Lessons learned from a review of PRO labeling (2011-2015)

8 December 2016

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Two publications

Patient-Reported Outcomes

A Review of Patient-Reported Outcome Labels in the United States: 2006 to 2010
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Objectives

• Review the ‘state of the science’ in regard to approved PRO labeling in the United States

• To estimate the percentage NDAs approved by the FDA with PRO labeling (2011-2015)

• Compare findings with previous finding (2006-2010)

• Summarize characteristics of select PRO labels
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

PRO Dependent

Non-PRO Dependent

Traditionally depends on PROs to demonstrate treatment benefit for regulatory decision making
PRO labeling (PRO dependent)

- **2006 - 2010**
  - 53% (n = 26)
  - 47%, (n = 23)
  - (n = 49)

- **2011 - 2015**
  - 54% (n = 27)
  - 46% (n = 23)
  - (n = 50)

Legend:
- Blue: PRO labeling
- Green: No PRO labeling
PRO labeling (non-PRO dependent)

- **2006 - 2010 (n = 67)**
  - 93% (n = 62)
  - 7% (n = 5)

- **2011 - 2015 (n = 132)**
  - 95% (n = 125)

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%)

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 - 20015
• This rate is lower than anticipated given, 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

- 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)
- SF-36
Labeling is sometimes based on specific domains of multidimensional PRO Measures

• Examples
  – International Index of Erectile Function (IIEF)
    • Sexual Encounter Profile
    • Erectile Function Domain
  – Cystic Fibrosis Questionnaire–Revised (CFQ-R)
    • Respiratory domain
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

• Many product approvals were based on daily event diaries without 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
  – Etc.
Labeling was common for proximal concepts

• 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)
  – Etc.

• Two exceptions
  – Satisfaction with treatment
  – Health-related quality of life
Case study: Pragmatic evaluation of evidence Fat below the chin (2015)

- PRO was a co-primary endpoint
- Early and frequent engagement with the FDA was critical
  - Dossier was 2,200 pages
- PROM was not optimal but acceptable
  - Within the context of use
  - As a co-primary with ClinRO
- Total score of a second PROM was appropriate to support the primary

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Patient-Reported Submental Fat Impact Scale (PR-SMFIS)

1. How happy are you with the appearance of your chin fat?
2. How bothered are you by the appearance of your chin fat?
3. How self-conscious are you about the appearance of your chin fat?
4. How embarrassed are you about the appearance of your chin fat?
5. How much older do you look because of your chin fat?
6. How much overweight do you look because of your chin fat?
Case study: Sponsor/regulator disagreement?
Non-24-hour sleep-wake disorder (2014)

• The sponsor insisted on using “entrainment” as primary endpoint
  – An unvalidated surrogate based on measures of the melatonin biomarker

• The division disagreed and did not accept the applicant’s proposal
  – Considered that showing a benefit on PROs was feasible

• Sponsor declined the advice
  – Used “entrainment” as primary endpoint in two pivotal studies
  – But included PRO-related endpoints as secondary

• The division considered PRO-related endpoints as the primary endpoint
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 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’
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
PROMs used for labeling
Secondary endpoints only (n = 7)

St. George’s Respiratory Questionnaire

Myelofibrosis Symptom Assessment Form

Cystic Fibrosis Questionnaire (Revised)–Respiratory domain

Cystic Fibrosis Questionnaire (Revised)–Respiratory domain

Psoriasis Symptom Diary

Daily rescue medication (diary)

Asthma Control Questionnaire-5 and St. George’s Respiratory Questionnaire
PROMs used for labeling
Secondary endpoints only (n = 7)

- 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?

Psoriasis Symptom Diary
Daily rescue medication (diary)
Asthma Control Questionnaire-5 and St. George’s Respiratory Questionnaire
Some recent examples of useful labelings

- “...effective in treating the symptoms of OAB”
- “...demonstrated statistically significant improvement in CF 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”

Manage the OAB symptoms of urgency, frequency, and leakage.
“Health-related quality of life was measured using the St. George’s Respiratory Questionnaire (SGRQ) in all six confirmatory COPD clinical trials. SGRQ is a disease-specific patient reported instrument which measures symptoms, activities, and its impact on daily life. At week 12, pooled data from these trials demonstrated an improvement over placebo in SGRQ total score of -3.8 with a 95% CI of (-5.3, -2.3) for the ARCAPTA NEOHALER 75 mcg dose, -4.6 with a 95% CI of (-5.5, -3.6) for 150 mcg, and -3.8 with a 95% CI of (-4.9, -2.8) for 300 mcg. The confidence intervals for this change are widely overlapping with no dose ordering. Results from individual studies were variable, but are generally consistent with the pooled data results.”
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, approximately 47% of new drug approvals are for diseases that traditionally depend on PROs to demonstrate treatment benefit for regulatory decision making
Observations

• Many PRO labels were based on legacy measures created before the release of the PRO guidance in 2009
• There were some newly created PRO measures, but not all had publically available evidence of validation
• Labeling was common for proximal concepts and for primary endpoints
• Only a few PRO labels were based solely on secondary endpoints
• Not all labeling languages was optimal for product promotion
Recommendations

• Formulate PRO strategies with high probability for success based on lessons learned

• Craft high impact value messages based on
  – Understanding treatment benefit to patients
  – Commercial input

• Start activities early in development
  – Phase 2 may be too late

• Involve regulators early to align PRO strategy

• Follow the spirit of the PRO guidance

• Continue to learn/evaluate share information publicly that advances the science
Lessons learned from a review of PRO labeling (2011-2015)

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