

# Genentech

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April 3, 2006

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

Subject: **Docket No. 2006D-0044**  
Comments on Patient-Reported Outcome Measures: Use in Medical Product  
Development to Support Labeling Claims (DRAFT GUIDANCE)

Dear Dockets Management Branch:

Enclosed are comments, provided by Genentech, for the Draft Guidance  
Patient-Reported Outcome Measures: Use in Medical Product Development to Support  
Labeling Claims.

Thank you for providing us the opportunity to comment on this Draft Guidance.  
We hope that you will find our comments useful and constructive.

Sincerely,

*for*   
Robert L. Garnick, Ph.D.  
Senior Vice President  
Regulatory Affairs, Quality,  
and Compliance

2006D-0044

Docket-025 ss

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**Draft Guidance for Review and Comment**

**Draft Guidance for Industry  
Patient-Reported Outcome Measures: Use in Medical Product Development to  
Support Labeling Claims**

**Docket No. 2006D-0044**

**Issued for Comment February 3, 2006  
Comments due April 4th, 2006**

Genentech, Inc.  
1 DNA Way  
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The following comments are provided by Genentech, Inc. on Docket No. 2006D-0044, "Draft Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims: We welcome FDA's efforts to provide direction on how sponsors can develop a patient-reported outcome (PRO) strategy in clinical drug development that would support a labeling claim.

We have the following **General Comments**:

The draft guidance document states that "FDA intends to consider a modified instrument as a different instrument from the original and will consider measurement properties to be version-specific." (lines 590-91). We are concerned that FDA will require such extensive evidentiary requirements for documenting the sufficiency of a modified instrument that sponsors will not pursue PRO instruments to assess the patient's perspective of treatment benefits. FDA appears to expect sponsors to submit documentation of the original development process of a PRO instrument, all modifications made to the instrument, and updated exhaustive assessments of the instrument's measurement properties (lines 176-181). It may be extremely difficult to collect documentation of the original development process, particularly if the data are not in the public domain. We request that FDA modify the final guidance document to acknowledge that documentation of the original development process may not be available to the sponsor and that verification of the validity of the instrument will be sufficient.

The draft guidance document suggests that, prior to the start of Phase III trials that will provide evidence to support the desired labeling claim, sponsors must validate the PRO questionnaire and develop criteria for specifying interpretation of the results. We recommend that FDA include a schematic depiction of the key milestones in PRO endpoint review during the drug development path. We believe that such a visual illustration will help clarify FDA's expectations.

We have the following **Specific Comments** in the following sections:

#### **Taxonomy of PRO Instruments (line 164)**

In Table 1 (Taxonomy of PROs Used in Clinical Trials), in the "Types of scores" block under "Attribute," we recommend that FDA provide specific examples for all of the types of scores identified. "Pain severity", an example of a single rating or single concept, is the only example currently provided in the table.

#### **Development of the Conceptual Framework and Identification of the Intended Application (line 194)**

##### *Identification of Concepts and Domains That Are To Be Measured (line 204)*

The draft guidance document states that FDA intends to review the conceptual framework of the PRO instrument (diagrammed in Figure 2, line 258), the association of domains supporting the concept, and the relationship among items in domains. FDA states in Section IV.B.9 of the draft guidance (line 460) that it expects sponsors to submit empirical data to confirm the conceptual framework. We recommend that FDA clearly state expectations about the nature and extent of empirical data that would be expected.

### *Identification of the Intended Population (line 273)*

This section of the draft guidance document states that FDA will compare the patient population used in the PRO instrument development to the intended study population. Population characteristics that will be compared are the patient age, sex, ethnic identity, and cognitive ability. We agree with this set of population characteristics to be compared. We note that the mode of administration of the study drug is not included in this list and we agree that it should not be compared. We request the FDA explicitly state in the final guidance that mode of administration should not be the basis for evaluating whether the PRO instrument is appropriate for assessing treatment benefit in a clinical trial.

### **Creation of the PRO Instrument (line 281)**

#### *Choice of the Recall Period (line 326)*

The draft guidance document recommends that PRO instruments not rely on recall, stating that there are potential problems with recall bias (lines 339-343). We believe that the final guidance should modify this recommendation to state that there are appropriate circumstances for PRO instruments to rely on recall. We agree that in general there are concerns with recall bias, but note that there are conditions for which it may be necessary to ask patients to recall their state. For example, when patients have episodic conditions such as lupus flare, migraines, multiple sclerosis episodes of flare or disease activity, and seizures, they may need to recall their last episode of illness to answer a question about their symptoms or functioning during that episode. An extensive discussion of this issue and validity of information provided over a recall period is provided in Dillman DA. Mail and internet surveys: the total design method. NY: Wiley, 2000.

Although there is always some bias in human measurement, and recall bias is likely to introduce some measurement error into PRO assessments, the added measurement error may not be substantial enough to mask treatment effects in a randomized controlled trial—if the treatment is effective. The recall bias represents a systematic error that affects both treatment groups. We recommend that FDA modify the guidance document to allow for use of recall when the sponsor provides a clear rationale for the recall period selected for the PRO measures.

### **Assessment of Measurement Properties (line 472)**

#### *Defining a Minimum Important Difference (line 537)*

We agree with FDA that a minimally important difference (MID) is usually specific to the population under study (lines 547-48). We believe that MIDs should be established for the intended study population because it is likely that an MID varies according to patient characteristics, particularly disease severity. To establish an MID for the study population, we recommend an approach that triangulates data to determine a narrow range of MID estimates. We believe the approach should use anchor-based methods with closely-related clinical anchors and supportive data from distribution-based methods. In addition, experience from previously completed clinical trials using the PRO instrument, when available, can also provide useful information supporting responsiveness evaluation and MID estimates. We note that this is consistent with recommendations presented at the recent Patient-Reported Outcome Consensus Meeting on this topic sponsored by FDA and the Mayo Clinic.

(Sloan et al. Analysis, Interpretation, and Reporting Results Based on Patient-Reported Outcomes. Presented at FDA Guidance on Patient-Reported Outcomes: Discussion, Dissemination, and Operationalization. Chantilly, Virginia, 24 February 2006.)

*Definition of Responders (line 569)*

FDA has asked specifically for comment on appropriate review of standards for the definition of a responder when applied to PRO instruments used in clinical trials (line 577, fn. 5). We believe that an appropriate review standard should be based on clinical anchors that have been established as measures of efficacy.

*Modification of an Existing Instrument (line 579)*

In addition to the General Comment made above to this section, we would like to make the following Specific Comments. The draft guidance document identifies instrument modification as including any of the following: revised measurement concept, application to a new population or condition, changed item content or instrument format, changed mode of administration, changed culture or language of application, and other changes. The draft guidance implies that a modified instrument must be revalidated in the specific population to be studied and states that the extent of validation recommended depends on the type of modification made. We request that the final guidance explicitly state the extent of validation that FDA expects for each category of possible modifications listed in the draft guidance (lines 595-670). Some relatively minor modifications of PRO instrument format and different modes of administration (paper and pencil versus telephone, paper and pencil versus ePRO) do not necessarily require full and comprehensive psychometric evaluation studies. We request that the guidance be modified to state that sponsors should provide a rationale, based on evidence, as to whether a full validation study is needed or not. We suggest that small cognitive debriefing and pilot studies may be sufficient.

We note that the additional validation requirement is very broad, applying to multi- and sub-domain instruments, to variations in how instruments will be administered, to modifications of scoring (even minor modifications), and to creation of a new instrument consisting of a series of already validated PRO measures. The draft guidance addresses the different types of modifications and states that when a PRO instrument is to be used in a new population of patients, sponsors may consider conducting a small randomized study to ascertain the measurement properties in the new population. FDA explains that sponsors may choose to conduct such a study to "minimize the risk that the instrument will not perform adequately in a Phase III study." (lines 587-88). We agree that sponsors may choose to conduct a small randomized study under those circumstances, but request that FDA not require sponsors to conduct the study. We ask that FDA explain in the final guidance that the sponsor has the option of conducting such a study or not, recognizing the risk of inadequate instrument performance in a Phase III study if the sponsor does not undertake the small randomized study. Sponsors should be permitted to confirm the measurement properties of the PRO instrument in the study population of interest using data from the Phase III studies.

We appreciate the opportunity to comment on this draft guidance document and look forward to reading the revised final guidance.

**U.S.: FDA—Genentech, Inc.**

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