An Overview of Biomarkers

BIOMARKERS CONSORTIUM

IMPROVING HEALTH THROUGH MEANINGFUL MEASUREMENTS

FNIH

Foundation for the National Institutes of Health

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Foundation for the NIH

Outline

- Quick FNIH and Biomarkers Consortium Background
- Terminology of biomarkers
- How do you know there is enough evidence?
- Important messages

About the FNIH

- The mission of the Foundation for the National Institutes of Health (FNIH) is to **support the mission of the NIH**. The FNIH creates and leads alliances and public-private partnerships that advance breakthrough biomedical discoveries and improve the quality of people's lives.

- The FNIH was **created by Congress** in 1990 as a not-for-profit charitable organization. The Foundation began its work in 1996 to facilitate groundbreaking research at the U.S. National Institutes of Health (NIH) and worldwide.

- Attract and share resources
- Enable insight and innovation
- Establish standards
- Distribute expertise
- Create consensus
- Drive competitiveness in marketplace
- Disseminate knowledge
- Enhance credibility
- Reduce costs
- Support training & education
- Manage complexity

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Select Partnerships at the FNIH

Accelerating Medicines Partnership NIH (OD), NIA, NIAMS, NIDDK, NINDS, 12 companies, 10 not-for-profit organizations	**$302 million**
Partnership for Accelerating Cancer Therapies NCI, PhRMA, 12 pharmaceutical companies	**$220 million**
Grand Challenges in Global Health (GCGH) Bill & Melinda Gates Foundation	**$201 million**
Lung-MAP: Master Lung Protocol Trial NCI (SWOG), FDA, Friends of Cancer Research, 5 companies to date	**$163 million**
Alzheimer's Disease Neuroimaging Initiative (ADNI) NIA, NIBIB, 25+ companies, 3 not-for-profit organizations	**$148 million**
The Biomarkers Consortium FDA, NIH, CMS, PhRMA, BIO, pharmaceutical and nutrition companies, not-for-profit organizations	**$95 million**
Helping End Addiction Long-Term (HEAL) Partnership Committee NIH contract	**$0.4 million**

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Biomarkers Consortium

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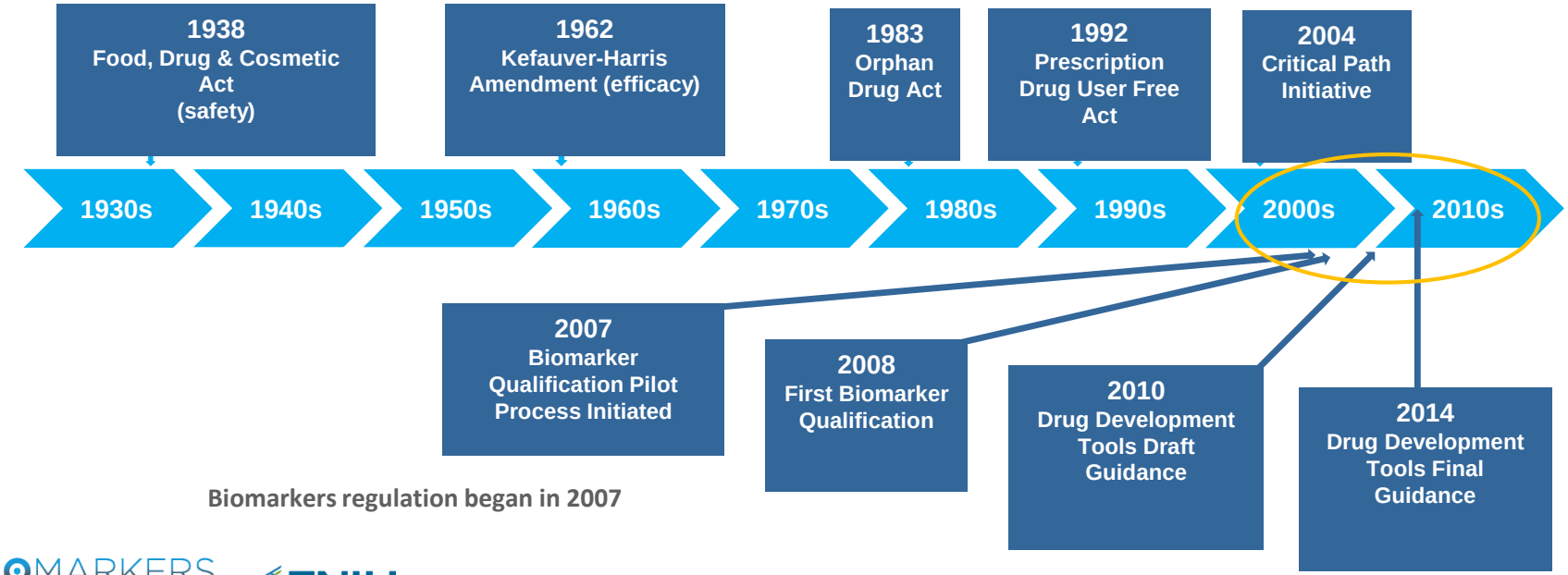
Why do we need a Biomarkers Consortium?

Biomarker qualification is new!

Answer: Precision Medicine

Drug development regulation preceded biomarkers regulation by almost 70 years

Drug development regulation began in 1938



Biomarkers regulation began in 2007

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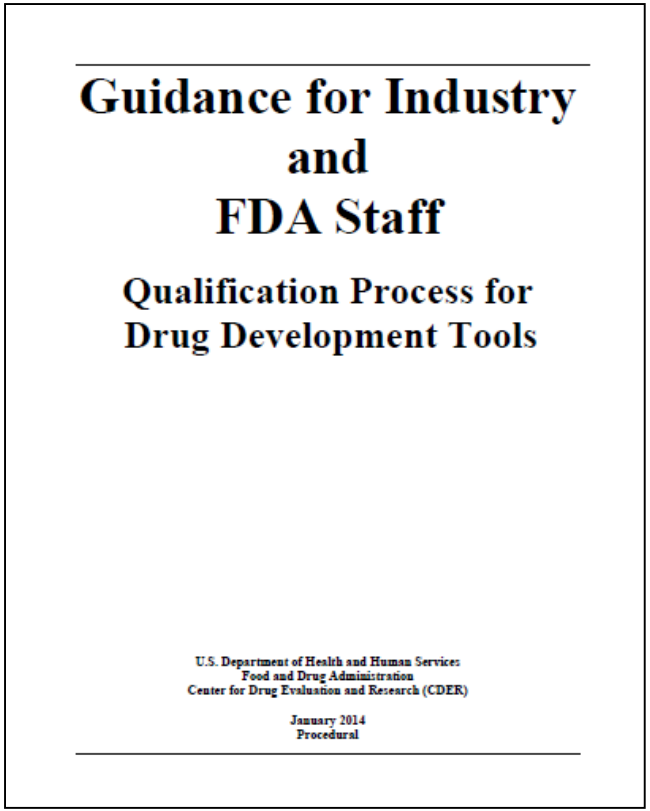
The consortium approach is encouraged by the FDA



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

"Because of the substantial work needed to achieve qualification, CDER [Center for Drug Evaluation and Research] encourages the formation of collaborative groups to undertake these tool-development programs… A variety of projects undertaken by consortia have demonstrated the usefulness of this approach."

Updated FDA Draft Guidance published
January 2014

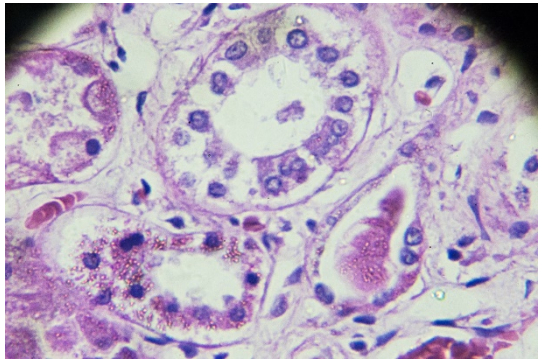
Biomarker Consortium

Vision

- Improving health through meaningful measurements

Mission

- To create and lead cross-sector efforts that validate and qualify biomarkers and other drug development tools to accelerate better decision making for the development of new therapeutics and health technologies.



Goals

- Facilitate the development and the seeking of regulatory approval for biomarkers using new and existing technologies;
- Develop evidence to help qualify biomarkers for specific applications in diagnosing disease, predicting therapeutic response or improving patient outcomes;
- Generate information useful to inform regulatory decision making;
- Make consortium project results broadly available to the entire scientific community.

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Biomarkers Consortium

12 years of collaboration, research and progress

14 therapeutics advanced based on tools generated

9 clinical tools being used in drug development

5 FDA guidance documents supported by work of the BC

1 Clinical safety biomarker Qualification

>50 publications

800+ citations

60 member organizations

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Biomarker Terminology

- **Basic terms comparison**
- **Type of biomarker**

Biomarker Terminology (SSA)

- **Biomarker:**
  - A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, the presence of disease, or pharmacologic responses to a therapeutic intervention.
- **Clinical endpoint:**
  - A variable that characterizes a study subject's wellbeing from his or her perspective (i.e., how the subject thinks he or she feels or functions).

Biomarker Terminology (BEST)

- **Biomarker:**
  - A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions. **Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers**.
- **Clinical endpoint:**
  - A precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question. *A precise definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined.*

Clinical Outcome Terminology (BEST)

- **Clinical Outcome:**
  - An outcome that describes or reflects how an **individual feels, functions or survives**.
- **Clinical Outcome Assessment:**
  - Assessment of a clinical outcome can be made through report by a clinician, a patient, a non-clinician observer or through a performance-based assessment.
  - There are four types of COAs.
    - clinician-reported outcome
    - observer-reported outcome
    - patient-reported outcome
    - performance outcome

BEST Resource

- NIH and FDA encourage stakeholders to join them in using BEST terms and definitions so that everyone can “speak the same language” when discussing biomarkers and endpoints.
- Consistent, mutually understood terminology can help accelerate development, validation, and qualification of medical product development tools.
- The BEST Resource will be updated periodically with additional terms, definitions, and examples.
- NIH and FDA welcome feedback, including specific proposed edits with rationales, from all stakeholders.
  - Email biomarkers@ncbi.nlm.nih.gov.

https://www.ncbi.nlm.nih.gov/books/NBK338448/

BEST (Biomarkers, EndpointS, and other Tools)
Classification: Range of Biomarker Types

- Susceptibility / risk biomarker
- Diagnostic biomarker
- Prognostic biomarker
- Monitoring biomarker
- Predictive biomarker
- Pharmacodynamic/Response biomarker
- Safety biomarker

Measures of disease presence and status

Measure aspects of response to treatment

BEST (Biomarkers, EndpointS, and other Tools)
Classification: *Disease Focused Biomarkers*

- **Susceptibility / risk biomarker**:

  Examples:
  - BMI or 2 hr post-meal glucose for diabetes risk
  - Apo E genotype risk for Alzheimer's disease

  Key uses:
  - Define population for more efficient prevention trials

- **Diagnostic biomarker**:

  Examples:
  - Blood pressure in hypertension
  - FEV1 for COPD

  Key uses:
  - Define disease population for study

- **Monitoring biomarker**:

  Examples:
  - HCV-RNA
  - PSA in prostate cancer

  Key uses:
  - Monitor patient status in trials

- **Prognostic biomarker**:

  Examples:
  - Gleason score in prostate cancer
  - Total kidney volume in AD-PCKD

  Key uses:
  - Define higher risk disease population, enhancing trial efficiency

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Adapted from:
Peter Stein, M.D.
Deputy Director
OND, CDER,
FDA

BEST (Biomarkers, EndpointS, and other Tools)
Classification: *Treatment-focused biomarkers*

- **Predictive biomarker**:

Examples:
- Cystic fibrosis genotypes response to ivacaftor
- Microsatellite-high predicts response to pembrolizumab

Key uses:
- Trial enrichment – improves efficiency, reduces sample size, increases response to treatment

- **Pharmacodynamic/Response biomarker**:

Examples:
- Blood pressure in hypertension
- FEV1 or 6 minute walk test
- LDL-C

Key uses:
- Demonstrating drug-target engagement, dose-ranging
- Surrogate endpoints (validated or reasonably-likely)

- **Safety biomarker**:

Examples:
- ALT, creatinine / eGFR
- Urinary kidney injury biomarkers (KIM-1, etc.)

Key uses:
- Detecting / assessing drug toxicity

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OND, CDER,
FDA

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Evidentiary Criteria Framework

Focus on regulatory decision-making

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How much data is enough?

While the amount of data is important, the type of data is essential.

Collecting more of the same data can be a waste of effort.

A stable framework requires a solid foundation

The 2016-2018 workshops were in a series of initiatives/discussions on evidentiary standards for biomarker qualification:

- *Evidentiary Considerations for Integration of Biomarkers in Drug Development*
  - U. of Maryland CERSI/FDA/Critical Path Institute, August 21-22, 2015
- *Facilitating Biomarker Development and Qualification*
  - Brookings Institution, October 27, 2015
- *Collaboratively Building a Foundation for FDA Biomarker Qualification*
  - National Biomarker Development Alliance, December 14-15 2015
- BEST (Biomarkers, EndpointS, and other Tools) Glossary
  - FDA/NIH Joint Leadership Council, NLM
- *Biomarker Qualification Workshop: Framework for Defining Evidentiary Criteria*
  - FNIH Biomarkers Consortium/FDA, April 14-15 2016
- *Biomarker Qualification Workshop: Evidentiary Criteria for Surrogate Endpoint Development*
  - FNIH Biomarkers Consortium/FDA, July 30-31 2018

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What does the framework provide?

- A clear set of steps needed for working toward Biomarker Qualification
- Identify key areas for defining biomarker need
- Specify and limit biomarker development focus to allow successful generation of appropriate evidence
- Provide consistent set of characteristics to describe and define the biomarker development program with the regulatory agency

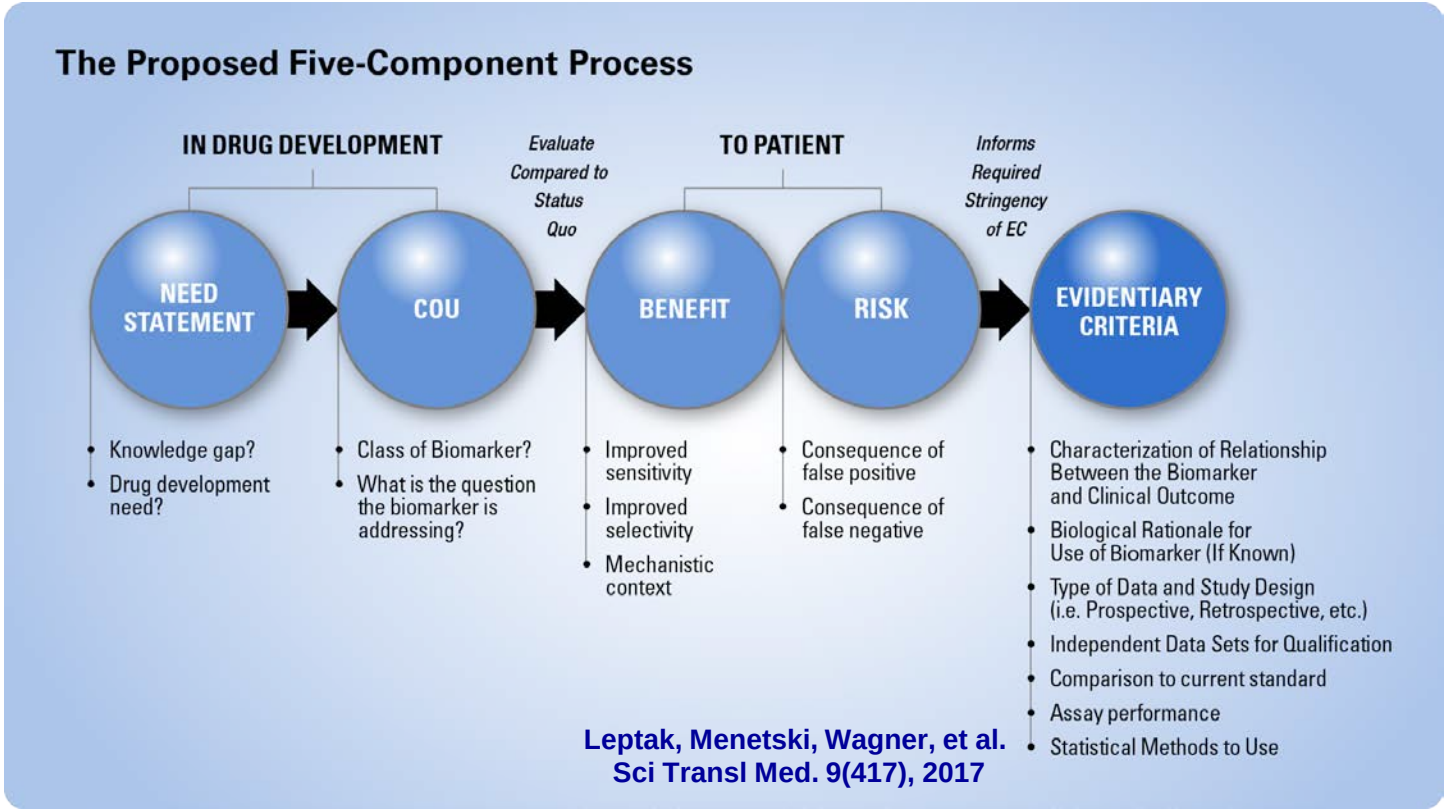
- **Goal: Enhance submission quality, predictability of the qualification process and clarify the type and amount of evidentiary criteria needed.**

Primary Assumption:

A clearly defined goal to the project will provide a better view of a path to ultimate drug development decision making and regulatory approval.

The framework provides a context for the discussion between sponsor and the agency.

Constructing a biomarker road map



Leptak, Menetski, Wagner, et al.
Sci Transl Med. 9(417), 2017

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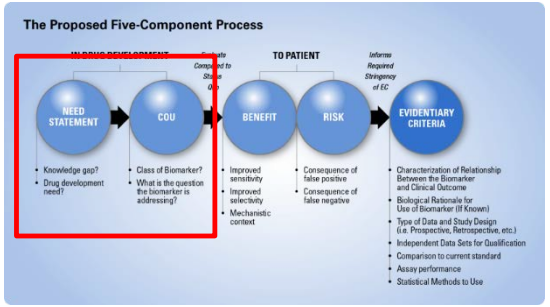
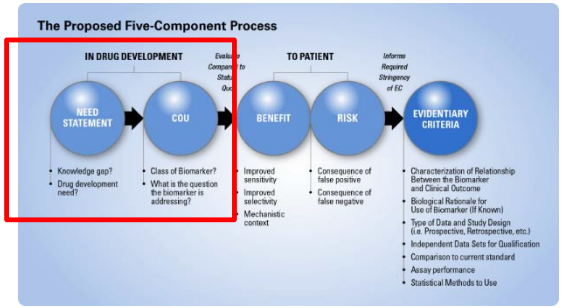
Need statement and context of use (COU)

- Need statement
  - The nature and extent of the need, drug development issue it addresses and target population
  - The major challenge(s) and unique aspects of these challenges the project is to address
  - The reasons and causes for the deficit being addressed
- COU statement – concise description of how a biomarker is intended to be used in drug development
- COU simplified to only 2 elements:
  - What class of biomarker is proposed and what information content would it provide?
  - What question is the biomarker intended to address? ("What is the biomarker's specific fit-for-purpose use?")



Examples of COU



BEST: identify likelihood of a clinical event

A prognostic marker for disease progression to be used as an inclusion criteria in a Phase 2 clinical trial of a novel drug to enrich for the likelihood of organ transplantation.

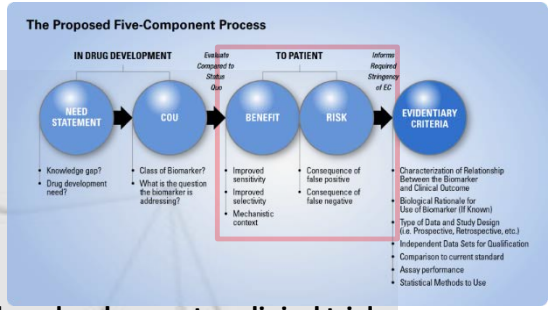
Clinical Trial Decision

BEST: response to an intervention or exposure.

A safety marker for organ toxicity to be used in a Phase 1 clinical trial of a novel drug in addition to a standard measure of organ toxicity to explore and refine the clinical trials stopping criteria.

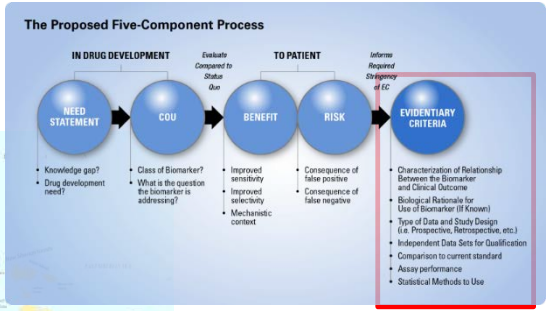
Clinical Decision

Benefit and risk



- The benefit and risk profile, given that the COU is related to the biomarker's value to drug development or clinical trials, is assessed from the perspective of patients
- Benefit assessment
  - What are the unmet needs of the population defined in the COU?
  - What is the mortality and morbidity of the disease's natural history in the absence of treatment?
  - What is the severity of the disease or condition?
  - What is the perceived benefit of the new biomarker vs. the current standard?
- Risk assessment
  - What is the potential consequence or harm if the biomarker's performance is not aligned with expectations based on the COU?
  - What is the perceived incremental risk, new biomarker vs. current standard?
  - When in the drug development lifecycle is the biomarker intended use?
  - What is the scope of the biomarker COU in terms of impacting drug development and regulatory review?

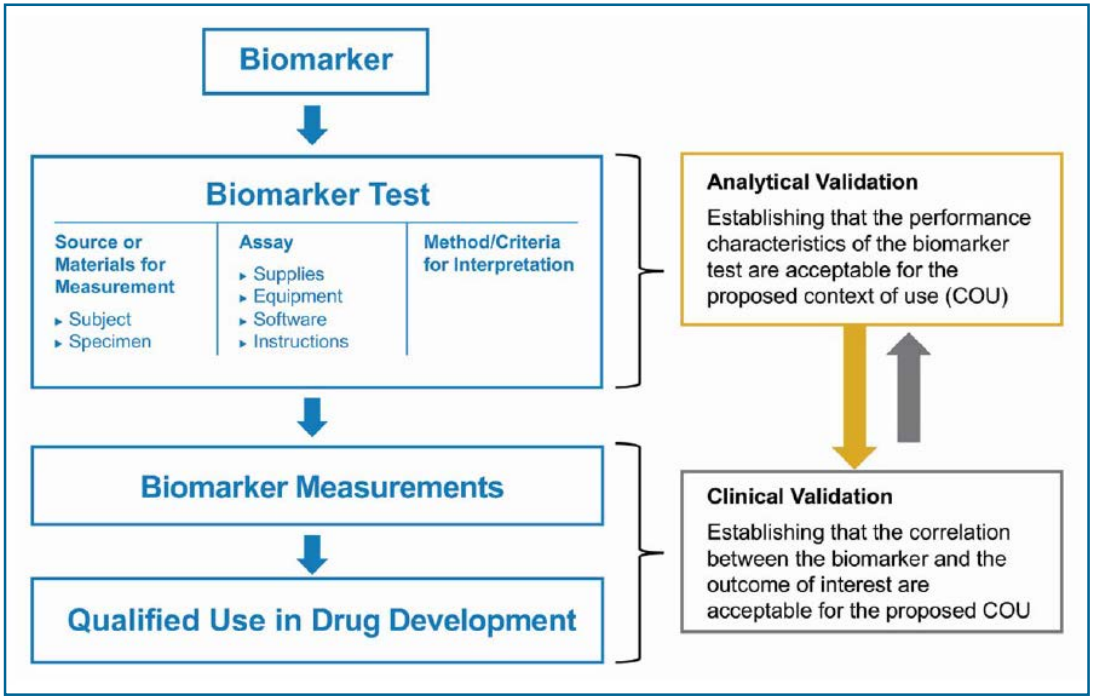
Evidence map



- The evidence maps in this framework are inspired by, but not identical to, the one used by Altar et al. (2008)
- The COU choices made determine the overall relative level of benefit and risk
- Benefit and risk determined as a result of the COU in turn determines the levels of evidence needed to evaluate the biomarker for qualification
- The evidence acceptable for satisfying evidentiary criteria in some cases may be partially or entirely composed of retrospective, literature, or other “real world” types of evidence
- The levels of evidence required to qualify the marker can be described according to a series of variables

Altar et al. CPT, 83:368-371, 2008

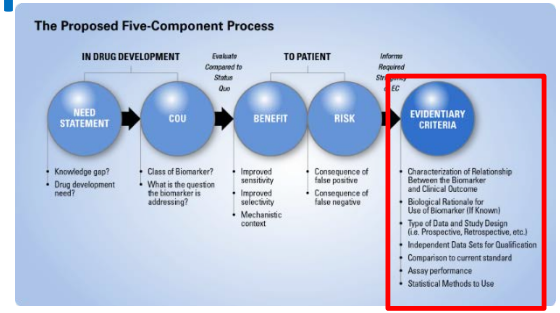
A view of Validation



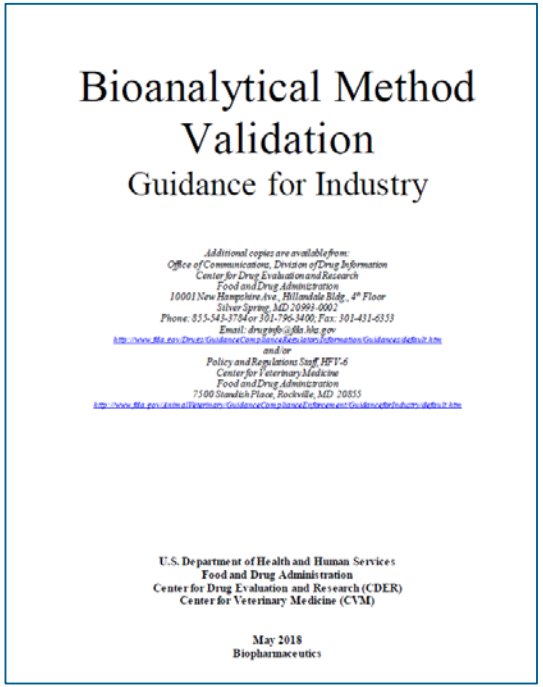
https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm628118.pdf

Analytical validation

- Accuracy
- Precision
- Analytical sensitivity
- Analytical specificity
- Reportable range
- Reference interval
- Reproducibility
- Stability



Very High Standard:	Minimum Requirements:
Regulatory Marketing Approval as Diagnostic	"Fit-for-Purpose" Validation
Parameters Evaluated During Validation	
Accuracy Precision Analytical sensitivity Analytical specificity Reportable range Reference interval Reproducibility Stability Other as required	Accuracy Precision Analytical sensitivity Analytical specificity Reportable range Reference interval Other as required


Bioanalytical Method Validation

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
and/or
Policy and Regulations Staff, HFV-6
Center for Veterinary Medicine
Food and Drug Administration
7500 Standish Place, Rockville, MD 20855
http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm

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

May 2018
Biopharmaceutics

https://www.fda.gov/downloads/drugs/guidances/ucm070107.pdf

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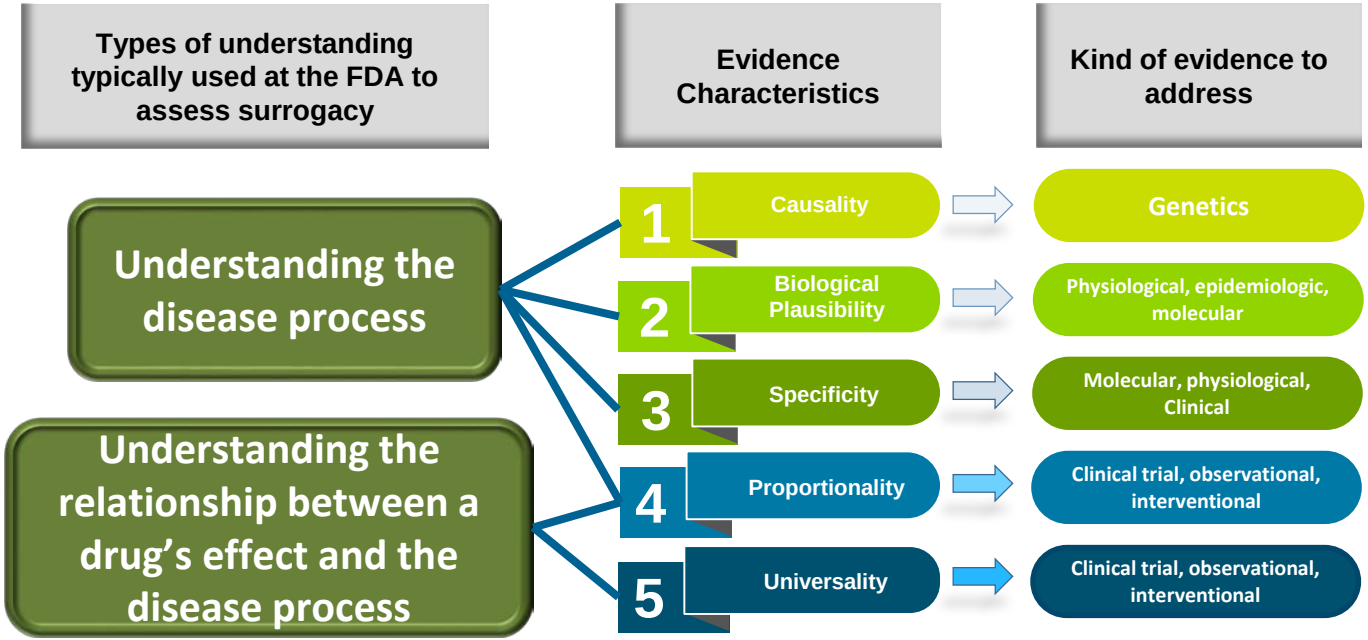
Clinical Validation:

Link to previous FDA vocabulary and framework terms



Issues of focus related to characteristics of (biomarker) evidence

- Causality
  - is there a compelling case for it being causal so there is less of a need for evidence of universality
- Plausibility
  - is the biology of the surrogate so compelling that it adds to the weight of evidence for acceptance
- Specificity and potential for complicating effects
- Proportionality
  - to what extent does the surrogate endpoint explain the disease or the change in disease
- Universality
  - to what extent is there evidence across drug mechanisms or across different populations

Different Biomarker Types are supported by different amounts and type of evidence

Take home messages from biomarker development in the drug development process

- Biomarker development can be as difficult and as resource intensive as drug development

- The correlation of a biomarker to a clinical observation is only as good as the precision that the observation can be quantified.
  - A biomarker for depression has been difficult. We now know that there are subdomains that all join to contribute to an overall diagnosis of depression. This lumping of characteristics will frustrate biomarker development.

- The type of biomarker you are trying to develop will dictate the type of data that will be needed to ensure **confident decision making**.
  - For biomarker development, you need to know who will be making the decision.

- The biomarker is not the test used to measure it. (this is always a difficult concept to explain)
  - Blood pressure is a biomarker. It doesn't matter if you measure it with an electronic cuff or an old fashion hand pump.
  - Body temperature is a biomarker. Mercury thermometer or forehead IR.
  - Serum CRP level is a biomarker. ELISA, mass spec, or fluorescent aptamer quenching

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