

Patient-Reported Outcomes Labeling for Products Approved by the Office of Hematology and Oncology Products of the US Food and Drug Administration (2010-2014)

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ABSTRACT

Purpose

To review the use of patient-reported outcome (PRO) data in medical product labeling granted by the US Food and Drug Administration (FDA) for new molecular entities and biologic license applications by the FDA Office of Hematology and Oncology Products (OHOP) between January 2010 and December 2014, to elucidate challenges faced by OHOP for approving PRO labeling, and to understand challenges faced by drug manufacturers to include PRO end points in oncology clinical trials.

Methods

FDA Drug Approval Reports by Month were reviewed to obtain the number of new molecular entities and biologic license applications approved from 2010 to 2014. Drugs approved by the FDA OHOP during this period were selected for further review, focusing on brand and generic name; approval date; applicant; indication; PRO labeling describing treatment benefit, measures, end point status, and significant results; FDA reviewer feedback on PRO end points; and study design of registration trials. First in class, priority review, fast track, orphan drug, or accelerated approval status was retrieved for selected oncology drugs from 2011 to 2014. Descriptive analyses were performed by using Microsoft Excel 2010.

Results

Of 160 drugs approved by the FDA (2010-2014), 40 were approved by OHOP. Three (7.5%) of the 40 received PRO-related labeling (abiraterone acetate, ruxolitinib phosphate, and crizotinib). Compared with nononcology drugs (2011-2014), oncology drugs were more likely to be orphan and first in class. The majority of oncology drug reviews by FDA were fast track, priority, or accelerated.

Conclusion

Although symptoms and functional decrements are common among patients with cancer, PRO labeling is rare in the United States, likely because of logistical hurdles and oncology study design. Recent developments within the FDA OHOP to capture PROs in oncology studies for the purpose of product labeling are encouraging.

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INTRODUCTION

Patient-reported outcomes (PROs) are an accepted source of evidence in evaluating and approving pharmaceutical interventions on the basis of their clinical efficacy.¹ The role of PROs in drug approval is particularly important for products developed to treat chronic disabling conditions for which the intention is not necessarily to cure but to ameliorate symptoms, facilitate functioning, or improve quality of life (QOL).^{2,3}

Better understanding of cancer biology and pathophysiology has led to an increase in targeted

therapies in smaller populations of patients. In addition, the introduction of the Orphan Drug Act in 1983 by the US Food and Drug Administration (FDA) has accelerated the development of orphan cancer therapies, and the approval of targeted therapies increased from 11% to 46% between 2003 and 2013.⁴

To shorten development timelines, drug manufacturers may also take advantage of one or more regulatory pathways, such as fast track, priority review, and accelerated review.⁵⁻⁸ Fast track is a process designed to facilitate the development of and expedite the review of drugs to treat serious conditions and fill an unmet

medical need. A drug is given priority review if there is potential to provide a significant advance in medical care. Accelerated approvals are for drugs used to treat serious conditions on the basis of surrogate end points.

The main focus of cancer treatment is to improve survival either through a cure or remission or by slowing or stopping progression, or to reduce cancer-related pain or other disease-specific symptoms.⁹ Patients with cancer experience multiple symptoms that may cause significant distress and impair physical, emotional, and social functioning, as well as health-related quality of life (HRQOL). Because most of patient experience can be reported only by the patient, many initiatives have called for inclusion of PROs in clinical trials.^{1,10-14}

The FDA is responsible for protecting and promoting public health by regulating and supervising pharmaceutical products and biopharmaceuticals. After animal studies and human clinical trials of an investigational new drug have been completed, manufacturers, through a process called New Drug Application, may propose that the FDA review and approve a new pharmaceutical for sale and marketing in the United States. In the case of oncology products, the approval of a new product will be based on the totality of the evidence reviewed by the FDA Office of Hematology and Oncology Products (OHOP). Expertise relating to the development and validation of PRO measures (PROMs) and interpretation of clinical benefit on the basis of PRO end points during the review process may be provided by Clinical Outcomes Assessment Staff (COAS).¹⁵ Importantly, although COAS may provide input regarding the validity of PROMs for a specific context of use and the interpretation of clinical findings, the decision regarding the final labeling language is entirely that of OHOP.

The FDA is also responsible for implementing the regulations that ensure that labeling is informative and accurate and not promotional in tone or false or misleading.¹⁶ Labeling is based on the totality of evidence submitted by the sponsor. For example, although “improvement in pain” may have been noted in the labeling for a particular product, the evidence supporting this labeling may be based on supportive data from multiple clinical trial end points, such as reduction in tumor size, as well as improvements in pain, fatigue, and reduced use of analgesics reported via various PROMs. Similarly, sometimes PRO data from clinical studies are found to be supportive of the overall product indication but are not included in labeling.

FDA product labeling, also known as the package insert (PI), is a product monograph approved by the FDA to provide complete and unbiased prescribing and safety information. PRO-related efficacy labeling on the basis of primary end points is typically found under the section titled “Indication and Usage” in the PI, whereas PRO labeling on the basis of nonprimary end points is typically found in the section of the PI titled “Clinical Studies.” Drug manufacturers use FDA-approved labeling to make claims about their products in marketing and promotional activities.

The PI is part of the Drug Approval Package (DAP), which is a summary of clinical study reports and related documents written by the FDA staff after data from pivotal studies submitted by the study sponsors has been reviewed. Documents in the DAP are structured and often updated when new information becomes available. The information made publically available in the DAP allows the rationale for a medication’s approval to be examined

and allows prescribers and researchers to appraise the data carefully.^{2,3}

Although end points that support symptomatic improvements have been used to support US regulatory approval in oncology,^{9,17} on the basis of previous research, there have been few instances of PRO labeling for oncology drugs. A review of PRO labeling in the United States between 2006 and 2010 showed that PRO labeling was granted for approximately one fourth of new products, whereas no oncology products received PRO labeling during this time period.³ Notably, certain clinical study designs (eg, randomized, double blind, placebo controlled) are more amenable to supporting FDA approval of PRO labeling; therefore, understanding pivotal trials designs is important for understanding reasons for higher or lower instances of PRO labeling.

The purpose of this article is to review the use of PRO data in medical product labeling granted for new molecular entities (NMEs) and biologic license applications (BLAs) by OHOP between 2010 and 2014, to elucidate challenges faced by OHOP for approving PRO labeling, and to understand challenges faced by drug manufacturers to include PRO end points in oncology clinical trials.

METHODS

A review of the FDA Drug Approval Reports by Month for new drug approvals (NDAs) was conducted in January 2015 to determine the number of NMEs and BLAs approved in the time period of interest (2010-2014). Reports were generated sequentially beginning with January 2010 through December 2014, sorted by the Center for Drug Evaluation Research NDA chemical classification, hand-reviewed by a single reviewer, and quality-checked by a second reviewer. Products containing substances previously marketed with a different brand name or a set of indications such as a different dosage form or strength or as a combination product of previously marketed entities were excluded. Indications for each product were then reviewed to select oncology drugs approved during this time period by OHOP. For the oncology products identified, DAPs and approved product labels were reviewed. As it became available, information was retrieved from the Medical Review, Summary Review, and other review sections of the DAP, as well as the Indication, Adverse Reactions, and Clinical Studies sections of the PI. The original PI and the most recent PI for each product were reviewed to assess any changes in PRO labeling that may have occurred. As available, the following information was collected for each product identified: brand name and generic name; date of FDA approval; applicant; indication; PRO-related language in the original and most recently FDA-approved PI; PROMs named in labeling or the DAP; PROs as primary, secondary, tertiary, or other end points in the PI or DAP; PRO results reported as statistically and/or clinically significant; comments or feedback from reviewers about PRO end points; and registration trial study design (ie, single arm, open label, randomized controlled trial, and fewer than or more than 200 patients).

In addition, first in class, priority review, fast track, orphan drug, and/or accelerated approval information was collected from FDA’s published Novel New Drugs Summaries for all NMEs and BLAs approved between 2011 and 2014.⁵⁻⁸ This information was not readily available for 2010.

PRO labeling was defined as any treatment benefit or harm on the basis of PRO data described in the PI. Aspects of the study design and regulatory pathways of oncology pivotal trials were compared with those for other diseases to determine whether there were differences that might have affected likelihood of success in obtaining PRO labeling. Descriptive analyses, including frequencies and cross tabulations of measured characteristics, were performed by using Microsoft Excel 2010.

RESULTS

A total of 160 NMEs and BLAs were reviewed between January 2010 and December 2014 (Table 1), of which 40 were approved by OHOP. Of the 40, only three (7.5%) received PRO labeling. As depicted in Table 2, two of the three instances of PRO labeling were based on data from randomized controlled trials (RCTs), whereas the third instance was based on a single-arm, open-label study. Furthermore, for the two instances of PRO labeling in the Clinical Studies section of the PI, one (abiraterone acetate [Zytiga]) was for improvement in pain related to prostate cancer measured on the Brief Pain Inventory–Short Form questionnaire, and the other (ruxolitinib phosphate [Jakafi]) was for improvement of symptoms associated with myelofibrosis assessed by the Myelofibrosis Symptom Assessment Form, a disease-specific symptom diary. The labeling relating to higher incidence of visual disturbances on the basis of the Visual Symptom Assessment Questionnaire-Anaplastic Lymphoma Kinase (VSAQ-ALK) was mentioned in the Adverse Reactions section of the PI for crizotinib (Xalkori).

Among the products reviewed, there was one instance in which a change in PRO labeling occurred between the original and the most recent PI. The original PI for abiraterone acetate (2011) included a single phase III study in the Clinical Studies section that did not include PRO labeling, whereas the 2014 PI included a second phase III study that supported PRO labeling (Table 2).

Notably, registration trials of 13 oncology drugs (32.5%) had some PRO measurement mentioned in the DAP but did not result in labeling (Table 3). For example, the DAP Medical Review for crizotinib (2011) states that secondary objectives for Study A8081005 (An Investigational Drug, PF-02341066, Is Being Studied In Patients With Advanced Non-Small Cell Lung Cancer With A Specific Gene Profile Involving The Anaplastic Lymphoma Kinase [ALK] Gene) are “To assess patient-reported outcomes (PRO) of health-related quality of life (HRQOL), disease/treatment-related symptoms of lung cancer, and general health status” and that the “EORTC QLQ-C30 and LC13, EQ-5D and VSAQ-ALK” are all listed as end points in the schedule of events for this study. Furthermore, published preliminary PRO findings from PROFILE 1005 (Phase 2, Open-Label Single Arm Study of the Efficacy and Safety of Crizotinib in Patients With NSCLC Harboring a Translocation or Inversion Event Involving the

Anaplastic Lymphoma Kinase [ALK] Gene) indicated high completion and compliance rates. Data also showed clinically significant reductions of ≥ 10 points in key symptoms of non–small-cell lung cancer, including pain, dyspnea, cough, fatigue, and insomnia (Quality of Life Questionnaire C30 scale), and well as maintenance of QOL.^{18,19} However, no additional PRO labeling was granted for crizotinib beyond that on the basis of the VSAQ-ALK.

Although all 13 registration trials included established PROMs, only 5 (38.4%) were RCTs. Significant deficiencies noted by the FDA reviewers within the DAP included unacceptable levels of missing values, use of inappropriate PROMs, and a lack of clinical significance.

Table 4 shows that oncology drugs, when compared with nononcology drugs, were more likely to be for orphan indications (73.7% v 22.0%) and considered to be first in class (50% v 39%). In addition, they are more likely to go through fast track (65.8% v 30.0%), priority (78.9% v 36.0%), or accelerated review (36.8% v 3.0%) during the FDA’s product review process.

Oncology registration trials, when compared with nononcology studies, are more likely to be single arm (37.5% v 8.3%) and open label (67.5% v 8.3%) and less likely to be double-blind RCTs (35% v 87.5%; Table 5). In addition, 35% of the oncology trials compared with 15.8% of the nononcology trials during the time frame reviewed had fewer than 200 patients in their registration trials (Table 5).

The review of brentuximab (Adcetris), an orphan drug for Hodgkin lymphoma, demonstrates the difficulties faced by regulators when they try to interpret data from small single-arm, open-label studies. The DAP Medical Review states “The efficacy evaluation is limited by the small size (N = 102) and single arm design. Time-to-event end points (i.e., progression free survival or overall survival) and patient reported outcomes cannot be adequately interpreted in a single arm trial.”

DISCUSSION

This analysis represents a comprehensive review of all oncology products approved by FDA OHOP from 2010 through 2014. Despite the symptomatic nature of many of the conditions being treated, only 7.5% of oncology products received PRO labeling. This is significantly less than the 24% reported for a similar review of all NMEs and BLAs approved by FDA between 2006 and 2010.³ As in previous reviews,^{3,20,21} instances of PRO labeling granted by the FDA OHOP within the Clinical Studies section of the PI were related to improvement of proximal (eg, symptoms) and not complex (eg, HRQOL) concepts and were based on RCTs.

The labeling for crizotinib was included, but notably, this use of a PRO was not specific to treatment benefit but rather to increased incidence of visual disturbances on the basis of VSAQ-ALK. This is a rare example of labeling on the basis of PROs in the Adverse Events section of a PI.³

Two major factors may contribute to the smaller number of PRO labeling instances in oncology drug development. First, oncology studies are significantly more likely to be small, single arm, and open label. Thus, these studies may not be perceived to be candidates for inclusion of PROs because of potential bias

Table 1. NMEs and BLAs Approved by FDA OHOP (2010-2014)

Year	No. of Oncology NMEs and BLAs Approved	No. of Oncology Products With PRO Labeling	No. of Nononcology NMEs and BLAs Approved
2010	2	0	20
2011	8	3	22
2012	12	0	26
2013	9	0	20
2014	9	0	32
Total (2010-2014)	40	3	120

Abbreviations: BLA, biologic license application; FDA, US Food and Drug Administration; NME, new molecular entity; OHOP, Office of Hematology and Oncology Products; PRO, patient-reported outcome.

Table 2. Oncology Products Approved With PRO Labeling (FDA OHOP, 2010-2014)

Generic Name	Brand Name	Year Approved	Disease	Study Design	PRO Concepts in Labeling	PRO Measures Used to Support Labeling	PRO Labeling Language
Abiraterone acetate	Zytiga	2011	Prostate cancer	Randomized controlled trial	Pain	Brief Pain Inventory–Short Form (BPI-SF)	Baseline pain assessment was 0-1 (asymptomatic) in 66% of patients and 2-3 (mildly symptomatic) in 26% of patients as defined by the BPI-SF (worst pain over the last 24 hours). The median time to opiate use for prostate cancer pain was not reached for patients receiving abiraterone acetate and was 23.7 months for patients receiving placebo (HR, 0.686 [95% CI, 0.566 to 0.833]; <i>P</i> = .0001). The time to opiate use result was supported by a delay in patient-reported pain progression favoring the abiraterone acetate arm.
Ruxolitinib phosphate	Jakafi	2011	Myelofibrosis	Randomized controlled trial	Symptoms of myelofibrosis	Myelofibrosis Symptom Assessment Form (MFSAF)	The modified MFSAF is a daily diary capturing the core symptoms of myelofibrosis (abdominal discomfort, pain under left ribs, night sweats, itching, bone/muscle pain, and early satiety). Symptom scores ranged from 0 to 10, with 0 representing symptoms "absent" and 10 representing "worst imaginable" symptoms. These scores were added to create the daily total score, which has a maximum of 60. At baseline, the mean Total Symptom Score was 18.0 in the ruxolitinib phosphate group and 16.5 in the placebo group. A higher proportion of patients in the ruxolitinib phosphate group had a 50% or greater reduction in Total Symptom Score than in the placebo group, with a median time to response of less than 4 weeks.
Crizotinib	Xalkori	2011	Non-small-cell lung cancer	Single arm, open label	Visual disturbances	Visual Symptom Assessment Questionnaire-Anaplastic Lymphoma Kinase (VSAQ-ALK)	Based on the VSAQ-ALK, patients treated with crizotinib in Study 1 reported a higher incidence of visual disturbances than patients treated with chemotherapy. The majority of patients in the crizotinib arm of Study 1 (> 50%) reported visual disturbances; these visual disturbances occurred at a frequency of 4 to 7 days each week, lasted up to 1 minute, and had mild or no impact (scores 0 to 3 out of a maximum score of 10) on daily activities as captured in a patient questionnaire.

Abbreviations: FDA, US Food and Drug Administration; HR, hazard ratio; OHOP, Office of Hematology and Oncology Products; PRO, patient-reported outcome.

Table 3. Oncology Products With Potential for PRO Labeling (FDA OHOP, 2010-2014)

Generic Name	Brand Name	Year Approved	Disease	Study Design	PRO Measures Used in Study	Significant Deficiencies Noted by FDA in DAP
Cabazitaxel	Jevtana*	2010	Prostate cancer	Randomized, open-label	MMPI	Inappropriate PROMs, too many missing values, inadequate measurement
Abiraterone acetate	Zytiga	2011	Prostate cancer	Randomized controlled trial	BFI, FACT-P	Too many protocol deviations
Crizotinib	Xalkori	2011	Non-small-cell lung cancer	Single arm, open label	EORTC QLQ C30, LC13, and EQ-5D	None noted
Axitinib	Inlyta	2012	Renal cell carcinoma	Randomized, open label	FKSI and EQ-5D	Poor data quality
Vismodegib	Erivedge	2012	Basal cell carcinoma	Single arm, open label	SF-36	Too many missing values
Pertuzumab	Perjeta*	2012	Breast cancer	Randomized controlled trial	FACT TOI-PFB, FACT-B	Inadequate content validity of PROMs, PROs were exploratory end point
Cabozantinib s-malate	Cometriq	2012	Medullary thyroid cancer	Randomized controlled trial	MDASI-THY	Lack of clinical significance
Ibrutinib	Imbruvica	2013	Mantle cell lymphoma, chronic lymphocytic leukemia, Waldenström macroglobulinemia	Single arm, open label	Health-related quality of life (instrument not reported)	Results not reported to FDA
Radium ra-223 dichloride	Xofigo*	2013	Prostate cancer	Randomized controlled trial	FACT-P, EQ-5D	Inappropriate choice of instruments, clinical relevance of findings not clear, too many missing values
Afatinib dimaleate	Gilotrif	2013	Non-small-cell lung cancer	Randomized, open-label	Health-related quality of life (instrument not reported)	Results not reported to FDA
Ado-trastuzumab emtansine	Kadcyla	2013	Breast cancer	Randomized, open-label	FACT-B TOI	Results not reported to FDA
Siltuximab	Sylvant	2014	Multicentric Castleman's disease	Randomized controlled trial	FACIT-F, SF-36, MCD-SS	Inadequate analysis plan
Olaparib	Lynparza	2014	Ovarian cancer	Single arm, open label	FOSI, FACT-O	Inappropriate instruments, lack of statistical significance

Abbreviations: BFI, Brief Fatigue Inventory; DAP, Drug Approval Package; EORTC QLQ C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; EQ-5D, EuroQol 5 Dimensions; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; FACT TOI-PFB, Functional Assessment of Cancer Therapy–Trial Outcome Index–Physical/Functional/Breast Subscale; FACT-B, FACT–Breast; FACT-B-TOI, FACT–Breast-Trial Outcome Index; FACT-O, FACT–Ovarian; FACT-P, FACT–Prostate; FDA, US Food and Drug Administration; FKSI, Functional Assessment of Cancer Therapy Kidney Symptom Index; FOSI, Functional Assessment of Cancer Therapy–Ovarian Symptom Index questionnaire; LC13, EORTC QLQ lung cancer-specific questionnaire; MCD-SS, Multicentric Castleman's Disease Symptom scale; MDASI-THY, MD Anderson Symptom Inventory–Thyroid Module; MMPI, McGill-Melzack Present Pain Intensity scale; OHOP, Office of Hematology and Oncology Products; PRO, patient-reported outcome; PROM, patient-reported outcome measure; SEALD, Study Endpoints and Labeling Development; SF-36, Short-Form Health Survey.
*Study Endpoints and Labeling Development input documented.

introduced by the open-label design.¹ Second, given that most oncology drugs are marketed first in the United States, oncology trials are likely to go through various regulatory pathways designed to speed up the development and regulatory process in the United States.²² Pressed for time and given the challenges involved in integrating PROs in clinical trials, sponsors may be unlikely to prioritize PRO end points.^{23,24} Therefore, sponsors may be more likely to include off-the-shelf measures rather than develop disease-specific tools, despite their possibly not fully complying with the FDA PRO guidance, for publication purposes and to satisfy European health authorities, which are more likely to grant PRO labeling.²⁵

However, despite fears of potential bias, PRO findings from single-arm, open-label studies can provide useful data to patients and physicians who may want to compare experience with supportive care or standard of care. These studies can be useful for reviewers who may want to study the experience of patients during progression-free survival. Such realization led one of the reviewers for brentuximab (a single-arm accelerated approval) to comment that “progression-free survival alone is a pyrrhic victory.”²⁶ However, overall improvement of HRQOL on the basis of a single

item may not provide enough detail to support labeling, particularly within an open-label study.²⁷

Given these challenges, coupled with downward pressure on budgets, resources, and rigorous application of the FDA PRO guidance, the challenges for study teams are exacerbated when they want to include PROs in clinical trials.^{28,29} Lack of time and resources may result in deprioritization of PRO-related end points, that is, they may follow a long list of other secondary end points or be included as an exploratory end point in the study protocol without any protocol-specific hypothesis or statistical analysis plans. The result of such limited implementation of PROs leads to protocol violations and missing values, which often result in data that cannot be analyzed.

Despite the standards outlined in the PRO guidance, the OHOP seems to recognize the flexibility needed to address the unique challenges encountered in oncology trials.³⁰ In a recent publication by both COAS and OHOP, sponsors were encouraged to assess three well-defined concepts that are proximal to a therapy's effect on patients and their cancers.³¹ These three concepts—symptomatic adverse events, physical function, and disease-related symptoms—are recommended to be assessed by

Table 4. Regulatory Characteristics of Oncology Versus Nononcology NMEs and BLAs (FDA OHOP, 2011-2014)

Year	Drug Type	No. of Products	First in Class		Orphan		Fast Track		Priority		Accelerated Review	
			No.	%	No.	%	No.	%	No.	%	No.	%
2011			6		7		7		8		2	
2012			4		6		7		8		3	
2013			4		6		7		5		2	
2014			5		9		4		9		7	
2011-2014	Oncology	38	19	50.0	28	73.7	25	65.8	30	78.9	14	36.8
2011-2014	Nononcology	100	39	39.0	22	22.0	30	30.0	36	36.0	3	3.0

Abbreviations: BLA, biologic license application; FDA, US Food and Drug Administration; NME, new molecular entity; OHOP, Office of Hematology and Oncology Products.

using items in contemporary PROMs such as Common Terminology Criteria for Adverse Events (PRO-CTCAE) for the description of symptomatic adverse events and the Patient-Reported Outcomes Measurement Information System (PROMIS) physical function assessments.^{32,33} The PRO Compendium, recently published by the FDA as part of an effort to foster patient-focused drug development, further recognizes the use of existing measures to demonstrate treatment benefit.³⁴ For example, item 3 of the Brief Pain Inventory is identified as a possible means to demonstrate improvement in pain or delay in time to pain progression for patients with metastatic castration-resistant prostate cancer. Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT–Fatigue) is identified as a possible measure to demonstrate improvement in fatigue in studies relating to paroxysmal nocturnal hemoglobinuria. Given that open-label trials are common in oncology research, the FDA recommends that sponsors demonstrate large magnitude of effect and use PROs in conjunction with other objective measures of antitumor effects to aid interpretation.³⁵

FDA's evolving position should not be interpreted by the sponsors as relaxing the standards for PROMs. End points must be valid and reliable, and the conclusions should be based on sound prespecified analysis plans.

There are eight steps sponsors can take to increase the chances of PRO labeling in oncology studies: (1) define the concept of interest within the context of use of the study; (2) assess concepts that are proximal to the disease, with specific emphasis on symptomatic adverse events, physical functioning and, where appropriate, a measure of the key symptoms of the disease; (3)

consider appropriate items or domains from widely available measures, such as the European Organisation for Research and Treatment of Cancer (EORTC), FACIT, the MD Anderson Symptom Inventory, PRO-CTCAE, and PROMIS, in the absence of disease-specific measures; (4) have early discussion with the FDA OHOP about the concept of interest, the proposed labeling language, PROMs to be used, frequency and timing of assessments, mode of administration (paper or electronic), and analysis plan (handling of missing values, methods of interpretation, and adjustment for multiplicity); (5) minimize missing data by using electronic data capture, placing emphasis on instructions to patients and providing adequate training for study coordinators²⁴; (6) document circumstances of missing data to assist in interpretation of data; (7) use a fit-for-purpose measure to demonstrate large magnitude of effect in open-label settings; and (8) consider follow-up studies with PRO as the primary end point if the main registration studies are not suitable for the purpose of collecting PRO data.

In conclusion, the small number of PRO labeling instances granted by the FDA OHOP is a reflection of the difficulties faced by regulators and the industry to capture the patient's voice in oncology drug development. However, recent developments within the FDA, and particularly within OHOP, to better capture PROs in oncology studies for the purpose of product labeling is encouraging. Sponsors should also make every effort to capture PROs in cancer drug development, and product labeling should not be the only goal for including PROs in drug development. PROs should be included in development programs to capture a comprehensive evaluation of the study participants' experience,

Table 5. Study Design Characteristics of Oncology Versus Nononcology NMEs and BLAs (FDA OHOP, 2010-2014)

Year	Drug Type	No. of Products	Single Arm		Open		RCT		< 200 Patients	
			No.	%	No.	%	No.	%	No.	%
2010			0		2		0		0	
2011			2		5		4		2	
2012			7		7		5		3	
2013			2		8		1		1	
2014			4		5		4		8	
2010-2014	Oncology	40	15	37.5	27	67.5	14	35.0	14	35.0
2010-2014	Nononcology	120	10	8.3	10	8.3	105	87.5	19	15.8

Abbreviations: BLA, biologic license application; FDA, US Food and Drug Administration; NME, new molecular entity; OHOP, Office of Hematology and Oncology Products; RCT, randomized controlled trial.

which can provide useful information on the impact of the new therapy for patients, regulators, health care providers, caregivers, and payers who need to choose between competing therapies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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