

A Review of Patient-Reported Outcome Labeling in the United States (2011-2015)

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Patient-Reported Outcomes

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

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A Review of Patient-Reported Outcome Labeling in the United States (2011–2015)

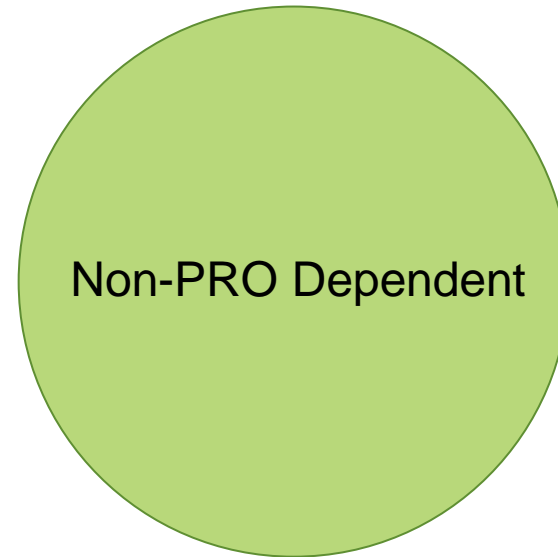
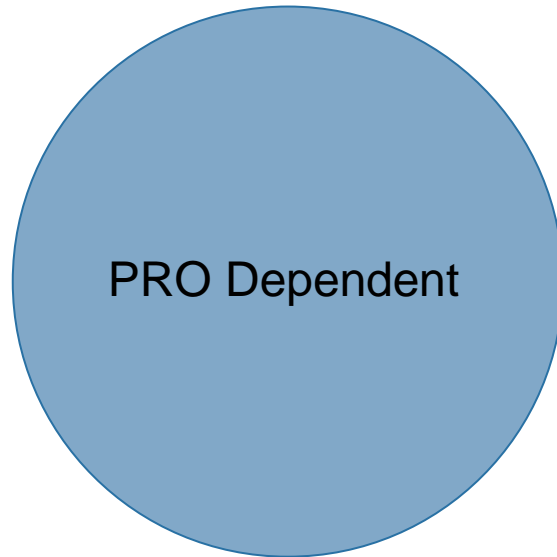
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Review of FDA PRO Labeling (2010-2015)

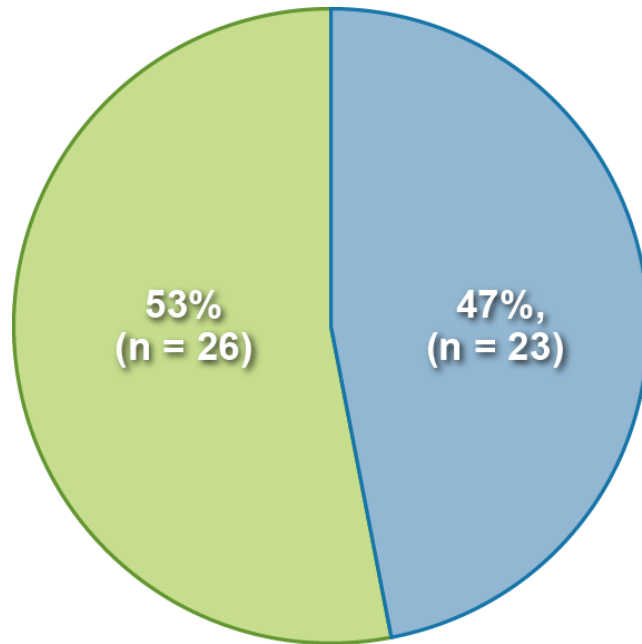
- Total number of new drugs approved (2006-2010) = 116
- New drugs with PRO labeling (2006-2010) = 24.1%
- Total number of new drugs approved (2011-2015) = 182
- New drugs with PRO labeling (2011-2015) = 16.5%

Two Categories of Diseases

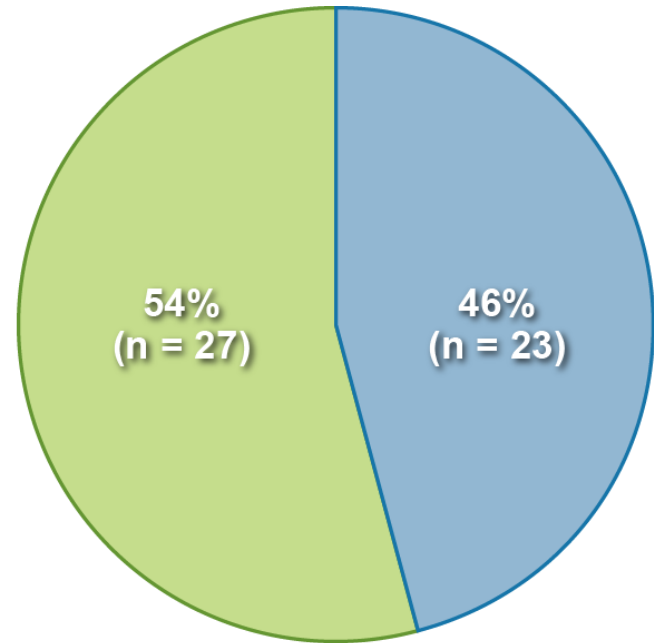


*Traditionally depends on
PROs to demonstrate
treatment benefit for
regulatory decision making*

PRO Labeling (PRO Dependent)



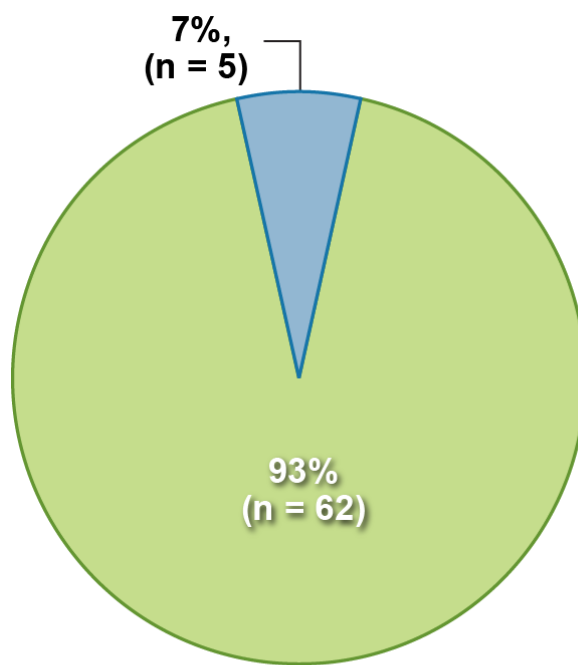
2006 - 2010
(n = 49)



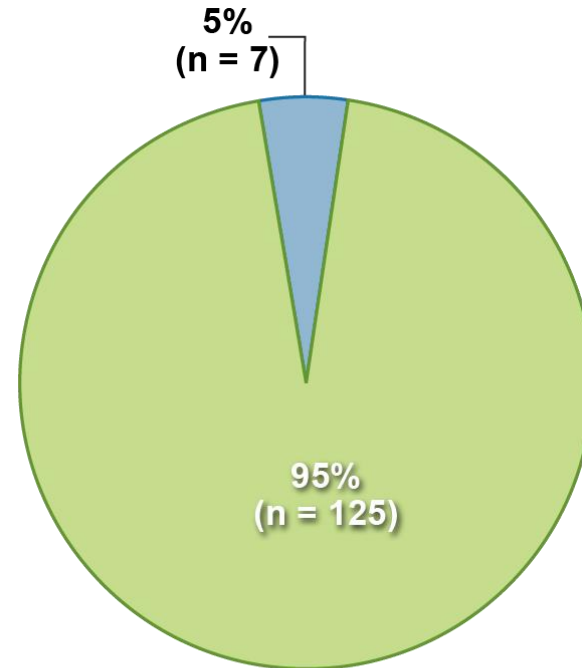
2011 - 2015
(n = 50)

 PRO labeling  No PRO labeling

PRO Labeling (Non-PRO Dependent)



2006 - 2010
(n = 67)

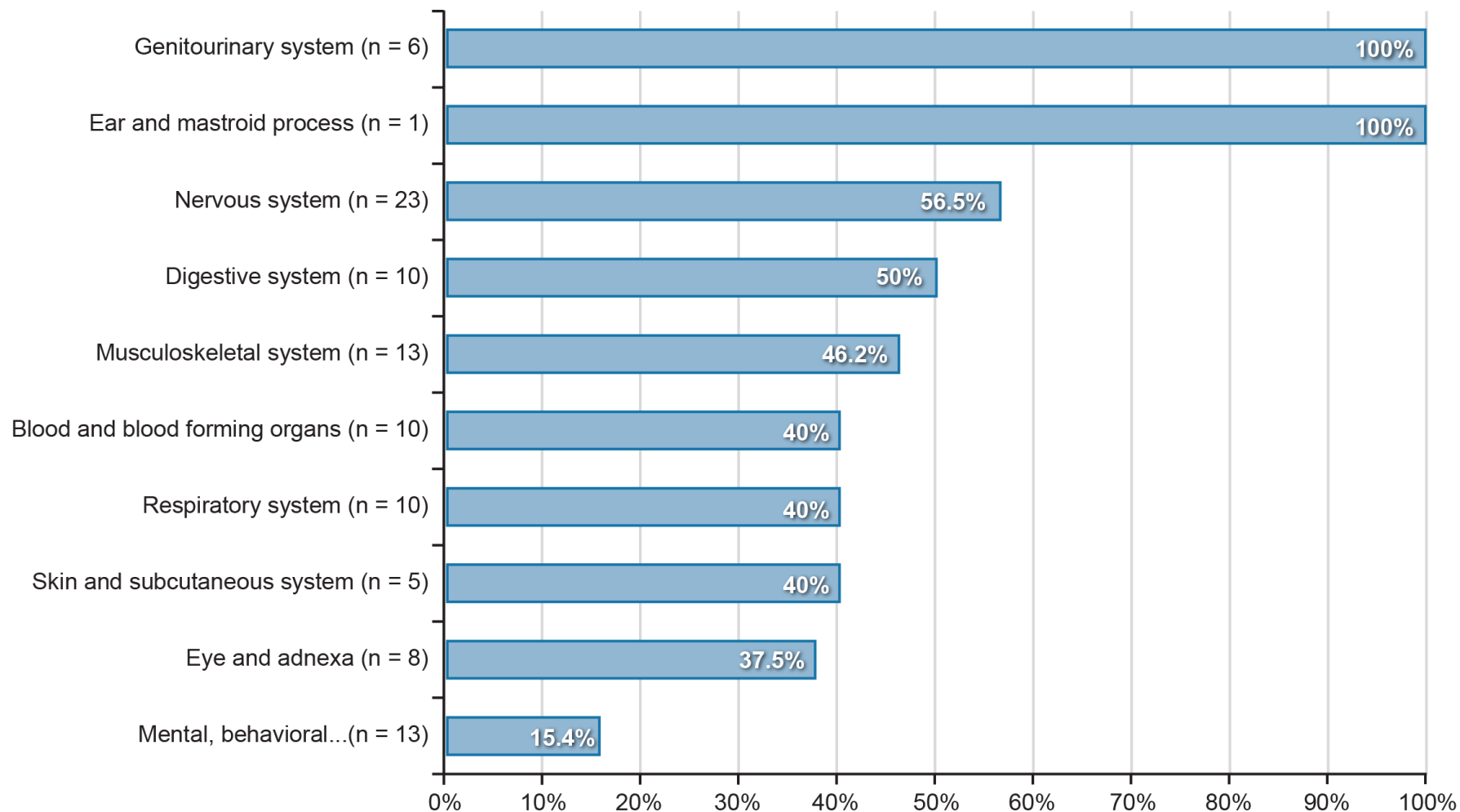


2011 - 2015
(n = 132)



PRO Labeling (FDA NDA, 2006-2015)

PRO-Dependent Diseases (N = 99, L = 46; 46.5%)

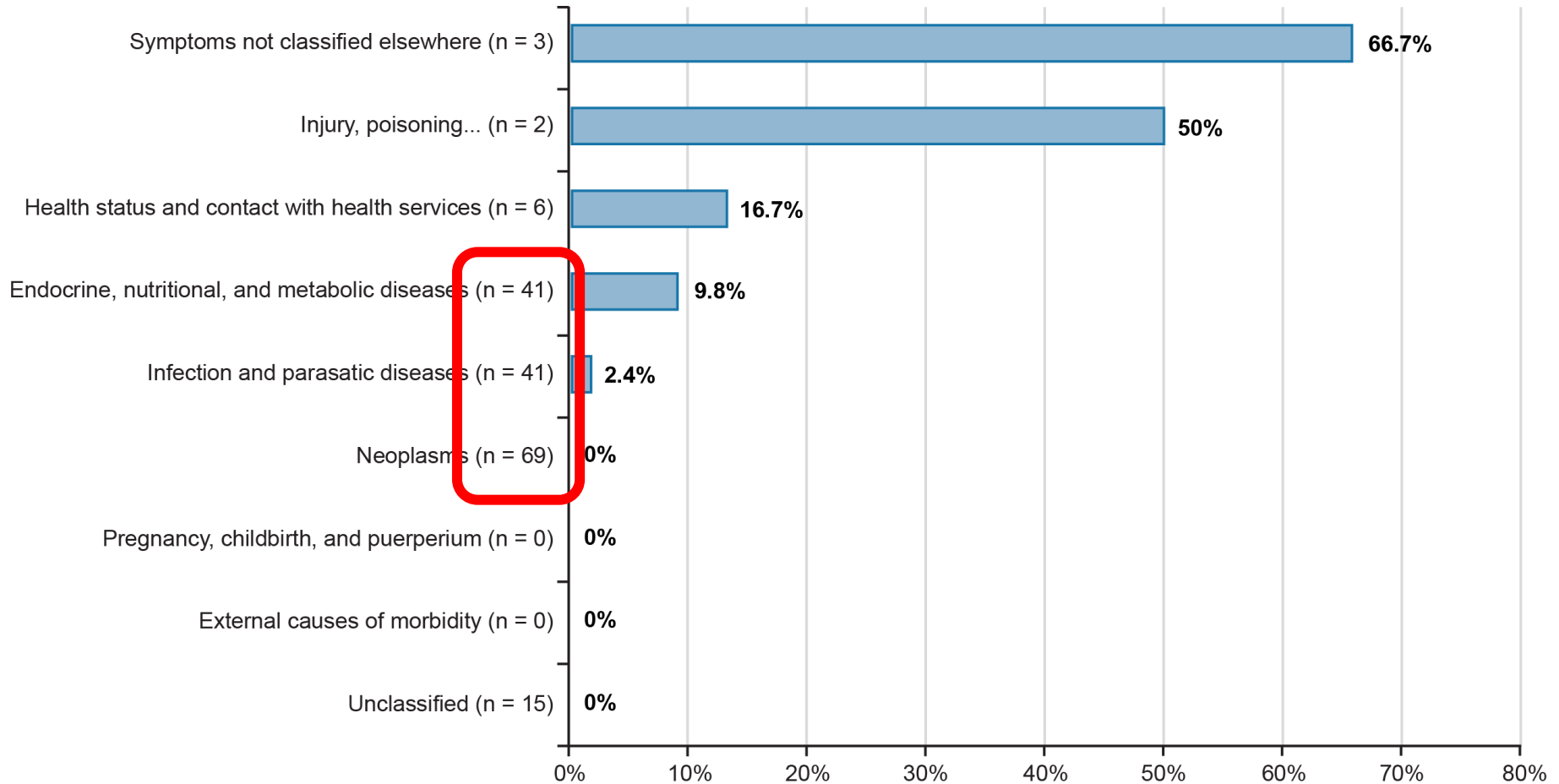


N=Number of new drugs approved by the FDA (2006-2015)

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 - 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

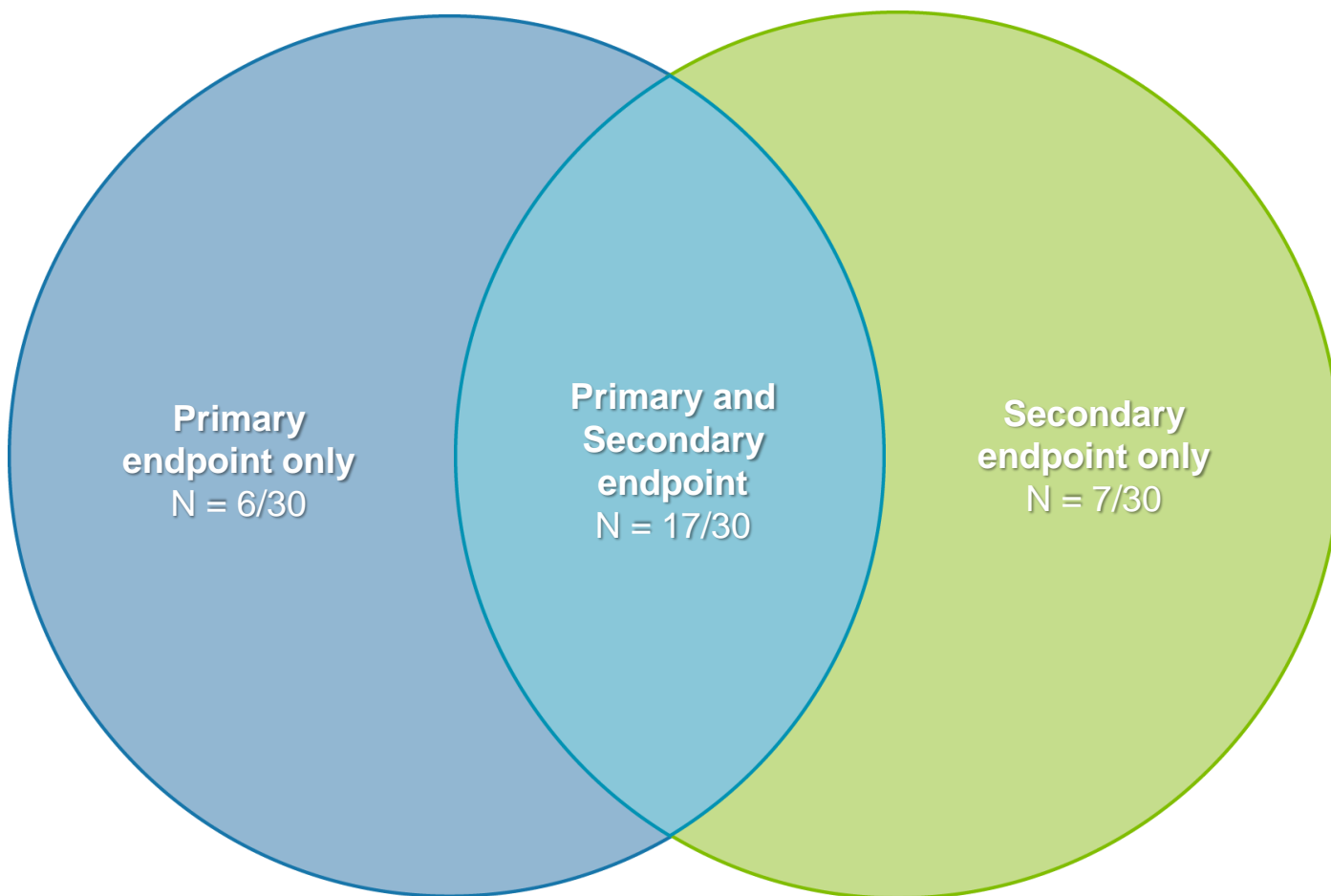
Labeling Was Common for Proximal Concepts

- 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



PRO Was Co-primary for Some Approvals

US brand name	Used for the treatment of...	PRO and...
Horizant	Restless legs syndrome	ClinRO
Belsomra	Difficulty falling and staying asleep	ClinRO
Kybella	Fat below the chin	ClinRO
Osphena	Pain during sexual intercourse	Biomarkers
Hetlioz	Sleep-wake disorder	ClinRO
Otezla	Psoriatic arthritis	ClinRO and biomarker

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. 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

PRO Measures Used for Labeling: Secondary Endpoints Only (n = 7)



St. George's Respiratory Questionnaire



Cystic Fibrosis Questionnaire
(Revised)–Respiratory domain



Psoriasis Symptom Diary



Daily rescue medication (diary)

Myelofibrosis Symptom
Assessment Form



Cystic Fibrosis Questionnaire
(Revised)–Respiratory domain



Asthma Control Questionnaire-5 and St.
George's Respiratory Questionnaire

PRO Measures 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 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 flashes...”



- “...improvement of itch severity...”



- “The overall patient-reported satisfaction and self-perceived visual attributes showed greater improvement...”

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

When your
**BLADDER
ACTS UP,**
it's time to
start talking.



Take charge by talking to your doctor to help manage the OAB symptoms of urgency, frequency, and leakage.

If you are experiencing these symptoms, ask your doctor about Myrbetriq® (mirabegron). Myrbetriq (mee-REE-trick) is the first and only medicine in its class for overactive bladder (OAB). In clinical trials, it was shown to be effective in treating OAB symptoms within the first several weeks. Those taking Myrbetriq made fewer trips to the bathroom and had fewer leaks than those not taking Myrbetriq. Your results may vary. So why give in to a demanding bladder? **Speak up—and ask your doctor if Myrbetriq is right for you.**

USE OF MYRBETRIQ

Myrbetriq® (mirabegron) is a prescription medicine for adults used to treat overactive bladder with symptoms of urgency, frequency and leakage.

IMPORTANT SAFETY INFORMATION

Myrbetriq may cause your blood pressure to increase or make your blood pressure worse if you have a history of high blood pressure. It is recommended that your doctor check your blood pressure while you are taking Myrbetriq. Myrbetriq may increase your chances of not being able to empty your bladder. Tell your doctor right away if you have trouble emptying your bladder or you have a weak urine stream.

Tell your doctor about all the medicines you take including medications for overactive bladder or other medicines such as thioridazine (Mellaril® and Mellaril S®), baclofen (Limbicor®), propofolone (Rythmol®), digoxin (Lanoxin®). Myrbetriq may affect the way other medicines work, and other medicines may affect how Myrbetriq works.

Before taking Myrbetriq, tell your doctor if you have liver or kidney problems. In clinical studies, the most common side effects seen with Myrbetriq included increased blood pressure, common cold symptoms (nasopharyngitis), urinary tract infection and headache.

Please see Brief Summary of Prescribing Information for Myrbetriq (mirabegron) on following page.

➔ To learn if you're eligible for
**A YEAR'S WORTH OF
PRESCRIPTION SAVINGS**
go to Myrbetriq.com/RxSavings.

Eligibility restrictions may apply.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

 **Myrbetriq®**
(mirabegron)
extended-release tablets
25 mg, 50 mg



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Manage the OAB
symptoms of
urgency, frequency,
and leakage