BIOMARKERS AND DRUG DEVELOPMENT: A 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
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

- **Drug programs**: 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.
**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)
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
- Improved sensitivity
- Improved selectivity
- Mechanistic context

Benefit
- Consequence of false positive
- Consequence of false negative

To Patient

Risk

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

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
21st CC: Acceptance of Biomarker Project into Qualification

- 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”
Biomarker qualification program (BQP) updates

- Program moved to OND for alignment with biomarkers developed under IND
- Legacy projects fully transitioned to 507 process
- Coordination with CBER for inter-Center consistency
- Continued collaboration with EMA for alignment on process and approach
- LOI, QP, and FQP submission content outlines now developed and posted
- In planning
  - New IT platform (submission portal, document knowledge management, business tools)
  - Guidances for DDT qualification process, BQ evidentiary framework, surrogate endpoints, and BQ analytical validation
- Public posting of information for transparency
Biomarker qualification program updates

BQP project overview metrics (Aug 2017 – April 2019)

- 19 LOI submissions
- 6 Legacy project transition summaries
- 3 QP submissions
- 2 new qualification determinations
  - Clinical nephrotoxicity safety panel to aid in dose escalation studies
  - Monitoring biomarker for treatment initiation in malaria challenge model clinical trials
- 5 Letters of Support issued
### 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