Improving Safety Testing By Qualification of New Biomarkers

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February 5, 2008

Toxicology Testing Related to FDA-Regulated Products

- Food contaminants, additives, etc
- Veterinary and animal feed products
- Medical devices and constituents
- Biological products
- Drugs and excipients
- Cosmetics

FDA Role in Alternative Methods

- FDA participates in ICCVAM in promoting development of alternative methods
- FDA scientists in each Center work on methods development
- FDA will update requirements and regulatory guidances as new methods become available
- Agency works with regulators worldwide to harmonize standards

Challenges with Current Toxicology Testing

- Predictive value
  - False negatives—not too common
  - False positives—may block development
- Species specificity
- Extrapolation to lower exposures
- Empirical nature of findings: lack of mechanistic data
- Use of animals

The Emerging Science of Safety

- Toxicological evaluation of new chemicals or products has been largely empirical in nature
- New science offers the opportunity of improved prediction
  - Genomics, proteomics…systems biology will provide mechanistic understanding
  - Feedback from healthcare outcomes will provide input from most relevant species for products subsequently used in humans

How Will This Play Out?

- Mechanistic understanding
  - Developing mechanistically-linked biomarkers
  - Use of in vitro systems to evaluate off-target effects on pathways
- Healthcare outcomes feedback
  - Epidemiologic studies (e.g., pharmacoepidemiology) linked to human mechanism studies (e.g. genomics)
  - Libraries of outcomes (benefits and harms) for construction of disease models
- Bioinformatics
  - Robust platforms needed to support above

Mechanistic Understanding

- In vitro systems—whole cell and others
  - Allows comparative profiling of effects of drugs with known toxicities and candidates
  - Build response libraries and structure activity relationships
- New safety biomarkers linked to mechanism
  - Use in animal studies for greater sensitivity
  - Bridge to human outcomes with same/related markers

Bioinformatics Needs

- New mechanistic information too complex for human memory
- Need informatics platforms that can integrate across molecules, pathways, species and setting
- Import information from clinical trials, health care data
- Develop in silico models

New Biomarker Development is Key to Utilizing the New Science

- Biomarkers can bridge mechanistic understanding and empirical outcomes
- Biomarker “qualification”: the process of determining that adequate evidence supports utilization of a biomarker for *a specific use*
- New, well-qualified safety biomarkers are needed to support FDA regulatory decision making around regulated product safety
- Science is now available to create these markers

Fate of Most Candidate Biomarkers

- Discovered in academic laboratory
- Results (animal or clinical) published
- Further small academic series published
- Some uptake in academic centers
- For clinical biomarkers, assay may be commercialized as laboratory service

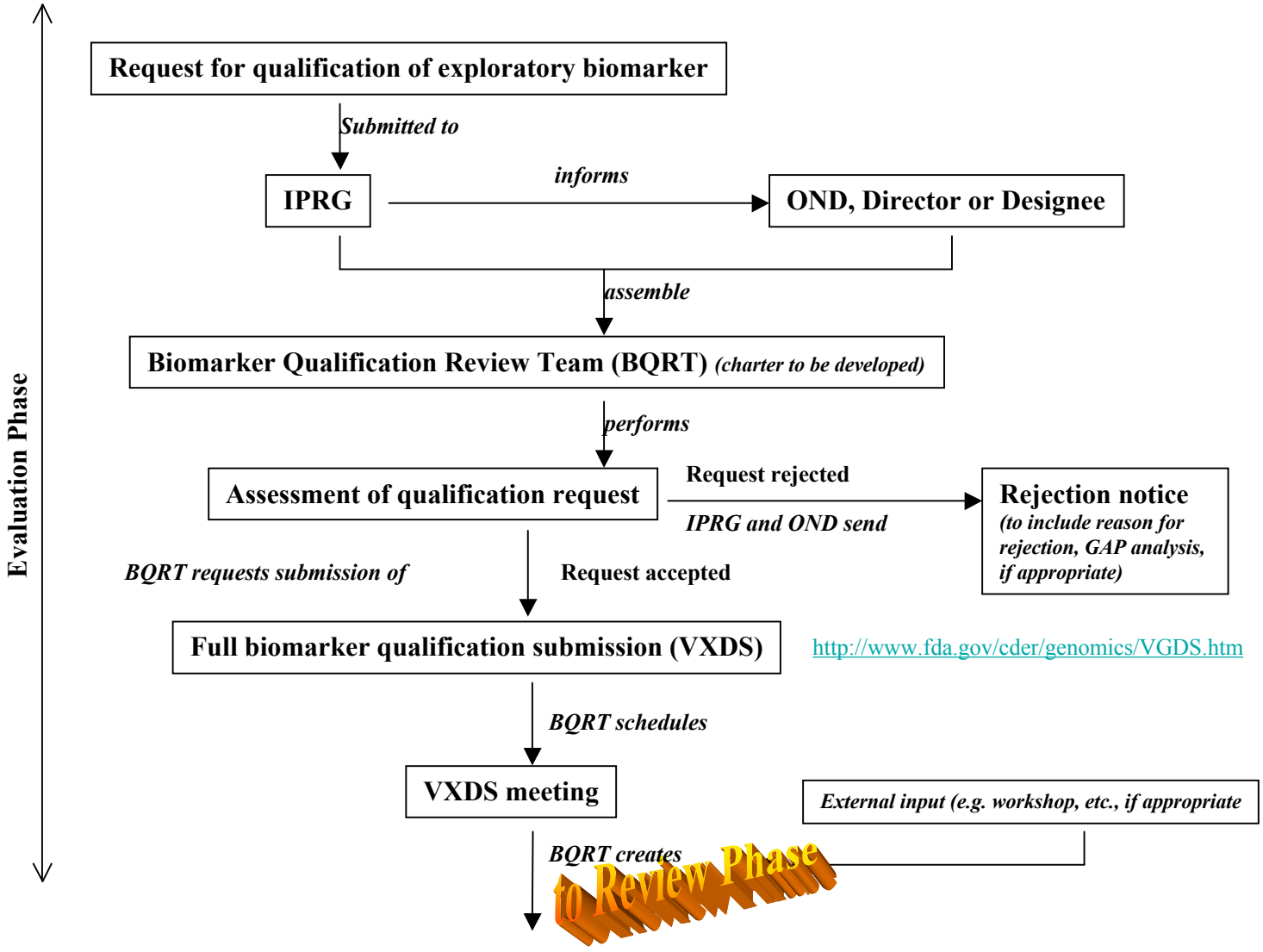
Fate of Most Candidate Biomarkers

- Small number may be developed into commercially available laboratory tests
- Fewer may become integrated into clinical or veterinary care
- Evidence base for use often remains slim/controversial
- Not adopted for regulatory use because of absence of needed evidence
- Other biomarkers developed by industry but not released for general use

Towards the Robust Use of New Biomarkers

- FDA's Critical Path Initiative: proposal to use consortia to qualify biomarkers through resource sharing
- Currently such consortia are being set up in areas such as animal safety testing and overall biomarker development
- Safety biomarkers of great interest
- FDA developing a qualification process

Biomarker Qualification Pilot Process at the FDA



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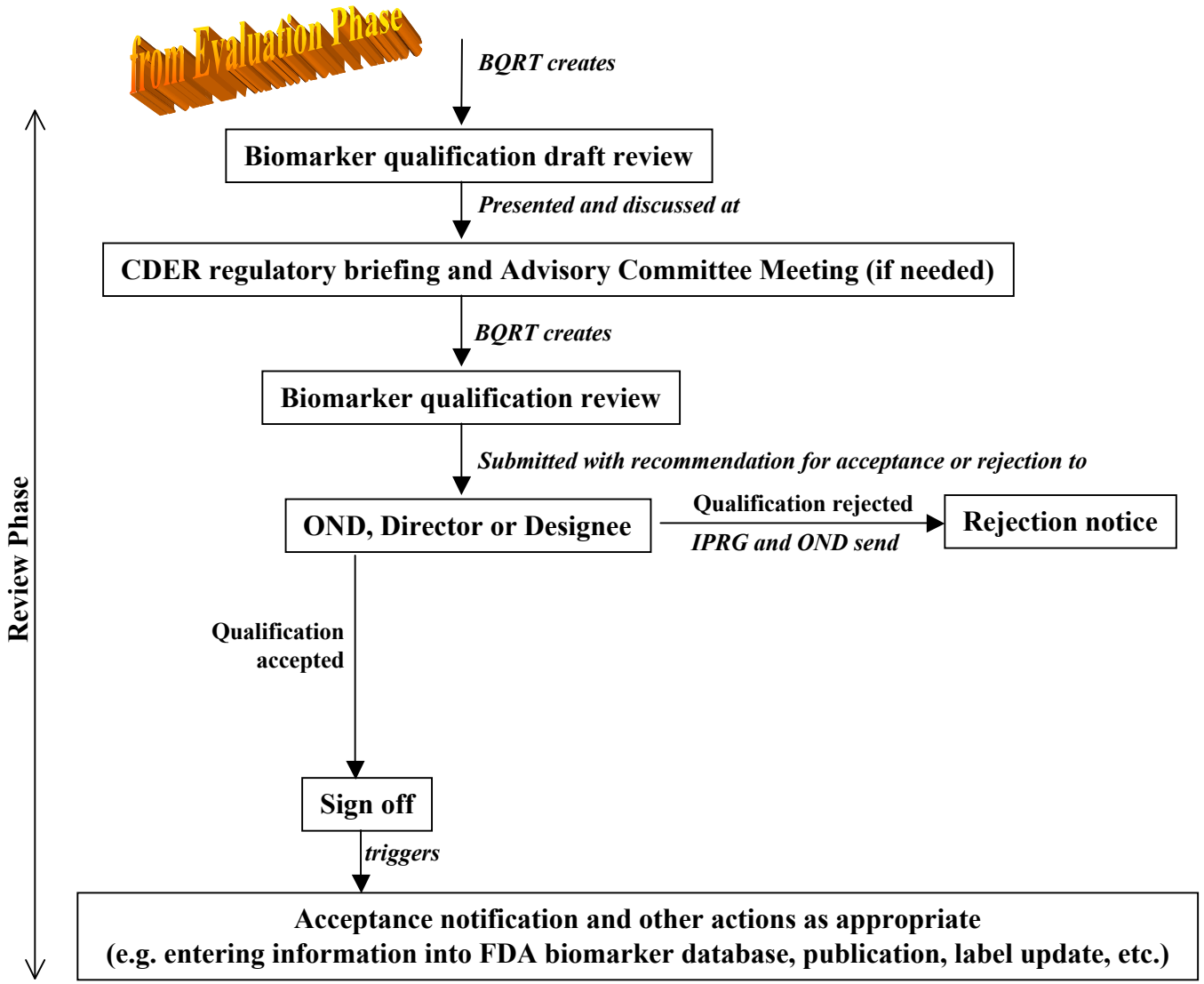
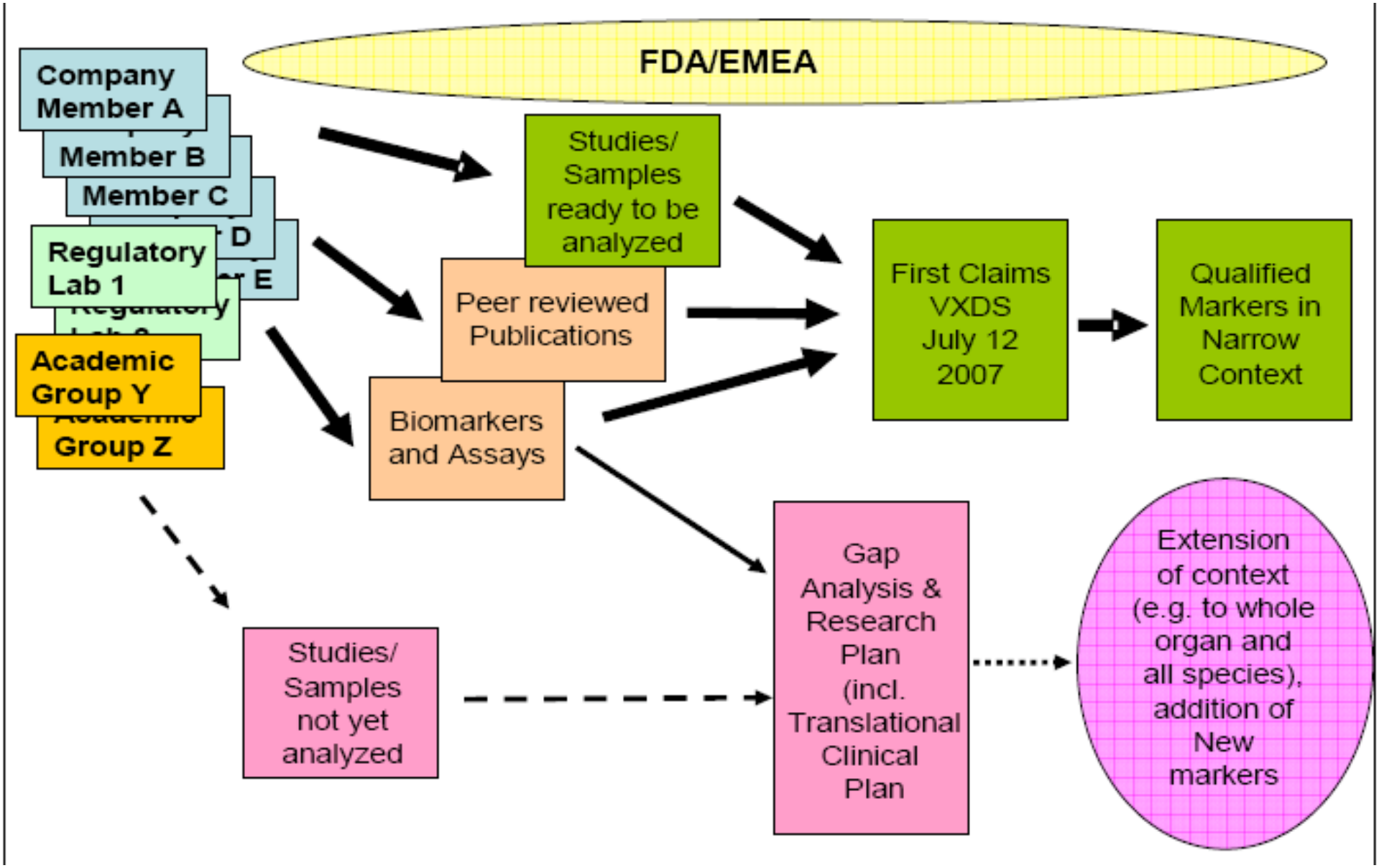


Biomarker Development Consortia

- Predictive Safety Testing Consortium
  - C-Path Institute, Tucson AZ
  - Animal safety biomarkers generated as a part of animal toxicology testing
  - Thousands of animal toxicology studies done each year in US for drug development purposes
  - Firms had developed in-house biomarkers but not shared them

Predictive Safety Testing Consortium

- Fourteen pharmaceutical companies joined consortium
- Agreed to cross-validate markers for organ-specific drug injury
- Have submitted first qualification package to FDA (renal injury markers)
- FDA reviewing along with EMEA


FDA/EMEA
Company Member A
Member B
Member C
Regulatory Lab 1
Academic Group Y
Group Z
Studies/ Samples ready to be analyzed
Peer reviewed Publications
Biomarkers and Assays
First Claims VXDS July 12 2007
Qualified Markers in Narrow Context
Studies/ Samples not yet analyzed
Gap Analysis & Research Plan (incl. Translational Clinical Plan
Extension of context (e.g. to whole organ and all species), addition of New markers

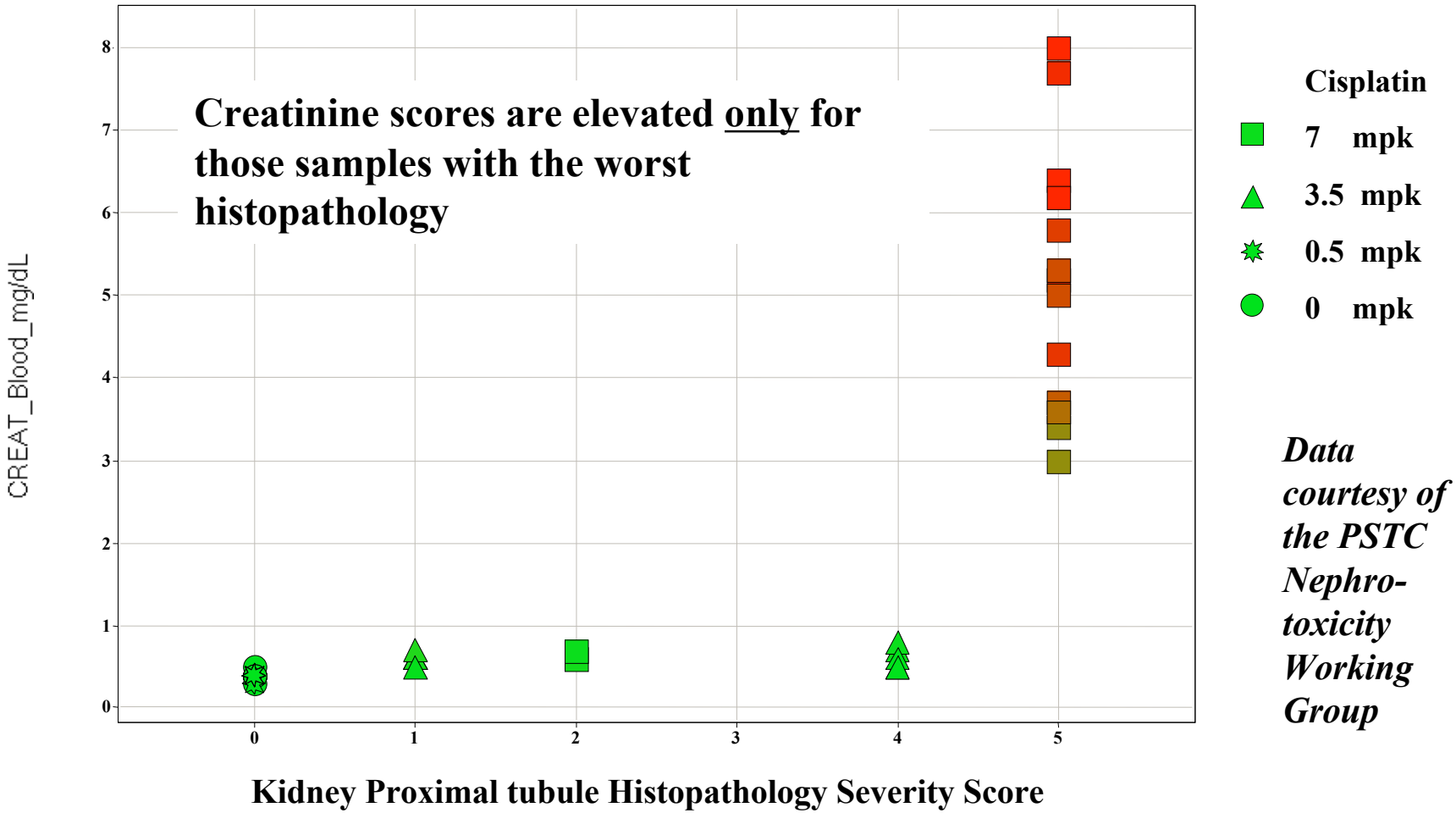
Biomarkers of Nephrotoxicity (*Predictive Safety Testing Consortium*)

- DEFINITION: set of protein biomarkers in urine mapped to specific areas in the kidney.
- CONTEXT: superior sensitivity and specificity than BUN and creatinine.

Why New Safety Biomarkers?

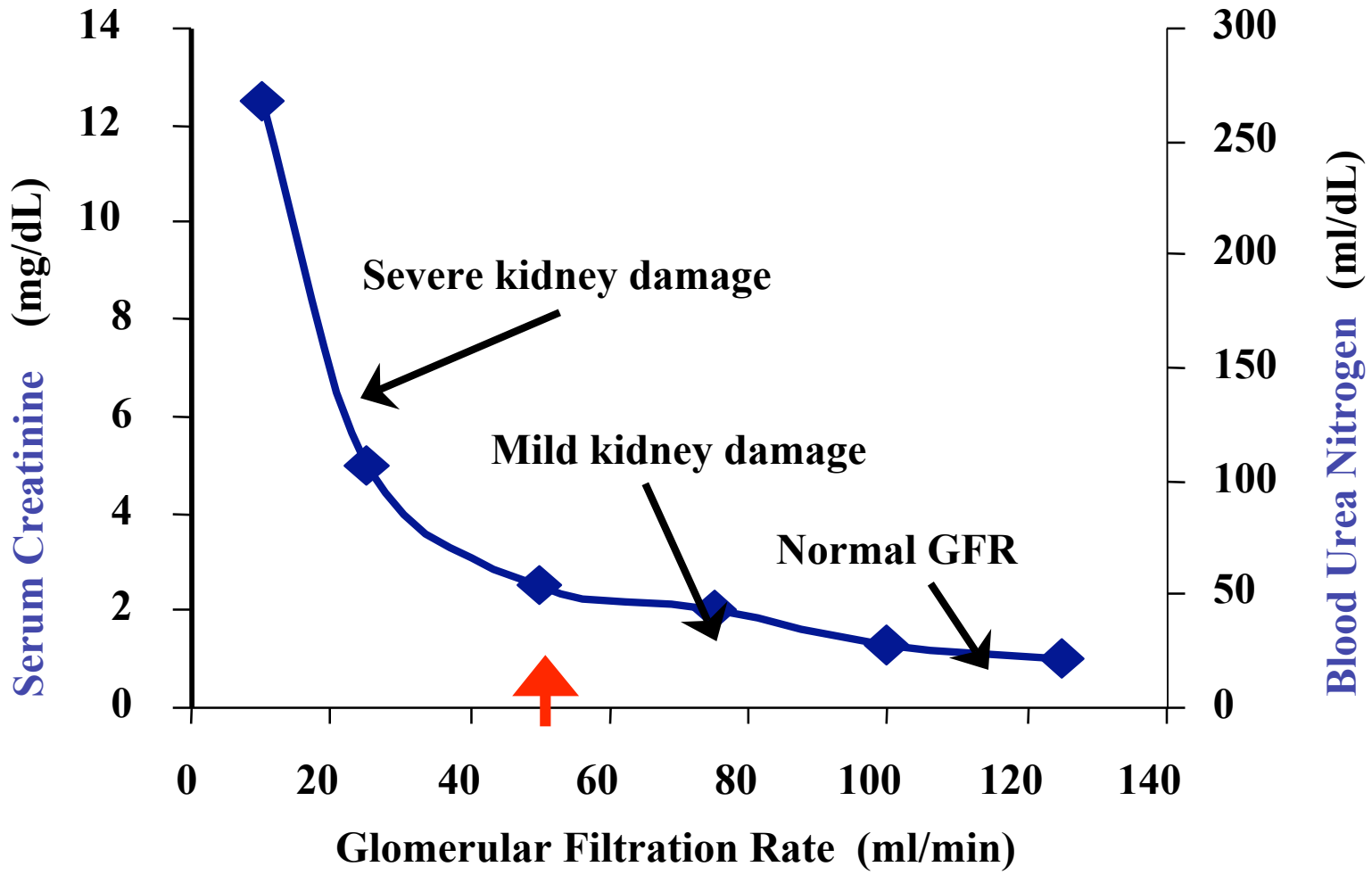
- Nephrotoxicity
  - Correct assessment of kidney function is important both for dosage adjustment of renally excreted drugs and for early detection of drug nephrotoxicity, that mostly is reversible if the offending agent is discontinued. **...Serum creatinine is a late marker of nephrotoxicity** that 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



Data courtesy of the PSTC Nephro-toxicity Working Group

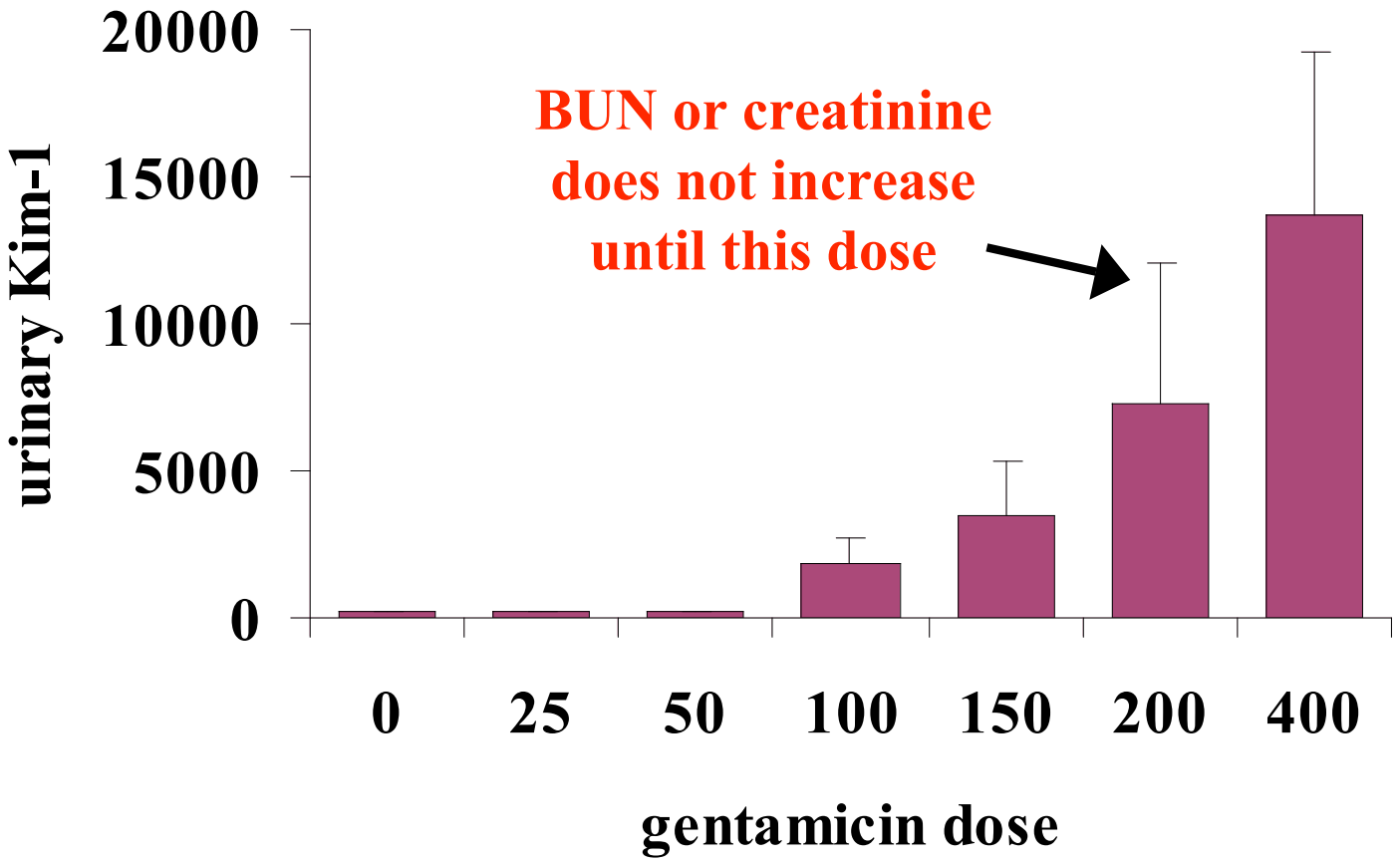
Are current tests for kidney damage adequate?



No. 50% of kidney function is gone before the current diagnostic tests are elevated. Need a better test.

Need for better tests

- Kidney injury molecule-1 (Kim-1) protein
  - Synthesis increases in proportion to kidney injury
  - Excreted into urine during kidney damage



Progress of Nephrotoxicity Biomarkers

- FDA concluding review of package
- Will make findings public
- Consortium has committed to making data public
- Next step will be to complete analytical validation in humans and initiate qualification protocols in the clinic or using stored samples

Other Promising Safety Biomarkers

- Drug Metabolizing enzyme status: markers for exposure
  - 6-Mercaptopurine (enzyme TPMT)
  - “Strattera” (enzyme CYP 2D6)
  - Irinotecan (enzyme UGT1A1)
  - Warfarin (enzyme CYP 2C9; pharmacodynamic biomarker VK0RC1)
- Genetic Basis of Adverse Event
  - Abacavir

Additional Biomarker Consortia

- SAE consortium
  - Industry consortium
  - Genetic basis of serious rare adverse events
- "The Biomarker Consortium"
  - NIH/FDA/PhRMA/BIO/patient groups/ many others
    - Discovery and qualification of biomarkers
- Cardiovascular Markers
  - Duke University/FDA/others
  - Research on digital ECG warehouse
  - Cardiac biomarker projects

Could These New Assays Substitute for Current Testing?

- Not yet
- Need to build mechanistic understanding
- Expectation that animal studies could become more efficient and targeted via use of biomarkers
- Construction of in silico models for preliminary testing and simulation, to get studies right the first time

Summary

- Important needs for development of additional biomarkers
- This requires identification of promising markers and formal qualification process
- Use of new qualified markers can build data and confidence about their performance
- Business model/regulatory path for such markers is not clear to industry
- Clarification and stimulus required

Summary

- FDA is developing these concepts as part of its “Critical Path” Initiative.

- Development will include process for refining general framework for biomarker qualification as well as individual projects on biomarker and surrogate endpoint development