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Impact Of The FDA Draft Guidance On Patient Reported Outcomes (PRO) Label Claims For Approved Drug Products In The US: Has It Made A Difference?

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Background

In February of 2006, the FDA Study Endpoints and Label Development (SEALD) group issued its Draft Guidance on Patient Reported Outcomes (PRO) measures[1], capturing the FDA's current thinking on PRO data capture in clinical research. The purpose of the guidance was to articulate standards under which claims can be made relating to patient reported outcomes such as, symptoms, functioning and health related quality of life (HRQL).

The box below outlines some of the critical points from the draft guidance:

- PRO instruments will be evaluated in the context of stated labeling goals.
- Instrument development must be based on patient input
- A recall period that captures the patient's current state is preferred
- Content validity is paramount and must be documented
- Instrument adequacy for one purpose does not guarantee its adequacy for another purpose
- In order to support claims, criteria for statistical analysis and interpretation of PRO results, including clear specification for a "positive" study conclusion should be clearly stated in the study protocol and statistical analysis plan
- Statistical adjustments for multiple endpoints and a plan for dealing with missing PRO data are required

Due to the level of rigor required by the guidance, concerns have been raised that the draft PRO guidance would stifle the number of PRO labels.

The ISPOR Task Force that reviewed the guidance called upon " . . . the FDA to recognize that an acceptable level of evidence may include less than the full set of criteria as outlined as best practice in the Guidance".

In addition, PhRMA pointed out that "... it is important that there be a balance between what may be considered ideal evidence and practical limitations of what can be accomplished in the context of the clinical trial setting".

"The FDA decides on a case-by-case basis whether existing documentation of content validity and other measurement properties is sufficient[2]"

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Objectives

To determine the influence of the FDA Draft PRO Guidance on obtaining PRO label claims, for drug products in the US, since its release in February 2006. Specifically the three following questions were addressed:

- What type of PRO label claims have been granted since the release of the draft guidance?
- Did the PRO label claims granted after Feb 2006 meet the standards set by the draft guidance? (Based only on the evidence submitted within each drug product's summary basis of approval)
- Has the FDA Draft PRO Guidance made a significant impact on the ability of new drug products in the US to obtain PRO claims?

Methods

All US drug products with a PRO label claim approved by FDA between Feb of 2006 and August of 2008, were identified from the MAPI PROLabels© database. Package inserts (indication, clinical trials sections) and medical review sections from publicly available summary basis of approvals (SBA) for these products were reviewed. 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 instruments named in label
- Type of claim
  - Signs and symptoms
  - Functioning
  - Health Related Quality of Life (HRQL)
  - Patient Global Rating (PGR)
  - Other
- Reviewing division
- Medical review available (Y/N)
- SEALD review (Y/N) & comments
- PRO measures mentioned and endpoint status (primary, secondary, tertiary/exploratory)
- PRO measure development included patient input (Y/N; based only on information in SBA)
- PRO measure validated for specific population (Y/N; based only on information in SBA)
- PRO results reported as statistically significant (Y/N)
- PRO results reported as clinically meaningful (Y/N)

Results

- 33 drug products were identified as having 44 total PRO label claims
- 24 of the 33 drug products had SBA Medical Reviews available for review
- SEALD was involved in the review of 4 of 24 drug products with an available Medical Review (based only on the evidence submitted within each drug product's SBA)
- SEALD written feedback within the SBA was available for 2 of 24 drug products

Table 1. Types of PRO label claims granted (2/2006 – 8/2008)*

Signs / Symptoms	32	72.7%
Functioning	4	9.1%
HRQL	5	11.4%
Patient Global Rating	2	4.5%
Other	1	2.3%
Total products / PRO label claims	33/44	100%

*Note: Based on our review, SEALD was involved with the review of 4 signs/symptoms and 1 HRQL label claim granted

Signs & symptoms PRO label claims (n=32) were based on:

- 10 pain related instruments
  - VAS (n=4), NRS (n=1), VAS & NRS (n=2), VAS & WOMAC (n=1), Modified Wong-Baker Faces scale (n=1), not specified (n=1)
- 5 allergic rhinitis related questionnaires
- 3 asthma symptom diaries
- 5 symptom diaries for the following product indications: GERD, premenstrual dysphoric disorder, Cryopyrin-Associated Periodic Syndromes, vasomotor symptoms due to menopause, COPD
- 3 patient diaries recording periods of "OFF," "ON," or "ON with dyskinesia" for Parkinson's disease
- 6 were based on various assessments for products with the following indications: smoking cessation (Brief Questionnaire of Smoking Urges and the Minnesota Nicotine Withdrawal scale "Urge to Smoke" item), insomnia (sleep duration, sleep latency, number of awakenings, and sleep quality), Crohn's disease (Crohn's Disease Activity Index), prevention of nausea (nausea VAS, Functional Living Index-Emesis), social anxiety disorder (Liebowitz Social Anxiety Scale), and paroxysmal nocturnal hemoglobinuria (Functional Assessment of Chronic Illness Therapy-Fatigue)

Functioning PRO label claims (n=4) were based on:

- Functional Living Index–Emesis (FLIE)
- Impact of disease-specific symptoms on activities of daily living (n=2)
- "Next day functioning" (i.e., self-assessment of next day residual effects and memory impairment due to drug therapy).

HRQL PRO label claims (n=5) were based on:

- "A Standard questionnaire (not specified). . ."
- Rhinitis Quality of Life Questionnaire (RQLQ)
- European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)
- Asthma Specific Quality of Life Questionnaire (AQLQ)
- Asthma Specific Quality of Life Questionnaire-Standardized Version (AQLQ(S))

Patient Global Rating PRO label claims (n=2) were based on:

- Patient-rated global impression of change
- Patient global assessment (not further specified)

"Other" PRO label claims (n=1) were based on:

- A patient's rating of medication helpfulness

PRO data collected that did not result in a label claim:

13 of the 33 drug products were found to have collected PRO data, as secondary endpoints, within the context of the registration trial that did not result in PRO claims (based on review of clinical trial information within the SBA for the 24 products identified with an available medical review)

- PRO endpoints were statistically significant and clinically significant (2 products)
- PRO endpoints were statistically significant but not clinically significant (4 products)
- PRO results were not significant (2 products)
- PRO results were not reported in the SBA (5 products)

Table 2. The Number and Type of PRO Label Claims granted by reviewing divisions

Reviewing division	Number of PRO labels granted by Type of Claim				
	Sign & symptoms*	Function	HRQL	PGR & Other	Total
Anesthesia, Analgesia and Rheumatology	8	0	0	0	8
Anti-inflammatory, Analgesic, and Ophthalmologic Products	1	1	0	2	4
Antimicrobial Products	1	0	0	0	1
Cardiovascular and Renal Products	0	0	1	1	2
Gastroenterology Products	4	1	0	0	5
Medical Imaging and Hematology Products	1	0	1	0	2
Neurology Products	3	2	0	0	5
Psychiatry Products	1	1	0	0	2
Pulmonary and Allergy Products	9	0	2	0	11
Reproductive and Urologic Products	2	0	0	0	2
Total	30	5	4	3	42

*Note: SBAs were not available and reviewing division could not be determined for two products. Each product received 1 claim for signs/symptoms.

Observations

- The vast majority of PRO label claims granted were for signs and symptoms endpoints, mostly based on symptom diaries with simple measurement tools such as VASs.
- Label claims for HRQL based on established instruments are still being granted
- Provision of PRO label claims remains inconsistent despite the Draft Guidance, and reflect the FDA's prerogative to evaluate PRO data on a case-by-case basis.
  - In some instances, PRO label claims were granted based on exploratory endpoints (e.g., Soliris - EORTC QLQ-C30) whereas for other products PRO label claims were not obtained for statistically and clinically significant secondary PRO endpoints (e.g. Voltaren, Fentora).
  - There are instances within our review timeframe where claims were granted based on positive (statistically significant) results even though SEALD reviewers commented that a PRO measure did not have content validity (e.g., "urge to smoke claim" for Chantix).
- Given the PRO-driven nature of the therapeutic areas, it is not surprising that the FDA Divisions of Anesthesia, Analgesia and Rheumatology Products (DAARP) and Pulmonary and Allergy Products (DPAP) granted the most PRO claims (45%)

Conclusions

- Since the release of the Draft PRO Guidance, many PRO claims continue to be approved by FDA reviewing divisions
- PRO label claims are most likely to be granted for data based on signs and symptoms
- Based on information available from the FDA website, SEALD was involved in the review of very few drug products that achieved PRO label claims
- Certain FDA reviewing divisions (e.g. DAARP, DPAP) appear to be more comfortable allowing claims using specific PRO measures (usually as primary endpoints)
- Reviewing divisions may or may not be adhering to the Draft PRO Guidance criteria when assessing PRO data for a claim

Limitations

- Very limited information was included in the SBAs about development and validation of the PRO measures upon which the 44 claims were based for the 33 drug products; thus, it was not possible to make conclusions about the content validity of the measures or whether they were "fit for purpose"
- Statements about SEALD involvement in reviewing PRO claims for the 33 drug products are limited by the information that is publicly available on the FDA website; undocumented informal consultations or conversations between SEALD and FDA Reviewing Divisions cannot be ruled out
- The date of the final drug product approval may reflect months or years of regulatory interaction

References

1. US Food and Drug Administration Draft Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims<http://www.fda.gov/Cder/guidance/5460dft.pdf. Accessed 1 April 2008

2. Burke, LA., Kennedy DL., Miskala, PH., Papadopoulos EJ., and Trentacosti, AM., (2008). The use of patient-reported outcome measures in the evaluation of medical products for regulatory approvals. Clinical Pharmacology & Therapeutics. 84 (2), p281-283.