Update on the Clinical Outcome Assessment Qualification Program and COA Compendium

Seventh Annual PRO Consortium Workshop April 27-28, 2016

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Office of New Drugs (OND)
Center for Drug Evaluation and Research (CDER)
Disclaimer

- The views expressed in this presentation are those of the speaker(s), and do not necessarily represent an official FDA position.
Topics to be Covered

• Update on FDA COA Qualification Submissions and Related Activities

• COA Qualification Program Website

• Biomarkers, EndpointS, and other Tools Resource (BEST)Glossary

• Future Direction

• COA Compendium

• Q&A
Presenters

Elektra Papadopoulos, MD, MPH
Acting Associate Director, Clinical Outcomes Assessment Staff

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Associate Director for Labeling, Division of Hematology Products
Update on FDA COA Qualification Submissions and Related Activities
COA Staff

• **Acting Associate Director for Clinical Outcome Assessments:**
  – Elektra Papadopoulos, MD, MPH

• **Regulatory Project Managers:**
  – Clinical Outcome Assessment
  – DDT Qualification:
    • Susan Montenegro, PharmD, MPH, BCPS
  – Clinical Outcome Assessment
  – Consults:
    • Jessica Voqui, PharmD, MS

• **DDT Qualification Scientific Coordinator:**
  – Michelle Campbell, PhD

• **Reviewers:**
  – Michelle Campbell, PhD
  – Wen-Hung Chen, PhD
  – Yasmin Choudhry, MD
  – Selena Daniels, PharmD, MS
  – Ebony Dashiell-Aje, PhD
  – Sarrit Kovacs, PhD
  – Nikunj Patel, PharmD

• **ORISE Fellow:**
  – Paula Chakravarti, MPH, MS, MA
PFDD MEETINGS
FDA’s Patient-Focused Drug Development Initiative

• A commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) that aims to more systematically gather patients’ perspectives on their condition and available therapies to treat their condition.

• Establishes the context in which a regulatory decision is made by analysis of the severity of the condition treated and current treatment options available.
<table>
<thead>
<tr>
<th>Fiscal Year 2013</th>
<th>Fiscal Year 2014</th>
<th>Fiscal Year 2015</th>
<th>Fiscal Year 2016-2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic fatigue syndrome/myalgic encephalomyelitis</td>
<td>Sickle cell disease</td>
<td>Female sexual dysfunction</td>
<td>Non-tuberculous mycobacterial lung infections</td>
</tr>
<tr>
<td>HIV</td>
<td>Fibromyalgia</td>
<td>Breast cancer</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Pulmonary arterial hypertension</td>
<td>Chagas disease</td>
<td>Neuropathic pain associated with peripheral neuropathy</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>Inborn errors of metabolism</td>
<td>Functional gastrointestinal disorders</td>
<td>(June 10&lt;sup&gt;th&lt;/sup&gt;)</td>
</tr>
<tr>
<td></td>
<td>Hemophilia A, B, and other heritable bleeding disorders</td>
<td>Parkinson’s disease and Huntington’s disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Idiopathic pulmonary fibrosis</td>
<td>Alpha-1 antitrypsin deficiency</td>
<td>To be announced</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Alopecia areata</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Autism</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Hereditary angioedema</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Patients who have received an organ transplant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sarcopenia</td>
</tr>
</tbody>
</table>
QUALIFICATION PROGRAM
UPDATES
Qualified for Exploratory Use

• Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease (E-RS: COPD)
• March 8, 2016
• Concept of Interest: Measures respiratory symptoms in stable COPD patients
## COA Qualification Projects

<table>
<thead>
<tr>
<th>COA DDT Qualification Program Stage</th>
<th>Number in Stage as of Q1-2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation Stage</td>
<td>11</td>
</tr>
<tr>
<td>Consultation and Advice (C&amp;A) Stage</td>
<td>38</td>
</tr>
<tr>
<td>Review Stage</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
</tr>
<tr>
<td>Qualified for Use in Exploratory Studies</td>
<td>2</td>
</tr>
</tbody>
</table>
Program Growth

Number of DDT Projects by Division as of 1st Q 2016
Continued Growth

Changes in COAQP from 2014 to 2015, represented by average response time in days and number of submissions received

<table>
<thead>
<tr>
<th>Year</th>
<th>Avg response time (days)</th>
<th># Submissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>209</td>
<td>32</td>
</tr>
<tr>
<td>2015</td>
<td>111</td>
<td>37</td>
</tr>
</tbody>
</table>
CLINICAL OUTCOME ASSESSMENT QUALIFICATION PROGRAM WEBSITE
Clinical Outcome Assessment Qualification Program Website

Qualification Submissions
Clinical Outcome Assessment (COA): Frequently Asked Questions

1. What is the standard of evidence for COA qualification?
   The measurement principles of content validity, reliability, construct validity, and ability to detect change apply to all types of COAs. The PRO guidance, while developed for patient-reported outcomes, provides many recommendations that are applicable to the development of all COAs, including clinician-reported outcome (ClinRO) assessments, observer-reported outcome (ObsRO) assessments, and performance outcome (PerfO) assessments. In addition, we often refer instrument developers to the ISPOR Task Force publications on content validity.

   The COA Wheel and Spokes (PDF - 1MB) provided here identifies the key components of various stages of instrument development and the points at which qualification may occur.

2. What is FDA’s position on use of modern psychometric methods (e.g., Rasch analysis and Item Response Theory) and qualitative research in an iterative approach in early instrument development to inform and guide thinking about content validity?
   FDA recognizes that different approaches to instrument development may be appropriate. FDA will consider different approaches to instrument development than what is described in the FDA PRO guidance.

   FDA does not require the use of modern psychometric methods in instrument development.

3. Is it necessary for an instrument to be qualified in order to use that instrument as the basis for a primary or secondary endpoint in a clinical trial?
   No. A tool that is not formally qualified may still be acceptable for use, and should be discussed with the review division within an IND. We recommend discussing outcome assessments and endpoints with the FDA as early as possible.

4. Are drug sponsors (IND/NDA/BLA holders) required to use qualified instruments when they exist?
   No. While we believe there are benefits of using a qualified tool, drug sponsors may select any well-defined and reliable tool(s) they believe will be best suited for their clinical trial(s). We encourage drug sponsors to discuss those decisions with the appropriate review division.
BEST GLOSSARY
BEST Glossary

- Biomarkers, EndpointS, and other Tools Resource
- Joint effort between FDA and NIH
- Harmonize terminology
BEST GLOSSARY

BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet].

Terms and Definitions

A

accelerated approval

Regulatory mechanism by which new drugs meant to treat serious, life-threatening diseases and that provide meaningful therapeutic benefit to patients over existing treatments can be approved on the basis of adequate and well-controlled clinical trials establishing that the drug has an effect on a reasonably likely surrogate endpoint or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity (intermediate clinical endpoint). Postmarketing confirmatory trials have been required to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit.

Relevant Links:

FDA/Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics

analytical validation

Establishing that the performance characteristics of a test, tool, or instrument are acceptable in terms of its sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol (which may include specimen collection, handling and storage procedures). This is validation of the test’s, tool’s, or instrument’s technical performance, but is not validation of the item’s usefulness.
FUTURE DIRECTIONS
Letter of ???

• Instrument is accepted into the qualification program and is currently in the advice and consultation stage

• FDA has reviewed and agrees with successful development of a draft instrument based on strong qualitative research that includes completion of both concept elicitation and cognitive debriefing

• There is a preliminary conceptual framework and preliminary scoring algorithm available
Potential for “Letter of ???”
Quantitative Analysis Plans

• The primary objective of the quantitative/psychometric analysis is, in conjunction with qualitative data, to select items and refine the conceptual framework of the instrument for further confirmatory evaluation.
Quantitative Analysis Plans

• Each quantitative analysis planned should:
  – Provide evidence that the items perform well psychometrically
  – Assess the instrument’s intent (i.e., the concept(s) described in the COA conceptual framework)

• Our goal is to develop an outline of what minimum evidence is required in these plans
Pilot FDA
Clinical Outcome Assessment Compendium
(COA Compendium)

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Acting Associate Director, Clinical Outcome Assessments Staff

Virginia Kwitkowski, MS, ACNP-BC
Associate Director for Labeling, Division of Hematology Products

April 27, 2016
Seventh Annual PRO Consortium Workshop
Objectives

Attendees will understand:

• What is a Clinical Outcome Assessment?
• What is the Pilot COA Compendium?
• The purpose for the creation of the Pilot COA Compendium
• How the Compendium was created
• What was included in the Compendium
• How the Compendium is organized
• Expected uses for the compendium
• Future Directions
Clinical Outcome Assessment

Assessment of a clinical outcome can be made through report by a clinician, a patient, a non-clinician observer or through a performance-based assessment. There are four types of COAs.

- clinician-reported outcome
- observer-reported outcome
- patient-reported outcome
- performance outcome

Please visit following website with a complete list of Glossary of Terms:
What is the Pilot COA Compendium?

A collaborative initiative by the FDA COA Staff & OND Review Divisions

The COA Compendium is a table that:

1. Describes how certain clinical outcome assessments have been used in clinical trials to measure the patient’s experience (such as disease-related symptoms) and to support labeling claims.

2. Identifies clinical outcome assessments that have been qualified for potential use in multiple drug development programs under the COA type of the Drug Development Tool (DDT) Qualification Program of the Center for Drug Evaluation and Research (CDER).

3. Recognizes ongoing qualification projects to encourage community collaboration in the development of clinical outcome assessments for unmet measurement needs.
Purpose of COA Compendium*

FDA’s effort to foster patient-focused drug development by collating and summarizing COA information for many different diseases and conditions into a single resource intended to:

- Identify patient-centered outcome measures and encourage their use in drug development and product labeling
- Identify unmet needs to encourage instrument development where gaps exist
- Provide transparency and consistency in FDA communications
- Encourage collaboration to develop measures for unmet needs

* Includes patient-reported, clinician-reported, observer-reported and performance based outcome measures
FDA's Review of COAs

Drug Development Tool Qualification Pathway

Qualified Clinical Outcome Assessments

Ongoing Qualification Projects

Clinical Outcome Assessments in Approved Labeling

IND/NDA/BLA Pathway

COA Compendium
How were COAs Selected for the Pilot COA Compendium?

**COA Qualification Program**

1. Collation of qualified and ongoing qualification projects
2. Permissions obtained from the qualification instrument developers for public posting

**Approved Drug Labeling**

1. Retrospective Review of Approved Drug Labeling (NMEs only 2003 – 2014)
2. Collaboration with OND review divisions

Pilot COA Compendium

NME = New Molecular Entity
ROLE OF THE REVIEW DIVISIONS: A DIVISION PROSPECTIVE
Input Sought From Review Divisions

• Reviewed the COAs identified for inclusion in compendium for the following:
  – Current acceptability for inclusion in compendium
  – Need for revision
Example of Review Division Input Into Compendium

• Disease/Condition: Myelofibrosis (MF)

• Labeled COA Selected from Jakafi label: “modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0”.
Review of Items in MFSAF v2.0

Figure 3: Proportion of Patients With Myelofibrosis Achieving 50% or Greater Reduction in Individual Symptom Scores at Week 24

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Jakafi</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal discomfort</td>
<td>4.0</td>
<td>2.7</td>
</tr>
<tr>
<td>Pain under left ribs</td>
<td>3.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Early satiety</td>
<td>3.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Night sweats</td>
<td>3.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Itching</td>
<td>2.8</td>
<td>3.3</td>
</tr>
<tr>
<td>Bone or muscle pain</td>
<td>1.8</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Baseline Mean:
- Abdominal discomfort: 3.9
- Pain under left ribs: 2.9
- Early satiety: 3.9
- Night sweats: 3.2
- Itching: 2.8
- Bone or muscle pain: 3.3

Baseline Median:
- Abdominal discomfort: 3.9
- Pain under left ribs: 2.7
- Early satiety: 4.0
- Night sweats: 3.0
- Itching: 2.5
- Bone or muscle pain: 3.1

Individual score range = 0 to 10
Input from DHP

• MFSAF v2.0 was acceptable for the approval of Jakafi
• Fatigue reported by 85% of patients with MF
• Fatigue is missing from MFSAF v2.0
• Fatigue should be included in a symptom measure in patients with MF
What is in the COA Compendium and what is not?

The pilot version is limited in scope to enable FDA to obtain public input.

The pilot includes:

- Labeled COAs from a retrospective review of a small subset of approved new molecular entity (NME) drug labeling between 2003 and 2014
- Qualified COAs and ongoing qualification projects as of December 31, 2015

The pilot does not include:

- Labeled COAs from efficacy supplement drug labeling
- Labeled COAs from approved drug labeling prior to 2003 or after 2014
- Labeled COAs in certain cases such as where FDA has issued guidance that provides recommendations for using different outcome measure(s)

Sponsors are strongly encouraged to seek the relevant Office of New Drug (OND) review division’s advice early (e.g., pre-IND meeting) and throughout drug development to discuss COA selection and implementation specific to their program, irrespective of whether the disease, condition, indication, claim, or COA is included in the COA Compendium.

IND = Investigational New Drug
The **COA Compendium** includes the following six columns

<table>
<thead>
<tr>
<th>COLUMNS</th>
<th>ELEMENTS</th>
<th>DESCRIPTION OF CONTENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Disease/Condition</td>
<td>Lists disease or condition and any relevant FDA disease-specific guidance.</td>
</tr>
<tr>
<td>2</td>
<td>Indication and/or Claim(s)</td>
<td>Lists key elements of indication and/or claim (either labeled or qualified). For ongoing COA qualification projects, targeted labeling or promotional claim(s) may not be yet known and may be described as “to be determined.”</td>
</tr>
<tr>
<td></td>
<td>Description</td>
<td><em>Inclusion of a clinical outcome assessment in the COA Compendium is not intended to indicate that the measure is or should be the sole (or primary) determinant of a clinical benefit in a particular clinical trial.</em></td>
</tr>
<tr>
<td>3</td>
<td>Outcome of Interest</td>
<td>Describes an outcome of interest that was assessed (labeled) or could be assessed (in our qualification program) by clinical outcome assessment(s) displayed in Column 4.</td>
</tr>
<tr>
<td>4</td>
<td>COA (COA Type)</td>
<td>• Lists a labeled, qualified, or ongoing qualification project clinical outcome assessment name and/or description.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Includes the clinical outcome assessment type (i.e., a patient-reported outcome, observer-reported outcome, clinician-reported outcome, or performance outcome).</td>
</tr>
<tr>
<td>5</td>
<td>COA Context of Use</td>
<td>Describes circumstances under which the outcomes of interest and the clinical outcome assessment have been used (i.e., labeled) or are targeted for use (i.e., they have been qualified or are part of an ongoing qualification).</td>
</tr>
<tr>
<td>6</td>
<td>COA Qualification Information</td>
<td>Lists ongoing and completed clinical outcome assessment qualification project information, if applicable.</td>
</tr>
</tbody>
</table>
COA Compendium Use

What it is:

• A communication tool to promote transparency between FDA and drug developers
• Method to improve collaboration by describing ongoing qualification efforts
• Method to encourage the development and use of COAs (especially those that are important to patients)

What it is not:

• All-inclusive list
• A way to stifle innovation
• A replacement for existing communication channels with review divisions (e.g., pre-IND, EOP 2 meetings)
• A replacement for existing disease-specific guidances or qualification

IND = Investigational New Drug
EOP2 = End of Phase 2
### Pilot Compendium Sample

#### HEMATOLOGY PRODUCTS

<table>
<thead>
<tr>
<th>Disease/Condition</th>
<th>Indication and/or Claim(s) Description</th>
<th>Outcome of Interest</th>
<th>COA (COA Type)</th>
<th>COA Context of Use</th>
<th>COA Qualification Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic lymphocytic leukemia (CLL)</td>
<td><strong>Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics</strong></td>
<td>Treatment of CLL</td>
<td>Incidence of palpable hepatosplenomegaly</td>
<td>Composite of clinician-reported outcomes, patient-reported outcome, and laboratory/imaging measures (biomarkers)</td>
<td>Adult patients with CLL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Size of lymph nodes; incidence of lymph nodes with nodularity</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>B symptoms evaluation (night sweats, fever, unexplained weight loss)</td>
<td>Note: B symptoms are assessed based on patient-reported outcome</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Laboratory measures (lymphocytes, neutrophils, platelets, histology)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutaneous T-cell lymphoma (CTCL)</td>
<td><strong>Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics</strong></td>
<td>Treatment of CTCL</td>
<td>Skin involvement</td>
<td>Capitalized Multidimensional Assessment Tool in addition to other outcomes (e.g., response duration, time to progression, time to objective response) (clinician-reported outcome)</td>
<td>Adult patients with CTCL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Physician’s global assessing improvement or worsening in overall disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis (DVT) and pulmonary embolism (PE)</td>
<td>Prophylaxis of DVT/PE</td>
<td>Incidence of venous thromboembolic events that includes deep vein thrombosis, non-fatal pulmonary embolism, and death due to thromboembolic in origin</td>
<td>Composite of thromboembolic events defined by a combination of biomarkers and clinician assessments (clinician-reported outcomes)</td>
<td>Adult patients at risk for DVT/PE</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
FUTURE DIRECTIONS
Future Directions

• Reviewing comments from the docket
  – Docket closed: March 14, 2016

• Comments will assist in determining the expansion and future scope of the Compendium
Public Comment Submissions on the Pilot (n=33)

- Academia, 2
- Consortia, 3
- CROs, 6
- Independent Consultants, 2
- Individuals, 1
- Industry, 9
- Patient Advocacy Groups, 4
- Professional Societies, 6
INITIAL THOUGHTS ON EXPANSION BASED ON DOCKET COMMENTS
Summary

• The COA Qualification Program continues to expand and grow.

• The COA Compendium is intended to facilitate communication and to provide clarity and transparency to drug developers and the research community.

• The FDA encourages the development and implementation of patient-focused clinical outcome assessments (COAs) in clinical trials to support drug approvals and labeling claims.
Relevant Resources

- FDA COA Staff Website: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm349031.htm#Endpoints
THANK YOU
ADDITIONAL SLIDES
What are key considerations of the COA Compendium?

- The **COA Compendium** is not a comprehensive list of clinical outcome assessments and is not intended to replace either existing disease-specific guidance or key interactions with FDA concerning drug development (e.g., during pre-IND meetings). Inclusion of a clinical outcome assessment in the **COA Compendium** is not intended to indicate that the measure is or should be the sole (or primary) determinant of a clinical benefit in a clinical trial.

- Drug sponsors are strongly encouraged to seek advice from the relevant Office of New Drug (OND) review division early in drug development to discuss the selection and implementation of the clinical outcome assessment specific to their program, irrespective of whether the disease, condition, indication, claim, or clinical outcome assessment is included in the **COA Compendium**.

- Some of the clinical outcome assessments listed in the **COA Compendium** may be protected by proprietary rights, and in some cases, a royalty and fee may be charged by the copyright owners for their authorized use. The inclusion of a clinical outcome assessment in the **COA Compendium** does not equate to an endorsement by FDA.