Adoption and Use of Biomarkers in Clinical Trials

Cardiac Safety Research Consortium Meeting
Washington, DC December 2013

Marc K Walton MD, PhD
Associate Director for Translational Medicine
Office of Translational Sciences
CDER-FDA

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

Biomarker Definition & Categories

- An objective patient characteristic that is measured as an indicator of:
  - Normal biologic processes
  - Pathologic processes (abnormal processes)
  - Biological responses to an intervention
  - Note small difference from wording of NIH Work Group for clarity
- A measureable characteristic that is not a clincal assessment of the patient
- Nomenclature of biomarker types within FDA

Types of Clinical Biomarkers (1)

- Categorize by *what it tells us* related to drug development
  - Other ways to categorize biomarkers as well

- 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 in observations
  - No connection to any particular new Tx
  - Tx may invalidate the preTx inference
    - Post-Tx marker-clinical relationship may differ among Txs

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
  - Prediction of beneficial or adverse potential

Types of Biomarkers (3)

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

Types of Biomarkers (4)

- Efficacy-response biomarker
  - ❖ Efficacy-surrogate biomarker, Surrogate endpoint
  - ➢ Subset of general pharmacodynamic biomarkers
  - ➢ Predicts the clinical outcome of the patient at some later time
  - ➢ Usually some prognostic utility so that placebo group measurements may be interpreted
  - ➢ Developed Tx by Tx

- Biomarkers applied differently for different characteristics – Eligibility criteria, variety of purposes as outcome assessments

How have Biomarkers Become Accepted?

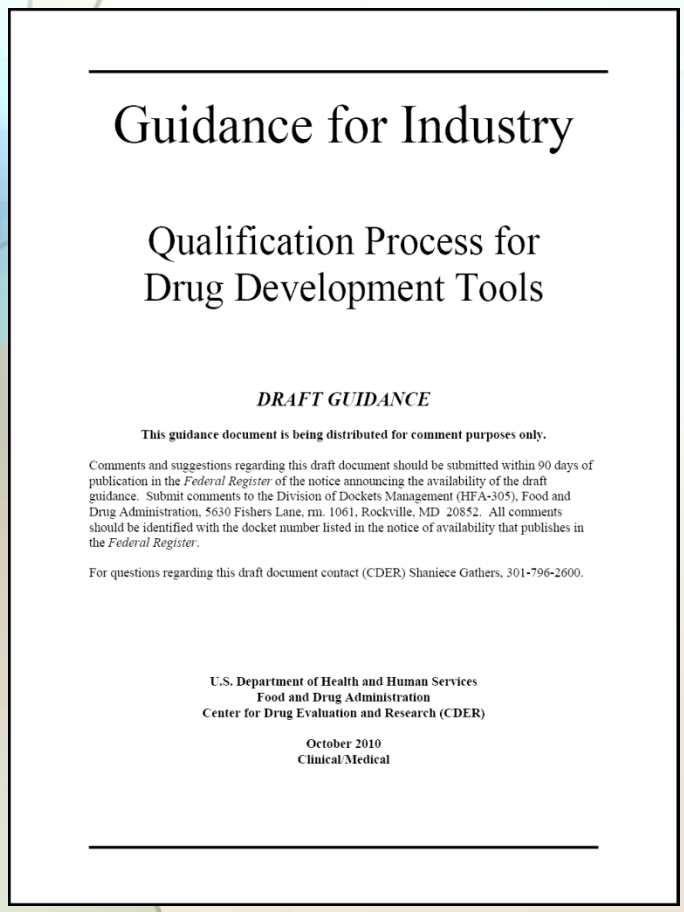
- Case by case
  - Within a specific IND/NDA/BLA/Labeling Update
  - For a specific drug
    - Evidence supporting use needs only to relate to the specific drug and specific study use
  - Driven by a specific drug developer's needs

- 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
  - Policy Guidance – July 2011
    - Others in development
- Biomarker Qualification Process
  - Developing program within CDER
  - Outgrowth of Critical Path Initiative

DDT Qualification Process Guidance (Draft)



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.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2010
Clinical/Medical

- Qualification process for drug development tools (DDTs):
  - Biomarkers
  - Clinical outcome assessments (PROs and other rating scales)
  - Animal models
  - 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

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 !
- Not how IOM decided to use term

What becomes Qualified?

- Biomarker is a measurement of a substance, analyte, anatomic image, or other 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

Context of Use (CoU)

- Biomarkers are qualified for a very specific context of use
- A comprehensive statement of the manner of use and the purpose, including how to apply results to decision making
- Identifies the limits of known reliability as shown by the evidence

- Biomarker may also have utility outside the currently qualified CoU
  - Accept on case by case (IND specific) basis
  - May 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

Effect of Qualification

- The biomarker can be applied in drug development programs without the need for submission of extensive biomarker-supportive information to each IND, and review division re-evaluation to confirm that application is justified
- May make the biomarker more attractive to use
  - Avoid slowing the drug development program
- May make developing a therapy for a disease more attractive
  - Development program may appear more tractable

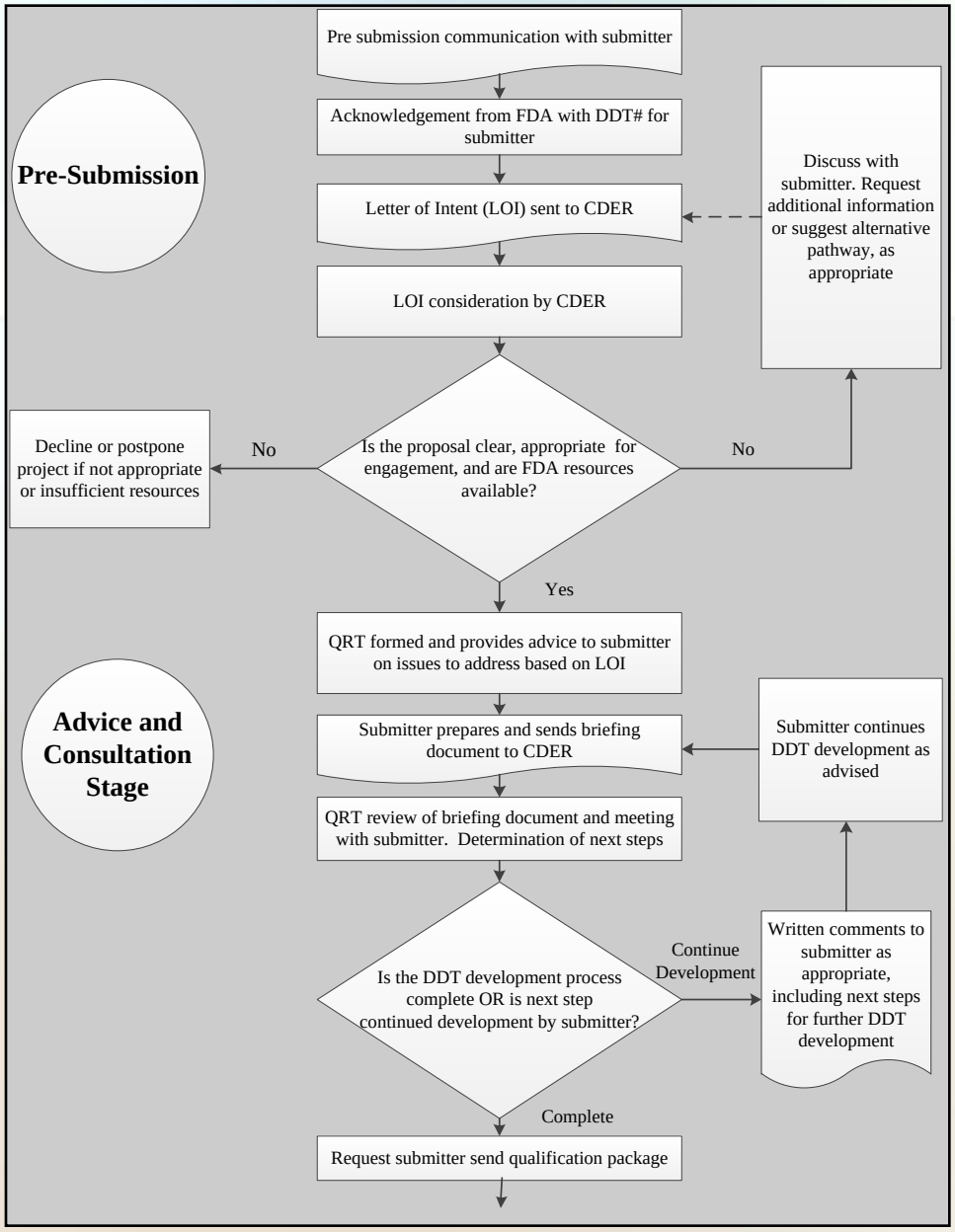
Qualification's Place in Therapeutic Development

- 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
- Interdisciplinary working team assembled
  - Working team will guide submitter, and ultimately review the complete evidence
- Qualification statements made public on FDA website as appendix to DDT Process Guidance
  - Initially as “draft” guidance statement; subsequently finalized

BQ Consultation and Advice Stage



BQ Review Stage