Meaningful Within-Patient Change in Patient-Reported Health Status: Comparison of FDA Guidance and Approved Label Claims

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INTRODUCTION

- Meaningful within-patient change (MWPC) describes the amount of individual-level change on an outcome that a patient would consider a meaningful change[1]
- Evaluation of MWPC can provide insight into treatment-related change beyond what is provided through analysis of mean change and significance testing
  - Analysis of mean change can mask variability in the outcome. Evaluation of MWPC can provide a better description of the underlying variability in observed scores
  - Very small amounts of change could be statistically significant, even if that level of change is not considered meaningful to patients. Evaluation of MWPC more clearly brings the voice of the patient into analyses that evaluate treatment efficacy
- The United States (US) Food and Drug Administration (FDA) encourages use of MWPC analyses to evaluate patient-reported outcomes (PROs) in clinical trials[2,3]
  - Recommendations related to MWPC analyses were made by the FDA as early as 2009 and continue to evolve through more recent draft guidance
  - Thresholds used for MWPC analyses are evaluated on a context-specific basis
  - The FDA may request evidence that the selected thresholds are applicable to the specific trial population and setting, increasing the burden of evidence placed on sponsors to justify their analytic approach

OBJECTIVE

To explore the degree to which FDA-approved labels that include PRO-based claims mirror the FDA's guidance on inclusion of MWPC analyses

METHODS

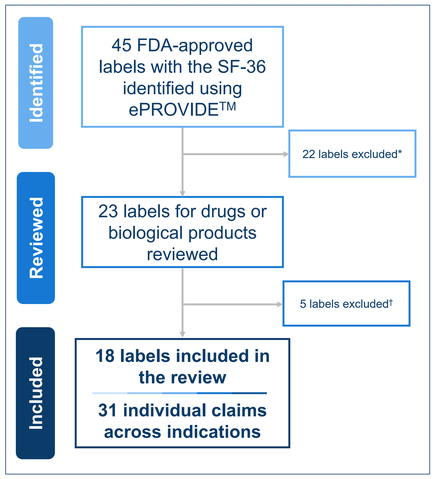
- The ePROVIDE™ PROLABELS database was used to identify FDA-approved labels for drugs or biological products that include claims about the SF-36® Health Survey (SF-36, either version 1 or version 2)
  - The SF-36 is one of the most widely used generic measures of health-related quality of life
  - MWPC thresholds for SF-36 scales and summary components have been published based on general population data[4] as well as for specific diseases (e.g., rheumatoid arthritis,[5,6] Crohn's disease[7])
- Relevant information from each label was extracted, including the positioning of the SF-36 in the endpoint hierarchy and descriptions of SF-36 analyses
- For each identified FDA-approved label, a search was conducted to identify a corresponding European Medicines Agency (EMA) label for the same treatment
- Information from FDA-approved claims regarding the SF-36 was summarized and compared to that from corresponding EMA-approved claims

RESULTS

FDA-Approved Label Claims That Include the SF-36

- **Figure 1** shows the results of the ePROVIDE™ PROLABELS search; a total of 18 FDA-approved labels and 31 individual claims were included
- **Table 1** provides an overview of the labels that were evaluated

Figure 1. FDA-Approved Labels for Medical Products That Include Claims Based on the SF-36



Reasons for exclusion: *Medical devices (n=22); †SF-36 not named in label (n=3), biosimilar or alternative administration method with same clinical study information as original product (n=2)

Table 1. Description of Evaluated Label Claims

Label Elements	N (%)
Therapeutic area	
Inflammatory/autoimmune*	29 (93.5%)
Hemophilia A	1 (3.2%)
Primary humoral immunodeficiency	1 (3.2%)
Approval year for SF-36 claim	
Prior to 2009	13 (41.9%)
2009 or later	18 (58.1%)
Position of SF-36 in endpoint hierarchy	
Primary	0 (0.0%)
Secondary	1 (3.2%)
Not specified	30 (96.8%)
SF-36 scores included in claim	
All 8 scales, PCS, MCS	18 (58.1%)
PCS and MCS only	9 (29.0%)
PCS only	4 (12.9%)
Other PROs included in the label†	
Incorporated into composite endpoint	28 (90.3%)
Analyzed as separate PRO-based endpoints	28 (90.3%)
Approved by the EMA	
Yes, with the SF-36 in the label	23 (74.2%)
Yes, without the SF-36 in the label	6 (19.4%)
No	2 (6.5%)

Abbreviations: MCS, Mental Component Summary; PCS, Physical Component Summary
*Includes: ankylosing spondylitis (n=4), non-radiographic axial spondyloarthritis (n=1), Crohn's disease (n=1), fibromyalgia (n=1), psoriatic arthritis (n=9), and rheumatoid arthritis (n=13)
†For the same indication(s) as the SF-36; both options could be true for a single label, so percentages sum to >100%

Claims Based on Evaluation of Mean Change Only, N=30

FDA-Approved Claims Using the SF-36

- Thirty claims **only** described SF-36 score **differences in change** for treatment compared to placebo
  - The amount of information included in claims varied, ranging from use of language that only implied evaluation of mean change to inclusion of mean scores and p-values

Corresponding EMA-Approved Claims

- Of the 30 SF-36 claims that were based on mean change alone, 23 had corresponding claims approved by the EMA
- Of these, 2 EMA-approved claims included reference to **clinically significant / clinically meaningful** improvements in SF-36 scores
  - This type of language did not appear in the corresponding FDA-approved claims
  - The thresholds used to evaluate meaningful improvement were not specified in the labels; few details were included to help interpret or understand how the analysis was conducted

Other PRO-Based Claims

- Of the 30 indications that evaluated the SF-36 on the basis of mean change / statistical significance only, 27 included claims based on other PROs (outside the context of a composite endpoint)
- Eleven of the 27 indications included claims based on MWPC analyses of the Health Assessment Questionnaire – Disability Index (HAQ-DI); all 11 reported the thresholds used to evaluate improvement
- The remaining 16 claims—which included the HAQ-DI, FACIT-Fatigue, Inflammatory Bowel Disease Questionnaire (IBDQ), and Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL)—only described differences in mean scores

Claims Based on Interpretation of Meaningful Change, N=1

- Only 1 SF-36 claim approved by the FDA (Savella [milnacipran], fibromyalgia) used an MWPC approach, incorporating the Physical Component Summary (PCS) score into a PRO-based composite endpoint:

> *"…a larger proportion of patients treated with SAVELLA met the criteria for treatment response, as measured by the composite endpoint that concurrently evaluated improvement in pain (VAS), physical function (SF-36 PCS), and patient global assessment (PGIC)…as compared to placebo."*

- Improvement in PCS was defined as an improvement ≥6 points
  - 6 points is larger than the threshold estimated from the general population, and is larger than thresholds that have been estimated previously for fibromyalgia
- The threshold used to define improvement and the percent of patients achieving it are provided in publications but not in the label itself
  - Information on the method used to derive this threshold are not included in the label or the original publication

SUMMARY & CONCLUSIONS

- Despite the FDA's guidance, approved claims based on the SF-36 rely almost exclusively on evaluation of mean differences and statistical significance, rather than MWPC
  - A small number of EMA-approved labels include what appear to be MWPC analyses, though these analyses are not included in the corresponding FDA-approved labels
  - Several labels include MWPC analyses for the HAQ-DI despite only presenting mean change analyses for the SF-36 (as well as for other PROs described in the label, such as the FACIT-Fatigue)
- Many possible reasons exist to explain the lack of MWPC analyses in claims related to the SF-36
  - The FDA's familiarity with the SF-36 and its score interpretation may result in a lower requirement for including MWPC analyses
  - Sponsors may not have the resources or guidance needed to plan for and implement MWPC analyses, particularly if disease-specific thresholds are needed
  - The decision to implement (or require) MWPC analyses may depend in part on the number of scores used; demonstrating meaningful change across 8 scales and 2 summary scores may be considered too high a burden
  - The FDA may not consistently require these types of analyses
- Most of the labels reviewed were for inflammatory/autoimmune diseases; expansion of label review to other PRO instruments and other therapeutic areas is needed for a more complete evaluation
- Overall, these findings point to differences between the FDA's emphasis on presenting patient experience data and the corresponding amount of detail that is ultimately included in labels
  - More consistent inclusion of MWPC analyses, along with sufficient detail to describe how the analyses were conducted, can help make more complete use of PRO data and provide more complete understanding of the patient experience

REFERENCES

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All FDA package inserts (labels) were downloaded in March 2023 from https://www.accessdata.fda.gov/scripts/cder/daf/ or https://www.fda.gov/vaccines-blood-biologics/licensed-biological-products-supporting-documents; the most recent inserts available at that time were used for evaluation. FDA labels that include claim language based on the SF-36: ACTEMRA (tocilizumab),* ADVATE (Antihemophilic Factor [Recombinant], Plasma/Albumin-Free Method), ARAVA (leflunomide)*, CUVITRU (Immune Globulin Subcutaneous [Human], 20% Solution), ENBREL (etanercept), HUMIRA (adalimumab),* KEVZARA (sarilumab),* KINERET (anakinra), OLUMIANT (baricitinib),* ORENCIA (abatacept),* REMICADE (infliximab),* RINVOQ (upadacitinib),* SAVELLA (milnacipran HCl), SIMPONI ARIA (golimumab),* SKYRIZI (risankizumab-rzaa),* TALTZ (ixekizumab),* TREMFYA (guselkumab),* XELJANZ/XELJANZ XR (tofacitinib)*

*Denotes the presence of a corresponding EMA-approved package insert that includes SF-36 claim language for the same indication(s) as the FDA-approved claim

Presented at the 30th Annual ISOQOL Conference; October 18-21, 2023; Alberta, Canada