VALUE IN HEALTH 22 (2019) 203–209

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/jval

Health Policy Analysis

A Review of Patient-Reported Outcomes Labeling for Oncology Drugs Approved by the FDA and the EMA (2012-2016)

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ABSTRACT

Objectives: To compare US Food and Drug Administration (FDA) and European Medicines Agency (EMA) labeling for evidence based on patient-reported outcomes (PROs) of new oncology treatments approved by both agencies. **Methods:** Oncology drugs and indications approved between 2012 and 2016 by both the FDA and the EMA were identified. PRO-related language and analysis reported in US product labels and drug approval packages and EMA summaries of product characteristics were compared for each indication. **Results:** In total, 49 oncology drugs were approved for a total of 64 indications. Of the 64 indications, 45 (70.3%) included PRO data in either regulatory submission. No FDA PRO labeling was identified. PRO language was included in the summary of product characteristics for 21 (46.7%) of 45 indications. European Organisation for Research and Treatment of Cancer and Functional Assessment of Cancer Therapy measures were used frequently in submissions. FDA's comments suggest that aspects of study design (eg, open labels) or the validity of PRO measures was the primary reason for the lack of labeling based on PRO endpoints. Both agencies identified missing PRO data as problematic for interpretation. **Conclusions:** During this time period, the FDA and the EMA used different evidentiary standards to assess PRO data from oncology studies, with the EMA more likely to accept data from open-label studies and broad concepts such as health-related quality of life. An understanding of the key differences between the agencies may guide sponsor PRO strategy when pursuing labeling. Patient-focused proximal concepts are more likely than distal concepts to receive positive reviews.

Keywords: European Medicines Agency (EMA), Food and Drug Administration (FDA), labeling, oncology, patient-reported outcome (PRO)

Introduction

In oncology clinical trials, patient-reported outcomes (PROs) are an important complement to other clinical endpoints such as survival and toxicity and are key to understanding overall treatment benefit. PROs help stakeholders understand the patient experience, particularly the impact of treatment on patients' functioning, and can help differentiate among products that offer similar survival benefits. In contrast, if a new regimen offers limited efficacy and no PRO advantages, then its clinical relevance may be questioned.[1,2]

Because measurement of PROs enables a holistic assessment of treatment benefit, the use of PRO measures (PROMs) is emphasized in many treatment guidelines. Moreover, both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) encourage the assessment of PROs in anticancer drug development.[3,4] Value frameworks proposed by the American Society of Clinical Oncology and the European Society for Medical Oncology for anticancer treatments indicate that PROs are a key component of evaluating value.[5,6] Payers worldwide also increasingly consider PRO data in decision making and anticipate the growing importance of PRO data.[7]

FDA product labeling and EMA summaries of product characteristics (SmPCs) for a drug product constitute the formal definition of a drug's benefits and risks.[8] The product labeling and SmPC, which are generated by manufacturers but require regulatory approval, define the boundaries of the legal promotion of a drug's properties.

Conflicts of interest: A. Gnanasakthy, A. Barrett, E. Evans, and C. Romano are salaried employees of RTI Health Solutions. D. D'Alessio is a salaried employee of Novartis Pharmaceuticals Corporation.

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1098-3015/$36.00 - see front matter Copyright © 2019, ISPOR—The Professional Society for Health Economics and Outcomes Research. Published by Elsevier Inc.

https://doi.org/10.1016/j.jval.2018.09.2842

Despite increasing recognition among regulators, payers, and other stakeholders of the importance of PROs in healthcare decision making, none of the 69 new oncology drugs approved for their first indication by the FDA between 2006 and 2015 included PRO-related language in the product labeling (ie, FDA PRO labeling).[8,9] Nevertheless, another review of approvals of new oncology drugs and subsequent updates to labeling showed that PRO labeling was granted in 2011 to abiraterone (for the treatment of prostate cancer), crizotinib (for the treatment of non–small cell lung cancer [NSCLC]), and ruxolitinib (for the treatment of myelofibrosis).[10]

The FDA is also more likely to grant labeling for proximal concepts such as symptoms, whereas the EMA also allows labeling for distal concepts such as health-related quality of life (HRQOL).[11] A recent review found PRO labeling included in SmPCs by the EMA for 47% of the 75 new drugs approved by the FDA and the EMA between 2006 and 2010, compared with 19% by the FDA.[11] To our knowledge, there have been no reviews of PRO labeling of oncology drugs recently approved by the EMA. The purpose of this study is to compare PRO labeling for new cancer drugs approved by the FDA and the EMA for any indication between 2012 and 2016.

Methods

Using the FDA Drug Approval Reports website,[12] drugs with oncology indications approved in the United States from January 2012 through December 2016 were identified. Drugs with one or more indications granted before 2012 were included. Drugs with only modifications to existing labeling during this time period, with no new indications granted, were excluded. The marketing authorization documents from the EMA website[13] for drugs and indications that matched those identified for the FDA during the 2012 to 2016 period were then identified and summarized.

For each drug and the corresponding indications, FDA product labeling and the medical and statistical reviews from the drug approval package (DAP) were identified and reviewed. Similarly, for the EMA, the SmPC and the European Public Assessment Report (EPAR) were reviewed.

Data collected included indication(s), approval date, applicant, confirmatory study design and comparator(s), number of patients, PROMs and claims in the FDA or EMA SmPC labeling, and reviewer commentary included in the DAP or EPAR. Statistical analyses consisted of frequencies and cross-tabulations of product characteristics and label content and were performed using Microsoft Excel 2007. All data extractions were performed by one researcher and were independently verified by another.

Results

Between 2012 and 2016, 49 drugs with 64 unique oncology indications were approved by both the FDA and the EMA; of the 49 drugs, 11 (22.4%) received 2 or more oncology indications (see Appendix S1 in Supplemental Materials found at 10.1016/j.jval.2018.09.2842).

Of the 64 reviewed indications, 45 (70.3%) included PRO data in submission documents (Table 1). Of the 45 indications with PRO data, 20 were double-blinded randomized controlled trials (RCTs) and 33 were for the treatment of solid tumors. Only 2 trials for these indications had fewer than 200 patients at baseline.

For the 45 indications with PRO data, none received PRO labeling from the FDA. Nevertheless, there were 21 indications (46.7%) with PRO-related language in SmPCs (EMA PRO labeling), amounting to roughly one-third (32.8%) of all 64 indications reviewed by the EMA.

Table 1 – Characteristics of oncology indications reviewed by the FDA and the EMA (2012-2016).

Characteristics	Indications reviewed (n = 64), n (%)	Indications including PRO data (n = 45), n (%)
Randomized controlled study	24 (37.5)	20 (44.4)
<200 patients at baseline visit	5 (7.8)	2 (4.4)
Cancer type		
Solid tumor	42 (65.6)	33 (73.3)
Hematological malignancy	22 (34.4)	12 (26.7)
PRO labeling		
FDA	0 (0.0)	0 (0.0)
EMA	21 (32.8)	21 (46.7)

EMA, European Medicines Agency; FDA, Food and Drug Administration; PRO, patient-reported outcome.

In Table 2 it can be seen that half of the indications that were granted PRO labeling were based on RCTs with more than 200 patients. PRO labeling was granted to 6 of 12 (50.0%) hematological malignancies and 15 of 33 (45.5%) solid tumor indications. Notably, 3 of 4 breast cancer submissions, 5 of 7 NSCLC submissions, and both prostate cancer submissions received EMA PRO labeling (see Appendix S2 in Supplemental Materials found at 10.1016/j.jval.2018.09.2842).

Table 3 presents the specific PROMs referenced in the reviews of 45 indications with PRO data. The EuroQol 5-dimensional questionnaire (EQ-5D) was the most commonly used PROM in submissions (53.3%) and was referred to in 7 of the 21 (33.3%) indications with EMA PRO labeling. There were no labels based on data from EQ-5D only.

The European Organisation for Research and Treatment of Cancer (EORTC) Core 30 Items (EORTC QLQ-C30) was included in more than half of the reviews (57.8%) and was referred to in labeling of 9 of the 21 (42.9%) indications. A Functional Assessment of Cancer Therapy (FACT) measure was included in 12 (26.6%) submissions and led to labeling for 8 (38.1%) indications. Notably, FACT measures led to a proportionately greater share of EMA PRO labeling when included in a submission (8 of 12 [66.7%]) than did EORTC measures (9 of 26 [34.6%]); moreover, these 2 commonly used measures with their disease-specific modules were granted PRO labeling in two-thirds of reviews (14 of 21 [66.6%]). The Lung Cancer Symptom Scale led to PRO labeling for 2 of the 4 submissions in which it was included.

Table 2 – Characteristics of oncology indications that were granted PRO labeling by the EMA (2012-2016).

Characteristics	Indications including PRO data (n = 45), n	Indications with PRO labeling (n = 21), n (%)
Randomized, blinded, controlled study	20	10 (50.0)
<200 patients at baseline visit	2	0 (0.0)
Cancer type		
Solid tumor	33	15 (45.5)
Hematological malignancy	12	6 (50.0)

EMA, European Medicines Agency; PRO, patient-reported outcome.

Table 3 – Summary of PRO measures included in oncology drug approvals (2012-2016).

PRO measures	Submissions with PRO data (n = 45), n (%)	EMA labeling (n = 21), n (%)
EQ-5D	24 (53.3)	7 (33.3)
EORTC QLQ-C30 with EORTC disease-specific module	13 (28.9)	7 (33.3)
EORTC QLQ-C30 without EORTC disease-specific module	13 (28.9)	2 (9.5)
FACT-G with FACT disease-specific measure	10 (22.2)	7 (33.3)
FACT-G without FACT disease-specific measure	2 (4.4)	1 (4.8)
Lung Cancer Symptom Scale	4 (8.9)	2 (9.5)
PRO-CTCAE	1 (2.2)	0 (0)
The Brief Pain Inventory—Short Form	3 (6.7)	1 (4.8)
MD Anderson Symptom Inventory	2 (4.4)	0 (0)
FKSI	2 (4.4)	1 (4.8)
Other non–cancer-specific measures	4 (8.9)*	1 (4.8)†

EMA, European Medicines Agency; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30 Items; EQ-5D, EuroQol 5-dimensional questionnaire; FACT-G, Functional Assessment of Cancer Therapy—General; FKSI, Functional Assessment of Cancer Therapy-Kidney Symptom Index; PRO-CTCAE, Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PRO, patient-reported outcome; PROM, patient-reported outcome measure; SF-36, short form 36 health survey.

* Diarrhea Assessment Scale, SF-36, Health Change Questionnaire, analgesic use.

† Symptom assessment, PROM not specified.

Critical comments in DAPs and EPARs give insight into the lack of potential labeling based on weaknesses of the PRO data submitted for review (see Table 4 and also Appendices S3 and S4 in Supplemental Materials found at 10.1016/j.jval.2018.09.2842). EMA reviewers' comments most commonly related to lack of treatment benefit demonstrated by PRO data (n = 17). FDA reviewers' comments most commonly related to study designs that compromised the interpretation of PRO data (n = 9). The FDA was mostly critical of the study designs used or the validity of the PROMs (13 of 23 [56.5%]), whereas EMA reviewers had no comments related to either of these study aspects. PRO results were not reported to the EMA for 6 (13.3%) submissions mentioning PROs.

Table 5 presents the concepts reported in EMA PRO labeling. Symptoms were referenced in 16 (76.2%) labels, although specific symptoms were not mentioned in 6 (28.6%) (eg, "Improvement in symptoms and prolonged TTD [time to deterioration] of symptoms"; afatinib, NSCLC). Broad concepts such as HRQOL, QOL, or global health status were mentioned in the labeling for 13 (61.9%) indications, with 5 (23.8%) including only such an outcome (eg, "Improved global health status"; carfilzomib, multiple myeloma). In Table 5, it can also be seen that function-related domains such as emotional functioning (from EORTC QLQ-C30) or physical well-being (from FACT-General) were rarely mentioned in EMA labeling.

Table 6 presents FDA reviewers' comments for 7 reviews that resulted in EMA PRO labeling. In 4 of the 7 reviews (cobimetinib, obinutuzumab, olaparib, and radium RA 223 dichloride), the FDA did not acknowledge the lack of difference in PROs between treatment, whereas the EMA labeling noted "no statistical significant differences were observed between olaparib and placebo in patient-reported symptoms or HRQOL."

Table 4 – Critical regulatory comments from submissions with PRO assessments (n = 45).

Critical comments	EMA, n	FDA, n
No statistical or clinical difference	17	6
Excessive missing data	3	4
Study design*	0	9
Invalid PRO measure	0	4
Inappropriate comparator	1	0
Worsening in PROs	1	0
Total number of comments	22	23

Note. PRO results were not reported to the EMA for 6 (13.3%) of the submissions using PRO measures.

EMA, European Medicines Agency; FDA, Food and Drug Administration; PRO, patient-reported outcome.

* Specific study design issues noted were open-label design, single-arm design, insufficient sample size, and problems with the PRO assessment schedule related to the timing of treatment administration.

Discussion

Despite evolving regulations and grassroot pressures to capture and amplify the patient voice in drug development,[14–16] little change has been demonstrated, as revealed in this analysis of FDA and EMA labeling based on PRO endpoints in oncology clinical trials. This analysis, as a previous review confirmed,[11] demonstrates that the FDA and the EMA use different evidentiary standards to assess submitted PRO data. During this time period, the EMA granted PRO labeling to one-third (32.8%) of all oncology reviews and approximately half (21 of 45 [46.7%]) of all oncology reviews with PRO data. The FDA did not grant any PRO labeling because of its emphasis on evidence from controlled trials, with few missing values, and on easily measurable endpoints reflecting the direct impact of the disease and the treatment.[4,17,18]

FDA and EMA: Areas of Misalignment

This review highlights 4 major areas of misalignment between the agencies, as summarized herein.

Study design

Although both agencies approve oncology drugs on the basis of single-arm studies, the FDA requires adequate and well-controlled studies to assess treatment benefit in PROs.[19,20] Among the indications reviewed, the FDA cited open-label study design as a concern, whereas the EMA granted PRO labeling based on open-label studies to approximately 50% of the indications reviewed. The presence of bias, mainly because of placebo effect from open-label studies, may seriously compromise the ability to draw valid conclusions from clinical trials.[21]

Common symptoms of cancer and its treatments may be affected by placebo or nocebo effect.[22,23] Heightened expectations may also have an impact on reporting of higher order concepts such as HRQOL or QOL. For example, patients may consider new or worsening symptoms, such as vitiligo when receiving immunotherapy, to be a marker of treatment efficacy.[24,25] Even in controlled settings, patients' perception of treatment benefit may be affected when treatment is unblinded because of adverse events (AEs). For example, EMA reviewers rejected claims for

Table 5 – Concepts in PRO labeling for oncology drug approvals by the EMA (2012-2016) (n = 21).

Concepts in EMA PRO labeling	n (%)
Symptoms	
Any symptoms	16 (76.2)
Symptoms, not further specified	6 (28.6)
Lung symptoms	3 (14.3)
Kidney symptoms	1 (4.8)
Leukemia symptoms	1 (4.8)
Pain	3 (14.3)
Cough	3 (14.3)
Dyspnea	3 (14.3)
Fatigue	2 (9.5)
Appetite loss	1 (4.8)
Bone pain	1 (4.8)
Chest pain	1 (4.8)
HRQOL	
HRQOL/QOL*	13 (61.9)
HRQOL/QOL* only	5 (23.8)
Global health status (EORTC QLQ-C30)	6 (28.6)
Health status (EQ-5D)	2 (9.5)
Functioning/functional well-being	
Physical functioning (EORTC QLQ-C30)	4 (19.0)
Emotional functioning (EORTC QLQ-C30)	1 (4.8)
Role functioning (EORTC QLQ-C30)	1 (4.8)
Cognitive functioning (EORTC QLQ-C30)	1 (4.8)
Social functioning (EORTC QLQ-C30)	1 (4.8)
Physical well-being (FACT-G)	1 (4.8)
Social well-being (FACT-G)	1 (4.8)
Functional well-being (FACT-G)	1 (4.8)
Usual activities (EQ-5D)	1 (4.8)
Mood	
Anxiety (EQ-5D)	1 (4.8)
Depression (EQ-5D)	1 (4.8)

EMA, European Medicines Agency; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30 Items; EQ-5D, EuroQol 5-dimensional questionnaire; FACT-G, Functional Assessment of Cancer Therapy—General; HRQOL, health-related quality of life; PRO, patient-reported outcome; QOL, quality of life.

* Includes all broad concepts such as HRQOL, QOL, health status, and global health status.

improved global health status in the review of palbociclib for the treatment of advanced breast cancer, noting that the unblinding due to the effects of palbociclib (on bone marrow) may potentially have an impact on "hopes with regard to the benefit of the experimental compound" (see Appendix S4 in Supplemental Materials).

Concepts assessed

Among the reviewed indications with EMA PRO labeling, symptoms were mentioned for 16 (76.2%) and broader concepts (eg, HRQOL) for 13 (61.9%). PRO labeling was granted by the EMA for concepts such as HRQOL, without reference to the impact of treatment on patients' experiences of symptoms or functioning, for 5 (23.8%) treatments.

It is widely accepted that HRQOL is an important aspect of cancer treatment.[26] There is, however, no uniformly accepted definition of HRQOL, QOL, or overall health status—concepts often seen in EMA labeling. Such concepts can also be affected by many factors, including age, comorbidities, and cultural norms, that may distort the impact of treatment.[27–31] In addition, the FDA does not consider HRQOL as a well-defined and reliable concept for the purpose of product labeling.[32]

Measures used for assessment

As confirmed by this review, PRO assessments in oncology studies largely rely on the EORTC and FACT questionnaires. The EQ-5D, a generic HRQOL measure used in economic evaluations, appeared in more than half of the EMA-reviewed submissions and was cited in 7 labeling claims (although none referred to EQ-5D alone). This review dispels a popular belief that the EMA prefers data based on EORTC modules and that the FDA prefers data based on FACT measures.[33] This review found that FACT measures, although included less often than EORTC measures in submissions, led to a greater proportion of PRO labeling by the EMA.

Use of EORTC and FACT measures in oncology trials irrespective of disease stage or therapies may be problematic for several reasons.[18,34] Some items may be irrelevant; for example, inclusion of items related to sexual desire and sexual activities, as in the EORTC QLQ-EN24, a commonly used PROM to assess HRQOL in endometrial cancer trials, may not be applicable in all settings.[35] Conversely, commonly used measures may not be sufficiently precise to capture patients' experiences with a particular therapeutic strategy in a meaningful way. For instance, a recent FDA-authored publication evaluating 18 studies of 5 immunotherapy agents that included PRO data (most commonly with the EQ-5D or the EORTC QLQ-C30) concluded that immune-related AEs (eg, fatigue, diarrhea, cough, shortness of breath, musculoskeletal pain, rash, pruritis, and fever) were not consistently assessed.[36] In addition, a clinically meaningful difference established years ago may not be appropriate for contemporary clinical trials.[37] The lack of sensitivity of PROMs measuring broad concepts such as HRQOL may lead to erroneous conclusions.[3,18,20]

Moreover, summary scores from these questionnaires, because of the equal weights given to individual items in PROMs in oncology, may not be meaningful because there is a possibility for dilution of important symptoms by irrelevant symptoms.[2,38] For example, in the coBRIM study comparing vemurafenib plus cobimetinib versus vemurafenib plus placebo in patients with advanced melanoma, HRQOL as assessed by the EORTC QLQ-C30 was reported to be similar between the 2 study groups. Nevertheless, the EORTC QLQ-C30 did not capture the impact of rash, alopecia, photosensitivity, and serious retinopathy, which differed markedly between treatment groups.[39]

In addition to cancer-specific symptoms, the FDA recommends assessment of physical functioning in oncology studies because it is a core concept in the evaluation of treatment impact.[18] Nevertheless, physical functioning items in the EORTC QLQ-C30 may not be applicable in all settings (eg, for frail older adults), and the validity of this domain itself may be questionable.[40] A PROMIS Physical Functioning short form may be a better alternative to physical functioning assessed by the EORTC QLQ-C30.[40] The physical well-being domain of the FACT-General does not address the core attributes of physical functioning.[40]

The limitations described here suggest that the PROMs currently used in oncology studies may be outdated and unsuitable for contemporary oncology clinical trials.

Missing data

Criticism of missing values affecting the analysis and the interpretation of PRO findings was a common theme for both agencies. Although missing PRO values are common in cancer studies, the amount and nature of missing data should be considered in the analysis and interpretation of results. A recent review of 33 RCTs showed that PRO data often contain a considerable quantity of missing PRO data, and some analyses did not consider the informative nature of the missing data in the interpretation of the

Table 6 – Comments by the FDA alongside EMA SmPC language related to PRO endpoints for oncology drug approvals (2012-2016).

Drug name	Cancer type	Comments by the FDA reviewers*	PRO language in EMA SmPC
Cobimetinib	Melanoma	No statistical or clinical difference	Changes in symptoms, functioning, and QOL were similar between the 2 treatment arms with no clinically meaningful change
Obinutuzumab	Chronic lymphocytic leukemia	No statistical or clinical difference	No substantial difference in any subscales assessing QOL during follow-up Fatigue assessments showed no statistically significant difference, suggesting that the addition of obinutuzumab to a chlorambucil regimen does not increase fatigue
Olaparib	Chronic lymphocytic leukemia	No statistical or clinical difference Excessive missing values	No statistically significant differences were observed between olaparib and placebo in patient-reported symptoms or HRQOL
Palbociclib	Breast cancer	Open-label study design Invalid PRO measures	Significantly prolonged TTD in pain compared with placebo
Pertuzumab	Breast cancer	Open-label study design Invalid PRO measures	No statistically significant differences were found between the 2 treatment groups in HRQOL
Radium Ra 223 dichloride	Prostate cancer	No statistical or clinical difference	Both groups had declining QOL, but QOL declined more slowly in treatment group vs placebo; difference did not reach the threshold of minimally important difference Positive effect of treatment on bone pain as shown by longer time to external beam radiation therapy for pain relief and fewer patients reporting bone pain as an AE
Sonidegib	Basal cell carcinoma	Open-label study design Excessive missing data	Most patients experienced maintenance or improvement in symptoms, functioning, and health status TTD in PRO scales mirrored the estimated PFS

AE, adverse event; EMA, European Medicines Agency; FDA, Food and Drug Administration; HRQOL, health-related quality of life; PFS, progression-free survival; PRO, patient-reported outcome; QOL, quality of life; SmPC, summary of product characteristics; TTD, time to deterioration.
* Abbreviated comments.

results or the potential for adjustment with appropriate statistical methods.[41] Although PRO data after disease progression is reached can be useful to assess the impact of treatments over time, a recent review of ovarian cancer clinical trials showed that none of the 35 phase 3 studies reviewed reported PRO findings after disease progression.[42]

Missing values, attributable to death, dropouts, and patients being too ill to provide data, may be addressed by performing sensitivity analyses. Nevertheless, missing values caused by administrative errors, which generally arise when the PRO assessments are for exploratory endpoints (which may lack priority during study planning and conduct), may be difficult to address in analysis.

In addition to these 4 areas of misalignments, 2 additional topics emerged for further discussion.

Assessment schedules

Findings from this review suggest that inappropriate assessment schedules can obscure key events pertinent to the analysis. In most oncology trials, patients complete PROMs at baseline and on the first day of each treatment cycle. Duration between cycles may vary from the treatment protocol if patients are not well enough to receive the next cycle; for example, dosing may be withheld for up to 4 weeks even for grade 2 skin toxicity for patients receiving immunotherapy.[43] Thus, the impact of treatment may be underestimated if PROs are assessed only when patients are well enough to receive the next treatment cycle, and not soon after an event that may have an impact on their feelings or function. For example, 19% of patients reported grade 2 nausea just before receiving high-dose cisplatin in the BTOG2 study. Nevertheless, the reporting of nausea, when captured daily for the first 5 days,

was much higher in a study of olanzapine for chemotherapy-induced nausea and vomiting.[44,45]

PRO data in context

Although this review focuses on PROs in labeling, it is important to recognize that overall assessment of treatment benefit is possible only if PRO data can be presented in the context of efficacy and safety evaluation.[1] Language used in EMA labeling often referred to a lack of treatment difference as a favorable outcome, but without the context of safety and efficacy of the experimental treatment. This trend was, however, not mirrored by the FDA. For example, in the FDA review of olaparib for the treatment of chronic lymphocytic leukemia, comments on the PRO data center on the lack of statistical and clinical significance between treatment groups. In contrast, the EMA appears to recognize the concept of no decrement as patient-relevant, with labeling that states "No statistical significant differences were observed between olaparib and placebo in patient-reported symptoms or HRQOL."

Use of inappropriate PROMs, assessment of broad concepts, and suboptimal assessment schedules in studies that are not powered to detect differences in PRO endpoints may result in higher likelihood of false-negatives. Such null PRO findings may not align with patients' true experiences of treatment in clinical trials. For example, in the coBRIM study, there were significantly higher incidences of grade 1/2 central serious retinopathy, gastrointestinal events, and photosensitivity among patients in the combination arm compared with patients in the placebo arm. The EMA PRO labeling based on this study ("Changes in symptoms, functioning, and QOL were similar between the 2 treatment arms with no clinically meaningful change") is not persuasive.[39,46]

Recent advances have led to a paradigm shift in the treatment of cancer. Novel therapies, including immunotherapy, targeted therapies, antibodies, and small molecules targeting various pathways, have dramatically different side-effect profiles from standard chemotherapy. With emerging cancer agents, there is also a greater likelihood of combination regimens, potentially resulting in new and as-yet-unknown AE profiles. In light of this evolving landscape, assessment of PRO data in oncology studies cannot rely on the cookie-cutter approach of the past.

Although a 2016 EMA guidance recommends the inclusion of symptoms and assessment of HRQOL in clinical trials, a recent FDA-authored article recommends the assessment of patient-reported symptomatic AEs, physical functioning, and disease-specific symptom data to support the safety and efficacy of cancer treatments.[3,18,36] Disease-specific symptoms must be applicable to the stage of the disease—symptomatic AEs may be assessed using items from the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events, for example—and patient-reported physical functioning impacts must be clinically meaningful in cancer settings.[18,38] This recent view from the FDA, coupled with the limitations of currently available PROMs described earlier, shows that the currently used PROMs in oncology clinical trials may be outdated and unsuitable for contemporary oncology clinical trials.

Although the FDA does not require PRO data after clinical progression is identified, the EMA in its recent guidance has emphasized the need for postprogression PRO data to enable decision making about the long-term impact of new cancer treatments.[3,47] Furthermore, although the focus of this review was to highlight the key differences between the FDA and the EMA to inform sponsors' formulation of PRO measurement strategies to achieve PRO labeling, sponsors should also be mindful of aspects of PROs that may influence stakeholders other than regulators. For example, payers consider PRO data after clinical progression to be important for decision making.[7]

Although this review did not identify any PRO labeling by the FDA between 2012 and 2016, the FDA granted PRO labeling in 2017 for imbruvica (chronic graft vs host disease), ceritinib (NSCLC), and crizotinib (NSCLC). Although crizotinib was approved for the treatment of NSCLC in 2011, this revised labeling is based on further evidence of symptomatic treatment benefit. It is notable that, for all 3 treatments, the PRO labeling was based on open-label studies (see Appendix S5 in Supplemental Materials found at 10.1016/j.jval.2018.09.2842). These recent labels suggest that the FDA may be pursuing a more pragmatic approach in evaluating PRO data from single-arm oncology studies than it has previously.

Conclusions

This review of PRO labeling of oncology drugs approved by the FDA and the EMA between 2012 and 2016 shows that different evidentiary standards are used by the agencies to assess PRO data from oncology studies. Although no labeling related to PRO endpoints from the FDA was identified between 2012 and 2016, the EMA during this period granted labeling to about a third (32.8%) of all oncology reviews and about half (46.7%) of all oncology reviews that had PRO data. EMA PRO labeling was frequently based on open-label studies, on broad concepts such as HRQOL, and based on PROMs that may be outdated and unsuitable for contemporary oncology clinical trials. The FDA relies on the evidence based on well-defined and reliable PRO assessments from adequate and well-controlled studies to be convinced of treatment benefit. Nevertheless, PRO labeling was granted in 2017 (outside the review period for this study) for 3 treatments on the basis of open-label study results, potentially suggesting that the FDA is adopting a more pragmatic and flexible approach to assessing PRO data.

This review has shown that the FDA and the EMA do not conceptualize treatment benefit in an entirely consistent manner. As such, the key differences between the agencies should be considered and may be useful to guide internal PRO measurement strategies as study sponsors prepare to seek and support requests for labeling. If sponsors aim to seek labeling from both agencies, considerations should include, at a minimum, using PROMs that assess patient-focused proximal concepts of core disease symptoms, treatment-related symptoms, and impacts on functioning. Assessment schedules must be optimized to capture pertinent data and appropriate mechanisms should be in place to minimize missing data. The approaches described earlier provide a higher likelihood of PRO labeling from both agencies. The addition of HRQOL assessments may also be useful for EMA reviews.

Acknowledgment

Medical writing services were provided by Kate Lothman of RTI Health Solutions and were funded by Novartis Pharmaceuticals Corporation.

Source of financial support: This study was performed under a research contract between Novartis Pharmaceuticals Corporation and RTI Health Solutions and was funded by Novartis Pharmaceuticals Corporation.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2018.09.2842.

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