Influence of Patient-Reported Outcomes on Regulatory, HTA, and Market Access Decisions: Obesity and Diabetes Case Examples

1. **Lynda Doward**
RTI Health Solutions, Manchester, United Kingdom

2. **Lise Højbjerre**
Novo-Nordisk, Søborg, Denmark

3. **Susan Hogue**
RTI Health Solutions, Research Triangle Park, NC, United States

4. **Maria Fernandez**
RTI Health Solutions, Research Triangle Park, NC, United States

5. **Amy Barrett**
RTI Health Solutions, Research Triangle Park, NC, United States

6. **Rebecca Crawford**
RTI Health Solutions, Manchester, United Kingdom

7. **Nana Kragh**
Novo-Nordisk, Søborg, Denmark

8. **Mark Aagren**
Novo-Nordisk, Søborg, Denmark

Objective

- To identify key drivers for the successful integration of patient-reported outcomes (PROs) in clinical programs to support regulatory label claims, health technology assessment (HTA), and market access in diabetes and obesity.

Methods

Case Example Products

- One case example product was selected for each therapeuticarea:exenatide(diabetes)andlorcaserin (obesity) (Figure 1).

Figure 1 Case Example Products

Diabetes	Obesity
Byetta/Bydureon (exenatide) • Byetta (twice-daily injectable) • Bydureon (once-weekly injectable) • Manufactured by Amylin Pharmaceuticals and codeveloped by Eli Lilly and Company • GLP-1 agonist • Indicated for the treatment of type 2 diabetes mellitus	**Belviq (lorcaserin)** • Manufactured by Arena and distributed by Eisai in the US • First-in-class 5HT2C receptor agonist • Indicated as an adjunct to reduced-calorie diet and increased physical exercise • Approved by the FDA in 2012 • EU submission withdrawn following Day 180 List of Outstanding Issues

5HT2C = 5-hydroxytryptamine; EU = European Union; FDA = Food and Drug Administration; GLP-1 agonist = glucagon-like peptide-1 agonist; US = United States.

Targeted Review

- An in-depth review was conducted of the PRO measurement strategy employed and the outcomes (both positive and negative) in terms of regulatory approval and market access.
- Relevant literature was identified for review by searching online literature databases (e.g., PubMed), clinical trials registries (e.g., ClinicalTrials.gov), regulatory websites (i.e., www.fda.gov and www.ema.europa.eu/ema), and the websites of reimbursement/HTA authorities in France, Germany, the United Kingdom (UK) in the EU, and in the US.

Payers and Economic Advisor Research

- Qualitative, one-on-one interviews were conducted via telephone with payer decision makers in key markets to determine perceptions of successful PRO strategies.
- Participants were selected based on the following inclusion criteria:
  - US: Current medical directors or pharmacy directors from large commercial health insurance plans
  - Europe: Current locally positioned academic health economists and advisors to national health systems

Results

Case Example Review

Regulatory Guidance

- General guidance:
  - The FDA issued guidance on the development and psychometric quality of PRO instruments used in support of labelling and promotional claims in the US.[1]
  - The EMA opted not to produce formal guidance but did publish a reflection paper on the value of health-related quality of life (HRQOL) in the drug evaluation process.[2]
- Diabetes-specific guidance:
  - FDA guidance does not provide recommendations for use of PROs. The guidance mentions the potential impact of unblinding on the interpretability of PROs included in studies.[3]
  - EMA guidance gives no recommendations or advice on use of PROs.[4]
- Obesity-specific guidance
  - FDA guidance recognizes the importance of PRO endpoints in studies of anti-obesity medications; it notes that "measures of quality of life from validated instruments also can be appropriate secondary efficacy endpoints."[5]
  - In the EMA guidance, quality of life is cited as one of several potential secondary efficacy endpoints for clinical trials; it notes that mechanical complications of obesity can severely impair quality of life and that obese patients have a "significantly impaired quality of life, as objectively measured by several independent tests." No advice is given on measures that would be deemed acceptable by the EMA.[6]

Review of PRO Measurement Strategy

- Registration trials included assessments of symptoms, HRQOL, depression, and psychological well-being.
- For exenatide, no PRO US or EU label claims were sought. For lorcaserin, PRO data supported US approval (no label claim). PRO data supported market access for the UK and US.
- An overview of the PRO measurement strategy employed for both products is set out in Table 1. Table 2 provides an overview of the positive and negative aspects of these strategies.

Table 1
Overview of PRO Measurement Strategy Results

Measurement Strategy	Diabetes (Exenatide)	Obesity (Lorcaserin)
PRO-based endpoints included in regulatory submissions	Symptoms, psychological well-being, HRQOL, utilities, treatment experience	Symptoms (depression, for safety), HRQOL
Regulatory approval	Appears that no PRO-based labelling claims were sought in the US or the EU; the long and complicated filing history may have diverted the focus from seeking such claims. The use of open-label studies may have weakened the position for seeking labelling claims in the US and the EU.	No FDA PRO labelling claims were granted, but HRQOL data were supportive of drug approval and considered by regulatory bodies, even where findings were not significant, and helped demonstrate the clinical meaningfulness of therapy. EMA submission was withdrawn.
HTA/market access	PRO data were widely used to support a communication strategy. NICE/UK: PRO data provided positive support for a NICE recommendation. IQWiG/Germany: decision to approve as a combination therapy influenced by PRO data HAS/France: no reference to PRO data in the HAS appraisal.	No HTA appraisal was conducted due to withdrawal in the EU. Publications report HRQOL benefits associated with Belviq.

HAS = Haute Autorité de Santé (National Authority for Health); IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Healthcare); NICE = National Institute for Health and Care Excellence.

Table 2
Positive and Negative Aspects of PRO Strategy

Diabetes (Exenatide)	Obesity (Lorcaserin)
Positive aspects	
• Inclusion of fit-for-purpose tools in studies – Diabetes Treatment Satisfaction Questionnaire (DTSQ and DTSQc) – Impact of Weight Change on Quality of Life (IWQOL-Lite) – Psychological and General Well-being Index (PGWB) – Binge-Eating Scale (BES) – EuroQol-5 Dimensions (EQ-5D) – 36-Item Short Form Health Survey (SF-36) – Hospital Anxiety and Depression Scale (HADS) – Well-Being Questionnaire 12 (WBQ12) • Dissemination of information through publications – Provided support for NICE recommendation – "Significantly greater improvements in IWQOL-Lite total score were reported for weekly prolonged-release exenatide…." – "Patients in both treatment groups reported improvements from baseline to end point in IWQOL-Lite, BES, and DTSQ total scores. Patients on weekly prolonged-release exenatide showed statistically significant gains in health-related quality of life as measured by EQ-5D"	• PRO results fully support efficacy endpoint and drug approval in the US – "Dr. Henderson agreed that lorcaserin is a promising drug and would encourage the sponsor to reapply. She "loves the quality of life data," but feels there is too much uncertainty surrounding cancer risk and the limited patient population studied."[7] • FDA guidance for industry: developing products for weight management notes: – "Measures of quality of life from validated instruments also can be appropriate secondary efficacy endpoints" • Strong publications strategy with positive PRO findings • PRO results were consistent and favorable across studies, supporting utilization of PROs in studies of anti-obesity medications
Negative aspects	
• Potential for missed opportunities for PROs to provide product differentiation – Open-label study design – No labelling claims appear to have been sought – Resources appear to have been diverted from PROs to other issues in the fillings • Minimal support for HTA in Germany – Data were considered by authorities: "Additionally, no benefit or additional benefit of exenatide in respect to patient reported outcomes was noted" • No support for HTA in France – No mention of PROs in the assessment – Gastrointestinal tolerability of exenatide may have impacted selection and use of PROs in clinical trials	• No labeling claims were granted – Lack of significant findings

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Table 3 Overview of Research Participants

EU (N = 6)	Lives Covered (Millions)	US (N = 4)	Lives Covered (Millions)
• France (n = 2) – Academic health economist; former member of the French Transparency Commission – Health economics professor at the University of Paris; advisor to HAS	60.5	• Regional Integrated Health Plan – Chief medical officer; active member of P&T committee	2.0
• Germany (n = 2) – Academic health economist; current advisor to IQWiG and numerous German sickness funds – Deputy member for arbitration and reimbursement and pricing negotiations at Zentrum für Gesundheitsökonomie Neumarkt	72.0	• National Health Plan – Chief medical officer; licensed OB/GYN; active member of P&T committee	7.1
• UK (n = 2) – Economist at the University of Glasgow; part-time member of SMC – Economist at Brunel University; former member of NICE appraisal committee; current consultant with NICE	61.4	• National Health Plan – Medical director; active member of P&T committee	13.0
		• National PBM – Active member of P&T committee	10.0

OB/GYN = Obstetrics and Gynecology; P&T = Pharmacy and Therapeutics; SMC = Scottish Medicines Consortium; PBM = Pharmacy Benefit Management

Value of PROs for HTA/Market Access

General Findings

- PROs were considered a valuable means of providing insight into patient experience with diabetes and obesity, but participants indicated that health care system differences influence payer preferences for PRO type (e.g., generic/disease-specific), influenced primarily by whether there is a need for a cost-effectiveness model.
  - Generic measures of HRQOL were rated highest by participants in France and the UK.
  - Disease-specific measures of HRQOL were rated highest by participants in Germany and the US.
- "A PRO that is deemed acceptable to FDA or EMA" was considered important for regulatory purposes by all participants in all countries.
- "A PRO in support of a lifestyle treatment" was only considered important by advisors in France and the US.
- "A PRO in support of a treatment first to market" was considered important for regulatory purposes by advisors in France and the US, and considered important for HTAs and market access by advisors in France and the UK.
- Participants recommended using PRO data to develop a value proposition that is patient centered. To support this, sponsors should be encouraged to complete the following tasks:
  - Use validated PRO scales and appropriate compators in clinical trials
  - Publish PRO data, even when these are not used to support a regulatory label claim
  - Develop relationships with patient associations and patient advocates
  - Investigate patient willingness to pay
- Participants indicated that data from postmarketing trials may provide an opportunity to change prescribing decisions.

Diabetes

- PROs were considered less important in HTAs, because the main outcome measure is glycated hemoglobin (HbA1c) levels.
- Generic measures of HRQOL were rated as the most useful for supporting HTA over other types of PRO measures.

Obesity

- PROs were considered less important in HTAs, because the main outcome measure is sustained and meaningful weight loss.
- UK advisors rated generic measures of HRQOL higher than other measures. Measures of psychological and general well-being were considered "short-term or transient."
- Obesity treatments are not reimbursed in Germany.

Table 4
Key Drivers for a Successful PRO Strategy

Regulatory	
FDA	**EMA**
• PRO measures used in support of label claims must meet the documentation and quality standards outlined in the FDA industry guidance for use of PRO measures to support labelling • FDA most likely to accept simple measures of a single concept (e.g., severity of a symptom) • Claims based on compelling PRO data may have a greater chance of success • Claims supported by open-label study designs are unlikely to support labelling claims in the US • Complications in the approval process and/or failure to disclose data can hinder PRO claims • PRO data can support approval even where a claim is denied	• Favors PRO data in submissions, even where label claim is not sought, and is less cautious in acceptance of measures of complex constructs (e.g., HRQOL) • Distinguishes "simple" measures (e.g., core disease symptoms), "intermediate" measures (multi-item, multi-concept), and "broad" multidimensional measures that go beyond efficacy and safety (e.g., HRQOL) • HRQOL claim must be supported by instruments validated for use in the corresponding condition (supported by publications) • Claims supported by open-label study designs are unlikely to support labelling claims in the EU • Complications in the approval process and/or failure to disclose data can hinder PRO claims • PRO data included in the EPAR can be used for market access purposes • EMA emphasizes the importance of seeking an early dialogue to discuss potential biomarkers, including PRO endpoints
HTA/Market Access	
HTA	**Broader Market Access**
• There is variation among HTAs on preferences for generic or disease-specific PRO measures; preference is largely dependent on whether there is a need to provide cost-effectiveness models (in which case, preference is for generic measures) ***Europe*** • Where utility data are required for cost-effectiveness models (UK and France), there is a preference for utility data derived from the EQ-5D • PRO data can support UK NICE submissions when included within the clinical evidence section of HTA submissions • Use of patient access schemes can boost relative cost-effectiveness of a drug and aide NICE approval • Productivity measures may influence UK HTA • For IQWiG (Germany), PRO data that measure impact (improvements/deterioration) on morbidity, side effects, or HRQOL are most likely to be considered ***US*** • Health plans are interested in PRO measures that are tied to adherence and persistence, tolerability, and reduction in costs or resource utilization	• PRO data can be a key component in the production of a value proposition that is truly "patient centered" • Publication of PRO data from clinical trials can facilitate market access: – A broad PRO publication strategy will not only support HTA submissions but also will support uptake by payers – Prescriber "pull-through" can be critical to success • "Nonlabel" PRO promotion is currently used by some sponsors for online and print advertisement

EPAR = European public assessment report.

Conclusions

- Sponsors must continue to bring data based on robust PROs to regulators, HTA, and market access, thus bringing the patient, the most affected stakeholder, to the forefront in decision making.

Key Learning Points

- Development of a strong PRO strategy is critical.
- PROs provide important insight into the patient experience in symptomatic disease, and this is clearly recognized by all stakeholders.
- It is critical to understand the five key decision makers and audiences (i.e., regulators, HTAs, prescribers, patients, patient advocates).

Key Takeaways

- Tie PROs to "actionable" measures (e.g., symptom reduction, improvement in adherence and outcomes) by completing the following tasks:
  - Develop a robust communication strategy
  - Publish, publish, publish
  - Partner with appropriate patient advocates
  - Provide field-based staff with data for direct-to-prescriber discussions
  - Utilize public relations press releases
  - Tailor messages to the five key audiences
  - Conduct stakeholder research with these audiences to understand needs

References

Please see handout for a complete reference list.

Contact Information

Lynda Doward, MRES
European Head, Patient-Reported Outcomes

RTI Health Solutions
E-mail: ldoward@rti.org
Phone: +44(0)161.447.6002

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