



**CRITICAL PATH INSTITUTE (C-PATH)  
& INNOVATIVE MEDICINES INITIATIVE (IMI)  
2<sup>ND</sup> ANNUAL MEETING**

**ACCELERATING THE DEVELOPMENT OF DRUGS,  
DIAGNOSTICS, AND DEVICES: PARTNERSHIPS TO EXPAND  
THE PRECOMPETITIVE SPACE**

**December 3, 2014**



**Session 2:**  
***Safety Biomarkers: The PSTC  
and SAFE-T Collaboration***

# Safety Biomarkers: The PSTC and SAFE-T Collaboration

Co-Chairs/Moderators: *John-Michael Sauer and Michael Lawton (Michael Merz)*

- The Past:** Key lessons learned from the SAFE-T/PSTC collaboration – *Denise Robinson-Gravatt*
- The Present:** Benefits from the ongoing collaboration; Preclinical and clinical qualification of markers for BSEP inhibition – *Douglas Keller*
- The Future:** How to build on a successful collaboration – *John-Michael Sauer and Michael Merz*
- Panel Discussion:** Panelists: *Maria Teresa DeMagistris (IMI SAFE-T)*  
*Douglas Keller (Sanofi)*  
*Ameeta Parekh (FDA)*  
*Denise Robinson-Gravatt (formerly Pfizer)*  
*Frank Sistare (Merck)*  
*Thorsten Vetter (EMA)*
- Expert Opinion: *ShaAvhrée Buckman-Garner (FDA)*

# Key Areas of Focus

- Setup and structure of the SAFE-T/PSTC collaboration
- Achievements through this collaboration (e.g. strategic and tactical benefits)
- Key lessons learned from the SAFE-T/PSTC collaboration
- Major obstacles in setting up the collaborative agreement
- Improvements to increase efficiency in the future
- Identifying additional areas which could benefit from more collaboration

# C-Path Predictive Safety Testing Consortium (PSTC)

## Scope & Expected Outcomes

Six organs in need of improved clinical monitoring of drug-induced injuries:



### **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*



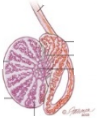
### **Liver:**

*Current biomarkers are not sufficiently sensitive and specific, and do not adequately discriminate adaptors from patients at high risk of developing liver failure*



### **Vascular System:**

*No biomarkers are available for detecting drug-induced vascular injury in humans*



### **Testicle:**

*No circulating biomarkers for seminiferous tubule toxicity*



### **Heart:**

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

**Biomarkers** and methods qualification (PMDA, EMA and FDA) for use in medical product development

Primarily nonclinical and translational expertise

# C-Path PSTC

## Participants and Collaborators

### Consortia Members (19)



### Partners (8)



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# IMI Safer and Faster Evidence-based Translation (SAFE-T) Consortium

## *Scope & Expected Outcomes*

Three organs in need of improved clinical monitoring of drug-induced injuries:

**Kidney:** current standards increase only once 50-60% of kidney function is lost.



**Liver:** current standards are not sufficiently sensitive and specific and do not adequately discriminate adaptors from patients at high risk to develop liver failure.

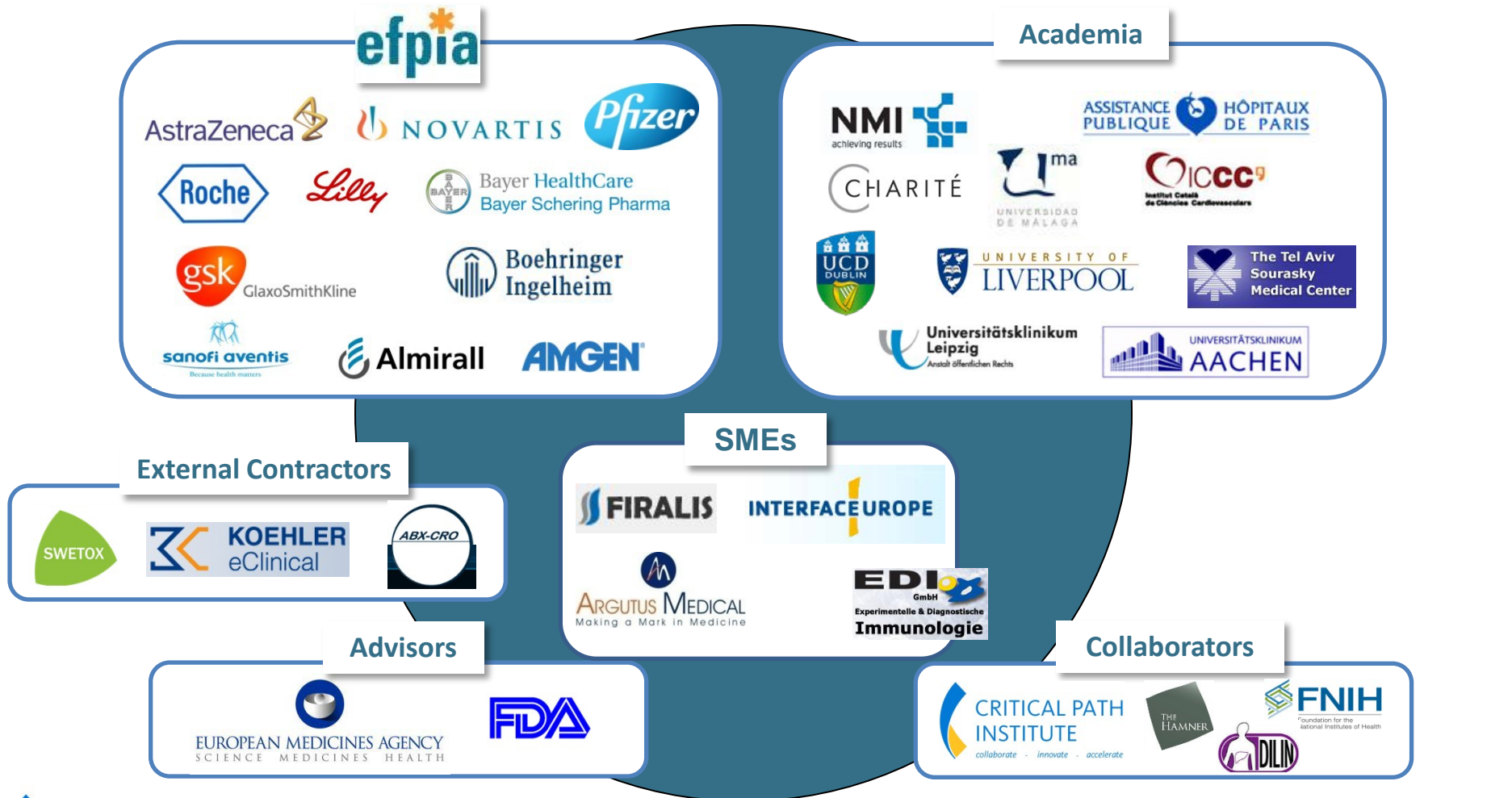


**Vascular System:** currently no biomarkers available for drug-induced vascular injury in human.

- Appropriate **DIKI, DILI and DIVI biomarkers** and methods qualified by the EMA and FDA for use in medical product development
- **Database for human safety biomarkers** with a detailed characterization of clinical, individual and drug-specific factors in the context of drug-induced toxicities and diseases
- **Biobank of human material**, obtained at different time points from patients enrolled in the clinical trials run by the consortium, to support future qualification of new biomarkers

# IMI (SAFE-T) Consortium

## Participants and Collaborators







# ***The Past: Key Lessons Learned from SAFE-T/PSTC***

**Denise Robinson Gravatt**

# Objectives

- Understand key elements of a successful collaboration in a consortium environment
- Recognize challenges and hurdles that may need to be overcome
- Describe how other consortia can capitalize on lessons learned

# A Tale of Two Consortia - Synergies

- Common objectives to improve the ability to address safety issues in early drug development
- Focus on similar organ systems (liver, kidney, vascular)
- Mutual desire for global regulatory partnerships
- Intent for information/tools in public domain
- Significant overlap in industrial participants
- Time/financial constraints
- **Note – in today's consortium-friendly environment, our scenario is increasingly likely**

# Collaboration Value Proposition

- Speed towards shared goals of improved translatable safety biomarkers
- Generate more robust dataset and increase impact through collaboration and coordination
- Optimize use of resources and minimize redundancy
- More effective regulatory engagement and consistency of decision making
- Enhance public awareness and scientific influence
- Increase acceptance and application of novel safety biomarkers

# How to Collaborate?

- Beyond participants' desire to work together...
- Recognized need for some type of legal framework
  - Need to protect integrity, IP and obligations of individual consortia
  - Specify terms of engagement
  - Structure for collaboration and decision making
  - Independent vs shared goals and activities
  - Transparency
  - Communication

# SAFE-T and PSTC Engagement Timeline

- Started informal discussions in late 2009
- Initiated interactions with a joint CDA (March 2010)
- Strategic meeting between heads of CPI and IMI (May 2010)
- Joint meetings of SAFE-T and PSTC consortia (from 2010 to present)
- Memorandum of Understanding signed between Critical Path Institute and Innovative Medicines Initiative (May 2011)
- PSTC/SAFE-T Legal Agreement approved (Nov 2012)
  - Framework approach to support explicit research collaboration
  - Collaboration Committee formed Dec. 2012
  - Specific Joint Project Plans developed and approved (April – Oct 2014); work in progress
- Engagement initiated between FNIH and SAFE-T (early 2013)
  - Determined that CDA would be most feasible form of agreement; finalized Sept. 2013
  - Joint regulatory strategy underway

# Successes

- Development of shared objectives and common vision of translational safety biomarker strategy
- Mutual respect and understanding of strengths of diverse participants, stakeholders
- Open information sharing and transparency
- Joint work plans addressing key regulatory feedback and requirements
- Open debate on emerging statistical practices
- Increased clarity and more harmonized regulatory processes

# Challenges - Legal

- Consortia have different legal frameworks
- Different intellectual property objectives
- Lack of common perspective between scientific participants and their respective legal experts
- Corporate vs public participant legal structures
- Differing perceptions of goals and value propositions
- Accountability to develop bridging legal documentation?
- Legal domains – US vs EU
- Terms and duration of agreement



# Challenges - Logistical

- Differing approaches (scientific, legal, resourcing)
- Non-overlapping members/participants
- Time zone differences
- Different project management models
- Assay providers within or external to projects
- Unformed regulatory processes
- Publication vs qualification strategy
- Commitment of key leadership roles and leadership changes

# Challenges - Cultural

- US vs. European models of partnership
- Industrial vs academic
- Regulatory vs. non-regulatory processes
- Drug development vs. clinical practice
- Commercialization vs. public domain

# Challenges - Regulatory

- How to engage regulators
  - participants, advisors, and/or customers
- When to engage regulators
- 3 different regulatory regions
- Unfamiliar territory and unformed processes
- Learning as we go in an evolving regulatory environment was necessary
  - but created delays, re-work and some confusion

# Challenges - Resourcing

- Sharing costs – a key impetus for consortia
- Complexity, diversity and extent of resources needed not fully envisioned
- Accountability and long-term commitment
- Sustain project over necessary time horizon
  - Participants departures, corporate restructuring, etc
- Evaluate different resourcing models
  - In-kind as well as direct financial resources needed
  - Project management essential

# Challenges – Achieving Impact

- Considering time frame from planning to execution to delivery to implementation
- Complex projects with multiple elements to align and complete
- Implementers need outreach and influencing
- Difficult to track use of biomarkers and impacts on drug development
- Proprietary vs public domain information
- Who is best able to collect metrics?

# Future Recommendations (1 of 2)

- Need sufficient project planning time
  - Define scenarios and contingencies
  - Match resource requests to project plan
  - Ensure core expertise (e.g., samples, assay development, data management, CROs, regulatory strategy, medical writing)
  - Anticipate need for changes to plan and flexibility
- Envision crucial collaborations at project design stage
- Establish collaboration framework at project inception
- Partnerships need to be aligned with requirements for expertise and resources
- Common understanding of IP and how to manage
- Early engagement of all stakeholders, esp. regulators

# Future Recommendations (2 of 2)

- Need for sustainable resourcing models
- Commitment of key leadership roles
- Optimize project management model(s)
- Sustainable knowledge management
  - databases, biobanking, implementation and metrics tracking
- Consider database maintenance as a continuing activity
  - Needs resourcing
- Set expectations to compile lessons learned and work towards best practices for consortia

# Benefits of SAFE-T and PSTC Collaboration

- Strong functional relationships developed
  - Among consortia leaders
  - Between respective WPs and WGs
  - Among consortia members
  - Between consortia and regulators
- Commitment to long range goals
- DIVI, DIKI, and DILI collaborative work plans are being executed across the consortia
- Overall strategies for biomarker qualification refined based on cross consortia interactions





***The Present: Benefits from the Ongoing  
Collaboration: Preclinical and Clinical  
Qualification of Markers for BSEP Inhibition***

**Douglas Keller (Sanofi)**

# Consortium Objectives

## PSTC

Regulatory qualification of safety biomarkers that inform preclinical and early clinical decision-making in drug development

## SAFE-T

Evaluate utility of clinical safety biomarkers for DIKI, DILI, DIVI. Develop and qualify assays for use in clinical drug development. Generate evidence for application to clinical practice and disease diagnosis.

# In the Beginning: Parallel workstreams on bile acids

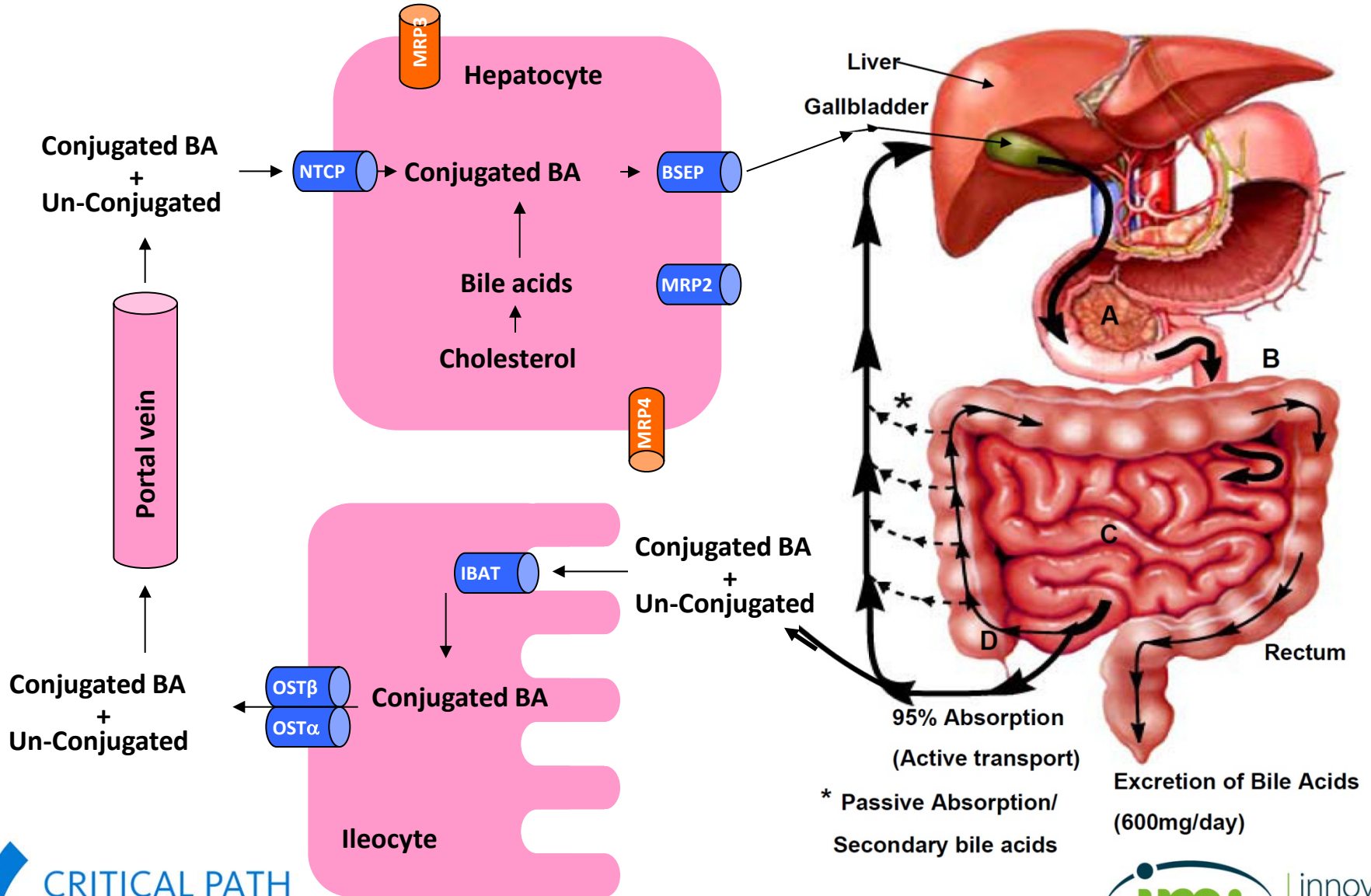


PSTC Hepatotoxicity Working Group  
BSEP Subteam – started in 2010



75 Bile acids as potential DILI biomarkers  
60 still of interest

# Bile Acid Trafficking: High Level



Courtesy of Ryan Morgan (Amgen)

# Why is a BSEP-Specific Biomarker Needed?

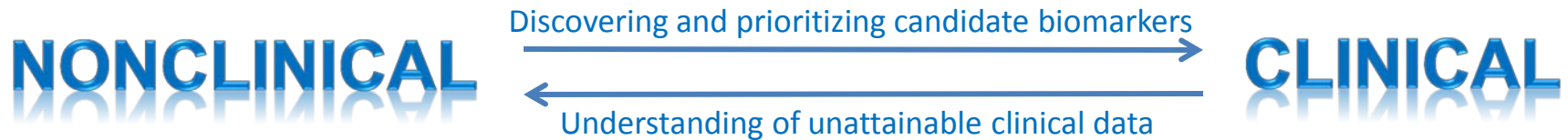
- Liver injury associated with BSEP inhibition often goes undetected during preclinical testing
  - Rodents are insensitive to liver injury due to this mechanism (e.g. Bsep knockout mice)
  - Humans are sensitive to liver injury due to this mechanism (e.g. genetic mutations in human BSEP)
    - Drugs that cause hepatotoxicity believed to be related to BSEP inhibition: AMG 009, bosentan, troglitazone, nefazodone, fusidic acid, and others
- In vitro assays can detect BSEP inhibition, but an in vivo model/biomarker to relate exposures needed to achieve clinically significant BSEP inhibition would greatly improve risk assessment
  - In vitro models often lack metabolic competency (e.g. membrane vesicle assay), do not account for protein binding, distribution, or other PK properties
  - An in vivo biomarker for BSEP inhibition may have clinical application and could help to generate a dataset that establishes causality between BSEP inhibition and drug induced liver injury (DILI)

# Regulatory Requests for Translational Studies

- EMA: “...there seems to be a lack of systematic evaluation of the preclinical work in order to inform and help design the clinical evaluation, and a retrospective data exchange is from this perspective not ideal.”
- FDA: “We recommend that you plan to support your clinical findings with the biomarker results, histopathology findings, and analyses from nonclinical toxicity studies in which the drug classes you intend to study in your confirmatory studies were used, when feasible.”
- “There may be great value in supporting your biomarker clinical findings with similar data and analyses from nonclinical toxicity studies in which other classes of hepatotoxic drugs were used (when feasible). We do recognize that nonclinical testing is an imperfect predictor of clinical toxicity, and that non-clinical toxicants selected for study should have relevance to clinical toxicants.”

# Moving Forward Using Translational Science

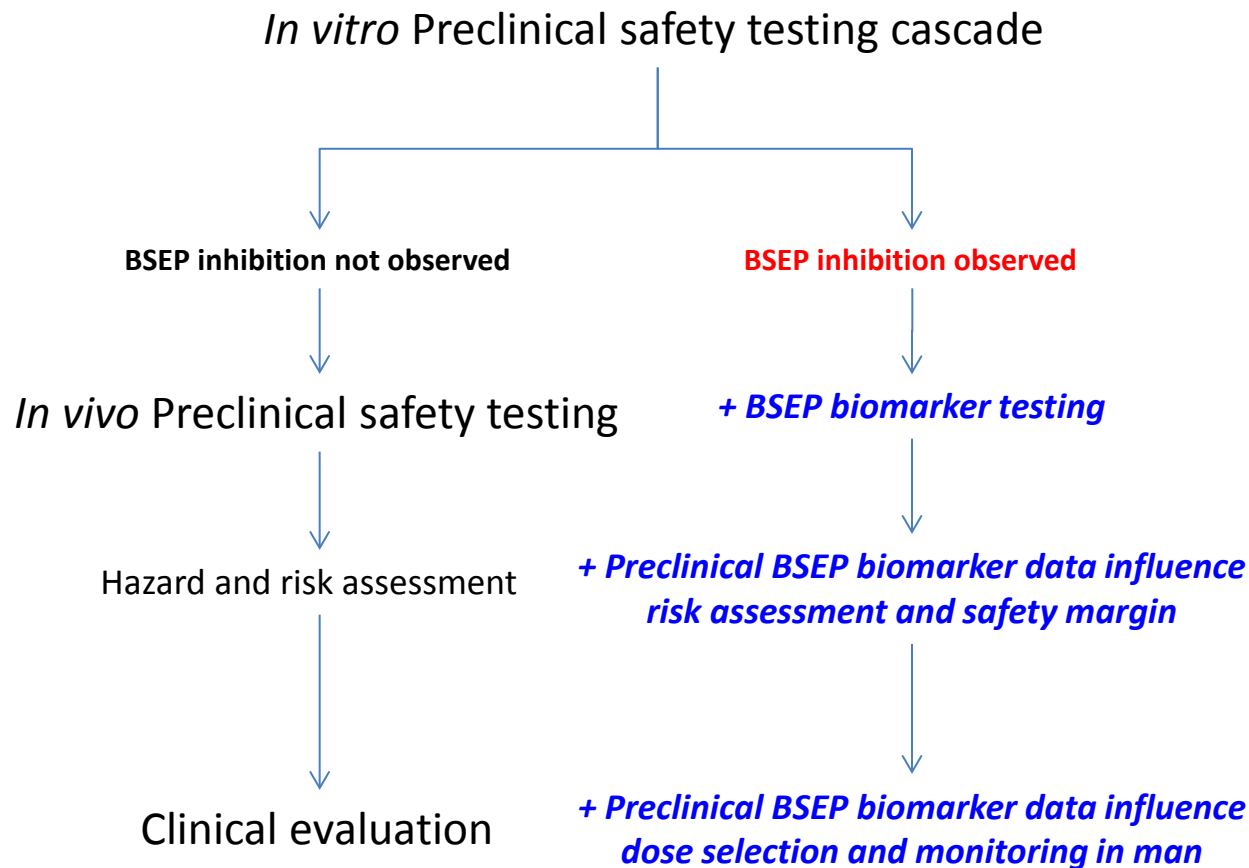
Translational opportunities for collaboration



- How does the onset of injury (histopathology) correlate with appearance of biomarker ?
- How does the resolution of injury (histopathology) correlate with normalization of the biomarker ?
- How does onset and development of adaptation (resolution of histopathology) with continued dosing correlate with biomarker levels ?
- What is the response of the biomarker when liver function is reduced ?
- Is the performance similar with different drugs ?
- How do confounding toxicities and health status affect biomarker performance ?
  - Do preclinical species exhibit different hepatic metabolism, pathophysiology and biomarker behavior and performance ?

# Biomarkers of BSEP Inhibition

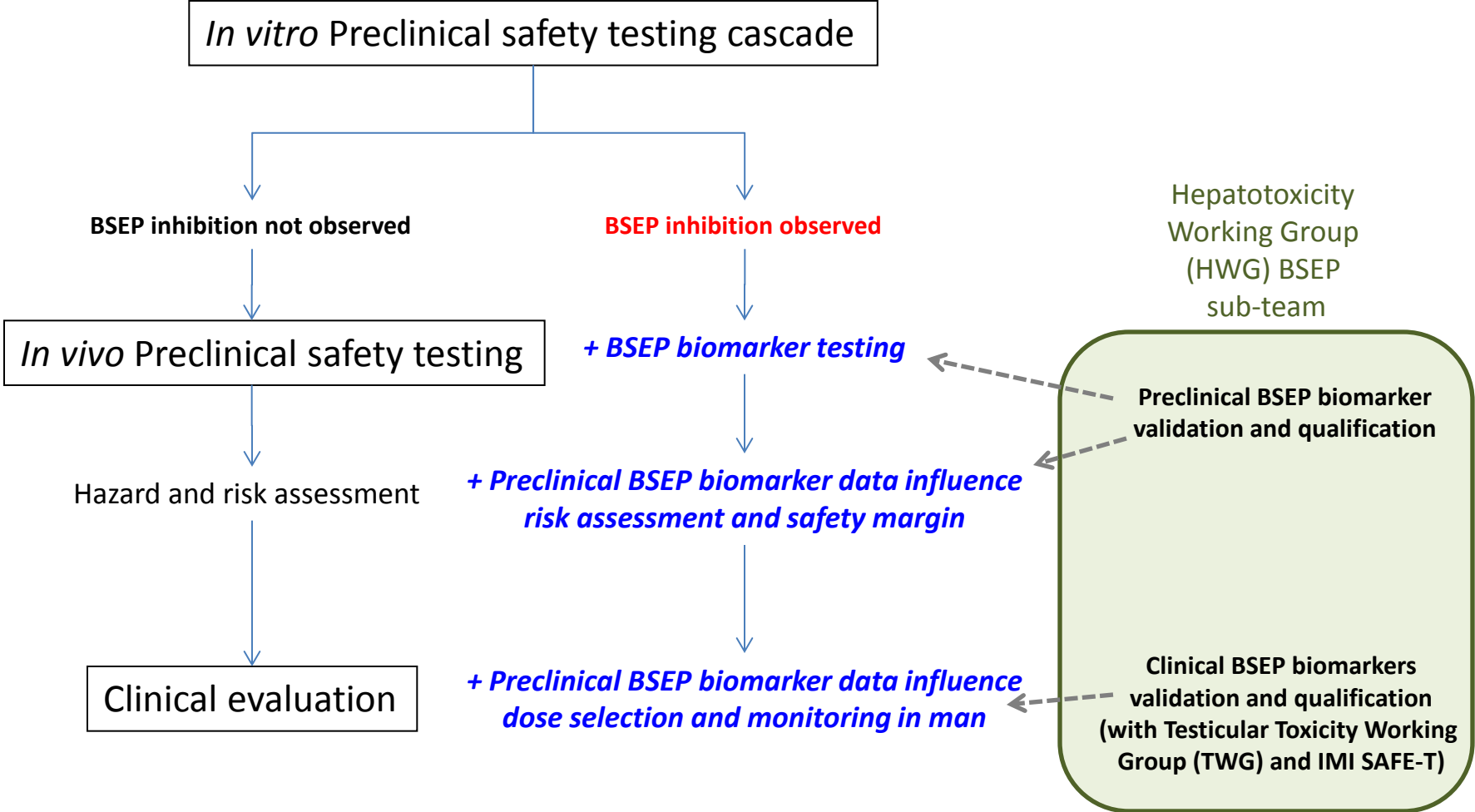
## Anticipated Utility and Impact





# Biomarkers of BSEP Inhibition

## Role of HWG BSEP subteam



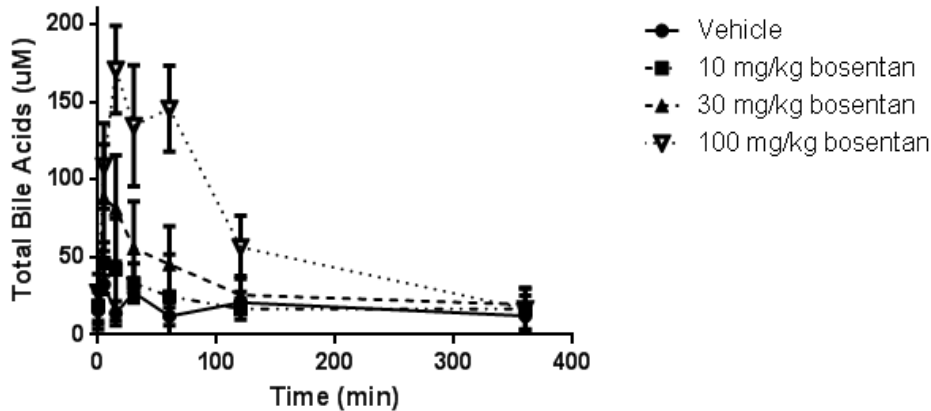
Hepatotoxicity Working Group (HWG) BSEP sub-team

Preclinical BSEP biomarker validation and qualification

Clinical BSEP biomarkers validation and qualification (with Testicular Toxicity Working Group (TWG) and IMI SAFE-T)

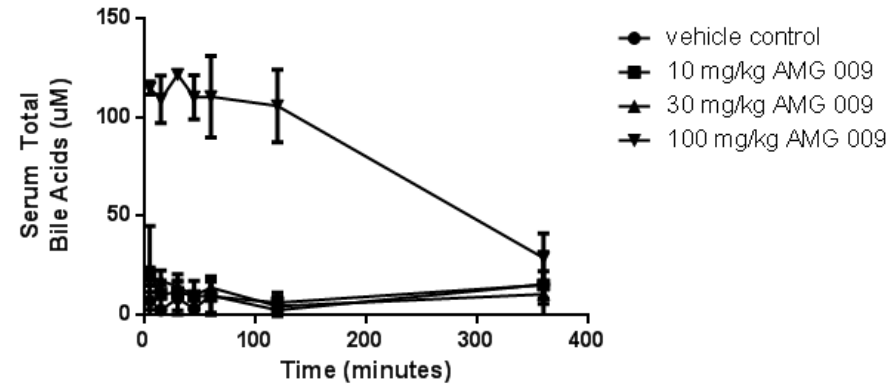
# IV administration of AMG 009 or bosentan causes dose-dependent elevations in serum total bile acids

**Serum Bile Acid Levels in Male Rats Following IV Administration of Bosentan**



IV exposure to 30 & 100 mg/kg bosentan = elevated total serum BA levels

**Serum Bile Acid Levels in Male Rats Following IV Administration of AMG 009**



IV exposure to 100 mg/kg AMG 009 = elevated total serum BA levels

PO exposure of up to 1500 mg/kg AMG 009 = no increase in total serum BA levels

PO exposure of up to 1000 mg/kg bosentan = no increase in total serum BA levels

Courtesy of Ryan Morgan (Amgen)

# SAFE-T WP 3 Data Summary

136 subjects - 61 are DILI and 75 are non-DILI

Single sample per subject (20 from DILI study)

Centre	Number of Subjects
Leipzig	12
Malaga	10
Liverpool	19
Paris	20
TASMC	50
SA	25

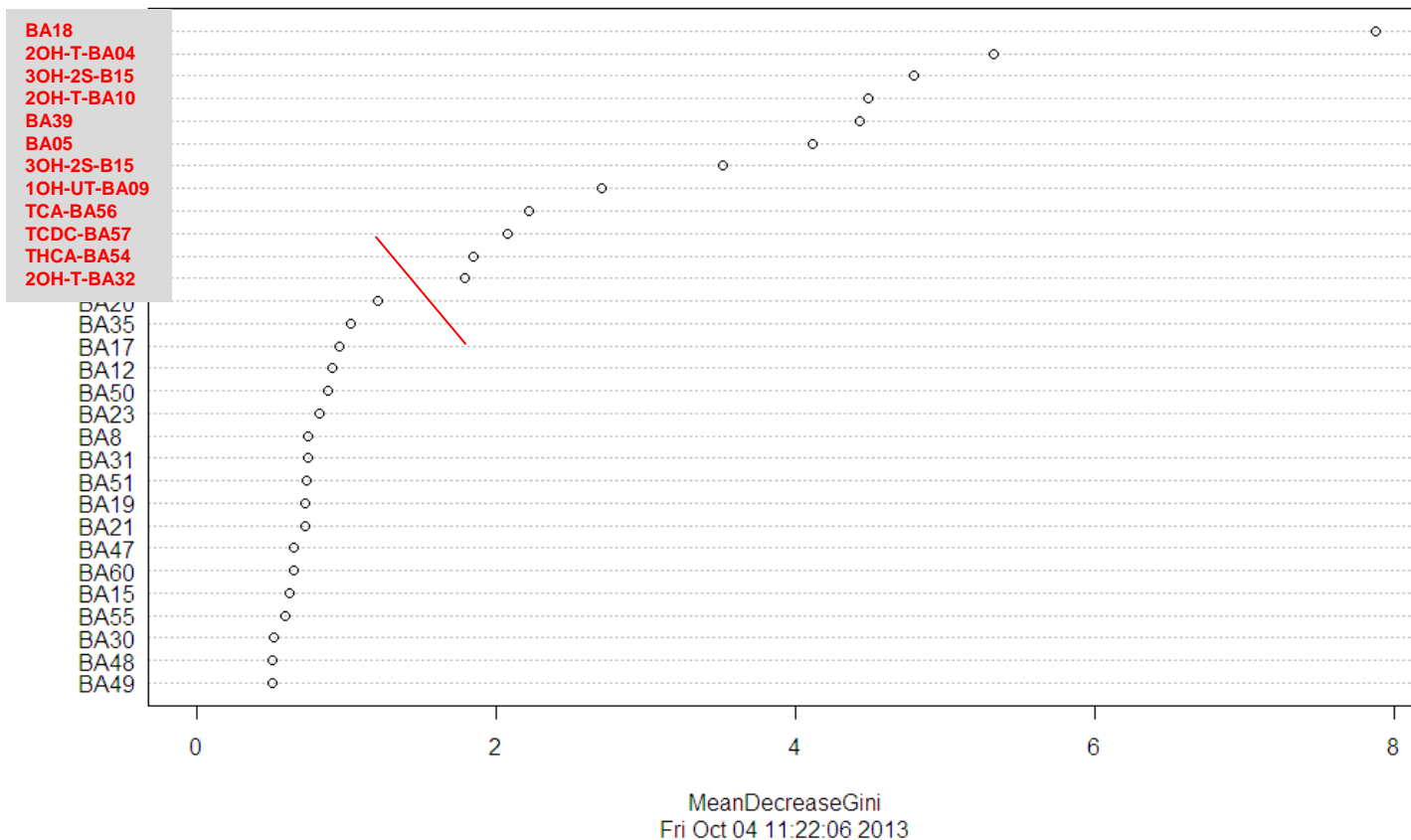
# Stage Gate Biomarkers

Albumin mRNA	miR122
Alpha-1-Fetoprotein	MCSF-R
Arginase 1	Osteopontin
GLDH	Paraoxonase 1
GST alpha 1	Paraoxonase 1 / Prothrombin
HPD	Prothrombin
HMGB1	ccKeratin 18
Hyperacetylated HMGB1	Regucalcin
Keratin 18	ST6Gal1
Keratin 18 / ccKeratin 18	SDH
LECT2	<b>75 Bile Acids (only 60 with DILI/non-DILI)</b>

# 1) Actual Bile Acid Species

From the initial DILI Stage gate analysis, a random forest analysis was performed on all 60 bile acids and 12 were selected

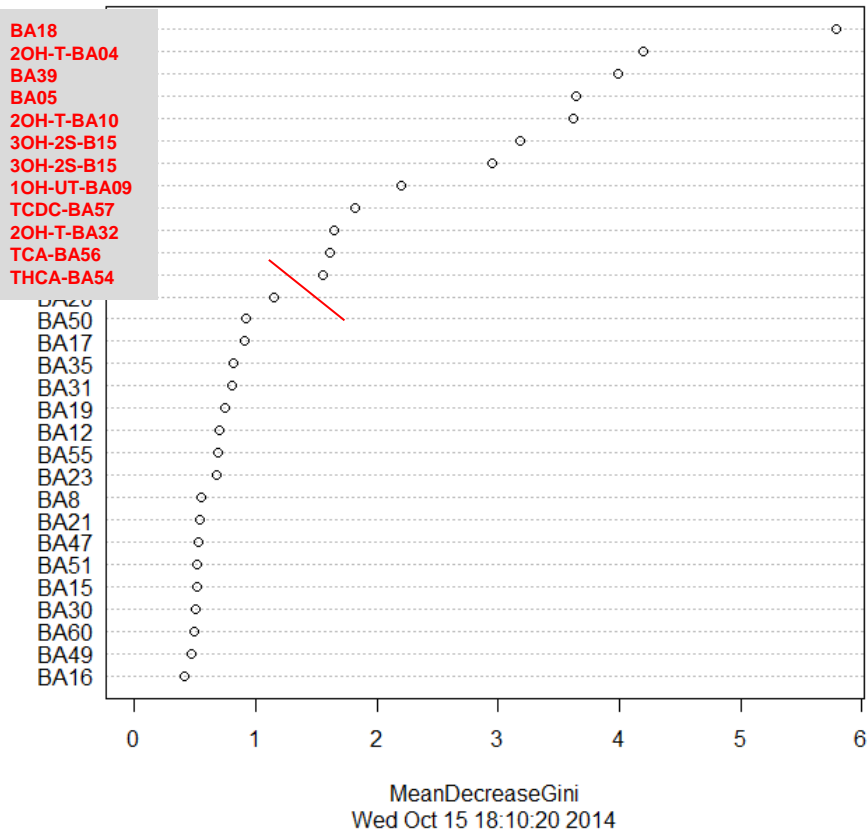
Random Forest Plot - All Bile Acids (No Imputation)



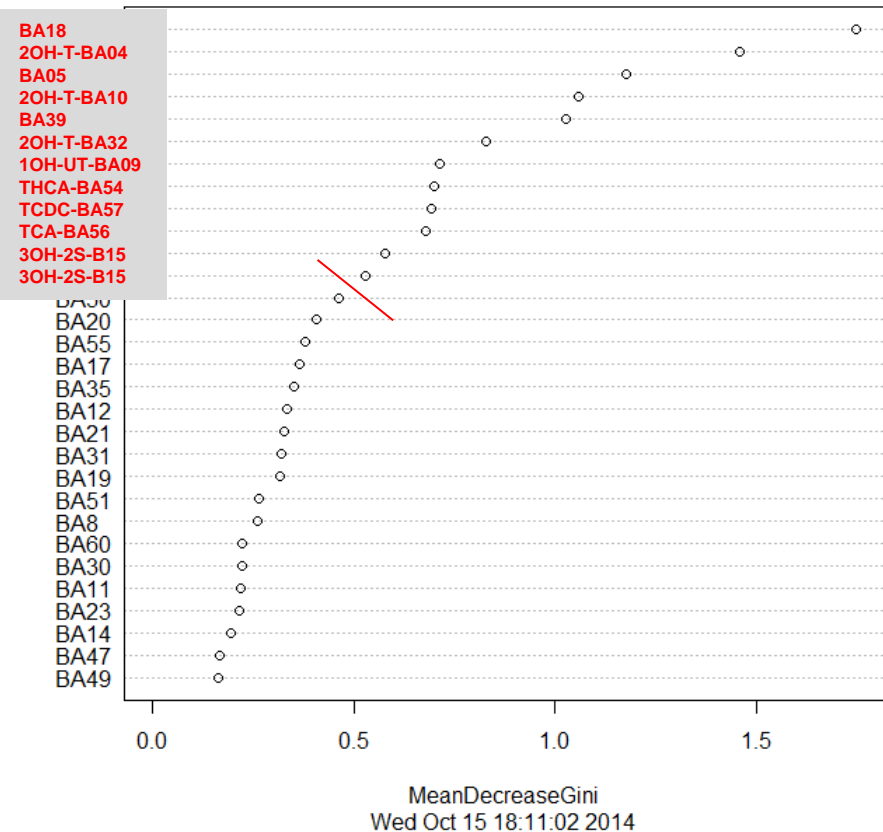
MeanDecreaseGini  
Fri Oct 04 11:22:06 2013

# 2. Stratifying by Liver Injury

Random Forest Plot - Hepatocellular - All Bile Acids (No Imputation)



Random Forest Plot - Cholestatic Injury - All Bile Acids (No Imputation)



The same 12 bile acids are coming out on top regardless of the type of liver injury

# Consortium Collaboration Points

- Discussion of clinically relevant compounds to use
- Similarity of analytical methods
- Sharing of study data and interpretations
- Discussion of study designs

# Benefits from Collaboration

- **What?**

- PSTC

- SAFE-T studies can provide avenue for clinical qualification that is unlikely to be attained by PSTC alone

- SAFE-T

- PSTC data on bile acids can provide mechanistic support for SAFE-T qualification
- PSTC studies can provide BSEP-specific data not planned on by SAFE-T

- **How?**

- Discuss study designs and analysis plans prior to study initiation



# Consortium Objectives

## Collaboration

### PSTC

Regulatory qualification of safety biomarkers that inform preclinical and early clinical decision-making in drug development

### SAFE-T

Evaluate utility of clinical safety biomarkers for DIKI, DILI, DIVI. Develop and qualify assays for use in clinical drug development. Generate evidence for application to clinical practice and disease diagnosis.

# Consortium Objectives

## Collaboration

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# Consortium Objectives

## Collaboration

### PSTC

Regulatory qualification of safety biomarkers that inform preclinical decision-making in drug development  
**evidence for application**

### SAFE-T

Evaluate utility of clinical safety biomarkers for DIKI, DILI, DIVI. Develop and qualify assays for use in clinical drug development. Generate to clinical practice and disease diagnosis. **and early clinical**

# Acknowledgements

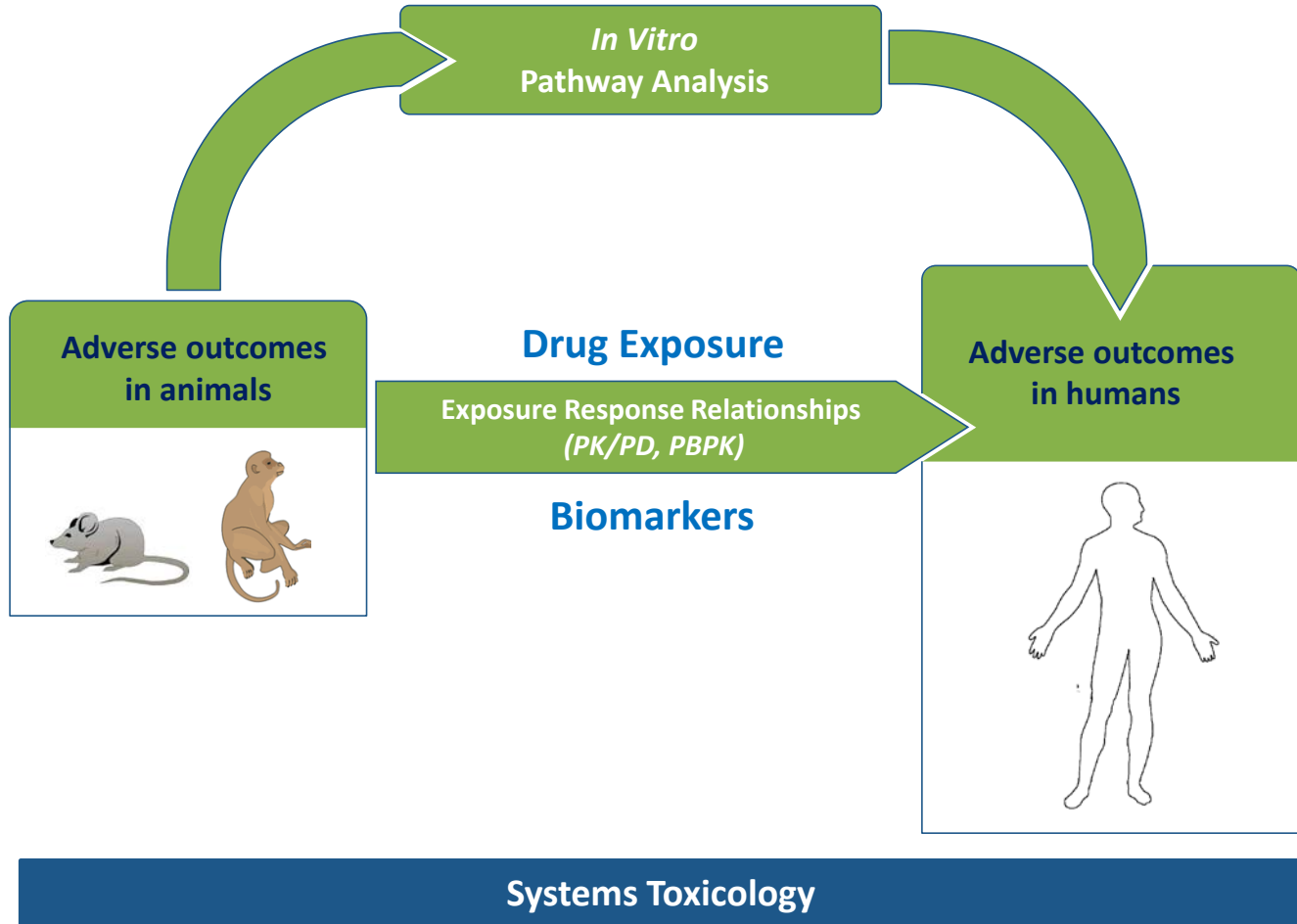
- PSTC
  - Jeff Lawrence
  - Patrick Kirby
  - Ryan Morgan
  - Jon Maher
  - John-Michael Sauer
  - Nick King
- SAFE-T WP 3
  - Michael Merz
  - Gerd Kullak-Ublick
  - Frances Hackman



# ***The future: How to build on a successful collaboration***

**John-Michael Sauer and Michael Merz**

# The Future of Safety Assessment (maybe)



# The Future of the PSTC and SAFE-T Collaboration

# SAFE-T Follow-up: A Call for Continuing Collaboration

*June, 2015*



# SAFE-T: Aspirations...

- Appropriate **DIKI, DILI and DIVI biomarkers** and methods qualified by the EMA and FDA for use in medical product development.
- **Database for human safety biomarkers** with a detailed characterization of clinical, individual and drug-specific factors in the context of drug-induced toxicities and diseases.
- **Biobank of human material**, obtained at different time points from patients enrolled in the clinical trials run by the consortium, to support future qualification of new biomarkers.

# ... and likely achievements

- Appropriate **DIVI biomarkers and methods qualified, and DIKI/DILI biomarkers and methods supported** by the EMA and FDA for use in medical product development
- Database for human safety biomarkers with a detailed characterization of clinical, individual and drug-specific factors in the context of drug-induced toxicities and diseases.
- Biobank of human material, obtained at different time points from patients enrolled in the clinical trials run by the consortium, to support future qualification of new biomarkers.

# Unmet Needs Beyond SAFE-T

- Full confirmatory qualification for DILI and DIKI safety biomarkers
- Broader CoUs for DIKI, DILI, and DIVI
- Validation, qualification, and calibration in larger and more diverse patient populations and across labs
- Point of care diagnostics for a subset of markers to support more flexible and less burdensome safety monitoring
- Additional markers closing remaining gaps, e.g. predictive vs diagnostic/prognostic markers, markers of hepatic *function*
- Mechanistic underpinning for key markers
- Translational link from *in vitro* to *in vivo* to *clinical* application of key markers
- A comprehensive reference safety database across key target populations, supporting calibration of new and standard safety biomarkers

# SAFE-T 2.0 (“SAFE-T PoC”): Expanded Safety Biomarker Qualification and PoC Assay Development

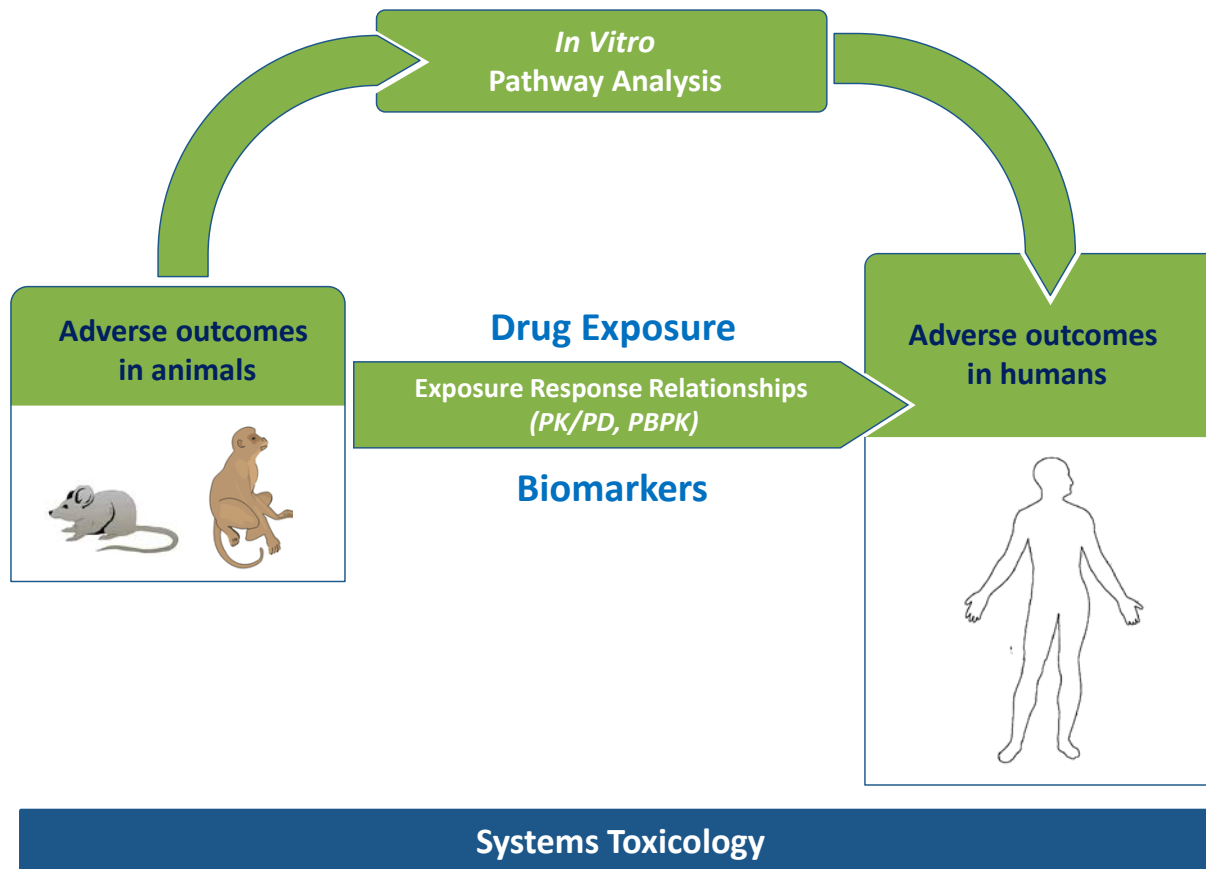
- Complete the qualification of new safety biomarkers for DIKI, DILI, and DIVI
- Expand biomarker qualification to larger and more heterogeneous patient populations, and to application in clinical practice, aiming at ISO certified, validated biomarker assays
- Develop point-of-care diagnostics for newly qualified biomarkers
- Support discovery of new biomarker candidates addressing gaps in existing panels, using technologies such as next generation sequencing, proteomics, and metabolomics
- Bridge preclinical and clinical biomarker assessment to *in vitro* models

# SAFE-T 2.0: Synergies and Deliverables

- Efficient collaboration between PSTC and SAFE-T, benefitting from significant synergies, to be continued from initiation onwards.
- Expected key deliverables:
  - A set of qualified new safety biomarkers for drug-induced liver, kidney, and vascular injury with practically meaningful contexts of use, across a variety of patient populations highly relevant to public health, approved by EMA and FDA
  - ISO certified standard assays for use in drug development and clinical practice
  - ISO certified point-of-care assay devices for a subset of new safety biomarkers
  - A comprehensive reference safety database with biomarker profiles across relevant target patient populations, including data on new and established safety biomarkers
  - A biobank of human serum, plasma, whole blood and urine samples for further medical research as defined at project outset
- **Additional synergies with European (MIP-DILI, Safer Medicines Trust) and US-based consortia (FNIH BC, DILIN, ALFS group) to be explored.**

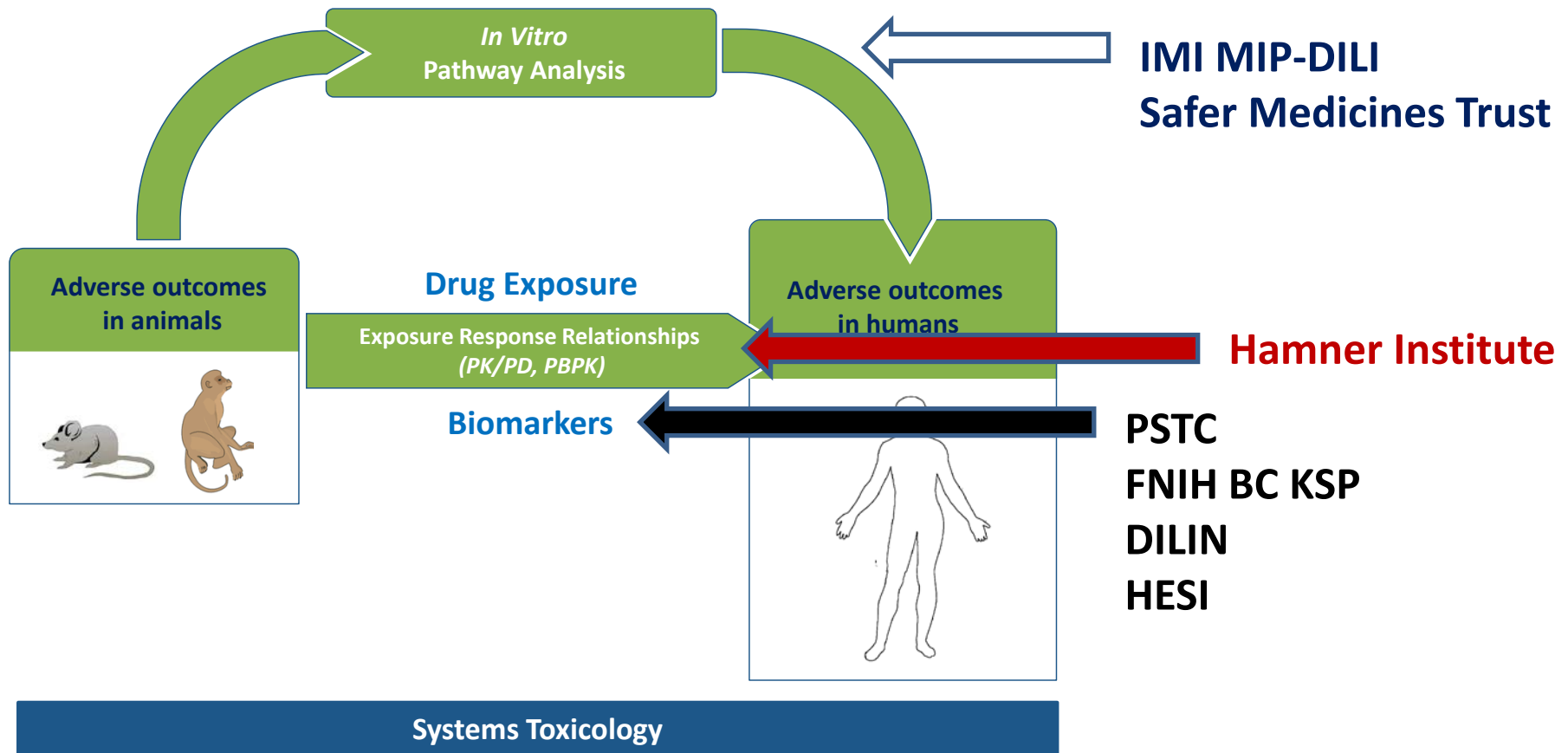
# Expanding Collaborations

## Defining a Translational Safety Strategy



# Expanding Collaborations

## Defining a Translational Safety Strategy



# Summary: SAFE-T and SAFE-T 2.0

- At project end, SAFE-T and PSTC will have generated a rich dataset on new safety biomarkers for drug-induced kidney (DIKI), liver (DILI), and vascular (DIVI) injury.
- Some of the most promising DIVI markers may receive a Qualification Opinion, some of the most promising DIKI and DILI markers may receive a Letter of Support.
- Completion of qualification of DILI and DIKI markers will be left for follow-up.
- **A respective proposal, relying on continuation of the successful collaboration with PSTC, is being prepared for IMI2.**



# Collaboration with Health Authorities

# Collaboration with Health Authorities

- A key attribute of a successful consortium with regulatory goals is a strong working relationship with health authorities
- PSTC, in partnership with SAFE-T and FNIH BC KSP, has been developing such relationships
  - Many regulators are “deep in the trenches with us” helping to facilitate biomarker qualification
- A primary goal has been to better define and refine the qualification process
  - Letter of support
  - Qualification with a limited context of use
  - Definition of evidentiary standards for biomarker qualification

# Collaboration with Health Authorities

- Qualification is far from a standardized locked in process at this point. We are still learning.

*“We are making this up as we go along”*

- It appears that the final definition of qualification will be based on a consensus-based process.
  - Thus, consortia and other stakeholders can directly participate in the evolution of the qualification process.



## ***Session 2: Safety Biomarkers: The PSTC and SAFE-T Collaboration***

**Panel Discussion and Expert Opinion**

# Accelerating the Development of Drugs, Diagnostics, and Devices: Partnerships to Expand the Precompetitive Space

**Moderators:** *John-Michael Sauer (C-Path)*  
*Michael Lawton (Pfizer)*

**Panelists:** *Maria Teresa DeMagistris (IMI SAFE-T)*  
*Douglas Keller (Sanofi)*  
*Ameeta Parekh (FDA)*  
*Denise Robinson-Gravatt (formerly Pfizer)*  
*Frank Sistare (Merck)*  
*Thorsten Vetter (EMA)*

**Expert Opinion:** *ShaAvhree Buckman-Garner (FDA)*

# Key Topics for Panel Discussion

- Is there an optimal path to follow in order to setup a successful collaboration between consortia?
  - What are the key attributes that allowed SAFE-T and PSTC to work successfully together?
  - What are the major obstacles that all consortia will face in establishing collaborations?
- How are key stakeholders (IMI, C-Path, FNIH BC, FDA, EMA) helping to drive cross consortia collaboration?
- How have both consortia cultivated successful relationships with health authorities?
  - Is there a regulatory “advantage” if consortia work together?



## ***Session 2: Safety Biomarkers: The PSTC and SAFE-T Collaboration***

# Thoughts on Biomarker Qualification Efforts

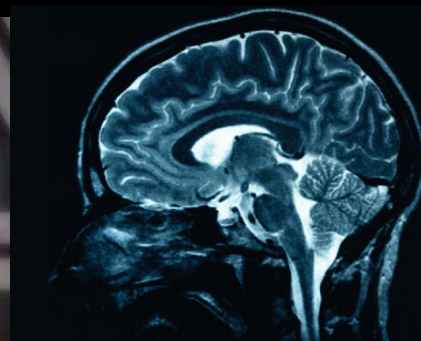
*ShaAvhrée Buckman-Garner, M.D., Ph.D., F.A.A.P.*

*Director*

*Office of Translational Sciences*

*Center for Drug Evaluation and Research*

*Food and Drug Administration*





## What we said in 2004:

A new product development toolkit — containing powerful new scientific and technical methods such as animal or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques — is urgently needed to improve predictability and efficiency along the critical path from laboratory concept to commercial product. We need superior product development science to address these challenges — to ensure that basic discoveries turn into new and better medical treatments. We need to make the effort required to create better tools for developing medical technologies. And we need a knowledge base built not just on ideas from biomedical research, but on reliable insights into the pathway to patients.

# What we said in 2006:

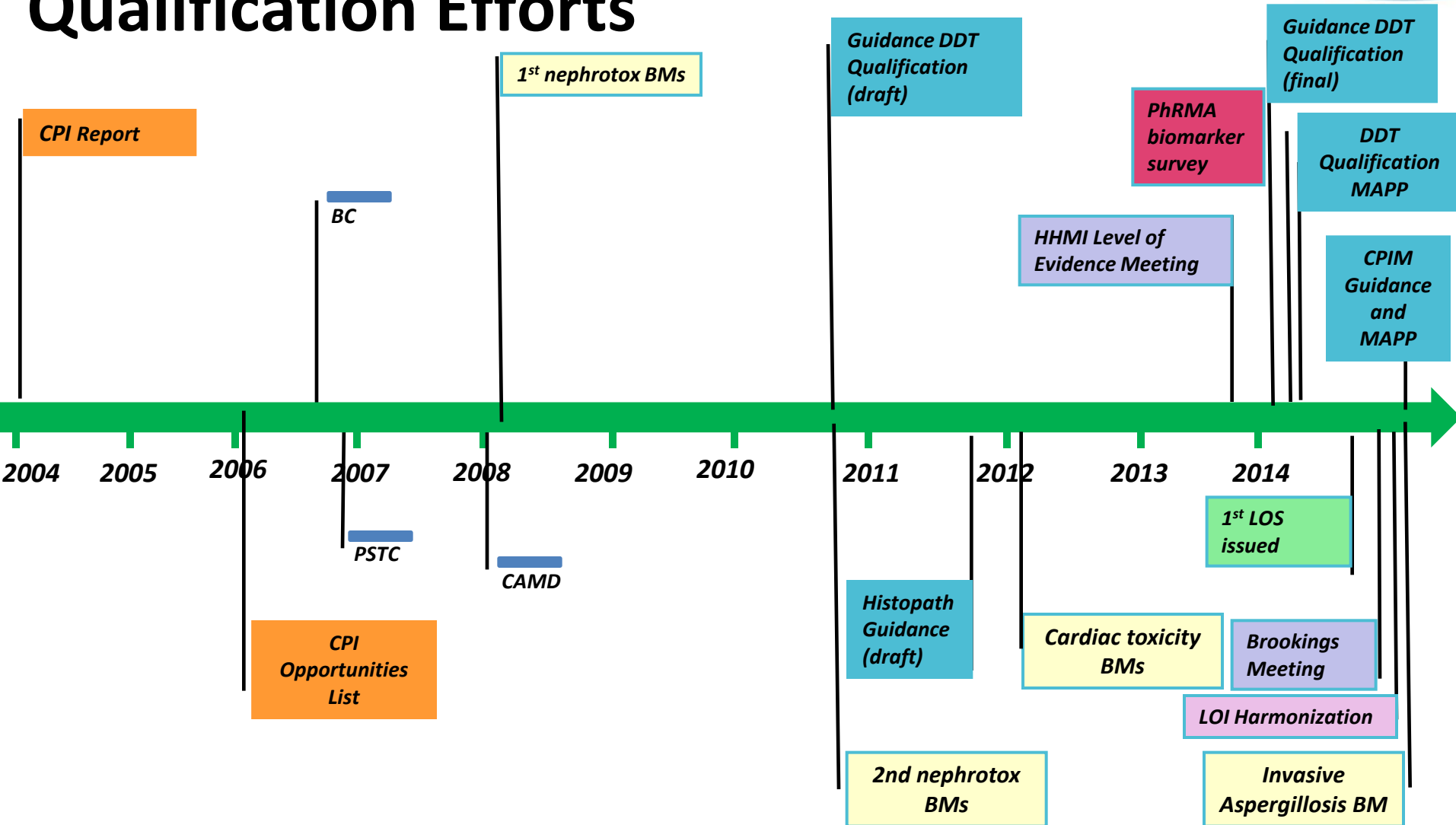
**1. Biomarker Qualification.** The process and criteria for qualifying biomarkers for use in product development should be mapped. Clarity on the conceptual framework and evidentiary standards for qualifying a biomarker for various purposes would establish the path for developing predictive biomarkers. Stakeholders, including industry, researchers, and patient groups would have a clear idea of what needs to be done to adopt a new biomarker for regulatory use. Such a framework could stimulate biomarker development and, consequently, shorten the time necessary to develop a successful marketing application.

Identifying the framework and evidence needed to qualify biomarkers for different purposes would put an emphasis on correlative and predictive science to accompany the current emphasis on biomarker discovery. Consensus on the following types of questions is needed to put such a framework in place:

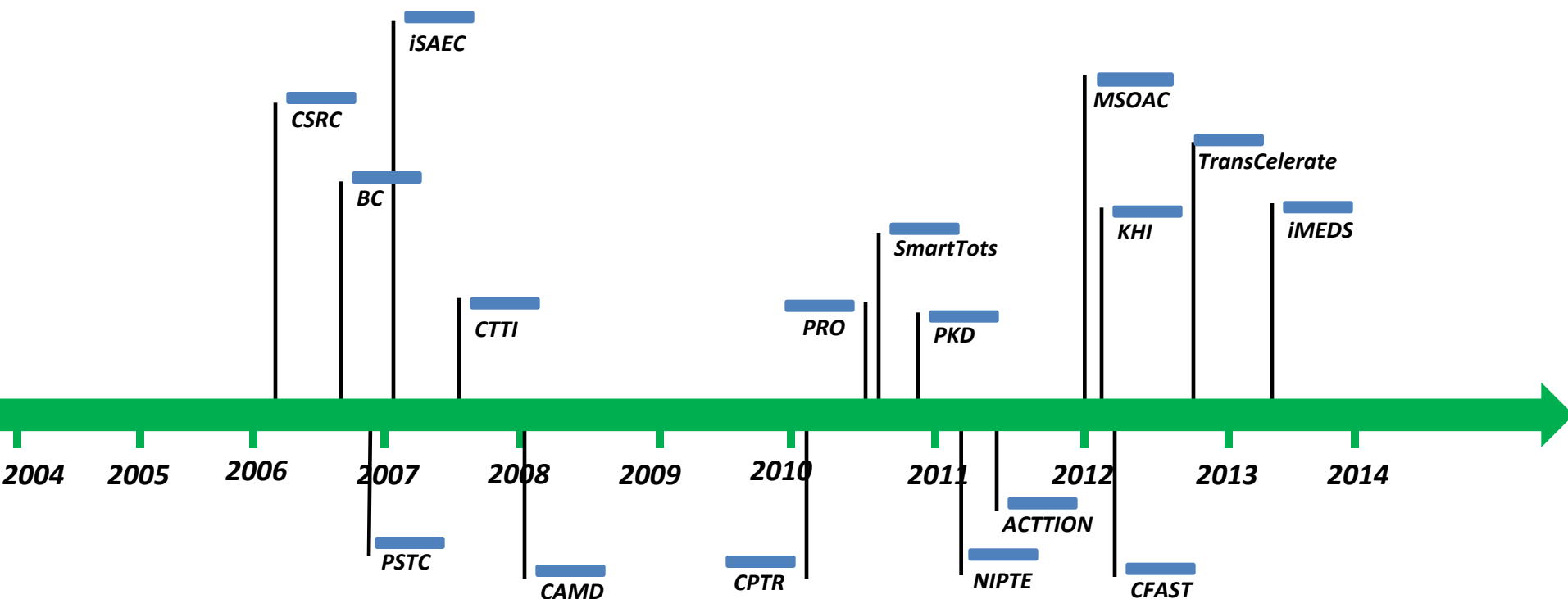
- How can biomarker evidence help demonstrate that a candidate product is not too toxic to test in humans?
- How can biomarkers be used to select dose ranges for initial human testing?
- How can biomarkers be used most effectively to evaluate dose response in later trials?
- What biomarker evidence is appropriate to guide selection of patients for clinical testing?
- What types and levels of evidence are needed to accept a biomarker as a surrogate endpoint for product efficacy?

# What has happened since then?

# Timeline for Salient Biomarker Qualification Efforts



# Examples of Consortia



*Cardiac Safety Research Consortium (CSRC), Biomarker Consortium (BC), Predictive Safety Testing Consortium (PSTC), Clinical Trials Transformation Initiative (CTTI), Coalition Against Major Disease Consortium (CAMD), Critical Path to TB Drug Regimens (CPTR) Consortium, Patient Reported Outcomes (PRO) Consortium, Polycystic Kidney Disease Outcomes (PKD) Consortium, National Institute for Pharmaceutical Technology and Education (NIPTE), Analgesic Clinical Trial Translations, Innovations, Opportunities, and Networks Initiative (ACTTION), Multiple Sclerosis Outcome Assessments Consortium (MSOAC); Kidney Health Initiative (KHI), Coalition For Accelerating Standards and Therapies (CFAST), Innovation in Medical Evidence Development and Surveillance (iMEDS) Program*

# Drug Development Tool Qualification Program

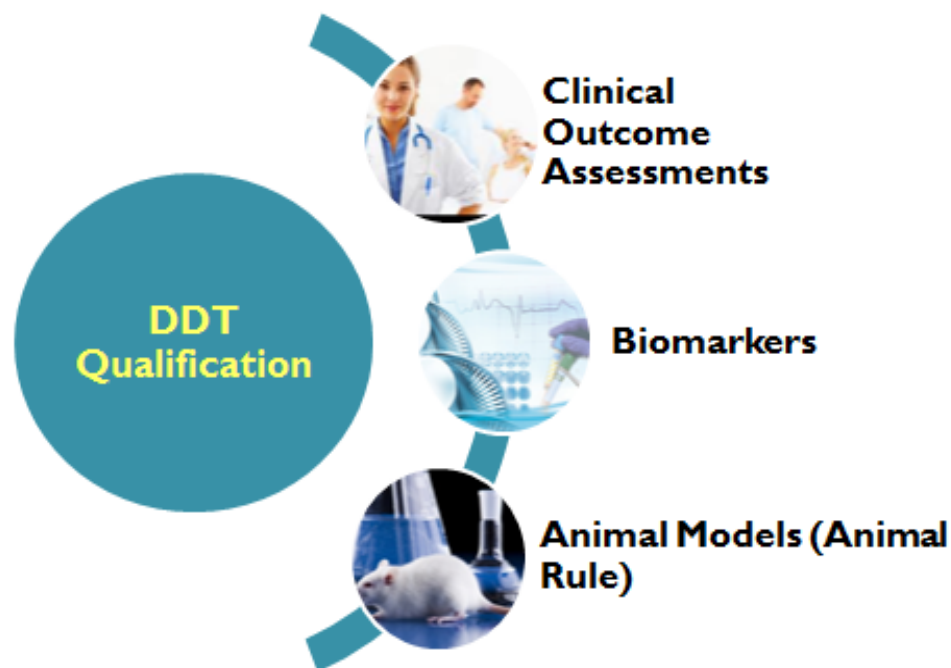
**Guidance for Industry  
and  
FDA Staff**

**Qualification Process for  
Drug Development Tools**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf>

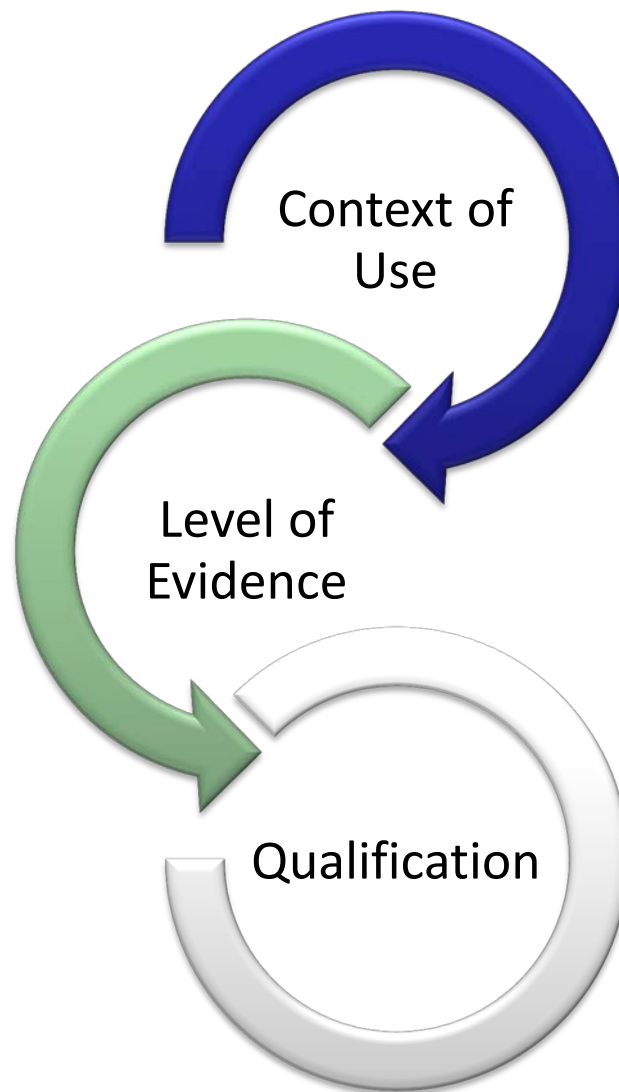
U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)

January 2014  
Final



# FDA-Qualified DDTs

DDT Type	Name	Submitter	Qualification Date
Biomarker	Seven Biomarkers of Drug Induced Nephrotoxicity in Rats	Predictive Safety and Testing Consortium (PSTC)	4/14/2008
Biomarker	Nonclinical Qualification of Urinary Biomarkers of Nephrotoxicity	International Life Sciences Institute(ILSI)/Health and Environmental Sciences Institute (HESI)	9/22/2010
Biomarker	Nonclinical Qualification of Circulating Cardiac Troponins T and I as Biomarkers of Cardiac Morphologic Damage	P J O'Brien, WJ Reagan, MJ York and MC Jacobsen	2/23/2012
COA/PRO	Exacerbations of Chronic Pulmonary Disease Tool (EXACT)	Evidera	1/09/2014
Biomarker	Galactomannan for Invasive Aspergillosis	Mycoses Study Group	10/24/2014





# Critical Path Innovation Meetings

- New CDER program
- Promotes understanding challenges in drug development and innovative strategies to address them
- Potential biomarkers not ready for DDT Qualification Program
- Natural history study design and implementation
- Emerging technologies or new uses of existing technologies
- Novel clinical trial designs and methods
- Nonbinding on FDA and other participants
- No advice on specific approval pathways



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# Critical Path Innovation Meetings

## Guidance for Industry

### *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Alicia B. Stuart 301-796-3852.

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)

October 2014  
Procedural

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Development & Approval Process (Drugs)

[Drug Development Tools Qualification Program](#)

[Animal Model Qualification Program](#)

[Biomarker Qualification Program](#)

[Clinical Outcome Assessment Qualification Program](#)

Resources for You

- [Biomarker Qualification Context of Use](#)
- [Biomarker Qualification FAQ](#)
- [Biomarker Qualification Contacts and Submitting Procedures](#)
- [Biomarker Qualification Templates and Examples](#)
- [Additional Resources](#)

## Letters of Support

### What is a Letter of Support?

This is a letter issued to a submitter that briefly describes CDER's thoughts on the potential value of a biomarker and encourages further evaluation. This letter does not connote qualification of a biomarker. It is meant to enhance the visibility of the biomarker, encourage data sharing, and stimulate additional studies.

### Why Issue a Letter of Support?

Encouraging the identification and qualification of new drug development tools has been recognized as one of the approaches to overcome hurdles in drug development programs. This approach has the potential to enhance the availability of useful information about drug safety and efficacy. To encourage further development of promising biomarkers which are not yet ready for qualification, FDA may issue a Letter of Support to submitters who have assembled this information about promising biomarkers.

### Where Can You Find Issued Letters of Support?

Letters of Support are made publicly available on the FDA's [DDT-Biomarker Qualification Program Website](#).

For more information, please contact [CDER-BiomarkerQualificationProgram@fda.hhs.gov](mailto:CDER-BiomarkerQualificationProgram@fda.hhs.gov).

### Issued Letters of Support

Submitter	Biomarkers	Area(s) for Further Evaluation	Issuance Date with Link to Letter of Support	Additional Information
Predictive Safety Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)	Urinary Biomarkers: Osteopontin and Neutrophil Gelatinase-associated Lipocalin (NGAL)	Early Clinical Drug Development	8/20/2014: <a href="#">Letter of Support (PDF)</a>	Refer to <a href="#">Predictive Safety Testing Consortium</a> Web Site for more information.

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- Development & Approval Process (Drugs)
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- Animal Model Qualification Program
- Biomarker Qualification Program
- Clinical Outcome Assessment Qualification Program

## Joint FDA/ EMA Letter of Intent (LOI) Submissions for Biomarker and Clinical Outcome Assessment Qualification Programs

A [Joint Letter-of-intent \(LOI\) template](#) to enable efficient parallel submissions to the US FDA and EMA for Drug Biomarker Qualification or Clinical Outcome Assessment Qualification.

The United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are launching a [joint letter of intent \(LOI\) template](#) to encourage parallel submissions to these agencies for qualification of biomarkers or clinical outcome assessments. As noted in the template, some sections of the form are specific for the FDA or EMA. This joint template is intended to reduce the submitter's preparation time. However, it is not a requirement for joint submission to FDA and EMA—the submitter may still choose to send in the agency-specific form for the LOI to each agency.

When joint LOIs for DDT qualification are submitted to FDA and EMA, the two agencies share scientific perspectives, advice, and response letters for the submitters.

There are three stages in the DDT qualification process at both the agencies, with minor differences in nomenclature as shown in the table below:

Stage	FDA	EMA
1	Initiation	Pre-submission
2	Consultation and Advice	Consultation and Advice by the Secretariat
3	Review	Review by the Scientific Advice Working Party

[Joint LOI template](#) submissions for FDA should be submitted via the following process:

- **Electronic Submissions only:** All DDT qualification correspondence and documents must be transferred to an optical disc storage media format (i.e., CD or DVD) and accompanied by a paper copy of the [Drug Development Tool \(DDT\) Cover letter \(PDF\)](#). A copy of the Cover letter should also be included in the electronic media.
- **Submission Mailing Address:** The paper copy DDT Cover letter and electronic media should be mailed to:  
 CDER Central Document Room  
 5901-B Amundale Road  
 Beltsville, MD 20705-1266

For additional questions please contact:

**Biomarker**  
 CDER-Biomarker Qualification Program  
 Email: [CDER-BiomarkerQualificationProgram@fda.hhs.gov](mailto:CDER-BiomarkerQualificationProgram@fda.hhs.gov)  
 Phone: (301) 796-2600

**Clinical Outcome Assessments**  
 Study Endpoints and Labeling Development (SEALD) - Study Endpoints Team  
 Email: [SEALD.ENDPOINTS@fda.hhs.gov](mailto:SEALD.ENDPOINTS@fda.hhs.gov)  
 Phone: 301-796-0900

# November 2014

FDA U.S. Food and Drug Administration  
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CDER Director's Mailbag

CDER Conversations

CDER Director's Mailbag: Answered Questions

From our perspective

Resources for You

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## From our perspective: Clinical biomarker qualification



Shashi Amur, PhD, Scientific Coordinator for CDER's Biomarker Qualification Program shares her perspective on CDER's first clinical biomarker qualification, and the need for more high-quality drug development tools.

### Biomarkers in drug development

Let me begin with the definition of a biomarker: a biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or biological responses to a therapeutic intervention. An example that is familiar to many people is the use of blood glucose levels to measure the effectiveness of a diabetes medication. In this case, glucose is the biomarker.

Biomarkers can be employed in many different aspects of drug discovery and development and also in the health care setting. Biomarker research can increase our understanding of the molecular underpinnings of a disease process, and this in turn can result in discovery of novel drug targets. A greater understanding of the disease process could also lead to biomarker-based enrichment strategies that enroll patients more likely to respond an investigational treatment in clinical trials. For example, human epidermal growth factor receptor 2 (HER2) is overexpressed in a subset of breast cancer patients who have a poor prognosis. This molecule has been used as a biomarker to identify patients who overexpress HER2 and thus are more likely to respond to monoclonal antibody treatments that block the HER2 protein.

In addition to influencing clinical trial design, biomarkers are also used in drug development for a variety of purposes including monitoring drug safety in preclinical or clinical studies, and identifying the optimal dose of a therapeutic. Clinical biomarkers are also useful in health care practice for the diagnosis and monitoring of a disease, or for identifying patients at risk for a serious adverse event or those who may be more likely to benefit from a drug treatment.

### Biomarker qualification

There are multiple pathways for biomarker acceptance and integration into drug development. Traditionally, biomarker acceptance has been achieved through submission of biomarker data in Investigational New Drug, New Drug or Biologics License applications. The challenge with this approach is that the supporting biomarker data is retained with the regulatory submission. To make drug development tools publicly available and subsequently expedite drug development and regulatory review, CDER established qualification pathways for biomarkers, clinical outcome assessments and animal models under the Animal Rule, as part of FDA's Critical Path Initiative.

Qualification is a conclusion that within the stated context of use, a biomarker can be relied upon to have a specific interpretation and application in drug development and regulatory review. Once qualified, the biomarker can be used for the specific context of use in regulatory submissions without having to reconsider and reconfirm its suitability. From FDA's perspective, qualification eliminates the need for repeated evaluations of similar supporting data.



November  
2014

# Challenges of the current state of data submissions...



***Massive amounts of clinical research data in extremely disparate formats***

***Using a variety of proprietary standards***

***Extremely difficult to do cross-study and application reviews***

# Guidance for Industry

## Providing Regulatory Submissions in Electronic Format — Standardized Study Data

### DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Ron Fitzmartin at 301-796-5333, (CBER) Office of Communication, Outreach and Development (OCOD) at 301-827-1800 or 1-800-835-4709.

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)

February 2014  
Electronic Submissions  
Revision 1

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FDA encourages the sponsor or applicant to discuss the waiver request prior to or at the pre-IND meeting with the appropriate review division in CDER or CBER and submit the request in writing prior to submitting the IND.<sup>11</sup> FDA will notify the sponsor or applicant in writing as to whether the waiver request is denied or granted.

### E. When will electronic submission of standardized study data be required?

For additional information on how FDA intends to implement the electronic submission requirements of section 745A(a) of the FD&C Act, including timetable for implementation, please see the 745A Implementation Guidance.

#### 1. Initial Timetable for the Implementation of Electronic Submission Requirements

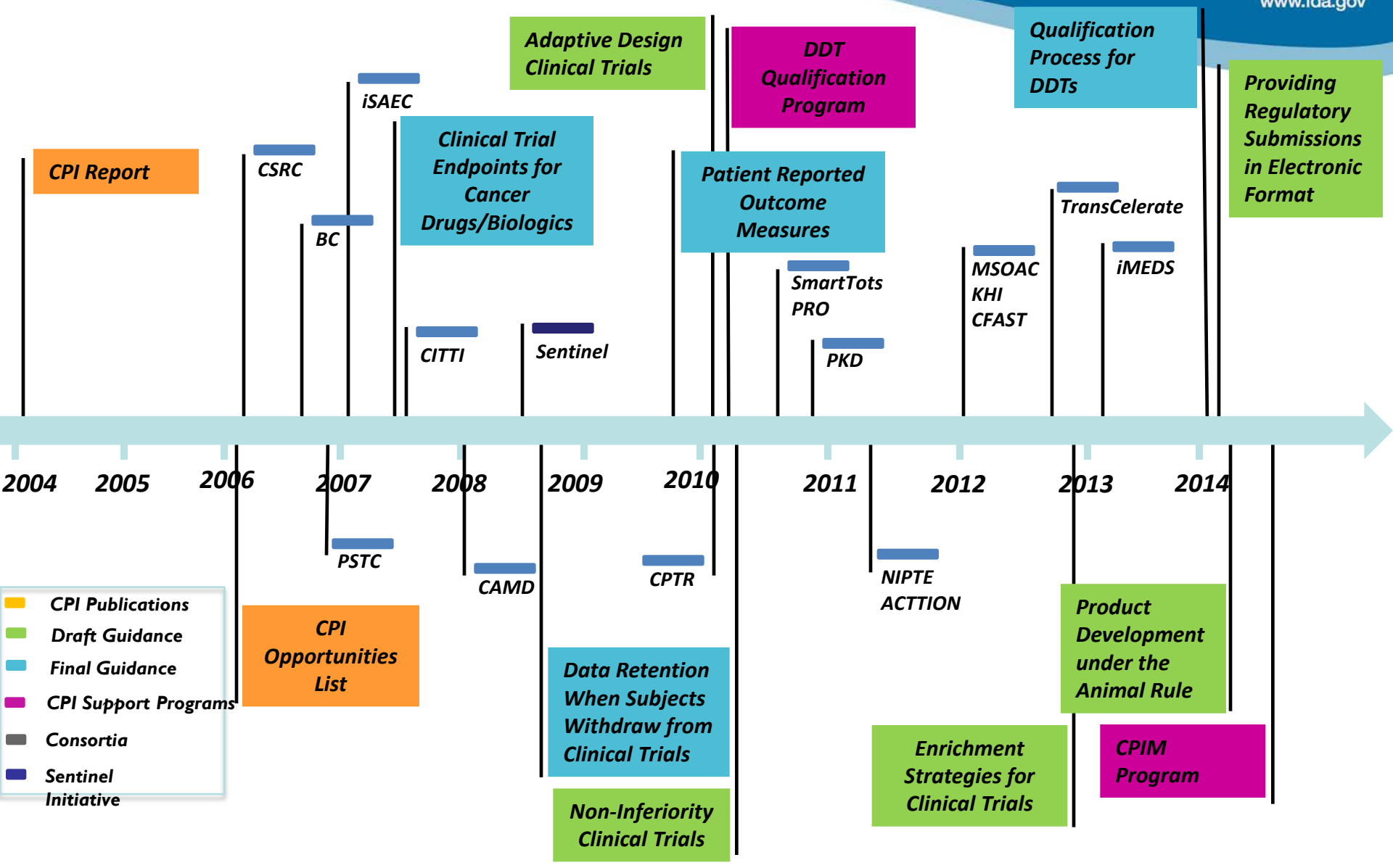
After we publish a notice of availability of the final guidance in the *Federal Register*, all studies with a start date<sup>12</sup> twenty-four months after the *Federal Register* notice must use the appropriate FDA-supported standards, formats, and terminologies specified in the Data Standards Catalog (see section I.I.C) for NDA, ANDA, and certain BLA submissions. Study data contained in certain IND submissions must use the specified formats for electronic submission in studies with a start date thirty-six months after the *Federal Register* notice of availability.

The following is an example of how a new electronic submission requirement would be implemented:

*On November 15, 2016, FDA publishes a Federal Register notice announcing the availability of the final eStudy Data Guidance. For studies with a start date after November 15, 2018, sponsors or applicants must use the appropriate FDA-supported standards, formats and terminologies specified in the Data Standards Catalog for NDA,*

<sup>11</sup> If no pre-IND meeting is held, sponsors or applicants are encouraged to contact the review division prior to the pre-BLA meeting to discuss a waiver request.

<sup>12</sup> For purposes of this guidance, the study start date is the earliest date of informed consent among any subject that enrolled in the study. For example, see Study Start Date in the SDTM Trial Summary Domain (TSPARMCD = SSTDTC), <http://www.cdisc.org>.





# Moving Forward...



# Next Steps...What is Needed

- Enhanced data sharing and collaborative efforts among consortia
- Qualification packages that don't try to “boil the ocean”
  - Limited vs Expanded Context of Use
- Data/specimen repositories which can support expanded contexts of use for biomarkers once additional data is aggregated
- Up front conversations around context of use—which drives the level of evidence needed
- More communication about the value and progress made by consortia efforts
- Greater clarity around levels of evidence for qualification—this takes the entire scientific community—not just FDA
- Patience...we are learning as we go...

# To Contact Us:

*Office of Translational Sciences/CDER/FDA*  
*301-796-2600*

*shaavhree.buckman-garner@fda.hhs.gov*



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