Collaborative Approaches for Developing Kidney Safety Biomarkers

John Michael Sauer, PhD
Executive Director of the Predictive Safety Testing Consortium (PSTC)

CRITICAL PATH INSTITUTE
a decade of excellence

10 YEARS

C-Path: A Public-Private Partnership

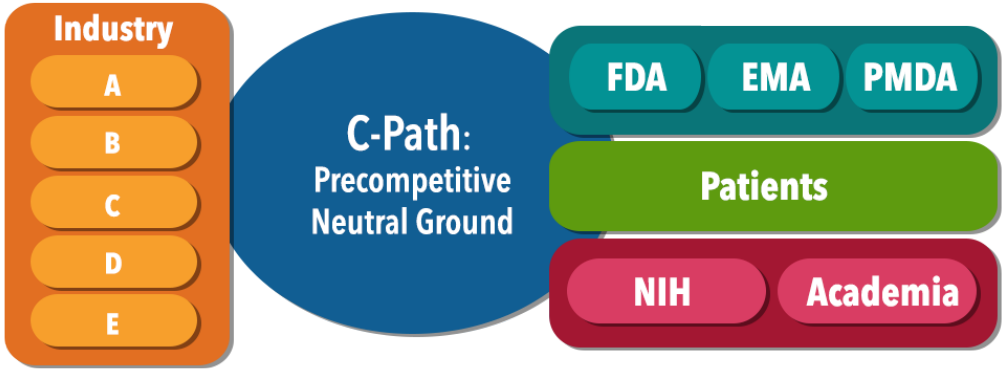
- Act as a trusted, neutral third party
- Convene scientific consortia of industry, academia, and government for sharing of data/expertise

  ✓ The best science

  ✓ The broadest experience

  ✓ Active consensus building

  ✓ Shared risk and costs



- Enable iterative EMA/FDA/PMDA participation in developing new methods to assess the safety and efficacy of medical products

- Official regulatory endorsement of novel methodologies and drug development tools

PSTC
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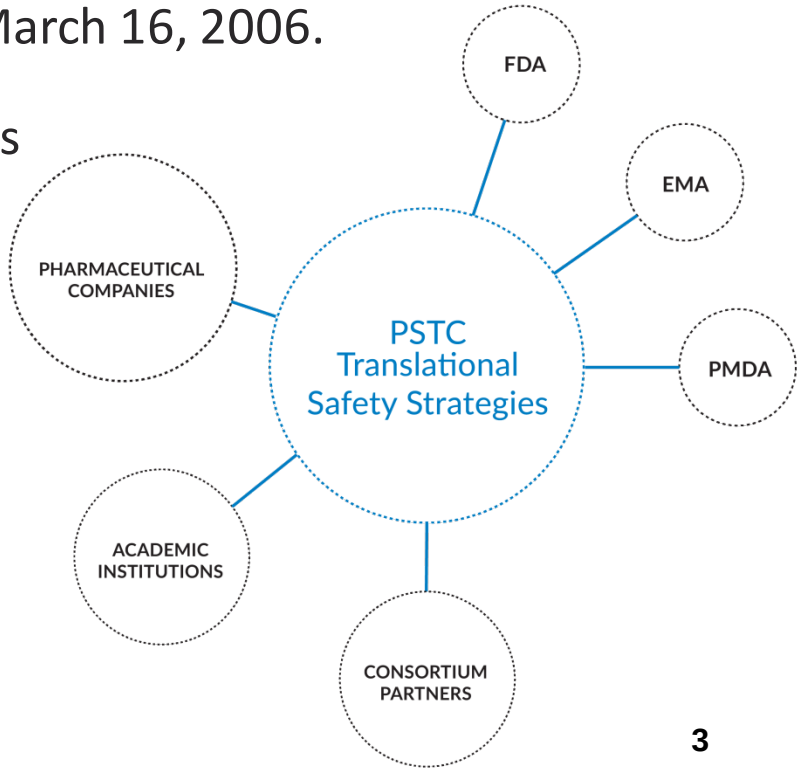
Translational Safety Strategies that Accelerate Drug Development

Predictive Safety Testing Consortium (PSTC)

PSTC was formed and officially announced on March 16, 2006.

PSTC brings together pharmaceutical companies to **share and validate innovative safety testing methods** under advisement of the FDA, EMA, and PMDA.

PSTC's eighteen corporate members have the same goal: to find improved safety testing approaches and methods.



PSTC Collaborators

Consortia Members (18)

abbvie
AstraZeneca
Daiichi-Sankyo
Genentech
A Member of the Roche Group
Johnson & Johnson
Otsuka
Takeda
Celgene
Lilly
gsk GlaxoSmithKline
MERCK
NOVARTIS
SANOFI
Bristol-Myers Squibb
Takeda MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY
Mitsubishi Tanabe Pharma
AMGEN
Roche
Pfizer

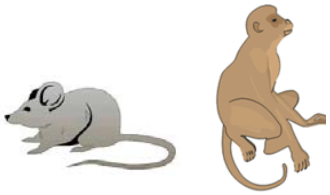
Partners (8)

FDA
Pmda JAPAN
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
THE HAMNER INSTITUTES FOR HEALTH SCIENCES
FNIH
Foundation for the National Institutes of Health
SRI International
SAFE-T
imi
Innovative Medicines Initiative
ILSI Health and Environmental Sciences Institute

PSTC's Current Focus

Monitorability of Drug Induced Tissue Injury in Humans

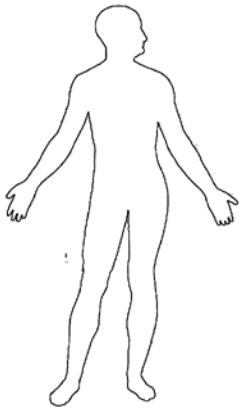
Adverse outcomes in animals



Histopathology

Better Monitoring of Potential Safety Liabilities in Humans

Adverse outcomes in humans



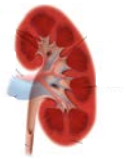
Fluid Based Safety Biomarker

Fluid Based Safety Biomarkers - similar to routine clinical pathology measure that can be used to *accurately* predict drug induced tissue injury

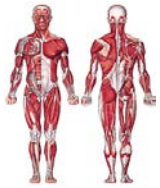
PSTC's Current Focus

Is there a need for improved safety biomarkers?

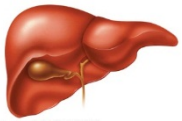
Current biomarker standards do not exist or have significant limitations



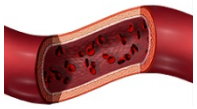
Kidney: Traditional safety biomarkers change only when 50 to 60 % of kidney function is lost



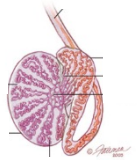
Skeletal Muscle: Current biomarkers are insensitive and nonspecific, as well as poorly predictive



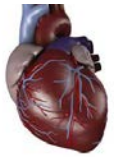
Liver: Current biomarkers are not sufficiently sensitive and specific, and do not adequately discriminate adaptors from patients at high risk to develop liver failure



Vascular System: No biomarkers are available for detecting drug-induced vascular injury in humans



Testicular: No circulating biomarkers for seminiferous tubule toxicity



Cardiac Hypertrophy: Currently no preclinical predictive markers for drug-induced hemodynamic stress leading to changes in cardiac mass

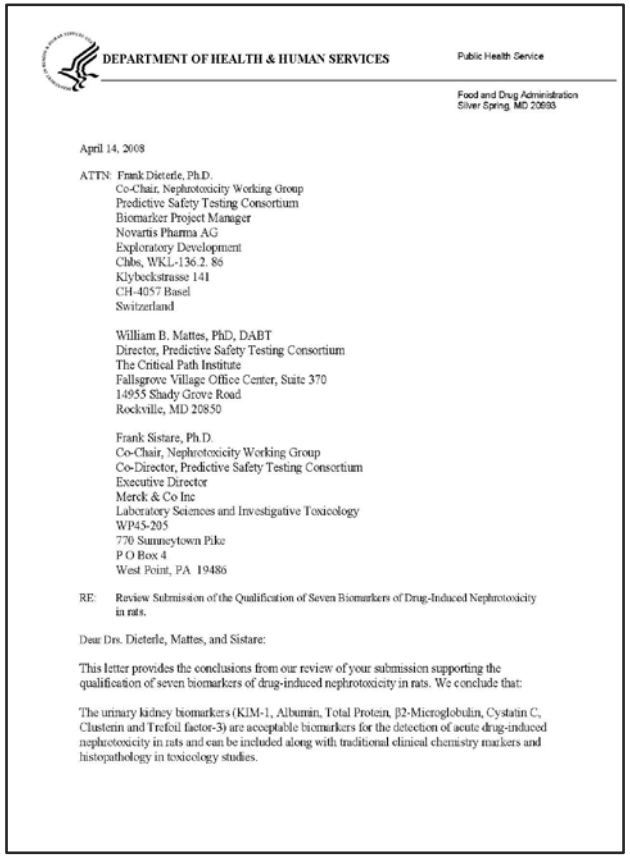
Current biomarkers used to monitor kidney safety have significant limitations

- These "gold standard" biomarkers (serum creatinine) change only when 50 to 60 % of kidney function is lost

Proposed urinary biomarker panel for drug-induced kidney injury:

1. Clusterin
2. Osteopontin
3. Microalbumin
4. Total Protein
5. N-acetyl-β-(D)-glucosaminidase (NAG)
6. Kidney Injury Molecule-1 (KIM-1)
7. Cystatin-C
8. Neutrophil gelatinase-associated lipocalin (NGAL)

FDA, EMA, and PMDA Qualification of 7 Kidney Safety Biomarkers



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

April 14, 2008

ATTN: Frank Dieterle, Ph.D.
Co-Chair, Nephrotoxicity Working Group
Predictive Safety Testing Consortium
Biomarker Project Manager
Novartis Pharma AG
Exploratory Development
Chbs, WKL-136.2. 86
Klybeckstrasse 141
CH-4057 Basel
Switzerland

William B. Mattes, PhD, DABT
Director, Predictive Safety Testing Consortium
The Critical Path Institute
Fallsgrove Village Office Center, Suite 370
14955 Shady Grove Road
Rockville, MD 20850

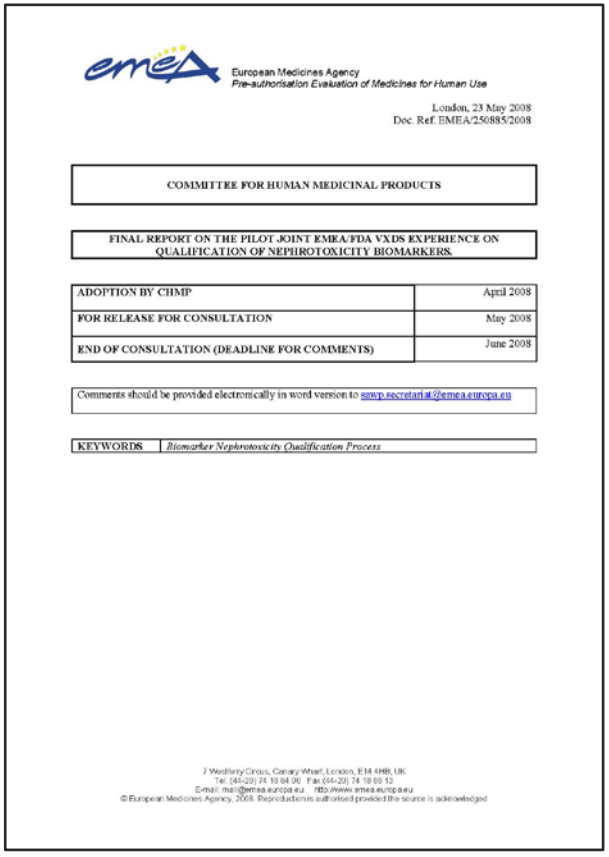
Frank Sistare, Ph.D.
Co-Chair, Nephrotoxicity Working Group
Co-Director, Predictive Safety Testing Consortium
Executive Director
Merck & Co Inc
Laboratory Sciences and Investigative Toxicology
WP45-205
770 Sumneytown Pike
P O Box 4
West Point, PA 19486

RE: Review Submission of the Qualification of Seven Biomarkers of Drug-Induced Nephrotoxicity in rats.

Dear Drs. Dieterle, Mattes, and Sistare:

This letter provides the conclusions from our review of your submission supporting the qualification of seven biomarkers of drug-induced nephrotoxicity in rats. We conclude that:

The urinary kidney biomarkers (KIM-1, Albumin, Total Protein, β2-Microglobulin, Cystatin C, Clusterin and Trefoil factor-3) are acceptable biomarkers for the detection of acute drug-induced nephrotoxicity in rats and can be included along with traditional clinical chemistry markers and histopathology in toxicology studies.



European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 23 May 2008
Doc. Ref. EMEA/250885/2008

COMMITTEE FOR HUMAN MEDICINAL PRODUCTS

FINAL REPORT ON THE PILOT JOINT EMEA/FDA VXDS EXPERIENCE ON QUALIFICATION OF NEPHROTOXICITY BIOMARKERS.

ADOPTION BY CHMP	April 2008
FOR RELEASE FOR CONSULTATION	May 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	June 2008

Comments should be provided electronically in word version to swwp.secretariat@emea.europa.eu

KEYWORDS	*Biomarker Nephrotoxicity Qualification Process*

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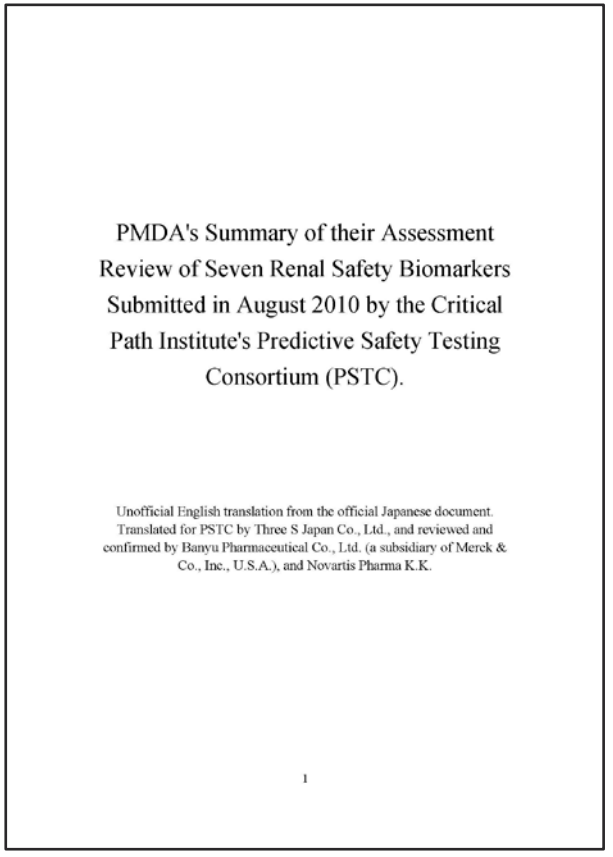

PMDA's Summary of their Assessment Review of Seven Renal Safety Biomarkers Submitted in August 2010 by the Critical Path Institute's Predictive Safety Testing Consortium (PSTC).

Unofficial English translation from the official Japanese document. Translated for PSTC by Three S Japan Co., Ltd., and reviewed and confirmed by Banyu Pharmaceutical Co., Ltd. (a subsidiary of Merck & Co., Inc., U.S.A.), and Novartis Pharma K.K.

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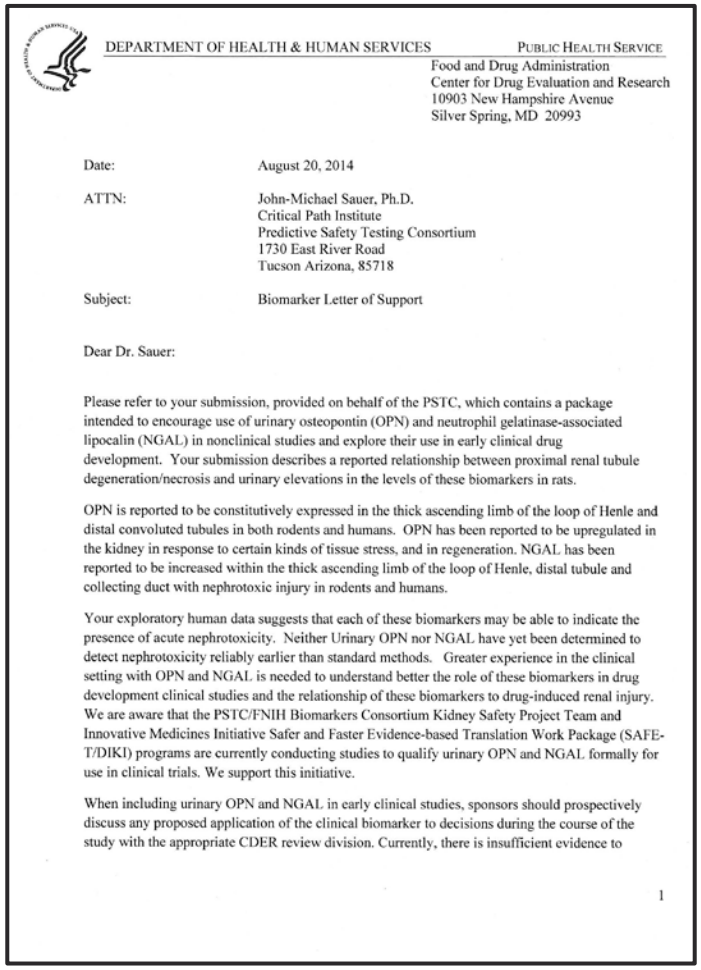
The Critical Path Institute's Predictive Safety Testing Consortium secures Qualification for 7 novel urine kidney biomarkers as preclinical biomarkers of kidney toxicity

FDA and EMA Letters of Support for Kidney Safety Biomarkers



DEPARTMENT OF HEALTH & HUMAN SERVICES — PUBLIC HEALTH SERVICE

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: August 20, 2014

ATTN: John-Michael Sauer, Ph.D.
Critical Path Institute
Predictive Safety Testing Consortium
1730 East River Road
Tucson Arizona, 85718

Subject: Biomarker Letter of Support

Dear Dr. Sauer:

Please refer to your submission, provided on behalf of the PSTC, which contains a package intended to encourage use of urinary osteopontin (OPN) and neutrophil gelatinase-associated lipocalin (NGAL) in nonclinical studies and explore their use in early clinical drug development. Your submission describes a reported relationship between proximal renal tubule degeneration/necrosis and urinary elevations in the levels of these biomarkers in rats.

OPN is reported to be constitutively expressed in the thick ascending limb of the loop of Henle and distal convoluted tubules in both rodents and humans. OPN has been reported to be upregulated in the kidney in response to certain kinds of tissue stress, and in regeneration. NGAL has been reported to be increased within the thick ascending limb of the loop of Henle, distal tubule and collecting duct with nephrotoxic injury in rodents and humans.

Your exploratory human data suggests that each of these biomarkers may be able to indicate the presence of acute nephrotoxicity. Neither Urinary OPN nor NGAL have yet been determined to detect nephrotoxicity reliably earlier than standard methods. Greater experience in the clinical setting with OPN and NGAL is needed to understand better the role of these biomarkers in drug development clinical studies and the relationship of these biomarkers to drug-induced renal injury. We are aware that the PSTC/FNIH Biomarkers Consortium Kidney Safety Project Team and Innovative Medicines Initiative Safer and Faster Evidence-based Translation Work Package (SAFE-T/DIKI) programs are currently conducting studies to qualify urinary OPN and NGAL formally for use in clinical trials. We support this initiative.

When including urinary OPN and NGAL in early clinical studies, sponsors should prospectively discuss any proposed application of the clinical biomarker to decisions during the course of the study with the appropriate CDER review division. Currently, there is insufficient evidence to

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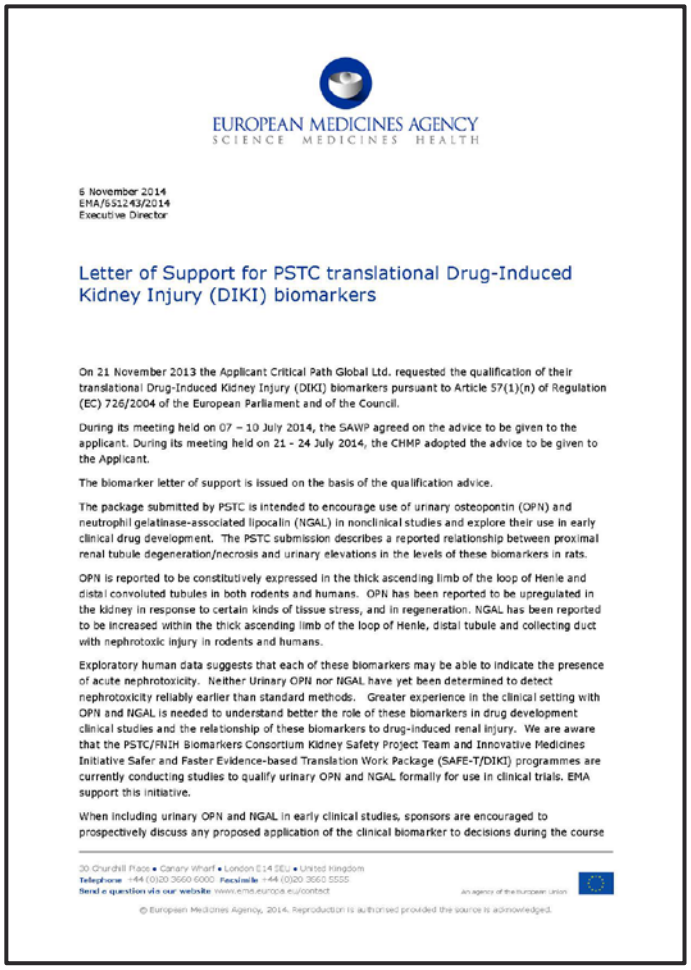

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6 November 2014
EMA/651243/2014
Executive Director

Letter of Support for PSTC translational Drug-Induced Kidney Injury (DIKI) biomarkers

On 21 November 2013 the Applicant Critical Path Global Ltd. requested the qualification of their translational Drug-Induced Kidney Injury (DIKI) biomarkers pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council.

During its meeting held on 07 – 10 July 2014, the SAWP agreed on the advice to be given to the applicant. During its meeting held on 21 - 24 July 2014, the CHMP adopted the advice to be given to the Applicant.

The biomarker letter of support is issued on the basis of the qualification advice.

The package submitted by PSTC is intended to encourage use of urinary osteopontin (OPN) and neutrophil gelatinase-associated lipocalin (NGAL) in nonclinical studies and explore their use in early clinical drug development. The PSTC submission describes a reported relationship between proximal renal tubule degeneration/necrosis and urinary elevations in the levels of these biomarkers in rats.

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When including urinary OPN and NGAL in early clinical studies, sponsors are encouraged to prospectively discuss any proposed application of the clinical biomarker to decisions during the course

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
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Send a question via our website www.ema.europa.eu/contact

An agency of the European Union

The Critical Path Institute's Predictive Safety Testing Consortium receives Letters of Support for 2 novel urine kidney biomarkers as preclinical biomarkers of kidney toxicity

Key Collaborations

FNIH
Foundation for the National Institutes of Health

Press Contact
Jenna R.M. Palfrey
301.435.2613
jmills@fnih.org

The FNIH Biomarkers Consortium Launches Project to Improve Diagnosis of Kidney Injury

Researchers aim to advance acceptance of new biomarkers for monitoring kidney safety in the clinic

Bethesda, MD (October 25, 2011) – The Foundation for the National
Biomarkers Consortium announced today the launch of a two-year
advance the acceptance of new biomarkers designed to detect
clinical trials. The study is being conducted in collaboration with
Consortium (PSTC), a public-private partnership founded by the
Path Institute (C-Path).

imi

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CRITICAL PATH INSTITUTE

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For Immediate Release
May 23, 2013

LEADING US AND EUROPEAN MEDICAL PUBLIC-PRIVATE PARTNERSHIPS ANNOUNCE AGREEMENT

Critical Path Institute and Innovative Medicines Initiative Collaborate on Development of Important New Drug Safety Tests

Tucson, AZ - The Predictive Safety Testing Consortium (PSTC) led by the Critical Path Institute (C-Path) and the Safer and Faster Evidence-based Translation (SAFE-T) consortium sponsored by the Innovative Medicines Initiative (IMI), announced today the

Learn and confirm (progressive) qualification strategy

Nonclinical Phase

- Cisplatin, aminoglycosides, dozens of other renal toxicants were used to demonstrate the superiority of novel biomarkers over sCr for monitoring renal tubular injury (using microscopic histopathology as gold standard)

Qualification of Seven Biomarkers (2008) and Letter of Support for Two Biomarkers (2014) of Drug-Induced Nephrotoxicity in rats

Clinical Learning Phase

- Prospective healthy volunteer study
- Archived samples from cisplatin study

Limited Context of Use Qualification (Submitted in July of 2015)

Clinical Confirmatory Phase

- Aminoglycoside study in cystic fibrosis patients
- Cisplatin study in cancer patients

Expanded Context of Use Qualification (Planned submission in 2017)

Limited Context of Use qualification for drug-induced kidney injury urinary biomarkers:

Claim

A Composite Measure (CM) of urinary biomarkers (all markers) is a qualified safety biomarker of kidney injury response for use in normal healthy volunteer trials supporting early drug development together with monitoring of conventional kidney biomarkers (e.g., serum creatinine and blood urea nitrogen).

Study Population

For use in healthy volunteers only, and for use in subject cohorts not on individual subject basis.

Data for Clinical Learning Phase

Normal healthy volunteer cohort

- N = 80, balanced on gender and age (~40/40, 20-39 years and 40-69 years)
- Longitudinal sample collections over 3 weeks

Cisplatin-treated mesothelioma patient cohort

- N = 58 patients treated with surgical resection and 250 mg/m^2 intraoperative intrathoracic cisplatin (3% <40 years; 80% males; 62% ≥ stage 2 CKD at baseline)
- Longitudinal sample collections over 6 days

Clinical Learning Phase Data Summary:

Eight (8) Selected Urinary Biomarkers Show Improved Sensitivity Over sCr to Identify Patients Exposed to Cisplatin

	Mesothelioma Patients: Number/N (%) >T_{SS}*		Normal Healthy Volunteers: % >T_{SS}
Biomarker	**Patients With Medically Relevant Increases in sCr**	**Patients Without Medically Relevant Increases in sCr**	**Normal eGFR No Cisplatin (N = 80)**
Clusterin	19/20 (95.0%)	**22/30 (73.3%)**	1.3%
Osteopontin	20/20 (100.0%)	**30/30 (96.8%)**	5.1%
Microalbumin	20/20 (100.0%)	**30/30 (100.0%)**	2.5%
Total Protein	20/20 (100.0%)	**30/30 (100.0%)**	3.8%
N-acetyl-β-(D)-glucosaminidase	20/20 (100.0%)	**27/30 (90.0%)**	0%
Kidney Injury Molecule-1	20/20 (100.0%)	**30/30 (100.0%)**	1.3%
Cystatin-C	19/20 (95%)	**22/30 (73.3%)**	5.1%
Neutrophil gelatinase-associated lipocalin	19/20 (95%)	**24/30 (80.0%)**	4.1%

*T_{SS} = statistically significant threshold.

Expanded Context of Use qualification for drug-induced kidney injury biomarkers:

Claim

Qualified kidney safety biomarkers are proposed to be used together with monitoring of conventional kidney biomarkers (e.g., serum creatinine and blood urea nitrogen), in early clinical drug development research to support conclusions as to whether a drug is likely or unlikely to have caused a mild injury response in the kidney at the tested dose and duration.

Study Population

For use in healthy volunteers and patients with normal kidney function.

Prospective clinical studies

Two prospective studies in patients currently using medications that have the potential to cause pancreatic injury.

- Aminoglycoside study in cystic fibrosis patients
  - Patients (n=100): Adult CF patients, acute pulmonary infection treated with IV tobramycin
  - Controls: Adult CF patients (n=25), acute pulmonary infection treated with IV fluoroquinolone; Adult CF patients (n=25), no pulmonary infection, no treatment
- Cisplatin study in cancer patients
  - Patients (n=100) : Patients with head and neck squamous cell carcinoma, and other cancers treated with cisplatin as single agent or part of chemo Tx cocktail
  - Controls (n=50): Cancer patients receiving non-cisplatin chemo Tx treatment, or radiation Tx

✓ Greater diagnostic predictivity compared to serum creatinine as defined by:

1. A formal adjudication procedure
2. A predefined statistical evaluation

The Future State of Biomarker Qualification

Improved definition for the implementation of the qualification process

- Progressive qualification approach – Letter of Support, as well as, Limited and Expanded Context of Use
- Better definition of what is required for qualification – Codified evidentiary considerations (evidentiary standards)

More innovative approaches to biomarker qualification

- Retrospectively collected samples with prospective analysis
- Biomarker data repository for biomarker data from IND studies and qualification projects – What should be considered precompetitive now (2015)?

Thank You

www.c-path.org

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FDA

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