PATHWAYS TO BIOMARKER QUALIFICATION AND ACCEPTANCE

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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
Key Contributors to Drug Development Success

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)
**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)
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 not reproducible
- Protracted time for consensus building
- Variability of study designs, populations, and analytics
- Applicability to regulatory paradigms

Scientific Community Consensus
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
Each of these elements share importance to drug approval. Since any element can lead to failure, it is important to optimize as appropriate and feasible.
What’s in a Word? Redefining the Lexicon of Biomarkers, Outcomes & Endpoints

The BEST (Biomarkers, EndpointS, and Tools) Resource

FDA-NIH Working Group, 2016
FDANIH JOINT EFFORT

• In the spring of 2015, the FDA-NIH Joint Leadership Council identified the harmonization of terms used in translational science and medical product development as a priority need, with a focus on terms related to biomarkers and study endpoints.

• Goals of improving communication, aligning expectations, and improving scientific understanding.

• The first phase of BEST comprises a glossary that clarifies important definitions and describes some of the hierarchical relationships, connections, and relationships among the terms.

• Meant to be a living document with periodic updates and opportunity for public input.
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
DEFINING A TERM:
GENERAL APPROACH

1. Identify existing definitions
2. Identify related terms and definitions
3. Propose a definition
4. Discuss and revise definition
5. Finalize definition
BIOMARKER CATEGORIES: GUIDING PRINCIPLES

• **Flexibility to accommodate** new concepts, methodologies, technologies and regulatory domains

• **Preserve distinctions** which are useful in achieving alignment with types of evidence and evidentiary standards

• **Amenable to unification** across stakeholder communities
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**
  - Susceptibility/Risk

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

- **Altered Physiology**
  - Descriptive
  - Threshold of concern

- **Clinical Disease**
  - Diagnostic Monitoring Prognostic

- **Improved Clinical Benefit**
  - Surrogate Endpoint

- **Non-Progression Or Reversal**
  - Response

- **Change in Physiology**
  - Pharmacodynamic
  - Predictive
  - Safety

- **Therapeutic Intervention**
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
- Class of Biomarker
- What is the question the biomarker is addressing.

Evaluate Compared to Status Quo

- Improved sensitivity
- Improved selectivity
- Mechanistic context

To Patient

- Benefit
- Consequence of false positive
- Consequence of false negative

Risk

Informs Required Stringency of EC

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