HEALTH-RELATED QUALITY OF LIFE AND REGULATORY INITIATIVES IN THE UNITED STATES: A SYNTHESIS

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Health-related quality of life outcomes reflects an assessment of the impact of treatment and underlying disease on patient functioning and well-being.

For the pharmaceutical and medical device industry HRQL outcome data is used to demonstrate value compared to existing competing treatments.

Frequently there is interest in using HRQL information in product labeling and advertising to physicians, health insurers, and patients.
In the United States, labeling and promotional claims must be approved by the Food and Drug Administration (FDA).

The FDA is responsible for ensuring that any claims related to clinical efficacy, safety or HRQL are based on scientific data and reproducible methods and instruments.

Although the FDA has extensive experience in reviewing and evaluating efficacy and safety data, the agency has less experience with HRQL outcomes.
Objectives

- Current status in Canada and the United States
- Review of the U.S. based initiatives on HRQL and regulatory issues
- Status report on FDA guidance on HRQL labeling and promotion claims
- Recommendations for HRQL and regulatory issues
Guidelines for economic evaluations available for Canadian provinces

- Economic analysis recommended, not required
- HRQL outcomes viewed as evidence of effectiveness and 'value'
- Quality-adjusted life years and cost-utility analysis
United States and Current FDA Regulatory Policy on HRQL

- No requirement for HRQL outcomes in FDA submissions
  - Viewed as supportive, secondary effectiveness endpoint
  - Some centers/divisions encourage use of HRQL outcomes
    - Oncology
    - Respiratory
    - HIV/AIDS

- Other centers/divisions highly skeptical of HRQL outcomes
Current FDA Regulatory Policy of HRQL Outcomes

- No consistent policy or guidelines for HRQL outcomes
  - Variable depending on specific center/division and disease area
  - Variable understanding of HRQL measures and methods

- DDMAC is currently working on guidance on HRQL for labeling and promotion
  - Draft guidance document will be issued sometime between November 1999 and infinity
“If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence...”
Substantial Evidence from Adequate and Well-Controlled Studies

Protocol Essentials

- Study objectives
- Precise study design that allows valid comparison
- How patients assigned to treatment groups
- Measures and criteria to assess response (validity of measures)
- Procedures for minimizing bias (binding)
- Data analysis plan
United States Initiatives on HRQOL and Regulatory Issues

- Leidy, Revicki and Geneste (1999)
- International Society for Quality of Life Research (ISOQOL)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
- PhRMA Health Outcomes Working Group (HOWG)
Recommendations for Evaluating Validity of HRQL Claims

- Leidy et al. (Value in Health 1999)

Main recommendations
- Include physical, psychological and social domains
- Well-documented rationale for HRQL domains and instruments
- Complete summary of psychometric evidence
- Training clinical center staff and implementation procedures
- Data analysis (a priori) plan with criteria for statistical and clinical significance
- Complete disclosure of all HRQL results
ISOQOL Policy and Regulatory Committee

- Constituted November 1998 at ISOQOL meeting in Baltimore

- Members: I. Barofsky; R. Berzon; D. Fairclough; N. Leidy; D. Osoba; D. Revicki (chair); M. Rothman

- Current Status
  - Draft report circulating for approval of ISOQOL Board and memberships
  - Publication in Quality of Life Research and other journals
ISPOR Quality of Life Regulatory Guidance Issues

- ISPOR Ad Hoc Quality of Life Guidance Committee
  - C. Acquadro; I. Wilkund; S. Fullerton; S. Coons; P. Erickson; P. Kind; E. Lydick; J. Osterhaus; L. Morris; R. Epstein

- Several meetings with the FDA and DDMAC

- Current Status
  - FDA questions and commentary/responses from committee members
Main Issues on HRQL and Regulatory Agency

- Terminology: quality of life, health-related quality of life, health status
- Stand-alone claims for HRQL endpoints
- Safety/adverse event reporting and HRQL
- HRQL domains: multidimensional versus more limited assessment
- Disease-specific versus generic HRQL instruments versus HRQL batteries
- HRQL research protocol and data collection
- Psychometric characteristics and evidence
- Responsiveness and clinical significance
- Statistical analysis
PHRMA Health Outcomes Working Group

Committee: J. Gagnon; K. Copley-Merriman; D. Miller; A. Baker; R. DeMarinis; J. Jackson; R. Mahmoud; M. Morgan; J. Osterhaus; N. Santanello; H. Tilson; R. Wilke

Multiple meetings of the HOW G

PhRMA/FDA Interactive Workshop on Regulatory Issues in HRQL Assessment (March 1999)

Represents industry perspective on HRQL outcomes

Current Status
- Document is under development
Legal Standards:

- Use consistent with FDA-approved product labeling

- Substantial evidence is required to claim effects for uses not specifically mentioned in approved product labeling

- Promotion may not be false, lacking in fair balance or misleading
Federal Food, Drug and Cosmetic Act: Sec. 505(d). New Drugs

“...substantial evidence [of drug effect] means evidence consisting of adequate and well-controlled investigations...”

“If...one adequate and well-controlled clinical investigation and confirmatory evidence ...are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence...”
FDA Policy Development Concerns

- Guidance must conform to substantiation requirement for other clinical endpoints in approved labeling and promotional materials.

- Guidance must be responsive to the developing nature of HRQL research.

- FDA cannot assess the adequacy of developing guidance before acquiring experience in the review of HRQL endpoints in submissions.
FDA Guidance that Mentions QOL

- Clinical development programs for treatment/clinical evaluation:
  - Osteoarthritis
  - Rheumatoid arthritis
  - Heart failure
  - Weight control drugs (draft)
  - Urinary incontinence (under development)

- Guidance on use of HRQL outcomes to support medical product claims in labeling and advertising (under development)
FDA Perspective: Key Elements

- Determine possible claims before clinical trials starts

- Complete documentation of the following:
  - HRQL instrument and scoring
  - Instrument development and psychometric evaluation
  - Clinical trial protocol
  - Data analysis plan
Recommendations for Standards of Evidence for HRQL Instruments

- Rationale for measuring HRQL

- Rationale for selecting specific HRQL instrument for clinical trial
  - Summarize evidence on psychometric characteristics
Evidence on Psychometric Characteristics

- Documentation of all evidence on reliability and validity of selected HRQL instruments
  - Previous studies and literature
  - Targeted studies for clinical trial

- Evidence must demonstrate psychometric characteristics
  - Internal consistency and test-retest reliability
  - Acceptable content and construct validity
  - Direct evidence of or rationale (based on data) supporting responsiveness
  - Definition of clinical significance
Recommendations for HRQL Research Protocol

- Provide rationale for and specify data collection protocol
  - Baseline and one or more follow-up assessments
  - Mode of administration (self, interviewer, computer)
Recommendations for HRQL Data Analysis Plan

Data analysis plan (a priori)

- Approach for handling missing items and missing endpoints
- Imputation techniques
- Between treatment group comparisons
  - Longitudinal data structure
  - Multiple endpoints
  - Primary and secondary endpoints
Recommendations for Reporting HRQL Findings

- Fair and complete disclosure of findings (positive, negative, neutral)
HRQL Labeling and Promotional Claims

- Approved indication(s)

- ‘Quality of life’ claims
  - Higher standard of evidence
  - Demonstrate connection with patient values

- HRQL and/or health status domain claims
  - Report on confirmed, demonstrated evidence
  - Full disclosure
Summary and Conclusions

- Government regulatory policy on HRQL outcomes is changing
- Most regulatory agencies view HRQL as secondary endpoints
- Physicians and patients view HRQL endpoints as important
- Regulatory agencies, based on existing information, often view HRQL as another way to show ‘value’
- Guidelines on HRQL outcomes are under development in the US
ISOQOL, ISPOR, and PhRMA are providing recommendations to the FDA.

Different perspectives are represented, i.e., academic and industry.

General guidelines and flexibility.

Focus on instrument development and validation, clinical trial protocol, and data analysis issues.