Drug Development Tools (DDTs)
Regulatory Perspective

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Disclaimer

- 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

Central Message

- Need for high quality DDTs to support successful drug development
  - Broad stakeholder engagement between regulators, academics and industry
  - Battery of tools for different level of concerns e.g. biochemical, physiological, morphological aspects of drug effects and respective safety and effectiveness
  - Develop critical mass of evidence to assure the DDT regulatory fitness for use

DDT Integration into Drug Development

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.

Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration; Published June 016, Duke-Margolis Center for Health Policy

DDTs Development Pathways

- **Drug-specific (IND)**: 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 program**: review and acceptance based upon appropriate submission qualification package; available for use in any development program within approved context of use

DDT, COU, and Qualification

- A **DDT** can be method, material, or measurement that can aid in drug development and regulatory review
- A DDT's **COU** describes the circumstances under which the DDT is to be used in drug development and regulatory review
- **Qualification** is a determination that a DDT and its COU can be relied upon to have a specific interpretation and application in drug development and regulatory review

Considerations for Biomarker Utility – Regulatory Fitness

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?

Analytical Assay and Clinical Validation Considerations

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)

Clinical Validation

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

- There will be different level of evidence and validation needed for DDT qualification depending on the specific COU, tool/technology novelty and complexity, currently available scientific knowledge and respective regulatory review experience.
- Example: Cardiac Troponins qualification was based on the literature review (magnitude of evidence) and reverse translation as the cardiac troponins are already accepted and used in both human and veterinary medicine as the preferred standard for detecting the presence and extent of myocardial necrosis and injury.

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-stage submission process. All stages must be completed; no skipping stages but FDA may add additional ones:
    - Letter of Intent (LOI)
    - Qualification Plan (QP)
    - Full Qualification Package (FQP)

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.

Content Focus for Submission Types

- 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

Note: For information on the content for these submissions, please contact the specific qualification program for examples and content outlines.

Content Focus for Submission Types

- 21CC specifically stated biomarkers and Clinical Outcome Once qualified, a DDT may be used within the qualified Context of Use (COU) as part of specific drug programs (IND/NDA/BLA) without need to resubmit information or FDA re-review
- A tool does not need to be qualified under the Section 507 to be used as part of an IND/NDA/BLA program

Note: Qualification is a voluntary process and FDA does not have a preference for one DDT development pathway over another

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

FDA DDTs Website

Three-step internal FDA review of DDT Submissions

- 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

Three-step internal FDA review of DDT Submissions

- 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

Note: Determination of "reviewability" and review clock dependent upon above

Transparency Provisions

Under 21CC, DDT qualification becomes a transparent public process:

- All interested parties know what tools are in development, stage of development, and FDA determinations including rationale
- Information about the submission and FDA's determination including recommendations will be posted on DDT website
- For legacy projects, we plan to post only new information after transition (e.g., we will not make public information prior to legislation enactment or to agreement to transition to 507)
- De facto Letter of Support (LOS) as part of DDT engagement

What information is publicly posted?

- Posted information includes:
  - Requestor (DDT developer) name and contact
  - DDT type (biomarker, COA, animal model), name and description
  - Proposed COU
  - Information about the requestor's submission (content outlines clearly indicate what information will be posted)
  - FDA's posted information
    - LOI and QP: FDA Decision Letter (Accepting or Not Accepting the submission), including recommendations for further DDT development
    - FQP: FDA Qualification Determination Letter, including reviews, final DDT, COU, any additional recommendations or considerations

Critical Path Innovation Meeting

- Discussion of the science, medicine, and regulatory aspects of innovation in drug development
- Non-binding meeting
- Not a meeting about a specific approval pathway
- Scope includes early biomarkers and clinical outcome assessments, 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

DDT Qualification Program Resources

- Biomarkers
  - List of Qualified Biomarkers
  - Biomarker Qualification Submissions
  - Table of Surrogate Endpoints

- COAs
  - List of Qualified COAs
  - COA Qualification Submissions