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April 06, 2006

Division of Dockets Management
HFA-305
Food & Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Reference: Docket Number 2006D-0044

Dear Sir/Madam:

The Society for Clinical Data Management (SCDM) is pleased to submit the attached Comment Document on the February 2006 issued Draft Guidance for Industry: Patient Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. SCDM represents over 1400 data management professionals from all facets of the drug development process. Members represent pharmaceutical, biotechnology, device, contract research, academic research, and technology organizations.

As the majority of the work that our members perform is affected by this guidance document, the SCDM board of trustees felt that our collective comments were necessary. This was felt to be especially important as clinical trials are being conducted more and more frequently with PRO instruments.

SCDM looks forward to the agency's response to these comments and is prepared to answer any questions that might come as a result of your review. We look forward to an open dialogue toward seeking concurrence on methods to assure the collection of quality data that will help to improve the lives of patients.

Sincerely,

David Borbas, R.N., MSN
ePRO Comments Task Force Coordinator
Director, Data Management
Jazz Pharmaceuticals, Inc.
Phone: 650-496-2637
Email: david.borbas@jazzpharma.com

Task Group Members:

Christine Lys
Director Business Development
eTrials, Inc.

Julie Rardon
Global Manager, Data Integration
Invivodata, Inc.

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I. Introduction

Line Number(s)	Comment
39	What evidence will be deemed acceptable? Who will be the responsible party to determine the evidence is acceptable?
43	How will reliability and validity be measured?

III. Patient Reported Outcomes – Regulatory Perspective

Line Number(s)	Comment
134-137	This statement does not apply to instruments measuring only subjective assessments (for example, pain.) We are not certain that purely subjective measures like pain can be completely validated. Lines 514 -516 seems to confirm this. At this point the document recognizes that “some times of validity testing is not possible due to the nature of the concept being measured”
141-151	We agree with the FDA that assessing complex, abstract, and multidimensional concepts places particular burdens on the developers and users of such measures. However, the distinction should be made clearer and stronger in the Guidance in order to give sponsors appropriate guidance with regard to these different domains. Although assessment of symptoms and HRQOL are both subject to similar considerations of reliability, validity, etc, as outlined in the draft guidance, assessment in these two domains are marked by substantial conceptual and practical differences that need to be identified. We encourage the FDA to expand on its distinction between measures of complex HRQOL concepts and measures of specific symptoms, which are often straightforward, concrete, interpretable, and uni-dimensional, and thus do not raise many of the same issues.

<p>160-162</p> <p>When the FDA reviews a PRO instrument, our goal is to determine whether its characteristics are appropriate and adequate to support the study objectives.</p>	<p>When will the FDA review a PRO instrument? Before or after protocol assessment or as a part of the protocol review?</p>
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IV. Evaluating PRO Instruments

Line Number(s)	Comment
<p>177-179</p> <p>When considering an instrument that has been modified from the original, the FDA generally plans to evaluate the modified instrument just as it would a new one.</p>	<p>As almost any anticipated use of PRO assessment will require at least some modification of an existing tool (e.g., it will never be the case that the same instrument will be administered within precisely the same populations or under precisely the same conditions), this standard seems to imply that all instruments must be revalidated for an additional time by additional validation studies.</p> <p>We suggest that the FDA revisit their draft language to clarify that minor modifications to PRO instruments do not require extensive revalidation. For example, clearly simple changes like changes in font (so long as the fonts are readable) would not require any empirical revalidation of any sort. At the other extreme, changes in the content of items or the content or number of response options would require considerable empirical evidence to support their validity or equivalence.</p>
<p>180-181</p>	<p>“Sponsor” should be changed to developer and/or license holder. A Sponsor could be a developer. Some PRO developers or license holders are not sponsors. Should this refer to the instrument developer or the license holder of the instrument?</p>

322-324	<p>Is this appropriate for all cases? (Ex.: Hamilton Depression Scale)</p> <ul style="list-style-type: none"> - Can this review method for comparability of data from multiple modes of administration be predefined? - "Comparability of data" What is the method to determine that? This statement may not apply to areas that are difficult to compare- subjective pain measures will differ from an objectively observed assessment of pain. How & when in the development process (at protocol development or after the study is complete) will the FDA determine 'appropriateness'?
334-335	<p>Which Protocol is referred to here? The Study Protocol or the instrument/device protocol?</p> <p>What are examples of 'measures' that should be discussed in a protocol that the FDA would deem appropriate?</p>
374-378	<p>Are cognitive debriefing reports required for modifications that include transferring an instrument from paper to electronic format? Who will be the responsible party to determine when these cognitive debriefing reports are required (the FDA, the developer or license holder?) What if the instrument is in the public domain?</p>
396-397	<p>What information will be expected for documentation purposes (especially for instruments in the public domain?)</p>
405-407	<p>The task force would recommend defining the term user manual in a glossary and cautions against its use in that it may lead to patients using it as a potential source for their answers</p>
457-458	<p>What is considered appropriate rates for assumed compliance? Non-compliance may also be a result of lack of efficacy. Could this missing data and refusal rate be due to a lack of efficacy?</p>

462-464	When does the agency intend to review this final version? Will it be in the context of a protocol review or NDA submission only? Or will this be done by an Advisory board or other group specifically charged to perform this?
580-588	The task force recommends defining adequate validation so that considerations for risk can be considered in determining the appropriate level of validation necessary
<p>590-593</p> <p>The FDA intends to consider a modified instrument as a different instrument from the original and will consider measurement properties to be version-specific. The FDA recommends additional validation to support the development of a modified PRO instrument when one or more of the following modifications occur.</p> <p>631-641</p> <p>Changed Mode of Administration An instrument's data collection mode is altered. For example: Paper-and-pencil self-administered PRO is modified to be administered by computer or other electronic device (e.g., computer adaptive testing, interactive voice response systems, Web-based questionnaire administration, computer)</p>	The task force is concerned that this recommendation may be too strong; We are concerned that the history of the instrument and its validity would be disregarded in the face of small changes.
667-668	The task force recommends that this line be modified since batteries of measures can be varied from study to study. As currently written, the sentence implies that each time an instrument is placed into a battery of measures it would have to be validated. How could individual PRO instruments be compared in the context of a battery of measures?

VI. Data Analysis

Line Number(s)	Comment
962-1017	<p>Missing data can occur at two levels: (a) items within an assessment can be missing and (b) entire assessments can be missing. Clearly, prevention of missing data is preferable to managing missing data after the fact. Therefore, we think it is important to note methods that can reduce the likelihood of missing data. Electronic data capture can address both sources of missing data. Electronic assessments can ensure presentation of all relevant items and require a participant to respond to an item before progressing on to the next item, therefore eliminating the possibility of missing data within an assessment. Although electronic data capture can not prevent study participants from missing clinic appointments or dropping out of a study, it is useful for diary studies, where participants are administered assessments outside of the clinic. Electronic platforms (e.g., PDAs, IVRS) can prompt patients to make required diary entries and increase compliance with protocols, resulting in fewer missing assessments.</p>
<p>966-968</p> <p>Rules for handling missing data should be specific to each PRO instrument and should usually be determined during the instrument development and validation process.</p>	<p>What will be the expectation for handling missing data if the instrument is available on the public domain?</p>

Glossary

Line Number(s)	Comment
	<p>Add a definition of "Developer" and License Holder. In some cases older measures have been licensed to organizations that hold and control the rights and development authority for those PRO measurements.</p>