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April 4, 2006

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

RE: Docket No. 2006D-0044 -- Notice: Draft Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

Dear Madam/Sir:

AdvaMed is pleased to provide both general and specific comments on the Draft Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.

AdvaMed, the Advanced Medical Technology Association, is the world's largest association representing manufacturers of medical devices, diagnostic products, and medical information systems. AdvaMed's more than 1,300 members and subsidiaries manufacture nearly 90 percent of the \$75 billion in health care technology products purchased annually in the United States, and more than 50 percent of the \$175 billion purchased annually around the world. AdvaMed members range from the smallest to the largest medical technology innovators and companies. Nearly 70 percent of our members have fewer than \$30 million in sales annually.

General Comments

The information outlined in the guidance document is extremely helpful. The guidance essentially acts as a primer on how to develop a new Patient-Reported Outcome (PRO) instrument even though many applications will use an established PRO. Because of the continued reliance on established PROs, AdvaMed also urges FDA to provide more clarity on what sponsors need to provide to document the validity of using an established PRO in a similar patient population. For example, what does a sponsor need to provide to FDA as justification for using SF-36 in a chronic pain study?

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In addition, to streamline the product development process, AdvaMed urges FDA to pre-review PRO instruments much like FDA reviews pre-Investigational Device Exemptions. Pre-review will not only improve the pace of new product development but will prevent the performance of inadequate studies. Inadequate studies may need to be repeated, potentially adding unnecessary cost to product development and leading to higher device costs and decreased funds for future innovation. Pre-review will also ensure that the patient-related outcomes that are measured will be the ones that give the medical community the best information about device use. The result will be better patient care.

Specific Comments

AdvaMed's specific comments on the guidance are included in the enclosed attachment.

In closing, thank you for the opportunity to comment on this draft guidance document. If you have any questions, please feel free to contact me.

Sincerely,



Tara Federici
Associate Vice President
Technology and Regulatory Affairs

Enclosure

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

Column Description:

ID # – Page, line number or other unique identifier

Recommended Change – AdvaMed recommended change

Reason – Rational or background behind the change as applicable

Edit #	ID #	Recommended Change	Reason
1	Pg 1-2 (lines 21 – 58)	Include the definition of HRQL and of QOL in the introduction of the document.	These concepts are too important to be buried in the glossary.
2	Pg 5 (line 164), Table 1, Types	Add “Use of healthcare resources” to Concepts measured.	This is a cost-effectiveness measure often collected in a patient diary.
3	Pg 8 (line 234)	The text should be revised to read “a general claim about improvements in physical function <u>would be supported</u> , provided there is no trend of a worsening response in other domains”.	If there is a significant improvement in the overall multi-domain PRO, then a claim for benefit in HRQL should be supported, provided no individual domain shows a trend of a worse response.
4	Pg 9 (line 275)	Delete text on lines 275 thru 279 and insert new text that reads as follows: “ <u>Sponsor will provide justification that the study populations enrolled in clinical trials are similar to the patient population used in the PRO instrument development process with respect to patient age, sex, ethnic identity and cognitive ability in order to demonstrate that the instrument is appropriate to that population</u> ”.	It is helpful to clarify that it is the sponsor’s responsibility to make the case that the PRO instrument is appropriate to the particular test population.
5	Pg 10 (Lines 295-300)	The text needs to be clarified. The current language implies that patients will know what is adequate on a scientific/study level. Presumably, FDA will review PRO instrument development and will want to see adequate numbers of patients to demonstrate support that the specific items are adequate to measure the concept.	Patients can not be expected to be knowledgeable in instrument adequacy. Patients will know what is important to them and what issues may be important to the disease but they are not experts in adequacy of information. This should be left up to the clinicians, who are experts in the disease process.

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6	Pg 15 (line 478)	Insert " <u>The FDA also plans to review . . .</u> " at the beginning of the sentence on line 478.	Run-on sentence.
7	Pg 16 (line 481, Table 4 Validity, FDA Review Consideration	In the section labeled FDA Review Considerations, eliminate the statement: "Have patients similar to those participating in the clinical trial confirmed the completeness and relevance of all items?"	As in suggested edit #5, patients do not have the expertise to comment on completeness.
8	Pg 17 (line 483, Table 4 Interpretability, What is Assessed)	Add new text: " <u>Would be acceptable to use a panel of patients or physicians familiar with the disease in question to provide input on MID</u> ".	This method can be used to obtain a criterion for objective clinical outcomes when there is no external medical standard.
9	Pg 18 (line 514)	Add an example to the following text: "In some cases, some types of validity testing are not possible due to the nature of the concept to be measured. For example...".	It would be very helpful to see some examples. Would pain be such an example?
10	Pg 18 (line 527-528)	Insert "and" after the parenthesis.	Typographical error.
11	Pg 19 (line 543)	The following text should be clarified to make clear whether the difference is a statistical difference or a MID: "For many widely used measures (pain, treadmill distance, HamD), the ability to show any difference between treatment groups has been considered evidence of a relevant treatment effect".	Clarification is needed. Is FDA suggesting there is no need to specify an MID in sample size/power calculations, but just show a statistical difference?
12	Pg 19 (line 547)	Add new sentence: " <u>Even within a disease class, the MID would vary depending on patient risk stratifiers, cost of the therapy and invasiveness of the intervention (e.g., pill vs. deep brain stimulation).</u> "	Many other factors contribute to MID definition, not just the population under study.
13	Pg 20 (577)	Add new sentence at end: " <u>In many cases, either there is a historical precedent or there are published</u>	Using published guidelines, when available, consistently allows across-study comparisons for

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		<u>guidelines for a particular disease area (e.g., IMMPACT guidelines for chronic pain) that specify a recommended percent change</u> .	a particular disease area.
14	Pg 20 (line 585)	<p>Revise and replace text to read: "On the other hand, if the PRO instrument is to be used in an entirely new population of patients, <u>the sponsor should verify the appropriateness of the PRO instrument to the test population</u>".</p> <p>FDA should clarify what is meant by "an entirely new population".</p>	<p>It seems unlikely that an instrument that hasn't been tested in a particular group will perform better than in the original population and thus result in a false positive rate. Further, it is a sponsor risk if background checks on appropriateness to the population have not been done.</p> <p>It is not clear when FDA believes a population is entirely new e.g., if PRO is validated in NYHA 1-2 patients, would NYHA 3-4 patients be considered an entirely new population for use of the PRO? Or if the PRO is validated in mild to moderate hypertension patients and used in severe hypertension patients?</p>
15	Pg 20 (line 602)	Revise and replace text to read: " <u>A newly constructed index or composite score is used to summarize multiple PRO concepts/domains when there is no existing validation on this summary score.</u> "	It is not clear whether this is the sum of scores of individual domains or a newly constructed measure which is a weighted combination of individual domains.
16	Pg 21 (line 636)	Add text: "The degree of validation is based on a risk analysis".	Current text implies that use of electronic diaries or computerized data collection could create a huge re-validation burden.
17	Pg 24 (line 766)	Add text at end: "It could also establish a process by which PRO measurement is ascertained before or shortly after patient withdrawal from treatment exposure due to lack of efficacy or toxicity, <u>or other reasons such as patient moved away, withdrew</u>	There are multiple reasons for study withdrawal, not just lack of efficacy or toxicity.

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		<u>consent, etc.</u>	
18	Pg 26 (line 835)	Add new sentence: <u>"If a PDA is used to transmit daily to a database with appropriate safeguards, audit trails and security, the database can serve as the electronic source documentation"</u> .	We may not need to retain the information on the PDA for FDA inspection if the database can serve as the electronic source documentation.
19	Pg 26 (line 848)	Add new text to read: <u>"Direct PRO data transmission from the PRO data collection device to the sponsor without prior validation of the transmission and without access granted to investigator to the transmitted data in sponsor's database (i.e., the sponsor should not have exclusive control of the source document)"</u> .	If the investigator is given access to the transmitted data in the sponsor's database, this should suffice as access to the source data.
20	Pg 29 (line 953)	Add new text to read: <u>"findings for the composite score would support a general claim (e.g., ...), provided there was no trend of a worsening response in individual component endpoints"</u> .	If there is a significant improvement in the composite endpoint, then a general claim for benefit should be supported provided no individual component endpoint shows a trend of a worse response.
21	Pg 30 (line 1012)	Add new sentence: <u>"The final label claim should indicate what data were missing and what were available"</u> .	It is reasonable to perform sensitivity analysis to examine the impact of missing data but the final label claim should indicate what data were missing and what were available rather than the worst case scenario which does not provide an accurate assessment of the effect of treatment or therapy. Physicians and patients may not have the proper information on which to base decisions if the ultra conservative or ultra radical result makes it into the label.
22	Pg 31 Glossary	Add definitions for clinical and non-clinical anchors.	These terms are used without definition in the guidance document.

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23	Pg 31 (line 1062)	Add new text to read: "(2) that improvement was demonstrated in all of the important domains <u>but not necessarily, all domains.</u>	<p>Improvement in overall HRQL and all important domains is still an improvement even if it doesn't affect all domains.</p> <p>Without this change, it seems like one would need to develop a new HRQL PRO for every application. Studies should use a standard and widely accepted measure of HRQL, so that results can be compared across interventions and changes can be measured relative to overall HRQL.</p>