Arnall Golden Gregory LLP

Client Alert

Contact Attorneys Regarding This Matter:

Alan G. Minsk
404.873.8690 - direct
404.873.8691 - fax
alan.minsk@agg.com

Jennifer S. Blakely
404.873.8734- direct
404.873.8735 - fax
jennifer.blakely@agg.com

Diana Rusk Cohen
404.873.8108 - direct
404.873.8109 - fax
diana.cohen@agg.com

Arnall Golden Gregory LLP
Attorneys at Law
171 17th Street NW
Suite 2100
Atlanta, GA 30363-1031
404.873.8500
www.agg.com

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

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

PRO data provides drug, device and biologics manufacturers with an opportunity to measure broader health and wellness product benefits. 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 overall quality of life. Patients taking the drug would be in the best position to report on how the drug accomplishes this quality of life improvement, for example, by easing pain, increasing flexibility or allowing for 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" is the means used to capture PRO data, such as a patient questionnaire or interview. Companies can only use PRO data to support labeling claims if FDA approves the underlying PRO instrument.

This Bulletin analyzes how the Guidance can help medical product companies that 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 insight into how FDA evaluates PRO instruments and the data they yield.

FDA's Expectations About the Appropriate Role for PRO Data

- Medical product companies typically use PRO instruments during the clinical trial phase of drug development. PRO data supplements other

1 This Bulletin summarizes key points from the 39-page Guidance; however, the Bulletin 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.

clinical trial data and serves to measure a drug's effect on variables, such as symptoms or biological and physical function.
- FDA advises that PRO instruments are most appropriate where the company seeks to measure a drug 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, assuming FDA approval.

The PRO Instrument Development Process

- FDA encourages companies to start developing PRO instruments early in the drug development process. Companies should carefully document the instrument development process. FDA 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 re-hypothesizing until the instrument can accurately and reliably measure the patient outcomes of interest. The agency provides a graphic in the Guidance that illustrates these points.

How FDA Evaluates PRO Instruments

FDA focuses primarily on the following issues when it evaluates PRO instruments: (1) the population enrolled in the larger clinical trial in which the PRO is being used; (2) the clinical trial's objectives and design; and (3) 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 – The Importance of the Endpoint Model:** A PRO endpoint is the measurement that 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

2 *Id.*
3 *Id.*

to use an "endpoint model." An endpoint model is a visual diagram showing the relationships between all endpoints, PRO and non-PRO, in the clinical trial. (See Appendix A of this Bulletin for sample endpoint models.)
    - In the endpoint model, PRO endpoints may be "primary" and support the drug's actual indicated use or "secondary" and support the drug'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 drug'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 drug's effectiveness.
- **The PRO Instrument's Conceptual Framework:** FDA advises that whether an instrument can support a labeling claim depends heavily on that instrument's "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 more 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 Appendix B of this Bulletin 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 more complex concepts, such as quality of life. The Guidance identifies issues unique to PRO instruments used in clinical trials including, but not limited to, 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 describes 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 prevent influencing patient perceptions, PRO instruments administered during a clinical visit should be administered before other clinical assessments or procedures.
- 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 until after data are unblinded to determine these criteria, FDA will not find the results credible. FDA advises companies not to selectively pick from among PRO endpoint results for inclusion in proposed labeling. In the generalized anxiety example, a company might have endpoints that measure nervousness and irrational fears. Both of these endpoints are vital to a claim about reduced anxiety and a company cannot make claims about general anxiety reduction unless both of these endpoints improve. Also, a company should not attempt fall back on labeling claims about a positive change in one PRO endpoint, such as nervousness, if irrational fears did not improve.
- **Specific Concerns When Using Electronic PRO Instruments:** The Guidance addresses specific FDA concerns relating to the use of electronic PRO instruments. The agency advises companies to do the following:
  - Comply with FDA regulatory requirements for sponsor and investigator record-keeping, maintenance, and access.
  - Avoid direct PRO data transmission from the PRO data collection device to a third party without an electronic audit trail that documents all changes to the data after it leaves the PRO data collection device.
  - Ensure that clinical investigators are able to maintain and confirm electronic PRO data accuracy.
  - Prevent persons other than the investigator (and/or site staff designated by the investigator) to modify the source data.
  - Secure against premature or unplanned access to unblinded data.
  - Enable FDA investigators to inspect, verify, and copy the data at the clinical site during an inspection.
  - Create a secure system where records are not easily altered.

Data Analysis

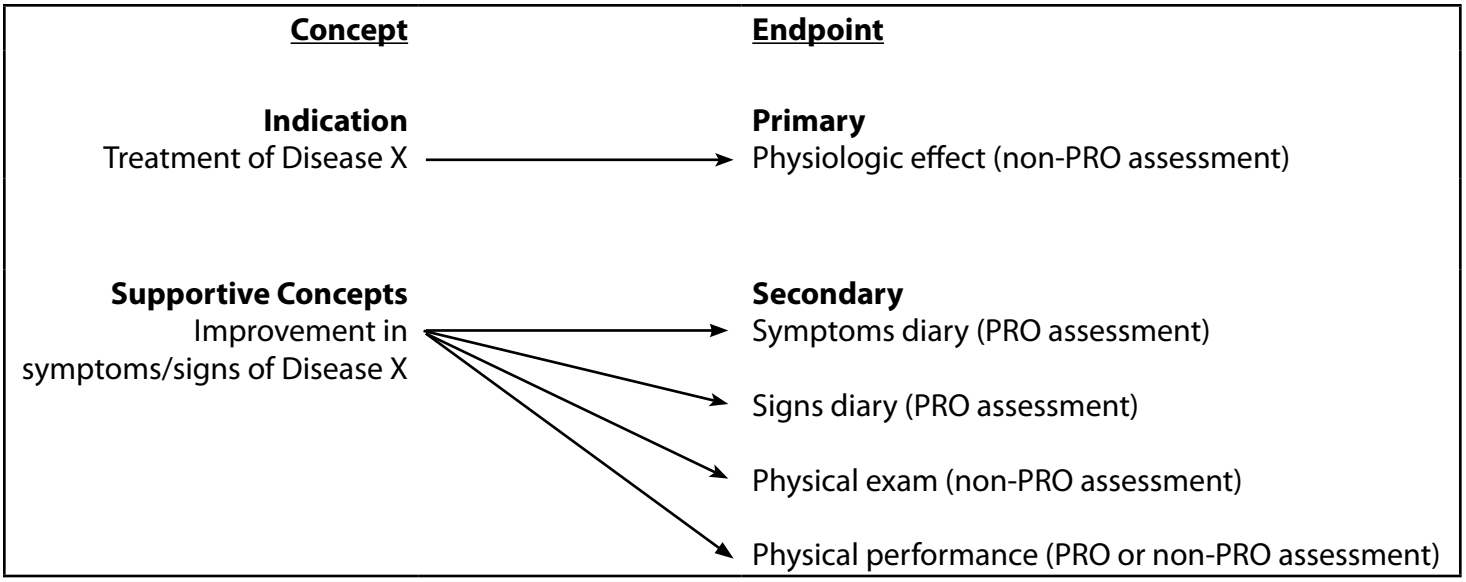
- **Interpretation of Clinical Trial Results:** Medical product companies are advised to avoid proposing labeling claims based on statistical significance alone. To demonstrate treatment benefit, FDA advises companies to compare responses between treatment groups. For example, a company might analyze 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 the following: (1) all relevant HRQL concepts and sub-concepts were measured; (2) a general improvement was demonstrated; and (3) no decline was demonstrated in any sub-concept.

Conclusion: How PROs Can Help Support Quality of Life Labeling

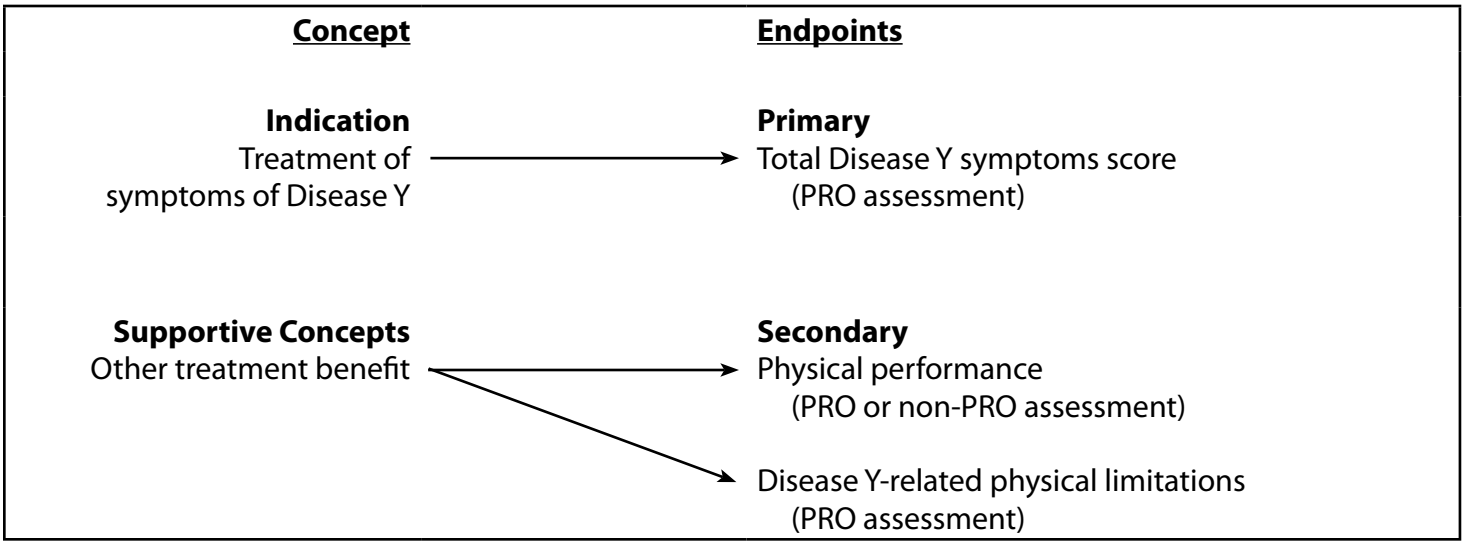
PRO data provides drug, device and biologics manufacturers with valuable insight into the quality of life benefits their products create for patients. Accordingly, PRO instruments can be a helpful tool for supporting quality of life labeling claims. However, as the Guidance indicates, medical product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

Appendix A – Sample Endpoint Models[4]

Sample 1: Treatment of Disease X



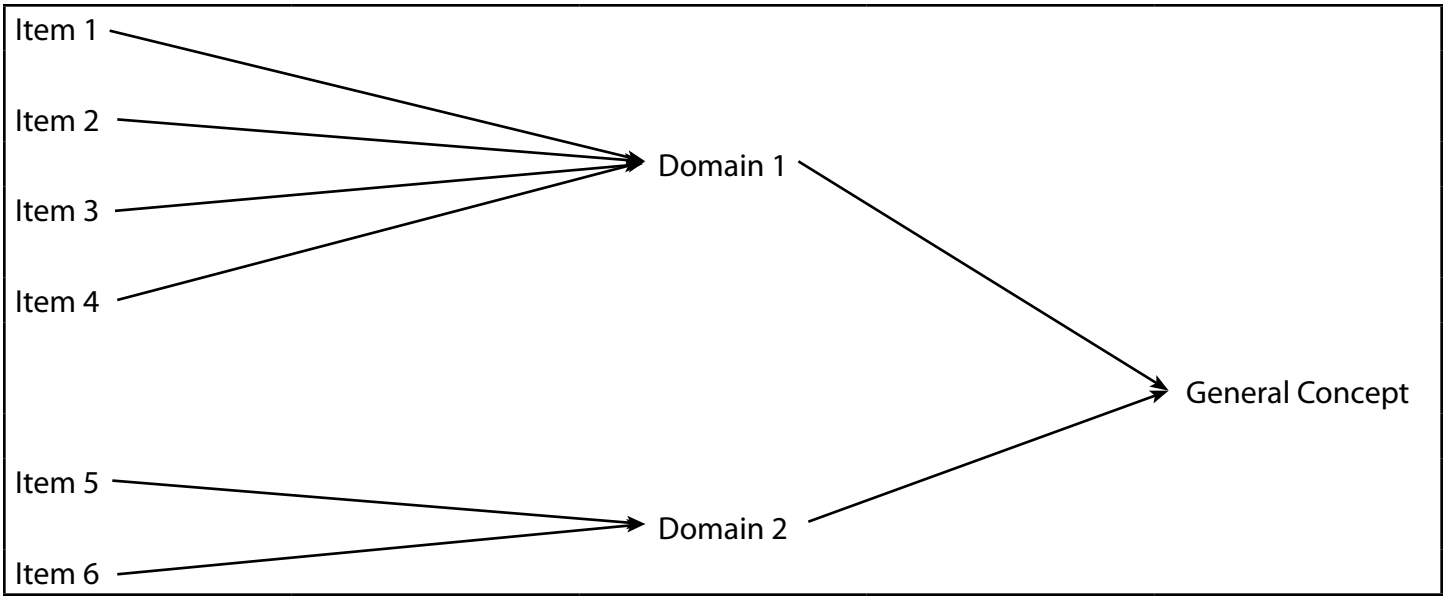
Sample 2: Treatment of Symptoms Associated with Disease Y



4 PRO Guidance, at 8.

Appendix B – Sample Conceptual Framework for a PRO Instrument[5]

Diagram of the Conceptual Framework of a PRO Instrument



5 PRO Guidance, at 8.