

# Addressing Methodological Challenges in International CNS Clinical Trials

ISCTM AUTUMN CONFERENCE WORKSHOP

**Boston Park Plaza** 

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Working Group Chairs: Richard Keefe, PhD; Amir Kalali, MD

### **Guidance for Industry**

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

A REVIEW: PURPOSE AND USE

## THE FDA PRO GUIDANCE

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# Presenter Disclosure

### Monika Vance - Founder & President, Santium

I have relevant financial relationships with the concepts described, reviewed, evaluated, or compared in this presentation.

Financial . financial compensation from Santium, with 100% ownership interest and income generated from government, healthcare and pharmaceutical industries; providing services centered on psychological assessment instrumentation, including management of psychometric and linguistic validations, and health outcomes research.

Non-financial - No relevant non-financial relationships to disclose.



### FDA PRO GUIDANCE

### A POSITION DOCUMENT

FDA's current thinking and attitude to dominant research trends in the pharma industry.

### FDA's expectations for:

- alignment in information exchange
- " optimal turn-around timeline

### Itos only a RECOMMENDATION

Think of it as a **communication guide** for the type of information FDA expects to see in your submissions.

Do NOT think of it as a methodology manual.

Draft: February 2006; Final: December 2009

### REMEMBER:

The Guidance could never be a set of concrete requirements that pharma must follow line-by-line to ensure approval from FDA. That is why the guidance is not overly specific. If it were, even if only interpreted as such, it would limit progress in CNS drug development, your scientific and medical objectivity and judgment, and also disregard a monumental volume of psychometric research.



### **INTENDED PURPOSE**

To accelerate evaluation of claims for medical product labeling.

### When...

PROs are used as clinical trial endpoints, and patients quoice is important in approval process.

*Claim* . statement or implication of treatment benefit

*Labeling* . packaging insert; description and summary of use, safety, and effectiveness of the medical product (i.e. drug, device, biologic etc.)

- Aimed at confirmatory trials
- Emphasizes need for supporting documentation:
  - . PRO development
  - . nature of modification
  - . psychometric properties and scoring
  - . statistical analysis and interpretation
- Supports industrycs view that PROs are important for insights into unobservable symptoms, and relevant patient experiences without clinical interpretation by observing physicians.
- Explains FDAcs SEALD division s logic and process when evaluating PRO label claims
- Passively implies application to ClinROs and ObsROs

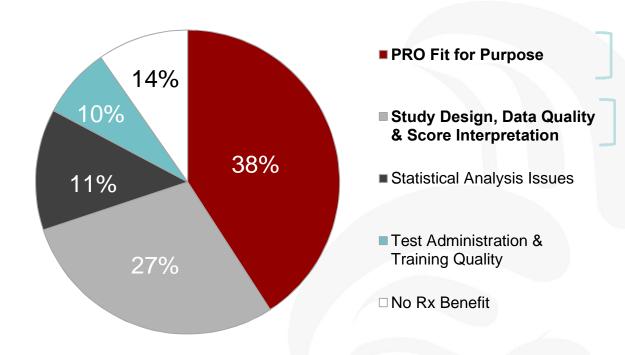


# WHY A GUIDANCE FOR PROs?

**HISTORY: DENIALS OF CLAIMS** 

### FDA 2006 - 2010 116 unique new brand drugs approved

52 with PRO label claims (44.8%) 26 denied (22%)



### FDA: 213 PRO Violation Notices

- " Use of individual items: 45%
- Insufficient evidence of content validity: 36%
- Broadening claim beyond PRO construct: 27%
- " Design & data interpretation: 49%
- " Broadening claim beyond trial scope: 55%
- " No PRO used: 50%

Rejection rates for PRO claims remain high across therapeutic areas.



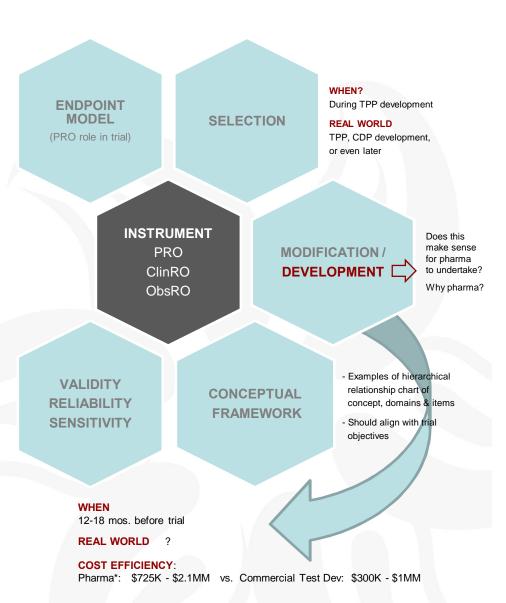
DeMuro C, Clark M, Mordin M, Fehnel S, Copley-Merriman C, Gnanasakthy A. Reasons for rejection of patient-reported outcome label claims: a compilation based on a review of patient-reported outcome use among new molecular entities and biologic license applications, 2006-2010. Value Health 15, 443-448 (2012).

Symonds T, Hackford C, Abraham L. A Review of FDA Warning Letters and Notices of Violation Issued for Patient-Reported Outcomes Promotional Claims between 2006 and 2012. Value in Health. Vol. 17. Issue 4, p433, 437 (2012).

### **CONTENT**

- 1. EVALUATION OF A PRO INSTRUMENT
- 2. CLINICAL TRIAL DESIGN
- 3. DATA ANALYSIS & INTERPRETATION
- 4. GLOSSARY
- 5. APPENDIX: DOSSIER TEMPLATE





# INSTRUMENT MODIFICATION & DEVELOPMENT: The Agile Way

LINGUISTIC VALIDATION

SPOKE I - V

#### Qualification of CLINICAL OUTCOME ASSESSMENTS (COAs) V. Modify Instrument I. Identify Context of Use (COU) and Concept of Interest (COI) Identify a new COU · Outline hypothesized concepts Change wording of items, response and potential claims options, recall period, or mode/method of Determine intended population administration/data collection · Determine intended · Translate and culturally adapt application/characteristics Evaluate modifications using spokes I - IV CONCEPT OF (type of scores, mode and · Document all changes frequency of administration) · Consider submitting to FDA for · Perform literature/expert review qualification of new COA, as appropriate · Develop hypothesized conceptual framework · Position COA within a preliminary IV. Longitudinal Evaluation of endpoint model **Measurement Properties**/ · Document COU and COI **Interpretation Methods** Assess ability to detect change and construct validity Identify responder definition(s) II. Draft Instrument and Evaluate · Provide guidelines for interpretation of treatment benefit and **Content Validity** relationship to claim · Document all results · Obtain patient or other reporter input · Update user manual · Generate new items · Submit to FDA for COA qualification as effectiveness endpoint · Select recall period, response options and format to support claims Select mode/method of administration/data collection · Conduct cognitive interviewing III. Cross-sectional Evaluation of Other Measurement Properties · Pilot test draft instrument · Finalize instrument content, format and scoring rule · Assess score reliability (test-retest or inter-rater) and construct validity · Document content validity Establish administration procedures & training materials · Document measure development Prepare user manual · Consider submitting to FDA for COA qualification as exploratory endpoint prior to longitudinal evaluation



# SOURCES OF CONFUSION RE: LINGUISTIC VALIDATION

- Inconsistency in detail across guidances
- Lack of specificity in method
- Scientifically compromising

### DHHS / FDA GUIDELINE (1988)

Guideline for the Format and Content of the Clinical and Statistical Sections of an Application

VS.

FDA PRO GUIDELINE (2009)

**USE THE SPOKE WHEEL!** 

### **DHHS / FDA GUIDELINE (1988)**

### Modifications of existing or new instruments

- For language translations and cultural adaptation processes, include:
  - a. Description of the expertise of the translators
  - b. Description of procedures used (forward, back, reconciliation, harmonization, assessment of measurement properties)
  - c. Description of patient testing
  - d. Results of translation / adaptation including clear description of all translation issues and how they were resolved
- 2. For content, wording, format, or mode of administration changes, describe results from studies conducted to evaluate modification, or rationale for not conducting studies.
- 3. For use in a new indication or new population, document instrument development and assessment of measurement properties as described above.

### **FDA PRO GUIDELINE**

### VIII. Language Translation and Cultural Adaptation

- A. Process used to translate and culturally adapt the instrument for populations that will use them in the trial.
- B. Description of patient testing, language- or culture-specific concerns, and rationale for decisions made to create new versions.
- C. Copies of translated or adapted versions.
- D. Evidence that content validity and other measurement properties are comparable between the original and new instruments.



FDA , DHHS (1988). Guideline for the Format and Content of the Clinical and Statistical Sections of an Application. Industry Guidance; July 1988. Retrieved from: www.fda.gov/downloads/Drugs/Guidances/UCM071665.pdf

FDA, DHHS, CDER, CBER, CDRH. (2009) Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Industry Guidance; December 2009. Retrieved from: www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf

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### LINGUISTIC VALIDATION METHODOLOGY

Where is it??

It's <u>not</u> in the PRO Guidance; or in the DDT Guidance, or in the 1988 Content/Format Guidance....

THE WILD PAPER+from ISPOR

Volume 8 · Number 2 · 2005

Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: Report of the ISPOR Task Force for Translation and Cultural Adaptation

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**Original Instrument Concept Elaboration Guid** Translator 1 Translator 2 **Harmonized Translation** Back Translation Project Manager Review Survey Research Expert Review Developer Review Client Subsidiary Review Approved Harmonized Translation Interviewer debriefs a diverse sample of subjects Translation Team, Interviewer, Project Manager, and Survey Research Expert analyze results Translation team amends translation if necessary based on debriefing results Linguistically Validated Translation



Wild D, Grove A, Martin M, et al. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR task force for translating adaptation. Value Health 2005;2:94-104.

Harmonization

Translation team amends translation after each review stage, if necessary

Cognitive Debriefing

### **IMPACT**

### Has it made a difference?

- Admirable intent with recommendations based on sound scientific principles.+\*
- Inconsistent implementation of guidance within SEALD and across other FDA reviewing divisions
- Some FDA reviewing divisions appear to prefer claims based on specific PROs (usually primary endpoints)

### YES, SOME, BUT...

‰vidence suggests that since the release of the Draft PRO Guidance, many PRO claims continue to be approved by FDA reviewing divisions; however, the reviewing divisions are not always adhering to the current standards when assessing PRO data for a claim.+

Mordin, M., Clark, M., Siersma, C., Copley-Merriman, K., & Gnanasakthy, A. (2009). Impact of the FDA draft guidance on Patient Reported Outcomes (PRO) label claims for approved drug products in the US: Has it made a difference?, Value in Health, 12 (3):A29-A29.

