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

BIOMARKERS AND DRUG DEVELOPMENT: REGULATORY PERSPECTIVE

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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 FDA-regulated products

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, digital, 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 information for that specified use. 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)

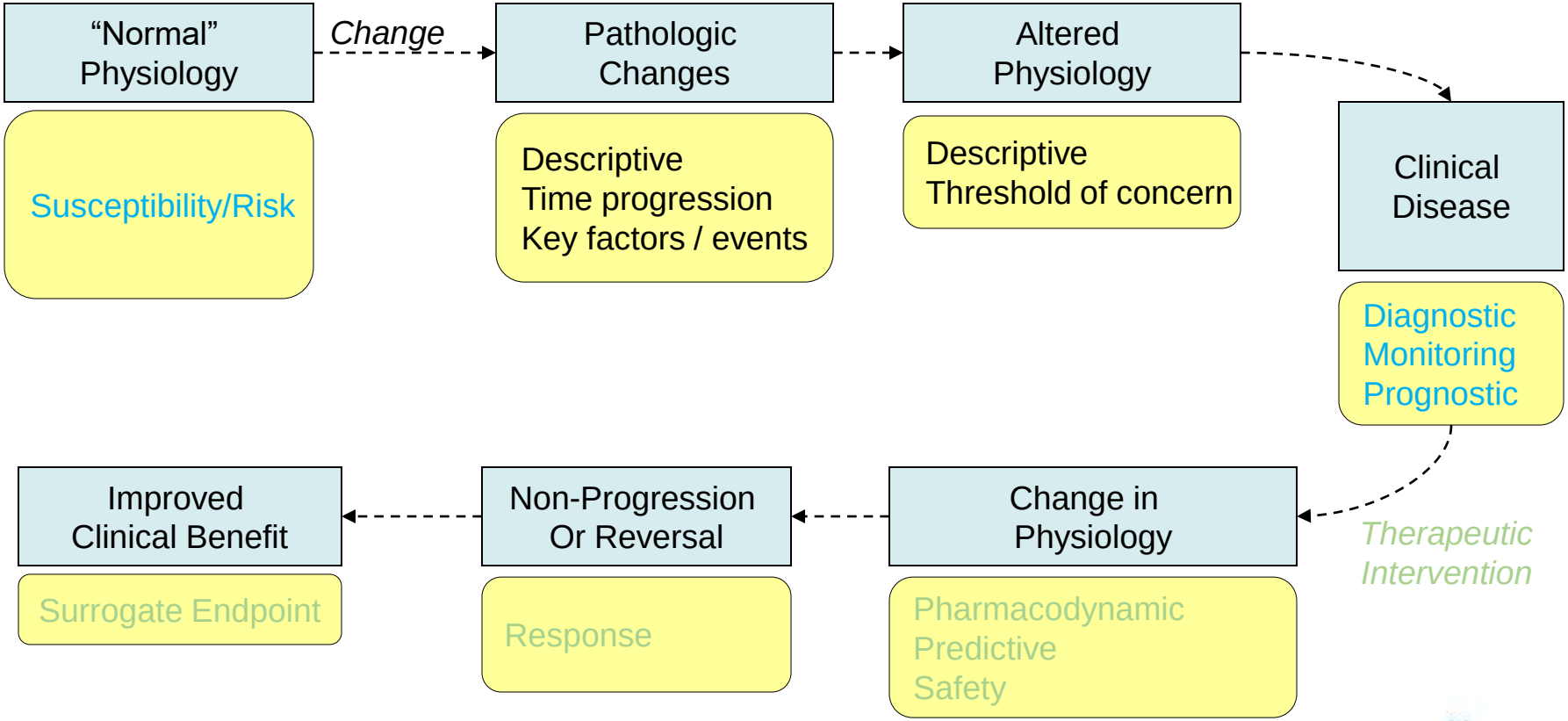
BEST: BIOMARKERS, ENDPOINTS, AND OTHER TOOLS RESOURCE

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

Biomarker Classes from a Drug Perspective

- **Susceptibility/Risk:** Indicates potential for developing disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition
- **Diagnostic:** Detects or confirms the presence of a disease or condition of interest or to identify individuals with a subset of the disease
- **Monitoring:** Assesses status, through serial measurement, of a disease or medical condition including degree or extent of disease
- **Prognostic:** Identifies likelihood of a clinical event, disease recurrence or progression, in patients who have the disease or medical condition of interest in the absence of a therapeutic intervention
- **Predictive:** Identifies patients who are more likely to experience a favorable or unfavorable effect from a specific treatment
- **Pharmacodynamic/Response:** Indicates that a biological response has occurred in a patient who has received a therapeutic intervention. May become clinical trial endpoints and for a very small subset, surrogate endpoints.
- **Safety:** Indicates the likelihood, presence, or extent of toxicity to a therapeutic intervention when measured before or after that intervention

"Fit for Purpose": BEST Biomarker Classes in Perspective -- Match Biomarker to a Drug Development Goal and Data-supported Relationship



CONSIDERATIONS FOR BIOMARKER UTILITY: WHAT IS ITS USE IN DRUG DEVELOPMENT

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

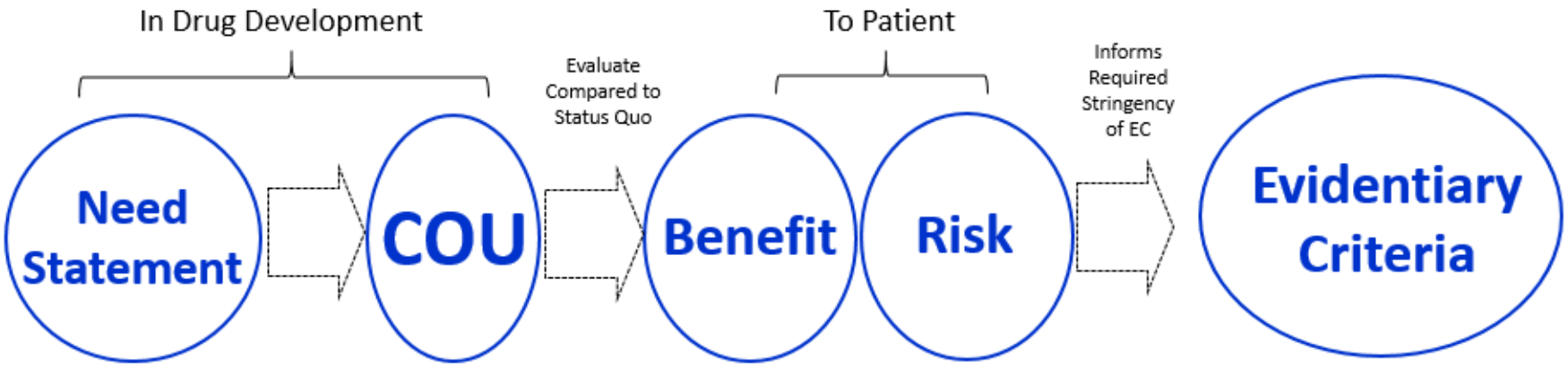
What question is the biomarker intended to address. Examples include:

- Inclusion/exclusion criteria for prognostic, predictive, or diagnostic 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."[1]

[1] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458483.pdf

CONCEPTUAL FRAMEWORK FOR BIOMARKER DEVELOPMENT FOR REGULATORY ACCEPTANCE



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

- *Improved sensitivity*
- *Improved selectivity*
- *Mechanistic context*

- *Consequence of false positive*
- *Consequence of false negative*

- *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*

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

ANALYTICAL ASSAY AND CLINICAL VALIDATION CONSIDERATIONS IN BIOMARKER QUALIFICATION

The Specific Context of Use for a Biomarker Drives the Extent of Evidence Needed for Qualification

Analytical Validation

(establish performance and acceptance characteristics of the biomarker assay)

- Reference Ranges/ Decision Points
- Pre-Analytical and Assay Performance Characteristics
- Analytical Rigor/ Reproducibility
- Sample Handling/ Stability

Clinical Validation

(establish that the biomarker acceptably identifies, measures, or predicts the concept of interest)

- Study Design Acceptability
- Clinical Meaningfulness/ Decision Points
- Benefit/Risk Assessment

21st Century Cures legislation: Section 507 Qualification of Drug Development Tools

- 21st Century Cures and PDUFA VI increasingly places FDA as an *active participant* in drug development, broadening our traditional regulatory role
- Formalizes a three-step submission process
  - Letter of Intent
  - ***Qualification Plan***
  - Full Qualification Package
- A transparent process – so all stakeholders are aware of tools in development, stage, and FDA determinations/recommendations
  - List of Qualified Biomarkers (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535383.htm)
  - Biomarker Qualification Submissions (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535881.htm)
- Requires setting and implementing “reasonable timeframes” for submission review/decision

CONTENT FOCUS FOR SUBMISSION TYPES

- LOI Submission:
  - Successful submissions include a clear drug development need, a COU to address that need, information about the proposed biomarker and summary level information that measurement of the novel DDT is, in fact, possible.
  - Information presented is in summary form (e.g., not a data analysis exercise)
- QP Submission: Project development plan from concept to information to be developed/provided to support the DDT's COU. For biomarkers, to determine clinical utility and clinical validation, important to know that the analytical validation has been completed (or a detailed plan of remaining validation to be done) and information submitted to QP.
  - QP needs to address FDA's comments/recommendations included in the LOI Determination Letter
- FQP Submission: Review of data to support the clinical validation of the DDT for the COU

THREE-TIERED INTERNAL REVIEW

- DDT Program Assessment and Recommendations
  - Work with requestor to clarify DDT, COU, and project proposal
  - Provide tool-specific recommendations based on past and ongoing projects

- Discipline-specific SME Assessment and Recommendations
  - Includes OND division management participation
  - Evaluate based on regulatory precedent, current disease-specific challenges, and level of impact on drug development programs

- CDER DDT Committee Assessment, Recommendations, and Decision
  - Opportunity for broad senior CDER input early and throughout in the process
  - Work towards greater consistency across therapeutic areas and divisions

TABLE OF SURROGATE ENDPOINTS

21st Century Cures Act, Subtitle B—Advancing New Drug Therapies

SEC. 507. QUALIFICATION OF DRUG DEVELOPMENT TOOLS.

"Transparency

"(E) A comprehensive list of—

"(ii) all surrogate endpoints which were the basis of approval or licensure (as applicable) of a drug or biological product (including in accordance with section 506(c)) under section 505 of this Act or section 351 of the Public Health Service Act."

- https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm613636.htm
- 101 adult and 56 pediatric disease/patient population/surrogate endpoint combinations
- 12 surrogate endpoints that may be appropriate for use in drug approval even though no successful drug program as of yet
- More disease/therapeutic areas use surrogates than commonly discussed
- Will be updated every 6 months

IND TYPE C MEETING FOR NOVEL SURROGATE ENDPOINTS

- https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm606684.htm
- PDUFA VI Commitment
- Meeting package due at time of request that includes preliminary human data indicating drug has an impact on the SE at a dose that is “generally tolerable”

- Package content examples include:
  - Rationale for use of surrogate endpoint (SE)
  - Relationship of SE with casual pathway(s)
  - Threshold for change required to demonstrate clinical relevance
  - Consistency of SE response
  - Reliability of quantifying changes in clinical outcome before and after tx
  - Predictive value of therapeutic-induced changes in SE
  - Off-target effects of therapy
  - Reliability of measurement tool to detect SE

THANK YOU FOR YOUR ATTENTION

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