



April 4, 2006

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

Re: FDA Draft Guidance "Patient-Reported Outcome Measures: Use in Medicinal Product Development to Support Labeling Claims"

Ladies and Gentlemen:

Reference is made to the Federal Register Notice dated February 3, 2006 (Docket No. 2006D-0044) requesting comments on or before April 4, 2006 on the guidance for industry entitled "Patient-Reported Outcome Measures : Use in Medicinal Product Development to Support Labeling Claims".

In accordance with the above mentioned Federal Register Notice, Hoffmann La Roche, Inc. (Roche) is pleased that the FDA has recognized the importance of Patient Reported Outcome (PRO) measures and the need for guidance on this issue. We appreciate the efforts put forth by the Agency and are providing the following recommendations on the above mentioned Draft Guidance. By way of background, Roche is a research based pharmaceutical company with extensive experience in conducting clinical trials in various therapeutic areas including primary care and specialty care. Many of these trials included and/or were specifically designed to assess patient-reported outcome (PRO) measures. Roche has a significant interest and recognizes the importance of the provisions addressed in the Draft Guidance and welcomes the opportunity to comment on the same. Roche is also a member of the Pharmaceutical Research and Manufacturers of America (PhRMA) and participated in the PhRMA working group which is also providing comments on this draft guidance. We fully support the recommendations that have been made by PhRMA.

Since this is the first regulatory guidance relative to PROs supporting labeling claims, the guidance will likely serve both as a US and global regulatory benchmark for PRO measures for researchers, the pharmaceutical industry and other health authorities. The guidance may also have a global impact on future PRO research and development, particularly for large international research based pharmaceutical companies. To-date there are no approved US marketed Rx products that include PRO measures in their approved labels which could serve as potential benchmarks, which further increases the interest and expectations of this guidance. Therefore, understanding the importance of this guidance and its' potential global impact on future research and development, we hope the Agency will carefully consider all comments/recommendations included in this communication.

Roche supports the recommendations being provided by PhRMA and are providing input on specific issues included in the draft guidance of importance to Roche. In this correspondence, we are providing both general and specific commentary on particular elements of concern to Roche which are delineated as follows.

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General Comments:

- Roche believes that PRO is still a developing field of research and professional opinions vary significantly regarding the science behind developing and validating PRO instruments. Understanding this issue, we support the guidance being flexible in its overall approach at this point in time and appreciate the FDA's recommendations to begin communication around PRO instruments and outcomes to be used in clinical trials as early in the development phase as possible. We appreciate the FDA making their staff available for these discussions and the desire to work together with industry on a case by case basis.
- Throughout, the guidance seems to be holding PRO instruments and validation to a higher standard than traditional clinical efficacy endpoints. We believe that there should be parity between clinical and PRO endpoints and that all endpoints should be held to similar scientific standards.
- The guidance should recognize and acknowledge that a balance is needed between ideal evidence for PRO measures and what can realistically be achieved in a clinical trial setting.
- Roche believes that the Agency, after reviewing the comments received from interested parties, consider additional review cycles for this guidance prior to its finalization.
- We clearly understand that to include specific information in an approved label, the data must be of acceptable scientific rigor. We also understand that the label should communicate useful information to healthcare providers and to patients. The Agency guidance entitled "Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" does provide to permit data in the label with qualifying statements if necessary to communicate the information appropriately. We believe such flexibility should also be considered for PRO data.

Specific Comments:

Specific comments on various aspects of the draft guidance are tabulated below identifying the section of the guidance for which comments are provided.

Section of Draft Guidance	Roche Comment
I. Introduction:	The definition of PRO needs to be clarified. In the Introduction this term is defined as measurement of health status made directly by the patient. This is not consistent with situations when, due to the patient's health status, input needs to be provided by others such as a care giver. The best scientific approach to collecting PRO information from vulnerable populations, such as children and those at the end of life, may be to have a proxy respond for the patient. In



	<p>some parts of the guidance, this appears to be disallowed and in others there is reference to proxy reporting. We strongly recommend that the FDA consider proxy reporting in special circumstances and make a statement to this effect in the guidance.</p> <p>In addition, some circumstances require that a patient be interviewed and we believe that the guidance should provide for trained interviewers to collect information/data directly from patients with the clear proviso that they do not interpret or coach the patients on their response.</p>
<p>II. Patient-Reported Outcomes –Regulatory Perspective:</p> <p>Regulatory Issues Not Addressed in Guidance:</p>	<p>The section of the Guidance entitled, “Patient-Reported Outcomes – Regulatory Perspective” seems to be a misnomer based on the information contained in that section which only addresses the rationale for PRO in product development. We recommend considering another title for this section, such as “Need for Patient Reported Outcomes”</p> <p>Since the goal of the FDA guidance is to provide guidance on the research needed to include the PRO claims in the label, we recommend that a section be added to the guidance that clarifies where in the label such claims might be placed and what supporting data or statements might be allowed. A specific, theoretical example would be helpful.</p> <p>There is no discussion of the regulatory process to obtain FDA input on the patient-reported outcomes in the study design process, for example does the Agency recommend or support using a Special Protocol Assessment-like process for outcomes study design, validation of the instrument etc. and if so what would be the review timelines associated with such a process?</p>
<p>III. Evaluating PRO Instruments:</p>	<p>In this section of the draft guidance as well as in numerous places throughout the guidance, the Agency indicates that revalidation of a PRO instrument may be needed if any changes are made to a previously validated instrument, including instructions for completion and training aspects. We strongly disagree that this is needed in all cases and request that the Agency remain flexible in its overall approach regarding revalidation and make an assessment on a case by case basis. In some cases, minor changes could</p>



	<p>simply be tested with cognitive debriefing versus a complete validation study. In the interests of conducting good science and using resources wisely, we believe that this needs to be addressed on a case by case basis. For example, minor clarifications in instructions would not require re-validation of an instrument. This issue is also discussed in section IV D of the guidance.</p>
<p>IV. Evaluating PRO Instruments: A. Development of the Conceptual Framework and Identification of the Intended Application</p> <p>3. Identification of the Intended Population.</p> <p>B. Creation of the PRO Instrument 3. Choice of Recall Period</p>	<p>The draft Guidance is not clear on what is meant by "adequacy of a PRO instrument from an FDA perspective." We recognize that there is significant variability in the field on this point and suggest that the FDA provide more information in the guidance in the form of an appendix that provides a summary of the state of art or literature on this matter. This would be similar to the glossary of terms that is currently included and is very helpful.</p> <p>The discussion regarding comparing the patient population vs PRO population seems very stringent as written and we suggest that the PRO instruments be created and validated using a comparable population and that the FDA consider this on a case by case basis as the plans for each trial are discussed and finalized.</p> <p>In Table 2 the statement in reference to Visual Analog Scales that states "These scales often produce a false sense of precision" should not be included. This is not a consensus view of the field and is a judgement about VAS rather than a description. Furthermore, patient recall periods and equally weighted scores need to be addressed on a case by case basis. There is not a single standard in the field and the best approach in a specific instance will depend on the specific patient population or issue under study. Again this is a very important point in certain therapeutic areas of clinical research.</p>



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<p>C. Assessment of Measurement Properties Table 4.</p>	<p>In Table 4, under validity one suggested test is the ability to predict future outcomes or "predictive validity". Again, depending on the patient population in question and the specific item under study, a patient's state at one point in time may or may not accurately predict a future state. The requirement regarding the ability to predict future outcomes is unrealistic for some PROs and the guidance should retain the flexibility to allow for such circumstances.</p> <p>In Table 4, under interpretability, guidance is provided regarding MID. Understanding that PROs is still a developing field, Roche strongly suggests that the methodology used in establishing a minimally important difference (MID) at this time also be flexible and be considered on a case by case basis.</p>
<p>D. Modifying an Existing Instrument</p>	<p>Please see the comments previously provided for section III. Evaluating PRO Instruments of the guidance.</p>
<p>E. Development of PRO Instruments for Specific Populations</p>	<p>Proxy reporting can be a necessary in some trials due to the cognitive ability or extremely frail nature of the patients. We applaud the FDA for recognizing that proxy reporting is sometimes needed, however the recommendation that all PRO instruments should be completed by <i>both</i> the proxy and the patient is unduly burdensome. In trials where some patients may degenerate to a point where proxy reporting is needed, it would be very costly and burdensome to the potential proxy to complete all PRO instruments at all data collection points. Rather, we recommend that proxy completion be considered at a PRO instrument level and that differences between proxy and patient reporting be understood for the instrument itself and that it only be completed by either a patient or a proxy for most studies. The FDA should remain flexible in this matter and be cognizant that for <i>some</i> studies the suggestion that both proxies and patients complete all PRO instruments may be a best practice, in others the proxy should only be used at the point when the patient cannot respond for themselves.</p>
<p>V. Study Design:</p>	<p>This section suggests that open label studies are not acceptable. Roche suggests that the guidance be more</p>



	<p>flexible regarding the overall utility of such data. In some therapeutic areas, open label studies are acceptable. As per several Agency labeling guidances which provide for qualifying statements to be included in a label, we believe it is possible to appropriately describe such data in the label. Again, this would be something that the FDA should be willing to consider as it works with industry in the early development of trials.</p>
<p>VI. Data Analysis: A. General Statistical Considerations</p>	<p>While we agree that analyses should be pre-specified in the statistical analysis plan, there are circumstances where post hoc analysis could be very useful. Roche suggests that the guidance be more flexible regarding the overall utility of such data. Again as per several Agency labeling guidances which provide for qualifying statements to be included in a label, we believe it is possible to appropriately describe such data in the label and the FDA should make provisions for this possibility.</p>
<p>C. Statistical Considerations for Composite Measures</p>	<p>Roche suggests that the guidance be more flexible regarding the overall utility composite measures and sample size requirements by engaging in discussions with the sponsor on a case by case basis to come to an acceptable recommendation for each study.</p>
<p>D. Statistical Considerations for Patient –Level Missing Data</p>	<p>Missing data is a complex topic and there are many reasons why data may be missing in a study. Because of the complexities in this matter, it is not possible to have a single solution that is applied in all circumstances. Roche strongly recommends that the FDA engage in a discussion with the sponsor about the reasons for missing data and seek to understand the patterns of missing data so as to identify the best analytic approach for the specific situation. As the FDA is interested in and willing to participate in constructive dialogue over the establishing the validity of a measure, we believe that addressing missing data issues is also something that is most constructively accomplished through dialogue on a case by case basis.</p>



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Since this is the first regulatory guidance relative to PROs supporting claims for medicinal products, and understanding that the guidance is likely to serve as an important benchmark for both US and global researchers, the pharmaceutical industry and other health authorities, we would like to conclude with the following additional recommendations.

1. We strongly suggest that the Agency carefully consider the all the comments received from interested parties and incorporate appropriate recommendations in the next version of the draft guidance.
2. Because of the potential broad local and global impact this guidance may have, we also suggest that the Agency consider additional review cycles for this important guidance before it is finalized and that periodic reviews of the guidance be established after finalization.
3. Understanding that the there is a lack of consensus in the scientific community on some topics addressed in the guidance, we strongly believe that the guidance needs to be consistently flexible throughout at this point in time. We applaud the recognition by the FDA that there is not a "one size fits all" solution to PRO's and that the field is still developing, thus flexibility around such issues should be consistently applied throughout the guidance.
4. Finally, Roche fully supports the input provided by PhRMA on this draft guidance.

We would like to thank the Agency for the efforts that have been put into developing the draft guidance and the opportunity to comment on the guidance. Roche would be happy to clarify any points included in this communication.

Sincerely,

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