

# **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
- A measurable characteristic that is not a clinical assessment of the patient
  - Clinical measures are those evaluating or closely relating to how a patient feels or functions, or survival

# Types of Biomarkers (1)

- Categorize by *how it is used* in drug development
- 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 connection to any particular new Tx
  - Tx may invalidate the preTx inference
    - ❖ Post-Tx marker-clinical relationship may differ among 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 Relate to Utility

- Biomarkers can have utility in more than one category
  - Depends on the specific characteristics of the particular biomarker
- Biomarker is applied differently for utilizing the different characteristics

# Biomarkers in Clinical Development Programs <sup>(1)</sup>

- Patient selection tool for enrollment
  - Enrichment study designs
  - Prognostic biomarkers
  - Predictive biomarkers
- Patient stratification tool
  - To ensure balance within strata across randomized groups in other characteristics
  - Prognostic, mildly predictive or unconfirmed major 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 selecting dose / regimen for later studies
  - Justify putting resources into further development

# Biomarkers in Clinical Development Programs <sup>(3)</sup>

- Phase 2 study outcome assessment
  - Pharmacodynamic biomarkers
  - Evaluate dose-response relationship
  - Identify other patient characteristics that are predictive markers
  - 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

# 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)

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## Guidance for Industry

### Qualification Process for Drug Development Tools

#### *DRAFT GUIDANCE*

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Shaniece Gathers, 301-796-2600.

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- 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

[http://www.fda.gov/downloads/Drugs/  
GuidanceComplianceRegulatoryInformation/Guidances/  
UCM230597.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf)

# 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 application in multiple different drug development programs
- Validation ??
  - Context of Use !

# 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
- May make the biomarker more attractive to use, avoid slowing the drug development program

# 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 does 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
- Comparative claim to another biomarker is not a CoU

# 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