ILSI Health and Environmental Sciences Institute (HESI)

Cardiac Safety Technical Committee

A Resource for Improving Cardiovascular Safety Through Collaboration

HESI Annual Meeting
May 2010

www.hesiglobal.org
Session Overview

- Introduction *you are here*
  - Dusty Sarazan DVM, Ph.D. (DSI)
- Functional CV Safety Evaluation
  - Dusty Sarazan DVM, Ph.D. (DSI)
- Cardiac Biomarkers
  - Eric Schultze, DVM, Ph.D. (Lilly)
- ProArrhythmia Model Evaluation
  - John Koerner, Ph.D. (FDA)
# CV Issues...How Real is the Problem?

<table>
<thead>
<tr>
<th>Phase</th>
<th>Nonclinical</th>
<th>Phase I</th>
<th>Phase 1-III</th>
<th>Phase III/Marketing</th>
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<th>Marketing</th>
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<tbody>
<tr>
<td>Information</td>
<td>Causes of attrition</td>
<td>Serious ADRs</td>
<td>Causes of attrition</td>
<td>ADRs on label</td>
<td>Serious ADRs</td>
<td>Withdrawal from sale</td>
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<td>Sample size</td>
<td>88 CDs stopped</td>
<td>1,015 subjects</td>
<td>82 CDs stopped</td>
<td>1,138 drugs</td>
<td>21,298 patients</td>
<td>47 drugs</td>
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<td>9%</td>
<td>21%</td>
<td>36%</td>
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<td>45%</td>
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<td>7%</td>
<td>21%</td>
<td>13%</td>
<td>0%</td>
<td>32%</td>
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<tr>
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<td>2%</td>
<td>4%</td>
<td>16%</td>
<td>10%</td>
<td>9%</td>
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<td>Nervous system</td>
<td>14%</td>
<td>28%</td>
<td>21%</td>
<td>67%</td>
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<tr>
<td>Immunotox; photosensitivity</td>
<td>7%</td>
<td>16%</td>
<td>11%</td>
<td>25%</td>
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<tr>
<td>Gastrointestinal</td>
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<td>23%</td>
<td>5%</td>
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<tr>
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<td>28%</td>
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<td>0%</td>
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<tr>
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<td>0%</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
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Source: Redfern WS et al. SOT 2010 Poster 1081 Tue 1 pm
Cardiac Safety Committee

Mission

• To develop and disseminate improved data, approaches, and resources for the evaluation of preclinical and clinical cardiovascular toxicity.

• Bring preclinical scientists and clinicians together to address issues of contemporary concern relative to clinical cardiovascular safety.
Quick History

- **July 2008**
  - Committee formation approved by HESI Board of Trustees

- **January 2009**
  - Committee officially initiated – integrates pre-existing ProArrhythmia Models Project Committee and Cardiac Biomarkers Working Group
  - First Committee meeting held

- **June 2009**
  - Committee organized workshop (June 2–4, 2009) on Structural and Functional Approaches to Cardiovascular Safety Evaluation held in Washington, DC

- **July 2009**
  - New working groups on Functional & Predictive Cardiovascular Safety Evaluation formulated as follow-up to workshop.

- **August 2009 – Present**
  - Committee provides structure and oversight of:
    - Proarrhythmia Models Working Group
    - Cardiac Biomarkers Working Group
    - Predictive Cardiovascular Safety Working Group
    - Functional Cardiovascular Safety Working Group
Advisory Team

Advisory Team of Senior Scientists Established to Provide Input on Overall Program Direction and Impacts

- Dr. Norman Stockbridge, US FDA (Dir. FDA CardioRenal)
- Dr. Jan Regnstroem, European Medicines Agency (clinician)
- Dr. Eugene Herman, US FDA
- Dr. Eric Schultze, Lilly
- Dr. Jean-Pierre Valentin, AstraZeneca
- Dr. Kendall Wallace, U. of Minnesota
- Dr. Brian Berridge, GlaxoSmithKline
- Dr. Dusty Sarazan, Data Sciences International
- Dr. John Koerner, FDA

Staff: Syril D. Pettit, MEM, HESI Associate Director
AN ACTIVE 16 MONTHS FOR ALL WORK GROUPS
A translational approach to detecting drug-induced cardiac injury with cardiac troponins: Consensus and recommendations from the Cardiac Troponin Biomarker Working Group of the Health and Environmental Sciences Institute

Brach Borgida, DM, PhD,a,b,c,d,e,f,g,h,i,j, Shengzhe Li, MD, PhD,a,b,c,d,e,f,g,h,i,j, Mary Metheny, MD, PhD,a,b,c,d,e,f,g,h,i,j, Benjamin Leber, MD, PhD,a,b,c,d,e,f,g,h,i,j, Andrew Davies, MD, PhD,a,b,c,d,e,f,g,h,i,j, and John-Pierre Valentinides6

Cardiac troponins (cTn) are established biomarkers of ischemic heart disease in humans. However, their value as biomarkers of cardiac injury from causes other than ischemic heart disease is now being explored, particularly in drug development. This is a workshop sponsored by the Cardiac Troponin Biomarker Working Group of the Health and Environmental Sciences Institute, preclinical, clinical, and regulatory scientists interested in the application of cTn in their respective environments, either in the translational application of cTn in clinical trials, and gaps in our understanding of cTn biology and pharmacology. Evidence indicates that cTn are sensitive and specific biomarkers of cardiac injury from several causes in both animals and humans. An effort is underway to establish cTn as routine monitoring in clinical practice. This consensus is an attempt to achieve consensus and to identify gaps in our understanding of cTn biology and pharmacology.

Original article
A call for more integrated cardiovascular safety assessment
S.H. Peter, R. Bridget, B.D. Susan

Cardiovascular safety concerns are a significant component of many drug development programs and are an area of ongoing concern for both pharmaceutical and device companies. The recent increases in patient safety concerns due to cardiovascular incidents, such as those reported in the literature, have caused an increase in the number of cardiovascular safety assessments. The use of integrated cardiovascular safety assessments is a critical component of the development of cardiovascular drugs that will be used for long-term treatment. The challenges in developing cardiovascular safety assessments are complex and require a multidisciplinary approach.

Current challenges in the evaluation of cardiac safety during drug development: Translational medicine meets the Critical Path Initiative

Current challenges in the evaluation of cardiac safety during drug development: Translational medicine meets the Critical Path Initiative

In this article, we present a call for more integrated cardiovascular safety assessment. We propose a framework for a comprehensive cardiovascular safety assessment that includes both traditional and novel approaches. This framework is intended to provide a comprehensive and consistent approach to assessing cardiovascular safety and to identify potential areas for improvement in current practices.

Journal of Pharmaceutical and Toxicological Methods

On this page, you can find articles related to cardiovascular safety, drug development, and translational medicine. The articles discuss the importance of integrated cardiovascular safety assessment and the challenges in evaluating cardiac safety during drug development.
Moving Forward

Enriched Portfolio

- Strong research, publication, and ‘think tank’ platform established within Committee.
- Expertise and interests shared across project teams – leading to focus on ‘integrated’ approaches to cardiovascular assessment in project portfolio.
- HESI Cardiac Technical Committee gaining recognition as a resource

Opportunity today to learn more and we invite you to participate with the program in the future!
The Cardiovascular System

Figure 13–5. The events of the cardiac cycle, showing changes in left atrial pressure, left ventricular pressure, aortic pressure, ventricular volume, the electrocardiogram, and the phonocardiogram.
Drug Safety Assessment: 1997-Present

Figure 13–5. The events of the cardiac cycle, showing changes in the electrocardiogram
Why The Obsession with ECGs?

- Terfenadine (Seldane®)
- Astemizole (Hismanal®)
- Cisapride (Propulsid®)
- Sertindole (Serlect®)
- Vardenafil (Levitra®)
- Ziprasidone (Geodon®)

This started a frenzy of regulatory activity in the 1990s, focused almost entirely on drug-induced QT interval prolongation!
CURRENT PRACTICE IN STRUCTURAL AND FUNCTIONAL ASSESSMENT OF CARDIOVASCULAR TOXICITY: ISSUES AND OPPORTUNITIES

S. Pettit, B. Berridge, D. Sarazan
Co-Chairs

JUNE 2-4, 2009
THE MADISON HOTEL
WASHINGTON, DC 20005
A call for more integrated cardiovascular safety assessment

S.D. Petit a,*, B. Bertridge b, R.D. Sarazan c

a E.R. Health and Environmental Sciences Institute, 1945 K Street, N.W., Washington, DC 20006, USA
b University of California, San Francisco, California, USA
c Genentech, 1900 Novato Blvd, South San Francisco, CA 94080, USA

ABSTRACT

Cardiovascular safety concerns are a significant cause of attrition in the development of new drugs (Laseter et al., 2002). These risks are present in a variety of ways from acute changes in cardiodynamics to long-term changes in cardiac contractility or compliance. Despite the relative frequency with which cardiovascular effects are observed during the drug development process, current approaches in the pharmaceutical industry and the regulatory (e.g., ICH 57a and b) guidelines that influence those practices are predominantly focused on QT prolongation and acute cardiovascular effects. Also, there is increasing concern about these unexplained and unexpected cardiovascular effects that emerge in high-risk patient populations not modeled in nonclinical studies.

The public health implications of cardiovascular safety-related attrition are significant but this attention also contributes to the rising cost of developing new drugs. Late stage (clinical) terminations or withdrawals put patent populations at risk. Inappropriate terminations during nonclinical phases of development for unproven risks may unnecessarily limit the future of a compound that could benefit a target patient population. In either scenario, a better understanding of the interaction between nonclinical and clinical predictors measures of cardiovascular risk as well as a more integrated and predictive development strategy could dramatically augment the development of safe and effective medicines for patients in need.

In response to this need, a consortium of industrial, academic, and government scientists designed and executed a three-day “think tank” under the auspices of the non-profit ERSI Health and Environmental Sciences Institute (ERSI HESI). The session was held from June 2 to 4, 2009, in Washington, DC. This highly interactive scientific forum provided a unique opportunity for experts with diverse cardiovascular-related expertise to cohesively discuss issues, challenges, and opportunities to improve the overall pharmaceutical cardiovascular safety assessment paradigm. The “think tank” drew approximately sixty scientists from the U.S., Europe, and Japan and included regulators, clinicians, academic research scientists, and industrial researchers (both clinical and nonclinical). The meeting agenda and areas of focus were specifically intended to integrate approaches to both cardiovascular structure and function as they relate to clinical and nonclinical drug development. The group discussed strategic gaps and formulated ideas for collaborative efforts to address these gaps. Specific sessions explored: evaluation of acute changes in cardiac hemodynamics and ionotropy, analytical sensitivity of contemporary cardiovascular parameters, current understanding of structural cardiotoxicity, the impact of therapeutic drug data for cardiovascular risk tolerance, unique challenges of assessing cardiovascular risk with large

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Consortia

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Toward an Integrated Approach to Cardiovascular Safety Assessment

D. Sarazan, S. Pettit, B. Berridge

Presented at the SPS 9th Annual Meeting
Strasbourg, France
21 – 24 September 2009

Poster and invited platform presentation
What has happened since?

- Functional CV Subteam has been meeting monthly via teleconference;
- Outline for paper on gaps, opportunities, recommended approaches developed collectively by work group and discussed in detail on series of teleconferences;
- Small writing team preparing initial draft document (D. Sarazan, J. Koerner, S. Mittelstadt, B. Guth, J. Zhang) based on outline developed by full work group;
- Draft of manuscript to be shared with full work group in June 2010 for input;
- Manuscript anticipated to be complete in August/September 2010.
Manuscript Outline

I. Introduction

II. Hemodynamics
   Background
   Current Status of Approaches
   Mechanistic Interpretation/Biology
   Recent Advances In Technology
   Recommendations for Further Actions

III. Cardiac Contractility (Inotropy)
   Background
   Current Status of Approaches
   Mechanistic Interpretation/Biology
   Recent Advances In Technology
   Recommendations for Further Actions

IV. Functional CV Assessment in Repeat Dose Toxicology Studies
   Background
   Current Status of Approaches
   Mechanistic Interpretation/Biology
   Recent Advances In Technology
   Recommendations for Further Actions

(continued)
Manuscript Outline Cont’d

V. Assay Sensitivity
- Background
- Definition of sensitivity
  - Statistical Power
  - Positive Control
- Types of Study Designs
- Recommendations

VI. Conclusions/Recommendations

VII. References
What happens after manuscript?

• Team will prioritize recommendations for next steps;
• Possible data sharing or experimental project proposed to assess the power of nonclinical functional studies to predict clinical functional outcomes;
• More specific direction to be determined following HESI Committee meeting June 2-3, 2010.
Thank You!
FOR BACKUP OR DISCUSSION
Discussion Questions

• What’s the scope of the problem?
  • What are the key CVS safety liabilities in Drug Discovery, Drug Development and Clinical Practice?

• How big is the problem?
  • How significant are CVS safety liabilities in affecting drug development, registration, clinical practice and marketability?

• What do we know about it?
  • Do we understand the mechanisms of CVS toxicities? If not…

• What can we do about it?
  • How effective are current strategies and BMs of CVS toxicities?
  • What are the gaps in our knowledge concerning CVS toxicities?
  • What is required to fill those gaps? Preclinically / clinically?
  • Where should effort be focused on in the next 5 years?

• What is the role for collaboration?
  • How have/can collaborative programs influence the development of new CVS science?
  • Are these programs reaching their potential? If not – how can these approaches be improved?