



April 4, 2006

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

**Re: Docket No. 2006D-0044 – FDA “Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims” -Draft Guidance**

Dear Sir/Madam:

On behalf of the Johnson & Johnson family of companies, I am providing the following comments and recommendations in response to the FDA , “*Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*” -Draft Guidance” released for comment in the Federal Register (FR Vol 71, pp 5862-5863 February 3, 2006). Johnson & Johnson is the world's most comprehensive and broadly based manufacturer of health care products, as well as a provider of related services, for the consumer, pharmaceutical, and medical devices and diagnostics markets. The more than 200 Johnson & Johnson operating companies employ approximately 114,000 men and women in 57 countries and sell products throughout the world.

Johnson & Johnson commends FDA on addressing this important topic. We agree that patient-reported outcomes (PROs) add a valuable component to the comprehensive determination of efficacy of new therapeutic products and that these measures should exhibit appropriate measurement properties in order to be properly interpreted. Johnson & Johnson companies have been using PRO measures in clinical trials for many years. The addition of the information in the Draft Guidance will help clarify and structure the information to be submitted in support of submissions to the FDA.

Overall, the discussion in the draft guidance regarding use of PRO measures in medical product development to support labeling claims is well written. Below we present our specific comments on the draft guidance, including suggestions to modify the text.

**Specific Comments:**

- The discussion on lines 302 to 308 regarding use of items that present a hypothetical or desired condition rather than something patients actually do would benefit from clarification. We agree with the FDA that, in general, items based

on hypothetical situations are to be avoided as they may introduce some level of measurement error. However, it is not completely clear what the FDA considers hypothetical. Some well-known instruments assessing mobility may ask if the respondent “can walk a mile.” This is an appropriate item for many respondents while beyond possibility for many others, while others may be able to walk a mile but have not done so in the past week or four weeks for reasons not related to their health status. In order to provide a range of function, the instrument must include items that cover a range of difficulty. If these items are phrased in such a way that responses suggest poorer health status for reasons other than physical incapacity (in this case), they will provide less valid data.

- The rationale for excluding community based preference weights is unclear. Some established instruments that assess generic health status do not use weights specific to the target population of a clinical trial, e.g., Sickness Impact Profile, SF-36 Physical and Mental Component Summary scores. It would be helpful to clarify the rationale for the exclusion of instruments using community preference weights (lines 424-430).
- J&J agrees that the choice of recall period is an important component of any PRO measure that should be based on the purpose and intended use of the instrument, the characteristics of the disease/condition, and the treatments to be tested (lines 328-332). However, there is insufficient evidence to conclude that it is “usually better to construct items that ask patients to describe their current state than to ask them to compare their current state with an earlier period or to attempt to average their experiences over a period of time (lines 341-343). J&J recommends that lines 339-343 be deleted because it conflicts with the previous paragraph.
- The use of the term “normal” on line 354 is ambiguous. It is not clear whether the reference group is the individual or the general population. An individual may be expected to know what is normal for him or herself, but not know what is normal for a population.
- The available evidence suggests that weighting does not influence scoring. J&J recommends that lines 416-422 be deleted from the Guidance.
- It is not clear from Table 4 whether the list of measurement properties are *required* for each instrument or viewed as “nice to have”. For example, it may be appropriate in some cases to assess predictive validity, while in other situations it may not be feasible. We suggest that FDA clarify whether all properties in Table 4 are required.
- Section IV (Evaluating PRO Instruments), D. Modification of an Existing Instrument appears to imply that each change to a PRO instrument should result in extensive revalidation. J&J believes that the level of validation for a modification should reflect the degree of modification and expected impact. In some cases, a qualitative study may be sufficient. For example, the impact of the fact that the PRO measure was not originally designed to be used in a clinical trial (line 666) or that it is included in a battery (lines 667-668) for the first time may be resolved with a small sample of subjects rather than a full-scale validation effort.
- A minor point is that the header on line 631 reads “changed mode of administration”. To many clinical trial researchers, this could mean a different route of delivery. We suggest changing to “changed data collection method”.

- The FDA notes in Table 4 that they are specifically seeking comments on interpretability issues. Because the methodological issues underlying the use of minimally important difference (MID) and responder analyses are still unresolved, it would be beneficial for the FDA to encourage the sponsor to engage in early dialog with the agency regarding assessment of clinical meaningfulness. J&J believes that any further discussion of MIDs or defining a responder analysis by the FDA in this Guidance is premature. Given the high importance of this topic, we encourage FDA to hold meetings with key stakeholders including academics, industry and regulators to explore critical issues and propose solutions going forward.
- The Guidance states that open label studies are “rarely credible” (line 717-718). While J&J agrees that blinded studies have greater credibility, it is often not feasible to conduct blinded studies, e.g., oncology and MD&D trials as noted in lines 735-737, thus there appears to be a conflict between these two statements. We recommend that this statement be deleted.
- The comment regarding an apparent preference for PRO instruments that include multiple items or do not require comparison of health status to a prior time point (lines 729-730) do not appear to be evidence based. This is further suggested by the comment on line 732-733, that this is “an area that could benefit from rigorous study”. We suggest that these comments be deleted from the Guidance until such data are available to make an informed decision.
- Missing data is a part of all studies even when stringent efforts are made to minimize the problem. We agree with the FDA on the need for flexibility in interpreting missing data. J&J believes that the sponsor should first describe the missing data and then identify the most appropriate approaches for handling these missing data, including specification of possible sensitivity analyses once the patterns are known. Such approaches should be based on scenarios that are clinically and medically reasonable, rather than hypothetically possible but highly unlikely, e.g., worst-case scenario.

In closing, we would like to thank the Agency in advance for its thoughtful consideration of our comments and recommendations.

Sincerely,



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