Biomarkers and Qualification

A focus on drug development

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The views expressed are those of the author, and do not necessarily represent an official FDA position

What is a 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 clinical assessment of the patient
• Clinical measures are those measures that intrinsically are not fully objective
  ➢ The ‘mind’ of the evaluator or patient is involved
Types of Biomarkers (1)

• Prognostic biomarker
  ➢ Indicates future clinical course of the patient with respect to some specified clinical outcome, in the absence of a Tx intervention
    ◆ Except standard care Tx, recorded
  ➢ No relationship to any particular new Tx
  ➢ Applying a new Tx may invalidate the preTx inference
    ◆ Marker-clinical relationship can change with a 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 (3)

- Pharmacodynamic biomarker (PD)
  - 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 (4)

- Efficacy-response biomarker
  - Efficacy-surrogate biomarker, Surrogate endpoint
  - Small 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
Biomarker Characteristics

- Biomarkers can have utility in more than one category
  - Depends on the specific characteristics of the specific biomarker

- Biomarker is applied differently for utilizing the different characteristics

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 through varied uses
  - Usually very extended time-frame
  - Evidence collection not cohesively directed
How can Biomarkers Become Accepted?

• Previous routes remain available

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

• Biomarker Qualification Process
  ➢ Developing program within CDER
  ➢ Outgrowth of Critical Path Initiative

DDT Process Guidance (Draft)

• Qualification process for drug development tools (DDTs):
  ➢ Biomarkers
  ➢ Clinical outcome assessments (PROs and other rating scales)
  ➢ Others
• New and existing DDTs
• Not required for tool use
  ➢ Intended to ease repeated use

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 drug development
  - Utility in drug development, particularly regulatory decisions, is central to purpose of qualification
  - Particularly for biomarkers expected to have repeated application in multiple different drug development programs

• Validation ??

Biomarker Qualification

• The biomarker can be applied in drug development programs without the need for submission of extensive biomarker-supportive information to each IND, and re-evaluation to confirm that application is justified

• Can be relied upon in the absence of:
  - Serious study flaws in collecting biomarker data
  - Attempt to apply the biomarker outside of the qualified context of use
  - New scientific evidence conflicting with prior conclusions
What becomes Qualified?

• Biomarker is a ‘substance’, analyte, or otherwise a ‘thing’
  ➢ 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 is not equal CDER qualification
  ➢ Different purposes

Context of Use (CoU)

• Biomarkers are qualified for a specific context of use
• A CoU is a comprehensive statement of the manner and purpose of use, including how to apply results to decision making and the impact on drug development
• The CoU identifies the boundaries of known reliability as shown by evidence
  ➢ Not all boundaries of non-reliability are known
• Biomarker may also have utility outside the currently qualified CoU
  ➢ Accept on case by case (IND specific) basis
  ➢ Expand qualified CoU as further data justifies
Context of Use (CoU)

• When, how the biomarker is sampled
• How the samples are analyzed
• How the data are analyzed and interpreted
• What decision is made based on the data
• What action, and how, drug development is altered by the biomarker results

• Adequately specifying the CoU is often a difficult first step towards qualification
  ➢ Determines what kind of data are needed

Qualification’s Place in Therapeutic Development

• Qualification is not required
  ➢ Case by case approach for accepting use in a single IND/NDA/BLA program remains valuable
• Qualification is voluntary
  ➢ Holder of biomarker data can choose to pursue or not pursue qualification
• Qualification is intended for biomarkers that will be used in multiple drug development programs
  ➢ Public knowledge and availability essential
  ➢ Consortia or collaborative groups likely to be source of biomarkers for qualification
DDT Qualification Process

• Three major parts
  ➢ Initial evaluation for agreement to collaborate
  ➢ Interactive Consultation and Advice Stage
  ➢ In depth Review Stage

• Initial contact - High level evaluation
  ➢ Submitter proposes project to FDA – Letter of Intent
    ❖ Identifies biomarker and proposed context of use
    ❖ Information on current state of development
  ➢ FDA decides to collaborate based on whether potential
    is sufficient to justify Agency resources

• Interdisciplinary working team assembled
  ➢ Working team will guide submitter, and ultimately
    review the complete evidence

Qualification Process within CDER

• Advice & Consultation stage begins

• Summaries of available information reviewed
  ➢ Advice to submitter on how to advance development
    for intended use
  ➢ Additional studies conducted as needed

• Summary results discussed with submitter as developed
  ➢ Advice on next steps for development
  ➢ Cycles of Briefing Document / Meeting / Conducting
    next steps as needed
  ➢ Ultimately development is thought complete
Qualification Process within CDER

- Biomarker Review stage begins
- Submission of full data package
- Full review and CDER decision on qualification
- Formal qualification granted if appropriate
- Qualification statements made public on FDA website as appendix to Guidance on process for development of Drug Development Tools
  - Initially as “draft” guidance statement; subsequently finalized

How do Biomarkers Become Developed?

- Disease biochemistry, pathophysiology, natural history as guide to selecting assessments to develop
  - Collection of scientific data related to a particular context of use justifies relying on the biomarker
- Substantial amount of effort may be required
  - Collaborative model for this work
    - Including pharmaceutical industry as “pre-competitive” space
  - Reduced resources per participant
    - Development resources needed well in advance of applying biomarker in drug development
BQ Projects

- Completed Qualification
  - Nonclinical – 2 from pilot phase
- Review Stage
  - Nearly completed – 2
- Advice & Consultation Stage
  - Nonclinical – 4; safety related
  - Clinical – 9 total
    - Response / Efficacy – 6
    - Population identification – 4
    - Safety response – 1
- Inquiries of interest

BQ & QIBA

- QIBA involved in two biomarker projects in C&A stage
- Imaging Biomarker Projects
  - 5 in C&A Stage
- Qualification inherently involves quantitative assessment of performance of a biomarker
  - Some biomarkers used in quantitated form
  - Some biomarkers used in qualitative manner
    - Dichotomous