Berkeley School of Public Health

EASL European Association for the Study of the Liver

Forum for Collaborative HIV Research

Session II: Focus on Biomarkers

FDA- Biomarker Qualification in drug development under IND or NDA/BLA

Presenter: Shashi Amur, Ph.D.
U.S. Food and Drug Administration

U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH

LIVER FORUM, AASLD MEETING
BOSTON, MA
NOVEMBER 10, 2016

FDA'S BIOMARKER QUALIFICATION PROGRAM

Shashi Amur, Ph.D.

Scientific Lead, Biomarker Qualification Program, Office of Translational Sciences, Center for Drug Evaluation and Research, FDA

OVERVIEW

- Biomarkers
- Integration of Biomarkers in Drug Development
- Drug Development Tool Qualification
  - Biomarker Qualification
- Summary

BIOMARKER

"Biomarker," or "biological marker," generally refers to a measurable indicator of some biological state or condition

A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.

Types: Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers.

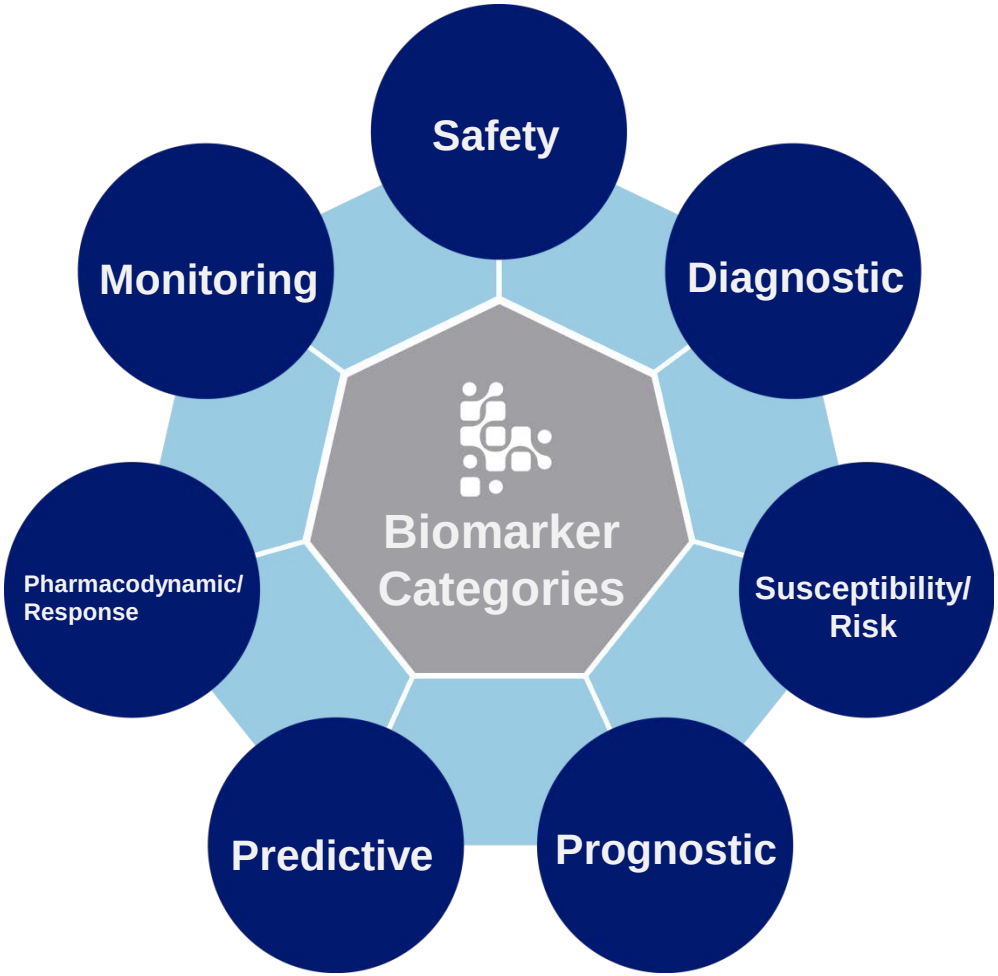
Examples:

- Blood glucose (molecular)
- Biopsy-proven acute rejection (histologic)
- Tumor size (radiographic)
- Blood pressure (physiologic)

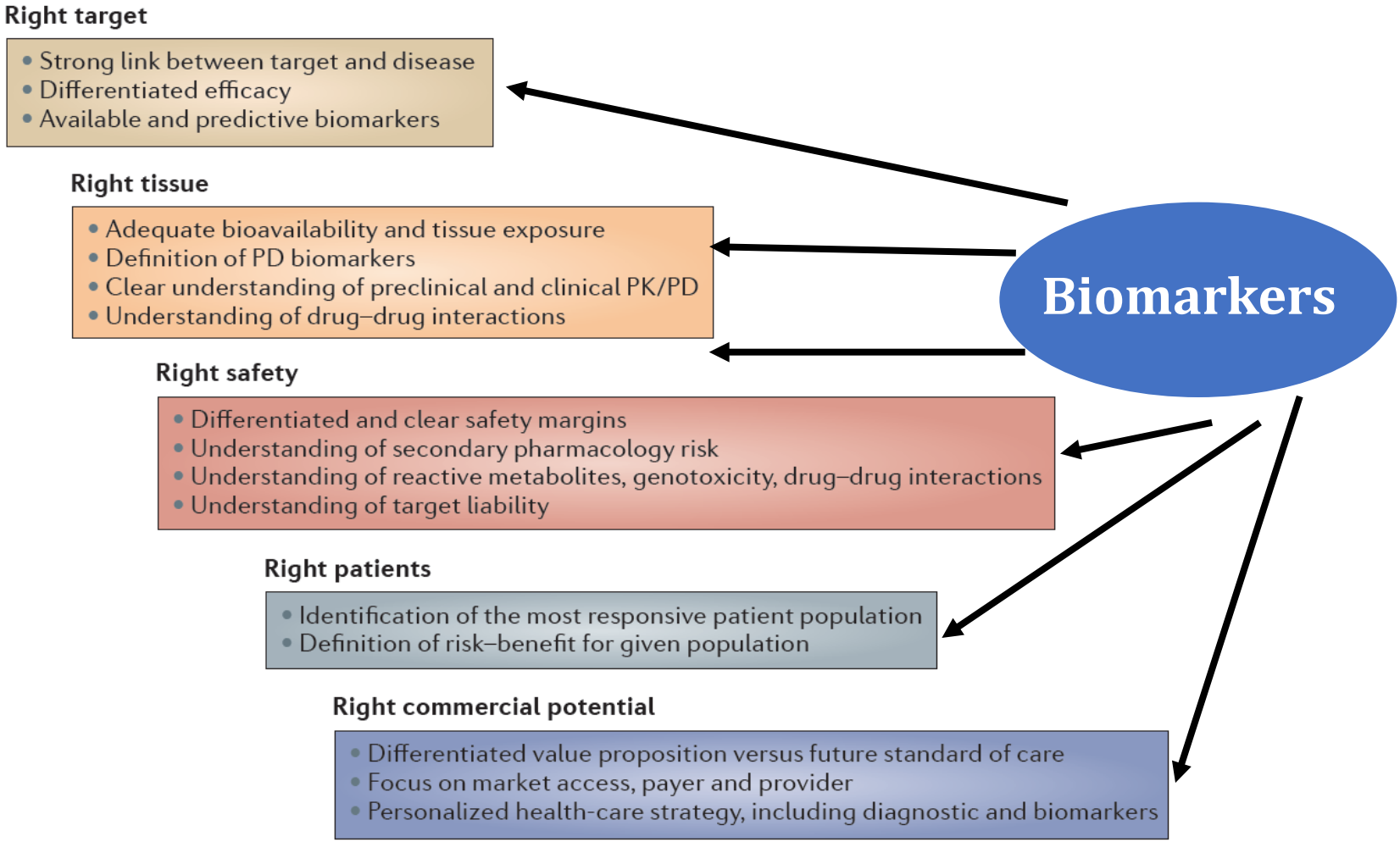
BEST: BIOMARKERS, ENDPOINTS, AND OTHER TOOLS RESOURCE

- 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
- Publicly available at http://www.ncbi.nlm.nih.gov/books/NBK326791/

BIOMARKER CATEGORIES

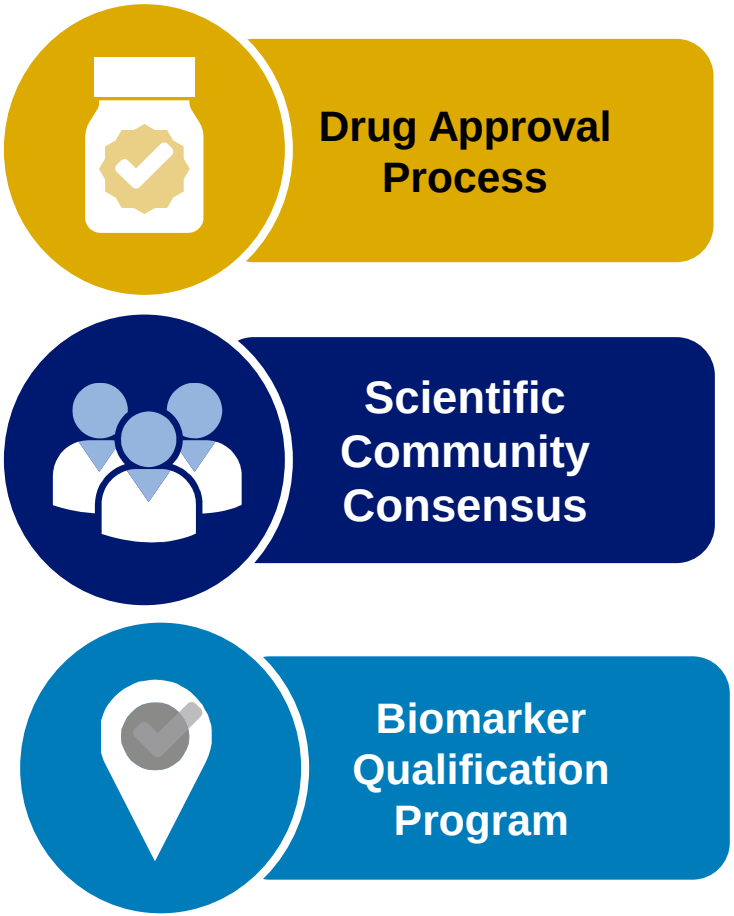


KEY CONTRIBUTORS TO DRUG DEVELOPMENT PROJECT SUCCESS



Cook et al., Nature Reviews Drug Discovery 13:2419-431 (2014)

BIOMARKER INTEGRATION INTO DRUG DEVELOPMENT



DRUG APPROVAL (IND/NDA/BLA) APPROACH FOR BIOMARKER DEVELOPMENT

Drug Approval Process

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 retains marketing advantage

Limitations

- Biomarker use 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

Reference:
Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration; Published June 2016, Duke-Margolis Center for Health Policy

SCIENTIFIC COMMUNITY CONSENSUS APPROACH FOR BIOMARKER DEVELOPMENT

Scientific Community Consensus

Strengths

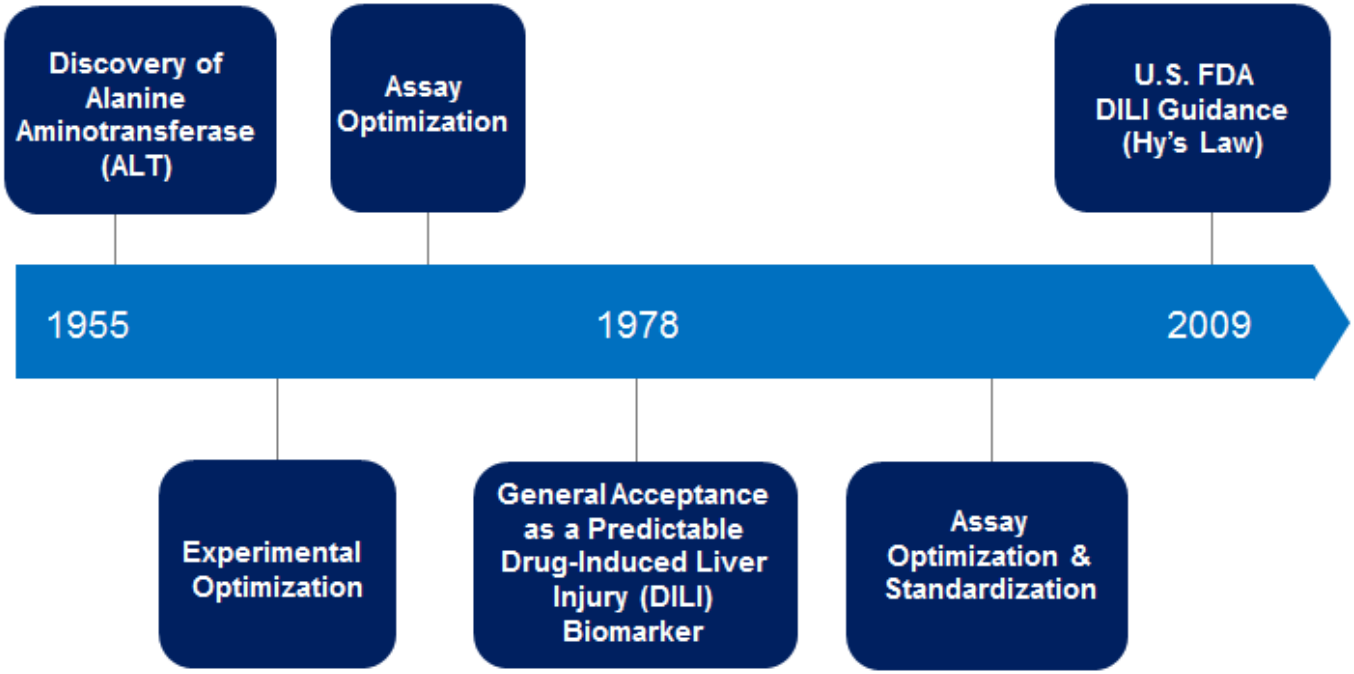
- Extensive knowledge base of exploratory biomarker data in published literature
- Opportunity for broad and multiple community inputs

Limitations

- Published data may not be not reproducible
- Time to regulatory acceptance
- Variability of study designs, populations, and analytics
- Applicability to regulatory paradigms

Reference:
Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration; Published June 2016, Duke-Margolis Center for Health Policy

ESTABLISHMENT OF ALT AS AN ACCEPTED BIOMARKER FOR REGULATORY USE



BIOMARKER QUALIFICATION APPROACH FOR BIOMARKER DEVELOPMENT

Biomarker Qualification Program

Strengths

- Biomarker use generalizable
- Opportunity to pool resources , share costs and bring outside experts
- Systematic biomarker development
- 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

Reference:
Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration; Published June 2016, Duke-Margolis Center for Health Policy

QUALIFICATION VS VALIDATION

Validation – Establishing that the performance of a (biomarker) test, tool, or instrument is acceptable for its intended purpose

Analytical validation: Establishing that the performance characteristics (including sensitivity, specificity, accuracy, and precision) of a test, tool, or instrument are acceptable.

Clinical validation: Establishing that the test, tool, or instrument acceptably identifies, measures, or predicts the concept of interest.

- Concept: In a regulatory context, the concept is the aspect of an individual's clinical, biological, physical, or functional state, or experience that the assessment is intended to capture (or reflect).

***BEST Glossary**: http://www.ncbi.nlm.nih.gov/books/NBK326791/*

DRUG DEVELOPMENT TOOLS (DDT) QUALIFICATION AT CDER/FDA

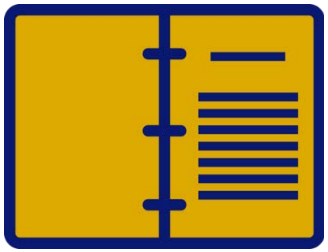
Clinical Outcome Assessments

Animal Models (Animal Rule)

Biomarkers

DDTs are methods, materials, or measures that aid drug development

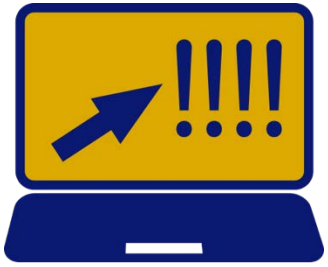
DDT QUALIFICATION AT CDER, FDA



Guidance for Industry and FDA Staff:

Qualification Process for Drug Development Tools

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



Drug Development Tools (DDT) Qualification Programs Webpage on FDA.gov

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

BIOMARKER QUALIFICATION (BQ)

Definition: 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

Context of Use (COU): A comprehensive statement that fully and clearly describes the manner and purpose of use for the biomarker in drug development

BIOMARKER QUALIFICATION: SUBMITTER ROADMAP

Stage 1: Initiation

Submit Letter of Intent (LOI)

FDA determines acceptability of LOI

Stage 2: Consultation and Advice

Submit briefing package

Collaborative discussion with FDA regarding the biomarker development plan

Stage 3: Review

Submit full qualification package

FDA reviews package and makes yes/no decision to qualify

FDA drafts guidance document

Publication of Guidance

Draft guidance document posted to Federal Register for public comment

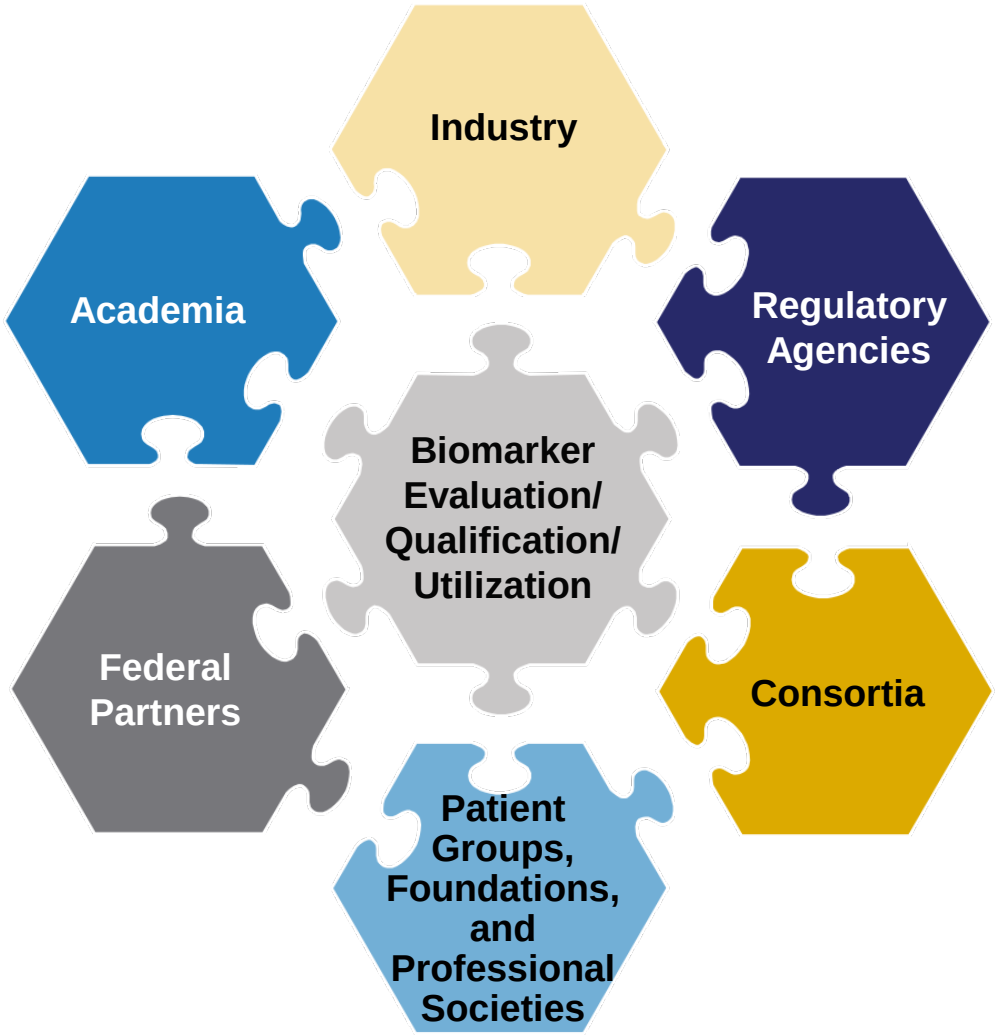
FDA publishes final guidance document

LIST OF FDA-QUALIFIED BIOMARKERS

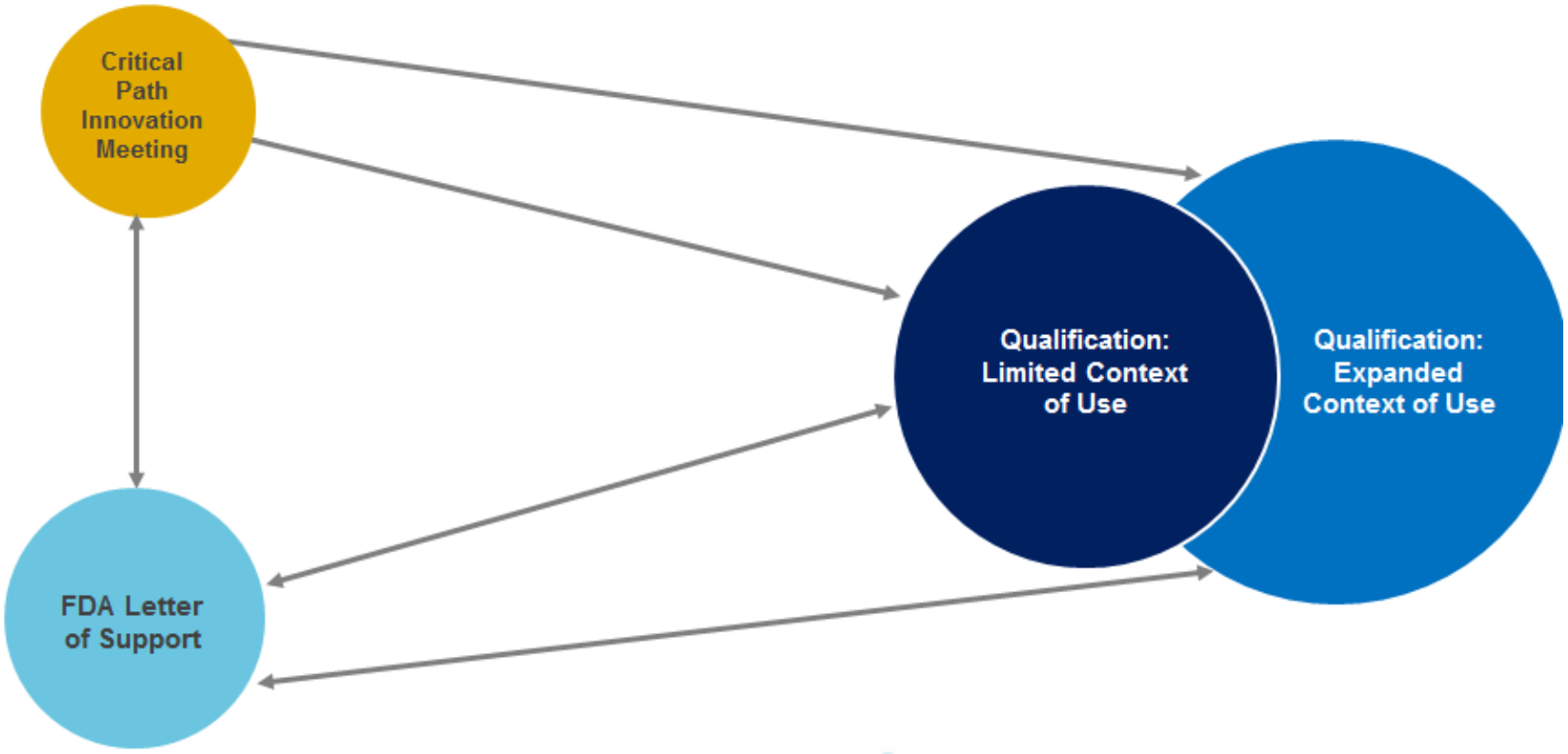
General Area	Submitter(s)	Biomarker(s) Qualified for Specific Contexts of Use	Issuance Date with Link to Specific Guidance	Supporting Information
Nonclinical	Predictive Safety and Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)	Urinary biomarkers: Albumin, β2-Microglobulin, Clusterin, Cystatin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

www.fda.gov/biomarkerqualificationprogram

STAKEHOLDERS IN BIOMARKER DEVELOPMENT



OPPORTUNITIES FOR ENGAGING FDA IN BIOMARKER DEVELOPMENT



Summary

- **BEST** (Biomarkers, Endpoints, and other Tools Resource) provides biomarker-relevant definitions, in an effort to harmonize biomarker terminology

- Biomarkers don't have to be qualified to be used in drug development and the drug approval pathway remains a valuable path for integration of biomarkers in drug development

- **Biomarker Qualification**
  - Submitter can be a person, a group, organization (including the federal government), or consortium that takes responsibility for and initiates a BQ proposal using the procedures described in the DDT guidance
  - No fees for submissions to the BQ program
  - Biomarker qualification is voluntary
  - Once qualified, it can be used in any drug development program under the context for which it obtained qualification.

- **New FDA initiatives**, such as LOS and limited COU qualification, can be utilized as early goal posts in biomarker development

ACKNOWLEDGEMENTS

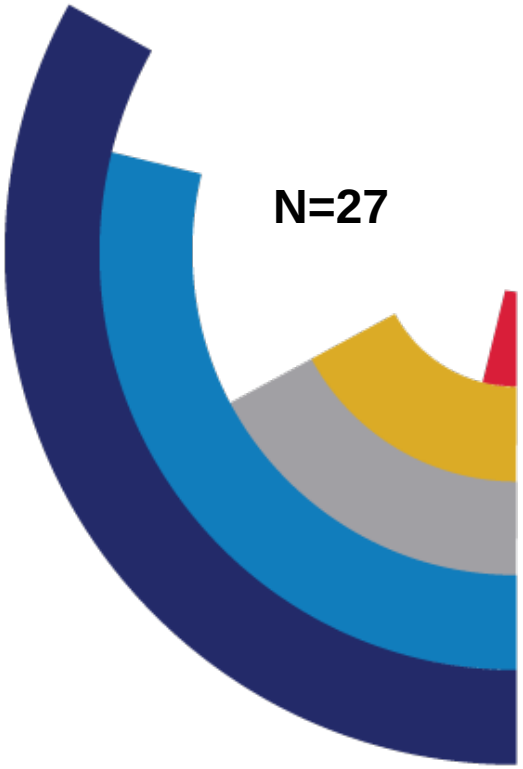
Janet Woodcock
ShaAvhrée Buckman-Garner
Suzie McCune
Chris Leptak
Marianne Noone
Sarmistha Sanyal
Kylie Haskins
Ru Chen

BIOMARKER QUALIFICATION (BQ) SUBMISSIONS

Biomarker Qualification Program Metrics	
Number in Initiation Stage	4
Number in Consultation and Advice Stage	19
Number in Review Stage	4
Total Number of Active Projects	27
Number Qualified	6

From the Drug Development Tool (DDT) Qualification Projects at CDER, FDA:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm409960.htm

TYPES OF SUBMISSIONS WE ARE SEEING FOR BIOMARKER QUALIFICATION



4% Monitoring

19% Patient Selection

22% Clinical Safety

26% Preclinical Safety

30% Response

SOME ENABLERS FOR BIOMARKER DEVELOPMENT

- Data standards
- Data quality
- Data reproducibility
- Statistical considerations
- Assay/imaging considerations/validation
- Assay/imaging protocols
- Establishing cut points