

PDUFA V Clinical Outcomes Assessment Workshop

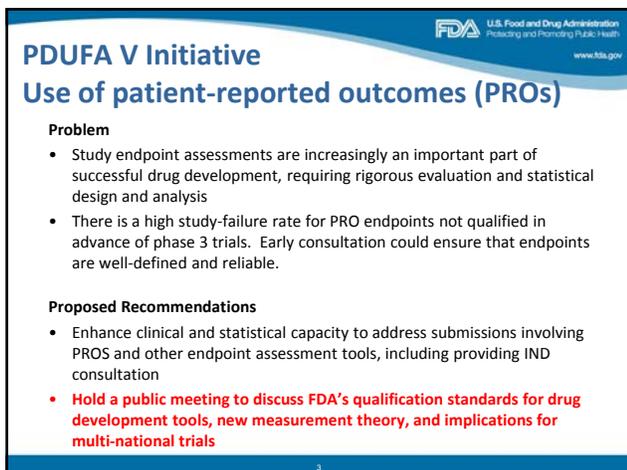
Theresa Mullin, PhD
Director, Office of Strategic Programs
FDA Center for Drug Evaluation and Research

April 1, 2015



**PDUFA V Commitments:
A Set of Targeted Program Enhancements**

- Review program for NME NDAs and Original BLAs
- Enhancing Regulatory Science/Expediting Drug Development
 - Promoting Innovation Through Enhanced Communication Between FDA and Sponsors During Drug Development
 - Methods for meta-analysis
 - Biomarkers and pharmacogenomics
 - **Use of patient-reported outcomes (PROs)**
 - Development of drugs for rare diseases
- **Enhancing Benefit-Risk Assessment**
- Enhancement and Modernization of the FDA Drug Safety System
 - Standardizing REMS
 - Using Sentinel to evaluate drug safety issues



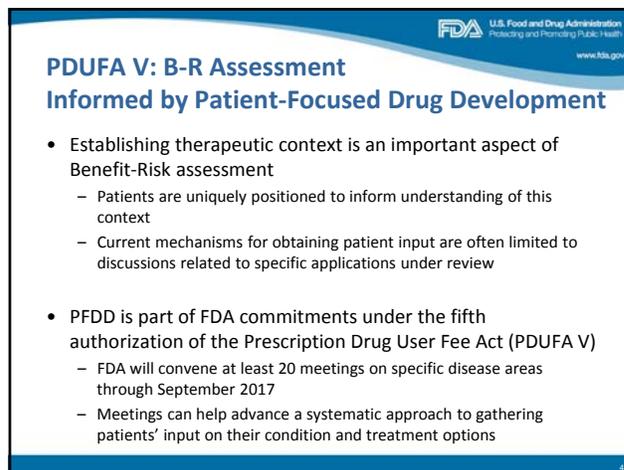
**PDUFA V Initiative
Use of patient-reported outcomes (PROs)**

Problem

- Study endpoint assessments are increasingly an important part of successful drug development, requiring rigorous evaluation and statistical design and analysis
- There is a high study-failure rate for PRO endpoints not qualified in advance of phase 3 trials. Early consultation could ensure that endpoints are well-defined and reliable.

Proposed Recommendations

- Enhance clinical and statistical capacity to address submissions involving PROs and other endpoint assessment tools, including providing IND consultation
- **Hold a public meeting to discuss FDA's qualification standards for drug development tools, new measurement theory, and implications for multi-national trials**



**PDUFA V: B-R Assessment
Informed by Patient-Focused Drug Development**

- Establishing therapeutic context is an important aspect of Benefit-Risk assessment
 - Patients are uniquely positioned to inform understanding of this context
 - Current mechanisms for obtaining patient input are often limited to discussions related to specific applications under review
- PFDD is part of FDA commitments under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V)
 - FDA will convene at least 20 meetings on specific disease areas through September 2017
 - Meetings can help advance a systematic approach to gathering patients' input on their condition and treatment options

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health www.fda.gov

Session 1: Experiences with FDA Guidance on Patient-Reported Outcome Measures and the Clinical Outcome Assessment Tool Qualification Process

Elektra J. Papadopoulos, MD, MPH
Associate Director (acting) for Study Endpoints
Office of New Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
April 1, 2015

1

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health www.fda.gov

Session 1 Participants

Speakers

- Elektra J. Papadopoulos, FDA
- Katarina Halling, AstraZeneca
- Bryce Reeve, University of North Carolina
- Paul Kluetz, FDA

Panelists

- Wen-Hung Chen, FDA
- Gabriela Lavezzari, PhRMA
- Bob Dworkin, University of Rochester Medical Center

2

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health www.fda.gov

Disclaimer

The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.

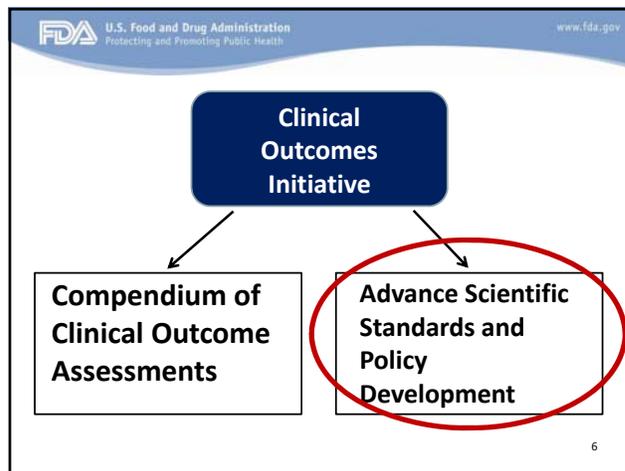
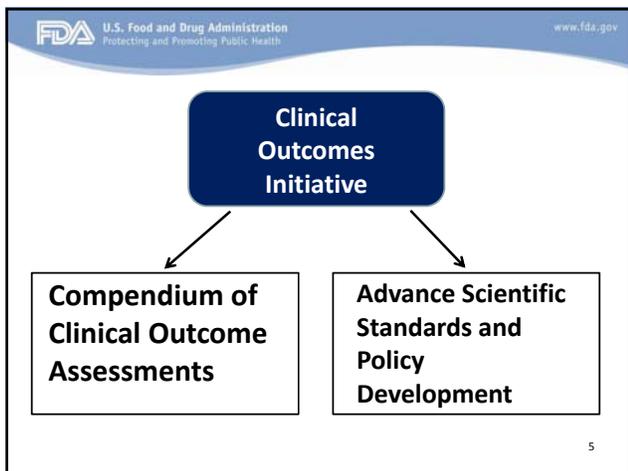
3

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health www.fda.gov

Brookings Meeting Take-away Points: What FDA Can Do

- Work with internal and external stakeholders to show how PRO development and implementation can be operationalized in real world
- Be more proactive in encouraging use of PROs
- Enhance communications, processes and transparency
 - Address need for earlier FDA/Industry communication (e.g., compound start up phase before pre-IND/IND submission)
 - Publish a list of “potentially acceptable” clinical outcome assessments
- Enhance consistency of advice
- Others

4



- FDA U.S. Food and Drug Administration Protecting and Promoting Public Health www.fda.gov
- Scientific Standards Development Needs**
- Operationalization of PRO guidance principles taking into account stages of drug development and need for greater regulatory flexibility
 - Description of good measurement principles for development of other COAs (e.g., ClinRO, performance-based)
 - Standards for analysis of PRO data and display of PRO data in labeling
 - Other research agenda items
- 7

- FDA U.S. Food and Drug Administration Protecting and Promoting Public Health www.fda.gov
- Study Endpoint Consultation Processes**
- Areas of focus for ongoing improvement include:
 - Clarity of advice
 - Provide high-level input early, rather than all details from get go
 - More clarity needed on what is "required" vs. "recommended"
 - Practicality of advice
 - Greater attention to need for concrete, actionable advice that fits into the overall drug development strategy
 - Timeliness of advice
 - Study Endpoint reviewers added to address workload needs

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health www.fda.gov

Critical Path Innovation Meetings*



- Provides an example of how FDA has responded to the request for earlier COA communications
- Voluntary process that can be used as a venue for a discussion of the potential approaches to developing COAs (and other to provide evidence of treatment benefit)
- What it's not:
 - Not a venue for regulatory advice on a specific product development program

*CPIM topics can include: biomarkers, COAs, natural history studies, innovative approaches to clinical trial design and analysis and others.

9

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health www.fda.gov

Questions for Panel 1

- What are the key areas of need for scientific standards development?
- How can the Agency further improve the quality of our COA advice with a focus on practicality in meeting drug development demands?

10

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health www.fda.gov

Addressing the challenges of clinical outcomes assessments in oncology:

Paul G. Kluetz, M.D.
Office of Hematology and Oncology Products

1

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health www.fda.gov

Acronym Dictionary

- COA: Clinical Outcome Assessments
 - Includes all types of clinical assessments for a patient, including reported by patients (PRO) or clinicians (ClimRO)
- PRO: Patient Reported Outcomes (Questionnaires to patients)

Key FDA Stakeholders for this Talk

- OHOP: Office of Hematology and Oncology Products
- SEALD: Study Endpoints and Labeling Development team.

2

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health www.fda.gov

Recent Meetings Highlighting Patient Reported Outcomes (PRO)

- May 2014: FDA co-sponsored AAADV PRO Plenary Session
- May 2014: PRO Consortium
- Jul 2014: Brookings "Enhancing the Development and Use of Patient-Reported Outcomes in Drug Development"
- Oct 2014: AACR Turning the Tide Against Cancer- Patient perspective panel
- Oct 2014: Brookings "Advancing Development and Use of Patient-Reported Outcomes in Drug Development: Near-Term Opportunities"
- Oct 2014: FDA co-sponsored NBTS "Brain Tumor Clinical Trial Endpoints Workshop 2 (Clinical Outcomes Assessments)"

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health www.fda.gov

Take Home Messages from These Meetings

- Capturing the patient perspective in drug development continues to gather momentum as a Priority
- What to measure, how to measure it and how to interpret what we have measured are very complicated issues.
- All parties appear dedicated to finding a way to improve PRO instruments, collection and interpretation across different disease areas

FDA U.S. Food and Drug Administration Protecting and Promoting Public Health www.fda.gov

Feedback I have heard from Industry, Advocates, PRO developers

- 2009 PRO Guidance is too unrealistic / infeasible
 - Lack of instruments (questionnaires) to use to gather PRO data
- Inconsistent advice about patient reported outcomes
 - Between SEALD and OHOP
 - Within different OHOP Divisions
- FDA Office of Hematology and Oncology does not put patient reported outcomes in labels as often as other therapeutic areas

FDA U.S. Food and Drug Administration Protecting and Promoting Public Health www.fda.gov

Challenges in Oncology include:

- Lack of agreed upon instruments (questionnaires)
- Trial designs not optimized for PRO
- Significant portion of PRO data frequently missing
- Lack of standardization in data analysis
- Lack of standardization in data presentation
- Lack of familiarity with PRO data analysis for Oncology clinical trial reviewers (both statistical and clinical) as we have relied on survival and radiographic evidence of treatment benefit

6

FDA U.S. Food and Drug Administration Protecting and Promoting Public Health www.fda.gov

Toward more Consistent PRO Advice

- Increased Collaboration Between OHOP and SEALD
 - OHOP-SEALD Working group with Monthly Meetings
- Improved OHOP PRO and Labeling Expertise
 - Office Level Dedication to advancing PRO in Oncology
 - PRO Leads and Associate Directors of Labeling in each OHOP clinical Division provide PRO and Labeling expertise and interact with SEALD: consistency between OHOP Divisions
- Overall OHOP PRO Educational Opportunities for Reviewers
 - Monthly Hematology/Oncology PRO Case Series
- **Goal: More detailed, consistent and proactive PRO advice to sponsors**

FDA U.S. Food and Drug Administration Protecting and Promoting Public Health www.fda.gov

We have Moved Away from a Parallel Process

```

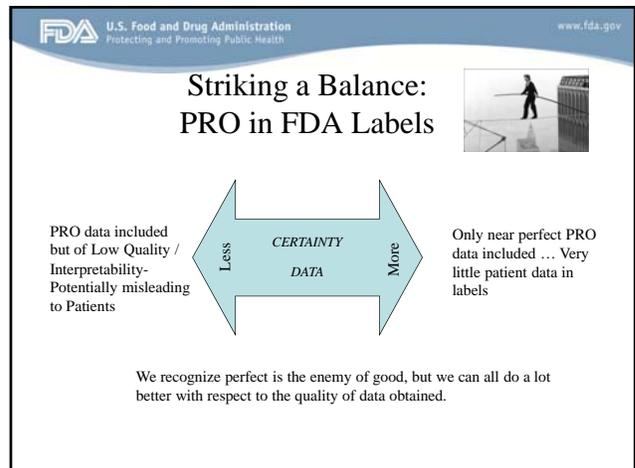
    graph TD
      Sponsor[Sponsor]
      SEALD((SEALD Review Team))
      Clinical((Clinical Division Review Team))
      
      SEALD -- Advice --> Sponsor
      Clinical -- Advice --> Sponsor
      
      Clinical -- Consult --> SEALD
      
      SEALD --- SEALD_exp[Expertise in PRO Instrument Development]
      Clinical --- Clinical_exp[Clinical knowledge  
Oncology Trial Design  
Statistical expertise]
    
```

8



- FDA U.S. Food and Drug Administration Protecting and Promoting Public Health www.fda.gov
- ### Identifying PRO Instruments
- This topic will be thoroughly discussed today, but my perspective briefly:
 - **Long Term:** Encourage New Instrument Development
 - **Short Term:** Identify existing instruments that can be used or modified as “reasonable” for use in trials
 - Optimal choices for instruments will be an iterative process
 - OHOP acknowledges that the PRO guidance is a roadmap for “gold standard” PRO instruments, but that flexibility may need to be exerted.
 - **We have concentrated very heavily on instruments and have MUCH we can do NOW to improve trial design, data capture, data analysis and presentation!**

- FDA U.S. Food and Drug Administration Protecting and Promoting Public Health www.fda.gov
- ### Moving Forward-
- More standardization of PRO in Oncology Trials is Needed
- What Core Concepts should we measure in all oncology trials?
 - May include: disease symptoms, treatment symptoms, physical function
 - HOW do we best measure these concepts?
 - Instrument identification
 - Optimal trial design and assessment frequency
 - Optimal methods to minimize missing data
 - Optimal statistical analysis methods
 - HOW do we most accurately PRESENT the results in a label?
 - Most informative... Least misleading way





Conclusion

- Office of Hematology and Oncology is working closely with SEALD and all stakeholders to improved the quality of patient-reported data obtained in cancer clinical trials
- Standardization of what is measured and how to measure it will be critical moving forward

Revisiting Guidance on PRO Measure Design and Evaluation



Bryce B. Reeve, Ph.D.

Associate Professor, Health Policy & Management
Member, Lineberger Comprehensive Cancer Center

Email: bbreeve@email.unc.edu

UNC Gillings School of Global Public Health



Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical Medical

Discussion of the PRO Guidance

- *“Only one PRO instrument has been fully qualified by the FDA, and the PRO label claim approvals have declined slightly since the publication of the guidance.”*
– Brookings Meeting Summary (10-6-2014)
- *“The requirements...are so onerous as to dissuade companies from pursuing PRO claims.”*
- *“...a sense that sponsors have to develop ‘perfect’ tools.”*
– Kate Rawson, “Getting with the PRO-gram: Making PROs work.” Pharma&MedTechBusinessIntelligence (Jan 2015)

*“What we observe is not nature itself
but nature exposed to our
method of questioning.”*

Werner Heisenberg 1958



There is no perfect
Clinical Outcome Assessment (COA)

- Patient-Reported Outcomes (PROs) measures
- Clinician-Reported Outcomes (ClinRO) measures
- Observer-Reported Outcome (ObsRO) measures
- Performance Outcome (PerFO) measures

Eight Attributes of a Quality Instrument

1. Conceptual and measurement model
2. Reliability
3. Validity
4. Responsiveness
5. Interpretability
6. Respondent and administrative burden
7. Alternate forms
8. Cultural and language adaptations

Source: Scientific Advisory Committee of the Medical Outcomes Trust. *Assessing health status and quality-of-life instruments: Attributes and review criteria*. QOL Research II: 193-205, 2002.

Guidance for Industry
Patient-Reported Outcome Measures:
Use in Medical Product Development
to Support Labeling Claims

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Veterinary Medicine (CVM)
Washington, DC
2013



ISPOR

Qual Life Res (2013) 22:1889–1905
DOI 10.1007/s11111-013-9411-1

Volume 12 - Number 8 - 2009
VALUE IN HEALTH

ISOQOL
outcome
and comp

Bryce B. Reeve
Caroline B. Ter
Carol M. Moyn
Pamela S. Haid
David Feeny - I
Sara Ahmed - N

The PCORI Methodology Report

PCORI Methodology Committee
David McLean, Joseph Follen, Wilfrid Burg, Katherine Pechter, R
Robin Newhouse, Editors

November 2013

COSMIN

COSMIN checklist manual
Consensus-based Standards for the selection of
health Measurement Instruments.

Lidwine B. Mokkink
Caroline B. Terwee
Donald L Patrick
Jordi Alonso
Paul W Stratford
Dirk L Knol
Lex M Bouter
Henrica CW de Vet

Bryce's 8 key areas to consider



1. Expand opportunities for patient engagement
2. e-PROs & interactive voice response (IVR) assessments
3. Disease-specific PRO vs PRO-specific measures
4. Item Response Theory (IRT)
 - Item Banking
 - Tailored static Short Forms
 - Computerized Adaptive Testing (CAT)
5. Pediatric PRO Measures
6. Patient-reported data for safety/AE monitoring.
7. Presentation of PRO data and standardization of the PRO metric
8. More methods research needs to be done....



Session 1: Experiences with FDA Guidance on Patient-Reported Outcome Measures and the Clinical Outcome Assessment Tool Qualification Process

Elektra J. Papadopoulos, MD, MPH
Associate Director (acting) for Study Endpoints
Office of New Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
April 1, 2015

1

Session 1 Participants

Speakers

- Elektra J. Papadopoulos, FDA
- Katarina Halling, AstraZeneca
- Bryce Reeve, University of North Carolina
- Paul Kluetz, FDA

Panelists

- Wen-Hung Chen, FDA
- Gabriela Lavezzari, PhRMA
- Bob Dworkin, University of Rochester Medical Center

2

Clinical Outcome Assessment to Demonstrate Treatment Benefit: An FDA Perspective

Elektra Papadopoulos, MD, MPH
Associate Director (acting) for Study Endpoints
Office of New Drugs, Immediate Office
Center for Drug Evaluation and Research (CDER), FDA

April 1, 2015

3

Disclaimer

The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.

4

Treatment Benefit

- Treatment benefit is demonstrated by evidence that the treatment has a positive impact on how a person with the condition or disease:
 - Survives
 - Feels or Functions in daily life

5

Types of Outcome Assessments

- Survival
- **Clinical outcome assessments (COAs)**
- Surrogates
 - Often a biomarker* that is intended as a substitute for how a patient feels, functions, or survives
 - Two types for use in clinical trials to support product approval:
 - Established Surrogates (for regular approval)
 - Reasonably likely to predict clinical benefit (for accelerated approval; require post-marketing studies to confirm clinical benefit)

**biomarker: a physiologic, pathologic, or anatomic characteristic that is objectively measured and evaluated as an indicator of some normal or abnormal biologic function, process or response to a therapeutic intervention*

6

Definitions

- Clinical Outcome Assessment (COA)*:
 - A COA is any assessment that may be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of treatment benefit.
- There are four types of COA measures:
 - Patient-reported outcome (PRO) measures
 - Clinician-reported outcome (ClinRO) measures
 - Observer-reported outcome (ObsRO) measures
 - Performance outcome (PerfO) measures

* As defined on the FDA website

7

Evidentiary Standards to Document Treatment Benefit

- Documented by “Substantial evidence” (21 CFR 201.56(a)(3))
- Evidence from “Adequate and well-controlled clinical trials”
- The methods of assessment are “well-defined and reliable” (21 CFR 314.126)

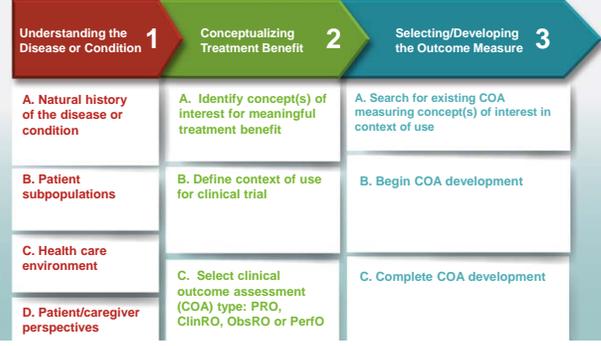
8

When is a Clinical Outcome Assessment Adequate for use?

- Regulatory standard: measures are *well-defined and reliable*
 - Empiric evidence demonstrates that the score quantifies the concept of interest in the targeted context of use
- What does this mean?
 - This means measuring the right thing (concept of interest), in the right way in a defined population (targeted context of use), and the score that quantifies that 'thing' does so accurately and reliably, so that the effects seen in the outcome assessment can be interpreted as a clear treatment benefit.

9

Roadmap to PATIENT-FOCUSED OUTCOME MEASUREMENT in Clinical Trials



FDA's PRO Guidance for Industry (2009)

Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

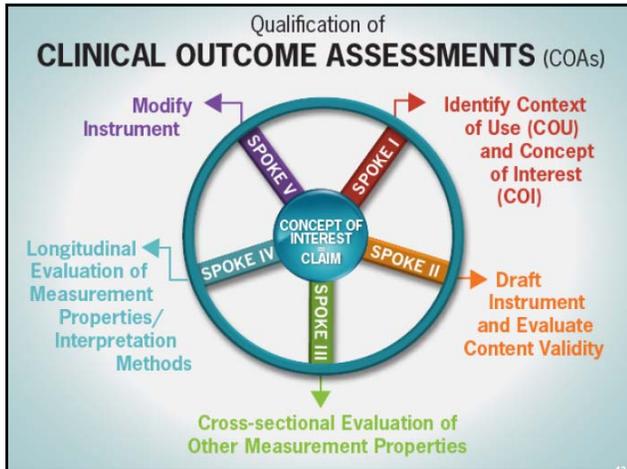
- PRO:** a measurement based on a report that comes from the patient about the status of a patient's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
- Describes good measurement principles many of which are also applicable to other types of clinical outcome assessment tools
- Provides an optimal approach to PRO development; flexibility and judgment needed to meet practical demands

11

Establishing Content Validity

- Content validity:** Evidence that the instrument measures the targeted concept in the context of use
 - And that the score represents the concept
 - Supported by literature review, expert input and patient input
- Begins after confirmation that the concept of interest and the context of use are appropriate
- Testing other measurement properties (e.g., test-retest reliability, construct validity and ability to detect change) will not replace or rectify problems with content validity

12



FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Drug Development Tool Qualification Guidance (Final January 2014)

Guidance for Industry and FDA Staff
Qualification Process for Drug Development Tools
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf>

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

- Qualification process described for Biomarkers, Animal Models, and Clinical Outcome Assessments (COA)
- COA qualification:
 - a conclusion that within the stated context of use, the results of measurement can be relied upon to represent a specific concept of interest with a specific interpretation when used in drug development and regulatory decision-making

14

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Ways FDA Provides COA Advice

- FDA provides advice under two pathways:
 - Specific drug development programs
 - Qualification program
- Formal qualification through COA drug development tool qualification program is completely voluntary and it in no way means that an instrument needs to be qualified to be acceptable for use in a clinical trial to support labeling claims.

15

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Helpful Links

- FDA's Patient-Reported Outcome (PRO) Guidance for Industry:
 - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071975.pdf>
- DDT Clinical Outcome Assessment Qualification Program webpage:
 - <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm>
 - Includes Roadmap and Wheel and Spokes diagrams
- FDA's DDT Qualification Program Guidance for Industry:
 - <http://www.fda.gov/downloads/drugs/guidancecomplianceinformation/guidances/ucm230597.pdf>

16

A Big Thank You to the Study Endpoints Team!

Medical Lead:

Ann Marie Trentacosti, M.D.

Regulatory Project Managers:

Susan Montenegro, Pharm.D.,
M.P.H., B.C.P.S.

Jessica Voqui, Pharm.D., M.S.
(interim)

ORISE Fellows:

Paula Chakravarti, M.S.

Nikunj Patel, Pharm.D.

Reviewers:

Michelle Campbell, Ph.D.

Wen-Hung Chen, Ph.D.

Yasmin Choudhry, M.D.

Selena Daniels, Pharm.D., M.S.

Sarrit Kovacs, Ph.D.

Ashley Slagle, Ph.D., M.S.

Jessica Voqui, Pharm.D., M.S.

Benefit-Risk Framework for human drug review

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Benefit-Risk Summary and Assessment		
Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Patient Focused Drug Development Provides the therapeutic context for weighing benefits and risks	
Current Treatment Options		
Benefit	Clinical Outcome Assessments (e.g., PROs) Incorporates expert judgments about the evidence of efficacy and safety, and efforts to further understand or mitigate risk	
Risk		
Risk Management		

5

- April 1 COA Workshop Outline**
- FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov
- Session 1:
 - FDA Guidance on PROs and COA Assessment Tool Qualification
 - Session 2:
 - Advancing Measurement Strategies for COA Tools
 - Session 3:
 - Use of COA Tools in Multinational Clinical Trials
 - Session 4:
 - Strategies Going Forward (Key learnings from PDUFA V)
- CDER - Office of Strategic Programs (OSP) 6

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Thank you!

CDER - Office of Strategic Programs (OSP) 7