

 COMPLEWARE® CORPORATION

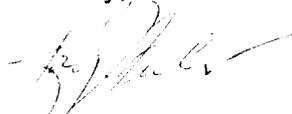
April 10, 2006

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

Re: 1006D-0044

Attached are comments submitted for the docket in reference to the above captioned draft guidance document titled "Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims - DRAFT GUIDANCE."

Sincerely,



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Vice President

2006D-0044

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Line number(s)	Comment(s)
NA	<p>ComplereWare views the publication of draft guidance addressing patient-reported outcomes (PROs) to be very important because such guidance provides a basis to select and adopt such measures. However, we are concerned that adoption of guidance that cannot be accomplished in the majority of clinical trials will cause a long delay in the general adoption of PROs for clinical trials in which PROs are the proper endpoints.</p>
NA	<p>There appears to be no basis in the draft guidance to bypass the validation requirement for PRO instruments that have been used in many recent previous studies (e.g. within the past 5 years) including registration studies. Such PROs (e.g. those used in allergic rhinitis as described in the allergic rhinitis guidance [Guidance for Industry - Allergic Rhinitis: Clinical Development Programs for Drug Products - DRAFT GUIDANCE]) do not appear to have been subjected to the validation required in this draft PRO guidance but are widely used and widely considered "valid" measures of the disorder both in clinical trials and in the clinic itself.</p>
NA	<p>Clinician reported outcomes (CROs) should be subjected to the same level of concern as is required for PROs. Otherwise, it is reasonable to presume that CROs will be more likely to be used in future studies even though such measures may be badly flawed. As described below in more detail, we suggest that each individual measure included in the conceptual framework be defined as a sign (readily observable activities or events) or a symptom (non-observable activities known only to the patient).</p>

Line number(s)	Comment(s)
61-72	<p>This section defines a PRO instrument as measuring "...how a patient feels or functions with respect to his or her health or condition. The concepts, events, behaviors or feelings measured by PRO instruments can be either readily observed or verified (e.g. walking) or can be non-observable known only to the patient and not easily verified (e.g. feeling depressed)." This section appears to differentiate signs (readily observable activities or events) from symptoms (non-observable activities known only to the patient). Physicians have long recognized a significant difference between signs and symptoms. Signs can be measured by an observer but symptoms depend on the patient's report. Why then does the guidance intermingle signs (e.g. number of steps walked) and symptoms (perception of gait stability)? Indeed signs can be either CROs or PROs or proxy observations and, as noted above, should be subjected to the same level of validation (whether recorded by a clinician as a CRO or by the patient him or herself as a PRO) as symptoms. Signs can be verified but symptoms cannot. Consequently, signs and symptoms should be validated using different processes. In summary, we recommend that the guidance differentiate between signs and symptoms.</p>
65	<p>The concept that a measure can be "readily observed" blurs the distinction between a PRO and an objective measure that is not a PRO. Are a hot flash demonstrated by a machine and a hot flash observed by the subject the same? If an activity can be measured then it should <u>not</u> be a PRO unless it is to be measured by the subject. This distinction should be made here.</p>
87	<p>In discussing a "change" in symptoms (e.g. in activities of daily living) it is important that such a change be meaningful to the subject. We suggest adding a comment that the change should be significant to the subject rather than just that a change occurs. In this case the MID should be the difference in the PRO that the subject detects as meaningful to himself or herself.</p>
Table 1, Concepts measured	<p>Consideration should be given to add: "Significance of adverse events." For example, a PRO instrument might ask the subject to rate the severity of drowsiness to determine the relative effect of two antihistamines on drowsiness. The adverse event might be elicited (rather than volunteered) on a PRO instrument to determine the relative frequency or severity of the event in patients under various conditions.</p>
Table 1, Mode of data collection	<p>Additional modes to collect data include: "Collected using hand held device"; and "Collected along with physiological data, such as peak flows."</p>

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178-181	We recommend that a comment should be made that a modification of an existing instrument should be evaluated using a risk based assessment. Some modifications of old validated instruments should require only minimal assessments to determine that there was no impact on the ability to collect valid data.
Figure 1	This figure uses inconsistent terminology. Specifically: 1) in ii the term "administration method" is used and yet in iv the phrase "method of administration" is used. Do these two phrases mean the same thing? If so, then only one phrase should be used for consistency; 2) In iv does the term "instrumentation" mean "method of administration" or does it mean the "instrument" identified in ii and iii? Again, the use of similar but not identical phrases is confusing.
304-307	Please clarify the intent of this section in assessing patient evaluation of daily activities. There is a fine line between asking if someone can perform a task and asking if they do perform the task. In some cases the subject has ancillary evidence that they can perform the task even if they are never asked to perform the task in the course of their daily lives.
322-324	We agree that it will be important to compare the validity of data collected by various methods. However, we recommend that this not be required with each trial. Once it has been demonstrated for a certain population, age and condition that a visual analog scale can collect pain data when used on a PDA, computer screen or paper, then this validation should not be required to be obtained subsequently. Such methods and instruments should be on a list of approved procedures. The FDA should determine if an instrument once standardized with one format for one sponsor or vendor: 1) can be used by another sponsor or vendor if the format is substantially the same for the second use as with the first sponsor or vendor; or 2) is an exclusive standard that can only be used once by anyone without revalidation; or 3) is an exclusive standard that can only be used by the first vendor or sponsor.
334-337	This statement seems to lead to a requirement that electronic methods must be used to prevent patients from recording data "...just before a clinic visit when their reports will be collected." Paper methods cannot readily achieve the goal of preventing "parking lot syndrome." Does this mean that paper and pencil PROs will no longer be acceptable to the FDA unless an embedded electronic device is included? What about PRO data recorded on paper when the device is not available (e.g. the soccer field, the grocery store)?

Line number(s)	Comment(s)
339-343	This section seems to imply that only instantaneous scores are useful and that reflective scores should not be obtained. For example, should all rhinitis studies depend only on how the subject feels at the time of the assessment and not also how the subject felt over the past 12 hours? The FDA should allow for flexibility in determining whether to allow reflective evaluations. In some cases, such an evaluation, if validation can be provided, should be allowed. Some disorders cannot be assessed by an instantaneous score only. It should be permissible for a subject to report when the onset of action of a drug was recognized if the instrument can be shown to collect valid data. Otherwise, constant assessments would be required.
Table 2, VAS	An electronic equivalent to a VAS should be described here: "Electronic VAS: Electronic device to collect a continuous scale similar to a paper VAS."
373-378	More discussion should be given about the instruction and training of subjects in the use of PROs. How can the data be compared from career patients who have used PROs frequently with data from new patients who have never used the PRO in the past? How is training to be accomplished and how is the adequacy of training to be documented (e.g. testing the patient)?
388-394	This section suggests that any change to an instrument will require revalidation. If the PRO instrument is validated for a computer application but a change is made between a black screen and a blue screen, does the instrument need to be revalidated? A risk based approach is preferable otherwise even trivial changes will appear to require full validation to assure that the change had no impact on the data.
416-422	This requirement will be difficult to implement. For example, the Total Nasal Symptom Score (TNSS) comprises adding four individual symptoms, which are correlated. The only reasonable way to construct this scale was to add all four items. Does this old scale, which is recommended in previous guidance, require revalidation and consideration that not all four symptoms be summed?
Table 3, Clarity or relevance	We suggest that missing data may be informative for reasons other than that the instrument is a bad instrument. Missing data may be indicative of death, severity of disease or other reasons that might be captured to explain the missing points.
Table 3, Variability	How do the first two bullets differ?
Table 3, Ability to detect change	Does this concept assume that some observable event is linked closely to each symptom? What happens if there is no such linkage? Otherwise, how should an "item" regarding a symptom (only the patient can describe) be validated?

Line number(s)	Comment(s)
475	The guidance document needs considerably more explanation about the MID. This should be an area for active investigation. The bottom line is that each scale should use patient perceptions to define the minimal important difference for each patient (responder) and for each population of patients (minimal important population difference). Statistical significance alone should not be used.
Table 4, Interpretability; 550-564	<p>“Any detectable difference” should not be accepted here. This would imply that very large studies can be conducted to show differences that have no biological or clinical significance. We suggest that the sponsor must state a minimal important difference and provide an objective basis for requiring this difference.</p> <p>We agree that MID should be differentiated from responder analyses. We strongly recommend against arbitrary rules (e.g. 0.5 times the standard deviation or 8% of the theoretical scores).</p> <p>The bottom line is: “Is the change meaningful to the patient?” We recommend that this single question be asked in the guidance and methods to respond to this question should be left for industry to provide. If the change in the endpoint makes a difference to the patient or to the course of the illness then it is important. If the change in the endpoint does not make a difference to the patient or to the course of the illness then no matter how statistically significant the difference, it is not important.</p>
571-577	We suggest that responder definitions will be different when applied to each indication and that the definitions be left to industry to propose. No general rules would seem to be applicable except that the differences again should be those that are meaningful to the patient or have an impact on the course of the illness.
590-670	We again suggest a risk based approach to the requirement that a modified instrument be considered as a different instrument from the original. Does changing the color of the paper on which the instrument is printed constitute a modified instrument that must be subjected to extensive revalidation?
664 -670	If the instrument was not validated for clinical trials but was validated for clinical practice, is this a problem? It would seem that a lofty goal is to make sure that each trial has applicability to clinical practice. In contrast, if an instrument is only validated for a clinical trial, it would seem reasonable to make sure that the instrument is also validated for clinical practice (where the therapeutic agent is to be used).

Line number(s)	Comment(s)
717-723	We strongly suggest that the blanket decision to reject most PROs used in open labeled studies be revisited. Some trials by their nature involve PROs even when the study is single blind or unblinded. We agree that in the majority of cases the placebo effect is important to assess but again the use of PROs in open label studies should be based on the protocol and not on a blanket prohibition. Open labeled studies are not necessarily entirely uncontrolled; historical controls may be relevant.
