FDA’s Biomarker Qualification Program

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Washington DC
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1. Introduction

2. Biomarker Qualification

3. Efforts to Support Biomarker Qualification

4. Take Home Points
Biomarkers

Definition: A 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”

Biomarker Types

- **Diagnostic Biomarkers**
  - Identify patients with a particular disease or a disease subset

- **Prognostic biomarkers**
  - Indicate future clinical course with respect to a specified clinical outcome, in the absence of therapeutic intervention

- **Predictive biomarkers**
  - Identify patients likely to respond (favorably or unfavorably) to a specific treatment
**Biomarker Types**

- **Response biomarkers**
  - Indicate that biological response has occurred in a patient after having received a therapeutic intervention

  - *Pharmacodynamic biomarkers*
    - Indicators of intended activity of the therapeutic
    - Not necessarily strong predictors of efficacy

  - *Efficacy-response biomarkers*
    - Predict specific disease-related clinical outcome
    - Could serve as primary clinical endpoints or surrogates for a clinical end point

- *Safety-related response biomarkers*
  - Indicators of potential adverse drug reactions
  - Likely to be specific for a type of drug toxicity, usually organ specific
Biomarkers in Drug Development

- Molecular pathways underpinning disease
- Mechanism of action of therapeutics
- Preclinical safety assessment
- Clinical trials
  - Safety Assessment
  - Dose selection
  - Stratification
  - Patient selection/enrichment
  - Surrogate end Point
- Companion Diagnostic
  - Selection of right patients for increased efficacy/safety
Pathways to facilitate integration of biomarkers in drug development
**Objective:** Use the biomarker in a single drug development program

Acceptance through IND, NDA and BLA submissions (Drug approval process)

- **Responsible Parties:** One sponsor contacts the review division
- **Process:** Discuss, provide rationale and data to the review division
- **Risk and resource:** burden on one sponsor
- **Biomarker Information:** Embedded in drug labels

**Objective:** Establish the biomarker for use in multiple development programs

**Biomarker Qualification**

- **Responsible Parties:** Generally, consortia contact the BQ Program
- **Process:** Submit letter of intent. Follow the BQ process
- **Risk and resources:** shared among consortia members
- **Biomarker Information:** qualified biomarkers announced as draft guidance

*Amur et al, Clin. Pharm. Ther. 98 (1) 34-46, 2015*
Biomarker Qualification (BQ)

Definition:
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.

Context of use:
“Context of use” is a comprehensive statement that fully and clearly describes the manner and purpose of use for the biomarker in drug development.

- **Use Statement:**
  Name, identity and purpose of use of the biomarker in drug development

- **Conditions for qualified use:**
  Comprehensive description of conditions and boundaries for the biomarker to be used
Biomarker Qualification Concept

Context of Use

Level of Evidence

Qualification
Considerations for Biomarker Qualification

• **Type and COU of the biomarker** for use in drug development

• **Biological rationale** for use of the biomarker (if available)

• Characterizations of the various **relationships** among the biomarker, the clinical outcomes, and the treatment (where applicable) required for the proposed COU.

• **Assay considerations** (analytically validated method and understanding of potential sources of variability in the measurement).

• **Type of data available** to assess the strength of association of the biomarker with its proposed clinical outcome: retrospective or prospective, registry data, and/or randomized controlled trial (RCT) data.

• **Reproducibility of data** (need for test dataset and confirmatory dataset).

• Use of appropriate, **pre-specified statistical methods** to demonstrate the hypothesized relationships for the COU.

• **Strength of evidence**: the level of evidence depends on the type of biomarker and its COU.
Biomarker Qualification Process

Initiation

- Letter of Intent (LOI) received, Biomarker Qualification Review Team (BQRT) formed, internal meeting, decision to proceed, send briefing document specifications to submitter.

Consultation and Advice Stage

- Biomarker Qualification Review Team (BQRT), is comprised of representatives from the appropriate review division, biostatistics, and others based on expertise needed to evaluate the submissions.

- Briefing document received, reviewed, internal meeting, pre-meeting comments, face-to-face Meeting Iterative process.

Review

- Full Qualification Package received, reviewed by BQRT, internal meetings, request additional information (if needed), qualification recommendations.

CDER Qualification Recommendation is issued as a draft guidance in federal register and posted on the FDA Guidance Web Page.

Public comments are received and the draft guidance revised, as needed and final guidance issued.
List of FDA-Qualified Biomarkers

<table>
<thead>
<tr>
<th>General Area</th>
<th>Submitter</th>
<th>Biomarker(s) Qualified for Specific Contexts of Use</th>
<th>Issuance Date with Link to Specific Guidance</th>
<th>Supporting Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonclinical</td>
<td>International Life Sciences Institute (ILSI)/Health and Environmental Sciences Institute (HESI), Nephrotoxicity Working Group</td>
<td>Urinary biomarkers: Clusterin, Renal Papillary Antigen (RPA-1)</td>
<td>9/22/2010 Drug-induced Nephrotoxicity Biomarkers</td>
<td>Reviews</td>
</tr>
<tr>
<td>Nonclinical</td>
<td>P J O’Brien, W J Reagan, M J York and M C Jacobsen</td>
<td>Serum/plasma biomarkers: Cardiac troponins T (cTnT) and I (cTnl)</td>
<td>2/23/2012 Drug-induced Cardiotoxicity Biomarkers</td>
<td>Reviews</td>
</tr>
<tr>
<td>Clinical</td>
<td>Mycoses Study Group</td>
<td>Serum/bronchoalveolar lavage fluid biomarker: Galactomannan</td>
<td>10/24/2014 Patient selection biomarker for enrollment in Invasive Aspergillosis (IA) clinical trials</td>
<td>Reviews</td>
</tr>
<tr>
<td>Clinical</td>
<td>Chronic Obstructive Pulmonary Disease (COPD) Biomarker Qualification Consortium (CBQC)</td>
<td>Plasma biomarker: Fibrinogen</td>
<td>7/6/2015 Prognostic biomarker for enrichment of clinical trials in Chronic Obstructive Pulmonary Disease (COPD)</td>
<td>Reviews</td>
</tr>
</tbody>
</table>

What types of submissions are we seeing for Biomarker Qualification?

N = 22

- Preclinical Safety: 32%
- Activity Response: 18%
- Patient Selection: 27%
- Clinical Safety: 18%
- Patient Compliance: 5%
Where are The Submissions in the BQ Process?

Drug Development Tool (DDT) Qualification Projects at CDER, FDA

This Table provides the current number of active CDER Drug Development Tool (DDT) Qualification projects overall and by program. Numbers are also provided by stage. Refer to DDT Contacts and Submitting Procedures for contact information for each DDT Program.

<table>
<thead>
<tr>
<th>August, 2015 Update</th>
<th>All Drug Development Tool (DDT) Qualification Programs</th>
<th>DDT - Animal Model Qualification Program</th>
<th>DDT - Biomarker Qualification Program</th>
<th>DDT - Clinical Outcome Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Active Projects</td>
<td>91</td>
<td>8</td>
<td>22</td>
<td>61</td>
</tr>
<tr>
<td>Number in Initiation Stage</td>
<td>30</td>
<td>5</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Number in Consultation and Advice Stage</td>
<td>55</td>
<td>3</td>
<td>18</td>
<td>34</td>
</tr>
<tr>
<td>Number in Review Stage</td>
<td>5</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Number Qualified</td>
<td>7</td>
<td>0</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>
16/24 submitters agreed to add their Submission information to the FDA webpage.

<table>
<thead>
<tr>
<th>Submitter</th>
<th>Biomarker</th>
<th>Date Accepted into BQ Program</th>
<th>Type of Biomarker</th>
<th>Proposed Biomarker Utility</th>
<th>Qualification Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Life Sciences Institute (ILSI) / Health and Environmental Sciences Institute (HESI)</td>
<td>Genomic Biomarker Approach for Positive Findings in the In Vitro Chromosome Damage Assays in Mammalian Cells</td>
<td>3/11/2010</td>
<td>Safety</td>
<td>Pre-Clinical Safety</td>
<td>Consultation and Advice</td>
</tr>
<tr>
<td>C-Path/ Coalition Against Major Diseases (CAMD)</td>
<td>Cerebral Spinal Fluid (CSF) Markers in Alzheimer’s Disease</td>
<td>1/25/2011</td>
<td>Prognostic</td>
<td>Patient Selection</td>
<td>Consultation and Advice</td>
</tr>
<tr>
<td>C-Path/ CAMD</td>
<td>Baseline Hippocampal Volume Measured by MRI in Alzheimer’s Disease</td>
<td>1/25/2011</td>
<td>Prognostic</td>
<td>Patient Selection</td>
<td>Consultation and Advice</td>
</tr>
<tr>
<td>C-Path PSTC Nephrotoxicity Working Group (NWG)</td>
<td>Drug-Induced Non-Clinical Kidney Injury Biomarkers</td>
<td>1/26/2011</td>
<td>Safety</td>
<td>Safety Assessment</td>
<td>Consultation and Advice</td>
</tr>
<tr>
<td>C-Path PSTC NWG/ Foundation for the National Institutes of Health (FNIH)</td>
<td>Drug-Induced Clinical Kidney Injury Biomarkers</td>
<td>2/24/2011</td>
<td>Safety</td>
<td>Safety Assessment</td>
<td>Review</td>
</tr>
</tbody>
</table>
Biomarker Qualification Process - Timeline

- **Initiation**
  - LOI Consideration: 2-4 months

- **Consultation & Advice**
  - Briefing Document Evaluation: 2-4 months per iteration
  - Full Qualification Package Evaluation: 9-12 months

- **Review**
  - Drafting the Biomarker Guidance: 2-4 months
  - Clearance of guidance and FR notice: 2-4 months

- **Clearance and Publication of Guidance and FR Notice**

- **Public Comment and Finalization of Miniguidance**
  - ~4 months

**Average time for biomarker qualification process (Expanded Context of Use): 2 – 3 Years**
In Preparation for Biomarker Qualification

- Identify promising biomarkers potentially useful in drug development
- Availability of a reliable method to measure the biomarker (preferably analytically validated at this stage)
- Context of Use of the biomarker - How (manner and purpose of use) can the biomarker(s) be used in drug development programs?
- Collect available data, evaluate gaps in the knowledge
- Usefulness of available data for qualification (retrospective data acceptable); which studies to select and why
- Additional studies needed? Plan studies - consult FDA early
- Consider resources needed
- Consider Design principles, data standardization, and data sharing needed
- Prospective statistical analysis plan
- Testing/confirmatory data sets
Guidance for Industry
Use of Histology in Biomarker Qualification Studies

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit comments to the Division of Device Management (HFA-395), Food and Drug Administration, 555 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact (CDER) Elizabeth Hanes 301-796-1044.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
January 2014
Procedural

Guidance for Industry
Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

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For questions regarding this draft document contact (CDER) Robert Twigg, 301-796-2179, (CDER) Office of Communication, Outreach and Development, 301-827-1800, or (CDER) Robert L. Brooks Jr., 301-796-0211.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 2012
Procedural


Efforts to Support Biomarker Qualification
Joint FDA/ EMA Letter of Intent (LOI) Submissions for Biomarker and Clinical Outcome Assessment Qualification Programs

A Joint Letter-of-intent (LOI) template to enable efficient parallel submissions to the US FDA and EMA for Drug Biomarker Qualification or Clinical Outcome Assessment Qualification.

The United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are launching a joint letter of intent (LOI) template to encourage parallel submissions to these agencies for qualification of biomarkers or clinical outcome assessments. As noted in the template, some sections of the form are specific for the FDA or EMA. This joint template is intended to reduce the submitter’s preparation time. However, it is not a requirement for joint submission to FDA and EMA—the submitter may still choose to send in the agency-specific form for the LOI to each agency.

When joint LOIs for DDT qualification are submitted to FDA and EMA, the two agencies share scientific perspectives, advice, and response letters for the submitters.

There are three stages in the DDT qualification process at both the agencies, with minor differences in nomenclature as shown in the table below:

<table>
<thead>
<tr>
<th>Stage</th>
<th>FDA</th>
<th>EMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Initiation</td>
<td>Pre-submission</td>
</tr>
<tr>
<td>2</td>
<td>Consultation and Advice</td>
<td>Consultation and Advice by the Secretariat</td>
</tr>
<tr>
<td>3</td>
<td>Review</td>
<td>Review by the Scientific Advice Working Party</td>
</tr>
</tbody>
</table>

Joint LOI template submissions for FDA should be submitted via the following process:

CDER provides an avenue to qualify a biomarker for a “limited” context of use in order to expedite the integration of the biomarker in drug development and to possibly generate additional data that can help in qualifying the biomarker for the “expanded” context of use.
Opportunities for Biomarker Development

- DDT-KD Consortium

- Level of Evidence
  - CPIM
    - Exploratory Discussions
  - Letter of Support
    - Pre-Qualification
  - 2 – 3 months
- Time

- Qualification – Limited Context of Use
  - Initiation
  - Consultation & Advice
  - Review
  - 1 – 2 years

- Qualification – Expanded Context of Use
  - Initiation
  - Consultation & Advice
  - Review
  - 2 – 3 years
Take Home Points

Biomarkers can be integrated into drug development through either of the two pathways:

1. Regulatory submissions for drug approval in the context of a single drug or
2. Biomarker qualification

Biomarker Qualification is a voluntary process intended for biomarkers that will be used in multiple drug development programs
➢ Once qualified, a biomarker can be used by drug developers for other applications without re-review, for the qualified COU

➢ Early engagement with CDER on biomarker qualification encouraged

➢ CDER has streamlined the BQ process, improved communication both internally and externally and has launched new initiatives to encourage biomarker development and qualification
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