrhythmia Assay

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ICH E14/ S7B: Current FDA Policy

**INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE**

**ICH Harmonised Tripartite Guideline**

**The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarhythmic Drugs**

E14

Current Step 4 version dated 12 May 2005

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**The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals**

S7B

Current Step 4 version dated 12 May 2005
Success of E14/S7B

• No QT-related withdrawals
• Reduction in post-marketing reports of TdP for non-anti-arrhythmic drugs
• Continued to approve some drugs with QT liability where benefits clearly outweigh apparent risks
False positives

- TQT assay limitations
- Small effects from blocking minor outward currents (not hERG)
- Real hERG blockers, but still not proarrhythmic
Cost

- $B in TQT studies (OK)
- Cautionary labeling when QT effect not from hERG (not good)
- Perversion of lead candidate selection (really bad)
  - Some true hERG blockers are not proarrhythmic
  - Selection against hERG forces other compromises
We can do better...

• TdP class of arrhythmias
  – Susceptibility in the form of derangement of the balance of inward and outward currents during repolarization
    • Very well understood
    • We know how to assay for this USING HUMAN CHANNELS, how to reconstruct the action potential, and how to probe for vulnerability during repolarization
  – Regional heterogeneity in electrical state across the ventricle
    • Role is well understood
    • Rare conditions (why you go hours to decades in susceptible state)
...and some firms already are

- AbbVie
- Astra-Zeneca
- GSK
- Lilly
- Others?
The assay

• Characterization of drug effects on human ion channels
• Reconstruction of the action potential from the summed effects of the drug
• Comparison of modeled effects with responses of cultured stem-cell-derived human cardiac myocytes
Cardiac action potential

- Human channels
- Cells overexpressing single channel types
- Amenable to high-throughput electrophysiology

Hoekstra et al., 2012
O’Hara-Rudy model

- Suffices to model single cell (not heart!)
- Exact proarrhythmia metric is under debate
- …but is likely to involve proximity to having EADs

T.J. O’Hara, L. Virág, A. Varró, Y. Rudy,
“Simulation of the undiseased human cardiac ventricular action potential: Model formulation and experimental validation”
doi:10.1371/journal.pcbi.1002061
Ion channel effects

A

- depolarizing current
- repolarizing current

0 1 2 3 4

100 ms

potential (mV)

I_{Na}

I_{Ca,L}

I_{Ca,T}

I_{to1}

I_{Cl(Ca)}

I_{Kur}

I_{Kr}

I_{Ks}

I_{K1}

I_f

I_{NCX}

B

potential (mV)

EAD

I_{Ca,L}

C

potential (mV)

DAD

I_{NCX}
MEA recordings from myocytes
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