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Patient-Reported Outcomes

A Review of Patient-Reported Outcome Labels in the United States: 2006 to 2010

Ari Gnanasakthy, MSc[1,], Margaret Mordin, MS[2], Marci Clark, PharmD[2], Carla DeMuro, MS[2], Sheri Fehnel, PhD[2], Catherine Copley-Merriman, MS[2]*

[1]*Novartis Pharmaceuticals Corporation, East Hannover, NJ, USA;* [2]*RTI Health Solutions, Durham, NC, USA*

A B S T R A C T

Objective: In 2004, Willke and colleagues reviewed the efficacy endpoints reported in the labels of new drugs approved in the United States from 1997 through 2002 to evaluate the use of patient-reported outcome (PRO) endpoints. Of the labels reviewed, 30% included PROs. Our study aimed to build on this work by describing the current state of PRO label claims granted for new molecular entities (and biologic license applications since February 2006 after the release of the US Food and Drug Administration (FDA) draft PRO guidance. **Methods:** All new molecular entities and biologic license applications approved by the FDA from January 2006 through December 2010 were identified by using the Web page of the FDA Drug Approval Reports. For all identified products, drug approval packages and approved product labels were reviewed to identify PRO endpoint status and to determine the number and type of PRO claims. **Results:** Of the 116 products identified, 28 (24%) were granted PRO claims; 24 (86%) were for symptoms, and, of these, 9 (38%) claims were pain related. Of the 28 products with PRO claims, a PRO was a primary endpoint for 20 (71%), all symptom related. **Conclusions:** The FDA continues to approve PRO claims, with 24% of new molecular entities and biologic license applications being granted. Successful PRO label claims over the past 5 years have generally supported treatment benefit for symptoms specified as primary endpoints.

Keywords: drug labeling, patient-reported outcomes.

Introduction

The content of package inserts from the US Food and Drug Administration (FDA) is vital to the commercial success of a medicinal product. These package inserts, also called product labels, constitute the formal, government-approved definition of a drug's benefits and risks. Package inserts are written by (and are the property of) the manufacturer but require FDA approval; they define the boundaries of the legal promotion of a product's properties [1].

Patient-reported outcome (PRO) is an umbrella term that comprises a range of potential measurement endpoints, but it is used specifically to describe outcomes collected directly from the patient, without interpretation by clinicians or others [2,3]. 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 endpoints 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.

Increase in the use of formal questionnaires in clinical trials [4], advances in methodological rigor in measurement science during the 1980s and the 1990s [5], and the need to standardize the terminology [2] led to the guidance on PROs from the FDA, especially because it is related to drug labeling and promotion.

For drug manufacturers seeking PRO claims, the FDA's release of a draft guidance in 2006 [6] and a final guidance in 2009 [7] (*Guidance for Industry. Patient Reported Outcomes: Use in Medical Product Development to Support Labeling Claims* [PRO guidance]) was a landmark event. The PRO guidance describes the use of PROs to support potential claims in product labeling. Based on this PRO guidance document, PROs may be used to support treatment benefit claims in FDA-approved product labeling. The claims must be supported by appropriately designed investigations using PROs that have been demonstrated to measure the concept underlying the claim [3].

International societies have held workshops to debate the impact of the FDA PRO guidance, and journals have hosted special issues devoted entirely to this topic [8]. It is generally agreed that the PRO guidance has set a high standard for developing and implementing PRO measures in clinical trials for new drug products and has also provided a blueprint for sponsors who wish to obtain PRO label claims for their products [9].

A review of PRO labels granted from 1997 through 2002 [10] showed that PRO evidence was cited in the Clinical Studies section of

* *Address correspondence to:* Ari Gnanasakthy, Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936, USA.
E-mail: ari.gnanasakthy@novartis.com.

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the label for 30% of the new product approvals and 11% of the new products were approved on the basis of PROs alone. Our study aimed to build on the work by Willke et al. [10] by describing the current state of PRO label claims granted for new molecular entities (NMEs) and biologic license applications (BLAs) from 2006 through 2010.

The purpose of this study was to compile and review the PRO label claims granted over the 5 years since the release of the draft PRO guidance (2006–2010) [6]. Moreover, we were interested in understanding the types of claims granted based on PROs. We hypothesized that PRO claims would be more likely for first-order impact assessments such as symptoms, rather than for more complex concepts such as HRQOL.

Methods

Products reviewed in this analysis included new drugs approved in the United States from January 2006 through December 2010. The Web page of the FDA Drug Approval Reports was used to determine the number of products approved in the time period of interest. The report options selected were original new drug approvals (NDAs) and BLAs by month; months were selected sequentially beginning with January 2006 and ending in December 2010. The reports include a specification of the Center for Drug Evaluation Research NDA chemical classification. Our review included products classified by the Center for Drug Evaluation Research as NMEs or BLAs. Therefore, we excluded products containing substances previously marketed with a different brand name or a set of indications, as a different dosage form or strength, or as a combination product of previously marketed entities.

Once products were identified, drug approval packages (DAPs) and approved product labels were reviewed. As available, information was retrieved from the Medical Review, Summary Review, Cross-Discipline Team Leader Review, and other review sections from the DAP, as well as the Indication and Clinical Studies section of the approved product label. The DAPs were located on the FDA's Web site Drugs@FDA (www.accessdata.fda.gov). In most cases, the product label was also found on this FDA Web site under approval history. In the event the approved label was unavailable for the specified time frame, the current label was evaluated. As available, the following information was collected for each US drug product identified:

- Brand name
- Generic name
- Date of approval
- Applicant
- Label indication
- PRO claim language
- PRO measures named in label
- Reviewing division
- Medical review available (yes/no)
- Indication in DAP of Study Endpoints and Label Development (SEALD) review (yes/no) and comments
- PRO measures mentioned in the label and DAP, and endpoint status (primary, secondary, tertiary/exploratory)
- PRO results reported as statistically significant (yes/no)

PRO claim language from the Indication and Clinical Studies sections of the label was reviewed and characterized as symptoms (yes/no), functioning (yes/no), HRQOL (yes/no), patient global rating (PGR) (yes/no), or other (yes/no). A single rater applied standard definitions to the review of the labels for characterization.

Symptoms were defined as any subjective evidence of a disease, health condition, or treatment-related effect that can be noticed and known only by the patient. Functioning claims related to restriction or lack of ability to perform an activity(ies) in the manner or within the range considered normal. HRQOL claims were defined as those referencing a multidomain concept representing the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life. A PGR was defined as any assessment or evaluation of the patient's disease or condition identified as "global." These classifications are in line with the definitions provided in the final PRO guidance and the work previously reported by Caron et al. [11]. A product label may contain more than one PRO claim.

Statistical analysis consisted of frequencies and cross tabulations of measured characteristics. Calculations were performed by using Microsoft Excel 2007.

Results

A total of 156 new drugs were approved during this period. DAPs were located and reviewed for all 156 products. The DAPs for all products contained medical reviews. Some DAPs also included summary reviews or cross team leader reviews or both. Product labels were located for all the products. Of the 156 approvals, 33 were granted tentative approvals and full approval will not be granted until after patent exclusivity expires. Because these were for generic products, we excluded them from our analysis. Some drugs approved during this period were subsequently removed from the market but were nonetheless included in this analysis. Denosumab, although registered as both Prolia and Xgeva, was considered a single new drug with the same clinical studies for registration and a single BLA supporting both. Similarly, Natazia was considered a single new drug because the same clinical studies were used in the registration files and a single NDA supported it. Sabril was considered a single new drug despite two unique NDA numbers supporting the different formulations. Finally, there were four new products approved with no data available on the FDA's Web site, including a label, at the time of our data extraction and analysis and so these products were excluded from this review. Therefore, a total of 116 products were included in this review.

Of the 116 products reviewed, the largest number (n = 16) was reviewed by the Drug Oncology division, followed by Neurology Products (n = 11), Cardiovascular and Renal Products (n = 10), and Anesthesia, Analgesia, and Rheumatology Products (n = 10) divisions (Table 1). PRO claims appeared in 28 product labels (24% of the 116 products reviewed) across 11 reviewing divisions. The indications for all 28 products with PRO claims in the label are available in Appendix A in Supplemental Materials found at doi: 10.1016/j.jval.2011.11.032). Among the 28 products with PRO claims in the label, Neurology Products (n = 7; 25.0%) and Anesthesia, Analgesia, and Rheumatology Products (n = 6; 21.4%) divisions granted the most PRO label claims. Approximately two-thirds of the products reviewed by the Neurology Products; Anesthesia, Analgesia, and Rheumatology Products; and Pulmonary and Allergy Products reviewing divisions received PRO claims in the label. The following reviewing divisions did not grant any PRO label claims: Drug Oncology; Biologic Oncology; Antiviral, Dermatology, and Dental Products; and Special Pathogen and Transplant Products.

The 28 products received a total of 38 PRO label claims (Table 2). The majority of the products (n = 20; 71%) received one PRO label claim. The products with one PRO label claim were characterized as follows: symptoms (n = 16), functioning (n = 1), HRQOL (n = 1), and other (n = 2). Of the eight products that received multiple PRO label claims, six received two PRO label claims and two products received three PRO label claims (symptoms, functioning, and PGR). Of the 28 products with PRO label claims in the Clinical Studies section of the label, 14 (50%) also contained PRO claims within their indication statements. Only one of the claims reviewed appeared in the medication guide. There were no PRO claims related to decrements in health.

Most PRO label claims granted were for symptoms (85.7%) and functioning (25%) (Table 2). A few products (n = 3; 10.7%) received PRO label claims on the basis of PGRs (e.g., seizure severity and

Table 1 – Number of products approved and number of PRO claims granted by reviewing divisions.

Reviewing division	Products reviewed	Number of products approved	Number of products that include a PRO claim
Anesthesia, Analgesia and Rheumatology Products	Chantix,* Arcalyst,* Nucynta,* Lusedra, Savella,* Uloric, Simponi,* Ilaris, Actemra,* Xiaflex	10	6
Antimicrobial Products	Durezol*	1	1
Anti-infective and Ophthalmology Products	Lucentis, Altabax, Doribax, Besivance, Vibativ, Bepreve,* Lastacaft,* Teflaro	8	2
Antiviral Products	Prezista, Tyzeka, Selzentry, Isentress, Intelence, PegIntron/Rebetol Combo Pack, acyclovir, hydrocortisone, Zidovudine	8	0
Biologic Oncology Products	Vectibix, Arzerra	2	0
Cardiovascular and Renal Products	Tekturna, Letairis,* Bystolic, Cleviprex, Samsca, Tyvaso, Effient, Multaq, Asclera,* Pradaxa	10	2
Dermatology and Dental Products	Veregen, Ulesfia, Stelara	3	0
Drug Oncology Products	Dacogen, Sprycel, Zolinza, Tykerb, Torisel, Ixempra Kit, Tasigna, Treanda, Firmagon, Mozobil, Afinitor, Folotyn, Votrient, Istodax, Jevtana, Halaven	16	0
Gastroenterology Products	Myozyme, Elaprase, Cimzia,* Relistor, Entereg, Vpriv, Carbaglu, Lumizyme	8	1
Medical Imaging and Hematology Products	Soliris,* Ammonia N 13, Mircera, Lexiscan, Eovist, Nplate, AdreView, Promacta, Ablavar	9	1
Metabolism and Endocrinology Products	Januvia, Somatuline Depot, Kuvan, Onglyza, Livalo, Victoza, Egrifta*	7	1
Neurology Products	Azilect,* Neupro, Xenazine, Vimpat,* Banzel,* Dysport,* Extavia, Sabril 500-mg tablet,* Ampyra,* Xeomin,* Gilenya	11	7
Nonprescription Clinical Evaluation Products	Anthelios SX, Cetirizine Hydrochloride Allergy,* Cetirizine Hydrochloride Hives Relief*	3	2
Psychiatry Products	Invega , Vyvanse,* Pristiq, Fanapt, Invega Sustenna, Saphris, Latuda	7	1
Pulmonary and Allergy Products	Omnaris,* Kalbitor,* Krystexxa	3	2
Reproductive and Urologic Products	Toviaz,* Rapaflo,* Natazia, Ella, Prolia	5	2
Special Pathogen and Transplant Products	Eraxis, Noxafil, Pylera, Coartem, Zortress	5	0
Total		116	28

PRO, patient-reported outcome.
* Products with PRO claims in the label.

global impression of change). Two products were granted PRO claims classified as other: these were patient satisfaction with treatment (Asclera) and distress associated with belly appearance (Egrifta). Pain continues to be a prominent symptom among the PRO label claims granted, ranking highest (n = 7) among the 16 symptoms label claims followed by allergy-related symptoms (n = 5). The concepts of pain and reduced pain appear straightforward, and as such, little was discussed in the DAPs regarding the measurement of pain itself. Pain assessments via visual analogue scales and numeric rating scales are common, with little (if any) discussion in the DAPs surrounding the question stem or anchors used.

Table 2 – Types of claims granted.

Type of claim	All products with PRO claims (N = 28)		Pain products excluded (N = 21)	
	n	%	n	%
Symptoms	24	85.7	14	66.7
Functioning	7	25.0	3	14.3
HRQOL	2	7.1	2	9.5
PGR	3	10.7	1	4.8
Other	2	7.1	2	9.5

HRQOL, health-related quality of life; PGR, patient global rating.

More than 30 different PRO measures were used to support the PRO claims received (Table 3). The bulk of the measures were designed to measure a single concept such as pain or seizure rates (n = 8) or diary assessments (n = 6). Another large proportion of the measures appears to be expected by the reviewing divisions given their familiarity with the measures (n = 9) (e.g., Health Assessment Questionnaire, Short Form 36 Health Survey, and International Prostate Symptom Score). We noted several hybrid measures that combined both clinician-reported outcomes and PROs into a single measurement tool (e.g., Toronto Western Spasmodic Torticollis Rating Scale and Activities of Daily Living and Motor subscales of the Unified Parkinson's Disease Rating Scale). Although these hybrid measures are not solely patient reported, they contain PROs that are critical to assessing efficacy in the given indications.

The extent of information identified in the label regarding the specific PRO measures used to support the label claim was variable. Some labels included very little information regarding the PRO assessment. For example, the assessment of ocular itching in the Lastacaft label is not described at all ("more effective than its vehicle in preventing ocular itching in patients with allergic conjunctivitis induced by ocular allergen challenge"). Other labels included more specific information regarding the PRO assessment. For instance, the Egrifta label has a subsection on PRO within the Clinical Studies section. The description of patient-rated degree of distress in the Egrifta label includes the following:

Table 3 – Measures used to support PRO label claims.

Type of claim/product	Measure description supporting claims
Symptoms	
Azilect	Diary: "On/off" periods
Chantix	Brief Questionnaire of Smoking Urges and Minnesota Nicotine Withdrawal Scale
Omnaris	Diary: Nasal symptoms (runny nose, nasal itching, sneezing, and nasal congestion)
Vyvanse	Conners' Parent Rating Scale
Soliris	Functional Assessment of Chronic Illness Therapy—Fatigue*
Arcalyst	Diary: Signs and symptoms of cryopyrin-associated periodic syndrome: joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue
Cimzia	Crohn's Disease Activity Index†
Durezol	Visual analogue scale—eye pain/discomfort*
Toviaz	Diary: Urge urinary incontinence episodes and number of micturitions (frequency)*
Rapaflo	International Prostate Symptom Score
Vimpat	Seizure frequency
Banzel	Seizure severity from the Parent/Guardian Global Evaluation of the patient's condition
Nucynta	Pain numeric rating scale
Savella	Pain visual analogue scale
Dysport	TWSTRS†
Simponi	Health Assessment Questionnaire—Disability Index and Bath Ankylosing Spondylitis Functional Index†
Cetirizine hydrochloride-allergy	Diary: Symptoms include sneezing, rhinorrhea, nasal pruritus, ocular pruritus, tearing, and redness of the eyes
Cetirizine hydrochloride-hives	Diary: Severity and duration of hives and pruritus
Sabril	Complex partial seizures—seizure frequency
Bepreve	Ocular itching
Kalbitor	Mean Symptom Complex Severity and Treatment Outcome Score
Actemra	Pain visual analogue scale
Xeomin	TWSTRS subscales†
Lastacaft	Ocular itching
Function	
Azilect	Activities of Daily Living and Motor subscale of the Unified Parkinson's Disease Rating Scale†
Savella	Physical function (Short Form 36 Health Survey physical component summary)
Dysport	TWSTRS subscales†
Simponi	RA and PSA: Health Assessment Questionnaire—Disability Index and AnkSpon: Bath Ankylosing Spondylitis Functional Index†
Ampyra	12-Item Multiple Sclerosis Walking Scale
Actemra	Health Assessment Questionnaire
Xeomin	TWSTRS subscales†
HRQOL	
Soliris	European Organisation for the Research and Treatment of Cancer—Quality of Life Questionnaire Core 30 Items*
Letairis	Short Form 36 Health Survey
PGR	
Banzel	Seizure severity from the Parent/Guardian Global Evaluation of the patient's condition
Savella	Patient global assessment of change
Simponi	Patient global assessment of change
Other	
Asclera	Patient satisfaction (verbal rating scale)
Egrifta	Distress associated with belly appearance

HRQOL, health-related quality of life; PGR, patient global rating; PRO, patient-reported outcome; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

* Not mentioned in label.

† Hybrid clinician-reported and patient-reported measure.

Patients rated the degree of distress associated with their belly appearance on a 9-point rating scale that was then transformed to a score from 0 [extremely upsetting and distressing] to 100 [extremely encouraging]. A score of 50 indicated neutral [no feeling either way]. A positive change from baseline score indicated improvement, i.e., less distress.

In addition, certain therapeutic areas included extensive information regarding the PRO assessment, where it was the primary efficacy endpoint (e.g., Omnaris label for seasonal allergic rhinitis).

A PRO was the primary endpoint for 20 of the 28 (71%) products with PRO label claims (Table 4). All 20 primary endpoints were based on symptoms. PRO label claims were granted for nonprimary endpoints for 8 of the 28 (29%) products. The four products for which a PRO was not a primary endpoint and where a symptom claim was not granted were those granted PRO claims for distress (Egrifta), satisfaction (Asclera), HRQOL (Letairis), and functioning (Ampyra).

Three products received PRO claims on the basis of PGRs. These included a measure of seizure severity from the parent/guardian global evaluation of the patient's condition (Banzel), a patient's global assessment of disease activity (Simponi), and a patient global impression of change (Savella). The Banzel label specifies the PGR as one of the three primary efficacy variables:

Table 4 – PRO primary endpoint and symptom claims.

	PRO primary endpoint		Total number of products
	Yes (n = 20)	No (n = 8)	
Symptoms claim: Yes	20	4	24
Symptoms claim: No	0	4	4
Total	20	8	28

PRO, patient-reported outcome.

> . . . seizure severity from the Parent/Guardian Global Evaluation of the patient's condition. This was a 7-point assessment performed at the end of the Double-blind Phase. A score of +3 indicated that the patient's seizure severity was very much improved, a score of 0 that the seizure severity was unchanged, and a score of 3 that the seizure severity was very much worse.

Results of the three primary endpoints, including the PGR, are presented within a table within the label.

Within the DAPs, SEALD was mentioned as providing a review for the following four products: Chantix, Soliris, Cimzia, and Egrifta. In the case of Chantix, SEALD personnel were named and their specific comments were directly available for review as part of the DAP, whereas for Soliris and Egrifta, a summary of the SEALD review and comments was referenced in the context of the medical team's review but specific comments from identified SEALD reviewers were not available. For Cimzia, only the names of FDA personnel involved with the product review revealed SEALD team involvement. There was no evidence in the other DAPs as to whether SEALD provided additional consultation to the reviewing division.

The extent of publicly available information regarding the labeling discussion itself is limited because proposed labeling language is considered proprietary. Nevertheless, the Egrifta DAP reveals that in response to the comments and recommendations made by the SEALD consult, the clinical and statistical team decided to include in the label only the results of the belly appearance distress. It was noted by the Reviewing Division that

> from a clinical perspective Belly Appearance Distress is an endpoint of higher significance as it does not measure the self-reported perception about changes in the size of the abdomen but rather the emotional impact and distress for the patient, an important proxy for QOL in HIV-patients with lipodystrophy. As recommended by the SEALD consult, the term XXX will no longer be included in Egrifta label description of this PRO since, although developed with advice, it no longer meets the new standard set by the December 2009 FDA PRO guidance.

Discussion

This review provides a compilation and categorization of PRO label claims granted since the release of the draft PRO guidance in 2006 [6]. Although a similar review of PRO labels for the 3 years immediately before the release of the draft PRO guidance is not available (2003–2005), this review provides an opportunity to compare the current state of PRO label claims over the 5-year period since the release of the draft PRO guidance (2006–2010) with that reported by Willke et al. between 1997 and 2002 [10].

Despite the hope that after the release of the PRO guidance the proportion of NMEs and BLAs with PRO label claims would increase given the established guidelines [12], our results indicate that this proportion has decreased slightly from 30% reported by Willke et al. to 24%. Our findings, based on NMEs and BLAs, are similar to the 21.5% reported by Marquis et al. [13], which was based on all products over the same time period as of our review.

The guidance from the FDA has provided the pharmaceutical industry with much more information regarding regulatory expectations than ever previously available. Our review, however, suggests that there is disparity across reviewing divisions in terms of the proportion of PRO label claims granted. Although several reviewing divisions have granted PRO label claims, others have yet to grant any since the release of the draft PRO guidance in 2006.

For example, although the FDA guidance for industry on oncology clinical trial design cites symptoms as a direct efficacy endpoint that can be used to support regulatory approval [14,15], only 4 of the 57 approvals from 1990 through 2002 were based on decrease in tumor-specific symptoms [16]. Gondek et al. [14] reported findings of an analysis of PRO claims among product labels for oncology. From a pool of 70 new or revised product labels (from January 2002 through September 30, 2006), there were six labels for a new product or a new indication that contained PRO assessments based on symptoms (n = 5) and functions (n = 1) [14]. Yet there have not been any PRO label claims for oncology products since the release of the draft PRO guidance.

Occurrences of symptoms are the most commonly reported PRO label claims granted. This finding, based on the analysis of NMEs and BLAs since the release of the draft PRO guidance in 2006 [6], is similar to the findings from previous analyses of all PRO labels in the United States [17] and Europe [11]. The dominance of symptom-based PRO claims may be twofold. First, symptoms are typically the first-order impact of many diseases and treatments. Second, most symptom occurrences that can be quantified by frequency, severity, and duration are easy to measure on simple scales and with patient diaries in clinical trials conducted in multiple regions.

Our analyses also show that many PRO measures used for the purpose of label claims can be considered to be well established in the literature on the basis of the frequency of use in clinical trials and available information on their development and psychometric measurement properties (e.g., Short Form 36 Health Survey and Health Assessment Questionnaire).

Patient diaries continue to be used prolifically in capturing PRO data. Diaries capture simple items, such as seizure frequency, severity and duration of pruritus, and the on/off cycle of Parkinson's symptoms, and thus tend to result in simple PRO labeling claims (e.g., reduction in 28-day seizure frequency and prevention of itching).

PRO label claims for nonprimary endpoints are uncommon from the FDA. There are three likely reasons for this.

1. Primary and nonprimary endpoints tend to measure the same domain. Furthermore, such claims, overemphasizing the efficacy of products, are often the target for warning letters from the Division of Drug Marketing, Advertising, and Communications [18].
2. Sponsors are unlikely to commit resources for nonprimary endpoints during the early stages of product development, which can be substantial for developing new PRO measures aimed at multinational studies, when the likelihood of changes to the target product profile and the rate of attrition are still high.
3. Sponsors may be reluctant to support the logistical complexities related to nonprimary PRO endpoints during the execution of a multinational study. For example, protocol amendments, such as changes to inclusion and exclusion criteria for patient characteristics while the study is ongoing, will preserve the integrity of the primary endpoint but may affect the validity of the nonprimary PRO endpoint. In addition, slow patient recruitment in studies may necessitate the need to close study centers in some countries and open new centers in other countries. Sponsors are unlikely to wait for the availability of new translations of PRO measures and take time to implement data col-

lection logistics, which may delay the study by months, to support nonprimary PRO endpoints.

This review was based on information publicly available in DAPs on FDA's Web site. Additional material, of which we were unaware or that was unavailable to us, may have been considered as part of the FDA review. Furthermore, SEALD acts on a consultancy basis and therefore not all reviews received (or required) their input regarding the PROs.

Conclusions

The percentage of NMEs and BLAs with PRO label claims has decreased from 30% [10] reported between 1997 and 2002 to 24% between 2006 and 2010. PRO label claims are granted mostly for primary endpoints that are also symptoms. The majority of accepted claims are supported by simple scales, such as a visual analogue scale, a numeric rating scale, or symptom diaries, or on the basis of measures that have been traditionally accepted by the reviewing divisions. Examination of future sponsor submissions and regulatory feedback for studies planned and executed since the release of the final PRO guidance may provide additional insight into how to increase success in obtaining PRO-based label claims.

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Supplemental Materials

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