Biomarkers in Drug Development

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Myotonic Dystrophy Patient-Centered Therapy Development
September 17, 2015
Overview

- Introduction
- Biomarker Qualification (BQ)
- Biomarker Survey
- Efforts towards developing evidentiary standards
- Take home points
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
**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  - **Biomarker Information:** Qualified biomarkers announced as draft guidance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
Biomarker Qualification Process - Timeline

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

**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.
**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>PJ O’Brien, WJ Reagan, MJ York and MC Jacobeen</td>
<td>Serum/plasma biomarkers: Cardiac troponins 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>7/9/2015 Prognostic biomarker for enrichment of clinical trials in Chronic Obstruction Pulmonary Disease (COPD)</td>
<td>Reviews</td>
</tr>
</tbody>
</table>

**Submitters:** Can be Individuals or groups; e.g., Academia, Consortia, Disease foundations, Patient advocacy groups

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.
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 received in the survey

<table>
<thead>
<tr>
<th>Disease</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne's Muscular Dystrophy (DMD)</td>
<td>- Dystrophin</td>
</tr>
<tr>
<td></td>
<td>- Skeletal MRI</td>
</tr>
<tr>
<td></td>
<td>- The assessment of upper extremity function based on the concept of 3-dimensional reachable workspace</td>
</tr>
<tr>
<td>Duchenne muscular dystrophy (DMD), Facioscapulohumeral muscular dystrophy (FSHD), Becker muscular dystrophy (BMD), and Amyotrophic Lateral Sclerosis (ALS).</td>
<td>A scalable and sustainable remote measurement platform for upper extremity function.</td>
</tr>
<tr>
<td>Myotonic dystrophy (DM)</td>
<td>- Biomarkers for cardiac and central nervous system.</td>
</tr>
<tr>
<td></td>
<td>- Predictive genetic biomarkers. CELF1 protein (upregulated in DM1 tissues, particularly in heart).</td>
</tr>
</tbody>
</table>
Efforts at Developing Evidentiary Standards

A Multiple stakeholder effort:
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
Acknowledgements

Janet Woodcock
ShaAvhrée Buckman-Garner
Chris Leptak
Suzie McCune
Marianne Noone
Sarmistha Sanyal
Back up slides
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
What types of submissions are we seeing for Biomarker Qualification?
Where are The Submissions in the BQ Process?

**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](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm409960.htm) 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 (FNHI)</td>
<td>Drug-Induced Clinical Kidney Injury Biomarkers</td>
<td>2/24/2011</td>
<td>Safety</td>
<td>Safety Assessment</td>
<td>Review</td>
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</table>
Opportunities for Collaboration

- Develop evidentiary standards for context-of-use-specific biomarker qualification

- Prioritize specific diseases and respective biomarkers whose development and qualification would advance drug development and satisfy unmet medical needs

- Expand qualification by developing and maintaining an accessible database for collecting biomarker data, and a repository for samples

- Develop standards for biomarker measurement tools...Reproducibility initiatives...

- Encourage and fund biomedical research that is necessary as the basis for development of new biomarkers

- Coordinate existing partnerships and consortia so that they effectively direct their efforts toward development and qualification of priority biomarkers

- Train investigators on regulatory considerations for biomarker development
Guidances

Guidance for Industry
Use of Histology in Biomarker Qualification Studies

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