



Developing a Qualified Biomarker: Regulatory Considerations

Janet Woodcock, M.D.
Deputy Commissioner/Chief
Medical Officer, FDA



Agenda

- n Definitions
- n Qualification of biomarkers
- n Qualification of surrogate endpoints
- n Applications in neurosciences
- n FDA's role



Biomarker Definition

- n "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.

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



Biomarker Qualification

- n Qualification= evaluation of “fitness for use”, i.e., do the data on the biomarker support its use for a given purpose
- n Level of evidence needed varies depending on the clinical situation
- n Both in vitro and in vivo biomarkers (e.g., imaging) are diagnostics and can be thought of using diagnostic paradigm



Clinical Endpoint Definition

- n “A characteristic or variable that reflects how a patient feels, functions or survives”
- n (Note that, except for survival, assessing these involves some sort of intermediary measurement)
- n Clinical endpoints are usually acceptable for evidence of efficacy for regulatory purposes
- n In contrast, many types of biomarkers are used for safety assessment



Surrogate Endpoint Definition

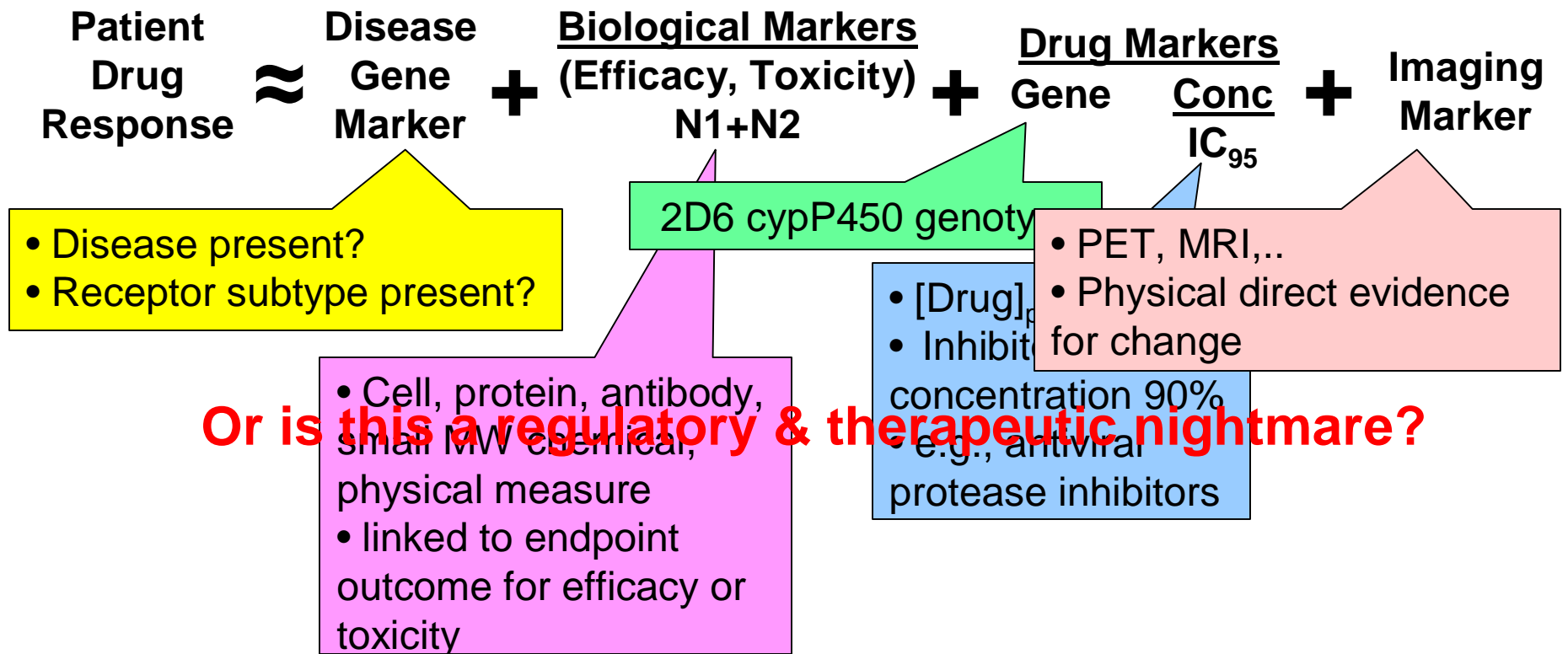
- n A biomarker intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm, or lack of benefit) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence



Why Are Biomarkers Important?

- n Diagnosis is the foundation of therapy
- n Biomarkers are quantitative measures that allow us to diagnose and assess the disease process and monitor response to treatment
- n Biomarkers are crucial to efficient medical product development
- n As a consequence of scientific, economic and regulatory factors, biomarker development has lagged significantly behind therapeutic development

Biomarkers in Future Clinical Practice: The Ultimate in Personalized Medicine





Fate of Most Candidate Biomarkers

- n Discovered in academic laboratory
- n Clinical series results published
- n Further small academic series published
- n Some uptake in academic centers in clinical care
- n Assay may be commercialized as laboratory service



Fate of Most Candidate Biomarkers

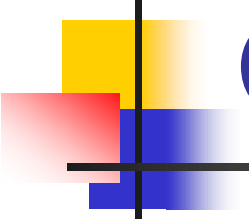
- n Small number may be developed into commercially available laboratory tests
- n Fewer may become integrated into clinical care
- n Evidence base for use often remains slim/controversial
- n Not adopted for regulatory use because of absence of needed evidence



Biomarker Qualification: Analytical Validation

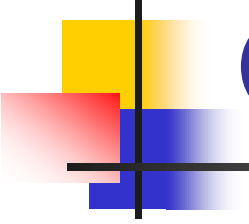
Biomarker usually embodied in a “test”:

- n Evaluate test parameters such as stability of reagents, interference, effects of various conditions etc.
- n Standardize assay:
 - n For imaging, stabilize acquisition parameters
 - n Develop standard protocols for use- e.g., sample acquisition, preservation, timing, etc.
- n Assess sensitivity, specificity, predictive value of standardized assay for detecting something
- n Assess robustness in various sites
- n All these activities usually not well compensated for or rewarded in academic sector



Biomarker Qualification: Clinical Validation

- n Evaluate performance in clinical samples or in people with varying characteristics
- n Does assay continue to measure the same thing with reasonable accuracy under varying conditions—i.e., different populations?



Biomarker Qualification: Clinical Utility (use dependent)

- n Show that the “test” results have some clinical significance (basis of claim)
- n “Stand-alone” diagnostic:
 - n Prognostic stratification (not a high bar)
 - n Outcomes (natural history) stratification
 - n Predict drug exposure: drug metabolizing enzymes
 - n Diagnose or contribute to diagnosis of pathology (diagnosis has higher bar)



Biomarker Qualification: Biomarker Result Linked to Therapeutic Intervention

- n Clinical utility finding will be in the context of the therapeutic use; contingent on trial design (drug-dx)
 - n Select patients to receive therapy
 - n Select patients to *not* receive therapy
 - n Select dose/regimen/other parameter
 - n Monitor response

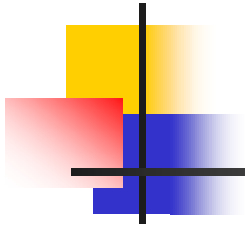
Above uses do not have extensive regulatory requirements



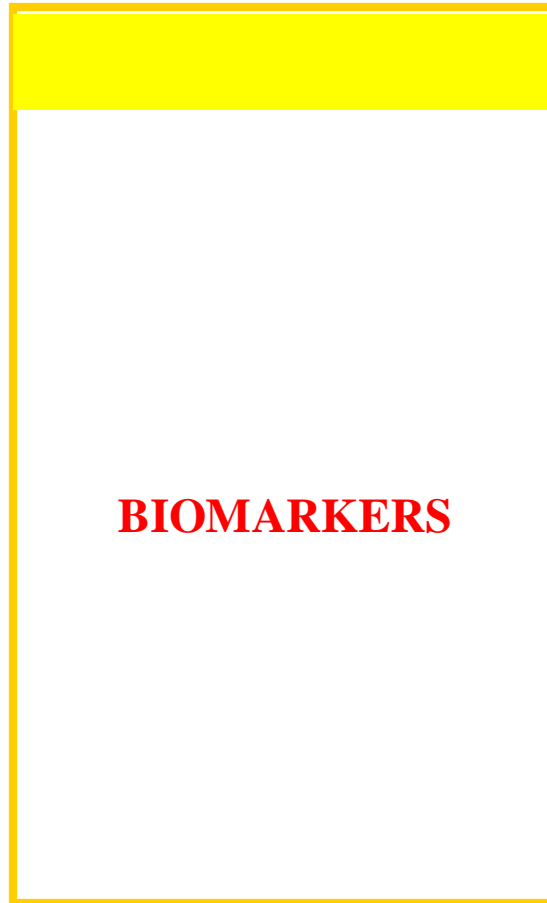
Biomarker Qualification: Use as Surrogate Endpoint

- n Pursuit of this goal has led to extensive problems and misunderstanding in the field of biomarker development
- n Development of new surrogate endpoint usually requires extensive use of and experience with marker in other contexts
- n Extremely useful markers such as for safety or disease stratification, may never become surrogate markers

This Concept is Incorrect: HIERARCHY OF BIOMARKERS



↑ VALIDITY



Surrogate
Endpoints



HIERARCHY OF BIOMARKERS*

**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.



Qualification of Biomarkers 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.**



Pursuit of Surrogacy

- § 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 surrogates
- § Fleming TR, DeMets DL: Surrogate endpoints in clinical trials: are we being misled?
Ann Intern Med 1996;125:605-13



Limitation of Current Conceptual Framework for Development of Surrogate Endpoints

- n Current model for surrogacy based largely on cardiovascular and HIV experiences in the 1990's

- n CAST outcome:

- n Surrogate: suppression of VBP's
- n Mortality increased in treatment arms

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



Surrogate Endpoint Development

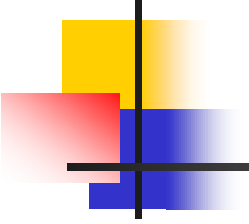
- n HIV epidemic spurred the use of new surrogate endpoints for antiretroviral therapy
- n Rigorous statistical criteria for assessing correlation of candidate surrogate with clinical outcome were published*
- n No surrogate EP has ever met these criteria

*Prentice. Stat in Med 8: 431, 1989



Surrogate Endpoint Development

- n HIV RNA copy number is now used as early drug development tool, surrogate endpoint in trials, and for clinical monitoring of antiviral therapy
- n Lack of complete correlation with clinical outcomes has not compromised utility
- n Successful development of antiretrovirals and control of HIV infection



Fundamental Problems with the Current Conceptual Framework for Surrogate Endpoints

- n There is no “gold standard” clinical outcome measurement – concept of “ultimate” clinical outcome is flawed
- n Survival: data show that desirability of longer survival dependent on quality of life, in many individuals’ estimation.
- n Generalizability of any single outcome measure (e.g., mortality) can be limited by trial parameters (e.g., who was entered)
- n 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

- n Patient outcomes are multidimensional—a single outcome measure (whether clinical or surrogate endpoint) can miss domains of interest.
- n Very difficult to capture both benefit and harm within a single measure—very unlikely for a biomarker.
- n 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



Future of Surrogate Endpoint Development

- n Composite outcome measurements: i.e., adding new imaging modalities to radiologic response measures in cancer therapy
- n Responder rather than population mean analyses
- n Individualized therapy based on biomarker-derived strata



Qualification of Biomarkers in the Neurosciences

- n Disorders with subjective diagnostic criteria
- n Disorders with highly variable responses to therapy
- n Disorders with high need for preventive interventions
- n Therapeutic interventions with safety or adherence problems



Role of FDA

- n Critical Path Initiative: encourage qualification and use of new biomarkers for preclinical and clinical product development
- n Encourage use of partnerships and consortia to share burden
- n Develop regulatory guidance on pathways and provide advice on design of qualification trials



Future of New Product Development and Biomarker Development Tightly Linked

- n Biomarkers represent bridge between mechanistic understanding of preclinical development and empirical clinical evaluation
- n Regulatory system has been focused on empirical testing: skewing overall clinical evaluation towards “all empirical”
- n Mechanistic clinical evaluation lacking



Summary

- n Clear definitions of biomarker and surrogate endpoint available
- n Information is being developed on how to qualify these for various uses
- n Neuroscience field a leading candidate for use of new biomarkers
- n Regulatory system is evolving to incorporate new science and opportunities
- n More extensive use of biomarkers will create a more quantitative basis for “evidence-based” medicine