FDA Patient-Reported Outcome Labeling of Novel Therapies (2011-2015)

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BACKGROUND

- Patient-reported outcome (PRO) data are defined by the Food and Drug Administration (FDA) as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."[1]
- The release by the FDA of a draft guidance in 2006 and a final guidance in 2009, Guidance for Industry Patient-Reported Outcomes: Use in Medical Product Development to Support Labeling Claims (PRO Guidance), provided the first guidance to drug manufacturers on use of PROs in product promotion.
- For the period covering the years 2006 through 2010, only 24.1% of new molecular entities (NMEs) had PRO-related labeling,[2] demonstrating a decrease from 30% reported by Willke and colleagues[3] from 1997 through 2002. This reduction in labeling was largely attributed to suboptimal implementation of the recommendations in the FDA PRO Guidance within the FDA and industry.[4]

OBJECTIVE

- To assess PRO labeling in the decade following the draft FDA PRO Guidance through an assessment of NMEs approved from 2011 through 2015 compared with the findings of the previous assessment of NMEs approved from 2006-2010.

METHODS

- New drugs approved from January 2011 through December 2015 were identified using the Drugs@FDA database.
- Data were extracted from publications related to the review of PRO labeling between 2006 and 2010.[2]
- Approved product labeling and medical review sections from FDA drug approval packages were reviewed to identify indication and the primary endpoint of confirmatory studies.
- ICD-10 codes were used to classify disease, and the primary endpoints were classified based on the type of outcome assessment (e.g., PRO, clinician-reported outcome [ClinRO], biomarker).
- Data were recorded in Microsoft Excel; frequency of measured characteristics was analyzed descriptively.

RESULTS

Overall NME Approvals

- A total of 182 NMEs were approved from 2011-2015; of these, 30 (16.5%) received PRO labeling.
- From 2011 through 2015, 58.8% of the NMEs approved were products for cancer; infectious and parasitic diseases; and endocrine, nutritional, and metabolic diseases (Table 1).
- NMEs approved for these three major categories of diseases also showed largest increases in approvals from 2006-2010 to 2011-2015. Table 1 shows that NME approvals related to cancer; infectious and parasitic diseases; and endocrine, nutritional, and metabolic diseases increased by 137.8%. The largest increase (177.8%) was in approvals of cancer drugs (Table 1).
- During review periods 2006-2010 and 2011-2015, the number of NMEs approved for all diseases, excluding the three major disease categories, was about the same (2006-2010, n = 71; 2011-2015, n = 75).

Table 1. NMEs Approved (FDA, 2006-2015)

Disease Categories	NMEs Approved (2006-2010) n	NMEs Approved (2006-2010) %	NMEs Approved (2011-2015) n	NMEs Approved (2011-2015) %	Change %
Cancer	18	15.5	50	27.5	177.8
Infectious and parasitic diseases	14	12.1	29	15.9	107.1
Endocrine, nutritional, and metabolic diseases	13	11.2	28	15.4	115.4
Subtotal	**45**	**38.8**	**107**	**58.8**	**137.8**
All other diseases	71	61.2	75	41.2	5.6
All approvals	**116**	**100.0**	**182**	**100.0**	**56.9**

PRO Labeling

- Table 2 shows that over the entire review period of 10 years (2006-2015), PRO labeling for approved NMEs for the three major disease categories was scarce (n = 7; 12.1%).
- Excluding the NME approvals related to the three major disease categories that showed the largest increases in approvals between period 2006-2010 and 2011-2015, the percentage of PRO labeling was comparable for the period 2006-2010 (38.0%) and 2011-2015 and 32.0% (Table 3).

Table 2. PRO Labeling (FDA, 2006-2015)

Disease Categories	PRO Labels (2006-2010) n	PRO Labels (2006-2010) %	PRO Labels (2011-2015) n	PRO Labels (2011-2015) %	All Labels (2006-2015) n	All Labels (2006-2015) %
Cancer	0	0.0	0	0.0	0	0.0
Infectious and parasitic diseases	0	0.0	3	10.0	3	5.2
Endocrine, nutritional, and metabolic diseases	1	3.6	3	10.0	4	6.9
Subtotal	**1**	**3.6**	**6**	**20.0**	**7**	**12.1**
All other diseases	27	96.4	24	80.0	51	87.9
All approvals	**28**	**100.0**	**30**	**100.0**	**58**	**100.0**

Table 3. NMEs Approved and PRO Labeling, Excluding Approvals in Diseases That Do Not Traditionally Rely on PROs to Assess Treatment Benefit[a] (FDA, 2006-2015)

Review Periods	NME Approvals n	PRO Labeling n (%)
2006-2010	71	27 (38.0)
2011-2015	75	24 (32.0)
2006-2015	146	51 (34.9)

[a] Cancer; infectious and parasitic diseases; and endocrine, nutritional, and metabolic diseases.

Endpoint Status

- The majority of PRO labeling (76.7%) during 2011-2015 was based on primary endpoints. PRO labeling for seven products was based only on secondary endpoints; for six of these products, the primary endpoints were biomarkers (Table 4).

Table 4. Approved NMEs With PRO Labeling Based on Secondary Endpoints Only (FDA, 2011-2015)

Drug Name (Generic)	Primary Endpoint Type	PRO Measure Used For Labeling
Indacaterol inhalation powder	Biomarker	St. George's Respiratory Questionnaire
Ruxolitinib	Biomarker	Myelofibrosis Symptom Assessment Form version 2.0
Ivacaftor	Biomarker	Cystic Fibrosis Questionnaire (Revised)—Respiratory domain
Aclidinium bromide inhalation powder	Biomarker	St. George's Respiratory Questionnaire
Secukinumab	ClinRO	Psoriasis Symptom Diary
Lumacaftor/ivacaftor	Biomarker	Cystic Fibrosis Questionnaire (Revised)—Respiratory domain
Mepolizumab	Biomarker	St. George's Respiratory Questionnaire

DISCUSSION

- Overall, the percentage of PRO labeling of NMEs decreased from 24.1% for the period 2006-2010 to 16.5% for the period 2011-2015.
- This reduction was likely due to the increase in drug approvals in three disease categories in which PROs traditionally do not play a role in the assessment of treatment benefit (cancer; infectious and parasitic diseases; and endocrine, nutritional, and metabolic diseases). PRO labeling for these three categories is difficult for the following reasons:
  - **Cancer**—development of cancer drugs relies largely on survival-related endpoints and single-arm or open-label study designs that may not be considered suitable for the interpretation of PRO data.[5]
  - **Infectious and parasitic diseases**—approval of drugs for these diseases mostly relies on some measure of pathogen activity (e.g., sustained virology response) and traditionally does not rely on PROs for assessing treatment benefit.
  - **Nutritional and metabolic diseases**—these are mostly asymptomatic (e.g., familial hypercholesterolemia or diabetes) and therefore do not traditionally rely on PROs for assessing treatment benefit.
- When these three major disease categories of NME approvals are excluded, the percentage of NMEs with PRO labeling for the periods 2006-2010 (38.0%) and 2011-2015 (32.0%) was comparable, as opposed to a comparison of PRO labeling based on the approvals of all products during these periods (2006-2010, 24.1%; 2011-2015, 16.5%).
- PRO labeling based only on secondary endpoints for 7 of the 30 products in the last 5 years (2011-2015) is perhaps indicative of sponsors' reluctance to allocate sufficient resources to secondary endpoints to meet the required regulatory standard.

CONCLUSIONS

- PRO claims continue to be approved by the FDA. While the overall percentage of products with PRO labels appears to have decreased from 2011-2015, this is due in large part to an increase in the number of products approved for cancer; infectious and parasitic diseases; and endocrine, nutritional, and metabolic diseases.
  - Ignoring these major disease categories reveals only a slight reduction in the percentage of PRO labeling granted between the 2006-2010 period (38.0%) and the 2011-2015 period (32.0%).

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Presented at: ISPOR 21st Annual International Meeting, May 21-25, 2016, Washington, DC, United States