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

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Invited oral presentation at the American Statistical Association Biopharmaceutical Section Regulatory-Industry Statistics Workshop, September 12-14, 2018, Washington, D.C.

Special Acknowledgment: Ari Gnanasakthy and Two Publications

VALUE IN HEALTH 15 (2012) 437–442

Available online at www.sciencedirect.com

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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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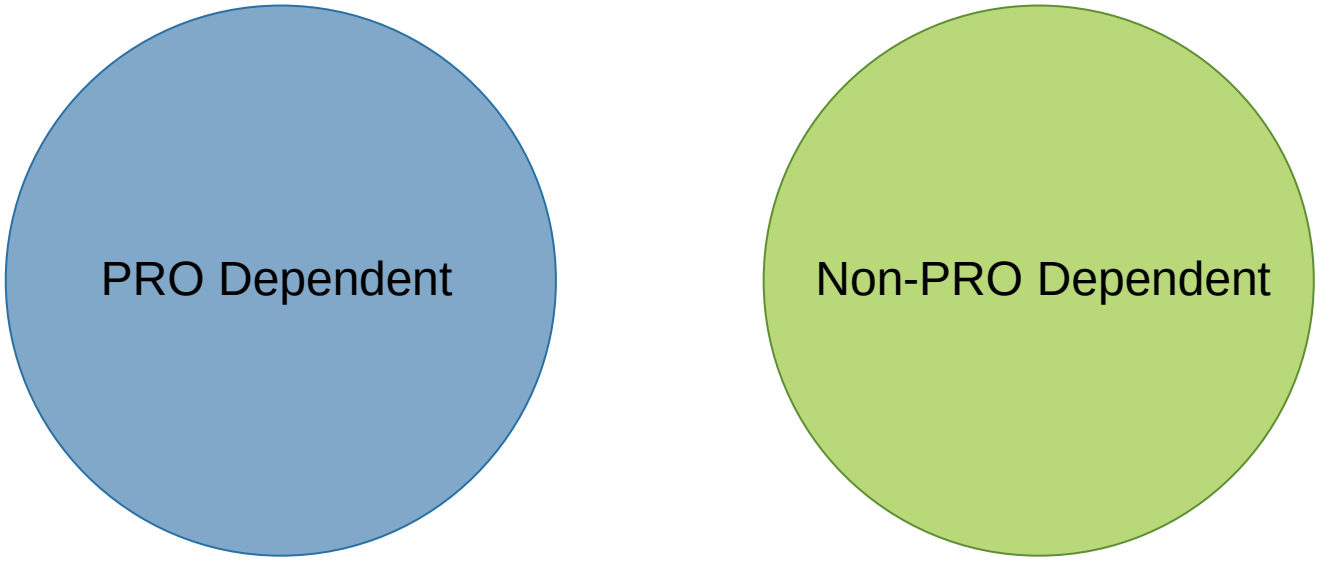
Review of FDA PRO Labeling (2010-2015)

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

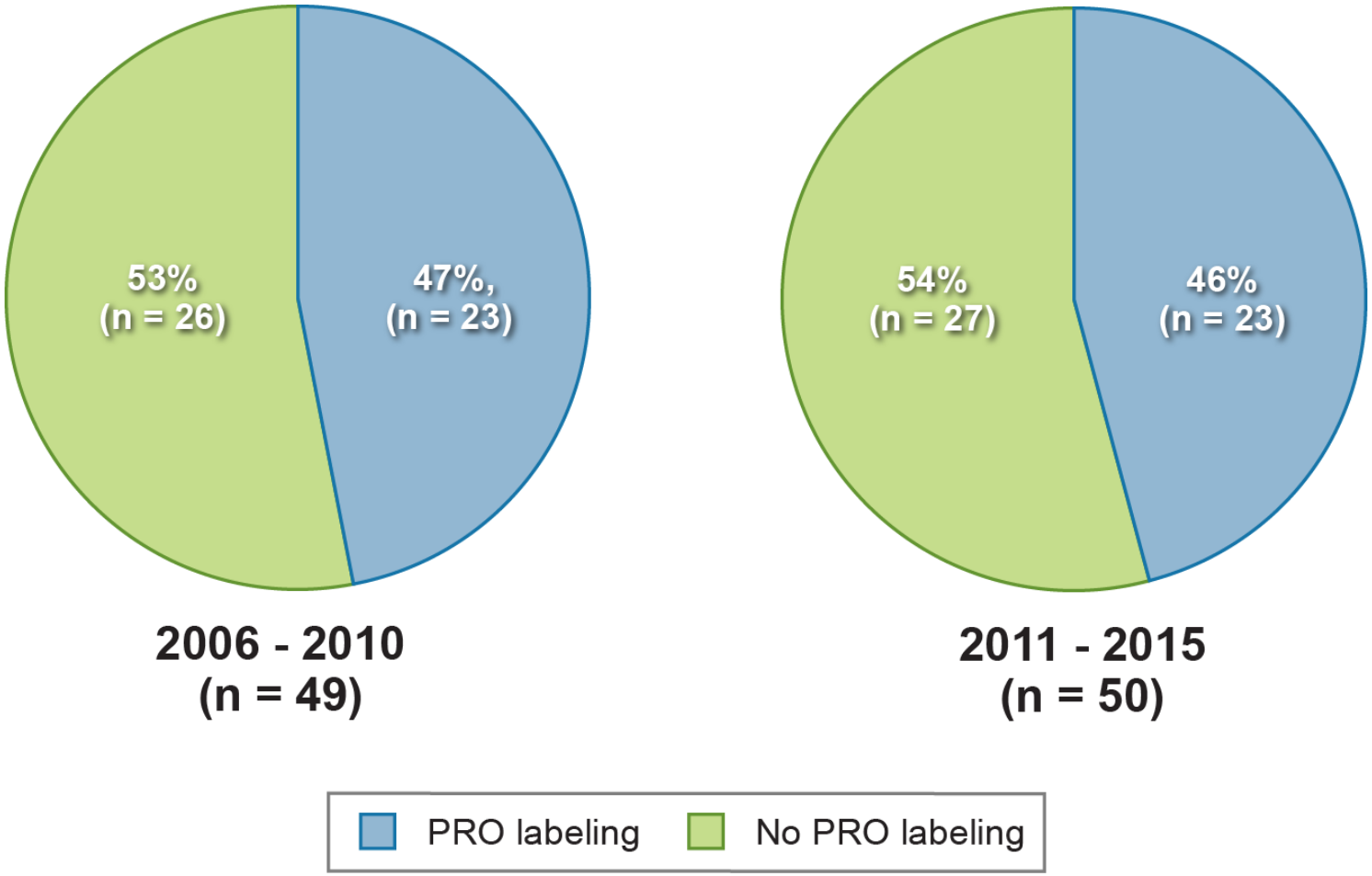
- Total number of new drugs approved (2011-2015) = 182
- New drugs with PRO labeling (2011-2015) = 16.5%

Two Categories of Diseases

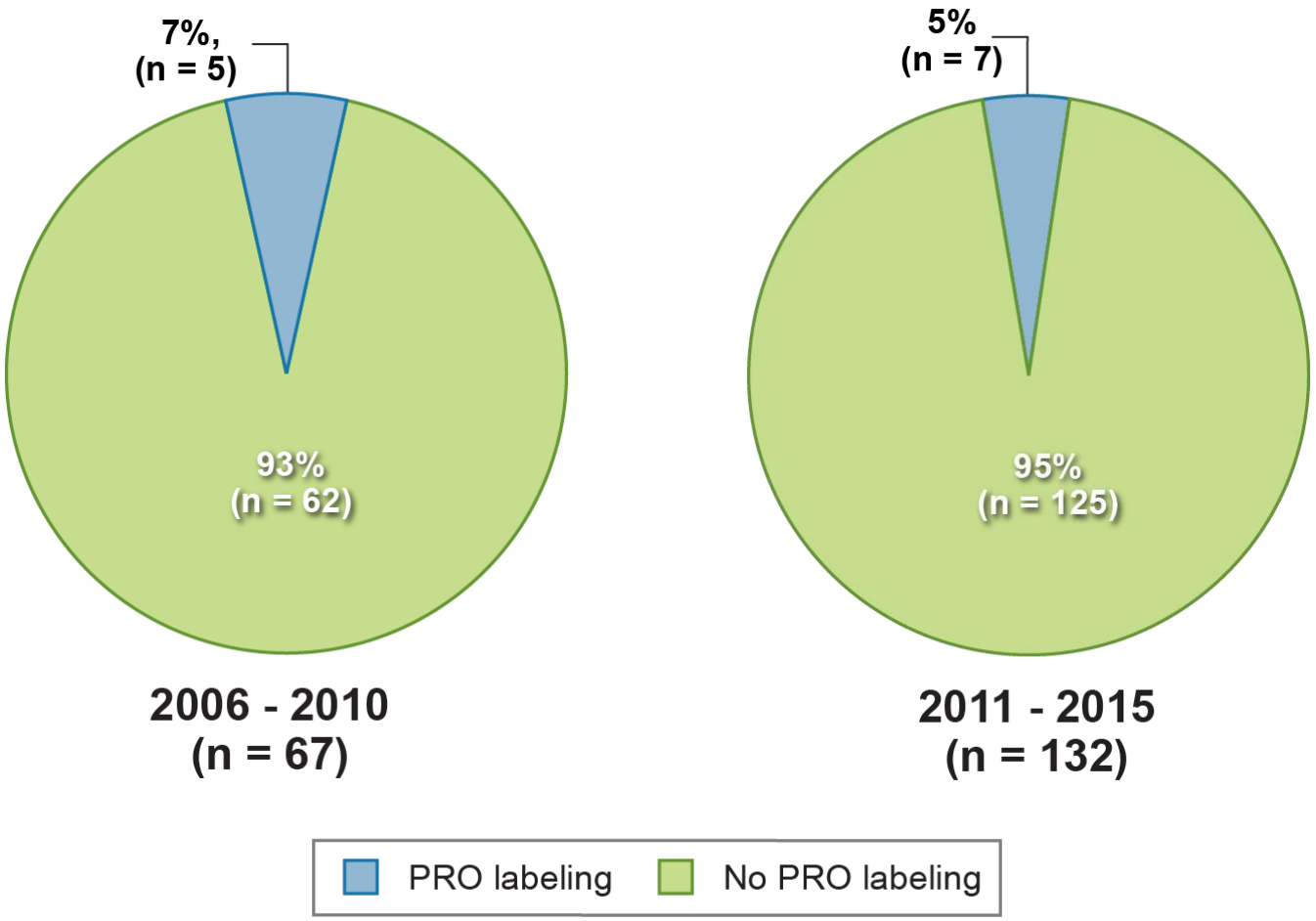


Traditionally depends on PROs to demonstrate treatment benefit for regulatory decision making

PRO Labeling (PRO Dependent)

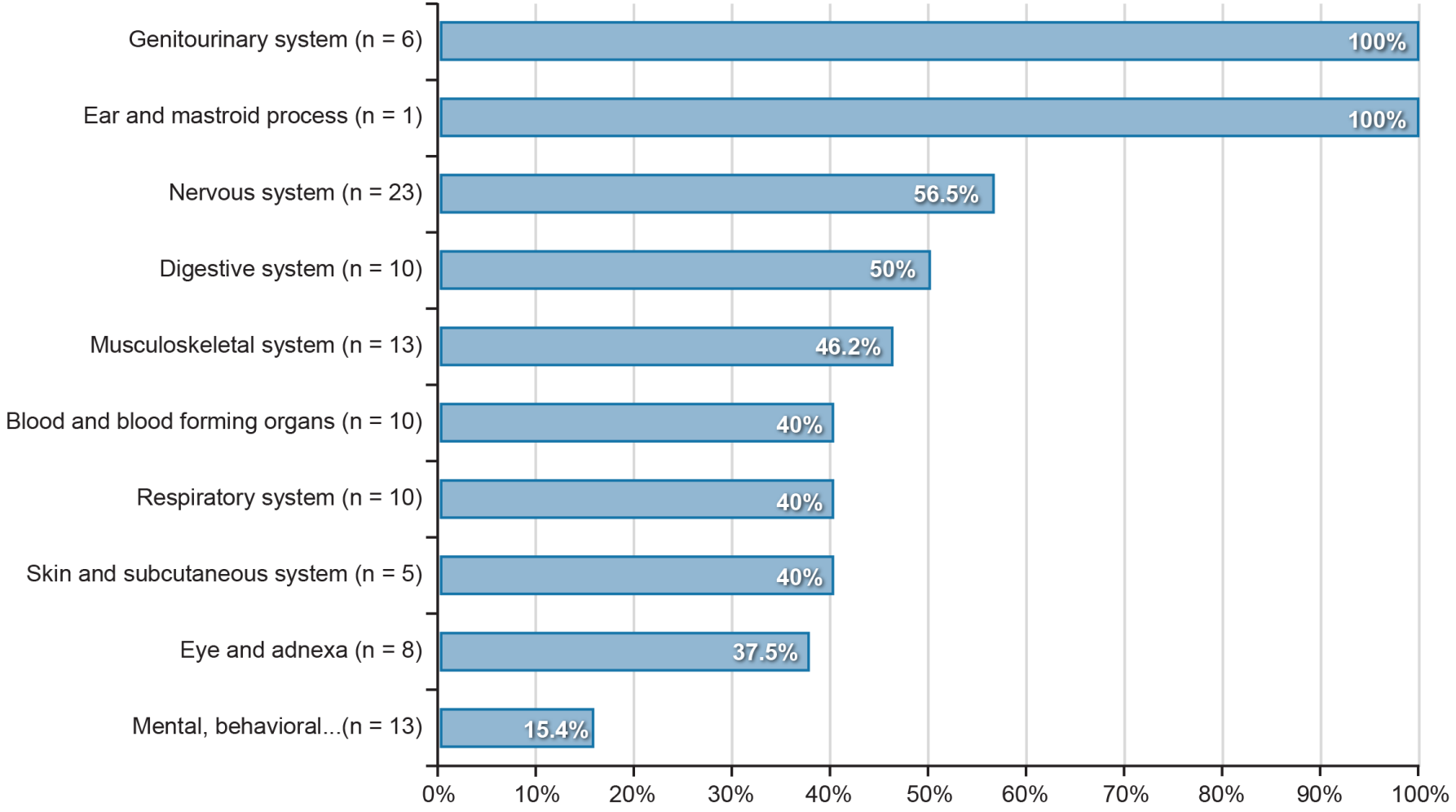


PRO Labeling (Non-PRO Dependent)



PRO Labeling (FDA NDA, 2006-2015)

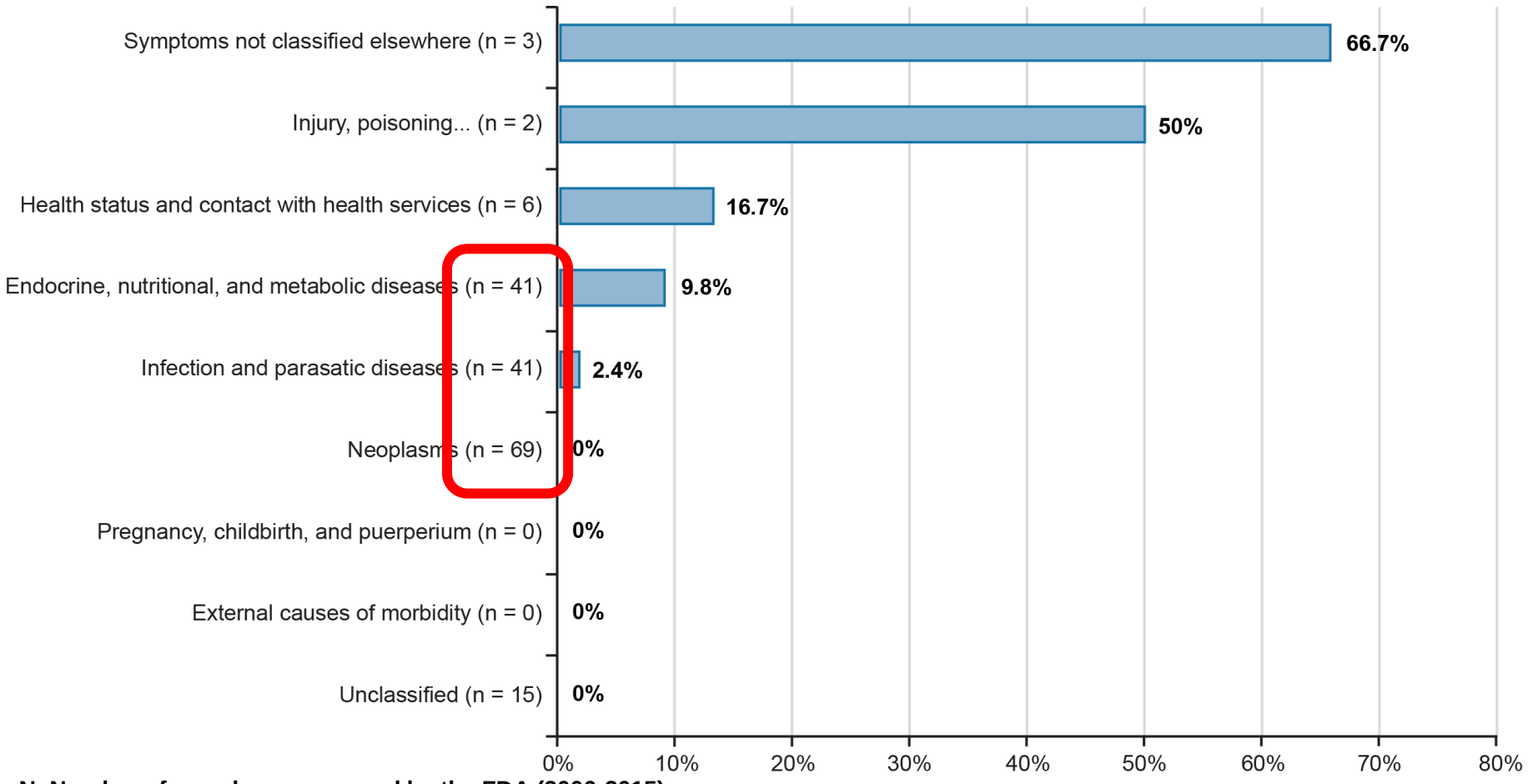
PRO-Dependent Diseases (N = 99, L = 46; 46.5%)



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

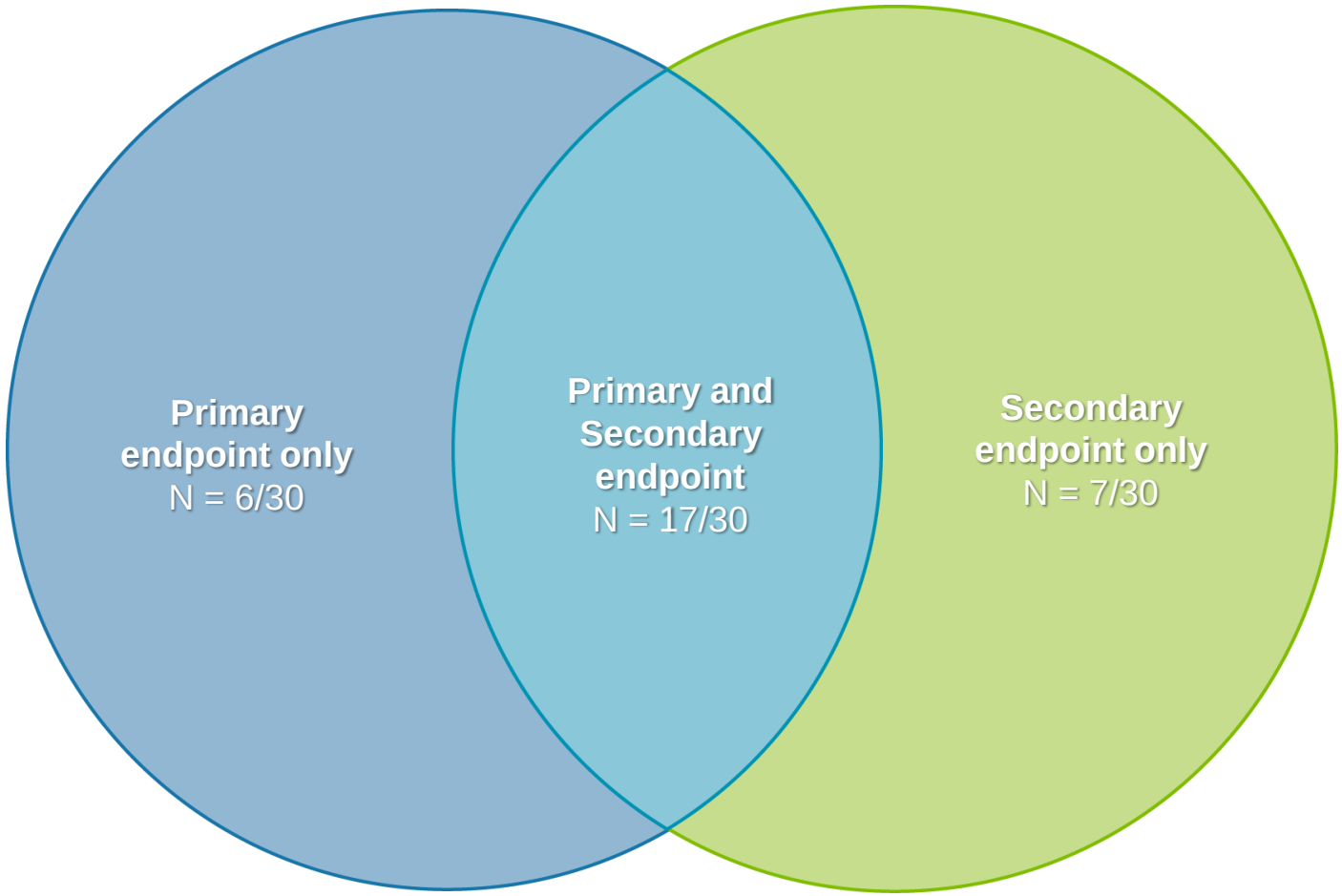
PRO Labeling for Primary and Second Endpoints

- 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 end points 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 end points 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’

Pink Sheet
Pharma intelligence | informa

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 en

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 man

clinical signs and symptoms of hypogonadism, such as low libido, erectile dysfunctio[illegible]ood disturbances and dec

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

Cystic Fibrosis Questionnaire (Revised)−Respiratory domain

ORKAMBI®
(lumacaftor/ivacaftor)
200 mg / 125 mg tablets

Psoriasis Symptom Diary

Daily rescue medication (diary)

Nucala®
(mepolizumab)
for Subcutaneous Injection
100 mg/vial

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?

ORKAMBI®
(lumacaftor/ivacaftor)
200 mg / 125 mg tablets

Psoriasis Symptom Diary

Daily rescue medication (diary)

Nucala®
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for Subcutaneous Injection
100 mg/vial

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

Some Recent Examples of Useful Labeling

Myrbetriq™ mirabegron

- "...effective in treating the symptoms of OAB"

kalydeco™ (ivacaftor) tablets

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

EQUINE DUAVEE™ CONJUGATED ESTROGENS/ BAZEDOXIFENE 0.45 MG/20 MG TABLETS

- "Significantly reduced the number and severity of moderate to severe hot flushes..."

taltz® (ixekizumab) injection 80 mg/mL

- "...improvement of itch severity..."

kybella® (deoxycholic acid) injection 10 mg/mL

- "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