



# Benefits and Limitations Overview

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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-  
ANTIARRHYTHMIC DRUGS**

**E14**

Current *Step 4* version  
dated 12 May 2005

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

ICH HARMONISED TRIPARTITE GUIDELINE

**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

# 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?

# Call to action

- Engineering specifications for the assay
- Pilot use
  - To set power calculations
  - To calibrate metric with a set of “known”s
- Goals
  - Abandon E14 by July 2015
  - Revise S7B by July 2016

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