A decisive step in the recognition of Patient Reported Outcomes in clinical trials
Meeting with the FDA: February 16, 2001 - Important Issues in Patient Reported Outcomes (PROs) Research

Co-organized by The Harmonization Meetings Coordination Committee
(ERIQA: Bernard Jambon, Patrick Marquis; FDA HRQL WG: Laurie Burke; ISPOR: Paul Kind; Nancy Kline Leidy; ISOQOL: Ivan Barofsky, Dennis Revicki; PhRMA HOC: Margaret Rothman, Nancy Santanello)

and Mapi Research Institute (Catherine Acquadro, ERIQA)

Background: At the initiative of Mapi Research Institute, the first two Harmonization meetings brought together members of ERIQA, ISOQOL, ISPOR, PhRMA HOC, and FDA observers on March 31st, 2000 in Pentagon City, VA and on September 14th, 2000, in Rockville, MD, to focus on issues related to Heath-related Quality of Life (HRQL) outcomes. One of the conclusions was to continue discussing issues related to outcomes research under the coordination of a Committee of representatives from each organization and the FDA.

The purpose of the February 16th 2001 Meeting Program was to continue to clarify aspects and components of Patient Reported Outcomes (PROs) evaluations, specifically to discuss the added value of this outcome, as it relates to regulatory authorities, as well as to suggest use of this information within labeling and promotional claims. It was the consensus of the group that the Program should succinctly address specific issues raised by government authorities and that it should be designed in such a way that it transcends any individual’s concerns, addressing questions that can arise from a variety of sources outside of the patient reported outcomes scientific field. This meeting was organized in collaboration with Laurie Burke (FDA/CDER/DDMAC), in agreement with Dr Robert Temple, Director of Office of Medical Policy, and of Drug Evaluation I (FDA/CDER).

The February 16th meeting entitled “Important Issues in Patient Reported Outcomes Research” addressed 4 key issues. Each of them included a group leader who coordinated the development of the argument:

Group 1: Conceptual and Definitional Issues
Ivan Barofsky, Pennifer Erickson, Paul Kind, Margaret Rothman, Donald Patrick

Group 2: The Value of Patient Reported Outcomes
Asha Hareendran, Nancy Kline Leidy, Charlotte, McMillan, David Miller, Dennis Revicki, Pierre-Philippe Sagnier, Ingela Wiklund

Group 3: Methodological considerations in obtaining Patient Reported Outcomes in clinical trials
Olivier Chassany, Dominique Dubois, Joe Jackson, Patrick Marquis, Nancy Santanello, Rhys Williams

Group 4: Interest in and Demand for Patient Reported Outcomes
Rick Berzon, Greg Boyer, Joyce Cramer, Haim Erder, Jean-Paul Gagnon, Richard Wilke, Albert Wu
The synthesis of the presentations was expressed in suggesting three Take Away Points:

1. Patient has a unique voice and valuable perspective that should play a role in medical decision making

2. PROs can be measured in reliable and valid ways

3. PROs are increasingly used as efficacy endpoints in randomized controlled trials

Outcomes:
It was clearly stated by the speakers that the field of PROs evaluation is still evolving. The audience did not question the definitions of PROs and HRQL, and expressed a great interest in the presentation of PROs added value, especially in the examples illustrating it. The audience also recognized that reliable and valid instruments are available to measure PROs, but deplored the lack of quality of some studies presented for review.

Some participants expressed the following concerns:
- There is a need to be clear in the use of PROs (clearly state what is measured, how the chosen PRO will be assessed, what the pre-specified hypothesis are).
- There is a need to clarify:
  - what is unique in PROs methodology as opposed to classical RCTs
  - what is meant by clinical significance, what are the meaningful data, what are the methods to handle missing data
  - what are the information needed to support a claim
  - what should be put in the label

Although it was stated that a FDA guidance on PROs Issues is not to be planned in the short term, and that some methodological issues still need to be clarified, the interest of including PROs in clinical trials seemed to be recognized.

To follow up, a meeting gathering all FDA agents willing to continue the discussion internally will be arranged by the FDA HRQL Working Group. At this occasion a format will be proposed to move forward on these issues with ERIQA, ISOQOL, ISPOR and PhRMA HOC. A step ahead will involve the study of PROs pathology per pathology.

To conclude, the FDA perspective seems encouraging for the future of the field. Although additional research is needed, this meeting can be considered as a crucial step in the future recognition and adoption of PROs as relevant evaluation criteria of drugs in clinical trials.
### APPENDIX

#### AGENDA

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tr>
<td>8:30-8:45</td>
<td>Introduction: Jean-Paul Gagnon, Aventis, Parsippany, NJ, USA</td>
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<td>8:45-9:15</td>
<td>Group 1</td>
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<tr>
<td>9:15-10:00</td>
<td>Group 2</td>
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<tr>
<td>10:00-10:15</td>
<td>Break</td>
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<tr>
<td>10:15-10:45</td>
<td>Group 3</td>
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<tr>
<td>10:45-11:00</td>
<td>Group 4</td>
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<tr>
<td>11:00-11:15</td>
<td>Next Steps: Jean-Paul Gagnon, Aventis, Parsippany, NJ, USA</td>
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<tr>
<td>11:15-11:45</td>
<td>Discussion</td>
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#### Audience (60)

FDA: Tom Abrams, Mark Askine, Julie Beitz, Laurie Burke, Judy H. Chiao, Jean-Ah Choi, Sarah Dawisha, Hung Du, Mary Furucker, Donna Griebel, Tarek Hammad, Lisa Kammerman, Peter A. Lechedbmuch, Marianne Mann, Kate Meaker, Bob Meyer, Robert O'Neil, R. Pazdur, Leah Palmer, Rupa Shah, Dan Shames, Jay Siegel, Jeff Siegel, Robert Temple, Grant Williams, Deborah Wolf

NCI: Joseph Lipscomb, Bryce Reeve, Claire Snyder. AHRQ: Sepheen Byron, Yen-pin Chiang Carolyn Clancy, Joanna Siegel

Coordinators: Catherine Acquadro (ERIQA), Marguerite Barberan (mapi Research Institute), Bernard Jambon (Mapi Research Institute)

Representatives of ERIQA, ISOQOL, ISPOR, PhRMA HOC not involved in Working Groups:

PhRMA HOC Chair: Catherine Copley-Merriman (Pfizer), ISPOR: Marylin Dix Smith, ERIQA: Bruce Crawford (Mapi Values)

#### ORGANISATION  REPRESENTATIVES (involved in Working Groups)

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Representatives</th>
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<tbody>
<tr>
<td>ERIQA</td>
<td>Olivier Chassany, Hôpital Lariboisière, France; Dominique Dubois, Janssen, Belgium; Asha Hareendran, Pfizer, UK; Patrick Marquis, Mapi Values, France; Ingela Wiklund, AstraZeneca, Sweden; Rhys Williams, Knoll-BASF, USA</td>
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<tr>
<td>PhRMA HOC</td>
<td>Haim Erder, Amgen, USA; Jean-Paul Gagnon, Aventis, USA; Joe Jackson, BMS, USA; Charlotte McMillan, AstraZeneca LP, USA; Margaret Rothman, Janssen Research Foundation, USA; Nancy Santanello, Merck, USA; Richard Wilke, Pharmacia, USA</td>
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<td>ISPOR</td>
<td>Joyce Cramer, Yale University School of Medicine, West Haven, CT, USA; Pennifer Erickson, Pennsylvania State University, PA, USA; Paul Kind, University of York, UK; Nancy Kline Leidy, MEDTAP International, Bethesda, MD, USA</td>
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<td>ISOQOL</td>
<td>Ivan Barofsky, Johns Hopkins University, Baltimore, MD, USA; Rick Berzon, Boehringer Ingelheim, Ridgefield, CT, USA; Donald Patrick, University of Washington, Seattle, WA, USA; Albert Wu, Johns Hopkins University, Baltimore, MD, USA</td>
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