FDA’s Efforts to Encourage Biomarker Development and Qualification

Shashi Amur, Ph.D.

Scientific Lead
Biomarker Qualification Program
OTS/CDER/FDA

August 21, 2015

M-CERSI Symposium, Baltimore, MD
Overview

- Biomarkers in Drug Development
- Integration of biomarkers in drug development
- FDA’s efforts to encourage biomarker development and qualification
- 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”

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

Pathways to incorporate biomarkers in drug development at US FDA

IND/NDA/BLA Review

Biomarker Qualification
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- **Biomarker Information**: qualified biomarkers announced as draft guidance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 in the qualified setting
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. 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.

**Consultation and Advice Stage**
Briefing document received, reviewed, internal meeting, pre-meeting comments, face-to-face Meeting- Iterative process

**Review**
Full submission package received, review 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

Qualified Biomarkers and Supporting Information:

<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>PJ O'Brien, WJ Reagan, MJ York and MC Jacobsen</td>
<td>Serum/plasma biomarkers: Cardiac troponin T (cTnT) and I (cTnI)</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>

Biomarker Qualification Process - Timeline

Note: The timeline is based on our experience to date and may vary. This timeline does not capture the time needed by submitters to generate the data and submit the necessary documents (LOI, Briefing document, and Final Qualification Package) or requested additional information.
FDA’s Efforts to Encourage Biomarker Development and Qualification
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 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 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 Hanauer 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 Tapiola, 301-796-2770, (CBER) Office of Communication, Outreach and Development, 301-827-1800, or (CDRH) Robert L. Buchanan, Jr., 301-796-2011.

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

January 2012

Procedural


New Initiatives
CPIM (Critical Path Innovation Meeting)

- Discussion of the science, medicine, and regulatory aspects of innovations in drug development; nonbinding
- Not a meeting about a specific approval pathway
- Scope includes early biomarkers & clinical outcome assessments, natural history studies, technologies (not manufacturing), clinical trial designs and methods
- Outcomes include CDER perspective on role of innovation in drug development; proposals for future collaborations
Letters of Support

This is a letter issued to a submitter that briefly describes CDER’s thoughts on the potential value of a biomarker and encourages further evaluation. **This letter does not connote qualification of a biomarker.** It is meant to enhance the visibility of the biomarker, encourage data sharing, and stimulate additional studies.

### Issued Letters of Support

<table>
<thead>
<tr>
<th>Submitter</th>
<th>Biomarkers</th>
<th>Area(s) for Further Evaluation</th>
<th>Issuance date with Link to Letter of Support</th>
<th>Submitter Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-Path, PTSC, Skeletal Muscle Working Group (SMWG)</td>
<td>Serum and Plasma Biomarkers: Myosin Light Chain 3 (MLC3), Skeletal Muscle Troponin I (KTN1), Tally Acid Binding Protein 3 (PABP3), Creatine Kinase, Muscle Type (CK-M, the Homodimer Ck-M1)</td>
<td>Early Clinical Drug Development</td>
<td>2/2/2016, Letter of Support (PDF)</td>
<td>Refer to Predictive Safety Testing Consortium Web Site</td>
</tr>
<tr>
<td>C-Path, Coalition Against Major Disease Consortium (CAMC)</td>
<td>Cerebral Spinal Fluid (CSF) Analytes Biomarkers: AB1-42, Tau, Phospho Tau</td>
<td>Exploratory Prognostic Biomarkers for Enrollment in Early Stage Alzheimer’s Disease Clinical Trials</td>
<td>5/10/2016, Letter of Support (PDF)</td>
<td>Refer to Coalition Against Major Disease Web Site</td>
</tr>
<tr>
<td>C-Path, CAMO</td>
<td>Magnetic Resonance Imaging Biomarker: Low Baseline Hippocampal Volume</td>
<td>Exploratory Prognostic Biomarkers for Enrollment in Early Stage Alzheimer’s Disease Clinical Trials</td>
<td>3/10/2016, Letter of Support (PDF)</td>
<td>Refer to Coalition Against Major Disease Web Site</td>
</tr>
<tr>
<td>C-Path, CAMO</td>
<td>Molecular Neuroimaging Biomarker: Dopamine Transporter (DAT)</td>
<td>Exploratory Prognostic Biomarkers for Enrollment in Early Stage Parkinson’s Disease Clinical Trials</td>
<td>7/5/2016, Letter of Support (PDF)</td>
<td>Refer to Coalition Against Major Disease Web Site</td>
</tr>
</tbody>
</table>

6 letters issued to date

Joint FDA-EMA LOI

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:

Limited COU

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**

- **CPIM**
  - Pre-Qualification
  - Exploratory Discussions
  - 2–3 months

- **Letter of Support**
  - 3–4 months

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

- **Qualification – Expanded Context of Use**
  - Initiation
  - Consultation & Advice
  - Review
  - 2–3 years
Communication
Communication

• Enhanced interaction with submitters
• Frontloading COU discussions
• Enhanced interactions with consortia, NCATS, FNIH, and Critical Path Institute
• International interactions (EMA/IMI)
• Presentations
• Publications
• FDA webpage- Information for submitters
FDA Webpage

Information for the Submitters

- Contact Information and Submission Procedures
- Submission Help
  - Cover letter template
  - LOI template
  - FDA-EMA Joint LOI template
  - Briefing Document template
  - Biomarker Qualification Submissions Checklist
  - Context of Use explanation
  - COU example for a hypothetical biomarker
  - FAQs
- Additional Information
  - BQ Presentation (recorded)
  - Relevant BQ-related Publications
Drug Development Tool (DDT) Qualification Projects at CDER, FDA

This Table provides the current[1] 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></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>87</td>
<td>7</td>
<td>24</td>
<td>56</td>
</tr>
<tr>
<td>Number in Initiation Stage</td>
<td>26</td>
<td>4</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>Number in Consultation and Advice Stage</td>
<td>54</td>
<td>3</td>
<td>18</td>
<td>33</td>
</tr>
<tr>
<td>Number in Review Stage</td>
<td>7</td>
<td>0</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Number Qualified</td>
<td>5</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

June, 2015 Update

[1] Updated as of June 2015

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>Contact: John-Michael Sauer</td>
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<tr>
<td>Contact: John-Michael Sauer</td>
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<td></td>
</tr>
<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>Contact: Reegan O’Lone</td>
<td></td>
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<td></td>
<td></td>
<td></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>Contact: Diane Stephenson</td>
<td></td>
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</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>Contact: Diane Stephenson</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Contact: John-Michael Sauer</td>
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</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>
Survey to identify biomarkers needed in drug development
FR Notice- Survey

- **Goal:** Identifying Potential Biomarkers for Qualification and Describing Contexts of Use to Address Areas Important to Drug Development

- **Logistics:** Published on February 13, 2015 with a deadline of April 14, 2015. Extended to May 15, 2015

- Two options given for providing responses
  - Docket (35 responses received)
  - Survey Monkey (38 responses received)
Survey Results

Number of Responses Obtained in Different Disease Areas
## Survey Results

<table>
<thead>
<tr>
<th>Disease Area/Organ Toxicity</th>
<th>Specific Areas in Critical Need for Biomarker Development</th>
<th>Biomarker Names</th>
<th>Context of Use</th>
<th>Why Is the Biomarker Useful in Drug Development?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological and Neuropsychiatric Diseases</td>
<td>Alzheimer's disease, Mood Disorders, Epilepsy, Huntington's disease, Alcohol Dependence, Schizophrenia and Parkinson's disease.</td>
<td>Tau imaging markers. Genetic &amp; epigenetic biomarker signatures (AD and Mood) Screen biomarkers for AD, Mood disorders (blood tests, neurofunctional and behavioral) Novel strategies to approach outcome measures (different than patient reported outcomes). Biomarkers of functional outcome measures. Imaging measures (PET, fMRI) and physiological (EEG). Translocator Protein (TSPO) PET ligand. Utilizing composite biomarker. Phosphodiesterase (PDE)-10A PET ligand</td>
<td>Diagnosis, stratification and outcome measures. Patient selection. Identification of target population based on disease biology and/or drug target for predicting drug efficacy/response. Diagnostic: Dose selection.</td>
<td>AD diagnosis and staging: progression monitoring, PD measurement. Disease risk. Patient enrichment for clinical trials. Objective measures for motor dysfunction. For stratification purposes in CNS disorders in general. Neuroninflammatory biomarkers such as the TSPO PET Ligand should thus be considered in the context of experimental medicine to potentially enrich clinical study designs and improve the testing of clinical hypotheses. The field acknowledges that given the heterogeneity and complexity of CNS disorders, a single biomarker (e.g., gene, SNP, micro RNA, protein or metabolite) will be unlikely to identify a subpopulation and/or explain. The PDE10A PET ligand will serve multiple purposes. Firstly it will confirm that a given drug enters the CNS, reaches and binds to the PDE10A enzyme. Furthermore, the PET ligand will enable the establishment of plasma exposure of a drug to target occupancy. This will be critical in determining the therapeutic dose range.</td>
</tr>
</tbody>
</table>
Initiating collaborative efforts aimed at developing evidentiary standards
Discussions on Evidentiary Standards

Workshops

• PhRMA-FDA workshop in 2007
• Institute of Medicine Workshop on Biomarker Qualification in 2009
• FDA-cosponsored “Biomarkers workshop” with HHMI in 2013
• FDA-cosponsored Brookings meeting on “Advancing the Use of Biomarkers and Pharmacogenomics” in 2014
• FDA-cosponsored workshop with M-CERSI and PSTC “Evidentiary Considerations for Integration of Biomarkers in Drug Development “held today (August 21, 2015)
• NIH-FDA Workshop planned for October, 2015
• FNIH-FDA Workshop planned for 2016
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 intended for biomarkers that will be used in multiple drug development programs

- Biomarker Qualification is a voluntary process
Early engagement with FDA on biomarker qualification encouraged

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

CDER has conducted a survey to identify potential biomarkers for qualification in areas important to drug development
Acknowledgements

Janet Woodcock
ShaAvhrée Buckman-Garner
Chris Leptak
Suzie McCune
Marianne Noone
Sarmistha Sanyal
Thank You!

Shashi.amur@fda.hhs.gov
Back-up Slides
Drug Development Tools (DDT) Qualification at CDER, FDA

DDTs are methods, materials, or measures that aid drug development.
DDT Qualification at CDER, FDA

Guidance for Industry and FDA Staff
Qualification Process for Drug Development Tools

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


MANUAL OF POLICIES AND PROCEDURES

CENTER FOR DRUG EVALUATION AND RESEARCH

POLICY AND PROCEDURES

OFFICE OF THE CENTER DIRECTOR

Drug Development Tool Qualification Programs

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