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Reasons for Rejection of Patient-Reported Outcome Label Claims: A Compilation Based on a Review of Patient-Reported Outcome Use among New Molecular Entities and Biologic License Applications, 2006–2010

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A B S T R A C T

Objectives: Previous analyses of patient-reported outcome (PRO) label claims concentrated only on successful label claims. The goal of this research was to explore the reasons why PRO label claims were denied and to compile regulatory feedback regarding the use of PROs in clinical trials. **Methods:** By using the Food and Drug Administration's Drug Approval Report Web page, all new molecular entities and biologic license applications approved between January 2006 and December 2010 were identified. For identified drug products, medical review sections from publicly available drug approval packages were reviewed to identify PRO end-point status and any Study Endpoints and Label Development team comments. **Results:** Of the 116 new molecular entities and biologic license applications with accompanying drug approval packages identified and reviewed, 44.8% of the products included PROs as part of the pivotal studies; however, only 24.1% received PRO label claims. Primary reasons for denial included issues of fit for purpose, issues of study design, data quality or interpretation, statistical issues, administrative issues, and lack of demonstrated treatment benefit. **Conclusions:** Based on drug approval packages, nearly half (45%) of new molecular entitity/biologic license application products in the years 2006 to 2010 included PROs in the clinical trials supporting their approval, yet this rate is not reflected by claims granted. Understanding the nature of PRO claims granted under the current regulatory guidance is important. In addition, a clear understanding of denied claims yields valuable insight into where sponsors may improve implementation of PROs in clinical trials and submission of PRO evidence to increase the likelihood of obtaining PRO label claims.

Keywords: label claims, patient-reported outcomes, rejection.

Introduction

Patient-reported outcomes (PROs) allow the voice of the patient to emerge within the context of a clinical trial or observational study and provide valuable insight into the patient experience beyond that which can be measured by clinical indices alone. In some diseases or conditions of interest, a PRO may be the sole source of data from which drug efficacy can be measured, whereas in others it may provide supplementary information on how the disease and its treatment impact patients' functioning and well-being.

PRO use is particularly common for products developed to treat chronic, disabling conditions where the intention is not necessarily to cure but to ameliorate symptoms, facilitate functioning, or improve quality of life. PROs are the primary end points in clinical trials evaluating drug products for disease areas such as irritable bowel syndrome, migraine, and pain. PROs provide key supportive data in many other disease areas, such as insomnia, asthma, and psychiatric disorders. In oncology, PROs are commonly used to assess both treatment benefits and toxicity to fully evaluate the impact of treatment on health-related quality of life (HRQOL). PROs can also be used in clinical trials to assess treatment satisfaction, compliance, and caregiver burden [1].

Sponsors (i.e., pharmaceutical or biotechnology companies developing a new product) may choose to include a PRO end point to support a label claim, to provide data supporting the primary endpoint, or as a source of data for communication and market-access strategies. Regardless of the reason for a PRO's inclusion in a clinical trial, it is unique in that it captures the viewpoint of the patient without input from others.

Willke and colleagues [2] conducted a review of drug labels to understand the use of PROs compared with other trial end points. That research identified the inclusion of PROs as efficacy end points in approximately 30% of all labels reviewed between 1997 and 2002. In 2006, the Food and Drug Administration (FDA) released a draft guidance for use of PROs in clinical trials, followed by a final guidance in 2009, *Guidance for Industry: Patient Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* [3], providing a blueprint for the use of PROs in clinical trials. The guidance documents were intended to influence the appropriate development, validation, and use of PRO measures to facilitate a positive regulatory review in support of label claims.

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The Study Endpoints and Labeling Development (SEALD) team coauthored the PRO guidance in collaboration with other colleagues from the FDA Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, and the Center for Devices and Radiological Health. SEALD acts as an advisory board to the 17 Office of New Drugs reviewing divisions within the FDA and provides guidance pertaining to the development and validation of study end points, clinical study protocol design, analysis, and interpretation of study end points to support drug development, labeling, and promotion.

According to the guidance, a claim is defined as a statement of treatment benefit. Furthermore, a claim can appear in any section of a medical product's FDA-approved labeling or in advertising and promotional labeling of prescription drugs and devices.

Since its release to the public, much interest has been paid to the impact of this guidance document on the use of PROs and the acceptance of PRO-based label claims [1,4,5,6]. Gnanasakathy and colleagues [1] built on the work previously conducted by Willke and colleagues [2] and reported the frequency of PROs in recently approved drug labels. Specifically, these authors found that PRO claims were granted for approximately 24% of all labels reviewed between January 2006 and December 2010.

To date, however, no formal review has been undertaken to examine PRO measures included in drug approval packages (DAPs) but not appearing in approved labeling. Hence, there is no compilation of feedback on the use of these PROs either by industry or by regulatory authorities. Examination of these submissions may provide an insight into the appropriate utilization of PROs by sponsors in clinical studies and additional guidance for preparing evidence dossiers. This information may also provide regulators with an overview to assess consistency in response across reviewing divisions. Therefore, the purpose of this research was to review the criticisms targeted at PRO end points for all new molecular entities (NMEs) and biological license applications (BLAs) from 2006 through 2010 that utilized PROs in their clinical trials supporting their approval but did not receive labeling claims for these measures.

Methods

Data collection methods for this research are fully described elsewhere [1]. Briefly, the FDA Drug Approval Reports Web page was used to review new drugs that were approved in the United States from January 2006 through December 2010, including only those products classified by the Center for Drug Evaluation and Research as NMEs or BLAs. Any product containing substances previously marketed with a different brand name or set of indications, as a different dosage form or strength, or as a combination product of previously marketed entities was excluded.

Once products were identified, DAPs and approved product labels were reviewed, and information was retrieved from the medical review, summary review, cross-discipline team leader review, and other review sections from the DAP as well as from the Indication and Clinical Studies section of the approved product label. The DAPs were located on the FDA Web site Drugs@FDA (www.accessdata.fda.gov). The following information was collected, as publicly available, for each US drug product identified:

- Brand name
- Generic name
- Date of approval
- Applicant
- Label indication
- Utilization of PROs
- PROs mentioned in the DAP but not appearing in the label
- Evidence of claims sought but not granted
- Significance of the PRO results
- Division reviewer or SEALD reviewer feedback

Statistical analysis consisted of frequencies and cross-tabulations of measured characteristics. Calculations were performed by using Microsoft Excel 2007. For analysis purposes, if a PRO appeared in the DAP, it was considered to be an attempt to seek a PRO label claim, despite sponsor intent, unless specifically noted otherwise.

Results

A total of 156 new drugs were approved between January 2006 and December 2010. Of these, 33 were generic products and were excluded from our analysis, as were 4 new products that were approved but had no data available on the FDA Web site at the time of review and three others were registered under multiple names so were considered single entities. Therefore, this review includes 116 products.

Of the 116 products reviewed, 52 (44.8%) included PROs as part of the pivotal studies; however, only 28 of the 116 (24.1%) received at least one PRO claim [1]. A total of 26 products were identified as having been denied a PRO label claim. For the purposes of analysis, this included any product that had a PRO included in the DAP, regardless of the sponsor's intention, because it was not always possible to determine whether a claim had been sought or whether PRO data had been collected for other reasons. A subset of products (n = 6) received some or partial PRO labeling while other requested PRO claims were denied within the same submission. These six products were Azilect, Chantix, Letairis, Ampyra, Bepreve, and Egrifta. Table 1 provides a listing of all 26 products described in this review, arranged by the FDA division that granted drug approval.

The filings for these 26 products included a wide range of PRO measures, for example, symptom diaries, event logs, measures of functioning and disability, symptom assessments (e.g., fatigue and pain), disease-specific measures of HRQOL, generic assessments of HRQOL, and utility measures. Table 2 provides an alphabetical listing of measures specified in the DAPs but not appearing in the approved labeling.

To determine the rationale behind decisions to reject PRO claims from the label, data specific to PROs mentioned in the DAP

Table 1 – Products with at least one claim denied by FDA reviewing division.

FDA reviewing division	Products reviewed
Anesthesia, analgesia, and rheumatology products	Chantix, Ilaris
Antiinfective and ophthalmology products	Lucentis, Bepreve
Biologic oncology:	Vectibix
Cardiovascular and renal products	Letairis, Samsca
Dermatology and dental products	Stelara
Drug oncology	Dacogen, Zolinza, Torisel, Ixempra kit, Treanda, Istodax, Jevtana
Gastroenterology products	Vpriv, Elaprase, Relistor
Medical imaging and hematology products	Promacta
Metabolism and endocrinology	Januvia, Egrifta, Somatuline
Neurology products	Azilect, Ampyra
Psychiatry	Invega, Pristiq

FDA, Food and Drug Administration.

Table 2 – Alphabetical listing of measures with claims denied.

Measure
Body Image Impact Module
Borg's Dyspnea Index
Caregiver Outcomes Assessment
Child Health Questionnaire–Child Form
Child Health Questionnaire, Parent Completed 50-Item Scale
Childhood Health Assessment Questionnaire
Chronic Idiopathic Thrombocytopenic Purpura Symptoms
Constipation Distress
Dermatology Life Quality Index
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Chronic Lymphocytic Leukemia 25
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–C30
EQ-5D
Functional Assessment of Chronic Illness Therapy Fatigue Scale
Functional Assessment of Cancer Therapy–Breast Symptom Index
Health Assessment Questionnaire–Disability Index
Hospital Anxiety and Depression Scale
Hunter Syndrome–Functional Outcomes for Clinical Understanding Scale
Hyponatremia Disease Specific Survey
Itch VAS
McGill-Melzack Present Pain Intensity scale
Modified Cigarette Evaluation Questionnaire
Multiple Sclerosis Walking Scale–12
Opioid Withdrawal Symptoms (modified Himmelsbach)
Pain Numerical Rating Scale (0–10 scale)
Parkinson's Disease Quality of Life Scale
Patient Impression of Change in Bowel Status
Patient Reports of Bowel Consistency and Difficulty
Pruritis relief VAS
Quality of Life assessments by proxy
Short form-36
SF-36 Physical Functioning Scale
Sleep VAS
Subject Global Impression of Change
Symptoms and Quality of Life in Schizophrenia
Visual Function Questionnaire–25
Work Limitations Questionnaire

EQ-5D, EuroQol five-dimensional questionnaire; SF-36, Short Form 36 Health Survey; VAS, visual analogue scale.

(but not appearing in the labeling) were extracted for further examination. The following coding convention was created and applied by a single rater to categorize the FDA reviewer's (division or SEALD) noted concerns regarding the PRO measure:

1. Fit for Purpose: lack of evidence of content validity (e.g., lack of link between concept and claim, insufficient documentation of validation in population of interest, and full constellation of symptoms not measured), recall period, or lack of evidence of proper translation or cross-cultural validation;
2. Study Design, Data Quality, or Interpretation of Results: issues of potential bias (open-label design, etc.), clinical meaningfulness, missing data, attrition rates, or improper completion;
3. Statistical Analysis: no adjustment for multiplicity or inappropriate or missing statistical analysis plan;
4. Administration Considerations: lack of documentation for training or instruction in use of measure or copy of measure not provided to the FDA; and
5. No Treatment Benefit: not supportive of treatment benefit, improvement in certain symptoms but worsening in others, lack of statistical significance, or FDA disagreed with sponsor.

Examination of the DAP for each product provided differing levels of detail regarding why a measure was not included in the approved labeling. Reasons for this included the proprietary nature of labeling discussions between sponsor and agency as well as differences between products receiving a review by SEALD. Detailed feedback for each submission, by product, is provided in the appendix in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2012.01.010.

"Fit for purpose" issues were the primary reasons for the denial of PRO labeling claims, accounting for more than 38% of regulatory feedback. A PRO measure that has been recognized by the FDA as appropriate to support claims in a specific context (i.e., the measure meets the qualifications for supporting claims outlined in the PRO guidance, specific to a study population and protocol and to the claim sought/hypothesis tested) is described as "fit for purpose" by the FDA.

As cited in the DAPs for 14 individual products, the FDA specifically questioned the content validity and/or validity of instruments in general, rationale in support of recall periods, and evidence of appropriateness of translations for use in multinational studies. This feedback was consistent, especially in regard to validity. Of the 14 products that fell within this category, 8 were noted to have potential issues with the validity of the PRO measure for the intended purpose. A SEALD review of the use of the SF-12 Health Survey (SF-12) and the Hyponatremia Disease Specific Survey as secondary end points in pivotal studies of Samsca provides an illustrative example. In these studies, the sponsor included the SF-12 and justified the use of the tool by pointing out that hypo-

natremia presents in a broad range of disease areas and that both the physical and mental component scores of the SF-12 were used. Reviewer feedback, however, noted: "The SF-12 was developed as a generic health status instrument for the general population and not as a symptom assessment tool or HRQoL tool in patients with hyponatremia. As such the instrument is not effective as an assessment of treatment benefit." Regarding the Hyponatremia Disease Specific Survey, the SEALD reviewer explained that "the information submitted by the sponsor concerning the psychometric properties of the HDS do not address the content validity and therefore do not support the use of the instrument." Similar feedback was provided in the Torisel review where FDA reviewers noted that the "applicant did not provide evidence of validation of the EQ-5D [EuroQol five-dimensional questionnaire] in the RCC [renal cell carcinoma] population. It was used in a setting for which it was not designed, and more frequently than intended."

Issues of study design, data quality, or interpretation of results was the second largest identified category and accounted for approximately 27% of the feedback for denied claims. In this category, reviewers questioned the clinical meaningfulness of patient responses, noted issues of bias introduced by open-label study designs, and commented on missing data/dropout rates and other indicators of data quality. These concerns were identified for nine individual products. Regulatory feedback on Zolinza and Torisel was illustrative of these points. The reviewer for the Zolinza submission stated, "PROs cannot be reliably measured in open label studies . . . a 3-point improvement was considered clinically significant, but the review does not state whether the proportion of patients obtaining this level of relief was clinically meaningful." Missing data and potential for bias were noted in the Torisel review. Neither Zolinza nor Torisel was granted PRO-related claims.

Statistical considerations that generated regulatory criticisms included lack of or inappropriate statistical analysis plans such as no planned adjustments for multiplicity. This issue is clearly described in the regulatory review of Azilect. The reviewer noted, "I cannot draw serious conclusions about the efficacy of these [PRO] end points because of issues of multiplicity whereby the sponsor did not make statistically appropriate adjustments for these multiple comparisons . . ." despite significant findings on the Parkinson's Disease Quality of Life scale in favor of Azilect. Although it is unknown how this adjustment may have impacted the result and subsequently the label claim, the expectations of the reviewing division are well documented.

In addition, administrative considerations impacted agency reviewer decision making. Concerns were noted regarding the lack of appropriate documentation describing training procedures, administration of the tool, and inadequate descriptions of measures. Examples of such concerns included the SEALD reviews of Egrifta where reviewers noted a missing user's manual, lack of description of the Caregiver's Outcome Assessment for Torisel, and confusion regarding patient instructions for using an itch visual analogue scale for Stelara.

A final category grouped agency reviewer feedback on PRO measures where discrepancies occurred between the agency and the sponsor regarding whether a measure appropriately demonstrated treatment benefit. Feedback in this category ranged from a straight-forward assessment of no demonstrated statistical difference between active treatment and placebo (e.g., Letairis and Relistor) to more detailed discussions of failure to demonstrate treatment benefit when some symptoms improved while others showed worsening (e.g., Chantix).

Figure 1 depicts the percentage of claims denied by each analytic category of reasons for rejections, and Table 3 describes regulatory feedback by product.

Case studies of each drug submission are detailed in the Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2012.01.010. Differing levels of information were provided in each DAP; likewise, review formats were somewhat inconsistent. Therefore, the level of detail extracted from the submissions varies by product. For the purposes of this review, it was assumed that the sponsor sought a claim based on the PRO(s) referenced in the DAP unless otherwise specified.

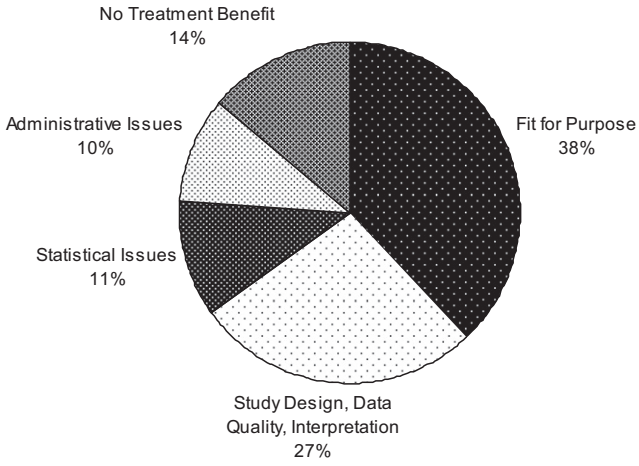

Fig. 1 – PRO label claim denials.

Discussion

To our knowledge, this is the first comprehensive compilation of FDA feedback on the use of PROs in clinical trials in support of label claims since the release of the draft FDA guidance in 2006. Reasons for rejection of claims varied, but the majority focused on whether a measure was fit for the purpose for which it was used and issues of study design, data quality, or interpretation of PRO results. Most denials and critical discussions were consistent with the spirit of the PRO guidance. The final PRO guidance places strong emphasis on interpreting PRO data and on developing PRO measures. Instrument validity, in particular content validity, is discussed in detail in the PRO guidance. The guidance notes that other measurement properties will not be considered until evidence of this property has been appropriately determined. Reviewers emphasized this in their criticisms in a number of product reviews, including several that utilized generic measures.

Concerns with study design and interpretation of PRO data persist. For example, reference to minimal important difference was removed from the final guidance and replaced with a discussion of individual responses to treatment or responder definitions. This change, however, does not completely address the issue of demonstrating a clinically relevant change. Clinical trial considerations are addressed in the guidance, but these issues do not always have a solution that is practical for all clinical trial conditions (e.g., single-arm study design in oncology studies).

Statistical considerations also remain paramount to obtaining PRO claims. Responses to submissions clearly demonstrate that PROs must be treated with the same rigor as other clinical end points. Prospective, adequate statistical analysis plans must be developed to address issues such as multiplicity and methods for dealing with missing data.

Importantly, as this review period is inclusive of the release of both the draft and final guidance documents, the level and type of documented feedback provided to the public by the FDA is inconsistent. First, the level of review varied across submissions. Not all submissions received a review from SEALD, because this group acts on a consultancy basis. Submissions with a SEALD review (e.g., Stelara, Chantix, Samsca, and Egrifta) received very detailed

Table 3 – Category of denial by product.

Product	Fit purpose	Study design, data quality, interpretation	Statistical issues	Administrative issues	No treatment benefit
Azilect			X		
Chantix	X				X
Dacogen*					
Luncentis	X				
Elaprase					X
Vectibix		XX	XX		
Zolinza		XX			
Januvia					X
Torisel	X	XXXX	X	X	
Letairis	X		X		X
Somatuline	X				X
Ixempra		XX			X
Relistor	XX				X
Samsca	XX				
Ilaris		X	X		
Stelara	XXXXXX			X	
Bepreve	X			X	X
Isodax	XX	XX		XXX	
Ampyra	X	X			X
Jevtana	XXX	XXXX		X	X
Egrifta	XXXX				
Invega			X		
Pristiq	X		X		
Treanda*					
Promacta*					
Vpriv		X			

* No information provided in the drug approval package. X, analytical category for denied claim.

comments and recommendations. Details on other submissions were much more difficult to discern and were found embedded within the medical review or cross-team leader review. Comments from the SEALD review of Egrifta illustrated the difficulties facing both industry and regulatory bodies in the review of studies utilizing PROs that were planned and executed prior to the release of the draft guidance. Specifically, the SEALD reviewer expressed reservations with respect to the content validity of the Body Image Impact Module, which does not meet the new standards articulated in the guidance; the reviewer stated that the instrument should not be recommended by FDA for future drug development, yet a claim was still granted. It is worth noting that the PROs evaluated in the Egrifta clinical trials had been incorporated with prior input from the FDA in advance of the final guidance. As experience with the guidance matures and both industry and regulatory bodies acclimate, such conflicts are expected to become less frequent.

Other inconsistencies in regulatory responses may be attributable to differences between reviewing divisions. For example, in some situations, a generic measure (e.g., the Short Form 36 Health Survey's physical component score) was accepted as a suitable end point by one reviewing division and rejected by another because of a lack of specificity. In addition, differences in the perceived acceptability of PRO measures to support labels claims may exist across FDA divisions. At the time of this analysis, no PRO claims have been granted by the oncology division, but PRO data for some oncology drugs (e.g., Dacogen) appear to demonstrate significant results regarding impact on HRQOL or symptoms such as fatigue and dyspnea. Although it is likely that these data were in some way confounded by the nature of the trial, sponsors would better understand the position of this division if details were provided in the reviews. Disclosing the measures used by sponsors and the reason for criticisms, if any, would greatly assist sponsors in refining their internal decision-making processes to include the right instrument to measure the right concept.

Several limitations should be noted for this review. First, for practical reasons we limited review of products to those classified as NMEs and/or BLAs. As such, products seeking approval for new indications were not included in our review. There may be instances where these submissions also have rejected PRO claims. A limitation of this analysis is that it is not clear, because of the confidential nature of labeling discussions, whether the comments by the FDA were for claims actively requested by sponsors or whether they were comments made in some other regard. PRO instruments are included in drug submissions not only for label claims but also to provide supportive data to the primary end point, to provide data requested by the FDA or the European Medicines Agency [5], for publication purposes, or to satisfy market-access needs (utility assessments). Unless actively seeking a label claim, the sponsor is unlikely to invest in new instruments to meet the standards outlined in the FDA PRO guidance. Therefore, although this analysis provides sponsors a means with which to assess and support the quality of their PRO strategies, our analysis is unlikely to be a measure of the quality of submissions targeted at PRO label claims to the FDA, because often the lack of access to a detailed response from the agency made it difficult to discern the rationale for these types of decisions.

Conclusions

The use of PROs as clinical trial end points continues to be widespread, with more than 45% of all NME or BLA submissions between 2006 and 2010 utilizing these instruments in some capacity [1]. Despite the commonality of PRO inclusion, rejection rates for PRO claims remain high. PRO label claims are denied for various reasons, some of which are addressed by the FDA in its PRO guidance. Although the learnings from this research are limited by the amount of information publicly available, review of denied claims

may provide an insight into how sponsors could improve the implementation of PROs in clinical trials and the level of PRO evidence submitted to increase the likelihood of obtaining PRO label claims. Such continuous learning and combined efforts between sponsors and regulatory bodies will allow the patient's voice to be heard in the drug development process.

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Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2012.01.010 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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