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FDA Perspective: Use of PROs in Product Labels – Objectives & Hurdles to New Methodologies

International Society for CNS Clinical Trials & Methodology (ISCTM)
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FDA Mission

- **Ensure the safety & efficacy of medical products**
- **Advance the public health by helping to speed innovations that make medical products more effective, safer & more affordable**
- **Help the public get accurate, science-based information they need to properly use medical products**

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Streamlining the "Critical Path"

"There is an urgent need to improve the efficiency and effectiveness of the clinical trial process, including trial design, endpoints, and analyses…much more attention and creativity need to be applied to disease-specific trial design and endpoints intended to evaluate the effects of medical products."

http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

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Streamlining the "Critical Path"

For many therapeutics, effectiveness criteria are best defined by the practitioners and patients who use the products. Much work needs to be done on clinical trial design and patient-driven outcome measures to ensure that endpoints in new therapeutic areas accurately reflect patient needs and values. Community (health professional and patient) consensus on appropriate outcome measures and therapeutic claims can lay a clear development path for new therapeutics, especially when there is international regulatory harmonization."

http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

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Challenges for the Critical Path Initiative

- New therapeutics with novel mechanisms targeting unique pathways or even diseases may demand novel assessments
- As new endpoints emerge, “validation” requires that we understand not only how these endpoints perform, but what they mean clinically
- Amongst the important considerations in interpreting the clinical meaning of an endpoint (i.e., assessing risk-benefit) is having an idea of the level of change that is important to the patient

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Labeling claims

Evidence of drug effectiveness is deemed substantial for claims in product labels, or advertising, if supported by adequate & well-controlled clinical trials using endpoint assessments that are well-defined and reliable to measure the specific concept(s) stated or implied by the claims.

Labeling must not be false or misleading in any particular.

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Use of PROs in clinical trials has a key role in drug development

Because:

1. **Some treatment effects are known only to the patient (e.g., pain, fatique)**
2. **There is a desire to know the patient perspective about treatment effectiveness**
3. **The patient can provide a unique perspective beyond clinical based measures**

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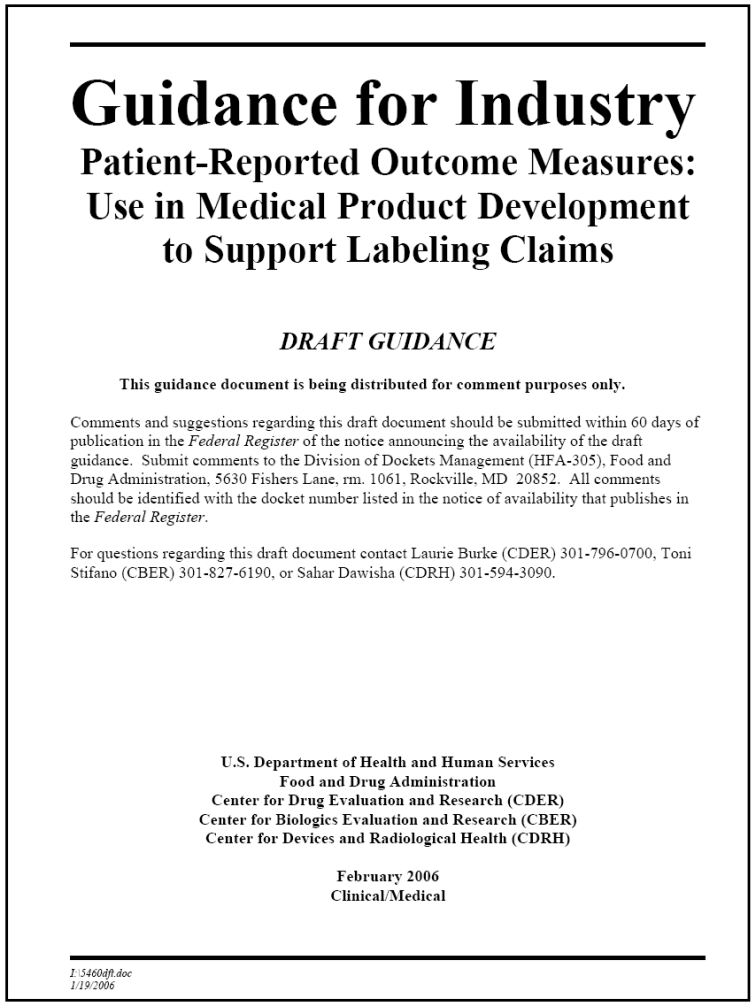

Guidance for Industry

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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 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 Laurie Burke (CDER) 301-796-0700, Toni Stifano (CBER) 301-827-6190, or Sahar Dawisha (CDRH) 301-594-3090.

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

To explain how FDA evaluates PRO instruments for their usefulness in measuring & characterizing benefit of medical product treatment as perceived by the patient.

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Labeling Claims

The adequacy of a PRO instrument as a measure to support medical product labeling claims depends on its developmental history & documented measurement properties.

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FDA Instrument Review

- **The most critical consideration during FDA's review of endpoints used to measure treatment effects is the adequacy & availability of a clearly established concept of measurement**
  - **What is the instrument measuring?**
  - **Is it meaningful as a treatment benefit?**
  - **Are measurement results truthful and not misleading?**

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Other Clinical Trial Design Issues

- **Study objectives correspond to the endpoint assessments and SAP**
- **Controlling for bias**
- **Quantification of meaningful effect sizes**
- **Calculation of study sample size to demonstrate treatment effects of that size**
- **Relationships among all trial endpoints**

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PRO use in clinical trials depends on the instrument's demonstrated ability to function as expected in all patient subgroups

- Consideration for all known and possible patient differences that may influence PRO results, e.g., age group, sex, language, culture, disease severity, co-morbidities, etc.
- If patient subgroup-specific versions are created, FDA considers whether each version conforms to the pre-specified conceptual framework and whether a version functions similarly between groups

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IRT, PRO Item Banks & CAT

- **FDA's experience with IRT is limited to its use as a substitute for factor analysis during instrument development**
- **No experience reviewing IRT/CAT to measure & compare medical product treatment effects in the clinical trial setting**
- **Not clear what the specific regulatory review issues will be when these methods are used**

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Specific concerns when using ePROs

- **Sponsors should ensure that FDA regulatory requirements are met for sponsor and investigator**
  - **Record keeping**
  - **Maintenance**
  - **Access**

*** See 21 CFR 312.50, 312.58, 312.62, 312.68, 812.140 & 812.145**

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Investigator record-keeping requirements

- **Preparation & maintenance of accurate case histories (including case report forms & supporting data)**
- **Record retention**
- **Provision for FDA to access, copy & verify records (i.e. source data verification)**
  - **Source documentation easily satisfied with paper PROs**

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Source documentation for ePROs

- **Can be a problem if direct control over source data is NOT maintained by the investigator**
- **To meet FDA requirements the investigator must retain control and be able to provide access to records that serve as the electronic source documentation.**
- **The investigators need to be comfortable with the methods and used and must remain accountable for confirming data accuracy.**

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Summary

- **Use of patient-reported information in clinical trials has always had a key role in drug development**
- **Patients increasingly demand better information about treatments in terms they can understand**
- **Many challenges exist with PRO endpoints—IRT, item banks & CAT has the potential to both resolve and add to those challenges**

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Concluding remarks

- **FDA encourages demonstrations of the application and added-value of item banks, IRT-based instruments and CAT in the clinical trial setting**
  - **to determine how to apply established measurement principles**
  - **to evaluate their performance against other known PRO testing and measurement paradigms**