

A Year of Working through a Pilot Process for Biomarker Qualification at the FDA

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The only thing you need to know is that you can't do anything with an airplane that hasn't already been done.



That includes making a smoking hole in the ground.

Chuck Yeager, *The Washington Post*, October 13, 2007.

November 1, 2007, 10:58 am

Drug Drought Deepens as FDA Approvals Lag

Posted by Scott Hensley

The malaise in Big Pharma is deepening, as 2007 shapes up as one of the slowest in years for new drugs.

Through Oct. 31, the FDA had approved just 15 drugs classified as “new molecular entities,” the designation for medicines that represent something really different. At that pace, the agency would greenlight just 18 new drugs (not counting vaccines or additional uses for existing drugs) by year-end, Peter Loftus of Dow Jones Newswires reports.

By comparison, FDA approved 22 NMEs last year, 20 in 2005 and 36 in 2004.

Some companies pin the blame on a skittish FDA. Safety worries since Merck withdrew painkiller Vioxx three years ago have put a chill on the agency, they say. FDA concerns have delayed several expected blockbusters, including Novartis’s diabetes drug Galvus and Sanofi-Aventis’s diet drug rimonabant, sold as Acomplia in Europe.

Companies say FDA is hunkering down against criticism. “It just indicates to you that when bureaucrats come under pressure, they tend to choose the path of asking for more data, as opposed to approving the drug,” Schering-Plough’s CEO Fred Hassan said in an interview last week.

If an experimental drug treats a condition for which there are already options for treatment, FDA seems to have raised the bar significantly, the industry says. Wyeth, for instance, has seen delays for approval Pristiq, a treatment for depression and menopausal symptoms. Treatments for both conditions abound, including some sold by Wyeth itself. “In categories where there are choices, the agency is making more demands for approval,” Joseph Mahady, a Wyeth executive said. “It’s across the board. Everybody’s got to adjust to that.”

FDA argues that its criteria for review haven’t stiffened substantially. “There have been no systematic changes in how FDA is approaching the approval standards for new drug applications,” a spokeswoman said. “Each application is reviewed on its own merit and judgments are made by the signatory authority as to whether the application meets the statutory standards.”

And it’s true that several companies have seen novel medicines approved this year. Merck’s Isentress and Pfizer’s Selzentry for HIV/AIDS stand out. So do three cancer treatments: Wyeth’s Torisel, GlaxoSmithKline’s Tykerb and Novartis’s Tasigna.

How do we know that a biomarker is valid?

- **What is a valid biomarker?**
 - *A biomarker that is measured in an analytical test system with well established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results.*
 - <http://www.fda.gov/cder/guidance/6400fnl.pdf>

**Guidance for Industry
Pharmacogenomic Data
Submissions**

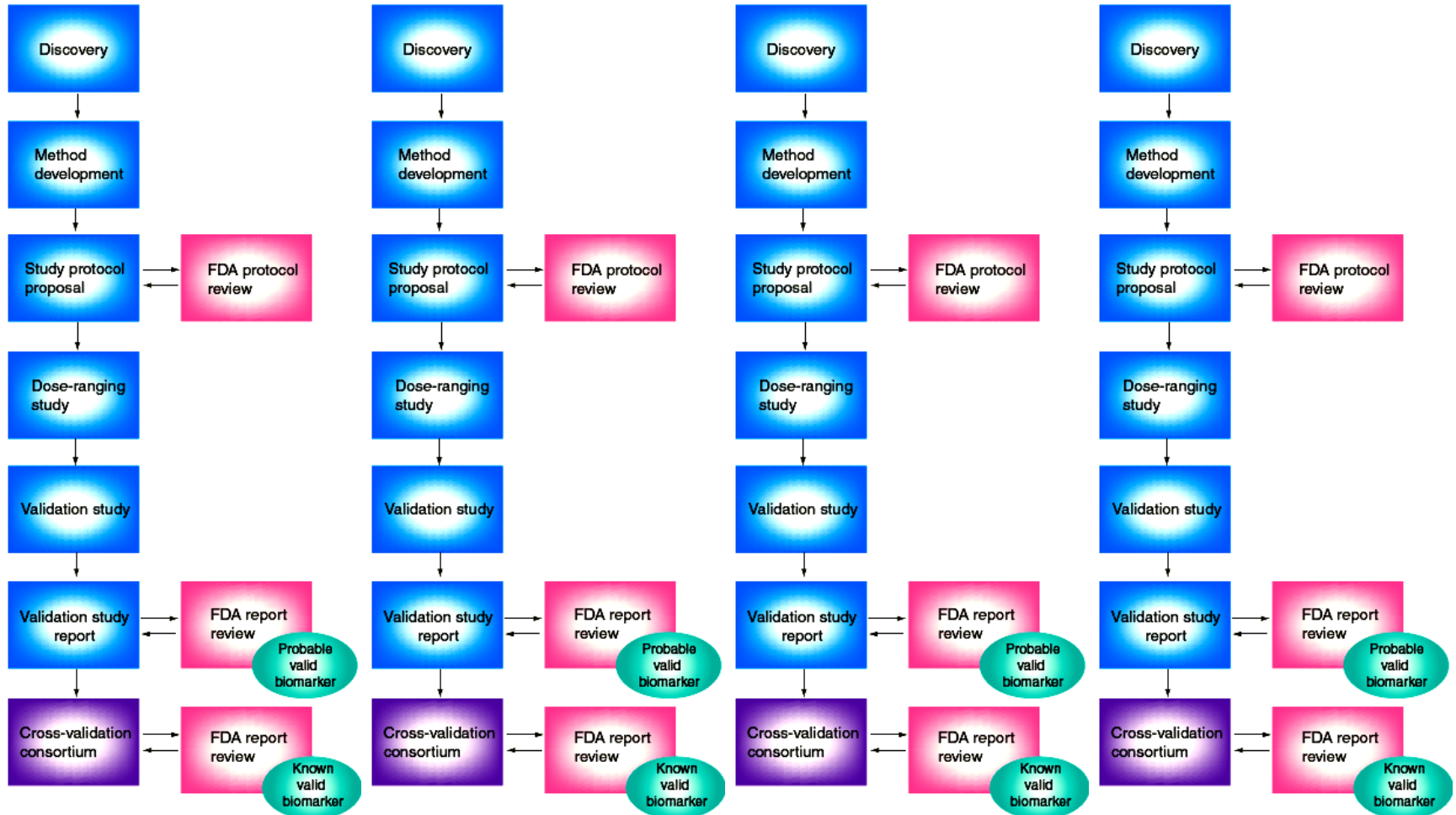
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Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels

Biomarker	Label Context		Examples of other Drugs Associated with this Biomarker	References (PubMed ID)
	Representative Label	Test Drug		
<i>C-KIT expression</i>	Gastrointestinal stromal tumor <i>c-Kit</i> expression “ <i>In vitro</i> , imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumor (GIST) cells, which express an activating c-kit mutation.” “Gleevec is also indicated for the treatment of patients	3 Imatinib mesylate		12851888 16226710 16294026

Biomarker Qualification: A Proposal

Process map proposal for the validation of genomic biomarkers. (Goodsaid F, Frueh F (2006).
Pharmacogenomics, 7, 773-782)



- **Biomarker qualification requires a collaborative approach between pharmaceutical companies and between the pharmaceutical industry and the FDA.**

Layers of fears and layers of facts: *paths to biomarker qualification.*



metus gravis = serious fear

"I've got it again, Larry ... an eerie feeling like there's something on top of the bed."

Fears associated with acceptance of biomarker qualification.

- **Added test burden.**
- **Replacement of well-established biomarkers.**
- **Exceptions in the sensitivity and specificity of exploratory biomarkers.**

Added Test Burden

- *Is this going to cost more?*
 - Biomarkers selected for qualification must be shown to reduce time, money or adverse events in drug development.
- *Will regulators know what these new biomarkers are for?*
 - An integral goal of the qualification process is a comprehensive training of reviewers on the context and data associated with qualified biomarkers.

Replacement of well-established biomarkers.

- *Why should we replace all these biomarkers for which we have massive databases to support control ranges?*
 - Because the new biomarkers work better.
- *How long will it take for these new qualified biomarkers to gain credibility?*
 - As soon as the first drug is approved supported by a biomarker measurement without which this drug would not have been approved.

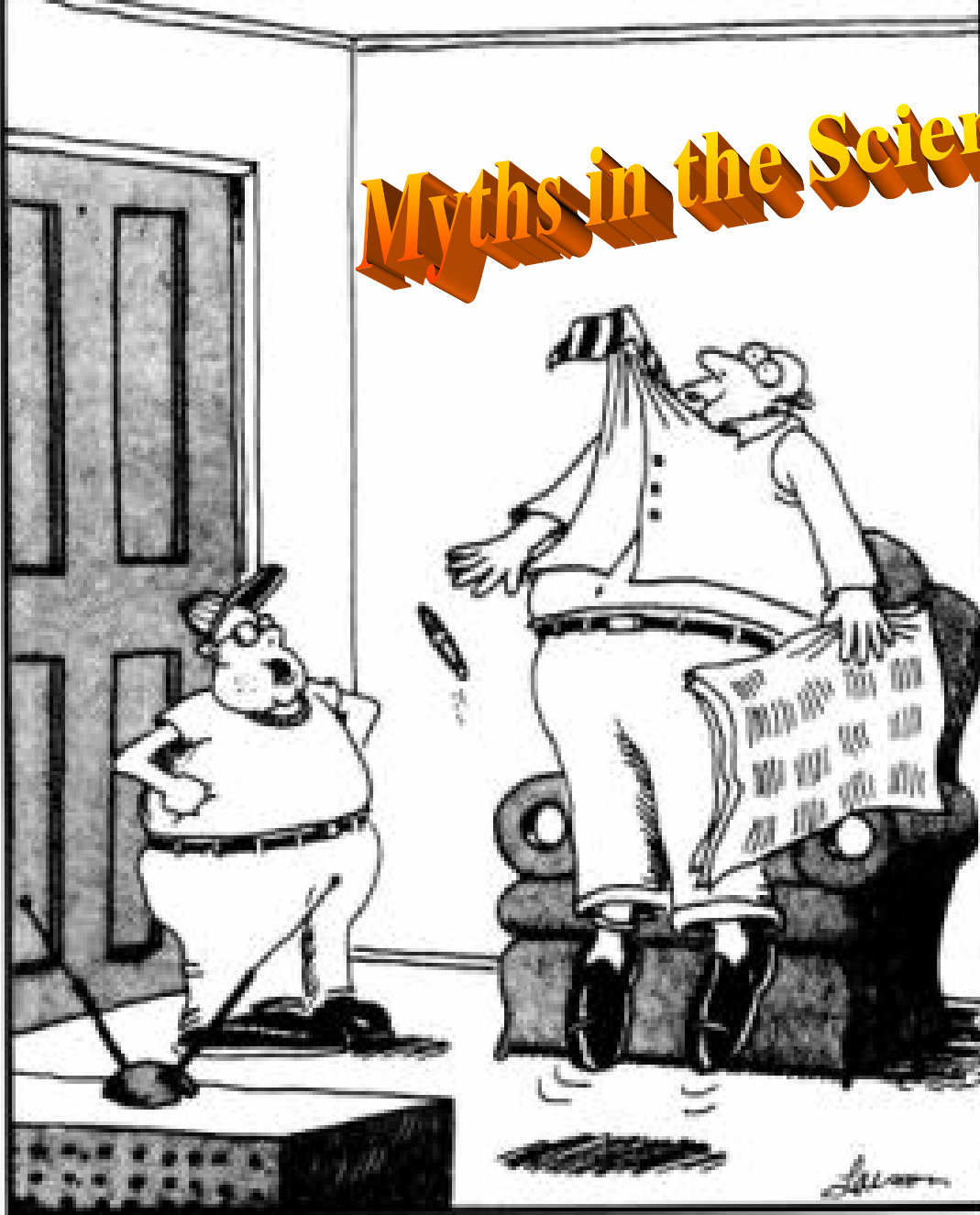
Exceptions in the sensitivity and specificity of exploratory biomarkers.

- ***I don't like this new biomarker. It is "too" sensitive.***
 - **That's because it tells you the outcome earlier, when you can still do something about it.**
- ***What standard should I use to qualify a new biomarker?***
 - **An accurate measurement of the outcome for which you are trying to develop the new biomarker.**
Histopathology data will often be a valuable standard in the development of biomarkers for preclinical drug safety assessment.

Biomarker Qualification: *Fear or Fact?*

- **Is it a *formidable impending peril?***
 - **The validity of preclinical and clinical biomarkers has been traditionally settled over the course of time, debate and consensus.**
- **Myths in biomarker qualification**
 - **Myths in the science**
 - **Myths in the industry**
 - **Myths in regulation**

Myths in the Science



"Big Bob says he's getting fired of you saying he doesn't really exist."

Myths in biomarker qualification

- **Myth in the science: *Test qualification precedes biomarker qualification.***
 - Analytical validation at level of commercial test.
 - *I won't test it if I can't buy it off the shelf.*
- **Fact in the science: *Biomarker qualification precedes test qualification.***
 - Analytical validation is an integral part of biomarker qualification.
 - Excellent chance that if it is a novel biomarker there is no off-the-shelf test available for it.

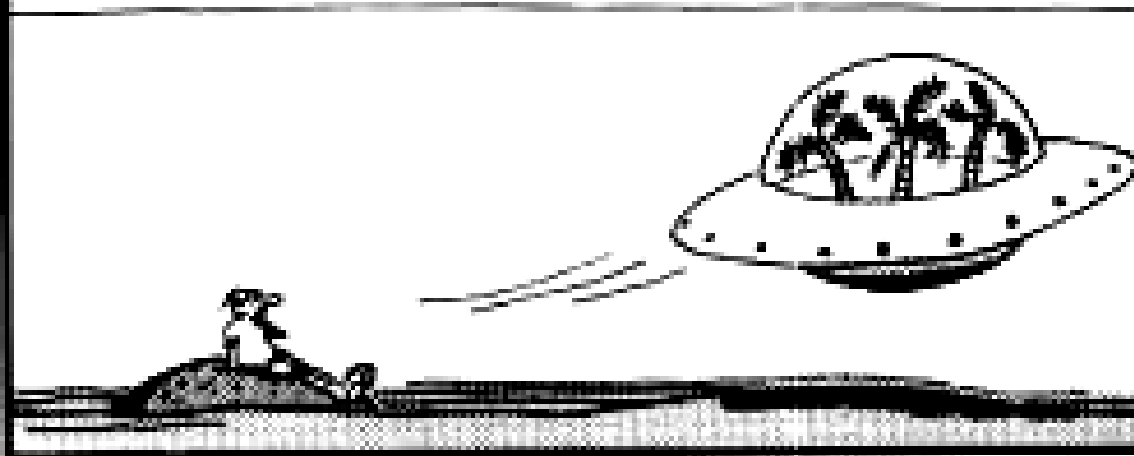
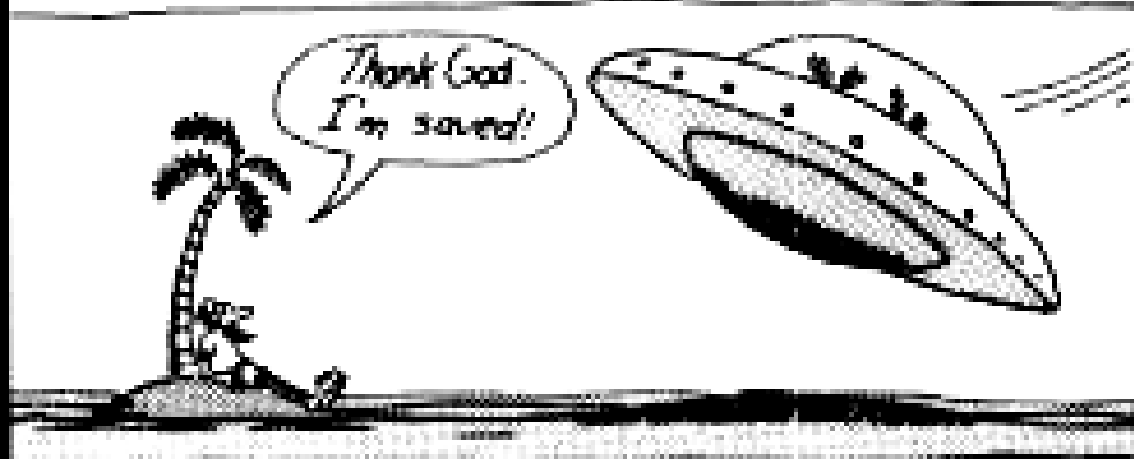
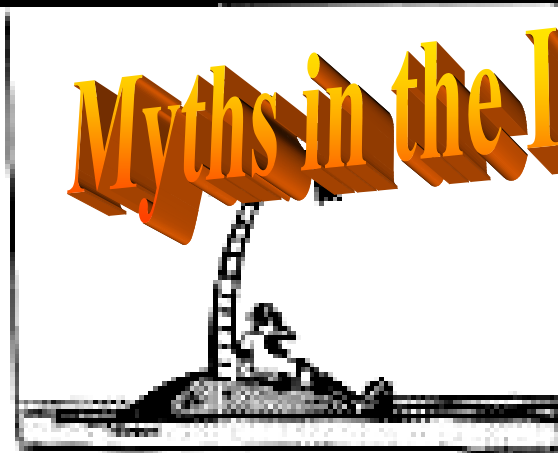
Myths in biomarker qualification

- **Myth in the science:** *If it's published, it's qualified.*
 - Qualification corresponds to impact metric of publications related to biomarker.
 - Qualification corresponds to quality of journals in which the data was published.
- **Fact in the science:** *If it's published, we may never know why.*
 - Proprietary data on key biomarkers in drug development may not reach publication until after data suitable for their qualification are available.
 - Successful biomarker contexts are strictly related to their impact on better, faster, cheaper drug development and safer drugs.

Myths in biomarker qualification

- **Myth in the science:** *If I heard about it, it's qualified.*
 - Biomarkers can be “voted” into qualification independently of whether sufficient data support their qualification.
 - Biomarkers should be “elected” by scientific or trade organizations.
- **Fact in the science:** *If I heard about it, I haven't heard enough.*
 - Biomarkers are qualified on the basis of the data that support their use in the context in which they are qualified.
 - Biomarker contexts are closely associated with the organizations that use them.

Myths in the Industry



Myths in biomarker qualification

- **Myth in the industry: *Evidentiary standards for biomarker qualification are different for preclinical and clinical biomarkers.***
 - **Preclinical biomarkers are not directly associated with therapeutic decisions and therefore need not be qualified to the same evidentiary levels.**
- **Fact in the industry: *Evidentiary standards are context-driven.***
 - **Evidence for biomarker qualification is associated, for example, with whether a biomarker is predictive, diagnostic, or mechanistic.**

Myths in biomarker qualification

- **Myth in the industry:** *Predictive preclinical drug safety biomarkers are the only ones worth qualifying.*
 - We have all the diagnostic and mechanistic biomarkers we need.
- **Fact in the industry:** *Newly qualified diagnostic and mechanistic preclinical drug safety biomarkers have the most immediate impact on drug development.*
 - Biomarkers that impact the sensitivity or accuracy of preclinical drug safety assessment add immediate value in drug development.

Myths in biomarker qualification

- **Myth in the industry:** *The cost of biomarker qualification must be borne by single pharmaceutical companies.*
 - *Not in my lifetime. It will take forever.*
 - **There is no organizational structure that could adequately define and protect ownership of intellectual property associated with biomarkers.**
- **Fact in the industry:** *Organizations such as the Predictive Safety Testing Consortium (PSTC) have developed the legal framework needed share the cost of qualification and to protect intellectual property associated with biomarker qualification.*
 - **The PSTC will be submitting a qualification package for biomarkers of nephrotoxicity to the FDA in July, within 18 months of its inception.**
 - **Pre-competitive sharing of qualification data is a cost-effective process with which to quickly reach a data threshold for qualification.**

Myths in Regulation



"You idiot! I said get the room freshener! That's the insecticide!"

Myths in biomarker qualification

- **Myth in regulation: *Qualification requires a public process.***
 - Biomarker qualification data must be published.
 - A single qualification process should work for all regulatory agencies.
- **Fact in regulation: *Qualification requires data generated by companies in industries regulated by specific regulatory agencies.***
 - Proprietary qualification data can be shared between companies in regulated industries and their regulatory agencies. These data may or may not be published.
 - Qualification processes are agency-specific.

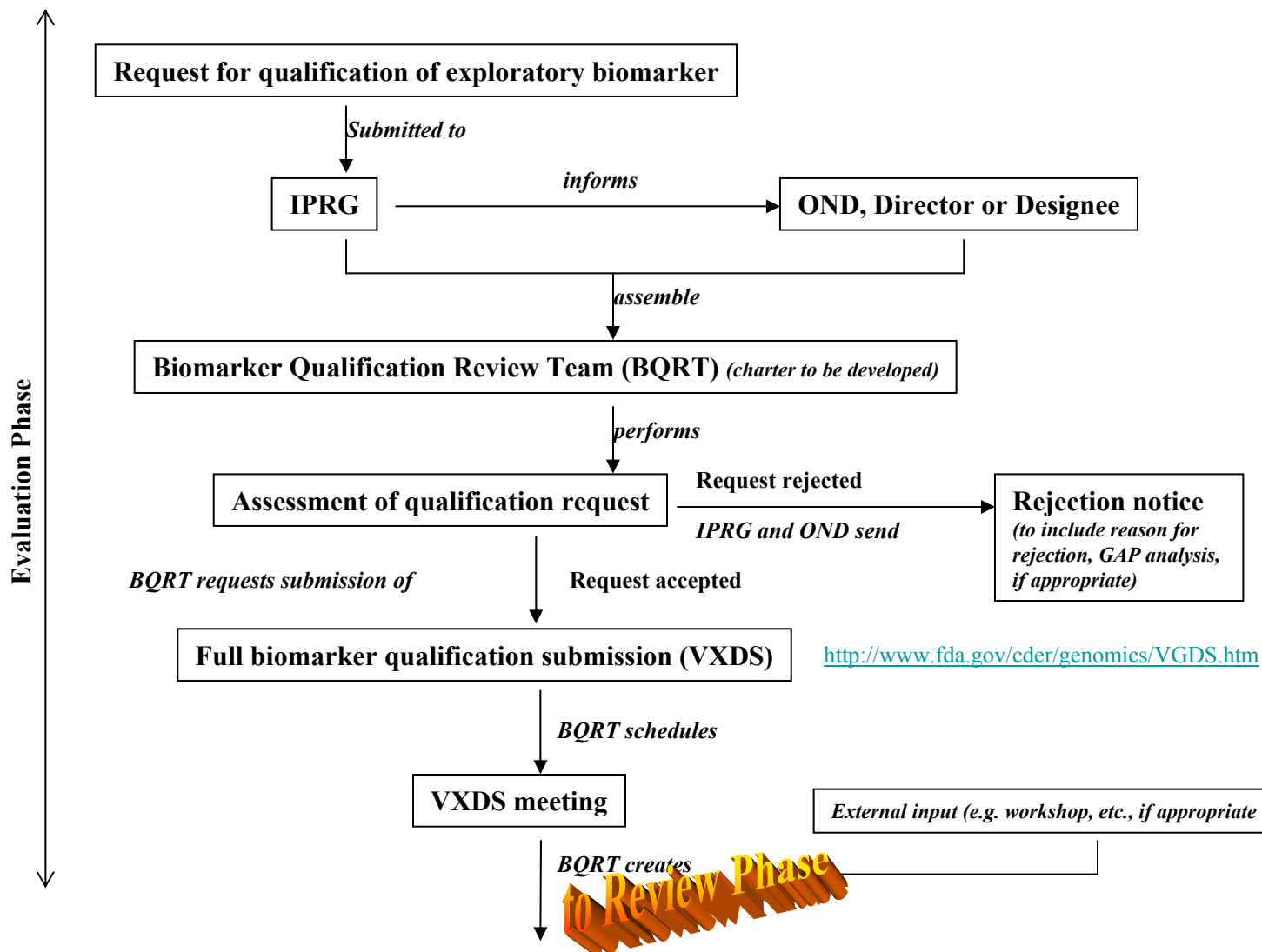
Myths in biomarker qualification

- **Myth in regulation: *Why should the FDA care?***
 - CDER evaluates drug submissions.
 - CDRH evaluates diagnostic submissions.
- **Fact in regulation: *The FDA has taken a proactive approach to develop a regulatory process for biomarker qualification.***
 - It is collaborating with individual companies to understand the process.
 - It is collaborating with the PSTC to test a pilot process for biomarker qualification.

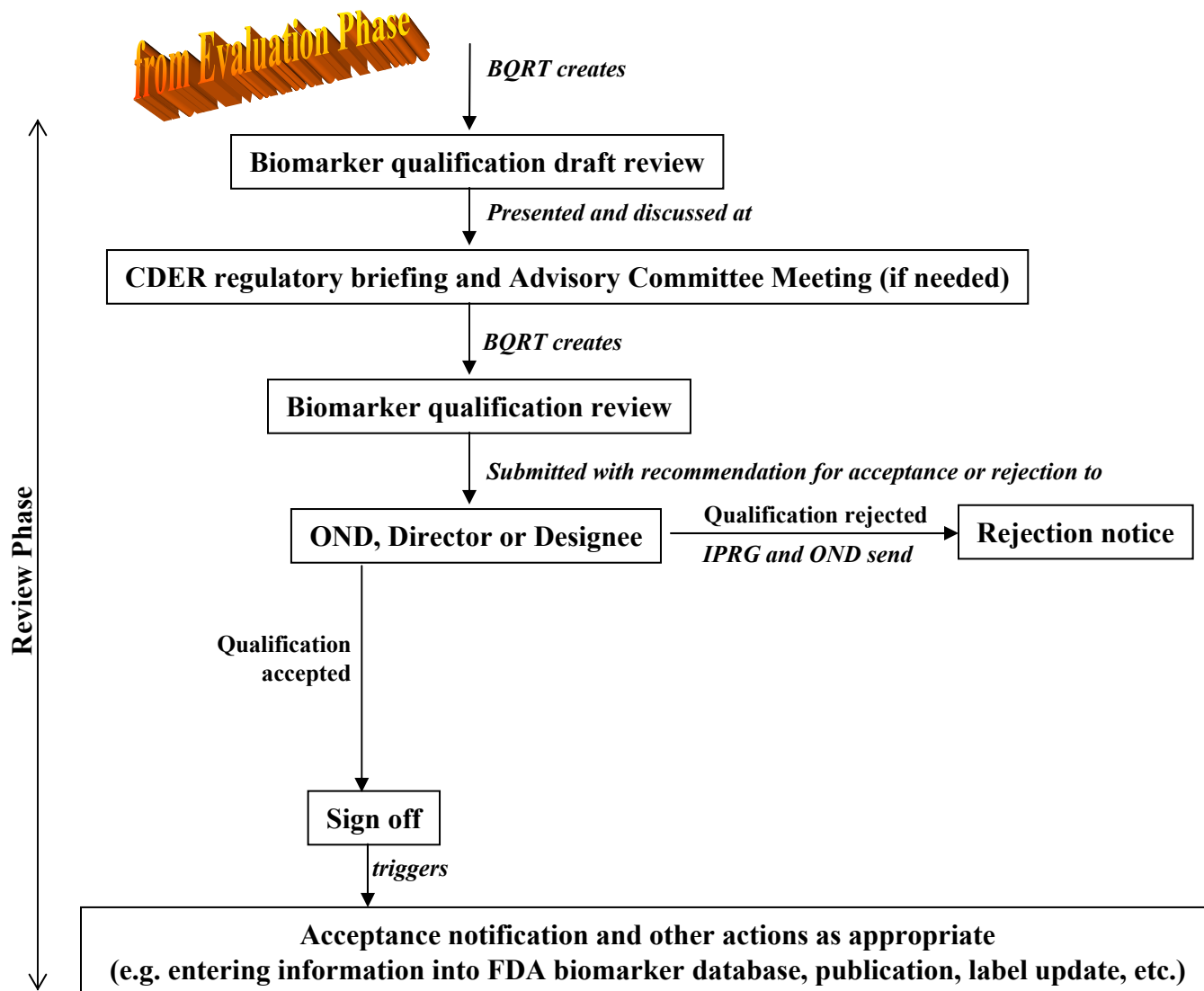
Myths in biomarker qualification

- **Myth in regulation:** *Regulatory agencies will never reach a consensus on a process for biomarker qualification.*
 - *Their reviewers don't talk to each other.*
 - *They've never done it before.*
 - *They don't have the expertise to do it.*
 - *I know a reviewer who says they don't want to do it.*
- **Fact in regulation:** *A consensus pilot process has been developed at the FDA.*
 - **This consensus has been reached over the past year.**
 - **This is a pilot process, which will need to be tested with as many qualification submissions as possible to assess its strengths and weaknesses.**

Biomarker Qualification Pilot Process at the FDA



Biomarker Qualification Pilot Process at the FDA



The First Year

First Wave

- **Galactomannan detection in broncho-alveolar lavage fluid as marker for invasive pulmonary aspergillosis.**
- **Galactomannan detection in blood as a biomarker for invasive aspergillosis.**
- **Preclinical Biomarkers of Nephrotoxicity (PSTC).**
- **Circulating Tumor Cells as biomarkers to aid in therapeutic decision-making in metastatic breast cancer.**

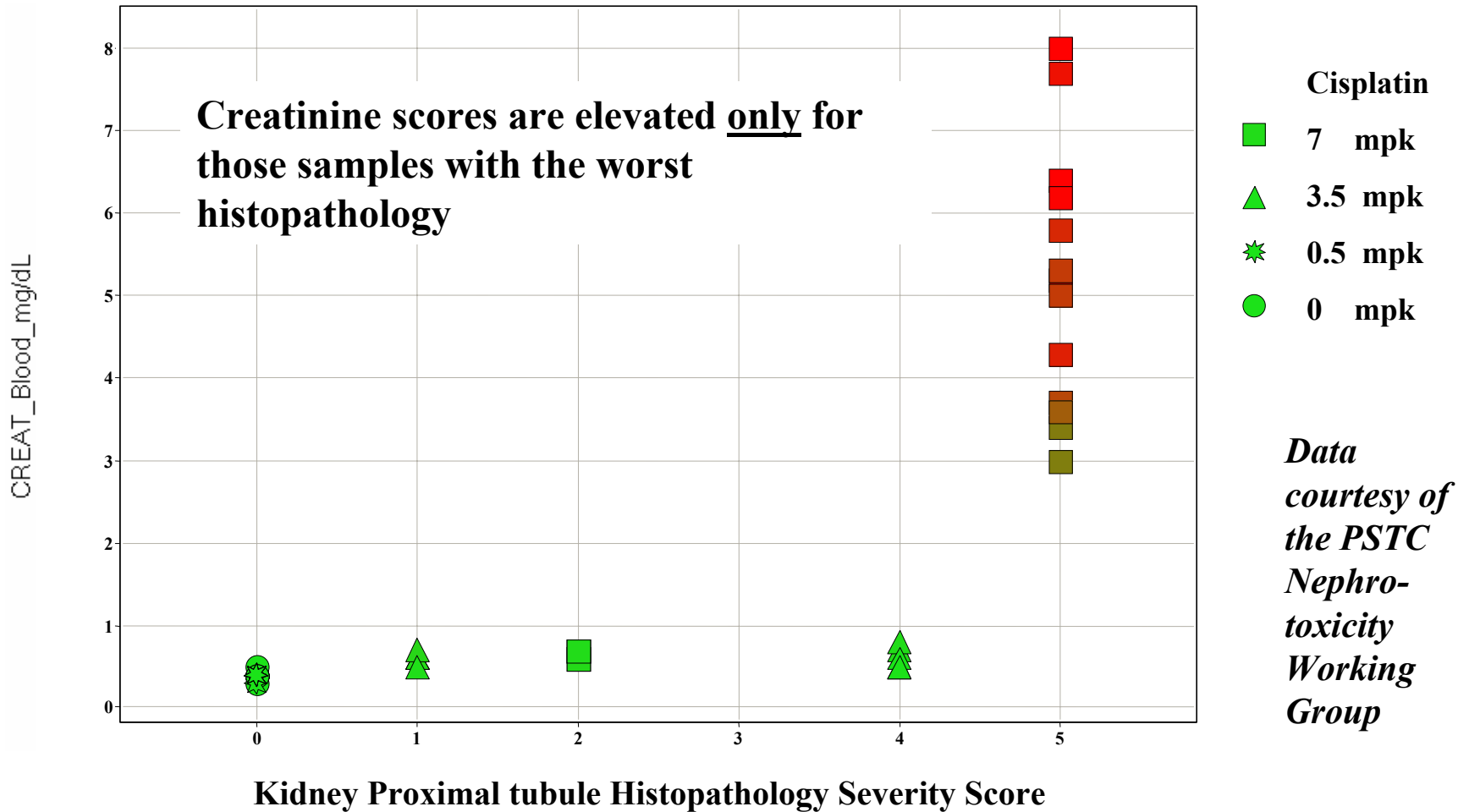
Biomarkers of Nephrotoxicity *(Predictive Safety Testing Consortium)*

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

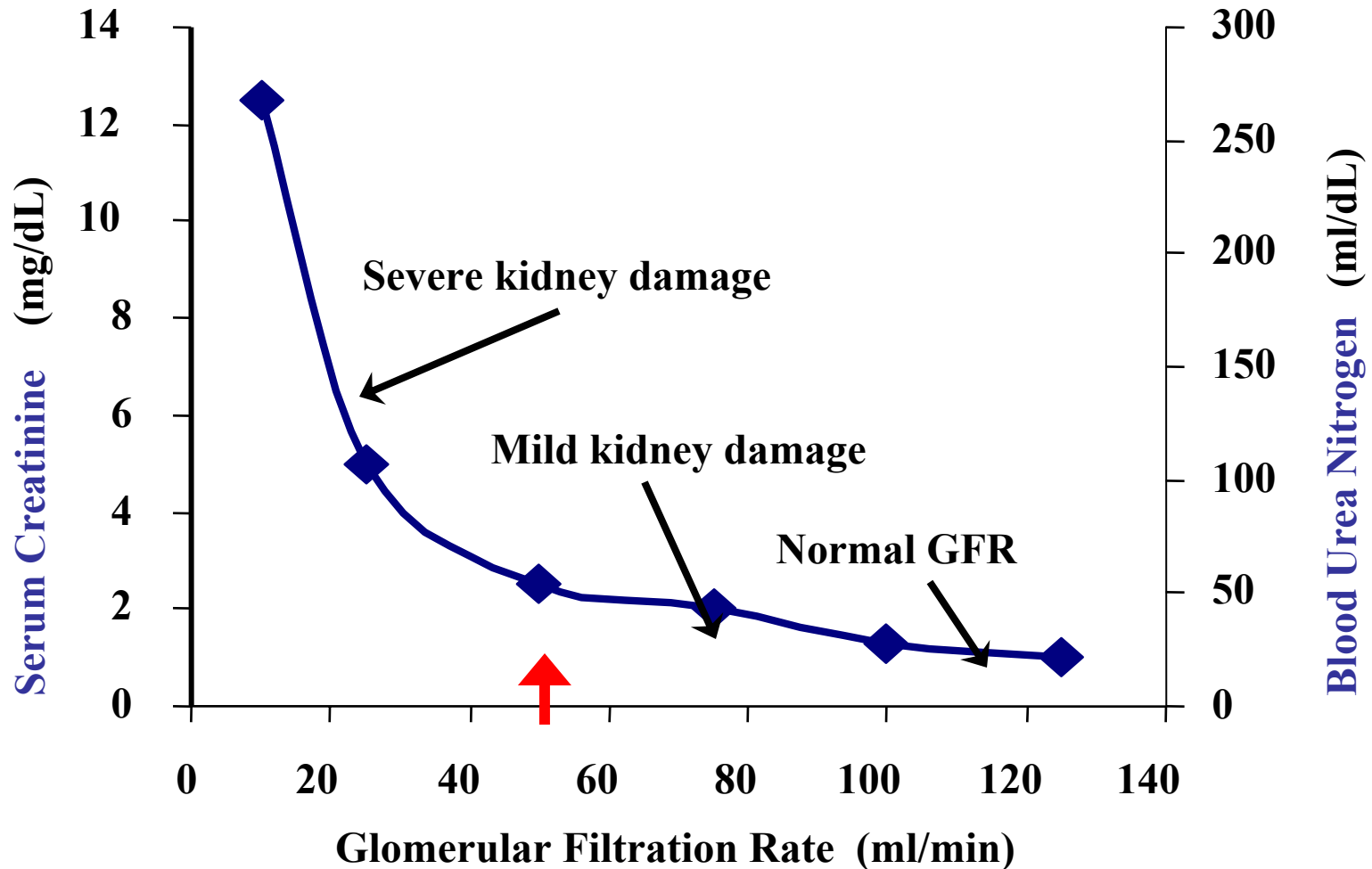
Why New Safety Biomarkers?

- **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



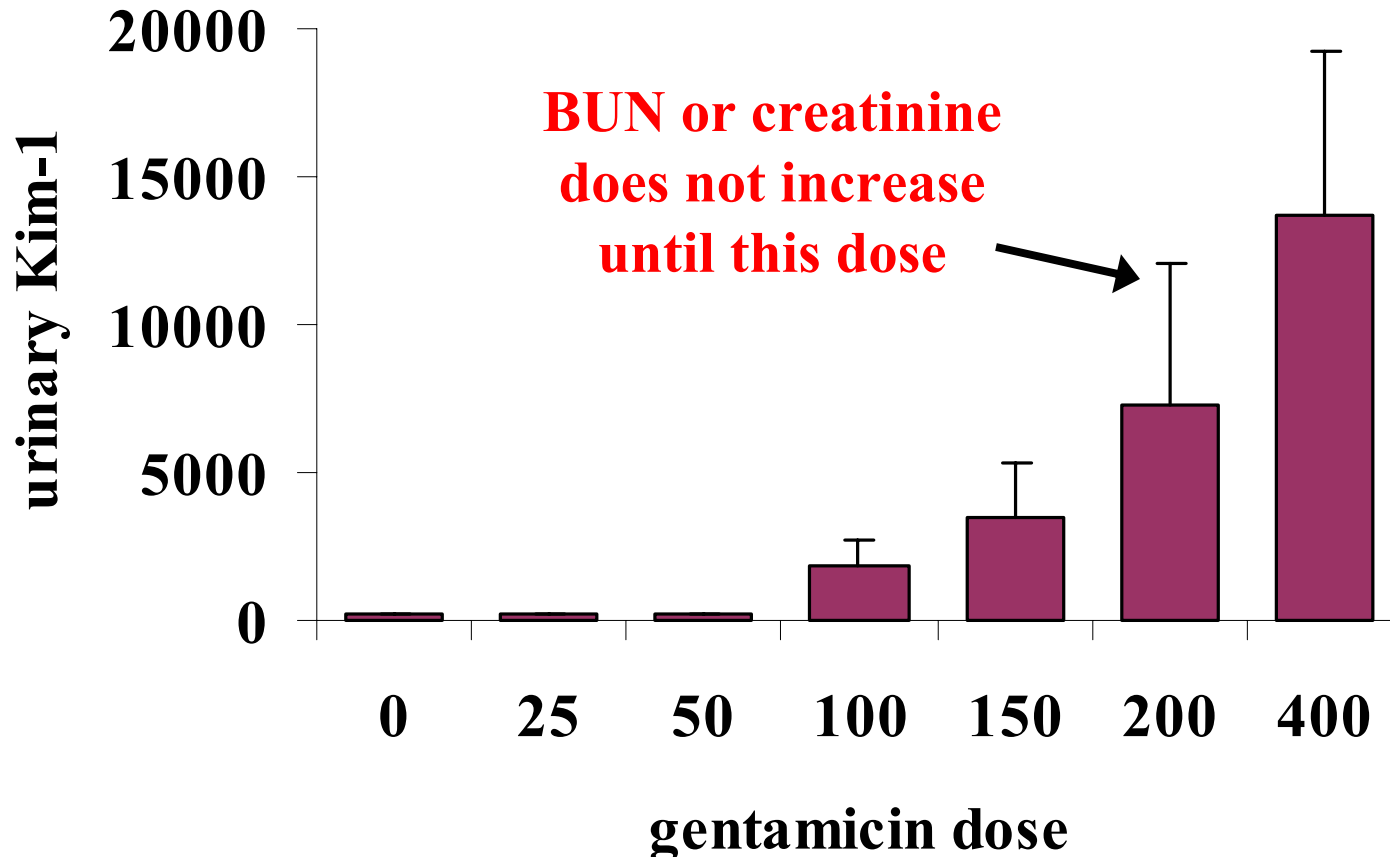
Are current tests for kidney damage adequate?

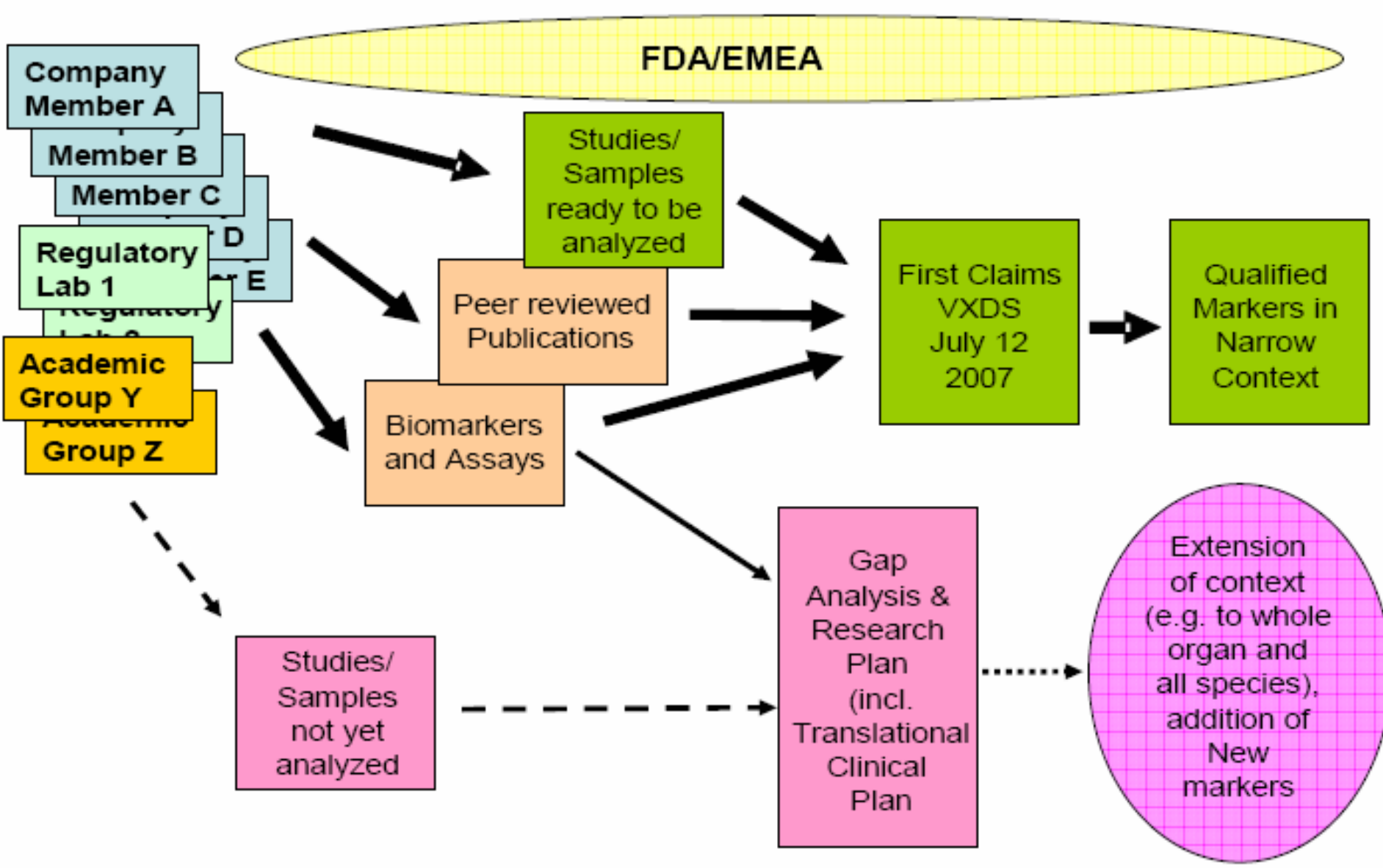


No. 50% of kidney function is gone before the current diagnostic tests are elevated. Need a better test.

A better test? We hope so.

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





Lessons Learned

- **Context for Use**
- **Data Submission Format**
- **Histopathology**
- **ROC Curves**
- **Analytical Performance**
- **Demonstrate a Basic Biological Relationship**
- **Need for recommendations on study designs, data and guidelines needed for qualification.**
- **Volunteer Reviewers**

Context for Use

- **State objectives clearly.**
- **Study should be designed to support the hypothesis.**

Data Submission Format

- **Individual animal data needed for thorough understanding of submission.**
- **Summary tables also useful.**
- **Discuss with reviewers if there are any questions about data needed.**
- **Formatting instructions needed.**

Histopathology

- **Common lexicon and metrics between different members of consortia.**
- **Histopathology reads for accurate assessment of biomarker performance.**
 - **Blinded**
 - **Randomized**
 - **Confirmed across multiple members of consortia and/or independent labs.**
- **Establishment of a pathology working group within consortia to monitor lexicon and metrics.**

ROC Curves

- **Metric to assess biomarker performance.**
- **Generated for different histopathology score ranges.**
- **Plots of AUC for ROCs as a function of histopathology score ranges help summarize biomarker score report.**

Analytical Performance

- **Sensitivity, reproducibility, threshold, dynamic range.**

Demonstrate a Basic Biological Relationship

- **Mechanistic relationship with observed endpoint.**

Need for recommendations on study designs, data and guidelines needed for qualification.

- **Recommendations in regulatory documents.**
- **Early interactions before study designs are completed.**
- **Data formats and content.**
- **Guidelines for histopathology.**

Volunteer Reviewers

- **Accomplished their reviews while developing simultaneously the process and tools for review and continuing their standard review tasks.**
- **Showed that an internal Biomarker Qualification Process will allow a better understanding of data supporting biomarker applications.**
- **Volunteer reviewers have scheduled open and frequent discussions with volunteer scientists in pharmaceutical companies working on biomarker qualification.**
- **Biomarker Qualification Review can develop into a standard review task.**
- **A full review team is required for biomarker qualification depending on context, including pharm/tox reviewers, clinical reviewers, chemists, microbiologists, statisticians, bioinformaticians and project managers.**

Acknowledgement

**The Nephrotoxicity Biomarker
Qualification Review Team**