DRUG DEVELOPMENT TOOLS: A REGULATORY PERSPECTIVE

CHRISTOPHER LEPTAK, M.D., PH.D.
DIRECTOR, CDER BIOMARKER QUALIFICATION PROGRAM

DIGITAL HEALTH TECHNOLOGIES IN DRUG DEVELOPMENT
March 24, 2020

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

21st Century Cures Section 3011 DDT Qualification

Per 21 USC §357(e):

"The term '**drug development tool**' includes—

- (A) a biomarker;
- (B) a clinical outcome assessment; and
- (C) any other method, material, or measure that the Secretary determines aids drug development and regulatory review for purposes of this section."

The term '**biomarker**'—

- (A) means a characteristic (such as a physiologic, pathologic, or anatomic characteristic or measurement) that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention; and
- (B) includes a surrogate endpoint.

The term '**clinical outcome assessment**' means—

- (A) a measurement of a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions; and
- (B) includes a patient-reported outcome."

Clarification of a DDT's components

The definition of a DDT is broad. While good for innovation and flexibility, the breadth makes it difficult to provide generalizable advice or approach.

- (C) any other method, material, or measure that the Secretary determines aids drug development and regulatory review for purposes of this section."

Some questions:

- What are the DDT's component parts?
  - The concept of value
  - Measurement of concept
  - Interpretation of concept
- What is new vs what can be repurposed?
  - Existing concept with existing measurement
  - Existing concept with new measurement
  - New concept with existing measurement
  - New concept with new measurement

DRUG DEVELOPMENT TOOL (DDT) INTEGRATION INTO DRUG DEVELOPMENT: Sources of Information to support regulatory use

Drug Approval Process

Scientific Community Consensus

DDT Qualification Programs

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.

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, 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)

BEST: <u>B</u>IOMARKERS, <u>E</u>NDPOINT<u>S</u>, AND OTHER <u>T</u>OOLS 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
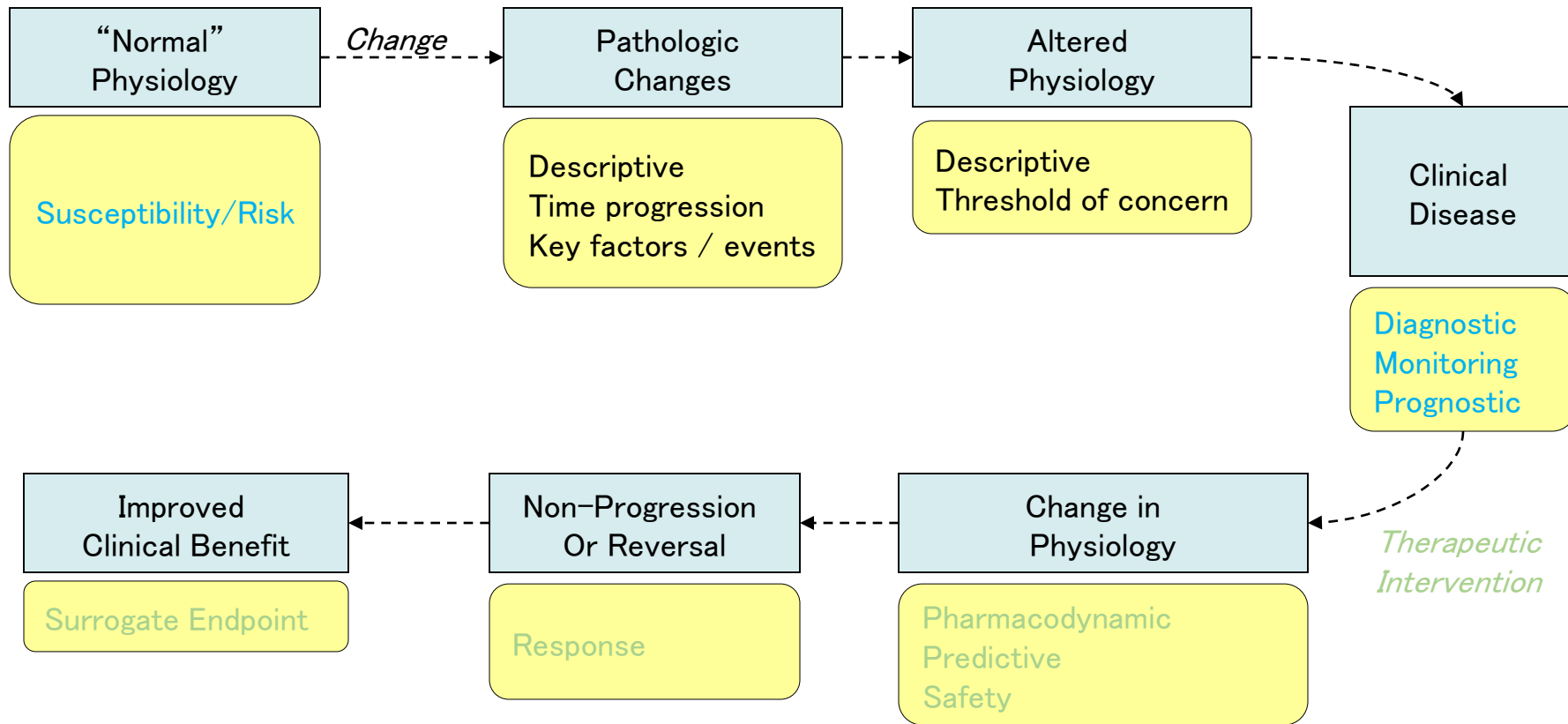
- Publicly available at http://www.ncbi.nlm.nih.gov/books/NBK326791/

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
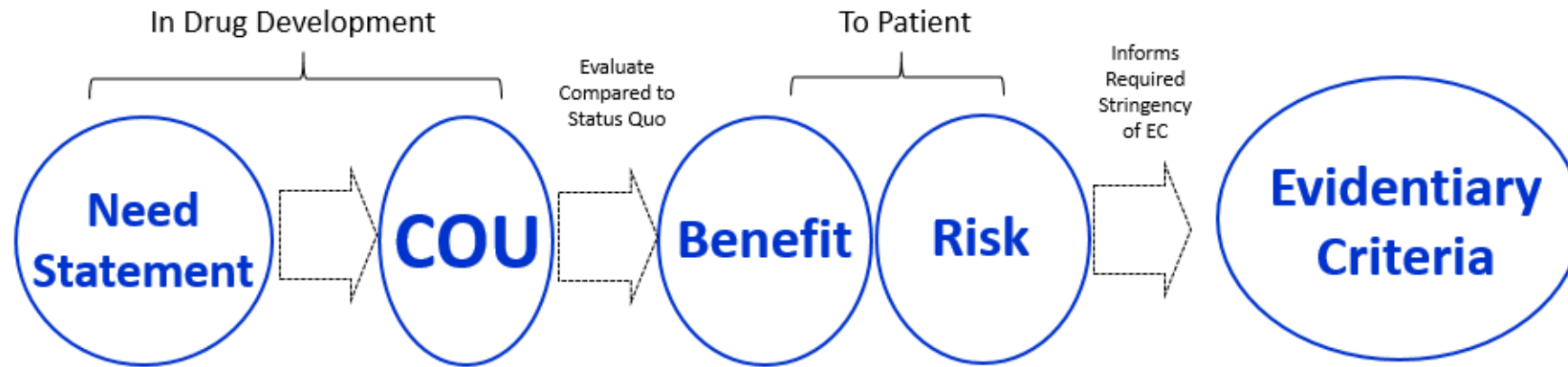
"Normal" Physiology

Susceptibility/Risk

— Change → Pathologic Changes

Descriptive
Time progression
Key factors / events

Altered Physiology

Descriptive
Threshold of concern

Clinical Disease

Diagnostic
Monitoring
Prognostic

Therapeutic Intervention

Change in Physiology

Pharmacodynamic
Predictive
Safety

Non–Progression Or Reversal

Response

Improved Clinical Benefit

Surrogate Endpoint

Components of Drug Development Success

Each of these elements share importance to drug approval

DDT

Method of DDT Measure

Clinical Trial Design

Patient Population
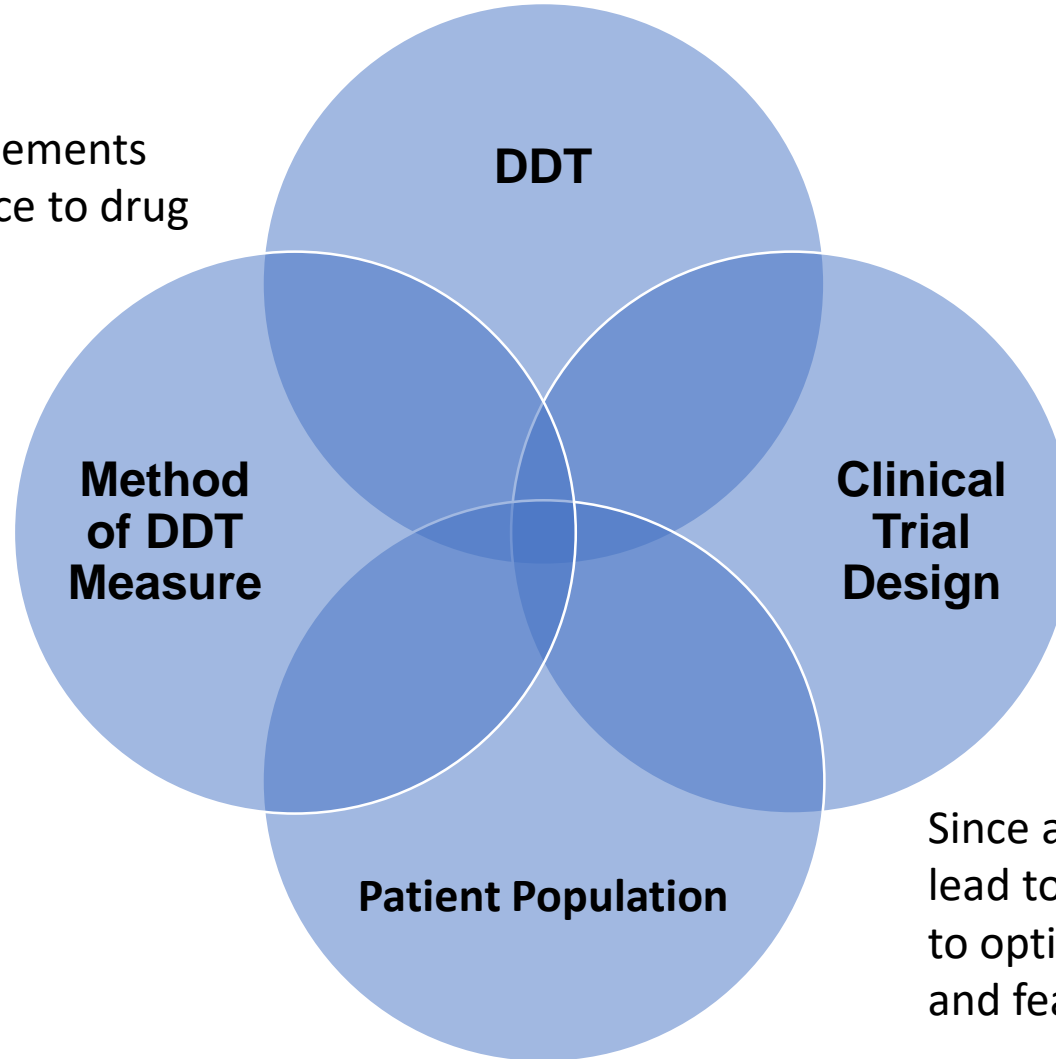
Since any element can lead to failure, important to optimize as appropriate and feasible

Conceptual Framework for Biomarker Development For Regulatory Acceptance

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

www.fda.gov

Drug Development Need

Unmet drug development need that may be addressed by the proposed DDT

When describing the need, a requestor may include discussion of the following:

- The current approach used in drug development for the intended population, highlighting the challenges and limitations of this approach.

- Identify the unmet need, such as the need to apply new technology or knowledge providing measures of disease severity, a lack of treatments for a specific condition for which a new diagnostic tool can aid in patient identification, or the lack of a system for characterizing sub-types of a condition which may exhibit different responses to the same therapy, or identification of toxicity resulting from exposure to an investigational drug.

- Include a description of the nature, severity, and prevalence of the disease or condition or other characteristics of the target population, and any other reasons for the need to be addressed.

- Describe the added value the DDT could provide to the current drug development and regulatory review processes, and address any potential public health benefit.

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."[1]

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. FDA can Accept/Not Accept at each stage:
  - 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

- Requires setting and implementing "reasonable timeframes" for submission review/decision

Content Focus for Submission types

- LOI Submission:

  - Identification of drug development need

  - Information to support that the proposed DDT and its COU would address that need

  - Feasibility assessment of proposal will include information to support that measurement of the novel DDT is, in fact, possible.

- QP Submission:

  - Define DDT development project plan to support the COU

  - Reach agreement on the interpretation and significance of existing information

  - Identify knowledge gaps and align on mitigation plan or additional data to address those gaps

- FQP Submission:

  - Data and analyses to support the DDT's COU

Composite biomarker Considerations

Terminology: Composite, panel, multi-modal, score, etc.

- As a start, list out the individual biomarker components

- The "final" list can evolve but plan accordingly

Strategies:

- Start with a single COU, explore biomarkers/measurement methodologies individually and then build into composite once value has been demonstrated

- Alternatively, again with a single COU, start with composite of most promising candidates and then refine

Measurement Scenarios:

- Each member of the composite is measure with a separate platform (each independently validated). The readouts are then "manually" transformed into a composite

  - Single composite readout/interpretation = cut points (ex. Mild, Moderate, Severe)

  - Group assessment. Still have cut points for "biomarker positivity" but interpretation simplified (ex., if any 2/7 positive, then composite is "positive")

- The individual biomarkers of the composite are measured by a single device

  - Does the device readout individual values (ex. Chem7) or combine (ex. Score)?

  - If score, then the algorithm which generates the score needs to be provided

DDT Qualification Program Resources

Biomarkers:

- 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)

- Table of Surrogate Endpoints
  (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm613636.htm)

COAs:

- List of Qualified COAs

  https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm450689.htm

- COA Qualification Submissions

  https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm625989.htm

Thank you for your attention