FDA Issues Final Guidance on Patient-Reported Outcome Measures Used to Support Labeling Claims

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In December 2009, the US Food and Drug Administration issued *Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. In appropriate circumstances, healthcare product manufacturers can rely on patient-reported outcome (PRO) data to support labeling claims. A PRO is a report on a patient’s health condition that comes directly from the individual, without amendment or interpretation of the response by a clinician or anyone else.

PRO data provide manufacturers with an opportunity to measure broader health and wellness benefits of a drug, device or biologic product. Often, patients are in the best position to explain any quality of life improvements they may be experiencing. Thus, PRO instruments are often the best tool for assessing and supporting quality of life labeling claims. For example, a company might want to claim that its arthritis drug improves overall energy levels in most patients, thereby enhancing quality of life. Patients taking the drug would be the best source of feedback on how the drug accomplishes this quality of life improvement, e.g., by easing pain, increasing flexibility or permitting more restful sleep.

The guidance focuses on how FDA evaluates PRO instruments that manufacturers use to support claims on medical product labels. A PRO instrument such as a patient questionnaire or interview is the means used to capture PRO data. Companies can only use PRO data to support labeling claims if FDA approves the underlying PRO instrument.

This article analyzes how the guidance can help healthcare product companies use PRO instruments to substantiate quality of life labeling claims.1 While the guidance is not legally binding and does not offer clear answers, it provides manufacturers with some insight into how FDA evaluates PRO instruments and the data they yield.

**FDA’s Expectations About the Appropriate Role of PRO Data**

- Healthcare manufacturers typically use PRO instruments during the clinical trial phase of product development. PRO data supplement other clinical trial data and serve to measure a product’s effect on variables such as symptoms or biological or physical function.
- FDA advises that PRO instruments are most appropriate in situations where the company seeks to measure a product benefit that is “best known by the patient or best measured from the patient perspective.”2
- Companies most often employ PRO data to support labeling claims about a patient’s signs, symptoms or functioning in direct relation to the particular disease. However, FDA acknowledges that PROs can also “represent the effect of disease on health and functioning from the patient perspective.”3
- Claims based on PRO data may appear in any labeling section, if approved by FDA.

**PRO Instrument Development Process**

- FDA encourages companies to start developing PRO instruments at an early point in product development. Companies should carefully document the instrument development process. The agency will later examine this documentation to evaluate the instrument’s adequacy to support labeling claims.
- The guidance recommends that companies engage FDA in a “discussion about a new or unique PRO instrument before confirmatory clinical trial protocols are finalized.” This will allow the agency to review the company’s labeling goals and how they relate to the proposed PRO instrument.
- FDA’s vision of the ideal PRO planning process includes a series of cyclical steps that involve hypothesizing, testing, adjusting assumptions, modifying the instrument and rehypothesizing until the instrument can accurately and reliably measure the patient outcomes of interest. A graphic in the guidance illustrates these points.

**How FDA Evaluates PRO Instruments**

FDA focuses primarily on the following issues when it evaluates PRO instruments: the population enrolled in the clinical trial in which the PRO is being used; the clinical trial’s objectives and design; and the PRO instrument’s “conceptual framework.”

- Population issues—An instrument cannot support a labeling claim unless it reliably measures the claimed benefit or outcome in the relevant patient population. The agency advises companies to involve patients in the PRO instrument development process and to submit evidence to FDA that the company incorporated patient input to improve the instrument’s performance.
- Clinical trial design and importance of the endpoint model—A PRO endpoint is the measurement the company will compare among treatment groups to assess a particular treatment effect. For example, a company may want to show that a drug reduces muscle pain associated with the flu. In this example,
the endpoint would be the change in patient-reported muscle pain.

• Most clinical trials measure multiple endpoints. FDA will evaluate how the PRO endpoint fits into the overall scheme of trial endpoints. FDA states that “it is critical” for medical product companies to use an “endpoint model.” An endpoint model is a visual diagram showing the relationships among all endpoints, PRO and non-PRO, in the clinical trial. See Figure 1 for sample endpoint models.

• In the endpoint model, PRO endpoints may be “primary” and support the product’s actual indicated use, or “secondary” and support the product’s other treatment benefits, such as overall physical performance. FDA indicates that secondary PRO endpoints are likely the best candidates to support quality of life-related claims because these endpoints often relate to a product’s other benefits, distinct from its primary indication.

• The endpoint model is a critical tool for FDA in evaluating whether a PRO instrument is adequate. Based on the endpoint model, FDA will know what the PRO instrument intends to assess and how it relates to other measurements supporting the product’s effectiveness.

The PRO instrument’s conceptual framework—FDA advises that an instrument’s ability to support a labeling claim depends heavily upon its “conceptual framework.” A conceptual framework is a visual diagram that lists every item in the PRO instrument (e.g., every question in a patient survey) and connects each item to the concept...
it measures. For example, a company might want to show that its drug product reduces generalized anxiety. The concept in this case is anxiety. The items in this example might be a series of questions that assess anxiety.

- PRO instrument conceptual frameworks must adequately reflect the complexity of the quality of life claims a company seeks to make. Quality of life labeling claims often require complex conceptual frameworks because they typically rely on general concepts.
- Complex conceptual frameworks subdivide larger and more complicated concepts into smaller concepts or “domains.” In the example where generalized anxiety is the main concept, the subconcepts or domains might include unexplained nervous feelings and irrational fears.
- The guidance defines “health-related quality of life” (HRQL) as a multi-domain concept that represents the patient’s general perception of the effect of illness and treatment on physical, psychological and social aspects of life.

See Figure 2 for a sample PRO instrument conceptual framework.

**PROs and Clinical Trial Design**

In clinical trials, a PRO instrument can be used to measure the effect of a medical intervention on simple or complex concepts, such as quality of life. The guidance identifies issues unique to PRO instruments used in clinical trials, including the following:

- **General protocol considerations**—If a company seeks to use PRO data to support labeling claims, it should state the PRO measurement as a specific clinical trial objective or hypothesis. Further, the guidance makes the following general points:
  - Open-label clinical trials, where patients and investigators are aware of assigned therapy, are rarely adequate to support labeling claims based on PRO instruments.
  - To avoid influencing patient perceptions, PRO instruments should be administered before other clinical assessments or procedures during a clinical visit.
  - The quality of a clinical trial can be optimized at the design stage by specifying procedures to minimize inconsistencies in trial conduct.

- **Design considerations for multiple endpoints**—According to the guidance, it is critical to define the endpoint measures and the criteria for a positive clinical trial conclusion. If a company waits to determine these criteria until data are unblinded, FDA will not find the results credible.
- **Specific concerns when using electronic PRO instruments**—The guidance addresses specific FDA concerns relating to the use of electronic PRO instruments and advises companies to:
Data Analysis

FDA notes that manufacturers may face certain data analysis challenges when they incorporate PRO instruments in clinical trials. Some challenges FDA addresses in the guidance include:

- Interpretation of clinical trial results—Healthcare product manufacturers are advised to avoid proposing labeling claims based on statistical significance alone. To demonstrate treatment benefit, companies should compare responses between treatment groups. For example, a company might analyze how the average response and standard deviation from the average differ between female and male patients. This type of analysis will enable companies to better characterize the treatment effect and examine how different responses in patient subsets contributed to the average response for the whole patient population.

- HRQL—According to the guidance, a company claiming a statistical and meaningful improvement in HRQL must show that: all relevant HRQL concepts and subconcepts were measured; a general improvement was demonstrated; and no decline in any subconcept was demonstrated.

How PROs Can Support Quality of Life Labeling

PRO data provide drug, device and biologics manufacturers with valuable insight into the quality of life benefits their products create for patients. Accordingly, PRO instruments can be a helpful tool for supporting quality of life labeling claims. However, as the guidance indicates, medical product companies must carefully design and administer PRO instruments and utilize the data according to FDA’s extensive criteria.

References

1. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (December 2009). This article summarizes key points from the 39-page guidance; however, it reorganizes the information in the guidance into topical sections that are most relevant to medical product companies seeking to support labeling claims with PRO data.

2. Ibid.

3. Ibid.

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