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Patient-Reported Outcomes

A Review of Patient-Reported Outcome Labeling of FDA-Approved New Drugs (2016-2020): Counts, Categories, and Comprehensibility

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ABSTRACT

Objectives: A review of new drug approvals (NDAs) by the US Food and Drug Administration (FDA) for 2006 to 2015 showed that approximately 20% of new drugs had labeling based on patient-reported outcomes (PROs). The purpose of this study was to review labeling text based on PRO endpoints for NDAs from 2016 to 2020, with a special focus on the comprehensibility of such statements when included.

Methods: We reviewed drug approval reports on the Drugs@FDA web page of the FDA website to determine the number of NDAs from 2016 to 2020. For all identified NDAs, drug approval package and product labels were reviewed. NDAs from 2016 to 2020 were grouped by disease category as per International Classification of Diseases 10th Revision. Data were summarized for diseases that traditionally rely on PROs for evaluating treatment benefit (PRO dependent) and for diseases that traditionally do not rely on PROs (non-PRO dependent). Results were compared with NDAs from 2006 to 2010.

Results: NDAs amounting to 228 were identified from 2016 to 2020, 26.3% of which had labeling statements based on PRO endpoints. From 2006 to 2015 and from 2016 to 2020, PRO labeling statements were included in 46.5% (46 of 99) and 50.0% (47 of 94), respectively, of NDAs for PRO-dependent new molecular entities and in 6.0% (12 of 199) and 9.7% (13 of 199), respectively, of NDAs for non–PRO-dependent new molecular entities. Comprehensibility of labeling statements based on PRO endpoints was judged to be complex in 56.7% of product labels.

Conclusions: The increase in labeling text based on PRO endpoints in product labels is encouraging. However, there is room for improvement on the comprehensibility of labeling statements based on PRO endpoints.

Keywords: PRO labeling, drug labeling, patient-reported outcome, FDA, comprehensibility.

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Introduction

The benefits and risks of new prescription drugs are communicated to healthcare professionals (HCPs) and other stakeholders through US Food and Drug Administration (FDA)–approved prescribing information, also known as "package inserts" (PIs) or "prescription drug labeling."[1] The FDA is responsible for ensuring that drug labeling is informative and accurate and does not contain any false, misleading, or implied claims.[2] For drugs marketed in the United States, product labeling enables promotional activities, serving as the foundation for direct-to-consumer advertising and other marketing activities. In addition to direct-to-consumer advertising, such marketing activities include communication with HCPs by sales representatives, advertisements in medical journals, and discussion of new products by key opinion leaders at conferences or in professional working groups.[3]

PIs include data related to the safety and efficacy of drugs based on clinical trial endpoints, which, at times, may include patient-reported outcomes (PROs). The FDA defines a PRO as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."[4] Concepts assessed by PRO measures typically include symptoms, functional outcomes, and multidimensional constructs such as health-related quality of life (HRQOL) and treatment satisfaction.[5] Of the 298 new drugs approved from 2006 to 2015, ~20% included PRO-related statements in the drug labeling.[6,7]

The FDA has specifically indicated that labeling is intended for use by physicians and other practitioners.[1] Nevertheless, over time, as members of the general public have become more active participants in their own medical decision making, stakeholders such as patients and caregivers have begun to review PIs for data to inform their understanding of the benefits and risks of a treatment and inform discussions with providers on medical treatment decision making. Because PRO-related data are intended to reflect the patient experience with a condition or while on treatment, text in PIs describing the results of a treatment on PROs is often of particular interest to these stakeholders. Hence, to optimize multistakeholder understanding of treatment benefits

and risks, PRO data are presented ideally in a way that is understandable to various stakeholders who may review the PI.

Therefore, PIs that are transparent and written in simple language enable the development of effective communication tools but may also empower patients to be informed and active participants in treatment decision making by helping them understand the benefits and risks of a drug, especially for newly approved products. To the best of our knowledge, no study has examined the comprehensibility of PRO-related text that appears in PIs.

The purpose of this study was to review labeling statements based on PRO endpoints for new drugs approved from 2016 to 2020, with a special focus on the comprehensibility of such statements.

Methods

A review of the FDA drug approval reports by month for new drug applications (NDAs) or new biologics license applications that were approved in the period of interest (2016-2020) was conducted to determine the number of new molecular entities (NMEs) in that period. The number of NMEs was confirmed by reviewing published summary reports.[8,9] Reports were generated sequentially in January 2021, from January 2016 to December 2020.

Once products were identified, product labels were obtained from the FDA website Drugs@FDA (www.accessdata.fda.gov) and reviewed.

For each newly approved product identified, the following information was collected, as available:

1. Brand and generic names
2. Date of FDA approval
3. Indication
4. PRO-related statements in the labeling
5. PRO endpoint designation (primary, nonprimary)

Based on the Indications and Usage section of the PIs, drugs were classified according to the International Classification of Diseases, Tenth Revision code. Diseases that traditionally rely on PRO assessments to derive or construct the primary or secondary endpoints for the evaluation of treatment benefit by regulators (eg, diseases of the digestive system) were classified as PRO dependent; diseases that traditionally rely on survival, biomarkers, or clinical outcome assessments other than PRO measures, where scores are used as primary or secondary endpoints (eg, cancers) for the evaluation of treatment benefit, were classified as non–PRO dependent. See Appendix A in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.10.006 for a complete list of the 2 categories by disease area.

Results of this analysis were compared with a similar analysis of PRO labeling of NDAs approved by the FDA from 2006 to 2015.[7]

Once a PRO-related statement was identified in labeling, the comprehensibility of the text (eg, syntax, vocabulary) was classified into 2 categories: “simple” or “complex.” PRO-related texts in which treatment benefits were clearly described in terms of effect on specific symptoms of a disease were considered to be simple. All other PRO-related statements were classified as complex. In general, labeling that was classified as complex described treatment benefit using one or more of the following:

1. Assumed familiarity with a PRO measure
2. A total or composite score rather than domain or concept score
3. A domain score presented without description of the concept(s) assessed
4. Advanced statistical methodology
5. Expert or field-related terminology

Categorization of PRO-related statements was designed to include independent review by 2 authors (AG and CR), comparison of results, and, if necessary, resolution of disagreements through consensus. Examples of each category are provided in Table 1.

Descriptive analyses, including frequency counts and cross-tabulations of measured characteristics, were performed in Microsoft Excel 2010 (Microsoft Corporation).

Results

Table 2 shows that PRO-related labeling was identified in 60 of the 228 drugs (26.3%) approved by the FDA from 2016 to 2020 (Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.10.006). Consistent with previous categorization,[7] PRO-related statements were found in 47 of the 94 PIs (50.0%) for PRO-dependent NMEs and in 13 of the 134 PIs (9.7%) for non–PRO-dependent NMEs (Table 2).

Notably, PRO-related statements were commonly found in PIs for new drugs approved in diseases of the respiratory system (100.0%), digestive system (62.5%), musculoskeletal system and connective tissue (60.0%), and skin and subcutaneous system (58.3%).

Endpoints

Of the 60 PIs that included PRO-related statements, 40 (66.7%) were based on primary endpoints related to PROs (Table 3). A subset of 9 PIs (15.0%) were based on multiple PRO-related endpoints, including both primary and nonprimary endpoints. For example, labeling for solriamfetol—a treatment for excessive daytime sleepiness associated with narcolepsy and obstructive sleep apnea—included evidence based on both the Epworth Sleepiness Scale (a PRO measure used to support a coprimary endpoint) and a patient global impression of change rating of symptom severity (a key secondary endpoint).

The remaining 20 PIs that included PRO-related statements (33.3%) were based on PRO-related endpoints specified as only nonprimary endpoints. For example, although an investigator’s global assessment of disease severity supported the primary endpoint in confirmatory trials of dupilumab for the treatment of moderate to severe atopic dermatitis in adults, the FDA-approved labeling for dupilumab also mentions one of the secondary endpoints: improvement in patient-reported itch, as measured by a numerical rating scale.[10]

Measures

A total of 12 drug approvals (20.0%) used newly developed measures, such as the Psoriasis Symptom Inventory, which appears in the labeling for brodalumab (Table 3). The majority of labeling that included PRO-related statements (n = 28; 46.7%) mentioned established (commonly used or well-known) PRO measures (eg, St. George’s Respiratory Questionnaire [SGRQ], Epworth Sleepiness Scale) or efficacy assessments recommended in FDA guidance documents (eg, pain and “most bothersome symptom” for acute treatment of migraine).

The remaining labeling (n = 20; 33.3%) was based on the patient-reported frequency of events such as daily bowel movement (eg, plecanatide for treatment of chronic idiopathic constipation) or patient-reported time to alleviation of symptoms (eg, lemborexant for treatment of adult patients with insomnia).

Table 1. Classification criteria of comprehensibility of PRO-related labeling.

Comprehensibility	Classification criteria	Examples
Simple	Treatment benefits are clearly described in terms of effect on specific symptoms of a disease.	Deutetrabenazine prescribing information: "A patient-rated global impression of change assessed how patients rated their overall Huntington's disease symptoms. Fifty-one percent of patients treated with AUSTEDO rated the symptoms as "Much Improved" or "Very Much Improved" at the end of treatment, compared to 20% of placebo-treated patients." Brodalumab prescribing information: "At Week 12, compared to subjects in the placebo group, a greater proportion of subjects in SILIQ 210 mg Q2W group achieved a Psoriasis Symptom Inventory (PSI) score of 0 (not at all) or 1 (mild) on every item (itch, redness, scaling, burning, stinging, cracking, flaking, pain)." Plecanatide prescribing information: "[…] improvements in the frequency of CSBMs/week were seen as early as week 1 with improvement maintained through week 12. The difference between the TRULANCE group and the placebo group in the mean change of CSBMs/week frequency from baseline to week 12 was approximately 1.1 CSBMs/week." "Over the 12-week treatment period, improvements were observed in stool frequency (number of CSBMs/week and SBMs/week) and/or stool consistency (as measured by the BSFS), and/or in the amount of straining with bowel movements (amount of time pushing or physical effort to pass stool) in the TRULANCE group as compared to placebo."
Complex	Treatment benefits are described using the following: ■ Assumed familiarity with a PROM ■ A total or composite score rather than domain or concept score ■ A domain score presented without description of the concepts assessed ■ Advanced statistical methodology ■ Expert or field-related terminology	Solriamfetol prescribing information: "Compared to the placebo group, patients randomized to 150 mg SUNOSI showed statistically significant improvements… on the ESS (treatment effect difference: 3.8 points) at Week 12. These effects were apparent at Week 1 and consistent with the results at Week 12. The change on percentage of subjects reported as improved by PGIc was also statistically significant compared with placebo." Revefenacin prescribing information: "The St. Georges Respiratory Questionnaire (SGRQ) was assessed in Trials 1 and 2. In Trial 1, the SGRQ responder rate (defined as an improvement in score of 4 or more as threshold) for the YUPELRI treatment arm on Day 85 was 49% compared to 34% for placebo [OR: 2.11; 95% CI: 1.14-3.92]. In Trial 2, the SGRQ responder rate for the YUPELRI treatment arm was 45% compared to 39% for placebo [OR: 1.31; 95% CI: 0.72-2.38]." Pitolisant prescribing information: "EDS was assessed using the ESS, an 8-item questionnaire by which patients rate their perceived likelihood of falling asleep during usual daily life activities. Each of the 8 items on the ESS is rated from 0 (would never doze) to 3 (high chance of dozing); the maximum score is 24." "WAKIX demonstrated statistically significantly greater improvement on the primary endpoint, the least square mean final ESS score compared to placebo."

BSFS, indicates Bristol Stool Form Scale; CI, confidence interval; CSBM, Complete Spontaneous Bowel Movement; EDS, Excessive Daytime Sleepiness; ESS, Epworth Sleepiness Scale; OR, odds ratio; PGIc, patient global impression of change; PRO, patient-reported outcome; PROM, PRO measure; PSI, psoriasis symptom inventory; Q2W, once every 2 weeks; SGRQ, St. George's Respiratory Questionnaire.

Concepts Assessed

Table 3 also shows that disease-specific symptoms such as itch (in atopic dermatitis) or pain (in rheumatoid arthritis) were included in all but one of the PIs with PRO-related statements (98.3%). Function-related concepts, such as physical or visual functioning, were included in 19 PIs (31.7%).

A total of 3 PIs were identified that, based on the instrument or score used, implied treatment benefit on quality of life (QOL) or HRQOL, although the labeling did not refer to QOL or HRQOL explicitly. Outcomes in these PIs were based on established PRO instruments that are known to include or identify themselves as measures of QOL or HRQOL (ie, the Asthma Quality of Life Questionnaire and SGRQ)[11,12] or that included a QOL domain in the overall score upon which the endpoint was based (ie, the Kansas City Cardiomyopathy Questionnaire [KCCQ]).[13]

Other concepts in PRO labeling included patient satisfaction and preference. Patient satisfaction related to a specific treatment benefit was included in 2 PIs, bremelanotide for treating hypoactive sexual desire disorder (satisfying sexual events) and

Table 2. Labeling based on PROs of new drugs approved (FDA, 2016-2020).

Disease category*	No. of drugs approved	Drugs approved with PRO labeling, n (%)
Diseases of the nervous system	34	18 (52.9)
Diseases of the skin and subcutaneous tissue	12	7 (58.3)
Diseases of the respiratory system	5	5 (100.0)
Diseases of the digestive system	8	5 (62.5)
Diseases of the blood and blood-forming organs, and immune mechanism	16	4 (25.0)
Diseases of the musculoskeletal system and connective tissue	5	3 (60.0)
Diseases of the genitourinary system	4	2 (50.0)
Mental, behavioral, and neurodevelopmental disorders	5	2 (40.0)
Diseases of the eye and adnexa	5	1 (20.0)
Diseases of the ear and mastoid process	0	0 (0.0)
Total PRO-dependent NMEs	94	47 (50.0)
Endocrine, nutritional, and metabolic diseases	28	9 (32.1)
Neoplasms	62	2 (3.2)
Certain infectious and parasitic diseases	30	0 (0.0)
Others	14	2 (14.3)
Total non–PRO-dependent NMEs	134	13 (9.7)
All categories	228	60 (26.3)

FDA indicates US Food and Drug Administration; NME, new molecular entity; No., number of; PRO, patient-reported outcome.
*Based on International Classification of Diseases, Tenth Revision codes.

collagenase Clostridium histolyticum-aaes for treatment of moderate to severe cellulite of the buttocks (satisfaction with the appearance of cellulite). Patients' preference for mode of administration of a product (ie, preferring subcutaneous injection over intravenous administration) was a unique concept in labeling approved for rituximab.[14]

Comprehensibility of PRO Labeling

The initial categorization of PRO-related statements performed independently by the 2 reviewers showed complete agreement in identifying both categories of labeling text (n = 60; 100.0%); without discrepancies, no consensus discussion was ultimately required.

Findings of the comprehensibility review of PRO-related statements used in the labeling reviewed are presented in Table 4. Results indicated that the PRO statements met the criteria for simple classification in fewer than half of the PIs reviewed (n = 26 of 60; 43.3%). The remaining 34 PIs (56.7%) that included PRO-related statements were classified as complex, indicating that, although not necessarily prohibitive, the comprehensibility of the information provided would be largely dependent upon the reading ability, statistical knowledge, and health literacy of the reader.

Most PIs in which PRO-related statements classified as simple (n = 19 of 30; 63.3%) were for drugs approved to treat diseases of the nervous system (n = 10 of 18), digestive system (n = 4 of 5), or skin and subcutaneous tissue (n = 5 of 7).

Discussion

This review shows that the proportion of NMEs with PRO-related labeling statements has increased over the years. Of all new drugs approved from 2006 to 2015, ~20% included PRO-related labeling statements compared with ~26% of new drugs approved from 2016 to 2020 (Table 5). During the 15-year period included in these reviews (2006-2020), ~22% of new drugs included PRO-related labeling.

A more focused comparison of the 2 time periods (ie, 2006-2015 and 2016-2020) confirms that for diseases that traditionally rely on PROs to demonstrate treatment benefit, labeling that included PRO-related statements has increased from ~46% to 50%.

More significantly, perhaps, an increase from 6.0% to 9.7% was observed for diseases that do not traditionally rely on PRO assessments to demonstrate treatment benefit. For these diseases, the increase was largely caused by new drugs approved for treating endocrine, nutritional, and metabolic diseases, such as cystic fibrosis and obesity (n = 9 of 28; 32.1%). Nevertheless, PRO-related statements in drug labeling of new treatments approved for cancers (n = 2 of 62; 3.2%) and infectious and parasitic diseases (n = 0 of 30) remained rare (Table 2).

Overall, results of this review are consistent with the FDA's PRO guidance and previous findings[6,7]: the majority of PRO-related labeling was based on disease-related symptoms (98.3%) and on primary endpoints (66.7%).

PRO Measures

From 2016 to 2020, labeling of 12 new drugs (20%) was based on measures developed specifically (de novo) to support assessment of key concepts for those drugs. For example, the Psoriasis Symptoms and Signs Diary was developed to support the approval of guselkumab, and the Migraine Physical Function Impact Diary was developed to support the approval of erenumab-aooe. The remaining 80% of PRO-related statements included in PIs were based on already established measures, FDA guidance recommendations, or patient-reported events.

The PIs described PRO measures inconsistently. Some PIs provided a brief description of the measure(s) used. For example, the labeling for tafamidis meglumine presents an overview of the KCCQ and its scoring approach. Nevertheless, labeling for benralizumab (indicated for treatment of asthma) and revefenacin (for treatment of chronic obstructive pulmonary disease) mentioned

Table 3. Characteristics of labeling based on PROs (FDA, 2016-2020).

Disease category*	NMEs with PRO labeling (N = 60), n (%)
Placement of PRO endpoints leading to labeling	
Primary	31 (51.7)
Nonprimary	20 (33.3)
Primary and nonprimary	9 (15.0)
Type of PRO measure[†]	
New measures	12 (20.0)
Established	28 (46.7)
Other[‡]	20 (33.3)
Type of concept assessed	
Symptoms	59 (98.3)
Function[§]	19 (31.7)
HRQOL[‖]	3 (5.0)
Other	3 (5.0)

FDA indicates US Food and Drug Administration; HRQOL, health-related quality of life; NME, new molecular entity; PRO, patient-reported outcome.
*Based on International Classification of Diseases, Tenth Revision codes.
[†]Types of PRO measures are presented hierarchically. New measures are emphasized over all other assessment types; an established measure is emphasized over frequency. If multiple PRO measures were included in the label, only the category for the predominant measure was recorded.
[‡]The category "other" includes concepts such as satisfaction, preference, and frequency counts.
[§]The category "function" includes concepts such as physical functioning, activity limitation, and emotional function.
[‖]The category "HRQOL" includes high-level concepts such as quality of life, HRQOL, and perceived wellbeing.

only the names of the PRO measures used without providing any further description. This lack of description surrounding the PRO measures used and how to interpret changes in the scores on such measures indicates that the language around the PRO-derived endpoints is intended for an audience already familiar with the PRO measures.

In fact, drug manufacturers' desire to use PRO measures that HCPs might be familiar with but that lack evidence supporting the appropriateness in the context of use may be partly responsible for the appearance of null or negative PRO-related statements in 5 PIs identified in this review (Table 6). This is often the result of using a multidimensional measure that is widely recognized but does not completely align with the experience of disease or failing to deprioritize less relevant concepts during analyses. In these instances, PIs included text acknowledging that there was "no difference" or "no improvement" associated with the product in one or more domains of a PRO measure included in the pivotal trials. For example, PRO labeling for sarilumab and baricitinib, both products approved for the treatment of rheumatoid arthritis, explicitly stated that although improvements were noted in physical domains assessed by the 36-Item Short Form Health Survey, other domains (such as emotional role) did not show improvement. Results for both domains are presented in the PIs because the physical functioning domain was not prioritized over emotional role domain in the endpoint hierarchy. Therefore, the PRO-related statements included in the drug labeling present a seemingly mixed message that may confuse or undermine the intended messaging regarding treatment benefit.

Distal Concepts

Drug manufacturers, driven by their interest in understanding and demonstrating the holistic value of new therapies, often desire to pursue labeling for concepts that are distal from the core signs and symptoms; such concepts may include complex constructs such as QOL or HRQOL, patient satisfaction with treatment, and treatment preference. Although the FDA PRO guidance emphasizes that measurement of distal concepts may be more difficult to associate directly with treatment benefit (and, therefore, less likely to be included in drug labeling), PRO-related statements in this review show that such labeling may be supported in certain situations.

QOL, a broad concept lacking a universal definition, has not traditionally been used by regulatory bodies to evaluate treatment benefit.[15,16] In part, this is because the term QOL is considered too general to be included in drug labeling.[4] HRQOL, in contrast, is a multidomain concept that represents a patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of an individual's life.[4] Despite being more consistently defined than QOL, HRQOL is also a relatively distal concept, and unlike disease-specific symptoms, the experience it reflects is both individual and diverse.[17,18] For these reasons, HRQOL rarely appears in FDA-approved drug labeling. Nevertheless, in the present review, statements related to QOL or HRQOL were identified in three PIs,[19] all of which implied or referred to domain or total scores of the established measures used (ie, the Asthma Quality of Life Questionnaire, SGRQ, and KCCQ).

Treatment satisfaction refers to a patient's satisfaction with medical care, and assessing the concept involves considering the interplay of expectations, preferences, and satisfaction with medical treatment.[20] Because it is both a distal concept and one that involves many separate factors, treatment satisfaction as defined earlier is rarely included in PIs. Nevertheless, in 2020, treatment satisfaction with a specific aspect of treatment benefit ("… patient-reported satisfaction with cellulite appearance showed a greater improvement…") was included in the labeling for collagenase clostridium histolyticum-aaes, an FDA-approved treatment for moderate to severe cellulite of the buttocks. It is likely that the approval of statements related to treatment satisfaction for this product is caused in part by the fact that it is prescribed to improve an aesthetic condition, an area in which treatment satisfaction is a key component. Some precedent exists to support this hypothesis: the concept of treatment satisfaction ("The overall patient-reported satisfaction and self-perceived visual attributes showed greater improvement… ") was similarly included in the drug labeling for deoxycholic acid, a treatment approved in 2015 for the reduction of fat under the chin.[21] These findings suggest that though satisfaction with treatment benefit may be recognized as a viable concept for inclusion in labeling for drugs approved in the aesthetic space, it is unlikely to be recognized elsewhere.

Patient preference assessments are defined as "qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions."[22] Such considerations may include treatment convenience, regimen, administration time, and costs. Because preference assessments are necessarily comparative in nature, outcomes related to preference appear infrequently in the clinical trials used to support NDAs.

This review identified a single PI that included patient preference: rituximab. The phase IIIb open-label crossover study used to support the PRO-related text in this PI included a PRO measure that evaluated preference for and satisfaction with subcutaneous injection or intravenous infusion of rituximab as an adjunct to chemotherapy in diffuse large B-cell lymphoma or follicular lymphoma. The primary objective, overall patient preference between the 2 routes of administration, was assessed using the Patient Preference Questionnaire. The study showed that most patients preferred subcutaneous administration over intravenous administration.[14] In addition to inclusion of the concept as a

Table 4. Comprehensibility of labeling statements based on PROs, by disease category (FDA, 2016-2020).

Disease category*	No. of simple statements	No. of complex statements	All statements
Diseases of the nervous system	10	8	18
Diseases of the skin and subcutaneous tissue	5	2	7
Diseases of the respiratory system	1	4	5
Diseases of the digestive system	4	1	5
Diseases of the blood, blood-forming organs, and immune mechanism	1	3	4
Diseases of the musculoskeletal system and connective tissue	0	3	3
Diseases of the genitourinary system	0	2	2
Mental, behavioral, and neurodevelopmental disorders	0	2	2
Diseases of the eye and adnexa	1	0	1
Diseases of the ear and mastoid process	0	0	0
Total PRO-dependent NMEs, n (%)	22 (46.8)	25 (53.2)	47 (100.0)
Endocrine, nutritional, and metabolic diseases	2	7	9
Neoplasms	1	1	2
Certain infectious and parasitic diseases	0	0	0
Others	1	1	2
Total non–PRO-dependent NMEs, n (%)	4 (30.8)	9 (69.2)	13 (100.0)
All categories	26 (43.3)	34 (56.7)	60 (100.0)

FDA indicates US Food and Drug Administration; NME, new molecular entity; No., number of; PRO, patient-reported outcome.
*Based on International Classification of Diseases, Tenth Revision codes.

primary endpoint in the study, the approval of labeling language related to patient preference for route of administration was also likely to have been influenced by the crossover study design, comparable efficacy and safety profiles of both formulations, and the fact that both formulations were of the same drug and from the same manufacturer; as such, results were more likely to represent a direct preference choice that was not influenced by other variables.

Patient Engagement and PROs

Perhaps one of the most influential factors in the increasing pursuit of the pharmaceutical industry for labeling that includes PRO-related text comes from the shifting culture embodied in recent patient engagement initiatives by the FDA and the explicit endorsement of patient experience data in the 21st Century Cures Act.[23]

Patient engagement initiatives are not new for the FDA, with initiatives of some form undertaken since the Office of AIDS Coordination was established in 1988.[24] Nevertheless, notably, the push to encourage and facilitate patient engagement has gained momentum in both healthcare delivery and research communities since the 2016 Affordable Care Act emphasized the importance of including patients' voice within the FDA regulatory process.[25-27] As part of this ongoing initiative, the FDA is increasingly supportive of patient-focused drug development (PFDD), an approach that systematically incorporates patient experiences and priorities into drug development and evaluation.[28] Such efforts are in part responsible for adding to the drug development lexicon terms such as "patient empowerment," "patient centricity," and "patient engagement." Although each of these terms denotes a subtle distinction in meaning, the core ideal embodied in such verbiage is a call to action for the healthcare industry to do things with patients rather than to them or for them.[29,30]

Although the increase in the number of PIs featuring PRO-related statements seen in this most recent review is encouraging, it does not seem to reflect the increasing emphasis being placed on patient centricity in drug development. Moreover, although the incorporation of patient experience data in trials—and, by extension, the inclusion of PRO-related statements in drug

Table 5. A summary of labeling based on PROs of new drugs approved (FDA, 2006-2020).

Disease category†	2006-2015*		2016-2020		2006-2020	
	No. of new drugs approved	PRO labeling, n (%)	No. of new drugs approved	PRO labeling, n (%)	No. of new drugs approved	PRO labeling, n (%)
PRO-dependent NMEs	99	46 (46.5)	94	47 (50.0)	193	93 (48.2)
Non–PRO-dependent NMEs	199	12 (6.0)	134	13 (9.7)	333	25 (7.5)
All categories	298	58 (19.5)	228	60 (26.3)	526	118 (22.4)

FDA indicates US Food and Drug Administration; NME, new molecular entity; No., number of; PRO, patient-reported outcome.
*Adapted from Gnanasakthy et al.[7]
†Based on International Classification of Diseases, Tenth Revision codes.

Table 6. Labeling based on PROs with null or negative messages.

Drug name	Disease	Labeling based on PROs
Telotristat etiprate	Carcinoid syndrome	"[Other] symptoms of carcinoid syndrome (abdominal pain or flushing) did not show improvement in the comparison of Xermelo to placebo." [Telotristat etiprate prescribing information, 2017]
Sarilumab	Rheumatoid arthritis	".... there was no evidence of a difference between the treatment groups in the mental component summary (MCS) at Week 24. Patients receiving KEVZARA 200 mg + MTX/DMARD reported greater improvement relative to placebo in the domains of Physical Functioning, Role Physical, Bodily Pain, General Health Perception, Vitality, Social Functioning and Mental Health, but not in the Role Emotional domain." [Sarilumab prescribing information, 2017]
Baricitinib	Rheumatoid arthritis	"General health status was assessed by the Short Form health survey (SF-36). In Studies III and IV, compared to placebo, patients treated with OLUMIANT 2 mg demonstrated greater improvement from baseline in the physical component summary (PCS) score and the physical function, role physical, bodily pain, vitality, and general health domains at Week 12, with no consistent improvements in the mental component summary (MCS) scores or the role emotional, mental health, and social functioning domains." [Baricitinib prescribing information, 2018]
Ravulizumab-cwvz	Paroxysmal nocturnal hemoglobinuria	"There was no observable difference in fatigue between ULTOMIRIS and eculizumab after 26 weeks of treatment compared to baseline as measured by the FACIT-fatigue instrument. Patient-reported fatigue may be an under-or over-estimation, because patients were not blinded to treatment assignment." [Ravulizumab-cwvz prescribing information, 2018]
Bremelanotide acetate	Hypoactive sexual desire disorder	"There was no significant difference between treatment groups in the change from baseline to end of study visit in the number of satisfying sexual events (SSEs), a secondary endpoint." [Bremelanotide acetate prescribing information, 2019]

DMARD indicates disease modifying antirheumatic drugs; MCS, mental component summary; MTX, Methotrexate; PCS, physical component summary; PRO indicates patient-reported outcome; SF-36, Short Form health survey; SSE, satisfying sexual event.

labeling—is a key aspect of PFDD, it is of no less importance that patients themselves have access to such data in a way that is both transparent and comprehensible.

Because of the expansion of healthcare and better access to information about diseases and treatments, patients are taking a more active role in making their own healthcare decisions.[31] Patients' clear and complete understanding of the benefits and risks of a treatment is an essential component in facilitating effective communication between care providers, regulators, and patients. Although the FDA maintains that prescribers are the intended audience for PIs, prescribers need access to information in a manner that is consistent, informative, and comprehensible; the information should be simple and clear enough to convey the intended message[32,33] to enable shared decision making, a process by which the patient and clinician work together to determine what is best for the patient.[34] This is critical in life-threatening diseases, such as cancer, in which a multitude of probabilistic information related to side effects, disease progression, and PROs need to be discussed between physicians and patients.

Nevertheless, as results of this review demonstrate, notable variation exists in the statements used to describe PRO-based treatment benefit. Although some PRO-related labeling statements may be simple enough to be understood by informed patients, many PIs included scientific or statistical jargon that might be accessible only to experts in the field and that therefore might impede comprehension for patients with limited reading ability or health literacy.

Nevertheless, it is not simply the benefit of a treatment described in the drug labeling that may be lost on patients. Recent studies have shown that patients with cancer find it difficult to comprehend the various concepts and the endpoints used in oncology studies to assess efficacy, making it difficult to make informed treatment choices.[35,36] Research shows that other FDA-approved documents, including medication guides designed to help patients avoid serious adverse events, are written, on average, at a 10th to 11th grade reading level, exceeding national recommendations for health-related materials.[37] Studies have also shown that patients often fail to fully comprehend instructions related to their prescription drugs.[37,38]

While regulatory agencies move, overwhelmingly, toward an acknowledgment of the value of PRO data—data that patients provide about their own experience that are not subject to interpretation by a third party—drug development cannot be truly "patient-focused" until the results of those patient-reported data are made accessible—without interpretation—to the same groups of people whom we trust to provide it. If, in its current form, FDA-approved drug labeling cannot present this information in a way that is comprehensible to patients, it may be time to envision a patient-facing document written specifically for members of the general public. Certainly, there is some precedence for this approach on the global stage: the European Medicines Agency, for example, publishes "lay summaries" that are intended to provide information for study participants, patients, and other stakeholders who have an interest in clinical study results, but who may have limited health literacy or scientific expertise.[39]

Limitations

This study of PRO-related statements in drug labeling for new therapies approved by the FDA from 2016 to 2020 has some limitations. Because the scope of the review was limited to new approvals for NMEs and biologics license applications, the data cannot claim to reflect the extent to which such statements are incorporated into supplemental or extended approvals for drugs already on the market, potentially misrepresenting the overall incorporation of PRO-related text in approved labeling. Another limitation is that the assessment of the perceived comprehensibility of PIs was based on the development and application of

the reading criteria by 2 authors (AG and CR), without direct input from the various stakeholders (most notably, patients). Although a detailed study that captures patients' view would help to support the validity of these findings, this study has demonstrated a significant variation in the PRO-related statements in drug labeling.

A formal readability assessment of the PRO-related statements, which may lend greater insight into lay understanding of PRO-related statements, was not conducted at this stage of the research.

Conclusions

This review showed an increase in the percent of PIs of new FDA-approved drugs that included PRO-related statements, which were included in ~26% of FDA-approved PIs for new drugs in 2016 to 2020 compared with ~20% for new drugs approved in 2006 to 2015.[7] Overall, 98.3% of PRO-related statements in labeling referred to aspects of symptoms and almost half of the PIs (46.7%) were based on evidence generated by established PRO measures.

This review also demonstrated notable variation in the perceived comprehensibility of the statements used to describe PRO-based treatment benefit in FDA-approved PIs. With more than half of the approved PIs identified as complex, questions arise about whether the product labeling is sufficient in providing patients with information to make complicated treatment decisions. Although PIs have traditionally been intended for an informed audience of HCPs, the shifting landscape of patient engagement (and patient centricity) makes the creation of accessible labeling a unique opportunity to foster patients' agency to participate in their own healthcare decision making. The underrepresentation of patient-centered language found in this review challenges the notion that patients are included among the intended audience for PIs, pointing to a gap in our realization of PFDD, and creates an opportunity for regulatory bodies and manufacturers to consider the potential value of a more accessible patient-facing document that will be informative and held to the same standards of accuracy as the approved drug labeling.

Supplemental Material

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