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

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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

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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

“Normal” Physiology
- Descriptive
- Variability range
- Demographic diffs

Pathologic Changes
- Descriptive
- Time progression
- Key factors / events

Altered Physiology
- Descriptive
- Threshold of concern

Clinical Disease
- Disease
- Diagnosis
- Prognosis

Improved Clinical Outcome
- Surrogate

Non-Progression Or Reversal
- Efficacy Endpoint

Improved Physiology
- PD
- Receptor engagement
- Dose selection

Change

Therapeutic Intervention
“Fit for Purpose”: Match Biomarker to Your Goal, Your Data and Causal Relationship

- **Normal** Physiology
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- Pathologic Changes
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  - Time progression
  - Key factors / events

- Altered Physiology
  - Descriptive
  - Threshold of concern

- Clinical Disease

- Disease
  - Diagnosis
  - Prognosis

- Drug Approval
  - Improved Clinical Outcome
  - Surrogate

- Non-Progression Or Reversal
  - Efficacy Endpoint

- Improved Physiology
  - PD
  - Receptor engagement
  - Dose selection

- Therapeutic Intervention
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

DDT Qualification at CDER, FDA

Guidance for Industry and FDA Staff

Qualification Process for Drug Development Tools


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?
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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
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
Resources:

www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/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?