ILSI Health and Environmental Sciences Institute (HESI)

# Cardiac Safety Technical Committee

# A Resource for Improving Cardiovascular Safety Through Collaboration

HESI Annual Meeting
May 2010

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# 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?

| Phase | Nonclinical | Phase I | Phase 1-III | Phase III/ Marketing | Marketing | Marketing |
|---|---|---|---|---|---|---|
| Information | Causes of attrition | Serious ADRs | Causes of attrition | ADRs on label | Serious ADRs | Withdrawal from sale |
| Source | Car (2006) | Sibille et al. (1998) | Olson et al. (2000) | BioPrint® (2006) | Budnitz et al. (2006) | Stevens & Baker (2008) |
| Sample size | 88 CDs stopped | 1,015 subjects | 82 CDs stopped | 1,138 drugs | 21,298 patients | 47 drugs |
| Cardiovascular | 27% | 9% | 21% | 36% | 15% | 45% |
| Hepatotoxicity | 8% | 7% | 21% | 13% | 0% | 32% |
| Haematology/BM | 7% | 2% | 4% | 16% | 10% | 9% |
| Nervous system | 14% | 28% | 21% | 67% | 39% | 2% |
| Immunotox; photosensitivity | 7% | 16% | 11% | 25% | 34% | 2% |
| Gastrointestinal | 3% | 23% | 5% | 67% | 14% | 2% |
| Reprotox | 13% | 0% | 1% | 10% | 0% | 2% |
| Musculoskeletal | 4% | 0% | 1% | 28% | 3% | 2% |
| Respiratory | 2% | 0% | 0% | 32% | 8% | 2% |
| Renal | 2% | 0% | 9% | 19% | 2% | 0% |
| Genetic tox | 5% | 0% | 0% | 0% | 0% | 0% |
| Carcinogenicity | 3% | 0% | 0% | 1% | 0% | 0% |
| Other | 0% | 0% | 4% | 16% | 2% | 2% |

Redfern WS et al. SOT 2010 Poster 1081 Tue 1 pm

0% 1-9% 10-19% >20%

# 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

# Recent Pubs

AHJ American Heart Journal



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Volume 158, Issue 1, Pages 21-29 (July 2009)

previous 7 of 34 next

**A translational approach to detecting drug-induced cardiac injury with cardiac troponins: Consensus and recommendations from the Cardiac Troponins Biomarker Working Group of the Health and Environmental Sciences Institute**

Brian R. Berridge, DVM, PhD[a], Syril Pettit, MS[b], Dana B. Walker, DVM, PhD[c], Alan S. Jaffe, MD[d], Albert E. Schultze, DVM, PhD[e], Eugene Herman, PhD[f], William J. Reagan, DVM, PhD[g], Steven E. Lipshultz, MD[h], Fred S. Apple, PhD[i], Malcolm J. York, MPhil[j]

Received 23 April 2009; accepted 23 April 2009.

ABSTRACT
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Cardiac troponins (cTns) 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. In a workshop sponsored by the Cardiac Troponin Biomarker Working Group of the Health and Environmental Sciences Institute, preclinical, clinical, and regulatory scientists discussed the application of cTns in their respective environments, issues in translating the preclinical application of cTn to clinical studies, and gaps in our understanding of cTn biology and pathobiology. Evidence indicates that cTns are sensitive and specific biomarkers of cardiac injury from varying causes in both animals and humans. Accordingly, monitoring cTns can help ensure patient safety during the clinical evaluation of new drugs. In addition, preclinical characterization of cardiac risk and cTns as biomarkers of that risk can guide relevant clinical application and interpretation. We summarize here the outcomes of the workshop which included consensus statements, recommendations for further research, and a proposal for a cross-disciplinary group of clinical, regulatory, and drug development scientists to collaborate in such research.

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Original article

## A call for more integrated cardiovascular safety assessment

S.D. Pettit [a,*], B. Berridge [b], R.D. Sarazan [c]

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ABSTRACT

Cardiovascular safety concerns are a significant cause of attrition in the development of new drugs (Lasser et al., 2002). This attrition has significant public health implications and also contributes to the rising cost of developing new drugs. However, a better understanding of the inter-relationship 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 ILSI Health and Environmental Sciences Institute (ILSI HESI) in June 2009 in Washington, D.C. This highly interactive scientific forum provided a unique opportunity for experts with diverse cardiovascular-related expertise to collectively discuss issues, challenges, and opportunities to improve the overall pharmaceutical cardiovascular safety assessment paradigm. This article identifies the major points of consensus and recommendations stemming from this workshop.



Cardiovascular safety concerns are a significant cause of attrition in the development of new drugs (Lasser et al., 2002). These risks are present in a variety of ways from acute changes in electrophysiology or hemodynamics to longer term changes in cardiac contractility or cardiovascular structure. 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 S7a and b) guidances that influence those practices are predominately focused on QT prolongation and acute cardiac effects. Also, there is rising concern about those untoward 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 attrition also contributes to the rising cost of developing new drugs. Late stage (clinical) terminations or withdrawals put patient 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 inter-relationship 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 ILSI Health and Environmental Sciences Institute (ILSI HESI). The session was held from June 2 to 4, 2009, in Washington, D.C. This highly interactive scientific forum provided a unique opportunity for experts with diverse cardiovascular-related expertise to collectively 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 those gaps. Specific sessions explored: evaluation of acute changes in cardiac hemodynamics and inotropy, analytical sensitivity of contemporary

Abbreviations: ILSI HESI, International Life Sciences Institute Health and Environmental Sciences Institute; ICH, International Conference on Harmonization; QT, duration of the QT interval of the electrocardiogram.

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Original article

## A HESI consortium approach to assess the human predictive value of non-clinical repolarization assays

Elena S. Trepakova [a,*], John Koerner [b,1], Syril D. Pettit [c,2], and Jean-Pierre Valentin [d,3] on behalf of the HESI Pro-Arrhythmia Committee members

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QTc

ABSTRACT

Drug-induced ventricular arrhythmia and Torsades de Pointes remain a serious public health issues in bringing safe new pharmaceuticals to the market place. Under the auspices of the International Life Science Institute (ILSI)–Health and Environmental Sciences Institute (HESI), a consortium involving representatives from pharmaceutical companies, regulatory agencies and opinion leaders from the scientific and medical research communities has been initiated. The objectives are (1) to assess the concordance between signals in non-clinical repolarization assays and clinical QT interval prolongation; (2) to investigate the mechanisms for any discrepancy identified between non-clinical and clinical results and to determine viable and successful alternative approaches to identify these compounds; and (3) to assess the proarrhythmic potential of such compounds. At present, the consortium is conducting a retrospective analysis of non-clinical and clinical data from both FDA and contributing companies' databases and supplementing with a literature review. The overall objectives of these initial efforts are to establish a quantitative integrated risk assessment for each compound; to define criteria for concordance and apply them to the database in order to identify non-concordant compounds.



### 1. Introduction

It is recognised that a subset of drug-induced sudden deaths is associated with the development of a cardiac arrhythmia called Torsades de Pointes (TdP). Current scientific understanding of this issue is that the most common primary event underlying TdP is the inhibition of the rapidly activating delayed rectifier potassium current ($I_{Kr}$) encoded by hERG (human ether-a-go-go related gene). Since $I_{Kr}$ plays a key role in repolarization of the cardiac action potential (for review, see Tamargo, 2000), inhibition of this current can prolong the action potential. This event is manifested on the surface electrocardiogram as a prolongation of the QT interval (Vandenberg, Walker & Campbell, 2001). While QT interval prolongation is not proarrhythmic *per se*, under certain conditions and in a small percentage of patients it has been associated with TdP, which either spontaneously terminates or degenerates into ventricular fibrillation and may therefore lead to sudden death (Pugsley, Authier, & Curtis, 2008; Roden, 2008).

To address this serious health concern, in 2005 the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) issued the final version of the S7B guideline. This guideline recommends an in vitro assessment of hERG channel inhibition in conjunction with in vivo cardiac testing as two critical components of an integrated risk assessment for delayed repolarization (QT prolongation) for all new candidate drugs that are submitted to regulatory agencies for approval prior to conduct of clinical trials or for marketing (Anon., 2005a).

The ICH E14 guideline was introduced at approximately the same time as S7B and provided recommendations on the design, conduct, analysis and interpretation of clinical studies aimed at assessment of

Abbreviations: ECG, Electrocardiogram; FDA, Food and Drug Administration; FTIH, First Time in Human; GLP, Good Laboratory Practice; hERG, human ether-a-go-go related gene; HESI, Health and Environmental Sciences Institute; ICH, International Conference on Harmonization; $I_{Kr}$, delayed rectifier potassium current; ILSI, International Life Sciences Institute; QT, duration of the QT interval of the electrocardiogram; QTc, rate corrected QT interval duration; TdP, Torsades de Pointes.

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

for the CSRC/HESI Writing Group Jonathan P. Piccini, MD, MHS[a], David J. Whellan, MD, MHS[b], Brian R. Berridge, DVM, PhD[c], John K. Finkle, MD[d], Syril D. Pettit, MEM[e], Norman Stockbridge, MD, PhD[f], Jean-Pierre Valentin, PhD[g], Hugo M. Vargas, PhD[h], Mitchell W. Krucoff, MD[i]

Received 4 June 2009; accepted 4 June 2009. published online 24 July 2009.

In October 2008, in a public forum organized by the Cardiac Safety Research Consortium and the Health and Environmental Sciences Institute, leaders from government, the pharmaceutical industry, and academia convened in Bethesda, MD, to discuss current challenges in evaluation of short- and long-term cardiovascular safety during drug development. The current paradigm for premarket evaluation of cardiac safety begins with preclinical animal modeling and progresses to clinical biomarker or biosignature assays. Preclinical evaluations have clear limitations but provide an important opportunity to identify safety hazards before administration of potential new drugs to human subjects. Discussants highlighted the need to identify, develop, and validate serum and electrocardiogram biomarkers indicative of early drug-induced myocardial toxicity and proarrhythmia. Specifically, experts identified a need to build consensus regarding the use and interpretation of troponin assays in preclinical evaluation of myocardial toxicity. With respect to proarrhythmia, the panel emphasized a need for better qualitative and quantitative biomarkers for arrhythmogenicity, including more streamlined human thorough QT study designs and a universal definition of the end of the T wave. Toward many of these ends, large shared data repositories and a more seamless integration of preclinical and clinical testing could facilitate the development of novel approaches to both cardiac safety biosignatures. In addition, more thorough and efficient early clinical studies could enable better estimates of cardiovascular risk and better inform phase II and phase III trial design. Participants also emphasized the importance of establishing formal guidelines for data standards and transparency in postmarketing surveillance. Priority pursuit of these consensus-based directions should facilitate both safer drugs and accelerated access to new drugs, as concomitant public health benefits.

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# 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!**

# Functional Cardiovascular Safety Working Group

Fall 2009 - Present

# The Cardiovascular System

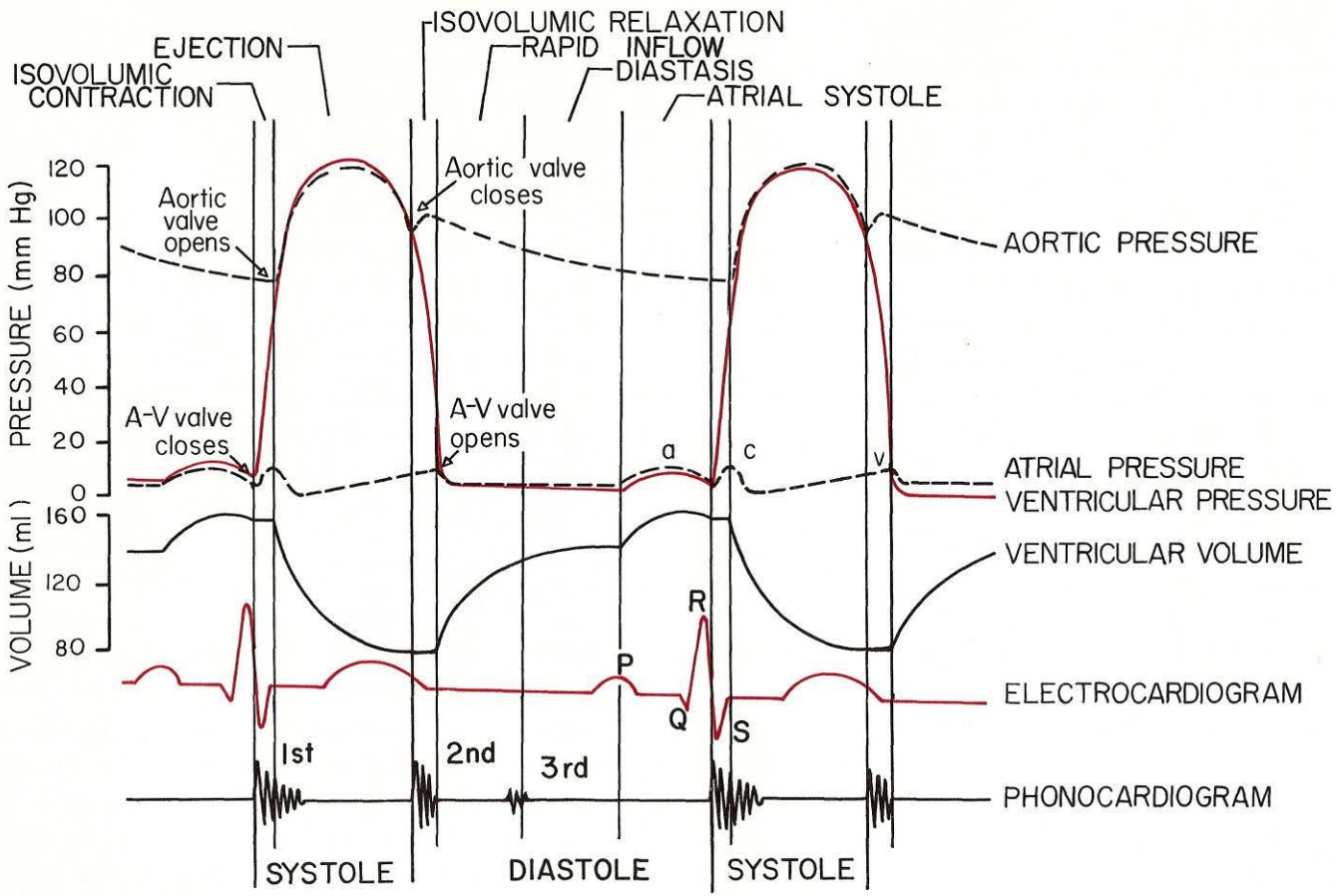


**Figure 13–5.** The events of the cardiac cycle, showing changes in left atrial pressure, left ventricular pressure, aortic pressure, ventricular volume, the electrocardiogram, and the phonocardiogram.

# Drug Safety Assessment: 1997-Present

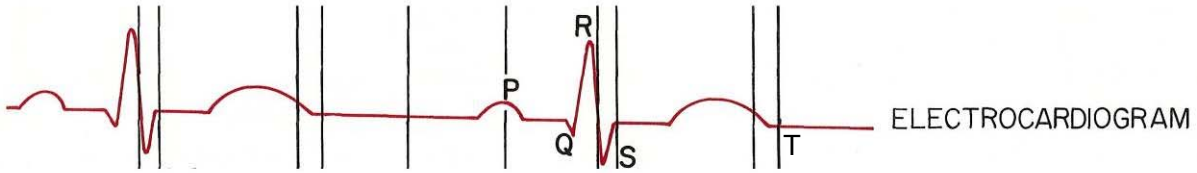


**Figure 13–5.** The events of the cardiac cycle, showing changes in the electrocardiogram

# Why The Obsession with ECGs?

- Terfenadine (Seldane®)
- Astemizole (Hismanal®)
- Cisapride (Propulsid®)

} Withdrawn

- Sertindole (Serlect®)

} Not Approved in U.S.

- Vardenafil (Levitra®)
- Ziprasidone (Geodon®)

} Approved with labeling

*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*


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**The Madison Hotel**
**Washington, DC 20005**

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Original article

# A call for more integrated cardiovascular safety assessment

S.D. Pettit [a,*], B. Berridge [b], R.D. Sarazan [c]

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*Abbreviations:* ILSI HESI, International Life Sciences Institute Health and Environmental Sciences Institute; ICH, International Conference on Harmonization; QT, duration of the QT interval of the electrocardiogram.

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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?