Role of biomarkers in drug development

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- Views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position
Overview

- Types of biomarkers
- Biomarker development process
- Surrogate endpoints – value and limitations
BEST Resource: **Biomarkers, EndpointS, and Other Tools**

- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
- Created by the NIH-FDA Biomarker Working Group
- BEST harmonizes terms and definitions and addresses nuances of usage and interpretation among various stakeholders, including:
  - Biomedical scientists
  - Translational and clinical researchers
  - Medical product developers
  - Patient/disease advocacy groups
  - Government officials
  - Clinicians
Biomarker: definition

“A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. *Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers.*”
BEST (Biomarkers, Endpoints, and other Tools)

Classification: Range of Biomarker Types

- Susceptibility / risk biomarker
- Diagnostic biomarker
- Prognostic biomarker
- Monitoring biomarker
- Predictive biomarker
- Pharmacodynamic/Response biomarker – including surrogate endpoints
- Safety biomarker

Measures of disease presence and status

Measure aspects of response to treatment
CONSIDERATIONS FOR BIOMARKER UTILITY

Context of Use (COU): 1) BEST biomarker category and 2) how the biomarker impacts the clinical trial or drug development program

What question is the biomarker intended to address. Examples include:

- Inclusion/exclusion criteria for prognostic or predictive enrichment?
- Alter treatment allocation based on biomarker status?
- Result in cessation of a patient’s participation in a clinical trial because of safety concern?
- Result in adaptation of the clinical trial design?
- Establish proof of concept for patient population of interest?
- Support clinical dose selection for first in human or Phase 3 studies?
- Evaluate treatment response (e.g. pharmacodynamic effect)?
- Support regulatory acceptability of a surrogate endpoint for accelerated or traditional approval?

“Total Kidney Volume, measured at baseline, is a prognostic enrichment biomarker to select patients with ADPKD at high risk for a progressive decline in renal function (defined as a confirmed 30% decline in the patient’s estimated glomerular filtration rate (eGFR)) for inclusion in interventional clinical trials. This biomarker may be used in combination with the patient’s age and baseline eGFR as an enrichment factor in these trials.”

The Specific Context of Use for a Biomarker Drives the Extent of Evidence Needed for Qualification

Analytical Validation

(establish performance and acceptance characteristics of the biomarker assay)

Reference Ranges/Decision Points
Pre-Analytical and Assay Performance Characteristics
Analytical Rigor/Reproducibility
Sample Handling/Stability

Clinical Validation

(establish that the biomarker acceptably identifies, measures, or predicts the concept of interest)

Study Design Acceptability
Clinical Meaningfulness/Decision Points
Benefit/Risk Assessment
BIOMARKER INTEGRATION INTO DRUG DEVELOPMENT

Drug Approval Process

Scientific Community Consensus

Biomarker Qualification Program

Note: These pathways do not exist in isolation and many times parallel efforts are underway within or between pathways. All share common core concepts, are data-driven, and involve regulatory assessment and outcomes based on the available data.
BIOMARKER QUALIFICATION AND 21ST CENTURY CURES DDT LEGISLATION

Biomarker Qualification Process

Letter of Intent
- Is a request for the qualification of a specific biomarker for a proposed context of use (COU) in drug development

Qualification Plan
- Describes biomarker development plans for the COU and provides data on analytical validation of the biomarker measurement

Full Qualification Package
- Contains all accumulated data to support the qualification of the biomarker for the proposed COU

Qualification Determination
- Is FDA’s determination on qualification of the biomarker for the proposed COU based on a comprehensive review of the full qualification package.
To support approval, FDA expects substantial evidence of effectiveness – that shows that a drug improves meaningful clinical outcomes: how a patient feels, functions, or survives.

- A **validated surrogate endpoint**: accepted by FDA that the effect on the biomarker predicts a specific clinical outcome. Validated endpoints have strong and diverse evidence supporting the relationship of the BM and the outcome.

- A “reasonably likely” **surrogate endpoint**: an endpoint supported by strong mechanistic and/or epidemiologic rationale such that an effect on the surrogate endpoint is expected to be correlated with a clinical benefit, but not yet reaching the standard for validation.
The limitations of surrogate endpoints

- Not a direct measure of how a patient *feels, functions or survives*
- Intended to reflect and predict clinical benefit not measure the outcome
- With a surrogate endpoint, the benefit / risk assessment therefore must be based upon *assumptions / predictions of benefit*
  - Translating the extent of clinical benefit from an *indirect* measure, and also using a *limited* dataset on risk to assess harms
  - Challenging when a drug shows clear effects on a *surrogate endpoint* – but also has safety issues
- And biomarkers may *fail* to predict clinical benefit
The limitations of surrogate endpoints

Surrogate on **causal pathway** modulated by drug.

Surrogate *not on causal pathway* by which drug leads to benefit, or *multiple pathways of leading to clinical outcome*, BM *may or may not* reflect key pathways.

Drug may induce **adverse effects on desired clinical outcome** through a pathway *not reflected* by BM, or may lead to other toxicities = BM does not reflect benefit (or risk).

*After Fleming Statistics in Medicine 2012*
Challenges in biomarker clinical validation: Radiographic Progression in RA

DL Scott et al. Rheumatology 2000;39:122–132
Correlation between physical function & X-ray

- Disability in Truro cohort initially variable
- Later progressive
- Radiographs progressed throughout
- Correlation marked only after 5 yrs
- Other studies support strong correlation ($r = 0.31-0.68$) only in “late” RA

DL Scott et al. Rheumatology 2000;39:122–132
Type of Surrogate Endpoints

- Candidate Surrogate Endpoint
- Reasonably Likely Surrogate Endpoint (RLSE)
- Validated Surrogate Endpoint

Level of Evidence Supporting Use
Type of Surrogate Endpoints

- Candidate Surrogate Endpoint
- Reasonably Likely Surrogate Endpoint (RLSE)
- Validated Surrogate Endpoint

Level of Evidence Supporting Use

Traditional Approval
- Ex: sUA for gout
Type of Surrogate Endpoints

- Candidate Surrogate Endpoint
- Reasonably Likely Surrogate Endpoint (RLSE)
- Validated Surrogate Endpoint

Level of Evidence Supporting Use

Not appropriate for regulatory decision making
Type of Surrogate Endpoints

- Candidate Surrogate Endpoint
- Reasonably Likely Surrogate Endpoint (RLSE)
- Validated Surrogate Endpoint

Level of Evidence Supporting Use

Accelerated Approval
FDA’s Benefit-Risk Assessment

When efficacy is established via the effect on a surrogate endpoint with unquantifiable clinical benefit, the risk/benefit assessment must balance an unmeasured clinical benefit against measured risks.

Hypothetical Therapy

Benefit

Risks
Accelerated Approval

- For serious and/or life-threatening conditions
- Endpoint is often a RLSE
- Requires postmarketing studies to confirm clinical benefit
- Pros and Cons of Accelerated Approval:
  - **Pros**: Faster access to promising treatments
  - **Cons**: Patients may be exposed to the risks of a drug that does not show benefit; potential for less safety information; confirmatory trial may not be completed in a timely manner
Considerations for potential surrogates in OA

- What is the clinical benefit expected?
- How strong is the scientific evidence tying the biomarker to clinical outcomes?
- How much change in the biomarker would indicate a clinically meaningful benefit to patients?