Brief overview of biomarkers: value, limitations, and the Biomarker Qualification Program (BQP)

Peter Stein, MD

Deputy Director

Office of New Drugs / CDER / FDA

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- 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

Overview

- Types of biomarkers – a brief review
- Surrogate endpoints – value and limitations
- Challenges of biomarker development

BEST Resource: Biomarkers, EndpointS, and Other Tools

- 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/
- 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: definition

"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. *Molecular, histologic, radiographic, or physiologic characteristics* are types of biomarkers."

Why develop biomarkers?

- High quality biomarkers *can markedly accelerate and enable drug development in areas of unmet need*
- Biomarkers can improve trial *efficiency and feasibility*
  - Improve ease and accuracy of identifying patient population
  - Enrich the study population
    - Study population with *more events* – so detecting change in outcome with treatment becomes feasible
    - Study a *more responsive* study population to detect a drug effect
  - Improved monitoring
    - Enhanced patient safety – earlier detection of drug toxicity
    - Detect changes in patient status
  - Improve assessment of treatment response; predict clinical benefit
- Address unmet medical needs, where progress is halted or delayed by lack of adequate drug development tools, including biomarkers

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

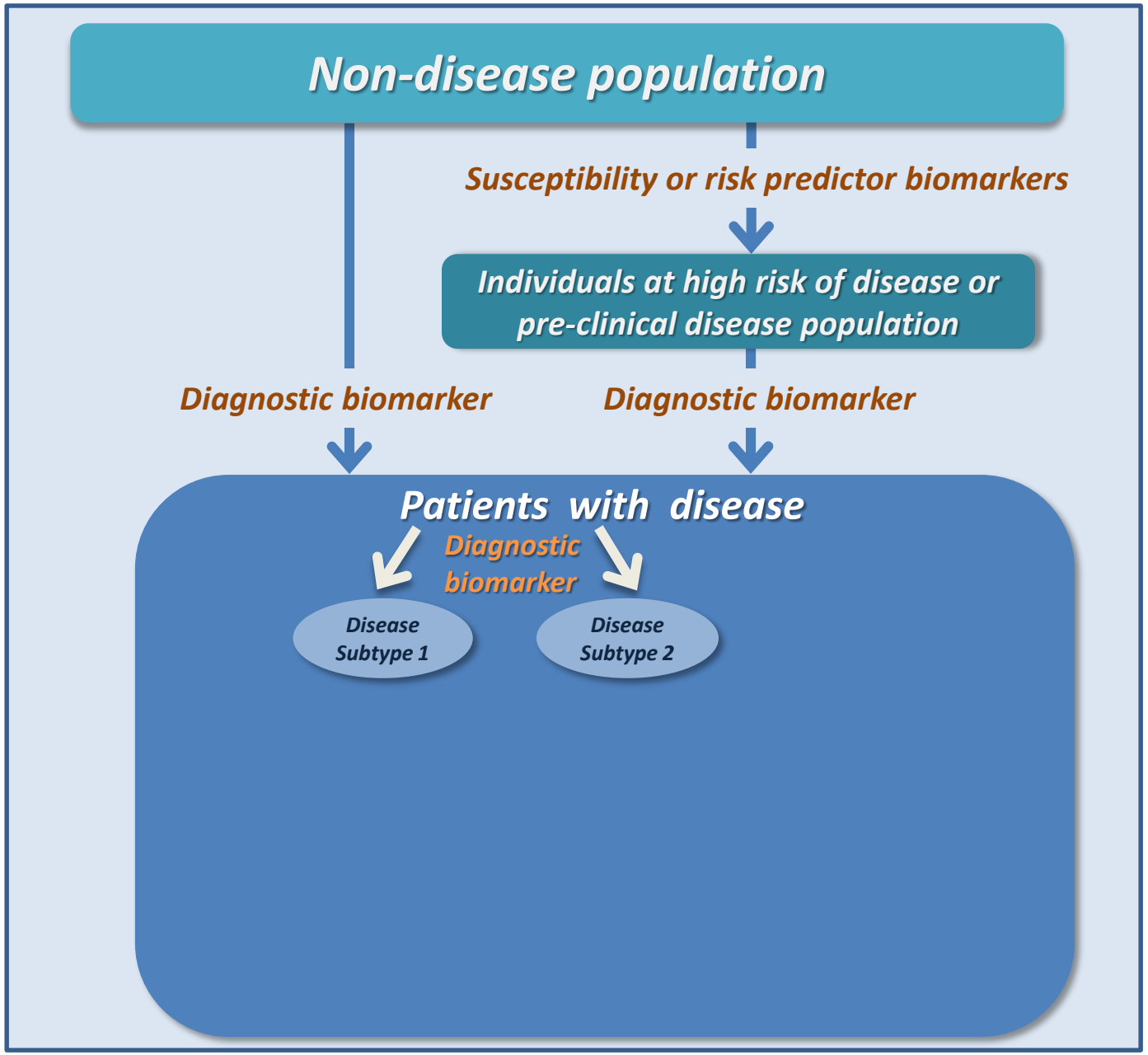
- **Susceptibility / risk biomarker**
- **Diagnostic biomarker**
- **Prognostic biomarker**
- **Monitoring biomarker**

Measures of disease presence and status

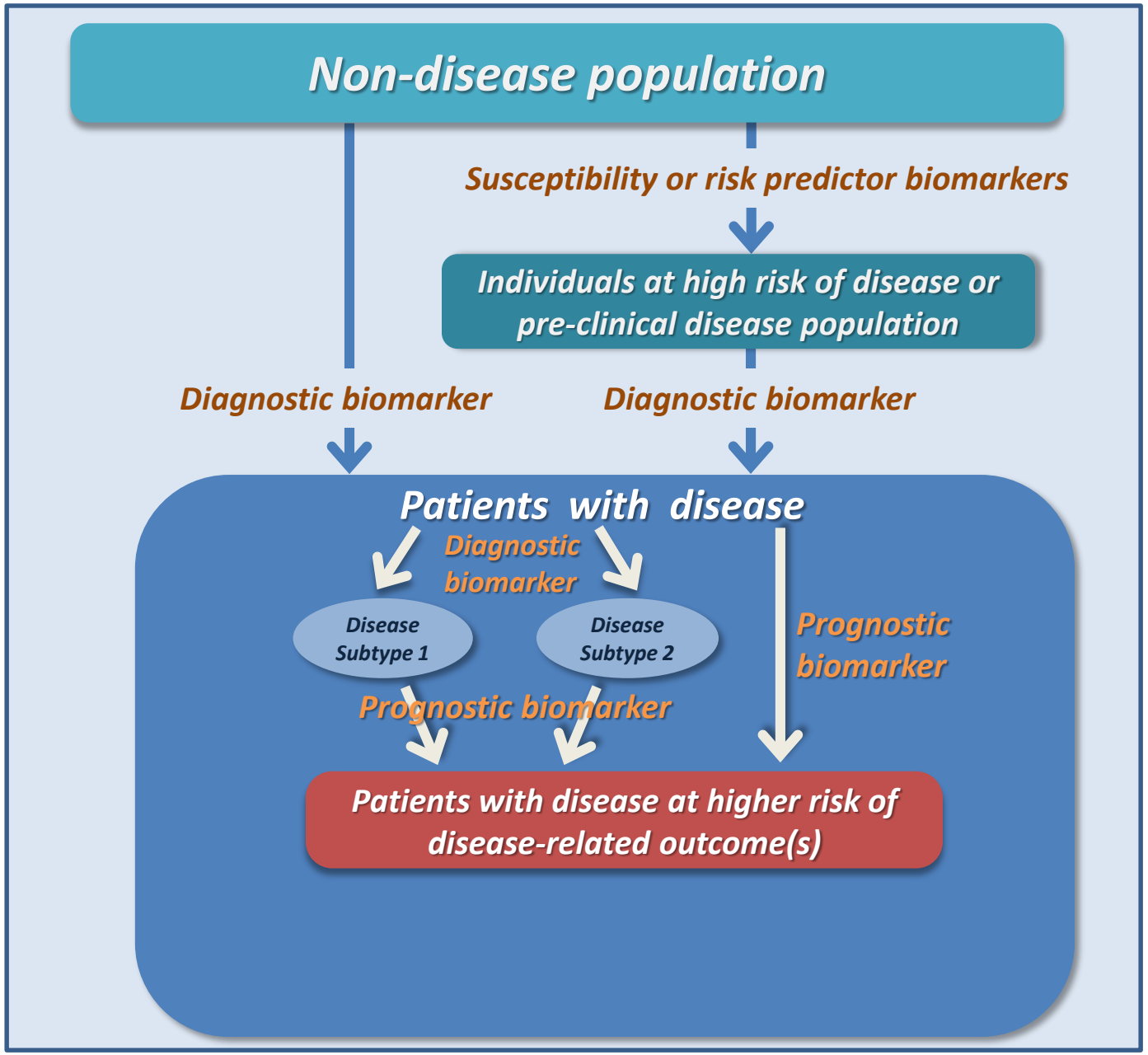
- **Predictive biomarker**
- **Pharmacodynamic/Response biomarker – including surrogate endpoints**
- **Safety biomarker**

Measure aspects of response to treatment

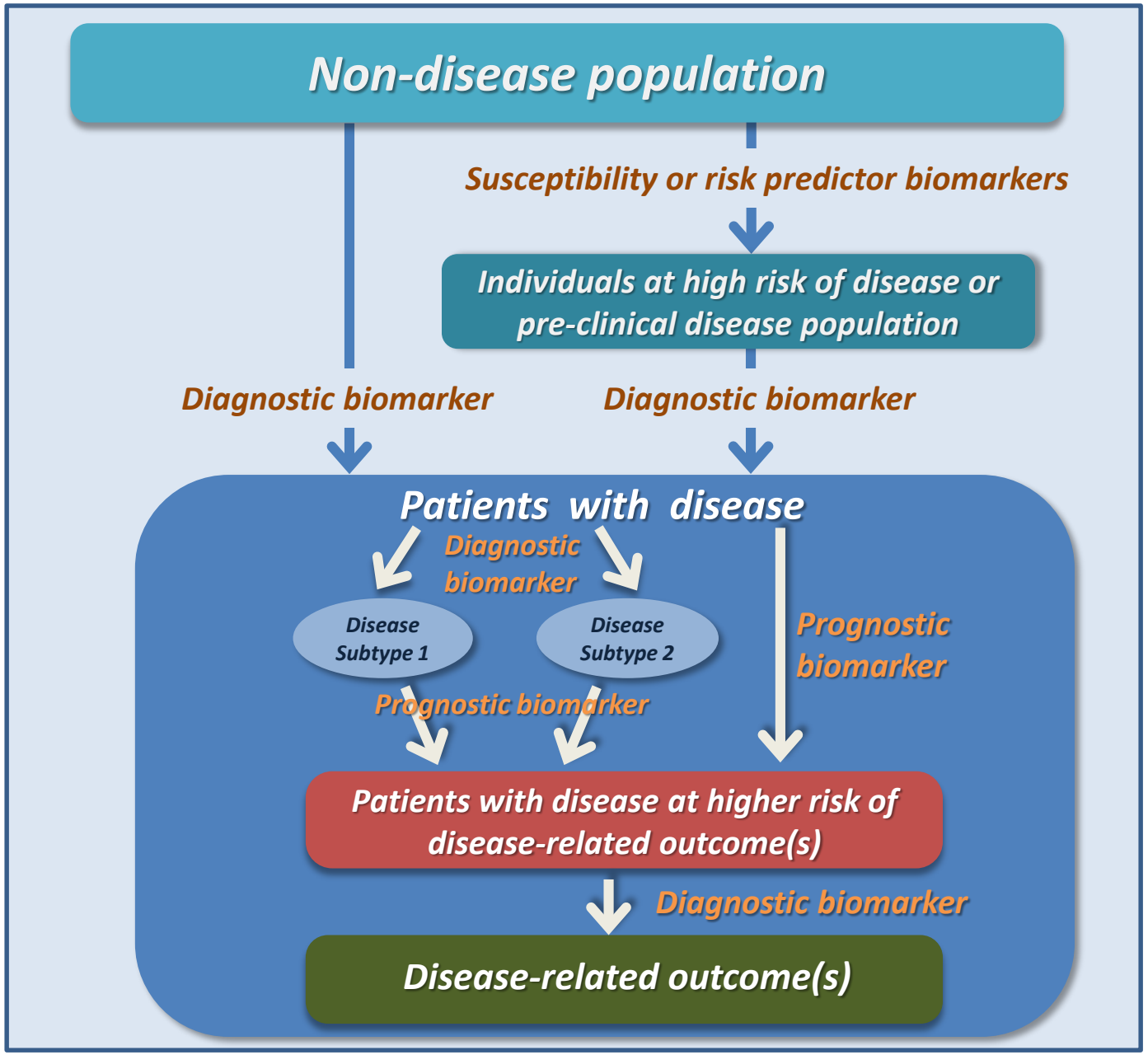
Disease-Focused Biomarkers



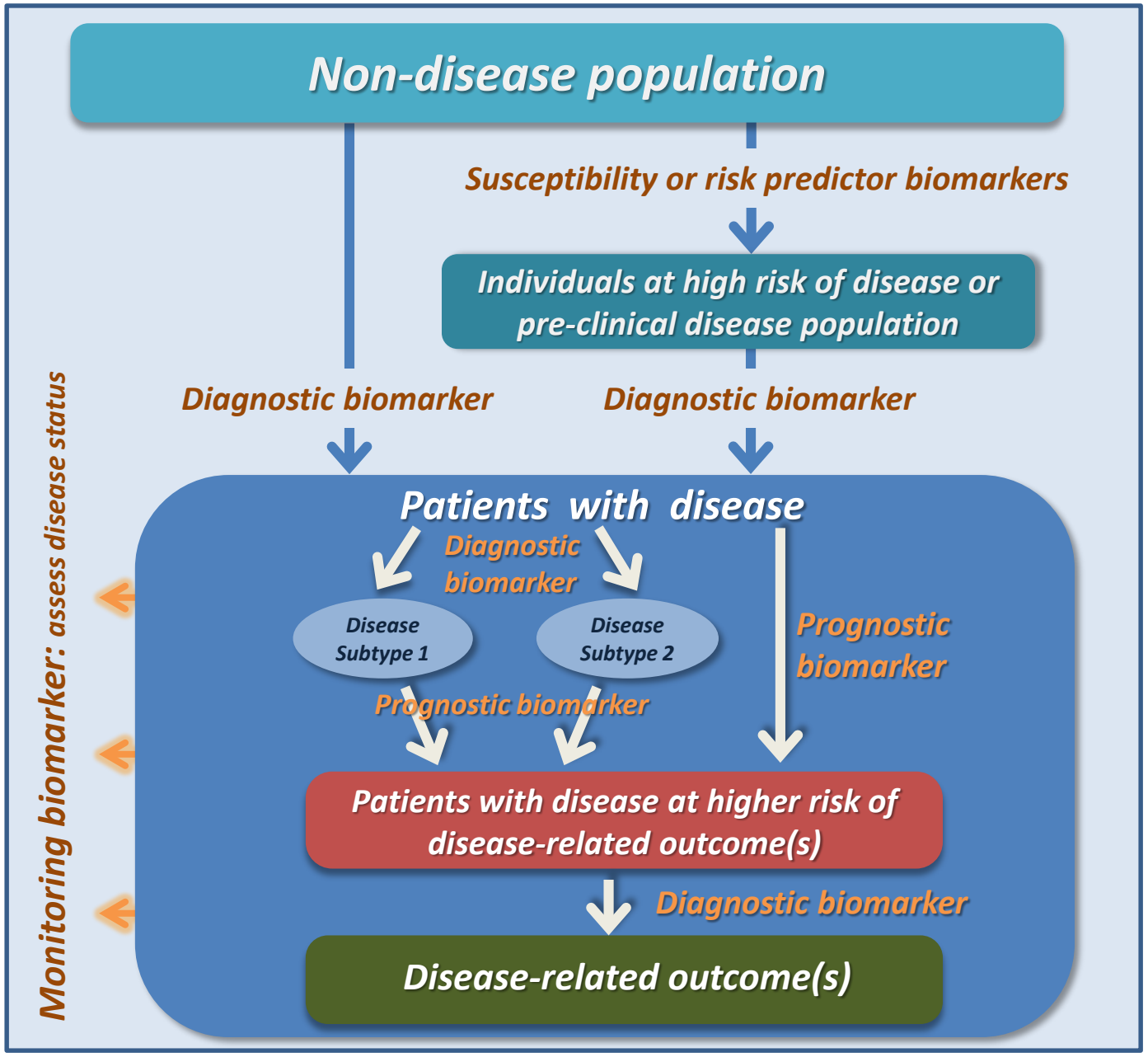
Disease-Focused Biomarkers



Disease-Focused Biomarkers



Disease-Focused Biomarkers



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

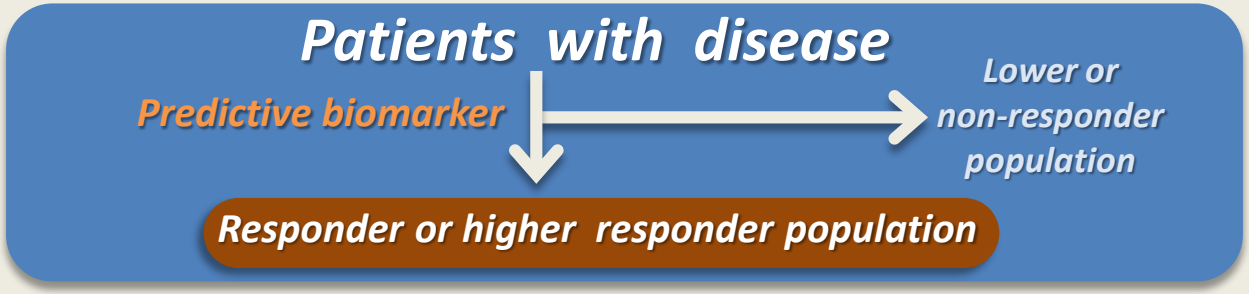
Key uses:
- Monitor patient status in trials

- **Prognostic biomarker**:

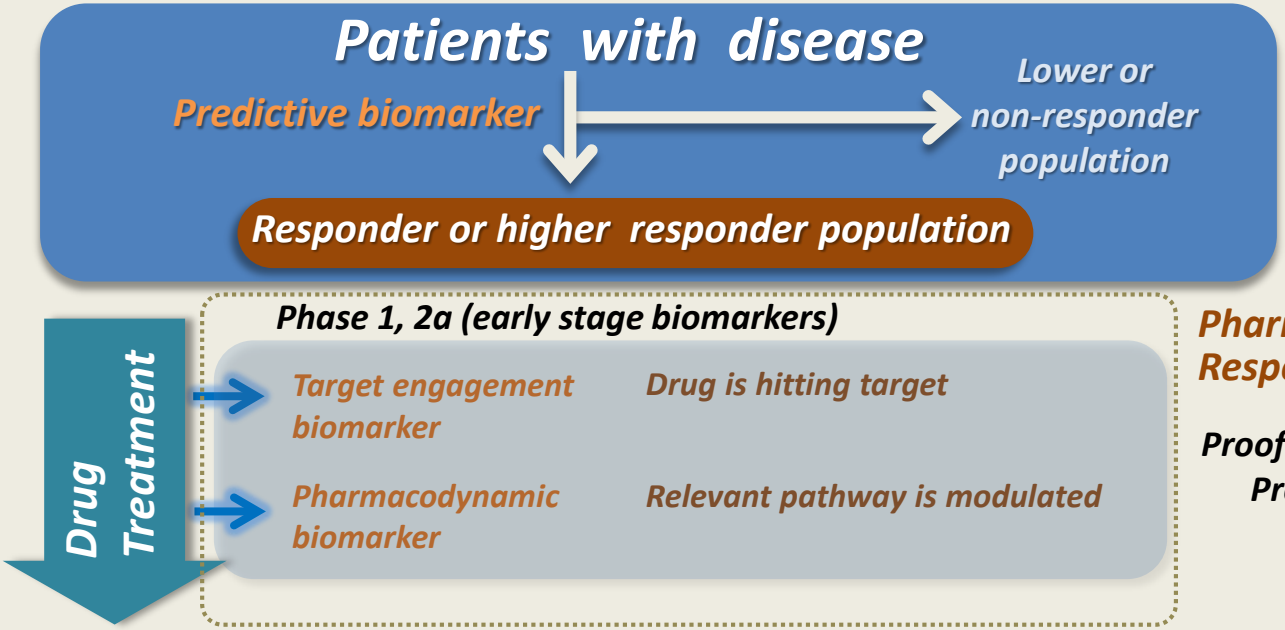
Examples:
- Gleason score in prostate cancer
- Total kidney volume in AD-PCKD

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

Treatment-Related Biomarkers



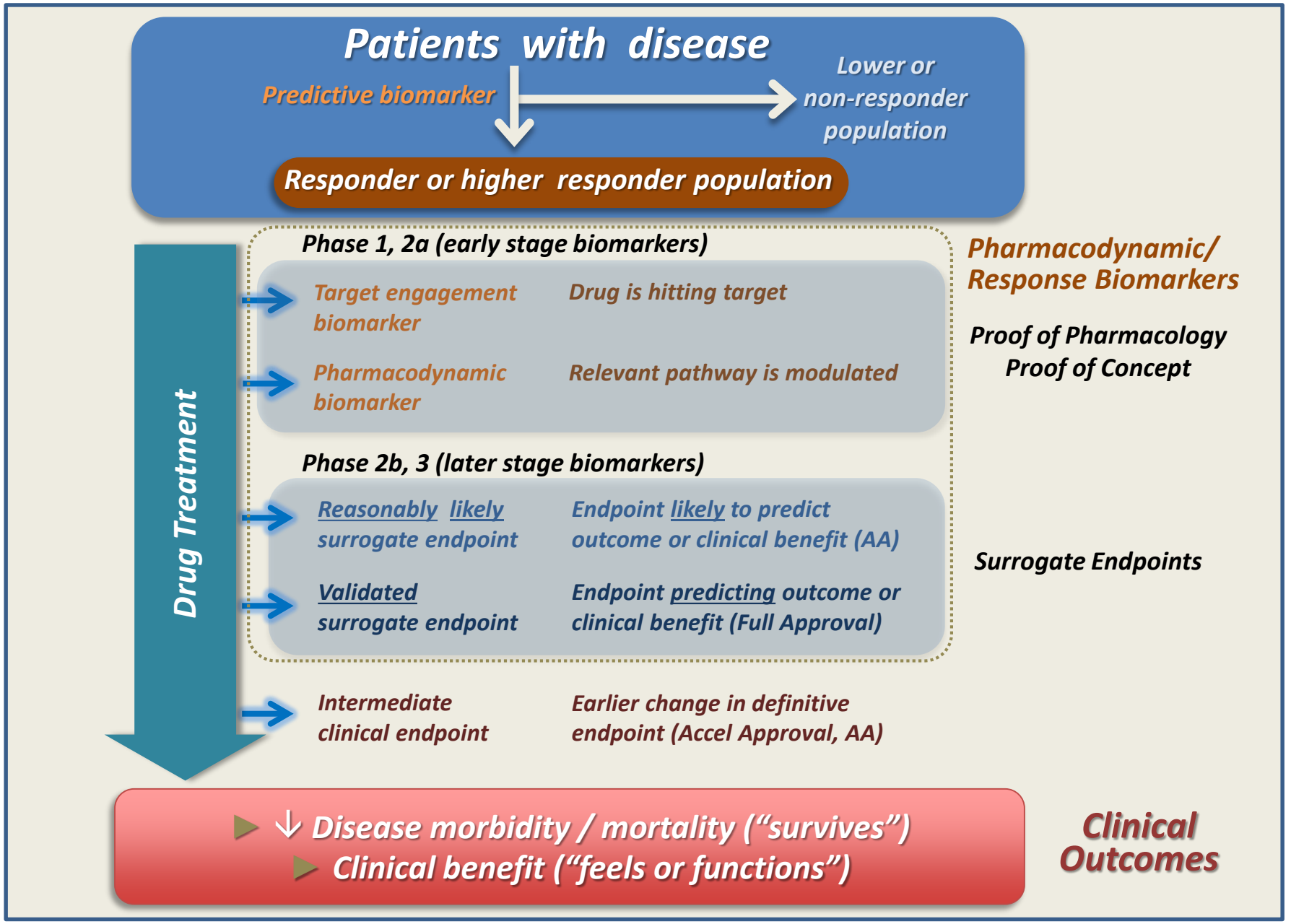
Treatment-Related Biomarkers



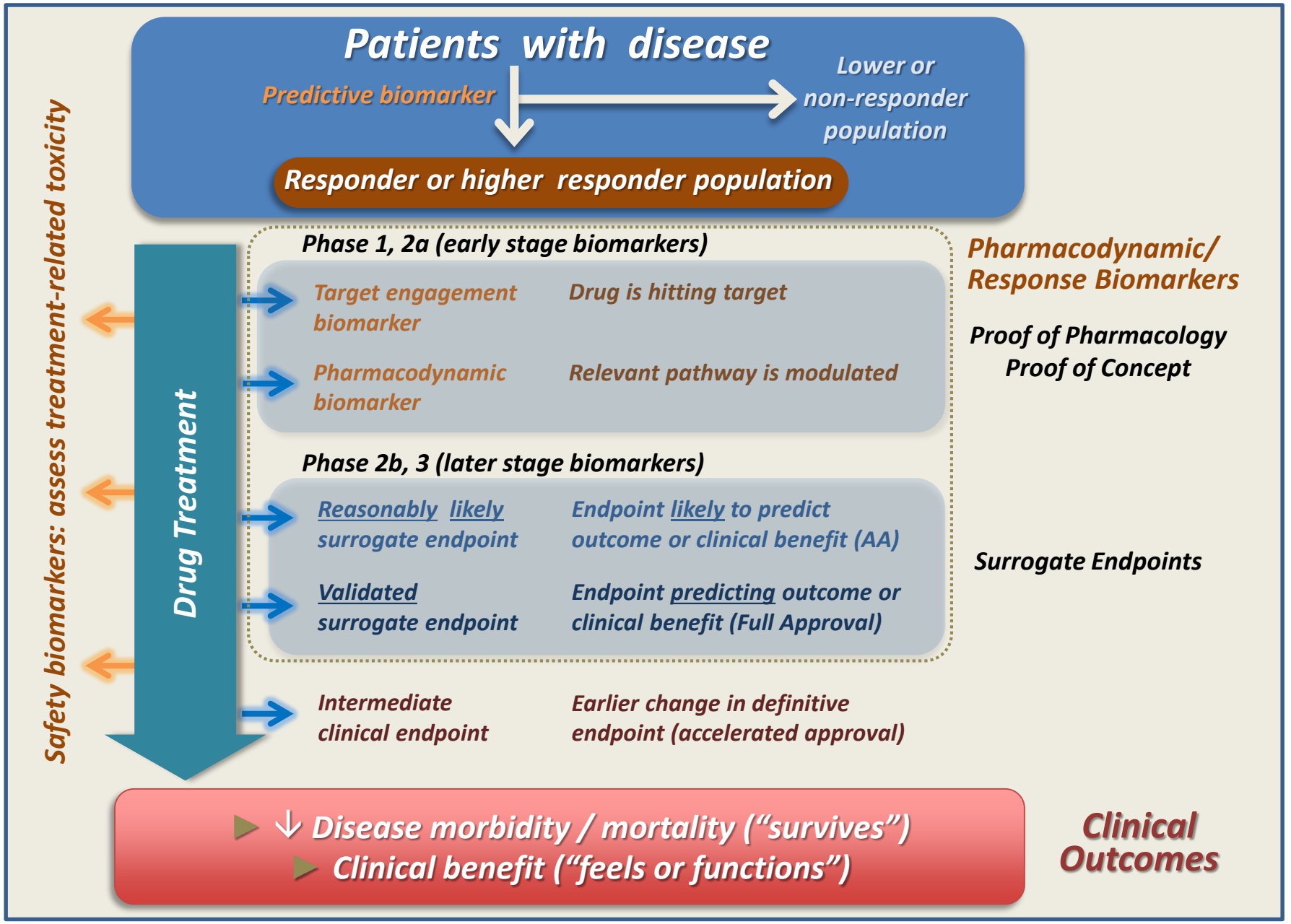
Pharmacodynamic/ Response Biomarkers

Proof of Pharmacology
Proof of Concept

Treatment-Related Biomarkers



Treatment-Related Biomarkers



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

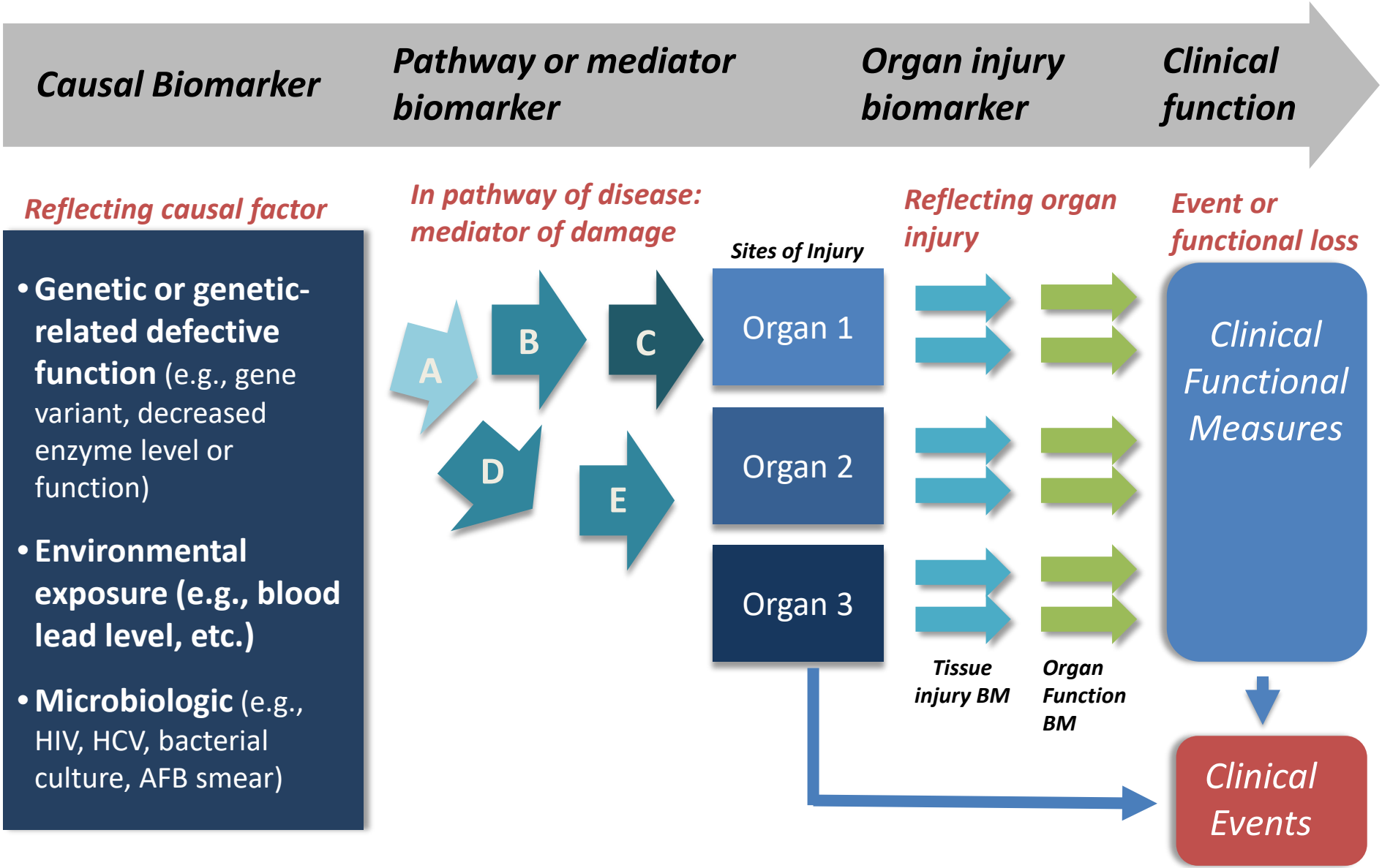
BEST (Biomarkers, EndpointS, and other Tools)
Classification: *Pharmacodynamic / Response BMs*

To support approval, FDA expects substantial evidence of effectiveness – that shows that a drug improves meaningful clinical outcomes: how a patient ***feels, functions, or survives***

- A **validated surrogate endpoint**: accepted by FDA that the effect on the biomarker *predicts* a specific clinical outcome. Validated endpoints have strong and diverse evidence supporting the relationship of the BM and the outcome

- A **"reasonably likely" surrogate endpoint**: an endpoint supported by strong mechanistic and/or epidemiologic rationale such that an effect on the surrogate endpoint is *expected* to be correlated with a clinical benefit, but not yet reaching the standard for validation.

Types of Surrogate Endpoints



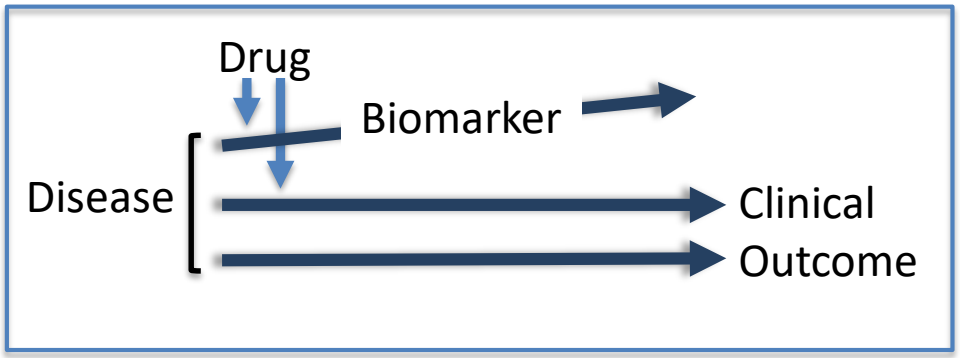
The limitations of surrogate endpoints

- Not a direct measure of how a patient *feels, functions or survives*
- Intended to reflect and predict clinical benefit not measure the outcome
- With a surrogate endpoint, the benefit / risk assessment therefore must be based upon *assumptions / predictions of benefit*
  - Translating the extent of clinical benefit from an *indirect* measure, and also using a *limited* dataset on risk to assess harms
  - Challenging when a drug shows clear effects on a *surrogate endpoint* – but also has safety issues
- And biomarkers may *fail* to predict clinical benefit

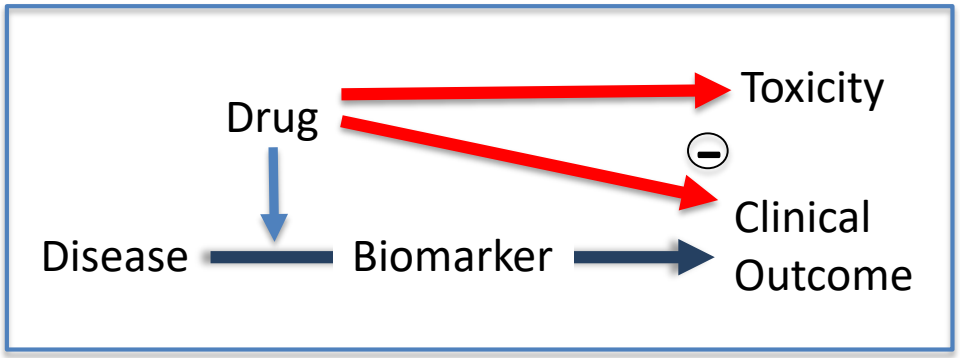
The limitations of surrogate endpoints

Surrogate on **causal pathway** modulated by drug

Surrogate ***not*** **on causal pathway** by which drug leads to benefit, or **multiple pathways of leading to clinical outcome,** BM *may or may* not reflect key pathways



Drug may induce **adverse effects on desired clinical outcome** through a pathway *not reflected* by BM, or may lead to other toxicities = BM does not reflect benefit (or risk)



After Fleming Statistics in Medicine 2012

Biomarker integration into drug development: 3 pathways

- **IND pathway**: based upon agreement with the division, in the context of a specific drug development program
- **Scientific community consensus**: broadly/widely used biomarker, appropriate scientific support, generally accepted by experts in the field
- **Biomarker qualification program**: review and acceptance based upon appropriate submission qualification package; available for use in any development program within approved context of use

The challenges of biomarker development

- Many disease areas with unmet needs have insufficient drug development tools to maximize trial efficiency (or even feasibility)
- Biomarker development *is a long and resource-intensive task*
  - Biomarker *discovery*: biased or unbiased screening in animal, clinical, epidemiological (include RWE)
  - Early animal *translational* models
  - Clinical or epidemiology observational studies
  - *Analytic validation* efforts: assure accuracy / reproducibility of measure
  - Interventional studies with "gold standard" endpoints compared to candidate – with multiple different treatments (different MOAs) to show that BM works across drug classes
- Many stakeholders in the mix:
  - Academic investigators at multiple institutions, US and ex-US
  - Often several academic societies in disease area with different viewpoints and membership
  - Different companies – both drug and device-focused may be working in the area
  - May be different patient stakeholder organizations
- The challenge: how to *prioritize* biomarker needs, *focus* resources, and *integrate* efforts across stakeholders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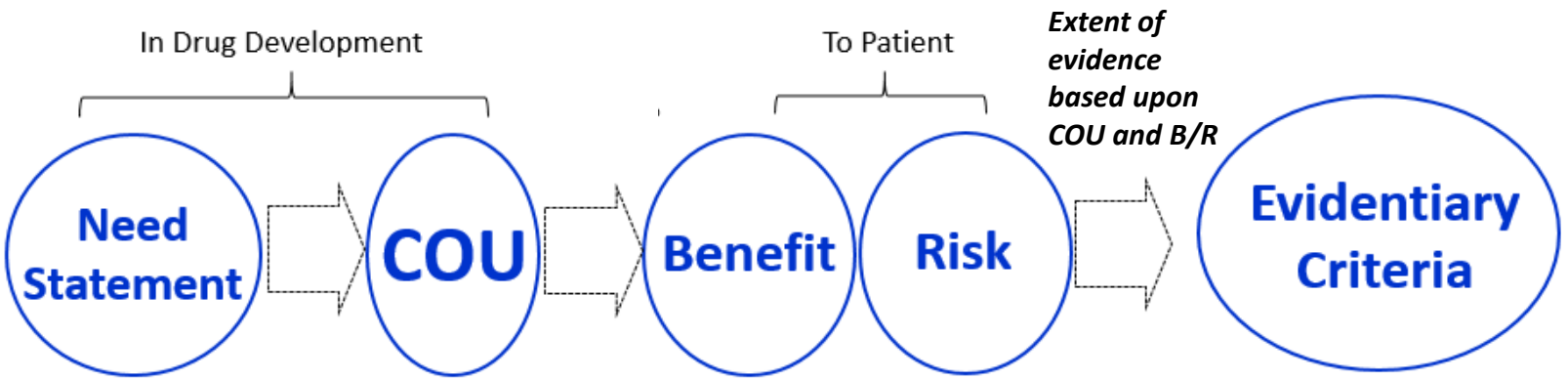
Conceptual Framework for Biomarker Development for Regulatory Acceptance



What is the "gap" in drug development this BM can fill? What are currently available tools and their limitations?

What is the intended *use* of the BM – for what purpose ("BEST" class), in what population and setting?

What is the expected *value* of the biomarker – how does it address unmet needs?

- *Need for this tool and unmet need for treatment in target disease?*
- *How important is the impact of the BM?*

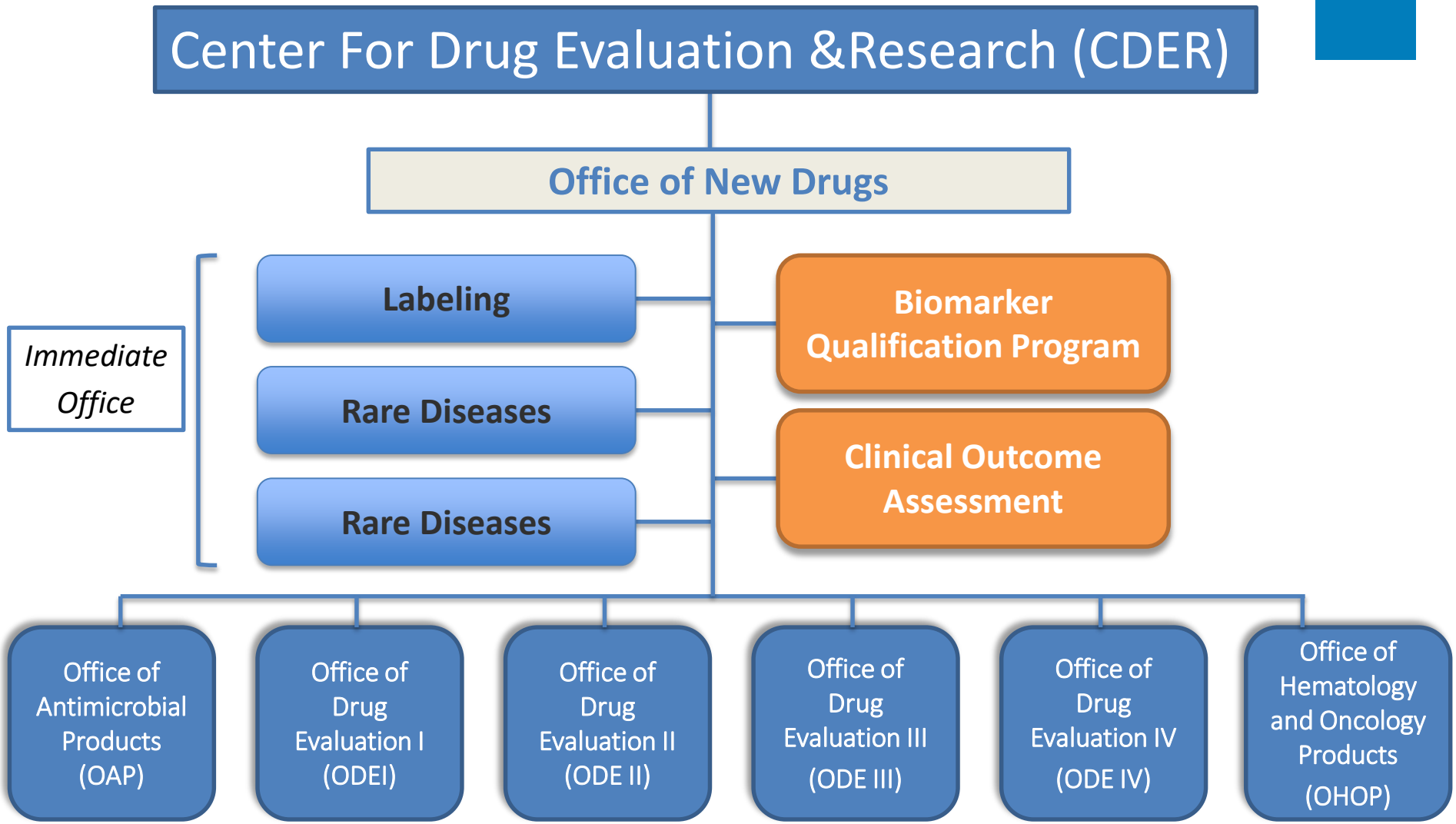
What is the consequence if the biomarker is inaccurate?

- *Used in conjunction with other endpoints or replacing other endpoints?*
- *Intended COU (e.g., enrichment vs a surrogate)?*

What is the evidence supporting the biomarkers proposed COU?

- *Where does the BM fit in the causal pathway?*
- *What is the biological rationale?*
- *What clinical data supports the relationship between the change in the BM and the clinical outcome?*
- *What are the analytic characteristics of the BM?*

https://fnih.org/what-we-do/biomarkers-consortium/programs/framework-for-safety-biomarkers


Center For Drug Evaluation &Research (CDER)
Office of New Drugs
Immediate Office
Labeling
Rare Diseases
Rare Diseases
Biomarker Qualification Program
Clinical Outcome Assessment
Office of Antimicrobial Products (OAP)
Office of Drug Evaluation I (ODEI)
Office of Drug Evaluation II (ODE II)
Office of Drug Evaluation III (ODE III)
Office of Drug Evaluation IV (ODE IV)
Office of Hematology and Oncology Products (OHOP)

Drug development tool qualification at CDER

- *Qualification* is a conclusion that within the stated *context of use*, the DDT *can be relied* upon to have a specific interpretation and application in drug development and *regulatory review*
- *Types of Tools:*

Potential for wide applicability to support drug development programs:

Clinical Outcome Assessments

Biomarkers

Usually in narrow context of use (biological, radiological threats)

Animal Models (Animal Rule)

21st Century Cures: Qualification of Drug Development Tools (Section 3011) - BQP

- Specifies the drug development tool qualification process, 3 stages
  - **Submission of LOI**
  - **Submission of qualification plan**
  - **Submission of full qualification package**
- FDA can accept or reject at each stage
- Time frames *for each review step* to be specified

21st CC: acceptance of biomarker into the BQP

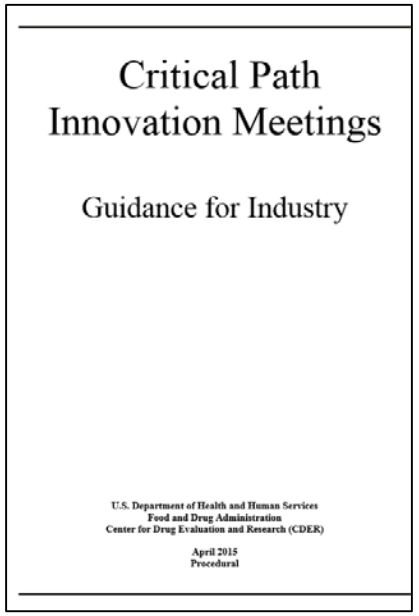
- Acceptance of each stage submission based upon scientific merit
- Prioritization of review
  - Based upon
    - "the *severity, rarity, or prevalence* of the disease or condition targeted by the drug development tool and *the availability or lack of alternative treatments* for such disease or condition; and
    - the identification by the Secretary or by biomedical research consortia and other expert stakeholders, of such drug development tool and its proposed context of use *as a public health priority*" (italics added)
- Effect of qualification: use of a qualified DDT "by any person" in:
  - Supporting or obtaining approval or licensure of a drug or biological product (under Section 505 of the FDC Act, or Section 351 of the PHS Act), or
  - Supporting the investigational use of a drug or biological product
- Recision or modification of qualification determination
  - Based upon new information that alters conclusions that supported qualification determination

21st CC: additional features of the BQP

- *Transparency*
  - Specifies providing information about each submission (stage, date of update, information about submission, formal written determinations, and reviews, etc.)
  - Supports a public, transparent process in DDT development – so that all interested parties know what tools are in development, stage of development, and FDA determinations (as appropriate)
- *Guidances* on DDTs to be issued – that "provides a conceptual framework describing the appropriate standards and scientific approaches to support the development of biomarkers delineated under the taxonomy established…" (within 3 years)
- A "*taxonomy*" of biomarkers to be established, in collaboration with biomedical research consortia and other interested parties through a public process, for use in drug development

Critical path innovation meetings (CPIM)

- A forum for an interactive discussion between FDA and outside organizations (including industry, academic or patient organizations) on specific drug development topics
- Discussion of the science, medicine, and regulatory aspects of innovation in drug development
- Intent is an forum for scientific communication – not to obtain regulatory advice ("non-binding" input)
- Not a meeting about a specific approval pathway
- Wide scope: biomarkers, COAs, natural history studies, technologies (not manufacturing), and clinical trial designs and methods


Critical Path
Innovation Meetings

Guidance for Industry

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

April 2015
Procedural

Office of Translational Sciences
Critical Path
Innovation Meeting

•http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformion/Guidances/UCM417627.pdf

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

- **Susceptibility / risk biomarker**: indicates the individual's potential for *developing* a disease or medical condition
- **Diagnostic biomarker**: used to detect or confirm presence of a disease or condition of interest or to identify individuals with a *subtype* of the disease
- **Prognostic biomarker**: used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest
- **Monitoring biomarker**: measured serially for assessing status of a disease or medical condition or for evidence of *exposure* to (or effect of) a medical product or an environmental agent

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

- **Predictive biomarker**: to identify individuals more likely to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent.

- **Pharmacodynamic/Response biomarker**: to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent. (A1C, LDL-C, BP)

- **Safety biomarker**: measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect. (ALT, eGFR, troponin)