Biomarker Applications and Development

Accelerating Therapies for Rare Diseases
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The views expressed are those of the author, and do not necessarily represent an official FDA position
Definition of Biomarker

• A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes (abnormal biologic processes), or biological responses to a therapeutic intervention

• Any measurable characteristic that is not a measure of the patient’s clinical functional status

• Clinical measures are those indicating how a patient feels or functions, or survival
Types of Biomarkers

• Prognostic biomarker
  ➢ Indicates future clinical course of the patient with respect to some specified clinical outcome, in the absence of a Tx intervention
    ❖ Except Tx interventions incorporated in the data that established the biomarker
  ➢ No relationship to any particular new Tx
  ➢ Applying a new Tx may invalidate the preTx inference
    ❖ Marker-outcome relationship can change with new Tx
Types of Biomarkers (2)

- Predictive biomarker
  - Measured prior to an intervention
  - Identifies patients who are relatively susceptible to a particular drug effect versus less susceptible patients
    - Benefit or harm
    - Exists only for a Tx with some effect
  - Developed Tx by Tx
  - Not necessarily prognostic of the Post-Tx clinical course
Types of Biomarkers

- Pharmacodynamic biomarker
  - Response-indicator biomarker
  - Post Tx measurement
    - Stand alone
    - Pre vs post Tx comparison
  - Marker that reveals whether, or how large, a biological response has occurred in that particular patient
  - May or may not be Tx-specific
    - Development occurs in a Tx by Tx manner
Types of Biomarkers

• Efficacy-response biomarker
   Efficacy-surrogate biomarker, Surrogate endpoint
    ➢ Subset of general pharmacodynamic biomarkers
    ➢ Predicts the clinical outcome of the patient at some later time
       Sometimes just a low-variance alternative measure indicating the current state of function
    ➢ Usually some prognostic utility or else placebo group measurements cannot be interpreted
    ➢ Developed Tx by Tx
Biomarkers in Clinical Development Programs

- Patient selection tool for enrollment
  - Prognostic biomarkers
  - Predictive biomarkers
- Patient stratification tool
  - To ensure balance between randomized groups
  - Prognostic or unconfirmed predictive biomarkers
Biomarkers in Clinical Development Programs (2)

- Phase 1 study outcome assessment
  - Pharmacodynamic biomarkers
  - Demonstrate drug is bio-active
    - May indicate actions on early cellular effects rather than clinical outcome
  - Aid in selection dose / regimen for later studies
  - Justify putting resources into further development
Biomarkers in Clinical Development Programs (3)

• Phase 2 study outcome assessment
  ➢ Pharmacodynamic biomarkers
  ➢ Evaluate dose-response relationship
  ➢ Identify other patient characteristics that are predictive
  ➢ Design of A&WC studies
    ✷ Selection of doses
    ✷ Selection of patient population
    ✷ Estimation of sample size
  ➢ Can be critical to efficient and successful development program
Biomarkers in Clinical Development Programs (4)

- A&WC Studies (Phase 3)
  - Pharmacodynamic biomarkers
  - Secondary endpoint
    - Supportive of primary EP findings
    - Objective, precise
  - Primary Endpoint
    - Surrogate endpoint
    - Well established relationship to clinical outcome
      - Conventional marketing approval
      - “reasonably likely to predict...” relationship
      - Accelerated approval provisions of regulations
Potential Advantages of Pharmacodynamic biomarkers

Compared to clinical outcome measures:

• More rapidly observed
• More easily measured
• Less intrinsic variability
• More objective measurement
• Less costly to measure
Potential Hazards of Pharmacodynamic biomarkers

• May mislead if discordant with clinical outcome
  ➢ False indication of presence or absence of benefit
  ➢ False optimization of dose / regimen / population
  ➢ Inaccurate estimate of size or frequency of benefit

• May result in a failed next trial for an effective drug
Understanding the Surrogate Measure: Idealized
Understanding the Surrogate: Silent Surrogate

Sequential Order of Processes

Pathophysiologic Processes

Drug Intervention

Surrogate Endpoint

Clinical Outcome

P1

P2
Understanding the Surrogate: Complexity

Drug Intervention

Sequential Order of Processes

P1 → Surrogate Endpoint → P2 → P3 → Clinical Outcome
Understanding the Surrogate Measure

Diagram:
- Y-axis: Clinical Status
- X-axis: Biomarker
- Red line indicating a positive correlation between Clinical Status and Biomarker
Understanding the Surrogate Measure: Idealized

Sequential Order of Processes

Pathophysiologic Processes

Drug Intervention

Surrogate Endpoint

Clinical Outcome

P1 → P2
Understanding the Surrogate Measure

Clinical Status

Biomarker Status

C2

C3

C4

C5

b2

b1
Understanding the Surrogate: Complexity

Sequential Order of Processes

Drug Intervention

P1

Surrogate Endpoint

P2

Clinical Outcome

P3
Potential Consequence of Complexity

Clinical Status

Biomarker Status

C_2

C_1

b_2

b_1
How have Biomarkers become accepted?

• Case by case
  - Within a specific IND/NDA/BLA/Labeling Update
  - For a specific drug
  - Driven by a specific drug developer’s needs

• General use accepted over extended period
  - Scientific experience accumulates in varied uses
  - Usually very extended time-frame
  - Evidence collection not cohesively directed
How can biomarkers become accepted?

• Co-development of drug and test
  ➢ Companion diagnostics
  ➢ Guidance in development

• Biomarker Qualification Process
  ➢ Developing program within CDER
  ➢ Guidance on process to publish soon
Biomarker Qualification at CDER

• Qualification vs Validation
  ➢ Emphasizes context of use
  ➢ Change in term aids awareness of need for specificity of intended use
• Outgrowth of Critical Path Initiative
  ➢ Developing program
  ➢ Particularly for biomarkers expected to have repeated application in multiple drug development programs
Biomarker Qualification

• A conclusion that within a carefully and specifically stated “context of use” the biomarker has been demonstrated to reliably support a specified manner of interpretation and application in decision-making

  ➢ Utility in drug development, particularly regulatory decisions, is central to purpose of qualification
What becomes Qualified?

• Biomarker is a ‘substance’, analyte, anatomic image, or otherwise a describable characteristic
  ➢ Assay methods are needed to measure the biomarker
  ➢ Assay method is not the biomarker
• One biomarker can have multiple assays that are capable of measuring the biomarker
  ➢ Assay method performance characteristics are important
• CDRH clears or approves commercial testing devices for clinical measurements
• CDRH clearance does not equal CDER qualification
  ➢ Different purposes
Qualification Process within CDER

• ‘Submitter’ proposes project to FDA
• Interdisciplinary working team assembled within CDER & FDA
• Information Package reviewed
• Advice given as needed on how to advance development for intended use
  - Additional evidence developed
  - Ultimately development is thought complete
• Submission of full data package
• Full review and decision on qualification
• Formal qualification granted if appropriate