REGULATORY GUIDANCE AND EVIDENTIAL CRITERIA FOR DRUG DEVELOPMENT TOOLS

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REMOTE MONITORING FOR MEDICAL PRODUCT DEVELOPMENT
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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
Overview

- Overview of Drug Development Tools (DDTs) including pathways and information sources
- Communicating from a common understanding: BEST resource
- Biomarker framework that may guide novel DDT development
- 21st Century Cures Qualification Process
- Biomarker-related resources
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.”
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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 qualification at CDER and CBER

• **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:**

  - **Clinical Outcome Assessments**
  - **Biomarkers**
  - **Animal Models (Animal Rule)**

*Potential for wide applicability to support drug development programs:*

*Usually in narrow context of use (biological, radiological threats)*
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.
DDT 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 DDT, appropriate scientific support, generally accepted by experts in the field

- **DDT qualification programs**: review and acceptance based upon appropriate submission qualification package; available for use in any development program within approved context of use
**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: 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
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

- **Diagostic**: 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
- **Pathologic Changes**
  - Descriptive Time progression
  - Key factors / events
- **Altered Physiology**
  - Descriptive Threshold of concern
- **Clinical Disease**
- **Improved Clinical Benefit**
  - Surrogate Endpoint
- **Non-Progression Or Reversal**
  - Response
- **Change in Physiology**
  - Pharmacodynamic
  - Predictive
  - Safety
- **Diagnostic Monitoring Prognostic**
- **Therapeutic Intervention**
Components of Drug Development Success

Each of these elements share importance to drug approval.

Since any element can lead to failure, important to optimize as appropriate and feasible.
Some Enablers for DDT Development

- Data standards (e.g., CDISC efforts)
- Data quality
- Data reproducibility
- Data sharing
- Assay/imaging pre-analytic standardization
- Assay/imaging protocols/SOPs
- Evaluating impact on clinical trial elements (e.g., choice of cut-point on number of patients screened vs enrolled)
Conceptual Framework for Biomarker Development For Regulatory Acceptance

In Drug Development

- Need Statement
  - Class of Biomarker
  - What is the question the biomarker is addressing.

- COU
  - Evaluate Compared to Status Quo

To Patient

- Benefit
  - Improved sensitivity
  - Improved selectivity
  - Mechanistic context

- Risk
  - Consequence of false positive
  - Consequence of false negative

Evidentiary Criteria

- 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

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.”

DDT Qualification: Value proposition

- Since DDT is developed independent from a specific drug program, opportunity for non-drug developers (academics, patient advocates, non-drug industries, other government organizations) to participate in DDT development through direct engagement with FDA.
- Opportunity for sharing resources, expertise, and data through consortia-led DDT development efforts that can include drug developers and/or others listed above.
- Qualification can advance scientific understanding in a non-competitive business environment that all stakeholder groups can then use and benefit from.
- DDTs may enable faster completion of studies at a lower cost and with fewer patients.
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
Acceptance decision for each submission (LOI, QP, FQP) based upon scientific merit:

- Does the proposal address an impactful drug development need?
- Is there enough information to suggest a likelihood of success?
- What is the feasibility of the proposed analytical biomarker measurement approach?

Prioritization of review of submissions 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)
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
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
### 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.”

- 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

- 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
DDT Qualification Program Resources

Biomarkers:

• List of Qualified Biomarkers

• Biomarker Qualification Submissions

• Table of Surrogate Endpoints

COAs:

• List of Qualified COAs

• COA Qualification Submissions
Thank you for your attention