# RESULTS OF THE SPRING 2000 HRQL HARMONIZATION MEETING

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## INTRODUCTION and BACKGROUND

Regulators need to understand the field of HRQL evaluation in order to make appropriate decisions. It is a matter of fact that they still have to be convinced that HRQL is a credible criterion of evaluation of medicines (especially in Europe).
A number of groups have considered the use of health-related quality of life (HRQL) assessments for regulatory purposes. Their work has been prompted by a desire to achieve credibility for HRQL as an evaluation criterion in clinical trials, which requires rationalization of the assessment of HRQL in clinical trials.
The groups, which have been involved in this work, are:

- The Pharmaceutical Research and Manufacturers of America (PhRMA) Health Outcomes Committee (HOC)
- The International Society for pharmacoeconomics and Outcomes Research (ISPOR)
- The International Society for Quality of Life Research (ISOQOL)
- The European Regulatory Issues on Quality of Life Assessment (ERIQA) group

The first three of these have considered the US regulatory situation, whilst the ERIQA group has looked at current circumstances in Europe. Each of these initiatives has produced a document describing their discussion and views on regulatory issues related to HRQL. These documents were compared by Mapi Values. Following this comparison, and considering the above regulatory context, it was decided to organize an Harmonization meeting on regulatory issues for HRQL, gathering members from each organization and FDA observers. This meeting was held on March 31st, 2000 in Pentagon City, VA, USA. This meeting was planned jointly by the members of the ERIQA Group, Mapi Research Institute with the support for logistics by the PhRMA HOC.
The list of topics (and issues within topics) developed at the occasion of the comparison of the four documents, was sent to representatives of each organization, 3 weeks prior the Harmonization meeting. In order to facilitate discussion, four important topics or issues were identified.

## OBJECTIVES

To highlight problematic topics/issues;
To harmonize recommendations/suggestions (if any) proposed by each organization;
To discuss about solutions when no recommendations have been suggested;
To propose future steps/collaboration to achieve consensus on problematic issues/topics.

## METHODOLOGY

The HRQL Harmonization meeting included an introductory presentation of the comparison to provide a brief update on what the four organizations have done. Representatives of the four organizations were split into four work groups corresponding to the four topics identified a priori:
Group 1: Concept -- Instruments; Group 2: Study Design; Group 3: Data Analysis -- Interpretation & Reporting; Group 4: Conditions for Claims -- Rationale

The morning session was devoted to work group discussions, while during the afternoon session each Group presented to all meeting attendees their conclusions, recommendations and research points to consider. Each presentation generated questions, comments from the audience. These presentations were followed by a discussion on next steps to be achieved and follow up of this first harmonization meeting.

## FINDINGS

**Group 1** focused on 3 particular issues: 1. Definition of HRQL, 2. Relationship between HRQL and patient satisfaction, 3. Relationship between HRQL measurement and adverse events (AEs).

### 1. Definition of HRQL

Two main ideas were developed:
**Concept is not absolute**
The way HRQL is defined will vary -- there is a wide range of definitions of HRQL depending on the context. There could be context-specific considerations, so HRQL could have a degree of malleability when it comes to these different contexts and their requirements. Contexts mentioned were: economic evaluations, practice (individual treatment decisions), clinical trial.
**Introduction of the concept of "fit for purpose"**

### 2. Relationship between HRQL and patient satisfaction

These are two different concepts to be treated separately and differently -- one cannot stand as a proxy for the other.

### 3. Relationship between HRQL measurement and adverse events (AEs)

- Recognition of a potential link between HRQL and AEs:
  - *HRQL evaluation could be used to trigger an adverse event. None of the documents that were considered and compared really address this effectively at all.*
  - HRQL should not stand as the surrogate for AEs.

- Inclusion of HRQL evaluation and AEs measurement at different phases of the drug development process: It was suggested that AEs would be most relevant in the earlier trials although there would also be room for some HRQL assessments during the early phases. Then, as things develop and as more is learnt about the impact of the treatment, it would be expected that adverse events would become less of an issue, and HRQL issues would become progressively more the focus of attention.

### Group 2 focused on the following:

✓ Planning for HRQL studies

*a) Recommended for consideration*
- Planning should be incorporated into the clinical development plan (to provide internal direction more than to request advice and direction from outside).
- Planning should begin relatively early in development -- phase II in general would make sense.

✓ HRQL hypotheses

*a) Essential:* To pre-specify hypotheses of what domains are expected to be affected and in what direction.
*b) Recommended for considerations:* To specify the size of a change and to provide information about what is an important change.

✓ Protocol requirements

*a) Essential*
- Protocol should contain hypothesis and details about the analysis plan including how missing data are to be handled.

*b) Recommended for considerations:*
- Protocol should include explanations or rationale for why the measures were selected.
- Need for data quality assurance measures to both prevent missing data and reassure anyone who is evaluating the study that the data would likely be trustworthy.
- Need for rationale for the timing of the measures.
- Need for specifying what the treatment regimen is, what the sample size for the overall study is to be, and what eligibility criteria are to be. If there are different eligibility criteria for participation in the QoL component of a study or obviously different sample sizes, or different timing, those things should be noted.

✓ Blinding

*a) Essential:* for drug approval, blinding is essential (if possible).
*b) Recommended for considerations*
- If blinding is not possible, efforts should be made to match either by design or by measurement, to account for biases which might exist, including expectations or other variables that could be related to a patients awareness of what treatment they are on.
- For promotional claims, blinding is recommended if possible.

✓ Sample size

*a) Essential:* If HRQL is a secondary end-point, it is essential to calculate power at study end.
*b) Recommended for considerations*
- To increase sample size to test HRQL hypotheses in order to make a claim on a secondary HRQL end-point

✓ Timing

*a) Essential*
- Timing of HRQL assessments should be pre-specified.
- A rationale for this should be provided in the protocol.

*b) Recommended for considerations*
- A baseline measure to help with interpretation.
- HRQL should be measured at the point of patient withdrawal.
- The timing of measures should be standardized within studies -- if possible in the same point within a study visit, perhaps at the beginning of the study.

✓ Respondent identity

Group 2 focused primarily on proxy respondents who might provide information about patients HRQL.
*a) Recommended for considerations*
- It might be legitimate to collect data from proxies in certain diseases, certain conditions where people cannot speak for themselves or it is very likely that at some point in the study, they might not be able to speak for themselves, though the patient data is still primary.
- If it were desired that proxy data be pooled with patient data, then it would be necessary to collect both proxy and patient data simultaneously at other points in the study.
  Other coupled strategies might be analyzing proxy data all by itself as an endpoint, though it is more difficult to do for certain dimensions of health that are more subjective than others are.
- Relationships with proxy should be recorded.
- Same proxy should be used throughout trial. If this is not possible, impact of using different proxies needs further study.

✓ Eligibility criteria

*a) Recommended for considerations*
- To either have inclusion / exclusion criteria to include patients with impaired QoL or to stratify randomization on baseline QoL.
- If not, then it is possible to have a priori plan of analysis of HRQL data stratified on baseline HRQL and not recommend to do a post-hoc.

✓ Design issues related to missing data and drop-outs

How missing data are to be handled was left to Group 3.

✓ Training of personnel

*a) Recommended for considerations:* Training will improve data quality.

✓ Comparison with other standards

*a) Recommended for considerations:* Standard procedures of data quality assurance should be specified

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### Group 3

1. Data analysis

*a) Absolutely Essential*
1- Follow clinical analysis procedures for HRQL, which should be considered as a primary or secondary endpoint
2- If it is a primary endpoint similar primary analyses should be followed
3- HRQL should be incorporated in a labeling claim like clinical endpoints
4- Primary or secondary end-points should be specified
5- If it is a primary endpoint, it should have hypotheses
6- Procedures for handling missing items and sample attrition should be specified, use sensitivity analysis to analyze for sample attrition
7- Multiple testing: need procedures to control Type I error. Researchers should specify procedure for controlling Type I error in protocol and report
8- Researchers need to consider secondary and primary endpoints together. Secondary endpoints can only be considered if there is a significant difference with the primary endpoint.
Comments: Statement 8 was severely questioned. Therefore, it was specified that this statement was not meant in terms of equivalence studies, but in terms of placebo controlled studies.
9- Based on the primary endpoint and sample size, researchers should state the power to detect the differences in the HRQL secondary endpoint

*b) Recommended for Consideration*
1- Analyze differences between patients with and without missing data
2- Study designs should support generalization, e.g., extended effectiveness studies in broad populations *(a clinical trial with very specific inclusion/exclusion criteria may not be adequate for a promotional claim because, although internal validity is highly supportive, the generalization of the study may be very limited).*

2. Interpretation and Reporting

*a) Absolutely Essential*
1- Statistical significance is required
2- Statistical measures of distance (meaning difference between comparator and treatment group divided by some measure of variation) are not equal to measures of clinical significance
3- A Minimal Important Difference (MID) does not equate to a patient global rating of change. An external variable is needed to determine MID, the external variable should be selected for the specific situation
4- Evidence from multiple external measures strengthens claims for clinical significance
5- Complete and balanced reporting of positive and negative data for summary scores and domains as appropriate for the instrument
6- Do not over interpret definitions of differences as being applicable to all instruments
7- Do not over interpret data

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### Group 4

Group 4 focused on conditions for claims.

Introduction
- The same requirements should apply irrespective of whether for approved labeling or promotional claims
- Evidence for claims of HRQL benefits need to be consistent with the standards for claims of clinical efficacy

How many trials
- If HRQL is the primary endpoint, the number of trials required should be the same as for clinical outcomes
- If HRQL is a secondary endpoint and if the trial is sufficiently powered, 2 trials are enough

Respect of the double-blind
- It is strongly encouraged. In some cases, it may be impossible to blind
- In those cases, the onus is on the sponsor to demonstrate that the data are not confounded

How many domains
- HRQL is a multidimensional concept
- In the protocol, the major domains, which are affected by the illness, must be substantiated
- The most important is to pre-specify a priori the major domains that are expected to improve, consistent with the disease. Domain specific claims require statistical significance within that domain. But it does not constitute a general HRQL claim

Psychometric evidence
- Evidence should be provided of the internal and test-retest reliability, content, construct, and criterion validity and responsiveness
- However, clinical trial (phase 3) can serve at the same time as a validation study, especially for responsiveness
- The same standard of psychometric evidence should apply to all patient-based assessments, including measures of self-report clinical efficacy

Data analysis
- Should be consistent with traditional clinical outcomes
- Analysis plan should include language consistent with patient self-reported clinical efficacy measures
- Plan should include a priori discussion: how to handle missing data and multiple comparison

Claims of difference
- Claims of differences in HRQL should be permitted if statistical significance is found in more than one domain and is consistent with the hypotheses
- It is the responsibility of the sponsor to provide guidelines for interpreting the results

Claims of equivalence
- It is highly desirable to employ a measure that has demonstrated responsiveness or at least discriminant validity.
- Demonstration of adequate power (80% with full disclosure) must be substantiated within the analysis plan

General
- Studies should be designed with intended claims in mind. Although a perfect relationship is not expected between HRQL and clinical measures, this should not conflict if a claim is to be made

**Table 1: List of Research Questions**

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| ♦ Concept<br>To explore in more details links between measurement of AEs and HRQL evaluation |
| ♦ Study Design<br>Respondent Identity: to study impact of using different proxies throughout trial |
| ♦ Data analysis<br>To explore in more details methods of imputation of missing data, methods for multiplicity of inter-related endpoints, and methods for multiple significance testing |
| ♦ Interpretation and Reporting<br>Investigation on types of external measures and their associated minimal important differences in various therapeutic areas |

**Table 2: List of Questions asked by FDA observers**

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| To Group 1<br>♦ Did you discuss the difference between a claim of HRQL supported by a one item global versus a claim of HRQL supported by multi-dimensional index?<br>♦ If we are willing to say that both could possibly measure the same thing, then why to develop these multiple items, multi-scale instruments?<br>♦ If you want to make a satisfaction with treatment claim, do you need a clinical trial to demonstrate that outcome ? Are satisfaction outcomes appropriate for clinical trials ? |
| To Group 2<br>♦ You commented that it is important to show the clinical relevance of results. Could you just explain that a little bit further, please ?<br>♦ I have a question about your proposed trial design of only including people who have a decreased QoL. Would not that have implications for the generalization of the results?<br>Would you then be proposing a claim that it improves QoL for patients who have an impaired QoL? |
| To Group 3<br>♦ How do we interpret a treatment effect ?<br>♦ What more are you learning from the QoL measure than you are getting from signs and symptoms or other outcome measures ? What is the Added Value of HRQL Outcomes ? |
| To Group 4<br>♦ Could someone clarify what is meant by a HRQL claim ? |

## Conclusions: Next Steps

This meeting raised a lot of interests from FDA observers, although some questions have remained unsolved.
Therefore, it was decided:
- To create a coordination committee, composed of 2 members from each organization/society (ERIQA, ISOQOL, ISPOR, PhRMA HOC), and one person from the FDA. Its role will be to

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organize future HRQL harmonization meetings, and facilitate the dissemination of the proceedings of each meeting.

- To organize a meeting on the Added-Value of HRQL outcomes at the FDA office, on September 14th, 2000 (with the same meeting attendees).