INTEGRATION OF PATIENT PERSPECTIVES IN DRUG EVALUATION: HARMONIZATION, CONSENSUS, AND DIVERGENCE

Health-Related Quality of Life and Patient-Reported Outcomes
A European Perspective

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The views expressed are my own and do not represent an official position or policy of EMEA or AFSSAPS

Part of the presentation is based upon work of ERIQA group (European Regulatory Issues on Quality of Life Assessment) Coordinator: Dr C. Acquadro, Mapi Research Institute
2.2.2. Primary and secondary variables:

“... Measurements relating to quality of life and health economics are further potential primary variables …”
EMEA RECOMMENDATIONS

Negative

- Crohn’s Disease (1999)
Other end-points such as...[...]...improvement in HRQL can be subsumed as response variables or outcomes measures of either the treatment of active disease or maintenance of remission.

Unless otherwise justified, they should not be mentioned in the indication

EMEA RECOMMENDATIONS

Study design issues

• Chronic PAOD (1995)
  In long-term therapeutic studies with an appropriate sample size of patients, the assessment of HRQL should also be performed by using general or disease specific questionnaires.

• Anticancer in Man (1995)
  The choice of scales should be justified and the validity of the scale for the specific study population and its reliability should be documented. Cultural aspects should be taken into account, especially in the case of multinational studies.

• COPD (1999)
  Care should be taken with respect to statistical multiplicity if secondary endpoints become the basis for specific claims.
EMEA RECOMMENDATIONS

Study design issues

Cardiac Failure (1995)

It is particularly important to consider whether

- the scale is linear over the range of measurements
- is sensitive to the changes anticipated
- it is valid and useful to adjust results using the baseline scores
- there is any correlation between the score and the objective responses
- the observer and the patients should be blinded and
- training of both the observer and the patient is necessary
EMEA RECOMMENDATIONS
Points to consider (CPMP/EWP/562/98) on clinical investigation of medicinal products in the chronic treatment of patients with COPD, 1999

- In the major efficacy studies of symptomatic benefit the primary endpoint should reflect the clinical benefit the applicant wishes to claim in the future SPC (Summary of Product Characteristics)

- It should include the \textit{FEV1} as a measure of lung function and include a measure of \textit{symptomatic benefit}

- A significant benefit for \textit{both endpoints}, should be demonstrated so that no multiplicity adjustment to significance levels is indicated

- \textbf{The primary symptomatic benefit endpoint} should be justified by referencing published data which supports its validity; one example is the \textit{St George’s Respiratory Questionnaire}

- There are number of \textit{secondary endpoints} which may provide useful information. ... e.g. symptom scales, ... and \textit{quality of life assessment}
CHECKLIST FOR DESIGNING, CONDUCTING AND REPORTING HRQL / PRO IN CLINICAL TRIALS


HRQL / PRO objectives
- Added value of HRQL / PRO
- Choice of the questionnaires
- Hypotheses of HRQL / PRO changes

Study design
- Basic principles of RCT fulfilled?
- Timing and frequency of assessment
- Mode and site of administration...

HRQL / PRO measure
- Description of the content of domains
- Evidence of validity
- Evidence of cultural adaptation

Statistical analysis plan
- Primary or secondary endpoint
- Superiority or equivalence trial
- Sample size
- ITT, type I error, missing data

Reporting of results
- Participation rate, data completeness
- Distribution of HRQL / PRO scores

Interpreting the results
- Effect size, MCID
- Comparison with other scores
- Comparison with external criteria
- Number needed to treat...
DISCREPANCIES MAKE APPRAISAL HARDER

- In the way to interpret HRQL data
- Between standard criteria and HRQL / PRO
- Among HRQL / PRO outcomes
- In direction and magnitude within HRQL domains
HOW TO EVALUATE DRUGS WHEN CLINICAL RELEVANCE OF RESULTS IS NOT OBVIOUS

- Mean score ± SD
  - p < 0.05 and IC₉₅
    - Clinically significant
      - YES
        - p < 0.05
          - OK
        - p = NS
          - STOP
      - STOP
  - p = NS
    - Clinically hard to perceive
      - NO
        - STOP
      - STOP
  - STOP

Responder's
- Consensual clinical definition and clear cut-off
% OF RESPONDERS (R) DEPENDS OF THE CUT-OFF OF MINIMAL CLINICALLY IMPORTANT DIFFERENCE (MCID)

<table>
<thead>
<tr>
<th>Cut-off : change unit</th>
<th>RA</th>
<th>RB</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 0.5</td>
<td>72%</td>
<td>50%</td>
<td>A &gt; B : + 44%</td>
</tr>
<tr>
<td>&gt; 1</td>
<td>22%</td>
<td>38%</td>
<td>B &gt; A : + 73%</td>
</tr>
</tbody>
</table>

Change of score (e.g. on a scale ranging from 1 to 7)

<table>
<thead>
<tr>
<th>Changes in AQLQ symptom-domain anchored to global</th>
<th>Asthma control global</th>
<th>Asthma change global</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global category</strong></td>
<td><strong>Average</strong></td>
<td><strong>n</strong></td>
</tr>
<tr>
<td>Worse</td>
<td>-0.04</td>
<td>3</td>
</tr>
<tr>
<td>Minimally worse</td>
<td>0.13</td>
<td>49</td>
</tr>
<tr>
<td>No change</td>
<td>0.35</td>
<td>102</td>
</tr>
<tr>
<td>Minimally improved</td>
<td>0.78</td>
<td>135</td>
</tr>
<tr>
<td>Improved</td>
<td>1.48</td>
<td>18</td>
</tr>
</tbody>
</table>

- 343 patients with mild to moderate asthma
- Global asthma control question: “How well is your asthma controlled?”
- Global asthma change question: “Overall has there been any change in your asthma since the beginning of the study?”
- Response from 0 to 6 (poorly controlled / much worse)
MCID MAY DEPENDS ALSO ON ...

• Characteristics of patients (age, gender…)
• Characteristics of disease (severity …)
• Setting of the trial
• Type of intervention
• Cross-cultural differences
• Baseline level of scores …
CURRENTLY, THERE IS NO CONSENSUS
Whether to be clinically relevant

• **Effect size** should be > 0.5

<table>
<thead>
<tr>
<th>Effect Size</th>
<th>Small</th>
<th>Moderate</th>
<th>Large</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benchmark</td>
<td>&gt; 0.20</td>
<td>&gt; 0.50</td>
<td>&gt; 0.80</td>
</tr>
</tbody>
</table>

• **MCID** should be > 0.5 on a range score from 1 to 7
• **Number needed to treat** should be < 10
**NUMBER NEEDED TO TREAT**

*Economic analysis of respiratory rehabilitation.*

<table>
<thead>
<tr>
<th>Chronic Respiratory Questionnaire</th>
<th>mean Δ</th>
<th>NNT to have 1 patient receive at least a small benefit</th>
<th>NNT to have 1 patient receive at least a moderate or large benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>0.61</td>
<td>4.1</td>
<td>5.8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>- 0.63</td>
<td>4.4</td>
<td>6.9</td>
</tr>
<tr>
<td>Emotional function</td>
<td>- 0.64</td>
<td>3.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Mastery</td>
<td>0.05</td>
<td>2.5</td>
<td>2.8</td>
</tr>
</tbody>
</table>

- Prospective randomized controlled trial of rehabilitation
- 84 subjects completed
- Intervention: 2 months of inpatient rehabilitation followed by 4 months of outpatient supervision
## NUMBER NEEDED TO TREAT

### Examples of literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Treatment duration</th>
<th>Criterion</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Woscops</strong></td>
<td>Pravastatin</td>
<td>5 yrs</td>
<td>Mortality (primary prevention)</td>
<td>111</td>
</tr>
<tr>
<td><strong>4S</strong></td>
<td>Simvastatin</td>
<td>5.4 yrs</td>
<td>Mortality (secondary prevention)</td>
<td>30</td>
</tr>
<tr>
<td><strong>LIPID</strong></td>
<td>Pravastatin</td>
<td>6.1 yrs</td>
<td>Mortality (secondary prevention)</td>
<td>32</td>
</tr>
<tr>
<td><strong>Left Ventricular dysfunction</strong></td>
<td>Enalapril</td>
<td>41 wks</td>
<td>Mortality</td>
<td>22</td>
</tr>
<tr>
<td><strong>MIRACL</strong></td>
<td>Atorvastatin</td>
<td>16 wks</td>
<td>Composite score</td>
<td>38</td>
</tr>
<tr>
<td><strong>CAPRIE</strong></td>
<td>Clopidogrel</td>
<td>1 yr</td>
<td>Composite score</td>
<td>196</td>
</tr>
<tr>
<td><strong>MUCOSA</strong></td>
<td>Misoprostol</td>
<td>6 months</td>
<td>Severe gastrointestinal complications (NSAID)</td>
<td>263</td>
</tr>
</tbody>
</table>
DISCREPANCIES MAKE APPRAISAL HARDER

- In the way to interpret HRQL data
- **Between standard criteria and HRQL / PRO**
- Among HRQL / PRO outcomes
- In direction and magnitude within HRQL domains
**DISCREPANCY WITH MORTALITY**


<table>
<thead>
<tr>
<th>MLwHF (0-105)</th>
<th>Placebo</th>
<th>6.25 mg</th>
<th>12.5 mg</th>
<th>25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>47.7</td>
<td>45.8</td>
<td>43.9</td>
<td>43.6</td>
</tr>
<tr>
<td><strong>Endpoint</strong></td>
<td>40.4</td>
<td>38.0</td>
<td>36.5</td>
<td>38.2</td>
</tr>
</tbody>
</table>

MLwHF : 21 items, 0 (best) - 105 (worst)

Double-blind, placebo-controlled trial (n=345), 6 months, 3 doses.
DISCREPANCY WITH PULMONARY FUNCTION


- Fluticasone dipropionate 500 µg bid leads to a lower decline in health-status (SGRQ)
- but does not affect the decline in FEV₁
LOW CORRELATION WITH WALK-TEST, $\text{SaO}_2$

Quality of life in elderly patients with COPD: measurement and predictive factors.

<table>
<thead>
<tr>
<th></th>
<th>$(n = 96)$</th>
<th>$r$</th>
<th>BPQ</th>
<th>CRQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-min walk test</td>
<td></td>
<td>0.17</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Pre $\text{SaO}_2$</td>
<td></td>
<td>0.14</td>
<td>0.17</td>
<td></td>
</tr>
</tbody>
</table>

BPQ : Breathing Problems Questionnaire
CRQ : Chronic Respiratory Disease Questionnaire

Variability in exercise capacity contributed to only 3% of the variability in BPQ score

<table>
<thead>
<tr>
<th>Fluticasone &gt; zafirlukast</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>0.001</td>
</tr>
<tr>
<td>Morning PEF</td>
<td>0.004</td>
</tr>
<tr>
<td>Evening PEF</td>
<td>0.002</td>
</tr>
<tr>
<td>% of symptom-free days</td>
<td>0.007</td>
</tr>
<tr>
<td>% of rescue-free days</td>
<td>0.001</td>
</tr>
<tr>
<td>Albuterol use</td>
<td>0.001</td>
</tr>
<tr>
<td>Combined symptom scores</td>
<td>0.001</td>
</tr>
<tr>
<td>Awakening-free nights</td>
<td>0.001</td>
</tr>
<tr>
<td>Asthma exacerbation</td>
<td>0.035</td>
</tr>
<tr>
<td>AQLQ</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Randomized, double-blind, parallel group
437 patients randomized (FEV1 % predicted: 74%)
DISCREPANCY WITH WALKING DISTANCE

European mutual recognition procedure

- Treatment in claudication (Peripheral Arterial Occlusive Disease)
- Phase II, RCT, DB, dose-ranging vs placebo, n = 340
- Primary endpoint: absolute change distance: **NO DIFFERENCE**
- HRQL assessment (secondary): SF-36

<table>
<thead>
<tr>
<th>Significant difference</th>
<th>No difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Social Functioning</td>
<td>• Bodily Pain</td>
</tr>
<tr>
<td>• Mental Health</td>
<td>• Physical Functioning</td>
</tr>
</tbody>
</table>

→ Can HRQL replace clinical end-point?
→ How many domains to be improved for a global HRQL claim?
DISCREPANCY WITH WALKING DISTANCE
Dossier for Approval - French Drug Agency (AFSSAPS)

- Treatment in claudication (Peripheral Arterial Occlusive Disease)
- Phase III, RCT, DB, vs placebo

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking distance</td>
<td>2.13</td>
</tr>
<tr>
<td>Specific HRQL questionnaire (CLAUS)</td>
<td>0.48</td>
</tr>
</tbody>
</table>
DISCREPANCY WITH CLINICAL OUTCOMES & AE
Dossier for Approval - French Drug Agency (AFSSAPS)

- Treatment in rheumatoid arthritis
- Phase III, RCT, DB, vs comparator & placebo, n = 485, 52 weeks
- Results: some modest improvement in clinical endpoint (ACR)

HRQL assessment (secondary endpoint: HAQ & SF-36) appears better with the new drug, but
- Only 280 patients analysed
- How many missing data?
- Multiple comparisons
- Type I error?
- Many adverse events
- Withdrawal 22% vs 8% placebo

→ is the impact of AE recorded by instruments?
→ are the patients with AE analyzed for HRQL?
DISCREPANCIES MAKE APPRAISAL HARDER

- In the way to interpret HRQL data
- Between standard criteria and HRQL / PRO
- Among HRQL / PRO outcomes
- In direction and magnitude within HRQL domains
DISCREPANCY PYROSIS VS HRQL (PGWB) AND SYMPTOM SCALE (GSRS) IN GERD

Comparison of several controlled randomized trials

<table>
<thead>
<tr>
<th></th>
<th>Festen 99</th>
<th>Havelund 99</th>
<th>Lind 99</th>
<th>Carlsson 98</th>
<th>Revicki 98</th>
<th>Galmiche 97</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Ome</td>
<td>Ome</td>
<td>Ome</td>
<td>Ome</td>
<td>Ome</td>
<td>Ome</td>
</tr>
<tr>
<td></td>
<td>Ran</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Ran</td>
<td>Cis</td>
</tr>
<tr>
<td>Nb of patients</td>
<td>448</td>
<td>408</td>
<td>424</td>
<td>506</td>
<td>294</td>
<td>423</td>
</tr>
<tr>
<td>Pyrosis resolution</td>
<td>24%</td>
<td>27%</td>
<td>25%</td>
<td>25%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>between groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGWB</td>
<td>0.26</td>
<td>NS</td>
<td>NS</td>
<td>0.22</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>GSRS total score</td>
<td>0.30</td>
<td>NS</td>
<td>NS</td>
<td>0.16</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>GSRS reflux score</td>
<td>0.72</td>
<td>0.55</td>
<td>0.43</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ome: omeprazole, Ran: ranitidine, Cis: cisapride
DISCREPANCY BETWEEN PRO OUTCOMES IN ERECTILE DYSFUNCTION

*Dossier for Approval - French Drug Agency (AFSSAPS)*

<table>
<thead>
<tr>
<th>Study</th>
<th>Cross-over vs placebo</th>
<th>Parallel vs placebo</th>
<th>Cross-over vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfaction (Fugl Meyer)</td>
<td>only sexual scale improved: ( \Delta ) of 0.7 (range 1-6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment satisfaction</td>
<td>( \Delta ) of 4 (range 1-42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRQL (SF-36)</td>
<td>No difference with placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
GENERIC VS SPECIFIC HRQL QUESTIONNAIRE

The influence of an inhaled steroid on quality of life in patients with asthma or COPD.


• Improvement of lung function (FEV$_1$, $p < 0.0001$) with added beclomethasone dipropionate (BDP)
• Temporary decrease of symptoms
• HRQL assessment: No improvement of NHP and ISP
  – NHP (Nottingham Health Profile): 38 statements, 6 domains: physical mobility, pain, social isolation, emotional reactions, energy, sleep. Binary Answer
    • Changes would have been better detected with a specific questionnaire
  – ISP (Inventory of Subjective Health): 21 items related to subjective complaints: tiredness, chest and heart problems, gastric problems, indigestion, headache…
• Is that measuring HRQL?
DISCREPANCIES MAKE APPRAISAL HARDER

- In the way to interpret HRQL data
- Between standard criteria and HRQL / PRO
- Among HRQL / PRO outcomes
- In direction and magnitude within HRQL domains
**WHICH DOMAINS ARE IMPAIRED?**


<table>
<thead>
<tr>
<th>FP 1000mg vs placebo</th>
<th>p</th>
<th>r (FEV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF</td>
<td>&lt; 0.001</td>
<td>0.44</td>
</tr>
<tr>
<td>RP</td>
<td>0.0001</td>
<td>0.29</td>
</tr>
<tr>
<td>GHP</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>VT</td>
<td></td>
<td>0.27</td>
</tr>
<tr>
<td>SF</td>
<td></td>
<td>0.23</td>
</tr>
</tbody>
</table>

- Only **Physical Functioning** and **Role-Physical** scales show large differences between drug and placebo groups.
- Only **Physical Functioning** shows a high correlation with FEV.
DISCREPANCY AMONG HRQL QUESTIONNAIRES

RESPONSIVENESS: AQLQ > LWAQ

AQLQ (32)
- Activities (11) 0.860
- Symptoms (12) 0.723
- Environment (4) 0.550
- Emotions (5) 0.302

Effect size

<table>
<thead>
<tr>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AQLQ</strong> (32)</td>
</tr>
<tr>
<td>Activities (11)</td>
</tr>
<tr>
<td>Symptoms (12)</td>
</tr>
<tr>
<td>Environment (4)</td>
</tr>
<tr>
<td>Emotions (5)</td>
</tr>
</tbody>
</table>

**LWAQ** 0.694
Health knowledge 0.625
Health appraisal 0.333

**SIP** 0.320

- 6-wk
- Salmeterol 50 µg or Salbutamol 400 µg bid
- 120 patients randomized
- FEV₁ % predicted: 59%

RESPONSIVENESS: LWAQ > AQLQ

Table 3. Effect sizes of changes in quality of life during treatment with formoterol in comparison to treatment with placebo

<table>
<thead>
<tr>
<th></th>
<th>Effect size</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AQLQ</td>
<td>0.128</td>
<td>-0.267–0.532</td>
</tr>
<tr>
<td>Activity</td>
<td>0.106</td>
<td>-0.343–0.559</td>
</tr>
<tr>
<td>Symptoms</td>
<td>0.316</td>
<td>-0.083–0.724</td>
</tr>
<tr>
<td>Emotional</td>
<td>0.132</td>
<td>-0.266–0.534</td>
</tr>
<tr>
<td>Environment</td>
<td>0.051</td>
<td>-0.347–0.451</td>
</tr>
<tr>
<td>LWAQ</td>
<td>0.394</td>
<td>-0.003–0.796</td>
</tr>
<tr>
<td>Physical problem</td>
<td>0.407</td>
<td>-0.015–0.809</td>
</tr>
<tr>
<td>Emotional problem</td>
<td>0.196</td>
<td>-0.192–0.589</td>
</tr>
<tr>
<td>SF36 total</td>
<td>0.008</td>
<td>-0.380–0.397</td>
</tr>
<tr>
<td>PGWB total</td>
<td>0.268</td>
<td>-0.120–0.664</td>
</tr>
</tbody>
</table>

CI: confidence interval; AQLQ: Asthma Quality of Life Questionnaire; LWAQ: Living with Asthma Questionnaire; SF36: Short Form 36; PGWB: Psychological and General Well-Being scale.

- 6 months, 110 patients
- FEV₁ % predicted: 65%
DISCREPANCY IN DIMENSIONS OVER TIME (AND MULTIPLICITY OF STATISTICAL TESTS)

Efficacy, tolerability, and effects on HRQL of inhaled Salmeterol in COPD.

- Open label
- Salmeterol 50 µg
- or SR Theophylline bid
- Randomized (n = 178)
- Completers (n = 145)
- HRQL (secondary) : SF-36
- Mean changes between baseline and the 4 assessments over time, for each single dimension : Student t test

<table>
<thead>
<tr>
<th>SF-36</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 (+1) dimensions</td>
<td>3 months</td>
</tr>
<tr>
<td>&quot;</td>
<td>6 months</td>
</tr>
<tr>
<td>&quot;</td>
<td>9 months</td>
</tr>
<tr>
<td>&quot;</td>
<td>12 months</td>
</tr>
</tbody>
</table>

Number of tests 36

<table>
<thead>
<tr>
<th>(n = ???) in favor of Salmeterol</th>
<th>Assessment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning (PF)</td>
<td>3 months</td>
<td>0.02</td>
</tr>
<tr>
<td>Change in Health Perception (HT)</td>
<td>9 months</td>
<td>0.03</td>
</tr>
<tr>
<td>Social Functioning (SF)</td>
<td>12 months</td>
<td>0.04</td>
</tr>
</tbody>
</table>
CONSISTENCY OF IMPROVEMENT OF THE SAME HRQL QUESTIONNAIRE THROUGH STUDIES


- Baseline AQLQ global score : 4.70
- 12-wk Global score AQLQ : 1 to 7 best

- Baseline AQLQ global score : 3.93-8
- 12-wk
HOW MANY DOMAINS AND WHICH DOMAINS SHOULD IMPROVE FOR A CLAIM IN PAOD?


- Broad HRQL claim? **Unlikely**
- Specific-domain claim?
  - If pre-specified
  - If consistency with standard criteria
  - If evidence of clinical relevance
WHY PHARMACEUTICAL FIRMS ARE SO INTERESTED IN HRQL / PRO?

Reimbursement / Price
France: “Transparency committee”
- Medico-economic evaluation of drugs
- Rank the new drug / indication according to
  - Efficacy
  - Therapeutic strategy (availability of other treatments)
  - Severity of disease, public health concern
  - Cost-efficacy, cost-utility
  - Quality of life, Patient-Reported Outcomes?
→ Score: “Amélioration du Service Médical Rendu”
- Propose a reimbursement rate

Advertising
- Physicians
- Patients - Consumers

Advertising

My Drug improves your Quality of Life in your everyday Life

WHY REGULATORS ARE RELUCTANT (SOME TIME)?

• To give the official global claim “Improvement of Quality of Life”, especially for drugs with overall weak efficacy

• To give a reimbursement / price on HRQL data which interpretation is no clear

• To authorize such advertising with the risk of abuse...