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Biomarker as a drug development tool (DDT) and biomarker qualification at CDER, FDA

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The views expressed are those of the author, and do not necessarily represent an official FDA position

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Overview

- Introduction
- Biomarkers in drug development
- Drug Development Tool Qualification at CDER, FDA
- **Biomarker Qualification**
- Other paths for integration of biomarkers in drug development
- Take Home Points

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Critical Path Initiative at FDA

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FDA Innovates….

2004

2006

2011

- Better Evaluation Tools
- Streamlining Clinical Trials
- **Use of Biomarkers in drug development**
- VXDS (Voluntary eXploratory Data Submission) Program
- Building Infrastructure to Drive and Support Personalized Medicine
- **Expedited Drug Development Pathway -Drug development tools**

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Biomarkers

- **A definition:** Biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or biological responses to a therapeutic intervention"

  BIOMARKERS DEFINITIONS WORKING GROUP: BIOMARKERS AND SURROGATE ENDPOINTS: PREFERRED DEFINITIONS AND CONCEPTUAL FRAMEWORK. CLIN PHARMACOL THER 2001;69:89-95.

- Needs to be an "objectively" existing characteristic since a "six minute walk" is not a biomarker, but is a COA
- **Application of Biomarkers**:
  - Diagnosis and Clinical Practice
  - **Drug (therapeutic-Drug/Biologic) Development**

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Biomarkers in drug development

- **Disease heterogeneity and molecular pathways underpinning disease**
- **Preclinical studies**
  - Safety assessment
  - Drug disposition
  - Mechanism of action
- **Clinical trials**
  - Safety assessment
  - Dose selection
  - Clinical trial design
    - Stratification
    - Patient selection/enrichment
    - Co-development of a test and drug/biologic (companion diagnostic)
  - Surrogate end Point

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Drug Development Tools (DDT) Qualification at CDER, FDA

DDTs are methods, materials, or measures that aid drug development

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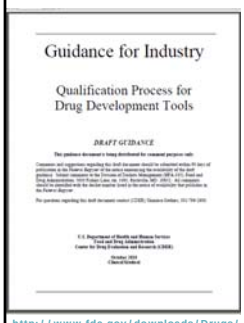
DDT Qualification at CDER, FDA


Guidance for Industry

Qualification Process for Drug Development Tools

DRAFT GUIDANCE


U.S. Food and Drug Administration

Drugs

Drug Development Tools (DDT) Qualification Programs

Resources for You

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/default.htm

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Definition of Biomarker Qualification (BQ)

Biomarker Qualification is a conclusion that within the stated context of use, the results of assessment with a biomarker can be relied upon to have a specific interpretation and application in drug development and regulatory review.

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm

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Context of Use (COU)

- "Context of use" is a comprehensive statement that fully and clearly describes the manner (*how*) and purpose (*why*) of use for the biomarker.
- The context of use statement describes the circumstances under which the biomarker is qualified.
- The qualified context of use defines the boundaries for the use of the biomarker in drug development

Qualification of the DDT is driven by the COU since the COU determines the type of data needed

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284620.htm

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Important Considerations

- Identify promising biomarkers to qualify
- Availability of a reliable method to measure the biomarker (preferably analytically validated at this stage)
- Context of Use of the biomarker- Can the biomarker(s) be helpful in drug development programs? How?
- Collect available data, evaluate gaps of knowledge
- Usefulness of available data for qualification
- If using available data, which studies to select and why
- Additional studies needed? Plan studies- consult FDA
- Prospective statistical analysis plan
- Testing/confirmatory data sets

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BQ Qualification Process

- **Initiation Stage**
  - Letter of Intent (LOI) received and reviewed, go/no go decision made by BQ Program
  - Submission-specific Biomarker Qualification Review team (BQRT) formed
  - LOI Reviewed, internal meeting
  - Specifications for briefing document, advice, comments
  - Clearance of the specifications document and sent to submitter
- **Consultation and Advice Stage**
  - Submitter sent initial briefing package reviewed and internal meeting commences
  - Pre-meeting comments finalized and sent to submitter
  - F2F meeting and meeting minutes sent

  Iterative process (as needed)
- **Review of the final submission package**

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List of FDA-Qualified Biomarkers

Qualified DDT:

DDT Type	Name	Submitter	Qualification Date	Link to Supporting Information
Biomarker	Seven Biomarkers of Drug-Induced Nephrotoxicity in Rats	Predictive Safety and Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)	4/14/2008	Predictive Safety Testing Consortium (PDF - 163KB)
Biomarker	Nonclinical Qualification of Urinary Biomarkers of Nephrotoxicity	International Life Sciences Institute (ILSI)/ Health and Environmental Sciences Institute (HESI), Nephrotoxicity Working Group	9/22/2010	HESI Nephrotoxicity Qualification (PDF - 234KB)
Biomarker	Nonclinical Qualification of Circulating Cardiac Troponins T and I as Biomarkers of Cardiac Morphologic Damage	PJ O'Brien, WJ Reagan, MJ York and MC Jacobsen	2/23/2012	Biomarker Qualification Decision (PDF - 144KB)

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm

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Biomarker Qualification at FDA

- **Submitter** can be a person, a group, organization (including the federal government) or consortium that takes responsibility for and initiates a BQ proposal using the procedures described in the DDT guidance
- **No fees** for submissions to the BQ program
- Once qualified for a specific **context of use**, a biomarker can be used by drug developers for other applications without re-review
- **Incremental expansion** of the qualified context of use over time may be undertaken
- Biomarkers considered for qualification are conceptually **independent of the specific test or device** performing the measurement
- Biomarker qualification is a tool for drug development, and **not for approval/clearance of diagnostics or for companion diagnostics for use in clinical practice**

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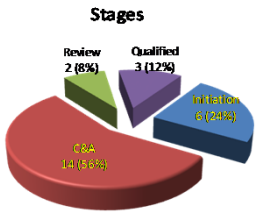
BQ Submissions Overview



14 Briefing Packages Received and Face to Face meetings after the packages are reviewed

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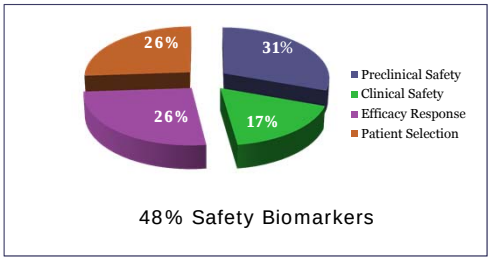
Categories of BQ Submissions



48% Safety Biomarkers

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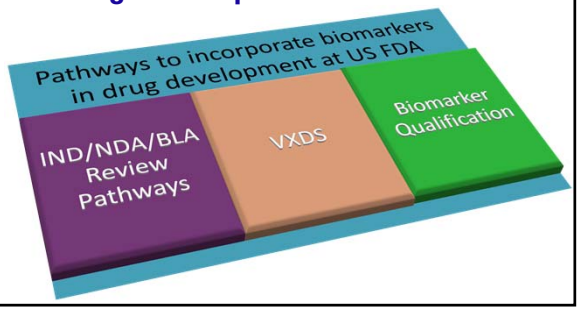
Regulatory Interaction Pathways to facilitate integration of biomarkers in drug development



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Take Home Points

- **Biomarker Qualification is not a requirement**
  - Case by case approach remains valuable
  - Currently well-established, widely used biomarkers do not require formal Qualification
- **Biomarker Qualification is intended for biomarkers that will be used in multiple drug development programs**
  - Consortia or collaborative groups likely to be source of biomarkers for qualification
- Biomarker Qualification is a **voluntary process** and **no definitive time clocks** are associated with the process

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Questions?

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For BQ Program/Process questions
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Back-Up Slides

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Clinical Outcome Assessment (COA) Qualification Program

- A clinical outcome assessment (COA) directly or indirectly measures how patients feel or function and can be used to determine whether or not a drug has been demonstrated to provide a treatment benefit
- COAs can also measure a safety benefit (e.g., fewer side effects) compared to other treatments
- COAs
  - Patient-reported outcome (PRO) assessment
  - Observer reported outcome (ObsRO) assessment
  - Clinician-reported outcome (ClinRO) assessment
  - Performance measures (e.g., six minute walk)

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Animal Model Qualification (AMQ) Program

- The AMQ program is jointly supported by both CDER and CBER
- The initial animal model to be qualified should demonstrate the natural history of the disease/condition caused by the threat agent and will therefore have a narrow context of use

  The context of use may be limited to the conclusions that the challenge agent induces a disease/condition in animals that is analogous to the human disease/condition, and that the human disease/condition and animal disease/condition share the same, or very similar, pathogenic mechanisms
- Qualification Steps for Animal Models
  - Natural history studies
  - Progression to efficacy studies

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Integration of biomarkers: Acceptance of Biomarkers in the Drug Development Process (IND/NDA/BLA)

- Drug Review Submissions within a specific IND/NDA/BLA/Labeling Update:
  - Exploratory studies
  - Stratification
  - Patient selection/enrichment
  - Co-development of therapeutic and test
  - Companion Diagnostics- Policy Guidance
- Advantages:
  - The biomarker becomes accepted in the context of the drug, through the drug review process
- Limitations:
  - Will be useful in the context of the approved drug alone, generally
  - Need to discuss the biomarker use in every new regulatory submission with the relevant review division

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Voluntary eXploratory Data Submission (VXDS) Program

- Established in 2004 as VGDS and expanded to VXDS in 2006- ongoing
- To stimulate the use of exploratory biomarkers in drug development
- Scientific exchange without regulatory impact
- More than 50 VXDSs have been received since 2004
- Led to increasing numbers of regulatory submissions with novel biomarker data
- Helped development of policy at the FDA

Submission types
- "-omics"
- Pharmacogenomics
- Proteomics
- Metabolomics

Therapeutic areas
- Alzheimer's Disease
- Cancer
- Cardiovascular diseases
- Depression
- Diabetes
- HIV
- Obesity
- Rheumatoid Arthritis
- Sepsis
- Systemic Lupus Erythematosus

Issues Discussed
- Clinical / analytical
  - Clinical trial design / statistical issues
  - Genetic association to adverse events
  - Genetic variants and response to drugs
  - Use of biomarkers in stratification
  - Impact on labels
- Preclinical
  - Toxicology markers
  - Renal toxicity
  - Vascular toxicity
  - Hepatotoxicity

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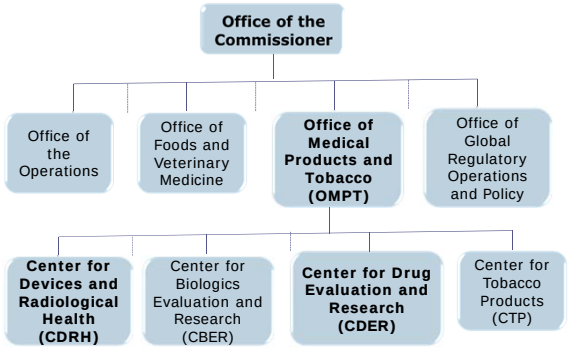
Food and Drug Administration (FDA)



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Challenges / Opportunities in Drug Development

- **Disease heterogeneity**
- **Target selection**
  – Incomplete understanding of the molecular mechanisms underpinning disease
- **Efficacy**
  – Varies from 25% to 80% depending on the therapeutic area*
  – Dosing
  – Inter-individual variability
- **Safety**
  – Inter-individual variability
  – Toxicity (dose)
  – Idiosyncratic serious adverse events in a small group of patients

*Spear et al., (2001)TRENDS in Molecular Medicine 7:201-4