Audience Quiz: Biomarker Context Definition

- 1) eECG/ABBIOS
- 2) Extraction of discrete 12-lead ECG strips from continuous Holter

Audience Quiz: Biomarker Data Examples

- 1) eECG/ABBIOS
- 2) Extraction of discrete 12-lead ECG strips from continuous Holter

CRITICAL PATH INSTITUTE

FDA's Critical Path Initiative,

The Critical Path Institute,
and the
Predictive Safety Testing Consortium

William B Mattes, PhD DABT
Director, Toxicology

Lecture Outline

CRITICAL PATH INSTITUTE

- Background: The Critical Path Initiative
- Aspects of the Critical Path Initiative
- The Critical Path Institute
- The Predictive Safety Testing Consortium

10 year Trend in Biomedical R&D Spending

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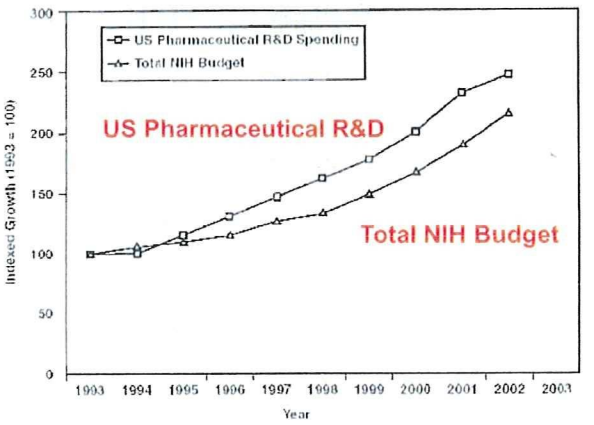
Figure 1: 10-Year Trends in Biomedical Research Spending



10 year Trend in New Applications to FDA

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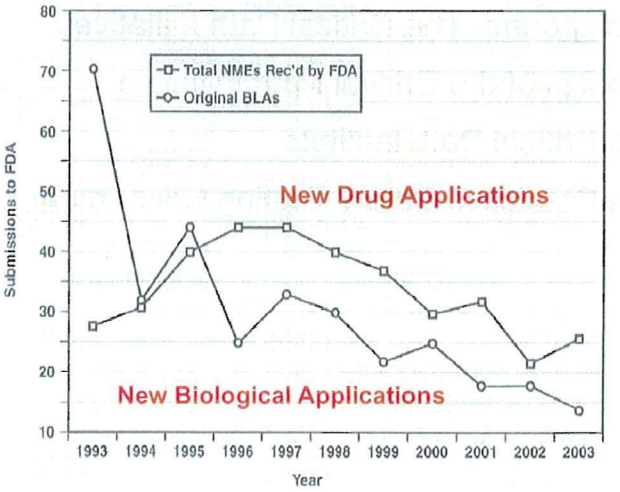

The Critical Path Initiative

CRITICAL PATH INSTITUTE

March 2004

Among other observations the FDA's Critical Path Initiative (CPI) finds
"The main causes of failure in the clinic include safety problems and lack of effectiveness: inability to predict these failures before human testing or early in clinical trials dramatically escalates costs."

The Critical Path Initiative

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- The Critical Path Initiative is FDA's effort to stimulate and facilitate a national effort to modernize the scientific process through which a potential human drug, biological product, or medical device is transformed from a discovery or "proof of concept" into a medical product.
- The CPI focuses on the scientific gap between discovery research and medical application

Critical Path Initiative: Priority Topics

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- Better Evaluation Tools
- Streamlining Clinical Trials
- Harnessing Bioinformatics
- Moving Manufacturing into the 21st Century
- Developing Products to Address Urgent Public Health Needs
- Specific At-Risk Populations — Pediatric

Better Evaluation Tools: Selected Projects

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- Develop a Concept Paper on Biomarker Qualification
- Improve Dosing of Warfarin
- Draft Drug-Diagnostic Co-Development Guidance
- Examine Genetic Basis of Adverse Events
- Broaden Our Understanding of Drug-Induced Liver Injury
- Participate in Microarray Standards Consortium
- Biomarker Development and Qualification
- Predictive Safety Testing

Better Evaluation Tools: Selected Projects

CRITICAL PATH INSTITUTE

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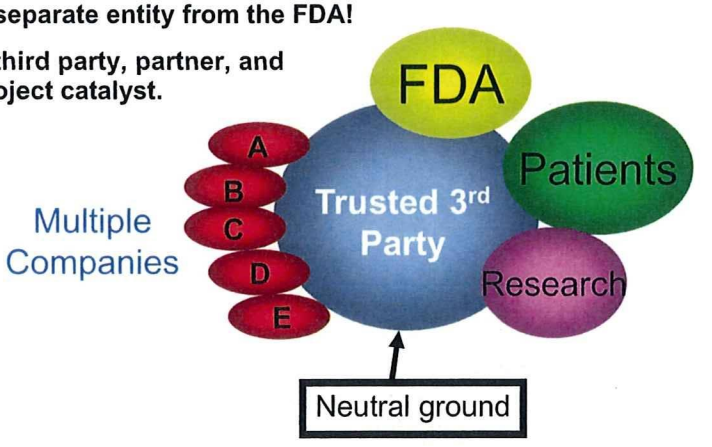
- Participate in Microarray Standards Consortium
- ***Biomarker Development and Qualification***
- ***Predictive Safety Testing***

The Critical Path Institute (C-Path)

CRITICAL PATH INSTITUTE

- **A separate entity from the FDA!**
- **A third party, partner, and project catalyst.**



Warfarin – Public Health Issue

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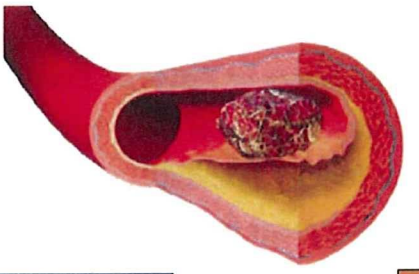
Management of thrombosis and embolism



US prescriptions
>2 million/year
>30 million total

Adverse events
- 40,000 ER visits
- $2B AE costs

Warfarin Dosing Optimization

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- Determine clinical / pharmacoeconomic benefit of routine genotyping to determine warfarin dose
- **Warfarin Summit I**
  - **C-Path** / NHLBI / FDA collaboration on clinical trial
  - **C-Path**-led technical assessment of genotyping assays

AutoGenomics · Nanosphere · Third Wave Technologies · Idaho Technology Inc. · paragon Dx · OSMETECH · COIGENICS · DNAFORM

  - Initial label change – highlight genetics, but not require/ recommend
- **Warfarin Summit II**
  - **C-Path** coordinated evaluation of cumulative pharmacogenetic information with experts/FDA to support additional label change

Genetic Basis of Adverse Events

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- Common Adverse Drug Reactions (CADRe)
- Goals:
  - Evaluation of evidence for genetic basis of adverse events associated with common drugs
  - Communication of pertinent information to clinicians and patients to guide safer use of these drugs.
- C-Path Staff
  - Maryellen de Mars
  - Marietta Anthony

Candidate Drug/ Adverse Event Pairs

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Drug	*Common Adverse Drug Reaction*
Protease inhibitors	lipodystrophy diabetes, liver toxicity
Statins, anticholesterol drugs and combinations such as statins and fibrates	myopathy, muscle pain, muscle necrosis to the extreme, rhabdomyolisis; elevated CPK
Beta-agonists	asthma
Atypical antipsychotics	glucose intolerance/diabetes, akathisia, weight gain, extrapyramidal syndrome
Tricyclics	neurologicaleffects
SSRI	sexual dysfunction, suicidal ideation, insomnia
NSAIDS	blood pressure elevation, GI pain
Stimulants for ADHD	weight loss, hallucinations, hypertension, adverse cardiovascular effects
Nevirapine (Viramune)	hepatotoxicity, severe skin reactions
Rosiglitazone	CVD
Methadone	QT prolongation, arrhythmia
Isoniazid	(NAT-2); hepatitis

Predictive Safety Testing Consortium (PSTC)

CRITICAL PATH INSTITUTE

FDA U.S. Food and Drug Administration U.S. Department of Health and Human Services

FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | FDA Centennial

FDA News

FOR IMMEDIATE RELEASE
P06-40
March 16, 2006

Media Inquiries:
301-827-6242
Consumer Inquiries:
888-INFO-FDA

FDA and the Critical Path Institute Announce Predictive Safety Testing Consortium
Consortium Will Share Tests to Understand Safety of Potential New Drugs Earlier

The Food and Drug Administration (FDA) and The Critical Path Institute (C-Path) today announced the formation of the Predictive Safety Testing Consortium between C-Path and five of America's largest pharmaceutical companies to share internally developed laboratory methods to predict the safety of new treatments before they are tested in humans. The FDA, while not a member of the Partnership, will assist it in an advisory capacity. This unprecedented sharing of potential early indicators of clinical safety may streamline the cost and time of preclinical drug safety evaluation and better inform the use of "personalized medicine". The Consortium was announced today at a press conference detailing the release of the Critical Path Opportunities List -- 76 initial research priorities that, if accomplished, will modernize the drug development process by 2010 and help get new medical discoveries to Americans faster and at a lower cost.

Pre-clinical Safety Testing?

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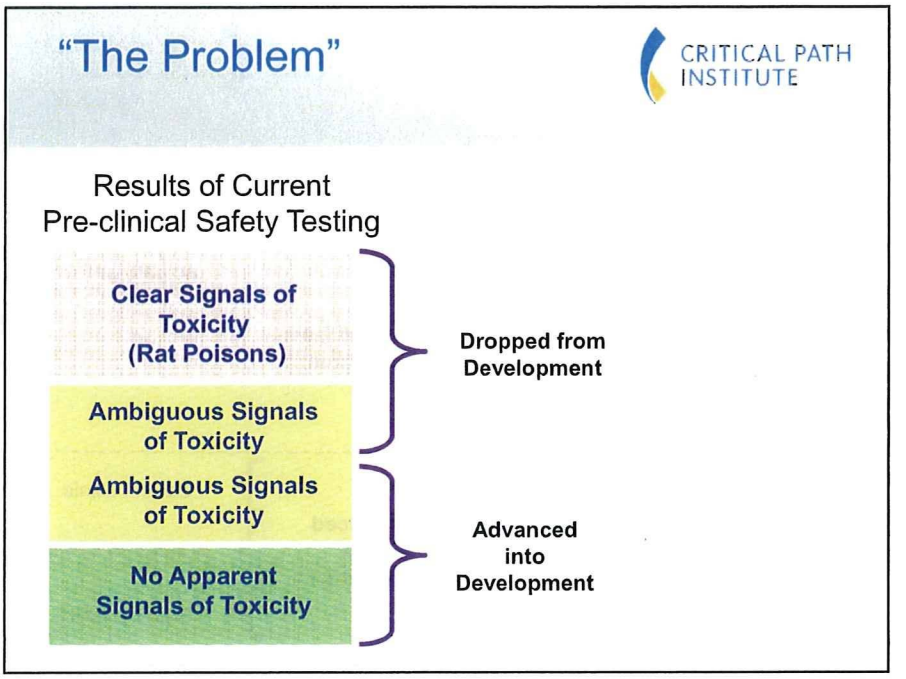
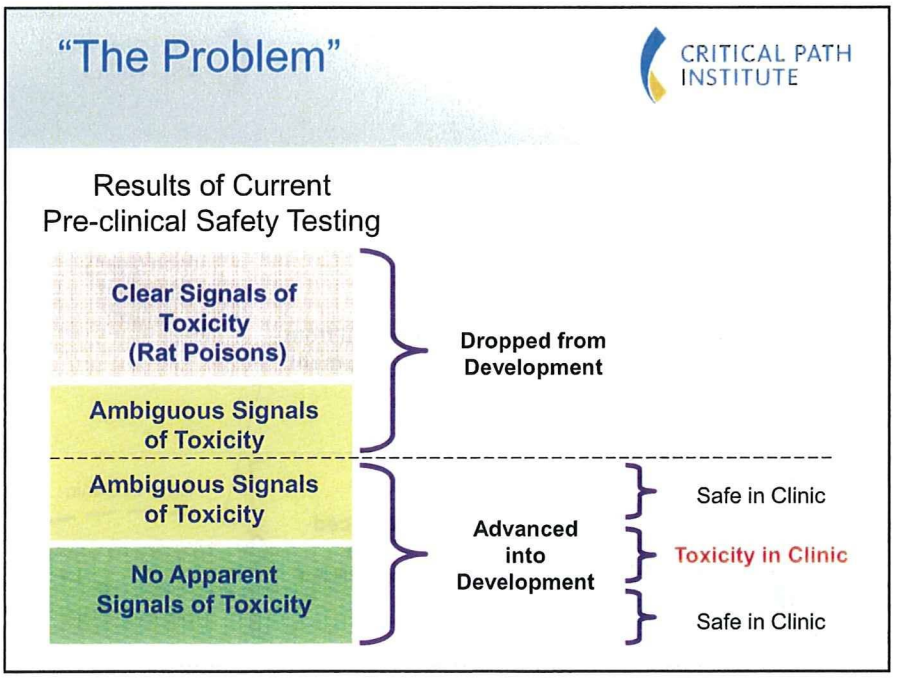
1937 Massengill distributed **Elixir Sulfanilamide** without testing for safety (which was not required by law). Because it contained diethylene glycol as a vehicle, 107 people died, many of whom were children.

1938 Federal Food, Drugs and Cosmetic Act

New drugs are required to be safe before marketing.


"The Problem"
CRITICAL PATH INSTITUTE
Results of Current
Pre-clinical Safety Testing
Clear Signals of Toxicity (Rat Poisons)
Ambiguous Signals of Toxicity
Ambiguous Signals of Toxicity
No Apparent Signals of Toxicity
Dropped from Development
Advanced into Development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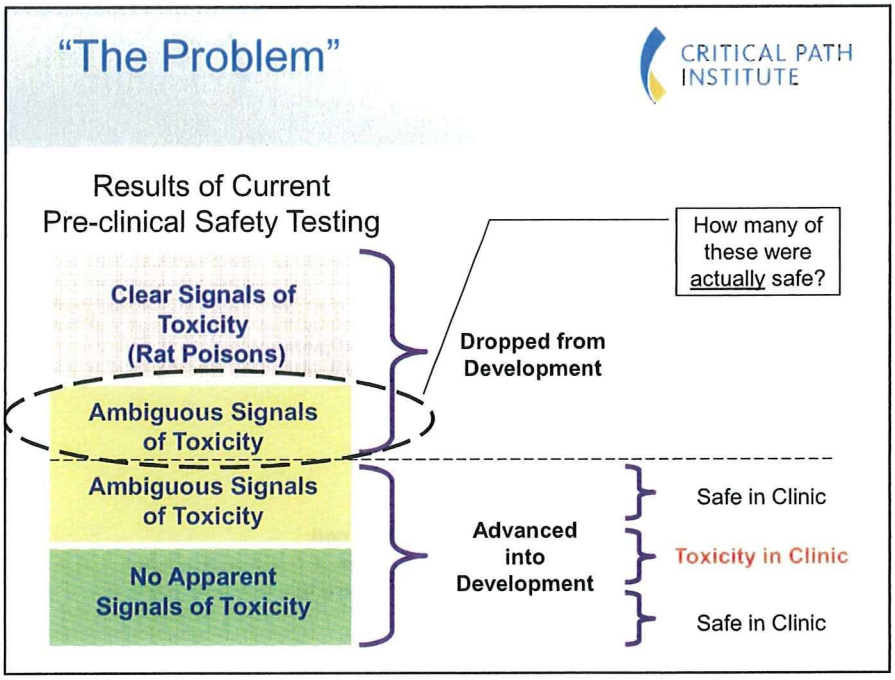
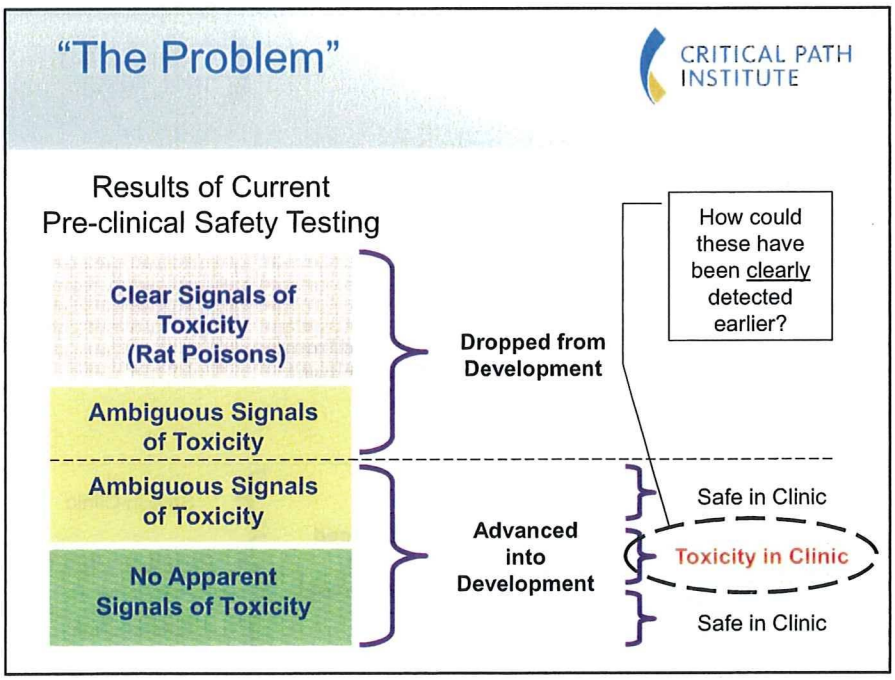
Dropped from Development
Advanced into Development
Safe in Clinic
Toxicity in Clinic
Safe in Clinic


"The Problem"
CRITICAL PATH INSTITUTE
Results of Current Pre-clinical Safety Testing
Clear Signals of Toxicity (Rat Poisons)
Ambiguous Signals of Toxicity
Dropped from Development
How many of these were actually safe?
Ambiguous Signals of Toxicity
No Apparent Signals of Toxicity
Advanced into Development
Safe in Clinic
Toxicity in Clinic
Safe in Clinic


"The Problem"
CRITICAL PATH INSTITUTE
Results of Current Pre-clinical Safety Testing
Clear Signals of Toxicity (Rat Poisons)
Ambiguous Signals of Toxicity
Dropped from Development
How could these have been clearly detected earlier?
Ambiguous Signals of Toxicity
No Apparent Signals of Toxicity
Advanced into Development
Safe in Clinic
Toxicity in Clinic
Safe in Clinic

Why New Safety Biomarkers?

CRITICAL PATH INSTITUTE

- Hepatotoxicity
  - Confounding factors in current tests

    "Muscular exercise can cause highly pathological liver function tests in healthy men"
    Br J Clin Pharmacol. 2008 65:253-9
  - Inability to assess risk of transient ALT elevations

    Mildly elevated liver transaminase levels in the asymptomatic patient.
    Am Fam Physician. 2005 71:1105-10

Why New Safety Biomarkers?

CRITICAL PATH INSTITUTE

- Nephrotoxicity
  - Correct assessment of kidney function is important both for dosage adjustment of renally excreted drugs and for early detection of drug nephrotoxicity, that mostly is reversible if the offending agent is discontinued. ...**Serum creatinine is a late marker of nephrotoxicity** that does not reflect rapid changes in renal function.

    M. Schetz, J. Dasta, S. Goldstein, T. Golper, Curr Opin Crit Care 11, 555-65 (Dec, 2005).

Creatinine vs Histopathology

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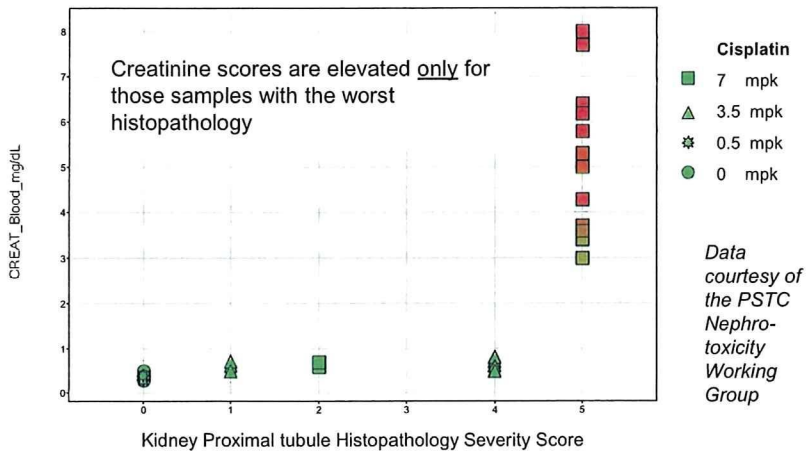

Data courtesy of the PSTC Nephro-toxicity Working Group

Reasons for Attrition

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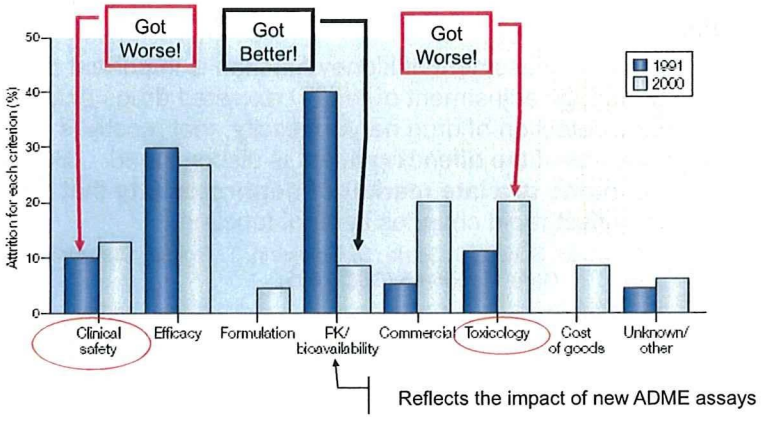

Nature Reviews: Drug Discovery, 3 (8): 711, 2004

Issues with New Biomarkers (in the real world)

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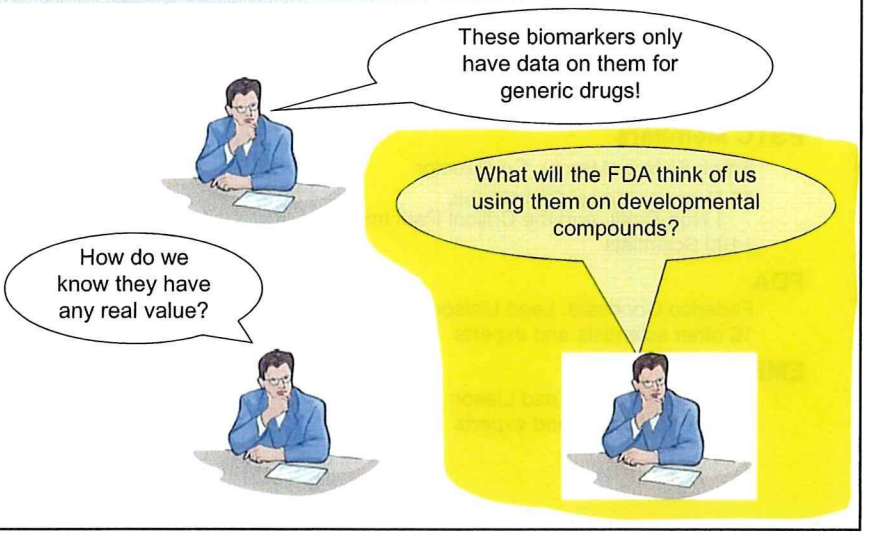

PSTC Goals

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- To cross-qualify pre-clinical animal model biomarkers aimed at reducing the cost and time of pre-clinical safety studies
- To use the **combined resources, sample sets, novel compounds, and expertise** to generate a biomarker data package convincing enough for **FDA/EMEA qualification** as a biomarker acceptable for regulatory safety decision making
- To provide potential early indicators of clinical safety in drug development and post-marketing surveillance.
  - Note the goal of translational biomarkers
- To develop new tools for FDA and EMEA to assist in regulatory decision making.

Who's Involved

CRITICAL PATH INSTITUTE

Critical Path Institute

Bill Mattes, Director
Elizabeth Walker, Assistant Director
Phil Rossi, Program Manager

PSTC Members

Frank Sistare (Merck), Co-Director

15 Pharmaceutical Companies,
1 Non-Profit, and the Critical Path Institute
>190 Scientists

FDA

Federico Goodsaid, Lead Liaison
16 other scientists and experts

EMEA

Sprios Vamvakas, Lead Liason
10 other scientists and experts

PSTC: An International Endeavor

CRITICAL PATH INSTITUTE

Working Groups and Teams

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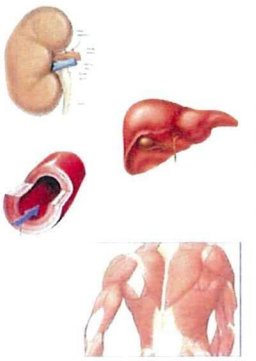
- Five Injury Area Working Groups
  - Nephrotoxicity
  - Hepatotoxicity
  - Vascular Injury
  - Non-genotoxic Carcinogenicity
    - Focus on carcinogenicity tests in rats and mice
  - Myopathy (Striated Muscle)
- Data Management Team
- Translational Strategy Team



Hepatotoxicity WG Progress

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- Four candidate biomarker assays identified for initial cross-qualification
  - PON-1, MDH, PNP, and GLDH
    - Standard auto-analyzer enzymatic assays
  - Significant preliminary internal data
- Three member laboratories identified for assay cross-qualification
- Cross-qualification samples inventoried
- Discussions with FDA planned for 1Q09
- Further discussions on potential candidate biomarkers ongoing

Paraoxanase 1 (PON1)as a Candidate Biomarker

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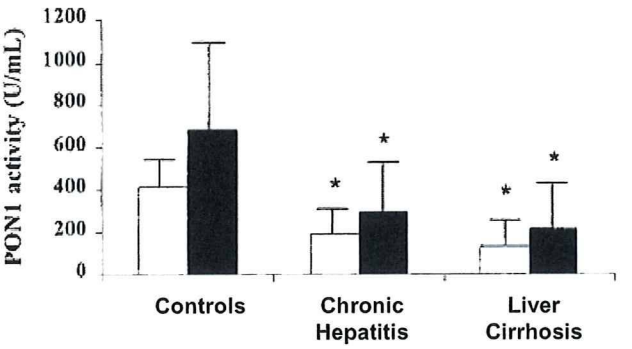

Baseline (*open columns*) and stimulated (*filled columns*) serum PON1 activity

From Ferre´et al (2002) *Clinical Chemistry* 48:261

Nephrotoxicity Biomarkers

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23 Proposed Exploratory Biomarkers of Kidney Toxicity

– 7 Prioritized for FDA/EMEA Submission

- Albumin
- β2-microglobulin
- Calbindin d28
- Clusterin
- Cystatin C
- EGF
- GSTa
- GSTmu
- Kim-1
- Lipocalin2 (NGAL)
- NAG
- Osteoactivin
- Osteopontin
- Podocin
- RPA1
- TFF3
- Timp1
- Total Urinary Protein
- Uromodulin (Tamm-Horsfall)
- VEGF
- Macrophage Migration Inhibitory Factor
- Monokine Induced by Interferon Gamma
- Interferon Gamma Induced 10Kda Protein

Kidney Injury Biomarker Qualification Submission

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- Data from 23 compounds for 7 biomarkers
- **First** establishment of a Biomarker Review process
- **First** joint submission (June, 2007) to both FDA and EMEA
- **First trilateral** (US- Europe-Japan) face to face meeting
- **First** cooperative FDA-EMEA (US-Europe) regulatory decision
- Favorable decision 2Q2008

Summary of Regulatory Decisions

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"..both regulatory agencies came to the conclusions that:"

- the renal biomarkers submitted were acceptable in the context of non-clinical drug development for detection of acute drug-induced renal toxicity;
- the renal biomarkers provide additional and complementary information to the currently available standards;
- the use of renal biomarkers in clinical trials is to be considered on a case-by-case basis…

From http://www.emea.europa.eu/htms/human/mes/biomarkers.htm

Translational Considerations

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- The first focus is on pre-clinical biomarkers
  - This allows a robust correlation between biomarker performance and histopathology
- If a biomarker is to be used to support safety in Phase-1 clinical trials:
  - Its performance in pre-clinical studies must be understood
  - *Its performance in clinical settings would, ideally, also be understood*

    (although in practice purely preclinical biomarkers may offer information on the preclinical toxicity that is useful for hazard characterization)

Translational Strategies

CRITICAL PATH INSTITUTE

- Key to developing strategies is a Translational Team that eliminates silos
  - Clinical scientists from member organizations
  - Preclinical scientists
  - Regulatory scientists
  - Outside advisors as determined

First PSTC Clinical Study

CRITICAL PATH INSTITUTE

Biomarkers of Nephrotoxicity
Final Draft Protocol 8 October 2008

The CPATH INSTITUTE clinXus

Predictive Safety Testing Consortium-PSTC

PHASE 1: OBSERVATIONAL BIOMARKER PROSPECTIVE STUDY:

CONTRAST INDUCED NEPHROPATHY (CIN) IN SUBJECTS UNDERGOING A CARDIAC CATHETERIZATION

- Draft discussed at FDA "Protocol Development Workshop" 10 Oct 2008
- Input obtained from academic scientists and FDA medical officers

Play It Again, Sam.

CRITICAL PATH INSTITUTE

- The Critical Path Initiative focuses on the scientific gap between discovery research and medical application
- Priority topics include "Better Evaluation Tools"
  - Improved Dosing of Warfarin
  - Genetic Basis of Adverse Events
  - Predictive Safety Testing
- The Critical Path Institute serves as a neutral third party to coordinate CPI projects such as these
- The Predictive Safety Testing Consortium is pursuing improved biomarkers of drug safety
- Better Evaluation Tools play a role not only in drug development but also in pharmacovigilance and risk management