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Ari Gnanasakthy and Two Publications

Patient-Reported Outcomes

A Review of Patient-Reported Outcome Labels in the United States: 2006 to 2010
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Review of FDA PRO Labeling (2010-2015)

- Total number of new drugs approved (2006-2010) = 116
- New drugs with PRO labeling (2006-2010) = 24.1%

- Total number of new drugs approved (2011-2015) = 182
- New drugs with PRO labeling (2011-2015) = 16.5%
Two Categories of Diseases

Traditionally depends on PROs to demonstrate treatment benefit for regulatory decision making
PRO Labeling (PRO Dependent)

2006 - 2010 (n = 49)
- 53% (n = 26): PRO labeling
- 47% (n = 23): No PRO labeling

2011 - 2015 (n = 50)
- 54% (n = 27): PRO labeling
- 46% (n = 23): No PRO labeling
PRO Labeling (Non-PRO Dependent)

<table>
<thead>
<tr>
<th>Period</th>
<th>PRO labeling</th>
<th>No PRO labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006 - 2010</td>
<td>7% (n = 5)</td>
<td>93% (n = 62)</td>
</tr>
<tr>
<td>2011 - 2015</td>
<td>5% (n = 7)</td>
<td>95% (n = 125)</td>
</tr>
</tbody>
</table>

**Legend:**
- Blue: PRO labeling
- Green: No PRO labeling
PRO Labeling (FDA NDA, 2006-2015)
PRO-Dependent Diseases (N = 99, L = 46; 46.5%)

- Genitourinary system (n = 6): 100%
- Ear and mastoid process (n = 1): 100%
- Nervous system (n = 23): 56.5%
- Digestive system (n = 10): 50%
- Musculoskeletal system (n = 13): 46.2%
- Blood and blood forming organs (n = 10): 40%
- Respiratory system (n = 10): 40%
- Skin and subcutaneous system (n = 5): 40%
- Eye and adnexa (n = 8): 37.5%
- Mental, behavioral... (n = 13): 15.4%

N = Number of new drugs approved by the FDA (2006-2015)
L = Number of new drugs approved with PRO labels (2006-2015)
PRO Labeling (FDA NDA 2006-2015)
Non-PRO Dependent Diseases (N = 199, L = 12; 6.0%)

- Symptoms not classified elsewhere (n = 3): 66.7%
- Injury, poisoning... (n = 2): 50%
- Health status and contact with health services (n = 6): 16.7%
- Endocrine, nutritional, and metabolic diseases (n = 41): 9.8%
- Infection and parasitic diseases (n = 41): 2.4%
- Neoplasms (n = 69): 0%
- Pregnancy, childbirth, and puerperium (n = 0): 0%
- External causes of morbidity (n = 0): 0%
- Unclassified (n = 15): 0%

N=Number of new drugs approved by the FDA (2006-2015)
L = Number of new drugs approved with PRO labels (2006-2015)
Conclusions from the Label Review

• The rate of PRO label claims granted has remained relatively stable over the period of 2006 - 2015

• This rate is lower than anticipated – given that approximately 47% of new drug approvals are for diseases that traditionally depend on PROs to demonstrate treatment benefit for regulatory decision making

• Questions
  – How can the probability for success in obtaining label claims for PRO-dependent products be increased?
  – Should the regulators be more proactive in encouraging (insisting on?) the inclusion of PROs, especially to support ClinROs or biomarkers as primary endpoints?
Many PRO Measures Were Created Prior to the Release of the PRO Guidance (December 2009)

• Examples
  – The Health Assessment Questionnaire Disability Index (HAQ-DI)
  – St. George’s Respiratory Questionnaire (SGRQ)
  – Asthma Control Questionnaire (ACS)
  – International Index of Erectile Function (IIEF)
  – Cystic Fibrosis Questionnaire—Revised (CFQ-R)
  – Bristol Stool Scale (BSS)
  – International Restless Legs Scale (IRLS)
  – Short-Form 36 (SF-36)

• Suggests regulatory reviewers were satisfied with these measures applicability to demonstrate treatment benefit in regulatory drug approval
In a Few Instances, Labeling Based on Specific Items or Domains of Multidimensional PRO Measures

- Examples (developed before release of PRO Guidance)
  - Only questions 2 and 3 of the Sexual Encounter Profile
  - Erectile function domain of IIEF
  - Respiratory domain of CFQ-R
There Were Some Newly Created PRO Measures

- Examples
  - Myelofibrosis Symptom Assessment Form (ruxolitinib)
  - Psoriasis Symptom Diary (secukinumab)
  - Composite measure of swelling, skin pain, and abdominal pain (icatibant injection)*
  - Patient-Reported Submental Fat Rating Scale (deoxycholic acid)*

*No publication related to validation found
Validity of Some PRO Measures Was Not Obvious

- Most labels were based on daily event diaries or simple one-item scales intended to evaluate severity, bother, or events of disease-defining concepts
  - Not much specific evidence of instrument validity
  - No publication available

- Examples
  - Daily diary of watery bowel movements
  - Diary to record seizures
  - Diary to record number and severity of hot flushes
  - Diary to record duration and timing of nighttime sleep and daytime naps
Labeling Was Common for Proximal Concepts

• In general, labeling related to PROs was granted for symptoms or functions that were proximal to the disease

• Examples
  – Seizures (anti-epileptics)
  – Vasomotor symptoms (associated with menopause)
  – Symptoms (influenza, psoriasis, myelofibrosis, etc.)
  – Emetic episodes (chemotherapy-induced nausea and vomiting)
  – Most bothersome symptom (moderate to severe dyspareunia)

• Two exceptions
  – Satisfaction with treatment
  – Health-related quality of life
PRO Labeling for Primary and Second Endpoints

• PRO labeling was based on primary endpoints for 23 of the 30 NDAs (76.7%) that received PRO labeling between 2011 and 2015

• PRO labeling was based on both primary and secondary endpoints for 17 of the 30 NDAs (56.7%)
  – For diseases such as overactive bladder and irritable bowel syndrome
  – Only patients can reliably inform treatment benefit

• PRO labeling was based on only secondary endpoints for 7 of the 30 NDAs (23.3%)
  – The primary endpoint for all but one of these NDAs was a biomarker.
Thus, Most Labels Were Based on Primary Endpoints

Primary endpoint only
N = 6/30

Primary and Secondary endpoint
N = 17/30

Secondary endpoint only
N = 7/30
# PRO Was Co-primary for Some Approvals

<table>
<thead>
<tr>
<th>US brand name</th>
<th>Used for the treatment of...</th>
<th>PRO and...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horizant</td>
<td>Restless legs syndrome</td>
<td>ClinRO</td>
</tr>
<tr>
<td>Belsomra</td>
<td>Difficulty falling and staying asleep</td>
<td>ClinRO</td>
</tr>
<tr>
<td>Kybella</td>
<td>Fat below the chin</td>
<td>ClinRO</td>
</tr>
<tr>
<td>Osphena</td>
<td>Pain during sexual intercourse</td>
<td>Biomarkers</td>
</tr>
<tr>
<td>Hetlioz</td>
<td>Sleep-wake disorder</td>
<td>ClinRO</td>
</tr>
<tr>
<td>Otezla</td>
<td>Psoriatic arthritis</td>
<td>ClinRO and biomarker</td>
</tr>
</tbody>
</table>
Is This The Beginning of a New ‘Normal’?

• PROs as co-primary endpoint
  – To provide clinical significance

• Recent recommendations
  – Female sexual dysfunction
  – Hypogonadism
  – Nocturia

• PROs becoming part of mainstream drug development?
  – To aid understanding of ‘clinical significance’
FDA’s Tough Stance On Patient-Reported Outcomes Underscored At Repros Meeting

07 Dec 2016 | ANALYSIS

Symptoms. Consequently, committee members emphasized the need for patients to be symptomatic prior to study entry, and normalization of testosterone levels should be shown to improve such symptoms.

FDA Won't Accept Just Any Outcome Assessment

However, FDA has acknowledged that selection of an acceptable symptom-based endpoint is challenging because many clinical signs and symptoms of hypogonadism—such as low libido, erectile dysfunction, mood disturbances, and decreased bone density—can improve with hormone replacement therapy.
PRO Measures Used for Labeling: Secondary Endpoints Only (n = 7)

St. George’s Respiratory Questionnaire

Myelofibrosis Symptom Assessment Form

Cystic Fibrosis Questionnaire (Revised) – Respiratory domain

Psoriasis Symptom Diary

Daily rescue medication (diary)

Asthma Control Questionnaire-5 and St. George’s Respiratory Questionnaire
Primary endpoint for all these labelings (except Cosentyx) was based on biomarkers.

Why only a few PRO labelings based on secondary endpoints?

Should regulators encourage sponsors to include PROs in protocols to provide evidence of clinical significance to the primary endpoints?
Some Recent Examples of Useful Labeling

- “...effective in treating the symptoms of OAB”

- “...demonstrated statistically significant improvement in cystic fibrosis symptoms (such as cough, sputum production and difficulty breathing)…”

- “Significantly reduced the number and severity of moderate to severe hot flushes…”

- “…improvement of itch severity…”

- “The overall patient-reported satisfaction and self-perceived visual attributes showed greater improvement…”
“...effective in treating the symptoms of OAB”