



Biomarkers: Physiological & Laboratory Markers of Drug Effect

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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 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"

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



Biomarkers Have Many Uses in Medicine

- 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



BIOMARKERS AND CLINICAL ENDPOINTS IN DRUG TRIALS: DEFINITIONS



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 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 pharmacokinetics
- 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

 **Biomarkers and Personalized Medicine**

- It is assumed that new biomarkers will enable personalized medicine
- Many of these markers will utilize new technology: genomics, proteomics, etc
- Individual markers for:
 - Drug metabolism
 - Interactions
 - Drug safety risks
 - Probability of response or non-response

 **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)



DEVELOPMENT AND QUALIFICATION OF BIOMARKERS



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)



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



Stimulating the 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 ongoing in areas such as animal safety testing and overall biomarker development
- Clinical safety biomarkers of great interest



Developing Biomarkers for Use in Drug Trials: a New Model

- Idea of "qualification":
 - Develop the evidence needed for a specific use: demonstrate "fitness for use"
 - Make evidence public
 - Process to submit evidence to regulatory agencies
 - Agencies review and, if indicated, publish findings of acceptance



Stimulating 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 surrogate endpoints
- Goal is understanding mechanistic bases for individual response to therapy to increase *informativeness* of development process
- Achieve more predictable drug development and therapeutic outcomes



Barriers to Progress

- Evidence development expensive: business model for diagnostic companies not compatible
- Frequently need multiple assays using many compounds/preclinical or clinical settings
- Science not considered as “innovative” as basic discovery



Promising Safety Biomarkers

- Drug Metabolizing enzyme status
 - 6-Mercaptopurine: enzyme TPMT
 - “Strattera”: enzyme CYP 2D6
 - Irinotecan: enzyme UGT1A1
 - Warfarin: enzyme CYP 2C9; pharmacodynamic biomarker VKORC1-- safety and efficacy
- Genetic Basis of Rare, Serious Adverse Event
 - Abacavir: HLA-B*5701 and hypersensitivity
 - Carbamazepine: HLA-B*1502 and Stevens-Johnson Syndrome
 - More to come, e.g., hepatic injury with lumiracoxib or exanta



Potential Imaging Biomarkers

- FDA Central and Peripheral Nervous System Drug Advisory Committee meeting: Oct 26, 2008
- Three sponsors presented development plans for 3 different imaging agents for detection of amyloid in diagnosis of Alzheimer’s disease
- Difficult challenge because of lack of a gold standard other than histologic verification



Potential Genomic Efficacy Biomarkers

- Metabolism of prodrugs: necessary for conversion to active drug in vivo
 - Clopidogrel
 - Tamoxifen
- Pathway markers in cancer: targeted therapy
 - Recent Oncology Drug Advisory Committee meeting on - RAS and 2 EGFR targeted drugs (Erbix, Vectibix) to treat colon cancer (Dec 16, 2008); label change to restrict treatment to individuals without mutated k-RAS



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 for renal injury markers
- FDA and EMEA have accepted for use in animal studies



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



Why Use Consortia for Biomarker Qualification?

- No group's "job" is to qualify biomarkers
- Requires significant resources and multiple experiments
- Often qualification can be "piggybacked" onto animal and clinical studies done for other purposes
- Multiple parties benefit from results



Regulatory Qualification of Biomarkers

- Until recently, regulators basically waited until a new biomarker was widely accepted in clinical practice and had a robust evidence base
- Unfortunately, this can take decades
- FDA has established a process whereby qualification packages can be submitted and reviewed for regulatory acceptance
- Process guidance will be issued soon



REGULATORY ACCEPTANCE OF SURROGATE ENDPOINTS



How are New Surrogate Endpoints Accepted for Regulatory Use?

- There is no standardized process
- In some cases, acceptance based on long time clinical use plus adequate data from trials
- In other cases (e.g., HIV) acceptance driven by crisis



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

- EPIDEMIOLOGIC 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.



History of Surrogate Endpoint Use

- Blood pressure measurements and cholesterol levels accepted in 1970s-80s based on epidemiologic data
- Problems with use of surrogate endpoints identified in late 1980s

CAST outcome:

- Use: antiarrhythmics 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

 **Result: 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 (under accelerated approval), 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
 - Dispute is misguided
- 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
- Can put "too many eggs" in the surrogate basket!



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



How Likely are New Surrogates?

- Clearly, need robust pipeline of new biomarkers being used in drug development
- Use in many drug development programs and in multiple trials adds generalizability
- New candidates will likely emerge
- Regulatory agencies need to better articulate how longer term safety evaluation would be performed



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
