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

Virginia Kwitkowski, MS, ACNP-BC

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

PFDD Meeting FY2013-2017

Fiscal Year 2013	Fiscal Year 2014	Fiscal Year 2015	Fiscal Year 2016-2017
• Chronic fatigue syndrome/ myalgic encephalomyelitis • HIV • Lung cancer • Narcolepsy	• Sickle cell disease • Fibromyalgia • Pulmonary arterial hypertension • Inborn errors of metabolism • Hemophilia A, B, and other heritable bleeding disorders • Idiopathic pulmonary fibrosis	• Female sexual dysfunction • Breast cancer • Chagas disease • Functional gastrointestinal disorders • Parkinson's disease and Huntington's disease • Alpha-1 antitrypsin deficiency	• Non-tuberculous mycobacterial lung infections • Psoriasis • Neuropathic pain associated with peripheral neuropathy (June 10th) *To be announced* • Alopecia areata • Autism • Hereditary angioedema • Patients who have received an organ transplant • Sarcopenia

QUALIFICATION PROGRAM UPDATES

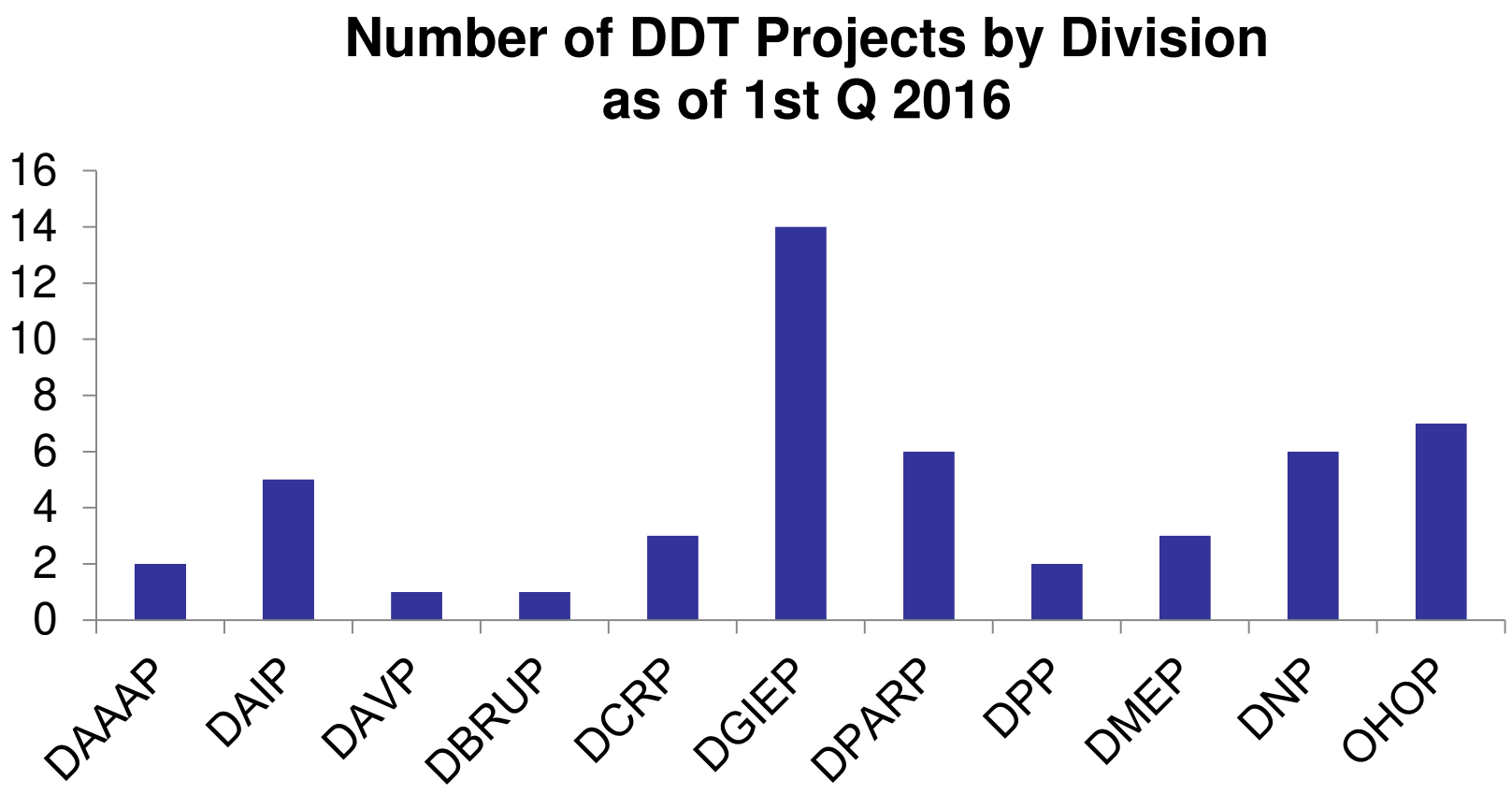
Qualified for Exploratory Use

- 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

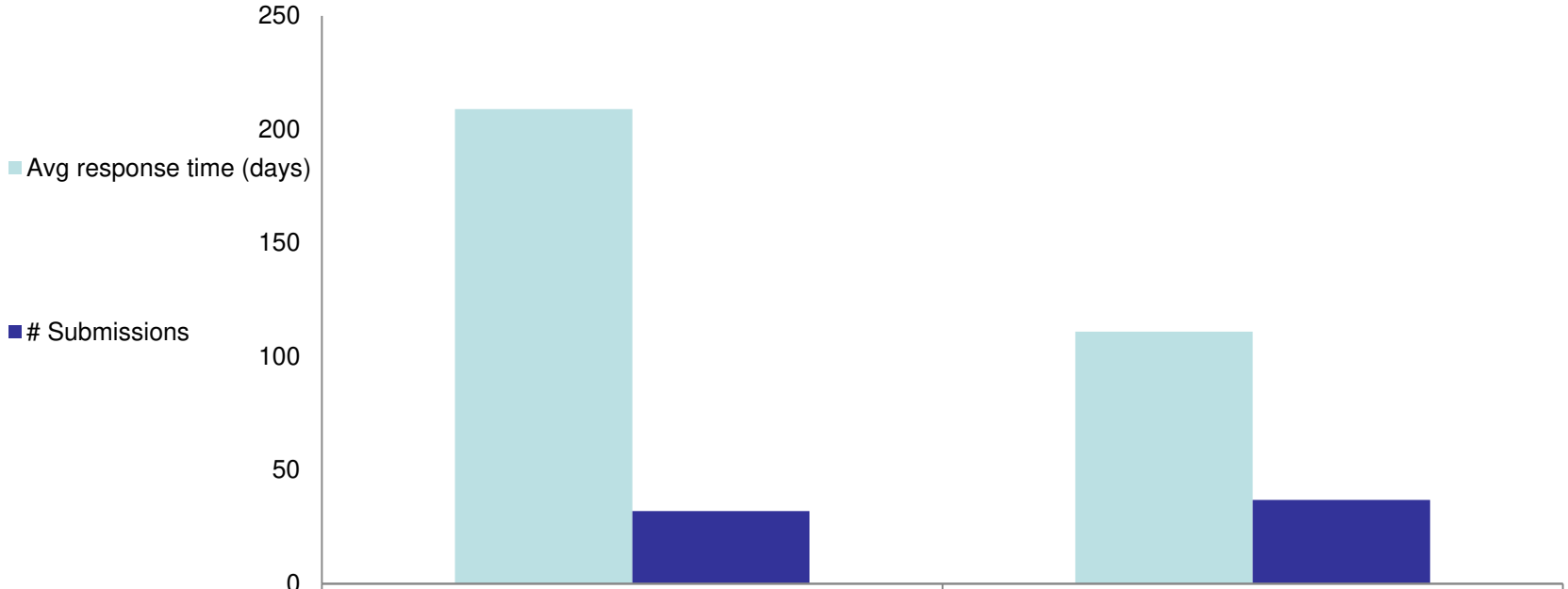
COA DDT Qualification Program Stage	Number in Stage as of Q1-2016
Initiation Stage	11
Consultation and Advice (C&A) Stage	38
Review Stage	1
Total	50
Qualified for Use in Exploratory Studies	2

Program Growth



Continued Growth

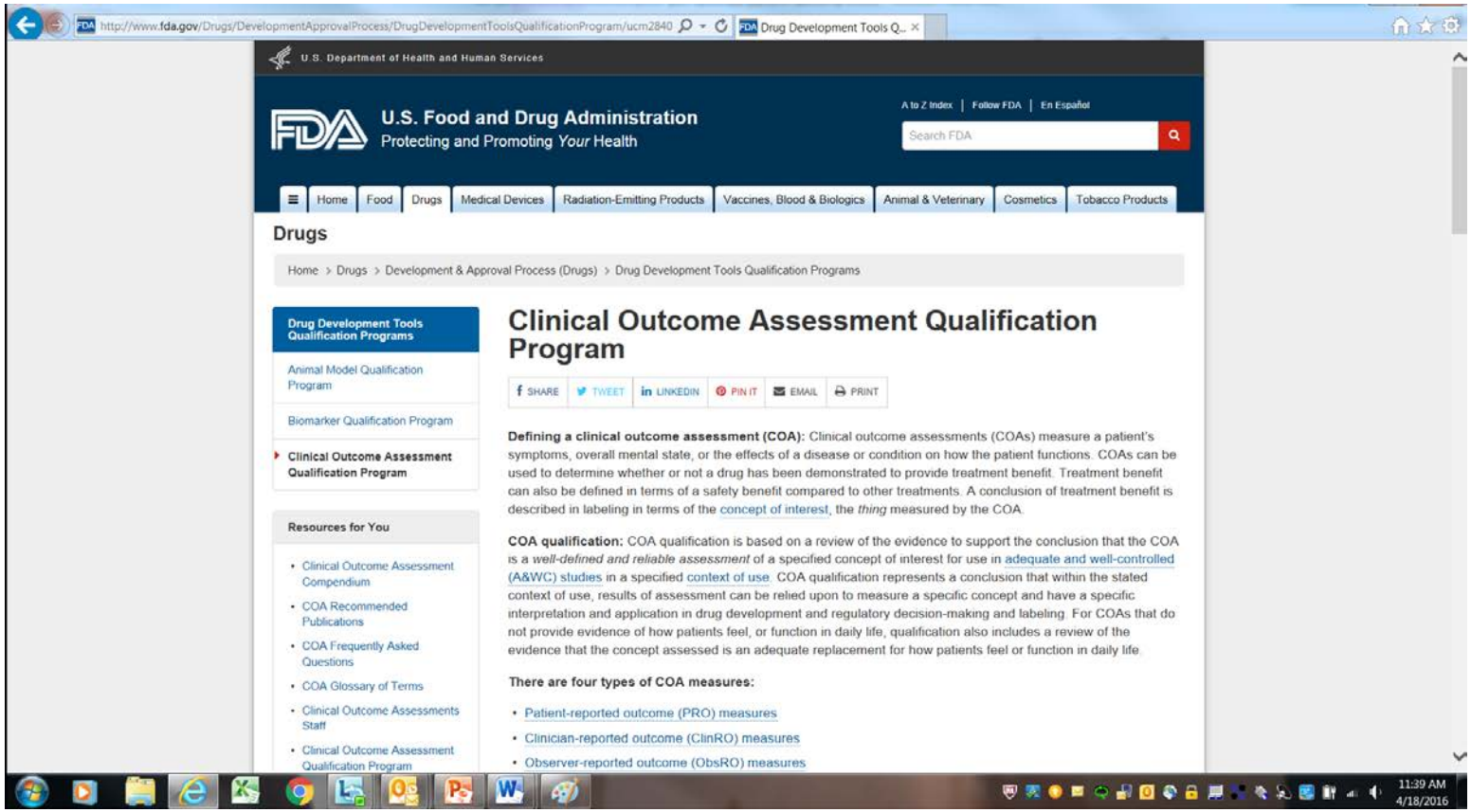
Changes in COAQP from 2014 to 2015, represented by average response time in days and number of submissions received



	2014	2015
Avg response time (days)	209	111
# Submissions	32	37

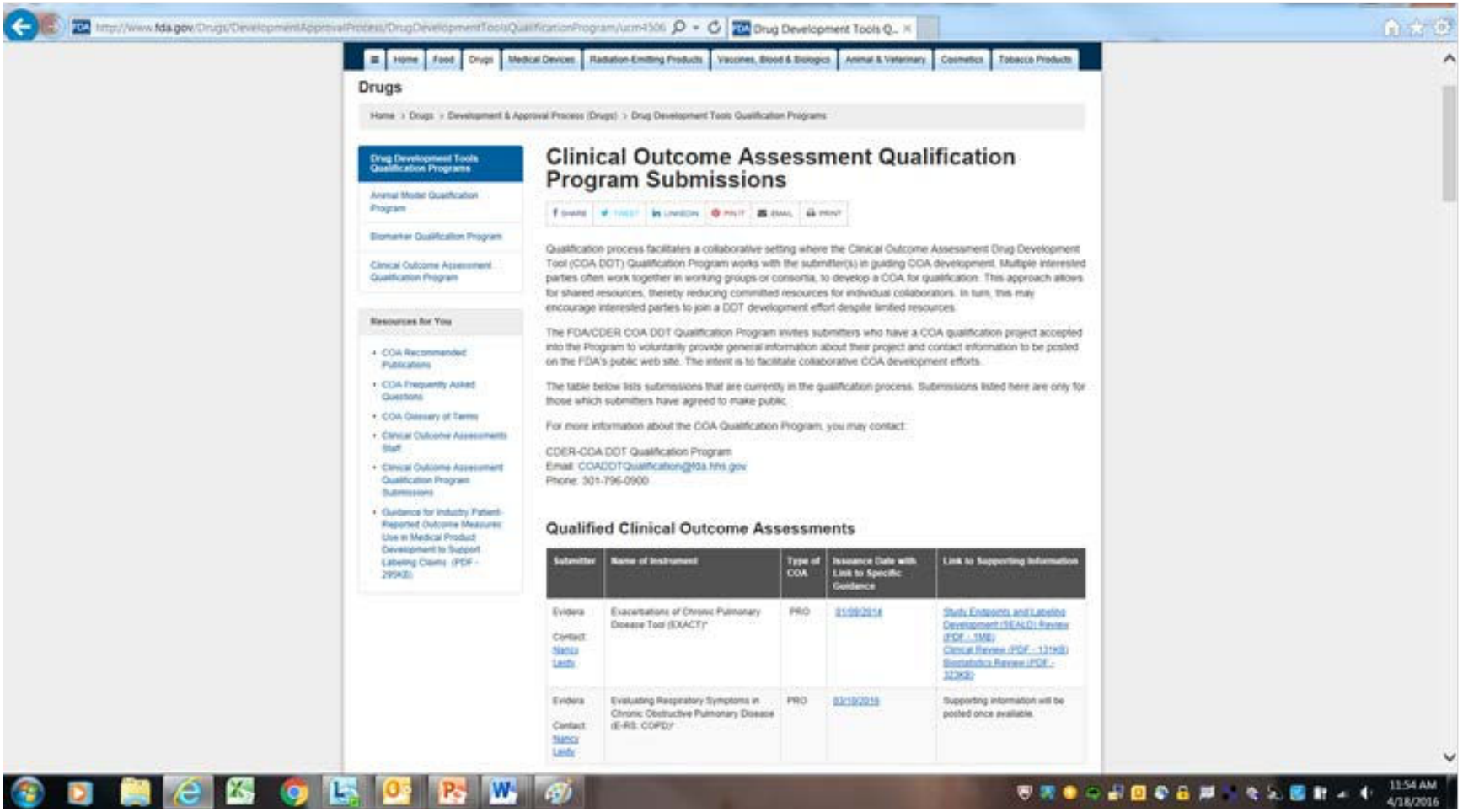
CLINICAL OUTCOME ASSESSMENT QUALIFICATION PROGRAM WEBSITE

Clinical Outcome Assessment Qualification Program Website

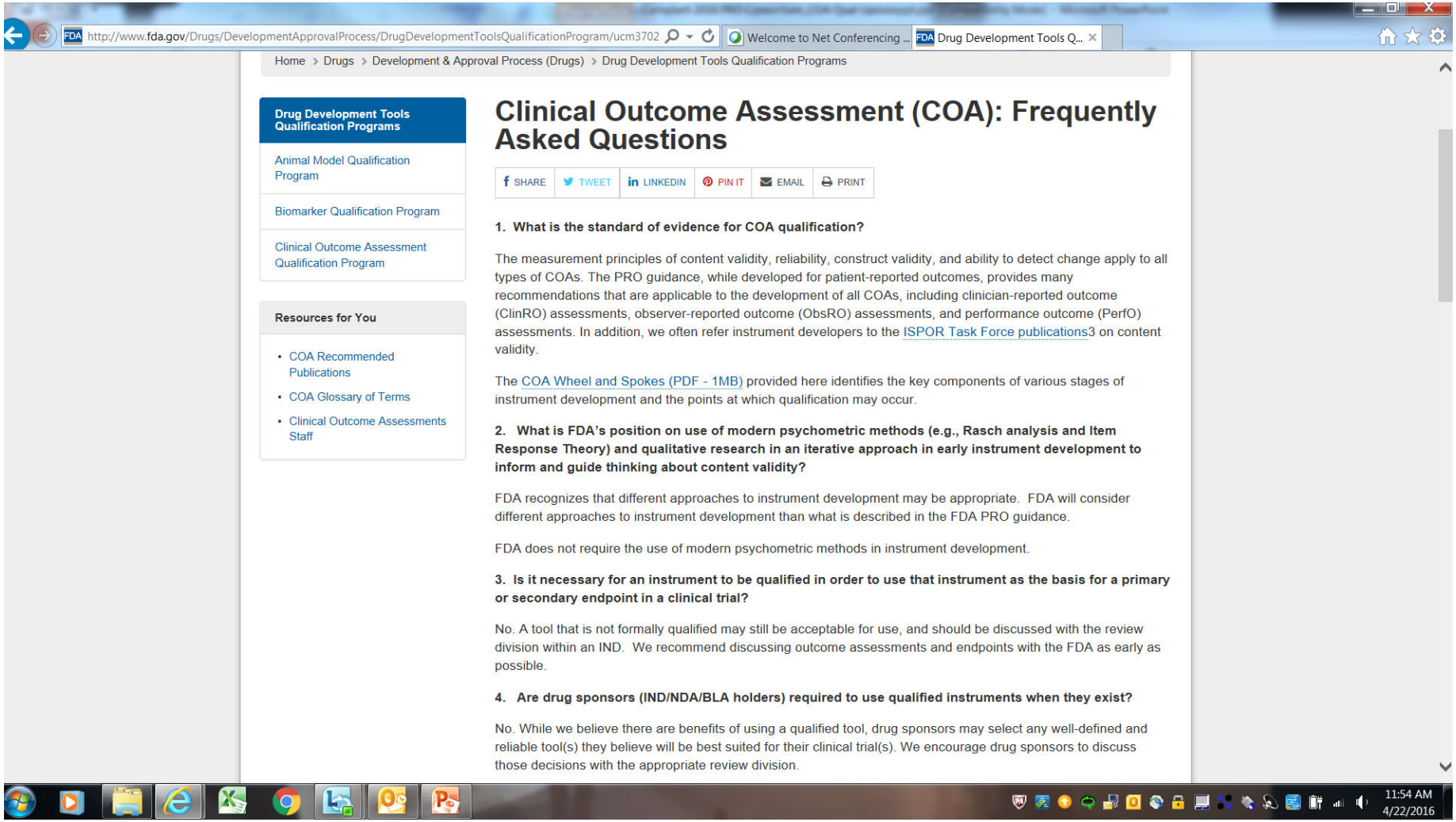


http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm

Qualification Submissions



FAQS



http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm3702

Welcome to Net Conferencing ...

Drug Development Tools Q...

Home > Drugs > Development & Approval Process (Drugs) > Drug Development Tools Qualification Programs

Drug Development Tools Qualification Programs

- Animal Model Qualification Program
- Biomarker Qualification Program
- Clinical Outcome Assessment Qualification Program

Resources for You

- COA Recommended Publications
- COA Glossary of Terms
- Clinical Outcome Assessments Staff

Clinical Outcome Assessment (COA): Frequently Asked Questions

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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 publications3 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.

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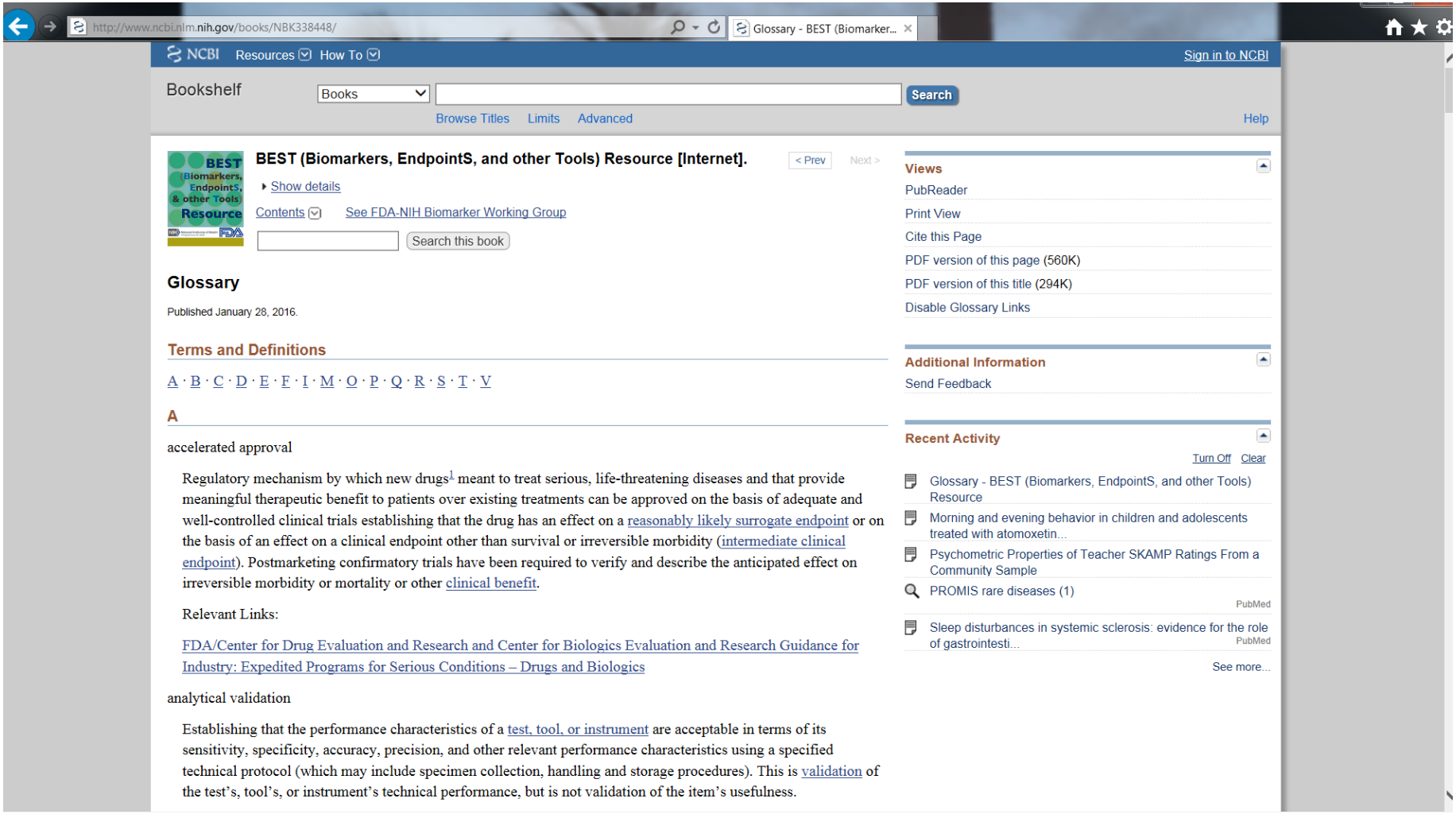
4/22/2016

BEST GLOSSARY

BEST Glossary

- Biomarkers, EndpointS, and other Tools Resource
- Joint effort between FDA and NIH
- Harmonize terminology
- http://www.ncbi.nlm.nih.gov/books/NBK338448/

BEST GLOSSARY



http://www.ncbi.nlm.nih.gov/books/NBK338448/ Glossary - BEST (Biomarker...

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BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. < Prev Next >

Show details

Contents See FDA-NIH Biomarker Working Group

Search this book

Glossary

Published January 28, 2016.

Terms and Definitions

A · B · C · D · E · F · I · M · O · P · Q · R · S · T · V

A

accelerated approval

Regulatory mechanism by which new drugs[1] 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.

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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

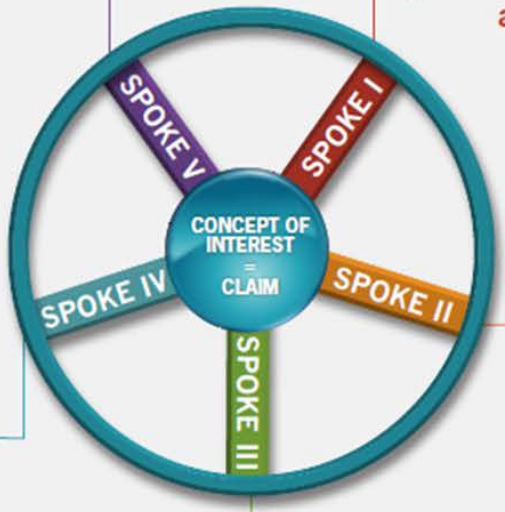
- There is a preliminary conceptual framework and preliminary scoring algorithm available

Qualification of **CLINICAL OUTCOME ASSESSMENTS** (COAs)

V. Modify Instrument

- Identify a new COU
- Change wording of items, response options, recall period, or mode/method of administration/data collection
- Translate and culturally adapt
- Evaluate modifications using spokes I - IV
- Document all changes

Consider submitting to FDA for qualification of new COA, as appropriate.



I. Identify Context of Use (COU) and Concept of Interest (COI)

- Outline hypothesized concepts and potential claims
- Determine intended population
- Determine intended application/characteristics (type of scores, mode and frequency of administration)
- Perform literature/expert review
- Develop hypothesized conceptual framework
- Position COA within a preliminary endpoint model
- Document COU and COI

IV. Longitudinal Evaluation of Measurement Properties/ Interpretation Methods

- Assess ability to detect change and construct validity
- Identify responder definition(s)
- Provide guidelines for interpretation of treatment benefit and relationship to claim
- Document all results
- Update user manual

Submit to FDA for COA qualification as effectiveness endpoint to support claims.

II. Draft Instrument and Evaluate Content Validity

- Obtain patient or other reporter input
- Generate new items
- Select recall period, response options and format
- Select mode/method of administration/data collection
- Conduct cognitive interviewing
- Pilot test draft instrument
- Finalize instrument content, format and scoring rule
- Document content validity

III. Cross-sectional Evaluation of Other Measurement Properties

- Assess score reliability (test-retest or inter-rater) and construct validity
- Establish administration procedures & training materials
- Document measure development
- Prepare user manual

Consider submitting to FDA for COA qualification for use in exploratory studies prior to longitudinal evaluation.

Potential for "Letter of ???"

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
http://www.fda.gov/Drugs

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:
http://www.ncbi.nlm.nih.gov/books/NBK338448/pdf/Bookshelf_NBK338448.pdf

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.**

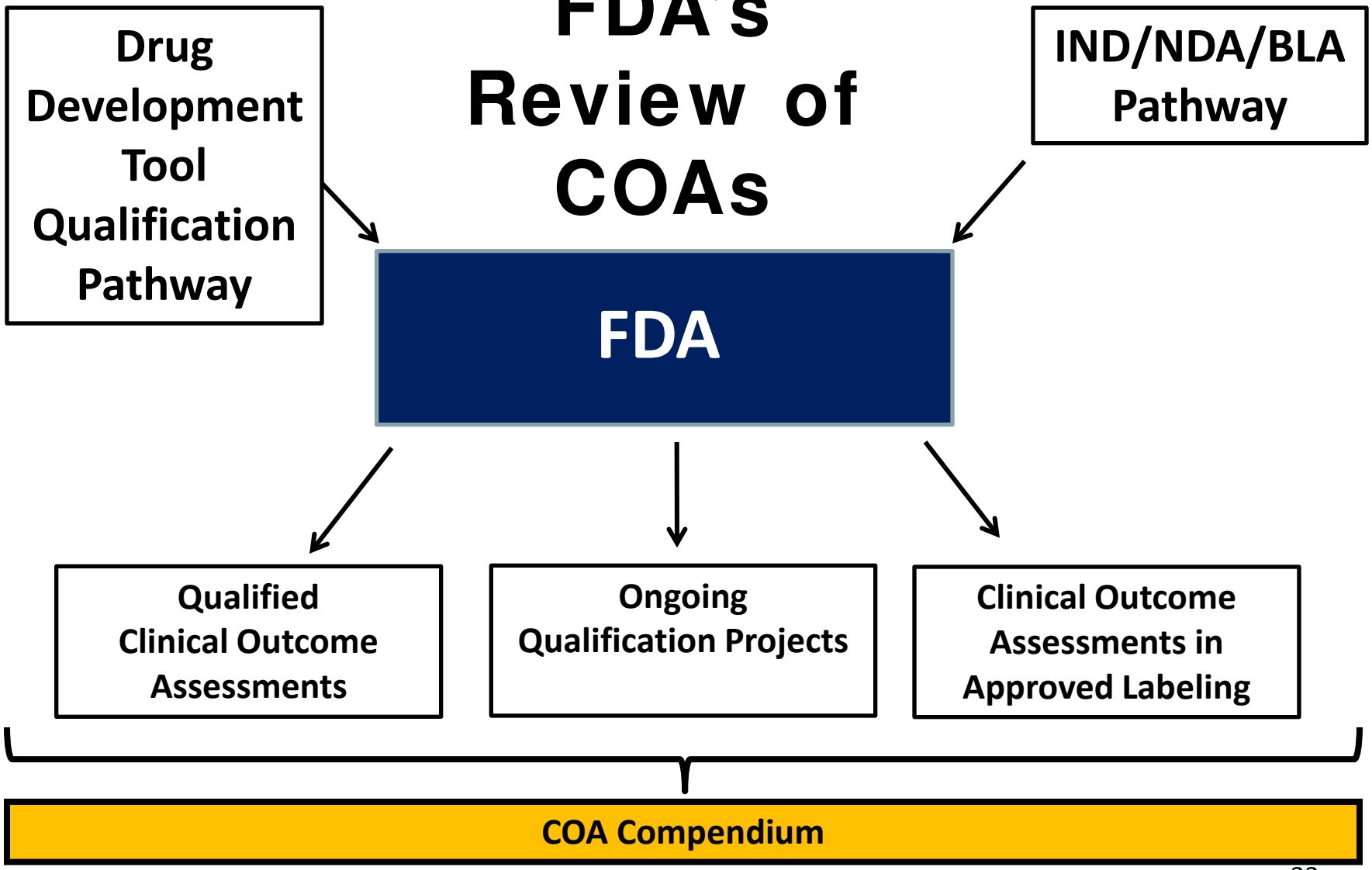
Purpose of COA Compendium*

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



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

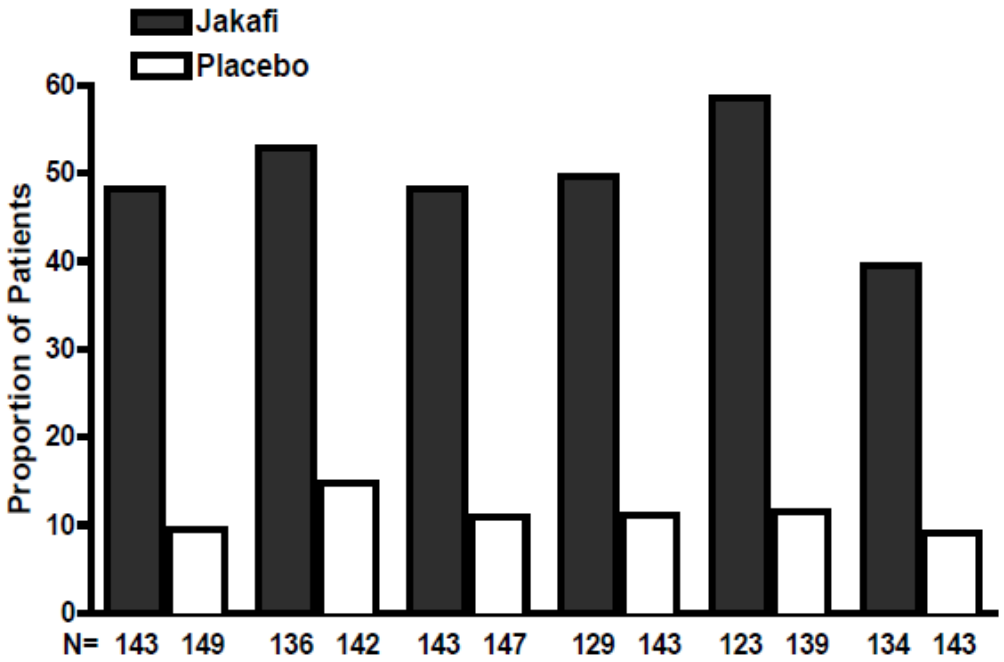
Example of Review Division Input Into Compendium

- 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



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

COLUMNS	ELEMENTS	DESCRIPTION OF CONTENT
1	Disease/Condition	Lists disease or condition and any relevant FDA disease-specific guidance.
2	Indication and/or Claim(s) Description	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." **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.*
3	Outcome of Interest	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.
4	COA (COA Type)	• Lists a labeled, qualified, or ongoing qualification project clinical outcome assessment name and/or description. • Includes the clinical outcome assessment type (i.e., a patient-reported outcome, observer-reported outcome, clinician-reported outcome, or performance outcome).
5	COA Context of Use	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).
6	COA Qualification Information	Lists ongoing and completed clinical outcome assessment qualification project information, if applicable.

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

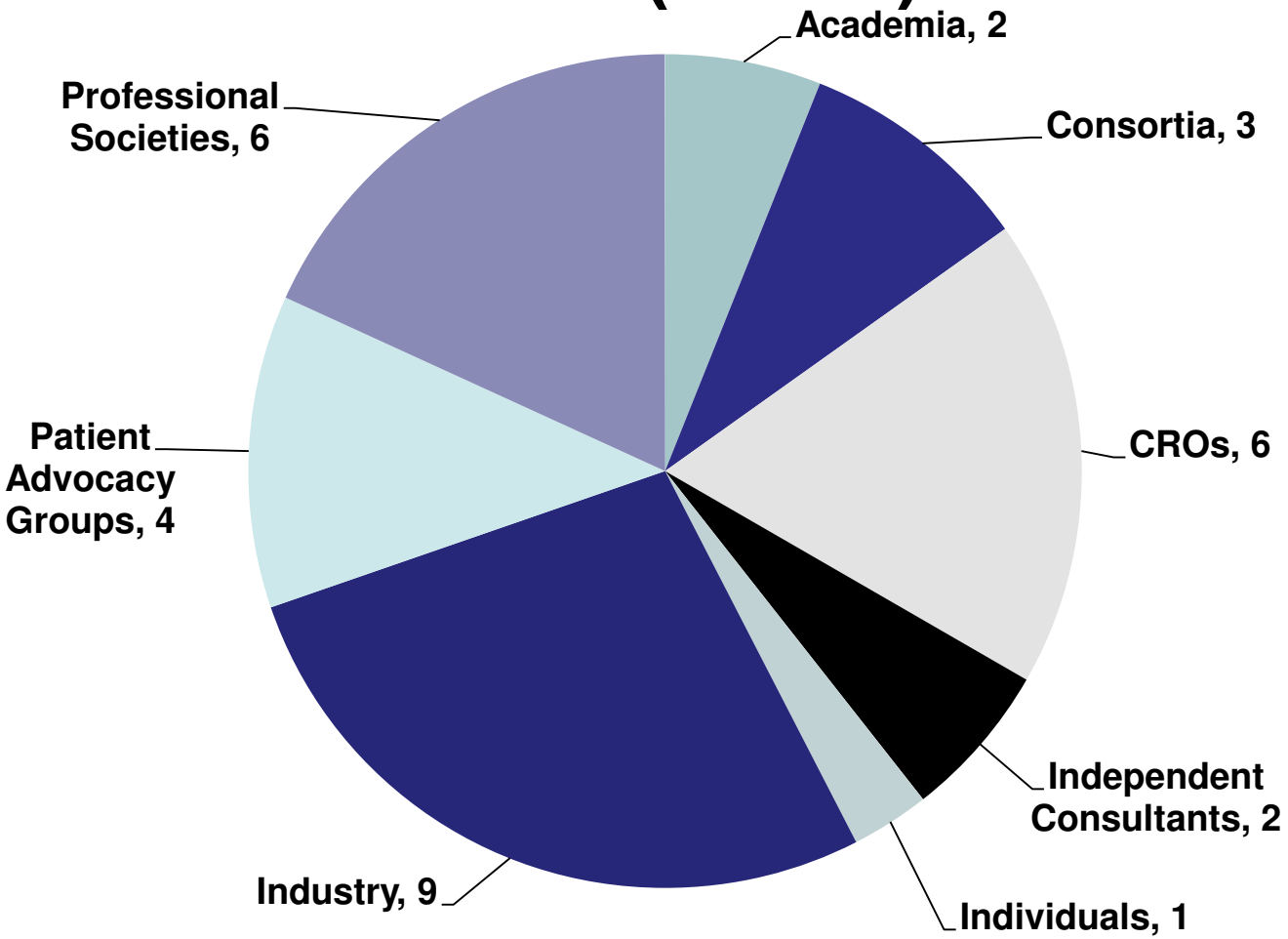
Disease/Condition	Indication and/or Claim(s) Description[36 37]	Outcome of Interest	COA (COA Type)	COA Context of Use	COA Qualification Information
Chronic lymphocytic leukemia (CLL) Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics	Treatment of CLL	Incidence of palpable hepatosplenomegaly	Composite of clinician-reported outcomes, patient-reported outcome, and laboratory/imaging measures (biomarkers) Note: B symptoms are assessed based on patient-reported outcome	Adult patients with CLL	Not applicable
		Size of lymph nodes; incidence of lymph nodes with nodularity			
		B symptoms evaluation (night sweats, fever, unexplained weight loss)			
		Laboratory measures (lymphocytes, neutrophils, platelets, histology)			
Cutaneous T-cell lymphoma (CTCL) Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics	Treatment of CTCL	Skin involvement	Severity Weighted Assessment Tool in addition to other outcomes (e.g., response duration, time to progression, time to objective response) (clinician-reported outcome)	Adult patients with CTCL	Not applicable
		Physician's global assessing improvement or worsening in overall disease	7-Point Physician's Global Assessment (clinician-reported outcome)		
Deep vein thrombosis (DVT) and pulmonary embolism (PE)	Prophylaxis of DVT/PE	Incidence of venous thromboembolic events that includes deep vein thrombosis, non-fatal pulmonary embolism, and death due to thromboembolic in origin	Composite of thromboembolic events defined by a combination of biomarkers and clinician assessments (clinician-reported outcomes)	Adult patients at risk for DVT/PE	Not applicable

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)



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
- **COA Qualification Website:** http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm
- **COA Compendium Website:** http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm459231.htm
- **PRO Guidance:** http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf
- **DDT COA Qualification Guidance:** http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf

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**