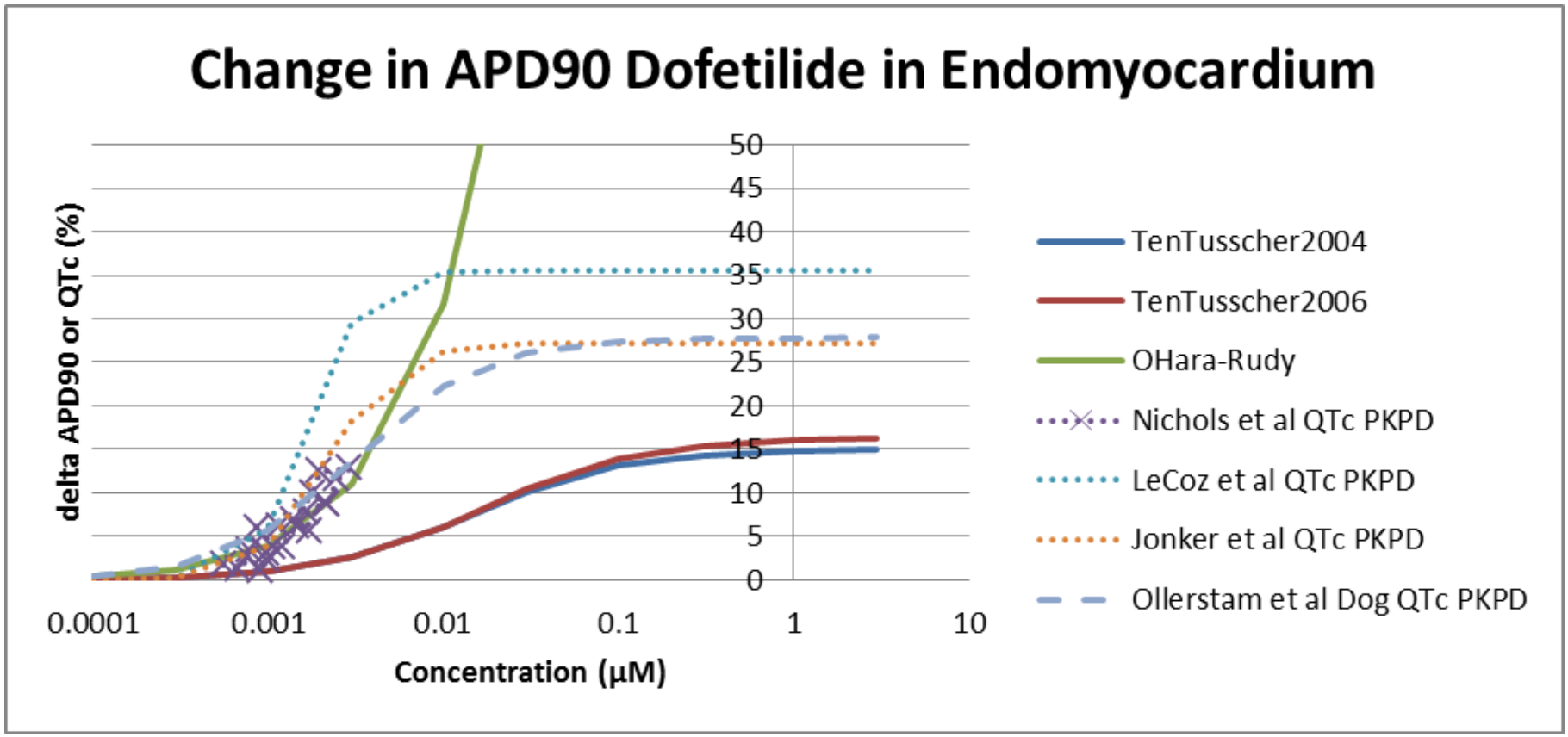
# CIPA Implementation in Large Pharma

- The problem CIPA will address?
  - Mixed channel block reducing TdP Potential?
  - **Which hERG potency value?**
  - **Indirect effect on QTc?**
  - Latter two are principal issues routinely faced
- Potency question may be addressed by patch-clamp protocol changes and *in silico* modeling
  - Modest changes to existing screening paradigm
- Indirect effect may be resolved by examining ECG morphology
  - Implications for implementation unclear at present
  - Data collection likely already appropriate

# Which *In Silico* Model Fits Best?



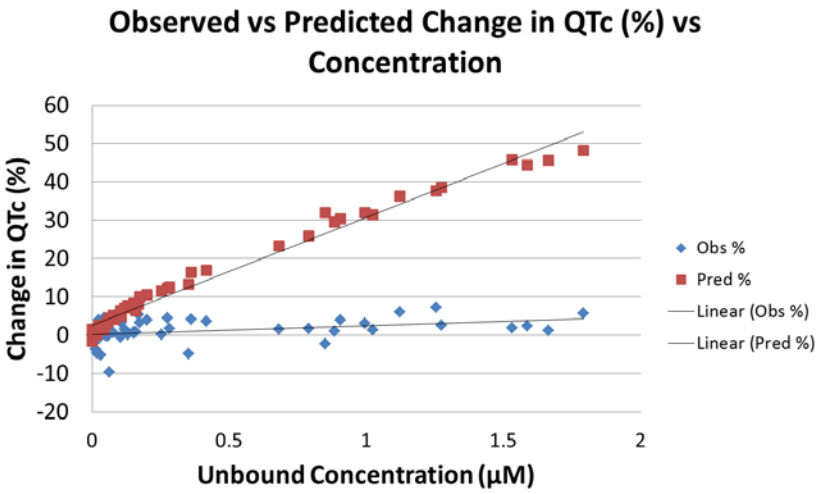

- Chose to examine dofetilide as a well characterized molecule
- Used patch-clamp $IC_{50}$ from Jonker et al 2005 – equivalent to value for dofetilide-binding
- 3 *in silico* APD models were compared Ten Tusscher 2004 & 2006, and O'Hara-Rudy
- 3 Human QTc PKPD models were used for comparison
- 1 Dog QTc PKPD model was used for comparison

# Simulated Human QTc Change Compound-X

**Simulation using hERG patch-clamp $IC_{50}$**

**1.1µM Potency**

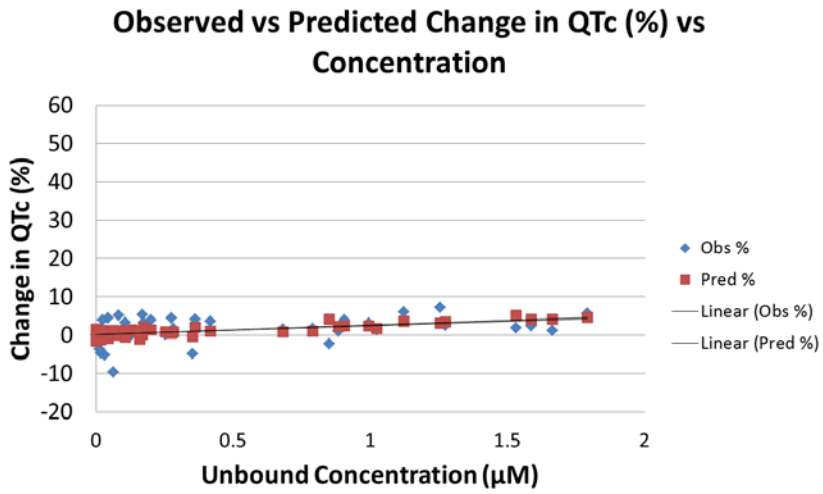
**Slope of simulated QTc Change vs Concentration 10-fold greater than observed**




**Simulation using Astemizole-binding $IC_{50}$**

**15.7µM Potency**

**Slope of simulated QTc Change vs Concentration matches that of observed**




Model used was O'Hara-Rudy Model. Modeling suggests Astemizole-binding is the potency value most representative of QTc change. This supports the empirical observation based on examining *in vivo* QTc and in silico modeling of *in vivo* data.