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

Overview

• Drug Development Tools at CDER, FDA
• Qualification definition and “Context of Use”
• Biomarker Qualification Program
• Imaging Biomarker Considerations
• Take home points
Drug Development Tool (DDT) Qualification Program at CDER

FDA’s Efforts to Improve Drug Development

- **2004**: “Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products” that identified scientific challenges underlying the medical product pipeline problem

- **2006**: “Critical Path Opportunities Report” identifies leading areas for scientific improvement in the drug development process

- **2010**: “Advancing Regulatory Science for Public Health”


DDT guidance

Guidance for Industry
Qualification Process for Drug Development Tools

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only. Comments and suggestions regarding this draft guidance should be submitted within 60 days of publication in the Federal Register. The agency will consider the comments received in the draft guidance.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 30, 2013

Drug Development Tools Qualification
Information on the DDT Website

Drug Development Tools (DDT) Qualification Programs

Introduction

The DDT Qualification Program is an integral part of the CDER development process. DDT Qualification Programs are intended to provide a framework for developing and evaluating the quality of tools for use in drug development. The DDT Qualification Program is intended to ensure that CDER has access to high-quality tools for use in regulatory decisions.

Resources for You

- DDT Frequently Asked Questions (FAQ)
- DDT Glossary
- DDT Contact and Submission Information

Drug Development Tool (DDT) Program at CDER- I

• **DDTs**: DDTs are methods, materials, or measures that aid drug development

• **DDT Qualification**: a conclusion that within the stated context of use, the results of assessment with a DDT can be relied upon to have a specific interpretation and application in drug development and regulatory decision-making

• **Qualification versus Validation**

Context of Use (CoU)

• “Context of use” is a comprehensive statement that fully and clearly describes the manner and purpose of use for the DDT

• The context of use statement would describe all important criteria regarding the circumstances under which the DDT is qualified

• The qualified context of use defines the boundaries within which the available data adequately justify use of the DDT

The CoU determines what kind of data are needed

Drug Development Tool (DDT) Program at CDER- II

• The Drug Development Tools (DDTs) Qualification Program was created by CDER as part of the FDA’s Critical Path Initiative (CPI) to provide a framework for development and regulatory acceptance of scientific tools for use in drug development programs

• Three DDT qualification programs are currently available:
  • Biomarker
  • Clinical Outcome Assessment
  • Animal models for use under the Animal Rule

Biomarker Qualification at CDER-I

• 2007: BQ Pilot Process initiated (PSTC-nephrotoxicity biomarkers)

• 2009: BQ Program within CDER introduced


Definition of Biomarker Qualification:
A conclusion that within a carefully and specifically stated “context of use” the biomarker has been demonstrated to reliably support a specified manner of interpretation and application in drug development

Contact: marianne.noone@fda.hhs.gov
Biomarker Qualification at CDER-II

- **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 DDT (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 performing the measurement

Bridging the Gap

**Exploratory Biomarkers**

**Regulatory Application of Biomarkers**

**Prior to Biomarker Qualification Effort:**
- Preliminary biomarker data and confidence in the usefulness of the biomarker in drug development
- A reliable method to measure the biomarker available (preferably analytically validated at this stage)
- How the biomarker(s) can be helpful in multiple drug development programs?
  - Considering aspects of the Context of Use
  - Gaps of knowledge
  - Additional studies needed
BQ Qualification Process

- **Initiation Stage (2 – 4 Months)**
  - Letter of Intent (LOI) received and reviewed, go/no go decision made by BQ Program
  - 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 (3 months to unknown—depends on time needed for completion of Biomarker development)**
  - 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 (TBD)**

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List of FDA-Qualified Biomarkers

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

BQ Submissions Overview

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

Categories of BQ Submissions

53% Safety Biomarkers
Imaging Biomarkers

• Currently, 6/16 BQ submissions are on imaging biomarkers

• The goals include confirming the diagnosis, aiding in patient selection or in monitoring therapy response

• General considerations for imaging biomarkers:
  • Technical performance (including)
    • What to measure, how to measure, Image acquisition, platform,
    • Reconstruction of image, QA/QC,
    • Reproducibility, changes in hardware/software
  • Technical limits of performance (including)
    • Setting a threshold or cut-off range or value
    • Impact of covariates/other factors
  • Collecting available data
  • If using available data, which studies to select and why
  • Statistical analysis plan
  • Testing/confirmatory data sets

Qualification’s Place in Therapeutic Development

• Qualification is not required
  • Case by case approach remains valuable
  • Currently well-established, widely used biomarkers do not require formal Qualification

• 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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