

FILED

MAR 31 2006

CENTRAL

Date: MAR 30 2006

Dockets Management Branch
(HFA-305)
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville MD 20705-1266

Re: Docket Number 2006D-0044
Response to FDA Call for Comments
Draft Guidance for Industry – Patient-Reported Outcome Measures: Use in Medical
Product Development to Support Labeling Claims

Dear Sir or Madam:

Reference is made to the February 3, 2006 Federal Register notice announcing the request for comments on Draft Guidance for Industry – Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.

AstraZeneca has reviewed this guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Natalie Doman, Associate Director, Regulatory Affairs, at (302) 885-1441.

Sincerely,



Debra N. Shiozawa, Ph.D., Regulatory Affairs Director
Regulatory Affairs
Telephone: (302) 886-3137
Fax: (302) 886-2822

dns\nsd

Enclosure

2006D-0044

C 8

US Regulatory Affairs

**AstraZeneca Response to FDA Call for Comments on Draft Guidance for Industry –
Patient-Reported Outcome Measures: Use in Medical Product Development to Support
Labeling Claims**

Docket Number 2006D-0044

General Comments

- Comment 1

Please clarify how evolving information obtained during the clinical development process and PRO identification and integration can be aligned with the appropriate Agency interactions. For example, how should a sponsor engage SEALD when separate meetings are required (i.e., to discuss a SAP)? What measures will assist a sponsor in obtaining timely feedback?

- Comment 2

Overall, the guidance is a well-written document, although some topics are subject to many variations in interpretation (e.g., MCID responder analysis). Conversely, there are areas where the requirements are more rigid (e.g., modification of an existing instrument). Please further clarify by ranking requirements in order of relative importance.

- Comment 3

The burden of proof for PROs is higher relative to that required for other endpoints. There should be a balance between the ideal as proposed in the guidance document and what is pragmatic. The ideal may not be the reasonable approach.

- Comment 4

The guidance has better defined what PRO information needs to be submitted in an NDA. Although not within the scope of this document, at some point in the near future we would appreciate clear direction regarding what the Agency defines as appropriate levels of navigation/linking.

- Comment 5

As a learning tool, please provide examples of cases where validated instruments appear to be applicable but are not; explain the reason(s).

Docket Number 2006D-0044 Response to FDA Call for Comments Draft Guidance for Industry – Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

- Comment 6

Current development standards need not be applied to well-established instruments.

Specific Comments on Draft Guidance for Industry – Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims		
Section	Page or Line Number	Comment or proposed replacement text
III.A.3	134-137	Many PROs (e.g., pain) cannot be validated by comparing with an expert assessment, as there are no external signs; therefore, we suggest amending the text.
III.B.	154-156	AstraZeneca does not agree that PROs should be used to elicit AE reporting as AEs are collected separately in clinical trials. PRO instruments to support “effectiveness” should measure the adverse consequences of treatment separately.
III.B.	Table 1	The terms “effectiveness” and “efficacy” are being used interchangeably. We recommend that that the term “efficacy” be used consistently in the document.
IV.	172-179	<p>As a principle, we agree that sponsors should work proactively, but often what we intend to measure early in the development program changes through the development phases. If a sponsor identifies an “appropriate” instrument in Phase II that is deemed “inappropriate” at the EOP2 meeting, then it is late to begin development of a new instrument.</p> <p>It is not clear how the process might be different when obtaining additional claims for new indications. How are instruments employed for additional indications? Is it necessary to develop a new instrument? We suggest that the dialogue to implement PROs should be operational at any phase of development. We agree with the need for early development discussions, but we encourage open dialogue throughout the planning for a product, rather than during early claim development only.</p>
IV.	179-181	<p>AstraZeneca does not agree that a modified instrument should be evaluated as if it were a new one, especially for minor PRO modifications. More flexibility is needed. A pragmatic approach would be to document small changes in an instrument and note why these changes were made. The documentation should include an explanation of why the changes made will not significantly bias the results.</p> <p>Who will arbitrate the importance of a change? The guidance would benefit from clarification regarding the criteria specifying the magnitude of a change that would trigger an update of the</p>

Docket Number 2006D-0044 Response to FDA Call for Comments Draft Guidance for Industry – Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

Specific Comments on Draft Guidance for Industry – Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims		
Section	Page or Line Number	Comment or proposed replacement text
		measurement properties.
IV.A.1.	212	Please ensure that the guidance provides clarification regarding what constitutes “suitable documentation”.
IV.A.1.	212-247	To support efficient drug development, more guidance is needed to enable the Agency and a sponsor to proactively identify and agree upon concepts and measured domains, as the process of concept and claim development is iterative.
IV.A.1.	214-216	On line 555 (page 19, section IV.C.4.a.), reference is made to a single question asking the patient to rate his or her global impression of change since the start of treatment. An effect on such an endpoint would indicate benefit from a patient’s perspective. Please provide guidance regarding whether such an endpoint could lead to a label claim on its own. If not, what supporting information would be needed?
IV.A.1.	255	Depending on the specific condition that is being studied and the specifics of the treatment effect, it may or may not be appropriate to aggregate items. Therefore, why must sponsors specify domain aggregation in advance?
IV.A.3.	275-279	“Ethnic identity” may not be a relevant category outside of the US where the populations are more homogenous and this requirement would impact multi-national trials. Linguistic validation takes care of cultural differences.
IV.B.1.	298-300	Determining whether an “adequate” number of patients support an opinion is subjective. How will the FDA determine what is “adequate”?
IV.B.1.	304-307	The Agency needs to provide specific guidance on the assessment of performance of daily activities. Asking patients whether or not they can perform specific activities is subject to the same biases as whether or not they can perform daily activities; patients may still over/under report on their performance of specific activities.
IV.B.2.	317-324	The Agency needs to provide guidance on pooling of responses from multiple modes of data collection. Sometimes data is collected electronically, but back-up methods are necessary (e.g., paper and pencil). Please provide clarity on these allowances to avoid excessive missing data or exclusion of important patient groups.
IV.B.3.	332-333	Clarity and guidance are needed regarding what is required in the protocol “to ensure that patients understand the appropriate recall period.”
IV.B.3.	334-337	Please advise regarding the appropriate measures to ensure that patients make entries according to the study design. We acknowledge

Docket Number 2006D-0044 Response to FDA Call for Comments Draft Guidance for Industry – Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

Specific Comments on Draft Guidance for Industry – Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims		
Section	Page or Line Number	Comment or proposed replacement text
		that this is an important issue, but it is extremely difficult to assess with certainty.
IV.B.3.	341-343	AstraZeneca does not agree with the Agency's recommendation of measurement of current states for all PROs. The measurement of current states over long periods presents implementation challenges and is subject to biases caused by response shift. Our recommendation is that the Agency be open to the results of cognitive debriefings, validation and past performance of instruments.
IV.B.4.	351-352, Table 2, Column Description, Row 2	We suggest deleting the sentence, "These scales often produce a false sense of precision".
IV.B.5.	373-378	Please provide clarity regarding what constitutes readability and understanding, as well as how they should be tested and evaluated.
IV.B.6.	385-386	Questionnaires are usually completed by the patient in confidence and missing data/unclear data would be discovered only when the data is entered onto the database, making re-administration during the same time period very difficult. Please provide some clarification on the meaning of this statement.
IV.B.6.	388-390	Conducting paper versus electronic comparison studies for validation purposes poses a big burden to the sponsor. Since there is available literature on paper versus electronic questionnaires, our recommendation is that a cognitive debriefing should be sufficient.
IV.B.6.	399-403	Please provide more clarity about how electronically administered PRO instruments will be reviewed.
IV.B.6.	405-407	The creation of a manual at this stage is desirable but could be interpreted as an obstacle to the development of a new instrument.
IV.B.7	413-414	More clarity and flexibility are required on the issue of appropriate intervals between response choices.
IV.B.7	416-420	Available evidence suggests that weighting does not influence scoring. This is an unnecessary burden that may result in difficulty in interpretation. Additional guidance is needed as it is necessary to understand the Agency's concerns and recommendations prior to large-scale implementation in clinical trials.
IV.B.7	424-430	When patient preferences are used to weight items, we suggest that a discussion with the sponsor should precede discouragement of the practice.
IV.C.	474-475	It should be possible to confirm the responsiveness of the PRO instrument during a Phase III trial, if it was not done during Phase II.

Docket Number 2006D-0044 Response to FDA Call for Comments Draft Guidance for Industry – Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

Specific Comments on Draft Guidance for Industry – Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims		
Section	Page or Line Number	Comment or proposed replacement text
		The risk rests with the sponsor.
IV.C.	478	The use of the term “sociodemographic” in this context might have strong implications. For instance, does it imply the re-validation of the instrument according to the age, gender, etc., of the Real Life Clinical Trial sample?
IV.C.	483, Table 4	It is important to acknowledge that MIDs are related to baseline severity, how well the treatment works and if an active or a placebo comparator is used.
IV.C.1.	492-493	We do not agree with the general statement that test-retest is the most important type of reliability for PRO instruments. We also need clarification on what the Agency means by “stability”. There is potential to confuse “non-response” with “stability”. Combining this concept with daily recall creates the problem of “learned responses”.
IV.C.2.	514-516	The Agency needs to be flexible in allowing instruments validated in broad populations to be used in smaller sub-populations. Revalidation in specific sub-populations is difficult as some of these patient populations are hard to enroll, which creates significant burden to the sponsor.
IV.C.3.	521-522	Does the Agency mean “responsiveness” versus “validity”?
IV.C.3.	528	See our comments on lines 275-279.
IV.C.3.	529-530	This sentence is should be deleted because the trial may not have enough power to assess the results in specific subpopulations.
IV.C.4.a.	550-564	A possible approach to obtaining the MID is to gain agreement from a panel of clinical experts prior to the start of the study. Would this be acceptable?
IV.C.4.a.	551-553	There is an underlying assumption here that non-PRO measures are sensitive to change. Available literature shows that spirometry measures do not correlate well with PRO measures. For example, PRO measures provide more information on changes in patients’ asthma control than spirometry does.
IV.C.4.a.	562-563	The Agency also needs to take into account the disease of interest, population severity, and comparator (active versus placebo), all of which impact on what is considered clinically meaningful. Therefore, a range of MCID scores may be more reasonable than a single number.
IV.D.	590-593	Sometimes the changes are minor and a cognitive debriefing with the modified instrument should be sufficient. Revalidating the entire instrument in such circumstances represents a significant burden to the sponsor.

Docket Number 2006D-0044 Response to FDA Call for Comments Draft Guidance for Industry – Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

Specific Comments on Draft Guidance for Industry – Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims		
Section	Page or Line Number	Comment or proposed replacement text
IV.D.2.	612-613	We agree that a disease-specific instrument cannot be used for a different disease; however, there are diseases/conditions that are similar or closely related where one disease-specific instrument could be applicable for another condition, e.g., GERD and dyspepsia.
IV.D.4.	637	Computer adaptive testing is not only a mode of PRO administration but also an algorithm driven, item response theory based item pool.
IV.D.5.	659	Please clarify the term harmonization. Is it harmonization as in “International Harmonization” or should it be understood as “reconciliation” when the forward versions are reconciled at the beginning of the linguistic validation process?
IV.D.5.	660	Psychometric validation for every translated version should not be mandatory. It should be sufficient to demonstrate that internationally endorsed standards and principles for translation and cultural adaptation have been used. Patients’ cognitive debriefing in the target countries is an important means to ensure that conceptual equivalence between the source and target versions have been retained.
IV.D.6.	666	This requirement seems to be unnecessarily restrictive. Consider removing it from the Guidance.
V.A.1.	717-718	Please consider rephrasing the term “rarely credible”, because there are many situations when blinding is not possible for ethical reasons.
VI.C.	924-954	Please clarify the use of “composite”. It might be more appropriate to refer to a global score in this context rather than to a composite score.
VI.D.2.	1000-1001	Please reconsider the phrasing. There are cases when LOCF is acceptable. Common causes of discontinuation are lack of efficacy or side effects or both. Unless the PRO outcomes are captured at the time of discontinuation and used in a LOCF the true difference might be overlooked.
VI.D.2.	1012-1016	In the event that the endpoint is a domain score or overall score from several domains, please provide guidance concerning what a worst-case approach would be if there were not enough questions answered to allow the score to be produced. Should we assume the worst/best score for each question not answered in the questionnaire (as opposed to assuming the worst/best score for the complete score)?