The Patient-Reported Outcome (PRO) Consortium:

A Collaborative Approach to PRO Instrument Development and Qualification

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Health Care Interventions

- Aimed at
  - Increasing longevity
  - Preventing future morbidity
  - Making patients feel and function better

Note: The FDA is required to base its evaluation of *treatment benefit* on how patients “feel, function, and survive.”

Endpoints in Clinical Trials

Clinical trial endpoints for assessing treatment benefit are:

- Survival
- Biomarkers
- Clinical Outcome Assessments
  - Clinician-Reported Outcomes (ClinROs)
  - Observer-Reported Outcomes (ObsROs)
  - **Patient-Reported Outcomes (PROs)**

Burke and Walton, 2011

Endpoints in Clinical Trials

- **Survival** – Example
  - Progression free survival in oncology trials

- **Biomarkers** – Examples
  - HbA_{1C} in diabetes trials
  - Hemoglobin and hematocrit in anemia trials

- **Clinician-Reported Outcomes (ClinROs)** – Examples
  - *Hamilton Depression Rating Scale* (*HAM-D*) in depression trials
  - *Expanded Disability Status Scale* (*EDSS*) in multiple sclerosis trials

Endpoints in Clinical Trials

- **Observer-Reported Outcomes (ObsROs)** – Examples
  - *Inattention/Overactivity with Aggression (IOWA) Conners* scale completed by schoolteachers in attention deficit hyperactivity disorder (ADHD) trials
  - *Activities of Daily Living Inventory* completed by caregivers/informants in Alzheimer's disease trials

- **Patient-Reported Outcomes (PROs)** – Examples
  - Number of incontinence episodes per week in overactive bladder trials
  - Relief of ocular itching in seasonal allergic conjunctivitis trials

Patient-Reported Outcomes

- Subjective well-being/quality of life
- Health-related quality of life (HRQoL)
- Health status
- Satisfaction with treatment
- Productivity
- Participation
- **Symptom experience**
- **Function/dysfunction**

PRO Endpoints in Clinical Trials

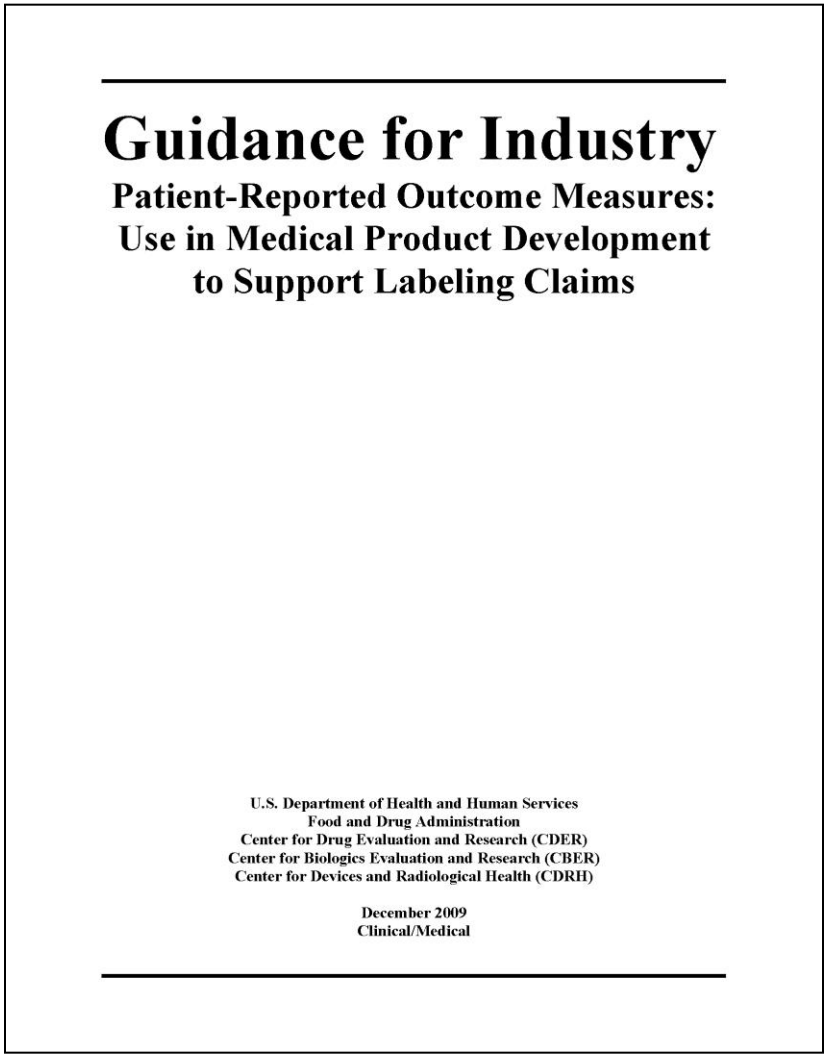
Regulatory Context

- To support drug approval for a specific indication
- To obtain a labeling claim

Regulatory guidance

- European Medicines Agency (EMA)
- US Food and Drug Administration (FDA)

FDA's PRO Guidance



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

- Clear acknowledgement of the importance of appropriately and effectively incorporating the patient's voice into the evaluation of medical products

- Draft: February 2006
- Final: December 2009

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM205269.pdf

FDA's PRO Guidance

- Describes how the FDA plans to evaluate PRO (and ClinRO and ObsRO) instruments used as efficacy endpoints in clinical trials.

- PRO assessment is "… a measurement of any aspect of a patient's health status that comes directly from the patient (i.e., without the interpretation of the patient's responses by a physician or anyone else)."

Note: Part of the impetus for the PRO Guidance was to bring consistency to the evaluation of PRO measures across the FDA review divisions.

PRO Endpoints in Product Labeling

A review of effectiveness endpoints reported in FDA-approved product labeling for new molecular entities approved from **1997 through 2002** found that PRO endpoints were included in **30% (64/215)** of the product labels examined. For 23 of the products, PROs were the only endpoints reported.

Source: Willke et al. *Controlled Clinical Trials* 2004

PRO Endpoints in Approved Labels: Examples

- Pain (e.g., severity, frequency, time to relief)
- Seizure frequency
- Micturation/urination and incontinence episodes
- Itching (i.e., ocular)
- Dry mouth symptoms
- Stool frequency and consistency
- Sexual function
- Time to flu symptom relief
- Nausea and/or vomiting

Source: Willke et al. *Controlled Clinical Trials* 2004

PRO Endpoints in Product Labeling

- Since release of the PRO Guidance:
- Data regarding new molecular entities and biologic license applications approved between **January 2006 and December 2010** show that **24% (28/116)** of the products had PRO endpoint-based labeling claims. For 20 (71%) of the 28 products, a PRO measure was the primary endpoint.

Source: Gnanasakthy et al. *Value in Health* 2012

Critical Path Institute (C-Path)

Established in 2005 by the University of Arizona and the US Food and Drug Administration (FDA)

An independent, non-profit organization

Dedicated to implementing FDA's *Critical Path Initiative* - A strategy for transforming the way FDA-regulated products are developed, evaluated, manufactured, and used

C-Path (www.c-path.org)

Provides a neutral, pre-competitive venue for collaboration aimed at accelerated development of safe and effective medical products

Primary sources of funding for C-Path operations:

- government agency grants (e.g., FDA grant no. U01FD003865)
- foundation grants/contracts (e.g., Science Foundation Arizona grant no. SRG 0335-08)
- private philanthropy
- membership fees from member firms

PRO Consortium

- Formed in late 2008 by C-Path, in cooperation with the FDA and the pharmaceutical industry

- **Membership**
  - Only available to medical product companies
  - 26 members in 2013

- **Non-Voting Participants**
  - Representatives of governmental agencies
  - Clinical consultants, patients, academic researchers, and CROs partnering in the development of the PRO instruments

PRO Consortium Members

Mission Statement

To establish and maintain a collaborative framework with appropriate stakeholders for the development of qualified, publicly available patient-reported outcome (PRO) instruments for use in clinical trials where PRO endpoints are used to support product labeling claims.

PRO Consortium: Goals

- Develop qualified, publicly available PRO instruments
- Enable pre-competitive collaboration that includes FDA input/expertise
- Avoid development of multiple PRO instruments for the same purpose
- Share costs of developing new PRO instruments
- Facilitate FDA's review of medical products by standardizing PRO endpoints

Current Working Groups

Asthma – 11 firms

- Actelion, Amgen, AstraZeneca, Boehringer Ingelheim, Forest, GlaxoSmithKline, Ironwood, Janssen, Merck, Novartis, and Roche/Genentech

Cognition – 9 firms

- AbbVie, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eisai, Janssen, Merck, Novartis, Pfizer, and Roche/Genentech

Depression – 8 firms

- AbbVie, Bristol-Myers Squibb, Lilly, Forest, Janssen, Pfizer, Shire, and Sunovion

Current Working Groups

Functional Dyspepsia – 3 firms

- Forest, Ironwood, and Shire

Irritable Bowel Syndrome – 3 firms

- Forest, Ironwood, and Takeda

Lung Cancer (NSCLC) – 6 firms

- AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Lilly, Merck, Roche/Genentech

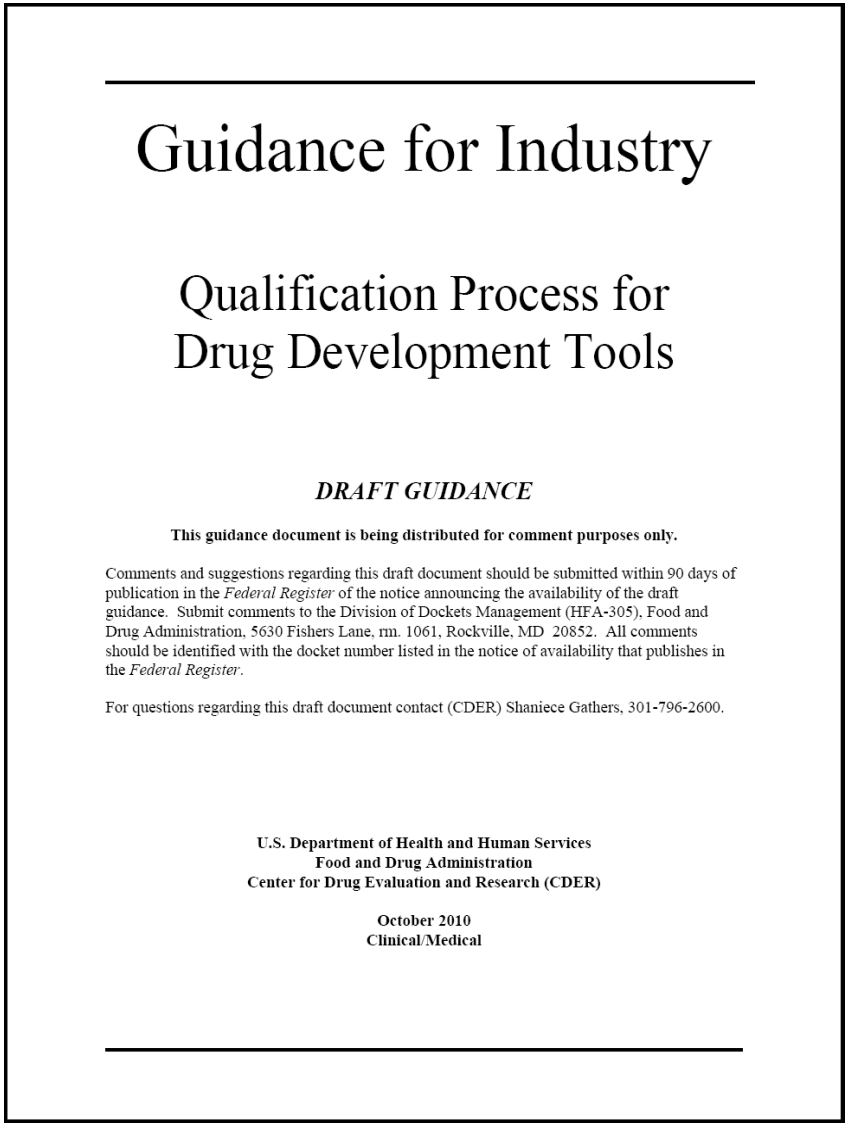
Rheumatoid Arthritis – 7 firms

- Boehringer Ingelheim, Lilly, GlaxoSmithKline, Janssen, Novo Nordisk, Roche/Genentech, and UCB

Goal of Working Groups

- To produce and/or compile the necessary evidence to enable new or existing PRO instruments to be “qualified” by the FDA for use in clinical trials where PRO endpoints can be used to support product labeling claims.

FDA Drug Development Tool (DDT) Guidance



Guidance for Industry

Qualification Process for
Drug Development Tools

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 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) Shaniece Gathers, 301-796-2600.

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

October 2010
Clinical/Medical

- Draft version currently available (October 2010)
- Final version coming soon; no major changes expected; will clarify of the process
- Describes the DDT qualification process

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf

FDA Qualification

- Qualification is based on an FDA review of evidence that supports the conclusion that a PRO instrument provides a **well-defined and reliable assessment of a targeted concept in a specified context of use**.

- FDA's *Guidance for Industry: Qualification Process for Drug Development Tools* (draft - October 2010)

FDA Qualification

- **…has the potential to:**

- More effectively incorporate the patient's voice into the evaluation of treatment effects
- Increase number of accepted PRO measures used to support claims in product labeling
- Enhance comparability/consistency of endpoints across clinical trial
- Improve efficiency for sponsors in endpoint selection
- Improve product labeling

Working Group Stages

Scoping Stage

FDA to review Scoping Stage Summary Document

Vendor Selection Stage (prepare/release RFP, proposal review, & vendor selection)

Content Validity Stage

FDA reviews Content Validity Summary Document

Psychometric Analysis Stage

FDA reviews Psychometric Analysis Summary Document

Qualification Stage

FDA to review "Qualification Dossier" and make "fit-for-purpose" determination

PRO Consortium: Summary

- A process for collaborative, pre-competitive PRO instrument development has been established in a neutral environment
- The FDA has agreed to a review structure for developmental milestone documents
- The process will be refined and improved as we learn what works and what doesn't
- The PRO Consortium approach has substantial benefits as well as challenges