

**Biomarkers for Drug Safety  
(Really Biomarkers for Drug Toxicity)**

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# Biomarker Definition

**U** A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention

**W** NIH Biomarkers Definitions Working Group, Clin Pharmacol Ther 2001;69:89-95

# Holy Grail of Drug Toxicity Biomarker Development

## u Preclinical

- | Biomarker elevation predicts clinical toxicity
- | Absence of elevation predicts future safety

## u Clinical

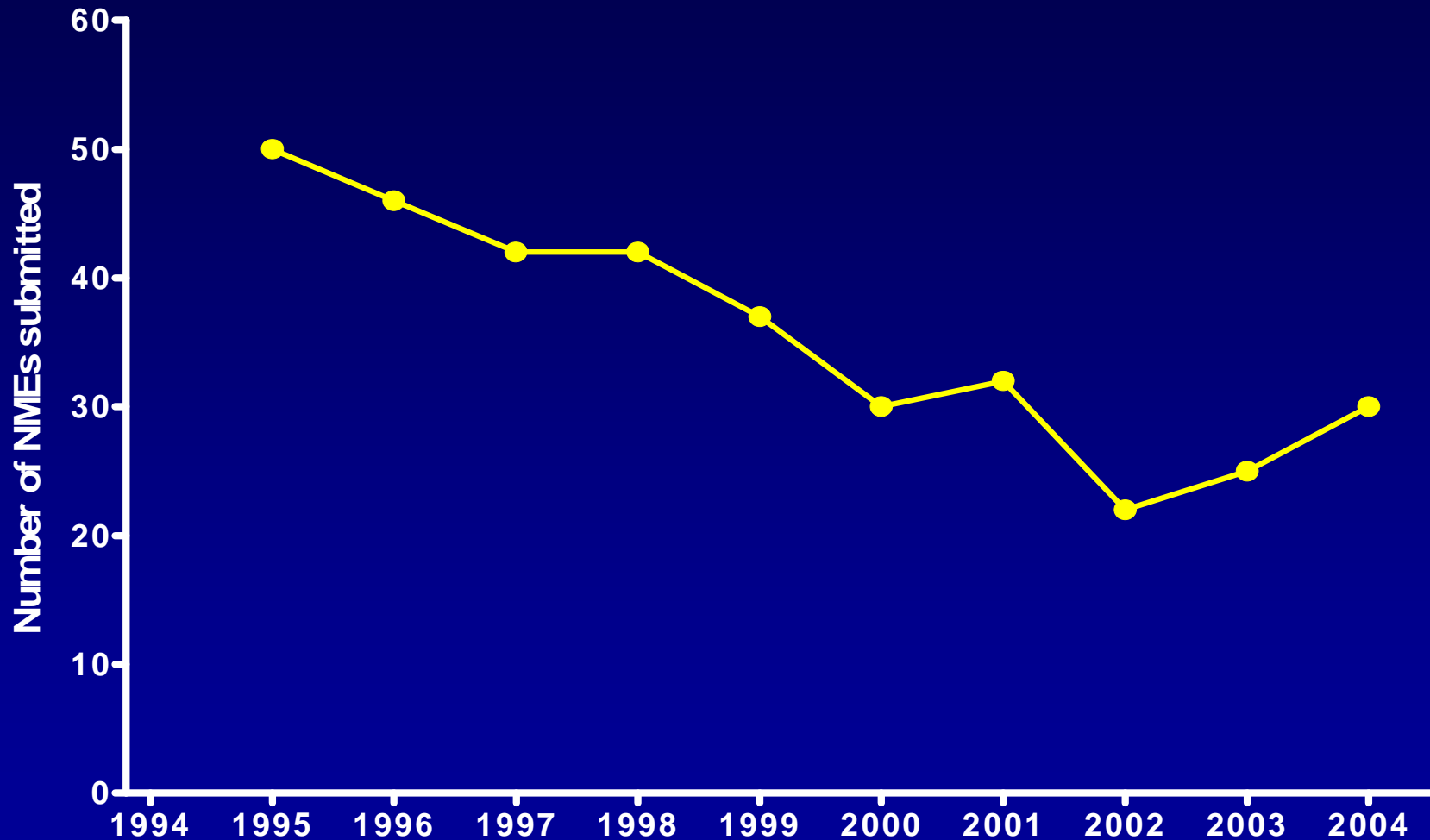
- | Individual biomarker elevation predicts
  - w Individual toxicity?
  - w Population risk?
  - w Often assumed to be the same but is not
- | Absence of elevation predicts future safety

# Why Identify Drug Safety Signals Early?

- u Inform decisions on future drug development
  - l Go/No Go decision
  - l Risk assessment
  - l Risk mitigation
- u Sensitivity/Specificity issues
  - l False negatives
    - w Future development costs wasted
  - l False positives
    - w Potentially successful drugs lost

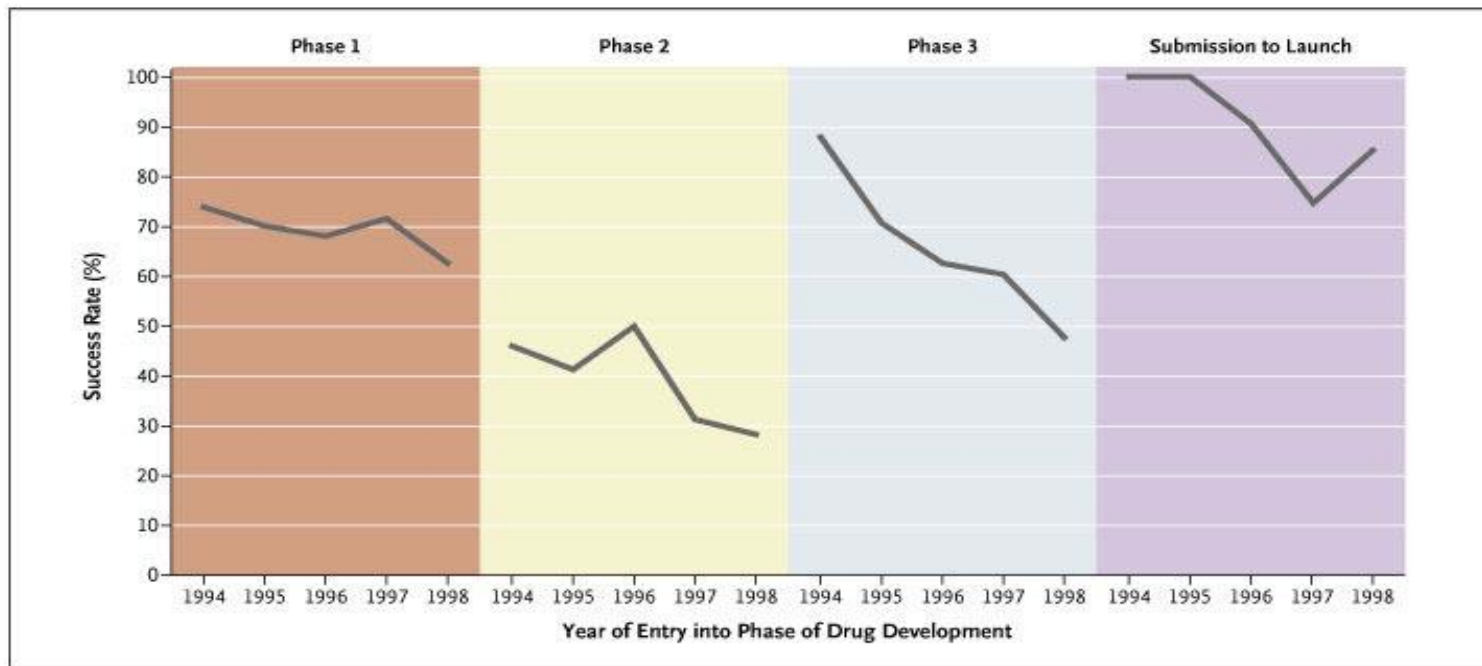
# Fall in NMEs Submitted to FDA

## We Can Ill Afford Misleading Signals



Frantz, Nature Reviews Drug Discovery 3:379, 2004

## Success Rates in All Phases of Drug Development



Wood AJJ N Engl J Med 2006;355:618-623



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# **Toxicity Biomarkers**

## **Sensitivity/Specificity Tradeoffs**

- U Setting the sensitivity too high at expense of specificity –too many false positives**
  - I Will reject many safe and potentially useful drugs**
- U Conversely increasing specificity may increase clinical safety failures**
  - I Too many false negatives**

# Toxicity Biomarkers

## Sensitivity/Specificity Tradeoffs

- u All drugs are not equal
  - l Sensitivity/specificity tradeoff varies by indication
  
- u Nasal allergy therapy vs. oncology cure
  - l Different tolerance for
    - w Failure to detect toxicity
    - w Calling toxicity where no clinical toxicity would occur

# Tolerance For False Positives?

- u 50 preclinical biomarker safety assays
  - | 1% random false positive in each assay
  - | 50% of drugs would be wrongly rejected in preclinical screening
- u Same issue with false negatives
  - | Large number of compounds fail in clinical
- u Would we define this as success?
- u How would we know?

# Safety Biomarkers

## Linear Reasoning vs. Pattern Recognition

- u QT prolongation—linear reasoning
  - l Mechanism understood
  - l Linked to TDP (actual toxicity)
  - l Linked to hERG channel
  - l Linked to “at risk” genotypes
  - l Manipulation of risk factors linked to toxicity
    - w Low Potassium
    - w Increased plasma concentration
    - w Even QT prolongation by drug linked to TDP

# Safety Biomarkers

## Linear Reasoning vs. Pattern Recognition

- U “Positive Array” with no underlying hypothesis
  - I What will our comfort level be?
  - I How do we avoid just replicating the “last war”
    - W Drug XXX did this so it must be bad because it was
    - W Real question is will this predict toxicity in a different molecule?
      - Y How will we know if we abandon compounds?
  - I In the absence of mechanism what level of specificity will we/should we tolerate?

# Knowledge of Mechanisms Helpful

## U Kinase inhibitors in oncology

- I Cardiac toxicity

- I Is it mechanism (cardiac kinase) based

- I Defining specific cardiac kinase linked to toxicity

  - w Would allow prediction of toxicity

  - w Develop molecules devoid of inhibition of cardiac enzyme.

# The Better Our Understanding of Mechanism

- u Better our ability to predict toxicity
- u Better our ability to exclude it
- u Best hope for improved productivity
- u Biomarkers may be an intermediate stop
  - l Same non-competitive structures could also jointly define mechanisms

# Safety Biomarkers Limitations

- u Likely success is predicting increased incidence of events that are very rare in background population
  - | Hepatotoxicity
  - | Nephrotoxicity
  - | Torsades
  - | Repro Tox

# Safety Biomarkers Limitations

- U Public health problem is increased incidence of events common in background population
  - I MI and COX-2 inhibitors
  - I 4X risk produces thousands of cases
  - I Not easy to detect
    - w Against background
    - w From spontaneous reports
    - w Preclinically

# Developing Safety Biomarkers

## Our Challenge for Today

- u How do we do it?
- u How do we measure success?
  - l Improved clinical drug safety?
  - l More drugs killed early?
    - w What if we are wrong (specificity/sensitivity)
    - w How will we know?
      - Y Positives will not progress
  - l Spawning a new industry is not the same as success
    - w If it just decreases the number of available drugs

# Developing Safety Biomarkers Our Challenge for Today

- u How do we validate safety markers?
  - | Across drugs
  - | Across companies
  - | Prospectively (when no one takes a drug forward with a signal)
  - | Retrospectively looking back from evidence of toxicity
  - | Different when there is a “linear relationship” like QT
  - | Different if we can understand mechanisms
  - | In most cases we won't have
    - w Linear relationship or mechanism

# **Developing Safety Biomarkers Our Challenge for Today**

- u How do engage all the stake holders?**
- u How do we share data pre/non competitively?**
- u How do we share/interpret data on drugs stopped early in development**
- u How do we make drugs safer without needlessly killing effective drugs in early development?**

