

# **Cardiac Safety Biomarkers: Lesson Learned and Challenges Ahead for QT, Troponins and Other Potential Biomarkers**

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# QT as a Safety Biomarker: Strengths and Weaknesses

	Strengths	Weakness
Biology	Knowledge of molecular mechanisms, ion channels, cellular models, in vivo models	Weak links between experimental models and clinical events,
Clinical experience/relevance	Genetic syndromes (LQT), documented clinical events	Rare clinical events, multifactorial etiologies, unpredictable
Measurable biomarker	Old technology, universally available	low freq/low amplitude signal, poor signal-noise, numerous methods of measurement, measured in static condition,
Multisector involvement	Interest from academia, clinical medicine, industry (technology, diagnostics, pharma), regulatory bodies	Insufficient data available to close gap between signal and rare events, lack of harmonization

# Effect of Regulatory Guidance on Decision Making in Drug Development

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- n Industry expressed concern based on a fear that very small signals in QTc would be identified in compounds where there was no theoretical risk and no preclinical evidence of QTc prolongation
- n The initial lack of understanding of what it means when a compound has a 5-10 ms increase in QTc generated considerable uncertainty in drug development
- n This uncertainty motivated some pharmaceutical and biotech companies to avoid developing compounds with any potential for this liability

# Effect of Regulatory Guidance on Decision Making in Drug Development

- n What was the clinical significance of such a small increase in QT<sub>c</sub>?
- n What additional studies would be necessary in later phases of drug development to further clarify the clinical significance of an increase in QT<sub>c</sub> of this magnitude?
- n How will do these additional studies affect the timelines and cost of drug development?
- n What is the likelihood that this additional data would be able to offset the perceived risk associated with the small but clearly documented increase in QT<sub>c</sub> from a TQT study?
- n How should a company weigh this potential increase in risk against the potential benefits of a drug?
- n How would these issues be described in the label?

# Effect of Regulatory Guidance on Physician Decision Making

- n How do physicians utilize the information in the product label?
- n How successful are physicians in measuring the QTc interval when instructed to do so in the label?
- n How do physicians make risk/benefit decision for an individual patient?
- n Are physicians avoiding potentially beneficial medications because of a fear of a small increase in QTc?
- n How do physicians respond to the observation of an increase in QTc interval?
- n What is the impact of including new warnings in the labels of drugs that have been used for a long period of time (e.g., methadone)

# How Can the CSRC Address Some of These Current Problems

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- n Enhance communication/education by promoting a dialogue between academics, pharma and regulatory – establish common ground and environment where difficult issues can be discussed outside of formal regulatory channels
- n Provide a meaningful dataset that will allow companies/scientists to enhance old measurements and develop new measurements
- n Enhance study designs and statistical assessments
- n Evaluate effect of moxi – outliers, non-responders – genomics
- n Need to develop first rate clinical epidemiology

# CSRC/HESI ANNUAL MEETING 2008

## *Integrating Pre-Clinical & Clinical Issues in Cardiac Safety: Translational Medicine Meets the Critical Path*

*October 6th-7th, 2008 in Bethesda, Maryland*

- n Educational collaboration between the Cardiac Safety Research Consortium (CSRC), the Health and Environmental Sciences Institute (HESI), and the FDA, to provide an open think tank forum integrating pre-clinical and clinical challenges of cardiac safety evaluation of new medical therapeutics.
- n Faculty experts from academia, industry and FDA will gather to discuss key topics in cardiac safety assessment from pre-clinical and clinical perspectives, with particular focus on the translational "gaps" between these two areas of expertise.

### *Plenary presentations:*

- n "Collaboration, Critical Path and Cardiac Safety: The FDA View" -- Doug Throckmorton
- n "How Can Collaborations in Cardiac Safety Efforts Best Impact the Regulatory Landscape?" – Norman Stockbridge

# CSRC Think Tank Meeting

## *Key agenda topics*

- n Organizational updates from HESI and CSRC
  - n Challenges and Solutions to Data Sharing Process: An FDA Perspective
  - n Data From the CSRC ECG Warehouse: First Proof-Of-Concept Report
- n Cardiotoxicity and troponin: Where do they fit in drug development?
- n Pre-clinical and clinical testing for QT proarrhythmia: How do they relate to one another and to risk of life-threatening arrhythmic events?
- n Pre-clinical and clinical testing for QT evaluation of non-QT proarrhythmia
- n Biologics and large molecules: How do we evaluate proarrhythmia and myotoxicity?
- n Risks & benefits developing drugs with safety signals-What are the challenges?
- n New horizons of cardiac safety programs: Do we need "thorough" blood pressure, heart rate, platelet and lipid studies?

# Catalog of Other Potential Cardiac Safety Biomarkers

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- n Blood pressure
- n Heart rate
- n Lipids
- n Troponins
- n BNP
- n CRP
- n Platelet aggregation
- n Imaging biomarkers
  - n Cardiac MR

# Troponins and Cardiotoxicity

- n Case studies
  - n Adriamycin
    - n Early toxicity associated with troponin release
    - n Potential reversibility in LV function
    - n Long term risk of developing heart failure
  - n Trastuzumab
    - n Cardiotoxicity not identified in preclinical studies
    - n Use of cardiac troponin under investigation
- n Cardiac troponins identify cardiotoxicity after the toxicity is already occurring
- n Is this the optimal paradigm for the development of safety biomarker?
- n How should cardiac troponins be used in drug development?

# Troponins and Cardiotoxicity

- n Which cardiac troponin assay should be used? When should it be measured and how should it be quantified?
- n What is the appropriate threshold to establish that the increase in cardiac troponin will be clinically significant?
- n How will that threshold be determined in the context of the potential benefits of a drug? What should be done with events that are biochemically detectable but below that threshold and therefore may be clinically insignificant?
- n How should investigators manage elevations in troponin in clinical studies?
- n Which compounds need to have a cardiac troponin evaluation preclinically?
- n Are the preclinical models sufficiently predictive? If not, which compounds warrant a cardiac troponin evaluation in clinical studies?
- n How can we define a negative cardiac troponin evaluation? Will a positive control be necessary to determine assay sensitivity? How would a positive control be used?

# Questions to Consider

- n What other safety biomarkers should be added to the catalog?
- n What paradigm should be used to validate a safety biomarker – ie how much prognostic data is sufficient to warrant using the biomarker in decision making (regulatory and within industry)?
- n How would a new measurement of ventricular repolarization get validated? What dataset would be necessary for it to displace QT?
- n What are the key steps necessary to develop a biomarker to evaluate cardiotoxicity?
  - n Would you develop doxorubicin or trastuzumab now (assuming there were no other agents with acceptable safety and efficacy) if you had the preclinical and early clinical data on cardiotoxicity and/or the human data out to 6 months?
  - n What data would you need to warrant an investment in a compound that might have cardiotoxicity in a small proportion of patients but is likely to have an overall benefit to the population?
- n What steps are necessary to make the most out of a collaboration between industry, academia, and regulatory agencies?
- n Is there even potential to develop biomarkers to pick up the drugs that cause an increase in background rates of common events (death, MI, stroke) as with coxibs, rosiglitazone, etc.