Biomarker Utility and Acceptance in Drug Development and Clinical Trials: an FDA Regulatory Perspective

Chris Leptak, MD/PhD
OND Biomarker and Companion Diagnostic Lead
CDER/Office of New Drugs, Immediate Office
Guidance and Policy Team

AASLD Liver Forum Meeting
November 6, 2014

Disclaimers

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

- **I do not have any financial disclosures regarding pharmaceutical drug products**

Outline

- Brief introduction to FDA structure and regulatory science
- Approach to biomarkers in regulatory science and drug development programs
- Best practices for biomarker development
- Opportunities for FDA engagement
- Resources

FDA Organizational Structure:

- CDER: Drugs
- CBER: Biologics
- CDRH: Devices
- CVM: Veterinary Medicine
- CFSAN: Food/Nutrition
- CTP: Tobacco
- NCTR: Toxicologic Research

FDA CDER Mission

To ensure SAFE and EFFECTIVE prescription, non-prescription, and generic drugs are available to the American public

Regulatory Science:
Bridging Basic Science, Clinical Practice, and Regulatory Authority

- Basic Science: Understanding of molecular pathways, inter-cellular communication, and organ system physiology
- Clinical Practice: Understanding disease pathology, diagnosis, and physiological response to treatment interventions
- Regulatory Authority: Endowed by Congress through laws, Codes of Federal Regulation are the backbone for over-sight of drug development and approval standards

CDER Drug Review Process: Multi-disciplinary team approach

"Trust but verify"

- **Clinical**
- **Chemistry, Manufacturing, and Controls (CMC)**
- **Microbiology**
- **Nonclinical pharmacology/toxicology**
- **Clinical pharmacology**
- **Statistics**
- **Regulatory project management**

Approach to Biomarkers in Regulatory Science and Drug Development Programs

OND Biomarker Lead

- **Biomarker data collection to determine impact on scientific and regulatory decisions**
  - Identification and qualification
  - Goals: consistency and standardization
- **Biomarker Resource Development**
  - Training for reviewers
  - Workshops planning
- **Policy and Process Development**
  - Guidance and MAPPs for biomarker-related endeavors
  - OND Liaison to Biomarker Qualification Program
  - CDER contact for Companion Diagnostics Guidance and co-development issues
- **Outreach and partnerships focused on common goals**

Christopher.Leptak@fda.hhs.gov

FDA Regulatory Approach to Biomarkers

- Broadly defined (i.e, serum protein, change in tumor size by imaging study, algorithm for QT determination on ECG)
- Consistent with long-standing goals and drug development processes (i.e., data driven)
- Definition: characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or biological responses to a therapeutic intervention (2001 NIH Consensus Group)
- Characteristic is not a *clinical* assessment of a patient (contrasted with Clinical Outcome Assessments [COAs])
  - *Not* a measure of how a patient feels or functions or of survival
- Categorized by *how used* in *drug development* (contrasted with clinical biomarkers used in doctor/patient treatment decisions)

Types of Biomarkers: Disease-focused

- Natural history of disease
  - **Diagnostic Biomarker**: presence or absence of pathology (progression: descriptive to diagnostic)
  - **Prognostic Biomarker**: predicts progression of pathology over time (focus on disease life cycle)
- Indicates future clinical course of a patient regarding a specified clinical outcome *in the absence of treatment intervention*
- Examples: For HIV, viral load, or CD4 count

Types of Biomarkers: Response to Therapeutic Intervention (1)

- **Predictive Biomarker**
- Measured *prior* to a therapeutic intervention
- Differentiates patients who are more or less likely to respond to a particular drug's effect *or* are more or less likely to develop an adverse event associated with a particular drug (efficacy- or safety-focused)
- By definition, therapeutic or therapeutic-class specific
- Not necessarily prognostic of the post-treatment course
- Example: Her2/neu and Trastusumab

Types of Biomarkers: Response to Therapeutic Intervention (2)

- **Pharmacodynamic (PD) Biomarker**
- Biologic response indicator to therapeutic intervention
- *Comparison* between pre- (baseline) and post-treatment
- Reveals if a response has occurred and degree of effect
- May or may not be treatment-specific
- Treatment response does *not* necessarily correlate with a clinical benefit. And if so, not necessarily a causal relationship
- Examples: BP, HbA1C, LDL

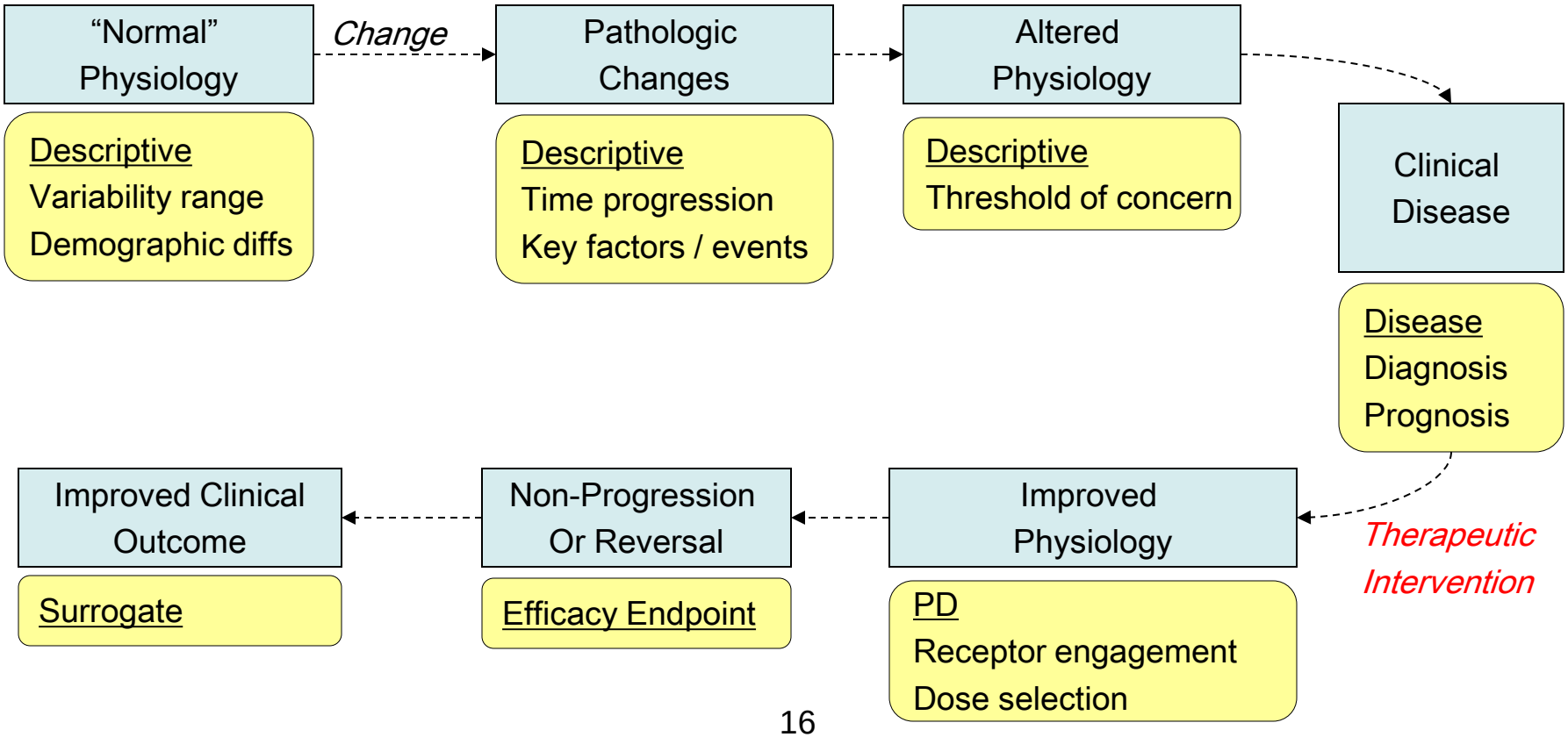
Types of Biomarkers: Response to Therapeutic Intervention (3)

- **Efficacy Response/Surrogate Biomarker**
- *Small* subset of PD biomarkers
- Intended to substitute for a clinically meaningful outcome measure
- Treatment-specific
- Predicts the clinical outcome of a patient over time after a given treatment
- Potential benefit: reduced lengths of clinical studies
- High bar for level of evidence

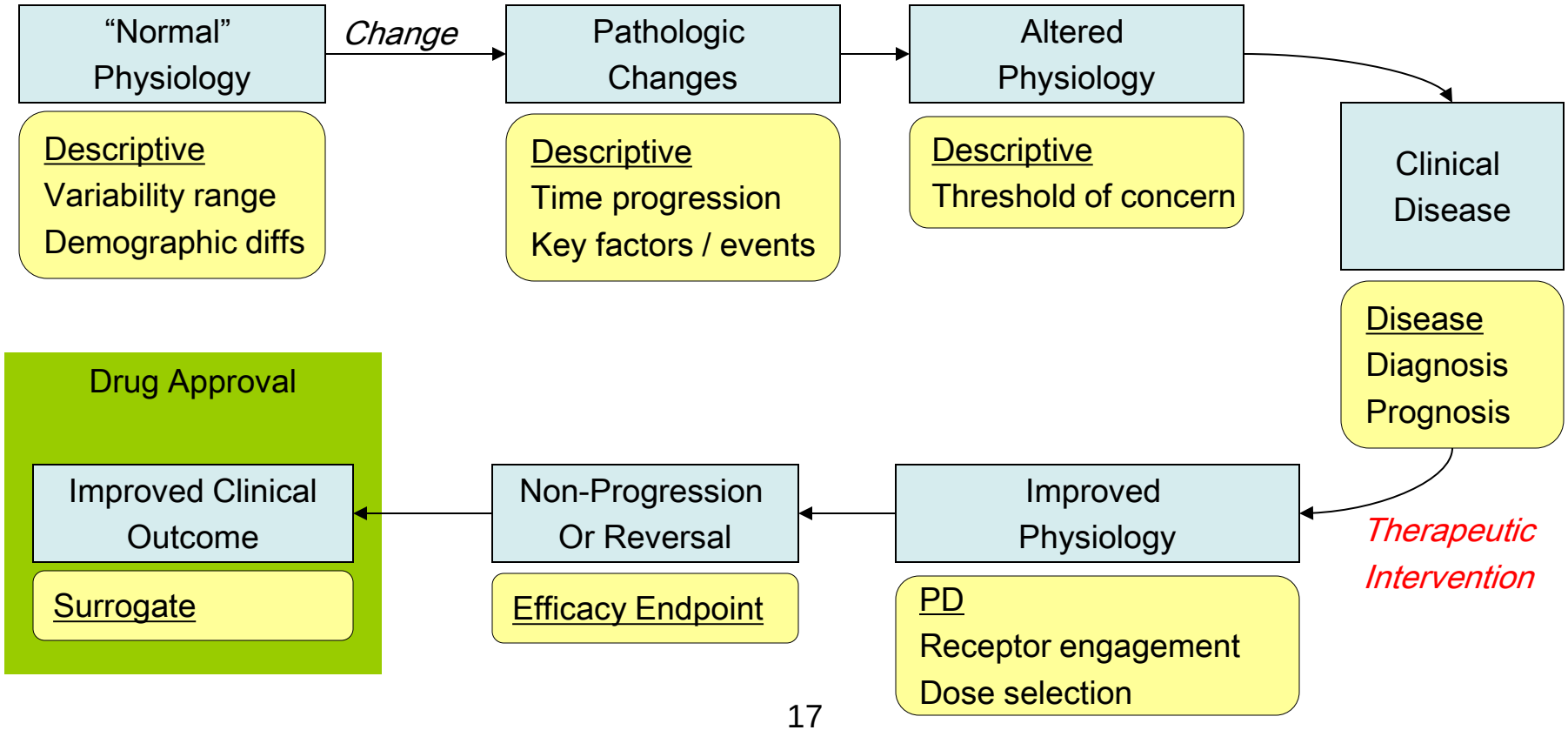
From a clinical trial perspective, what is a Surrogate Endpoint?

- Defined in the preamble to the Accelerated Approval Rule and mentioned under Fast Track in FDAMA
  - A surrogate endpoint is a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions, or survives
  - Changes induced by therapy on the surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint
  - Effect on the surrogate is, by itself, of no value to the patient. Value is imparted only if the effect leads to clinical benefit.

"Fit for Purpose": Match Biomarker to Your Goal, Your Data and Causal Relationship



"Fit for Purpose": Match Biomarker to Your Goal, Your Data and Causal Relationship



Two Approaches to Biomarkers in Regulatory Science and Drug Development Programs:

- **Drug-specific applications**
- **Formal qualification process**

Note: Both equally valid, use the same definitions, and can have the same types of uses in drug development programs

How can biomarkers become accepted?

- General use accepted over extended time period
  - Accumulation of scientific knowledge and experience
  - Information not cohesively collected and can delay recognition of potential utility
- Case by case development for a specific drug
  - As part of IND/NDA/BLA/labeling update
  - Driven by a particular drug developer's needs
- Biomarker Qualification Process

Drug Development Tool (DDT) Qualification Process:

Formalized process for multi-disciplinary review that involves a regulatory outcome that is data-driven

Intended for biomarkers that are broadly applicable and not product specific

Stages: Initiation, Consultation/Advice and Review

Guidance: Qualification Process for Drug Development Tools

DDT Qualification at CDER, FDA

Guidance for Industry and FDA Staff

Qualification Process for Drug Development Tools

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

January 2014
Procedural

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/default.htm

CDER's Interest in Biomarkers

- Use of biomarkers to impact and to improve drug development programs as well as regulatory and scientific decision making
- Inter-Office endeavor requiring communication and collaboration
- Goals of Biomarker Qualification efforts include:
  - Promotion and encouragement of external stakeholders to develop good biomarkers
  - Exploration of the possibility of personalizing therapy within the context of both safety and efficacy

What is Biomarker Qualification?

- *Definition:* Qualification is a conclusion that within the stated context of use, the results of patient assessment with a biomarker can be relied upon to have a specific interpretation and application in drug development and regulatory decision-making.

- *Regulatory implication:* Once qualified, drug developers will be able to use the biomarker in the qualified context in IND and NDA/BLA submissions without requesting that the relevant CDER review group reconsider and reconfirm the suitability of the biomarker.

"Context of Use"

- Short-hand term for a comprehensive statement of manner and purpose of use
- May include:
  - Range of animal species (nonclinical)
  - Range of clinical disorders
  - Range of drug classes
  - Procedures and criteria for how samples are obtained
  - How the results are interpreted
    - Limitations on the interpretation
- Defines boundaries of known reliability
- Potential of expansion of context of use with additional studies/data supporting future qualifications

Potential BQ Submitters

- Consortium of industry stakeholders
  - Use and share data in a pre-competitive environment (cost-effective, win-win approach)
  - Broad acceptance of biomarker context of use in multiple different drug programs
- Consortium of academic investigators
  - Potential translational application of basic science knowledge to clinical utility

Note: Importance and influence of professional societies and patient advocacy groups

Potential Applications of Biomarkers in Drug Development

- Nonclinical safety testing
- Clinical population enrichment
  - Ability to demonstrate an effect of any drug (disease characterization)
  - Potential for responding to the specific test drug (efficacy endpoint)
- Clinical safety
  - Exclusion of population at high risk for AE for a specific drug
  - Non-drug-specific monitoring during studies or clinical use
- Pharmacodynamic for dose selection

Emerging Best Practices for Biomarker Development

- Control for potential variability (sample collection and storage, analytical methods, inter-operator characteristics)
- Control for bias (blinding methods)
- Be careful of putting too much weight in a negative result especially if using stored samples (recommend hypothesis generation and testing with “fresh” samples whenever possible)
- Be careful of putting too much weight in a positive result if using pooled samples, collected over time, from multiple sources

Considerations for Safety Biomarker Development

What kinds of information can contribute to the evidence?

- Consistency of biomarker findings across many drugs in a drug class that cause injury
- Consistency of biomarker findings across many drugs that cause tissue injury through different mechanisms
- Is the biomarker associated with a specific type of injury (i.e., serum creatinine is useful to evaluate sustained injury, but not acute injury)
- Does the biomarker aid in the localization of injury (toxicity of different segments of nephron)

Translation of Nonclinical Safety Biomarkers to Clinical Application

Questions to ask…

- Is the animal organ similar to human organ (structure/function)?
- Is the type of injury similar in preclinical and clinical scenarios?
- Is data available from multiple animal species?
- Identical effect in multiple species? (higher trust)
- Similar in rats and mice, but different in monkeys/dogs? (lower trust)
- Data available in only one species (lower trust)

Central Question: Is the nonclinical data predictive of human pathology?

Imaging Biomarkers: A few regulatory considerations

- Is an imaging drug employed as a biomarker?
- Standardization between sites, devices, readers?
- Use of training sets?
- Blinded verses unblinded reads?

Considerations for Safety Biomarker Development

What kinds of information can contribute to the evidence?

- Consistency of biomarker findings across many drugs in a drug class that cause injury
- Consistency of biomarker findings across many drugs that cause tissue injury through different mechanisms
- Is the biomarker associated with a specific type of injury (i.e., serum creatinine is useful to evaluate sustained injury, but not acute injury)
- Does the biomarker aid in the localization of injury (toxicity of different segments of nephron)

Opportunities for Engagement in addition to Biomarker Qualification

Critical Path Innovation Meeting (CPIM)

What is a CPIM? Opportunity for industry, academia, patient advocacy groups, and govt to engage to improve efficiency and success in drug development. Topics are therapy independent and can include: natural history studies, emerging technologies, biomarker development, Clinical Outcome Assessments (COAs), innovative clinical trial designs

Why Request a CPIM? To have an opportunity to meet with FDA staff with expertise in an area for which you have questions

For more information, please contact

CPIMInquiries@fda.hhs.gov

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm395888.htm

New Pilot: Letter of Support (LoS)

What is a LoS? Describes CDER's thoughts on the potential value of a biomarker and encourages further evaluation to enhance visibility of the biomarker, encourage data sharing and stimulate additional studies that may support future qualification

Why Issue a LoS? Encourage identification, development and qualification of new drug development tools to overcome hurdles in drug development programs and to enhance drug safety and efficacy.

For more information, please contact

CDER-BiomarkerQualificationProgram@fda.hhs.gov

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm412833.htm

Resources:

www.fda.gov/Drugs/Guidance ComplianceRegulatoryInformation/Guidances/default

- Qualification Process for Drug Development Tools
- Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies
- In vitro Companion Diagnostic Devices
- Standards for Clinical Trial Imaging Endpoints
- Clinical Trial Designs Employing Enrichment Strategies to Support Approval of Human Drugs and Biological Products

Questions?