Biomarkers: Physiological & Laboratory Markers of Drug Effect

Janet Woodcock, M.D.
Deputy Commissioner and Chief Medical Officer
Food and Drug Administration
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Biomarker Definition

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

* FDA Pharmacogenomics Guidance further defines possible, probable and known valid biomarker categories depending on available scientific information on the marker

BIOMARKERS DEFINITIONS WORKING GROUP: BIOMARKERS AND SURROGATE ENDPOINTS: PREFERRED DEFINITIONS AND CONCEPTUAL FRAMEWORK. CLIN PHARMACOL THER 2001;69:89-95.

Types of Biomarkers

* Markers of drug effect or response (laboratory, physiological, or other) are a subset of the general class of biomarkers

* Other biomarkers may include diagnostic, prognostic or physiologic status information not linked to drug response

Clinical Endpoint Definition

* “A characteristic or variable that reflects how a patient feels, functions or survives”

* Clinical endpoints are usually acceptable as evidence of efficacy for regulatory purposes

Surrogate Endpoint Definition

* A biomarker intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm, or lack of benefit) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence

SURROGATE ENDPOINT

A surrogate endpoint of a clinical trial is a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives. Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint.

Robert J. Temple

SURROGATE MARKER

Use of this term is discouraged because it suggests that the substitution is for a marker rather than for a clinical endpoint

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Biomarkers in Drug Development

Use of Biomarkers in Early Drug Development and Decision Making

* Evaluate activity in animal models
* Bridge animal and human pharmacology via proof-of-mechanism or other observations
* Evaluate safety in animal models, e.g., toxicogenomics
* Evaluate human safety early in development

Examples of Biomarkers Commonly used in Drug Development

* Safety biomarkers: serum creatinine and blood chemistries; CBC, CXR, ECG
* Drug phamacokinetics
* Pharmacodynamic (efficacy) biomarkers:
  - Blood glucose
  - Urine, sputum, etc cultures
  - Pulmonary function tests

Use of Biomarkers in Later Drug Development and Decision Making

* Evaluate dose-response and optimal regimen for desired pharmacologic effect

* Use safety markers to determine dose-response for toxicity

* Select or deselect patients for inclusion in trials

* Determine role (if any) of differences in metabolism on above

Use of Surrogate Endpoints in Late Drug Development

* Use to assess whether drug has clinically significant efficacy: this is often faster than using clinical endpoint

* Surrogate endpoints may be used to support "accelerated approval" of a drug if the surrogate is deemed reasonably likely to predict a clinical endpoint of interest

* A few surrogate endpoints are acceptable for full approval (e.g., are "validated")

Biomarkers used as Surrogate Endpoints

* “Validated Surrogate Endpoints”
  - Blood pressure
  - Bone mineral density for estrogenic compounds
  - Hemoglobin A1C for glycemic control
* “Non-Validated Surrogates” used for accelerated approval
  - HIV copy number
  - Tumor shrinkage

The Most Widely Used Surrogate Endpoint*

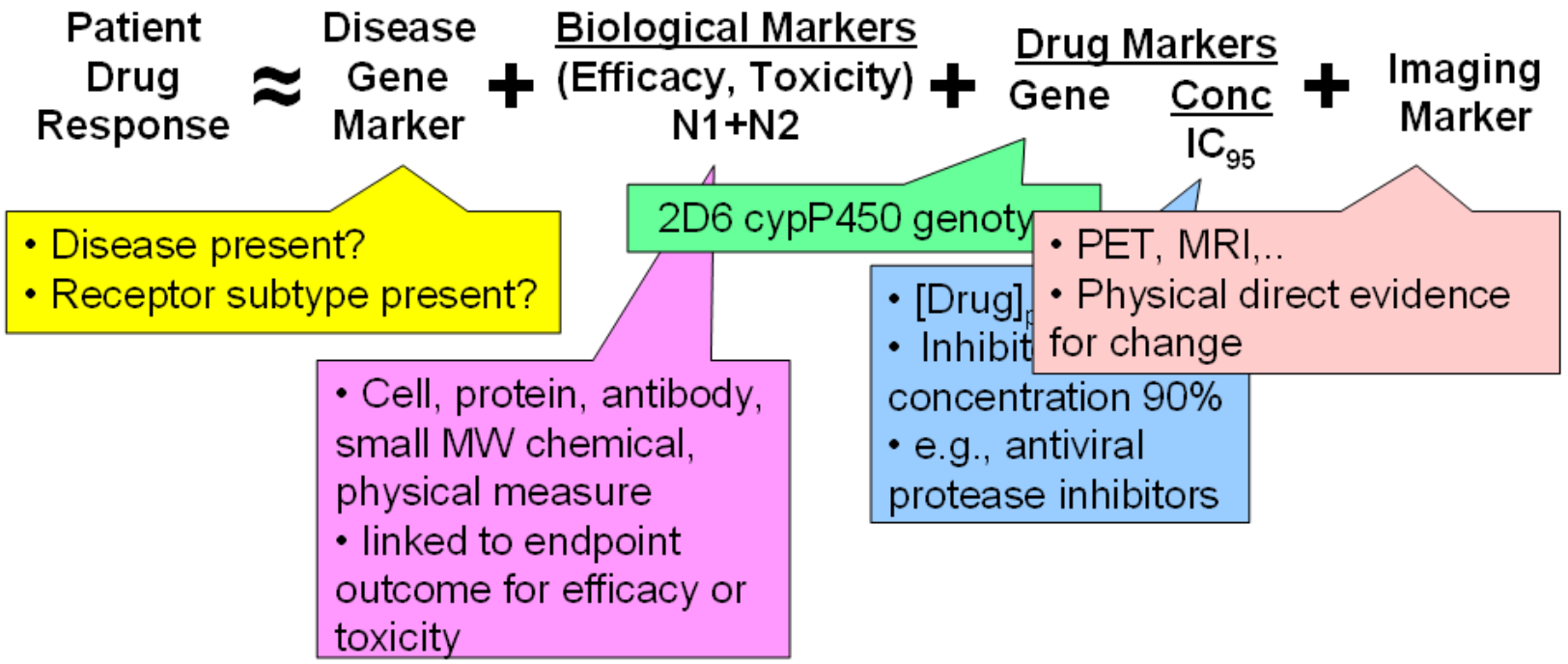
BLOOD LEVELS AS A SURROGATE FOR CLINICAL EFFICACY AND TOXICITY IN THE EVALUATION OF GENERIC DRUGS

*** Comment by Carl Peck: CDDS WORKSHOP, McLean, VA, May 13, 1998**

Use of Biomarkers in Clinical Practice

* Disease and disease subtype diagnosis
* Prognostic determination
* Selection of appropriate therapy
  - Maximize efficacy
  - Minimize toxicity
* Selection of correct dose
* Monitoring outcomes (good and bad)

Biomarkers in Future Clinical Practice: The Ultimate in Personalized Medicine



Or is this a regulatory & therapeutic nightmare?

Why Are Biomarkers Important?

* Diagnosis is the foundation of therapy

* Biomarkers are quantitative measures that allow us to diagnose and assess the disease process and monitor response to treatment

* Biomarkers are also crucial to efficient medical product development

* As a consequence of scientific, economic and regulatory factors, biomarker development has lagged significantly behind therapeutic development

Biomarker Development: More is at Stake than Efficient Drug Development

* Biomarkers are needed to create evidence-based medicine as well as personalized medicine: who should be treated, how and with what

* Absent new markers, advances towards more targeted therapy will be limited and treatment will remain largely empirical (i.e, trial and error)

* It is imperative that biomarker development be accelerated along with therapeutics

Problem: Classic Thinking about Biomarkers Inhibits New Biomarker Development

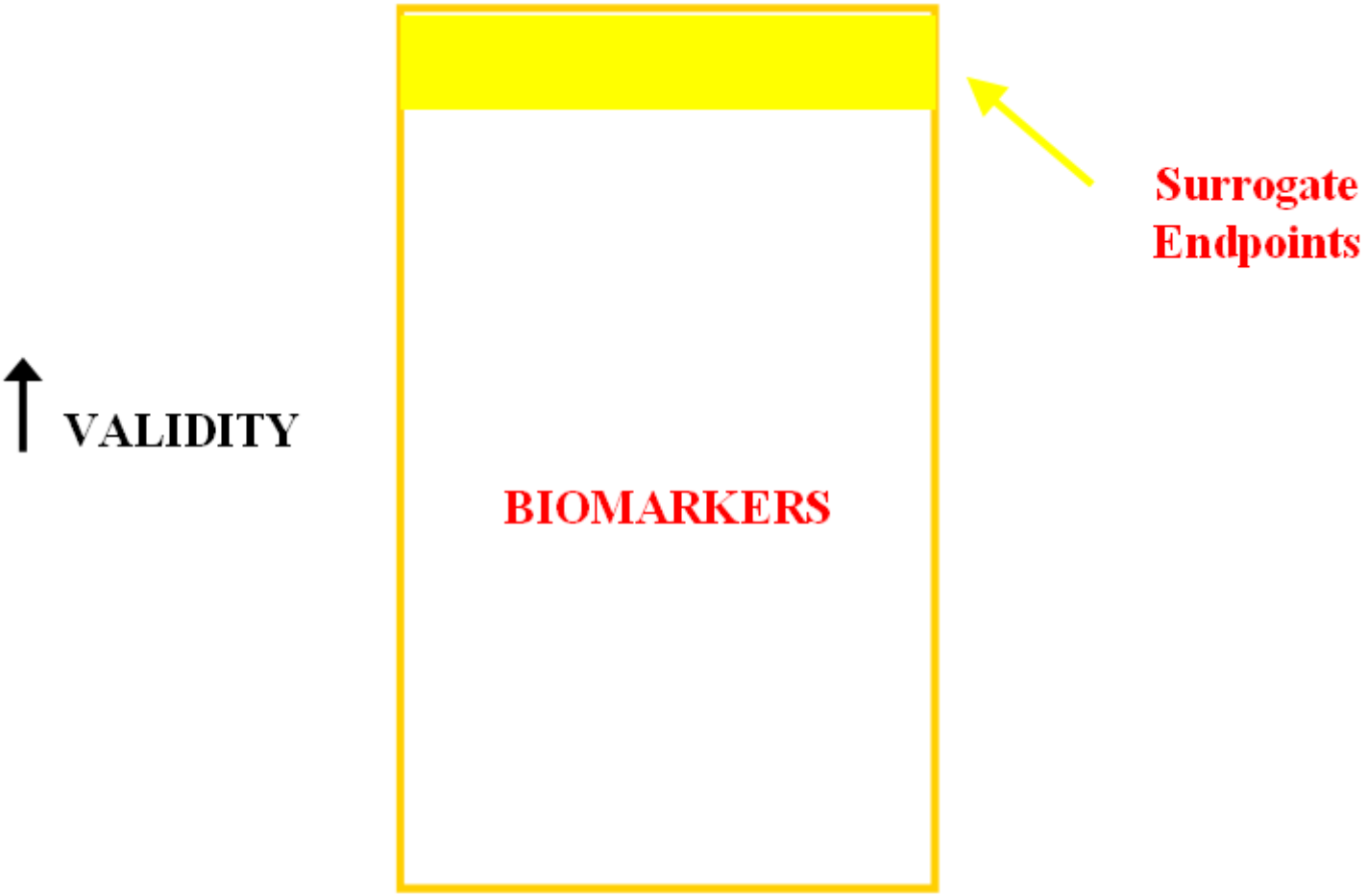
* Development of biomarkers “confounded” with the surrogate endpoint issue

* Near impossibility of “validating” new surrogates has created a significant barrier

* I will present the classic view first (slides courtesy of Dr. Art Atkinson) and then a proposal for a new framework

* Note: classic view not “wrong” as much as limiting

HIERARCHY OF BIOMARKERS (Classic view)



HIERARCHY OF BIOMARKERS* (Classic view)

TYPE 0: NATURAL HISTORY MARKER (Prognosis)

TYPE I: BIOLOGICAL ACTIVITY MARKER (Responds to therapy)

TYPE II: SINGLE OR MULTIPLE MARKER(S) OF THERAPEUTIC EFFICACY (Surrogate endpoint, accounts fully for clinical efficacy)

*** Mildvan D, et al.: Clin Infect Dis 1997;24:764-74.**

"Validation" of Biomarkers (e.g., for use as Surrogate

BIOLOGICAL PLAUSIBILITY

* **EPIDMIOLOGIC EVIDENCE THAT MARKER IS A RISK FACTOR**
* **MARKER MUST BE CONSISTENT WITH PATHOPHYSIOLOGY**
* **MARKER MUST BE ON CAUSAL PATHWAY**
* **CHANGES IN MARKER REFLECT CHANGES IN PROGNOSIS**

STATISTICAL CRITERIA

* **CHANGES IN MARKER MUST BE CORRELATED WITH CLINICAL OUTCOME** (but correlation does not equal causation)

(Not confounded by adverse drug effects)

ADDITIONAL SUPPORT FOR BIOMARKER as SURROGATE

SUCCESS IN CLINICAL TRIALS

* EFFECT ON SURROGATE HAS PREDICTED OUTCOME WITH OTHER DRUGS OF SAME PHARMACOLOGIC CLASS
* EFFECT ON SURROGATE HAS PREDICTED OUTCOME FOR DRUGS IN SEVERAL PHARMACOLOGIC CLASSES

OTHER BENEFIT/RISK CONSIDERATIONS

* SERIOUS OR LIFE-THREATENING ILLNESS WITH NO ALTERNATIVE THERAPY
* LARGE SAFETY DATA BASE
* SHORT-TERM USE
* DIFFICULTY IN STUDYING CLINICAL ENDPOINT

Temple R: JAMA 1999;282:790-5.

Limitation of Current Conceptual Framework for Development of Surrogate Endpoints

* Problems with use of surrogate endpoint identified in 1980s

* CAST outcome:
  - Use: antiarrhymics for prevention of sudden death
  - Surrogate: suppression of VBP's
  - Mortality increased in treatment arms

Temple. "A regulatory authority's opinion about surrogate endpoints". Clinical Measurement in Drug Evaluation. Wiley and Sons. 1995

Use of Surrogates Discouraged

* Surrogate EP supposed to “completely correlate with the clinical endpoint”

* This is not possible and has led to serious (but I would argue, misplaced) disillusionment with the use of biomarkers

* Flemming TR, DeMets DL: Surrogate endpoints in clinical trials: are we being misled?

Ann Intern Med 1996;125:605-13

Surrogate Endpoint Development: 1990s

* HIV epidemic spurred the use of new surrogate endpoints for antiretroviral therapy: highly controversial at first given CAST experience

* Rigorous statistical criteria for assessing correlation of candidate surrogate with clinical outcome were published*

* No surrogate EP has ever met these criteria

Prentice. Stat in Med 8: 431, 1989

Surrogate Endpoint Development: HIV

* HIV RNA copy number is now used as early drug development tool, surrogate endpoint in trials, and for clinical monitoring of antiviral therapy

* Lack of complete correlation with clinical outcomes has not compromised utility

* Successful development of antiretrovirals and control of HIV infection

Surrogate Endpoint Use: 2000s

* Controversy over use of glycemic control as efficacy endpoint: rosiglitazone
  - Wrong dispute
  - Real argument is over how much premarket cardiovascular safety data to accumulate
* Controversy over use of LDL cholesterol (as assessed by another biomarker, carotid artery intimal thickness on ultrasound): Vytorin

Fundamental Problems with the Current Conceptual Framework for Surrogate Endpoints

* There is no “gold standard” clinical outcome measurement – concept of “ultimate” clinical outcome is flawed

* Survival: data show that desirability of longer survival dependent on quality of life, in many individuals’ estimation.

* Generalizability of any single outcome measure (e.g., mortality) can be limited by trial parameters (e.g., who was entered)

* Confusion between desirability of prolonged observation (for safety and long term outcomes) and use of surrogate

Fundamental Problems with Current Conceptual Framework for Surrogate Endpoint Development

* Patient outcomes are multidimensional—a single outcome measure (whether clinical or surrogate endpoint) can miss domains of interest.

* Very difficult to capture both benefit and harm within a single measure—very unlikely for a biomarker.

* The concept of “ultimate clinical outcome” includes parameters such as duration of observation that are important dimensions. However, knowledge about these dimensions could be acquired outside of the biomarker measurement

Additional Problems with Surrogate Endpoint Framework

* Per-patient view of outcomes very different from population mean view of outcomes.

* For example, “ultimate” benefit in survival of 8% over placebo not meaningful to you if you are not in the 8% who actually respond

* Newer (and older, e.g., metabolizing enzymes) biomarkers provide information at the individual level

Summary:Problems with Current Biomarker Conceptual Framework

* Overemphasis on “surrogacy” as single objective of biomarker development
* Difficulty in achieving surrogate “validation” frustrates progress
* New science and technology will contribute numerous candidate biomarkers—require path forward

Fate of Most Candidate Biomarkers

* Discovered in academic laboratory
* Clinical series results published
* Further small academic series published
* Some uptake in academic centers in clinical care
* 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 care

* Evidence base for use often remains slim/controversial

* Not adopted for regulatory use because of absence of needed evidence (e.g., PSA)

Limitations of Current Conceptual and Developmental Framework

* Practical business and conceptual models for biomarker development are lacking

* Consequence: no rigorous pursuit of evidence to develop marker or to assemble data for regulatory approval

* Exploration of clinical relevance is generally ad hoc

Future of Drug Development and Biomarker Development Tightly Linked

* Biomarkers represent bridge between mechanistic understanding of preclinical development and empirical clinical evaluation

* Regulatory system has been focused on empirical testing: skewing overall clinical evaluation towards “all empirical”

* Mechanistic clinical evaluation lacking

Towards the Robust Use of Biomarkers in Drug Development

* Implement new biomarker use throughout preclinical and clinical development
* "Qualify" biomarker for intended use: less focus on surrogacy
* Goal is understanding mechanistic bases for individual response to therapy to increase *informativeness* of development process
* Achieve more predictable drug development and therapeutic outcomes

Towards the Robust Use of Biomarkers in Drug Development

* 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
* Clinical safety biomarkers of great interest

Promising Safety Biomarkers

* Drug Metabolizing enzyme status
  - 6-Mercaptopurine (enzyme TPMT)
  - “Strattera” (enzyme CYP 2D6)
  - Irinotecan (enzyme UGT1A1)
  - Warfarin (enzyme CYP 2C9; pharmacodynamic biomarker VK0RC1

* Genetic Basis of Adverse Event
  - Abacavir

Biomarker Development Consortia

* Predictive Safety Consortium
  - C-Path Institute, Tucson AZ
  - Animal safety biomarkers generated as a part of animal toxicology testing
  - Thousands of animal tox 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

Other 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

Summary

* Important public health need for development of additional biomarkers to target and monitor therapy
* This requires use in clinical trials during drug development
* Business model/regulatory path for such markers is not clear to industry
* Clarification and stimulus required

Summary

* Definitions for biomarkers, clinical outcomes and surrogate endpoints have been developed
* Further development of the model needed in order to increase use and utility of markers in drug development
* Single measurements will rarely capture all dimensions of clinical outcomes

Summary

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

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