BIOMARKERS AND DRUG DEVELOPMENT: REGULATORY PERSPECTIVE

CHRISTOPHER LEPTAK, M.D., PH.D.
DIRECTOR, OND REGULATORY SCIENCE PROGRAM
CO-DIRECTOR, BIOMARKER QUALIFICATION PROGRAM

Midwest Biopharmaceutical Statistics Workshop
May 23, 2017
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.
Precision Medicine Approach to Drug Development

Right target
- Strong link between target and disease
- Differentiated efficacy
- Available and predictive biomarkers

Right tissue
- Adequate bioavailability and tissue exposure
- Definition of PD biomarkers
- Clear understanding of preclinical and clinical PK/PD
- Understanding of drug–drug interactions

Right safety
- Differentiated and clear safety margins
- Understanding of secondary pharmacology risk
- Understanding of reactive metabolites, genotoxicity, drug–drug interactions
- Understanding of target liability

Right patients
- Identification of the most responsive patient population
- Definition of risk–benefit for given population

Adapted from Cook et al., Nature Reviews Drug Discovery 13:2419-431 (2014)
FDA Regulatory Approach to Biomarkers

- **Definition**: a defined characteristic that is measured as an 1) indicator of normal or pathogenic biological processes or 2) response to an intervention.

- Broadly defined, with multiple biomarker types including molecular, histologic, radiographic, and physiologic. (i.e., serum protein, change in tumor size by imaging study, algorithm for QT determination on ECG)

- Characteristic is not a *clinical* assessment of how a patient feels, functions, or survives (contrasted with Clinical Outcome Assessments or COAs)

- Although a biomarker may be used by clinical or basic science research communities, regulatory acceptance focuses on a drug development context that is supported by data for that context. Considerations include:
  - Reproducibility of data (e.g., high rate of discordant conclusions RE biomarkers in the published literature)
  - Adequacy of the analytic device to assess biomarker’s reliability
  - Feasibility of the biomarker should a drug be approved (e.g., will the analytic be widely available and capable of integration into clinical practice paradigms)
BEST: BIOMARKERS, ENDPOINTS, AND OTHER TOOLS RESOURCE

- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care

- Created by the NIH-FDA Biomarker Working Group


- BEST harmonizes terms and definitions and addresses nuances of usage and interpretation among various stakeholders, including:
  - Biomedical scientists
  - Translational and clinical researchers
  - Medical product developers
  - Patient/disease advocacy groups
  - Government officials
  - Clinicians
Biomarker Classes from a Drug Perspective

- **Susceptibility/Risk**: Indicates potential for developing disease before it is clinically apparent (e.g., BRCA mutations and development of breast cancer)

- **Diagnostic**: 1) Detects presence of a disease or condition or 2) identifies patient subsets (e.g., HbA1c to aid in diabetes diagnosis)

- **Monitoring**: Assesses disease status, including degree or extent, through serial measurement (e.g., INR and anti-coagulation status)

- **Prognostic**: Identifies likelihood of a clinical event, disease recurrence, or progression, in the absence of a therapeutic intervention (e.g., BRCA mutations and breast cancer recurrence)

- **Predictive**: Identifies patients who are more likely to experience a favorable or unfavorable effect from a specific treatment (e.g., HLA-B5701 and risk of severe AE with Abacavir)

- **Pharmacodynamic/Response**: Indicates that a biological response has occurred in a patient who has received a therapeutic intervention. May become a clinical trial endpoint and for a very small subset, surrogate endpoint. (e.g., sweat chloride and response to CFTR agents)

- **Safety**: Indicates the likelihood, presence, or extent of toxicity to a therapeutic intervention when measured before or after that intervention (e.g., QTc and Torsades)
“Fit for Purpose”: BEST Biomarker Classes in Perspective

- “Normal” Physiology
- Pathologic Changes
  - Descriptive
    - Time progression
    - Key factors / events
- Altered Physiology
  - Descriptive
    - Threshold of concern
- Clinical Disease
  - Diagnostic Monitoring Prognostic
  - Therapeutic Intervention
- Improved Clinical Benefit
  - Surrogate Endpoint
- Non-Progression Or Reversal
  - Response
- Change in Physiology
  - Pharmacodynamic
    - Predictive
    - Safety
BIOMARKER INTEGRATION INTO DRUG DEVELOPMENT

Note: These pathways do not exist in isolation and many times parallel efforts are underway within or between pathways. All share common core concepts, are data-driven, and involve regulatory assessment and outcomes based on the available data.
DRUG APPROVAL (IND/NDA/BLA)
APPROACH FOR BIOMARKER DEVELOPMENT

**Strengths**
- Generally, biomarker use has a well-defined purpose
- Data (clinical trial information) available to the biomarker developer
- Opportunities to bring in outside experts
- Company maintains proprietary rights

**Limitations**
- Biomarker may not be generalizable
- Limited opportunities for additional data sources
- Company responsible for development costs
- Limited opportunities for engagement with outside stakeholder groups
- Biomarker information in drug labels and reviews are available only upon drug approval
SCIENTIFIC COMMUNITY CONSENSUS APPROACH FOR BIOMARKER DEVELOPMENT

**Strengths**
- Extensive knowledge base of exploratory biomarker data in published literature
- Opportunity for broad and multiple community inputs
- Public access and cost-sharing approach (e.g., NIH and other grant funded research)

**Limitations**
- Published data may not be reproducible
- Protracted time for consensus building
- Variability of study designs, populations, and analytics
- Applicability to regulatory paradigms
**BIOMARKER QUALIFICATION APPROACH FOR BIOMARKER DEVELOPMENT**

**Strengths**
- Context of use clearly established
- Opportunity to pool resources, share costs and bring outside experts
- Leverage outside stakeholder groups
- Outcome is a public guidance with supporting reviews

**Limitations**
- If part of a group effort, stakeholders may have differing goals, level of commitment, and engagement
- Data (clinical trial information) may not be readily available
- Data sharing and aggregation may be challenging
DDT QUALIFICATION AT CDER

Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools

Drug Development Tools (DDT) Qualification Programs Webpage on FDA.gov
TYPES OF SUBMISSIONS WE ARE SEEING FOR BIOMARKER QUALIFICATION

- 19% Patient Selection
- 22% Clinical Safety
- 26% Preclinical Safety
- 30% Response
- 4% Monitoring

N=27
## LIST OF FDA-QUALIFIED BIOMARKERS

<table>
<thead>
<tr>
<th>General Area</th>
<th>Submitter(s)</th>
<th>Biomarker(s) Qualified for Specific Contexts of Use</th>
<th>Issuance Date with Link to Specific Guidance</th>
<th>Supporting Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonclinical</td>
<td>Predictive Safety and Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)</td>
<td>Urinary biomarkers: Albumin, β2-Microglobulin, Clusterin, Cystatin C, KIM-1, Total Protein, and Trefoil Factor-3</td>
<td>4/14/2008: Drug-Induced Nephrotoxicity Biomarkers</td>
<td>Reviews</td>
</tr>
<tr>
<td>Nonclinical</td>
<td>International Life Sciences Institute (ILSI)/Health and Environmental Sciences Institute (HESI), Nephrotoxicity Working Group</td>
<td>Urinary biomarkers: Clusterin, Renal Papillary Antigen (RPA-1)</td>
<td>9/22/2010: Drug-Induced Nephrotoxicity Biomarkers</td>
<td>Reviews</td>
</tr>
<tr>
<td>Nonclinical</td>
<td>PJ O’Brien, WJ Reagan, MJ York, and MC Jacobsen</td>
<td>Serum/plasma biomarkers: Cardiac Troponins T (cTnT) and I (cTnI)</td>
<td>2/23/2012: Drug-Induced Cardiotoxicity Biomarkers</td>
<td>Reviews</td>
</tr>
<tr>
<td>Clinical</td>
<td>Mycoses Study Group</td>
<td>Serum/bronchoalveolar lavage fluid biomarker: Galactomannan</td>
<td>10/24/2014: Patient Selection Biomarker for Enrollment in Invasive Aspergillosis (IA) Clinical Trials</td>
<td>Reviews</td>
</tr>
<tr>
<td>Clinical</td>
<td>Chronic Obstructive Pulmonary Disease (COPD) Biomarker Qualification Consortium (CBQC)</td>
<td>Plasma biomarker: Fibrinogen</td>
<td>7/6/2015: Prognostic Biomarker for Enrichment of Clinical Trials in Chronic Obstruction Pulmonary Disease (COPD)</td>
<td>Reviews</td>
</tr>
<tr>
<td>Clinical</td>
<td>Polycystic Kidney Disease Outcomes Consortium</td>
<td>Imaging biomarker: Total Kidney Volume (TKV)</td>
<td>8/17/2015: Prognostic Biomarker for Enrichment of Clinical Trials in Autosomal Dominant Polycystic Kidney Disease</td>
<td>Reviews</td>
</tr>
</tbody>
</table>

[www.fda.gov/biomarkerqualificationprogram](www.fda.gov/biomarkerqualificationprogram)
CONSIDERATIONS FOR BIOMARKER UTILITY

Context of Use (COU): 1) BEST biomarker category and 2) how the biomarker impacts the clinical trial or drug development program

What question is the biomarker intended to address. Examples include:

- Inclusion/exclusion criteria for prognostic or predictive enrichment?
- Alter treatment allocation based on biomarker status?
- Result in cessation of a patient’s participation in a clinical trial because of safety concern?
- Result in adaptation of the clinical trial design?
- Establish proof of concept for patient population of interest?
- Support clinical dose selection for first in human or Phase 3 studies?
- Evaluate treatment response (e.g. pharmacodynamic effect)?
- Support regulatory acceptability of a surrogate endpoint for accelerated or traditional approval?

“Total Kidney Volume, measured at baseline, is a prognostic enrichment biomarker to select patients with ADPKD at high risk for a progressive decline in renal function (defined as a confirmed 30% decline in the patient’s estimated glomerular filtration rate (eGFR)) for inclusion in interventional clinical trials. This biomarker may be used in combination with the patient’s age and baseline eGFR as an enrichment factor in these trials.”

CONCEPTUAL FRAMEWORK FOR BIOMARKER DEVELOPMENT FOR REGULATORY ACCEPTANCE

In Drug Development

Need Statement

COU

Evaluate Compared to Status Quo

To Patient

Benefit

Risk

Evidentiary Criteria

• Characterization of Relationship Between the Biomarker and Clinical Outcome
• Biological Rationale for Use of Biomarker (if Known)
• Type of Data and Study Design (i.e. Prospective, Retrospective, etc.)
• Independent Data Sets for Qualification
• Comparison to current standard
• Assay performance
• Statistical Methods to Use
OPPORTUNITIES FOR ENGAGING FDA IN BIOMARKER DEVELOPMENT

Critical Path Innovation Meeting

FDA Letter of Support

Qualification: Limited Context of Use

Qualification: Expanded Context of Use
CRITICAL PATH INNOVATION MEETING

• Discussion of the science, medicine, and regulatory aspects of innovation in drug development

• Non-binding meeting

• Not a meeting about a specific approval pathway

• Scope includes early biomarkers and clinical outcome assessments, natural history studies, technologies (not manufacturing), and clinical trial designs and methods

Clinical Trial Endpoints

- Biomarker Development
- Drug Development Tools
- Innovative Trial Designs
- Clinical Trial Networks

Natural History Studies

- COA Development
- Rare Diseases
- Databases
- Registries

Development and Adoption of Biomarkers for Molecularly Targeted Cancer Therapies: Workshop Summary
LETTER OF SUPPORT

LETTER OF SUPPORT

• This is a letter issued to a requester that briefly describes CDER’s thoughts on the potential value of a biomarker and encourages further evaluation.

• This letter does not connote qualification of a biomarker. It is meant to enhance the visibility of the biomarker, encourage data sharing, and stimulate additional studies.


11 letters issued to date
SOME ENABLERS FOR BIOMARKER DEVELOPMENT

- Data standards (e.g., CDISC efforts)
- Data quality
- Data reproducibility
- Data sharing
- Assay/imaging pre-analytic standardization
- Assay/imaging protocols/SOPs
- Evaluating impact on clinical trial elements (e.g., choice of cut-point on number of patients screened vs enrolled)

• 21st Century Cures and PDUFA VI increasingly places FDA as an active participant in drug development, broadening our traditional regulatory role

• Requires expanded efforts to enhance drug development
  • Patient-focused drug development: collect / analyze patient experience, to use in designing drug development programs (endpoints), and in regulatory decision making (endpoints and risk/benefit considerations)
  • Novel, innovative trial designs: use of complex adaptive and other novel trial designs – and how such clinical trials can be used to satisfy the substantial evidence standard
  • Real world evidence: using data regarding use or potential benefits and risks of a drug derived from sources other than randomized clinical trials – in support of new indications and post-approval study requirements
  • Drug development tools: biomarkers and COAs
Each of these elements share importance to drug approval.

Since any element can lead to failure, important to optimize as appropriate and feasible.