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# Concordance of PRO Labeling Claims Between the FDA and EMA

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## ABSTRACT

**Objectives:** Recent reviews have examined the differences in patient-reported outcome (PRO) labeling claims comparing United States (US) Food and Drug Administration (FDA) decisions to those of the European Medicines Agency (EMA). However, little research has been conducted to understand where there is concordance between agencies with regard to PRO labeling decisions. This analysis seeks to examine where similar PRO labels are granted by each agency to determine if there are precipitating factors that would increase the likelihood of claims granted by both agencies.

**Methods:** A listing was created of drug approvals granted by both the FDA and EMA. A total of 75 products were identified. PRO claims were compared using US drug approval packages and European public assessment reports packages to determine whether claims made for the same product by the same company were similar or different. For analysis purposes, PRO claim language was categorized as symptoms, functioning, health-related quality of life, patient global rating (PGR), or other.

**Results:** A total of 75 products had been approved by both agencies. Of these, a total of 35 (47%) were granted at least one PRO claim by the EMA as compared with 14 (19%) by the FDA. Of the 14 products with PRO claims granted by both agencies, only 4 (11%) had the same claim types granted, without deviation. However, despite these discrepancies, upon dissection of the labels, commonalities were identified. Symptom claims were granted in 12 of 14 products by both agencies as were 5 functioning and 3 PGR claims.

**Conclusions:** While there is not perfect agreement between agencies on PRO labeling claims, upon close examination there appears to be greater concordance then previously recognized. Precipitating factors such as therapeutic area, PRO measure, and order of regulatory submission may influence the agreement between agencies. Further investigation is warranted to support effective PRO strategies.

## BACKGROUND

- United States (US) Food and Drug Administration (FDA)
  - In late 2009, the FDA issued a formal guidance, *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.[1]
  - The document set standards for the use of patient-reported outcome (PRO) measures in support of product labeling claims.
    - The guidance was intended to "increase efficiency of discussions with the FDA during the medical product development process, streamline the FDA's review of PRO instrument adequacy and resultant PRO data collected during a clinical trial, and provide optimal information about the patient perspective for use in making conclusions about treatment effect at the time of medical product approval."[1]
  - A second initiative for drug development tools (DDTs), including PROs, was created by the Center for Drug Evaluation and Research (CDER) as part of the FDA's Critical Path Initiative, *Draft Guidance for Industry: Qualification Process for Drug Development Tools*.[2]
    - The purpose of this initiative was to provide a framework to facilitate the development and regulatory acceptance of scientific tools used in drug development programs.
    - The initiative was intended to encompass multiple levels of instrumentation, including PROs, biomarkers, animal models, and other clinical outcome assessments.
- European Medicines Agency (EMA)
  - The EMA, unlike the FDA, has not opted to issue a formal guidance specific to PROs but instead has authored a reflection paper.[3]
    - The paper provides broad recommendations on the use of PRO measurement in clinical trials.
  - Additionally, the EMA has developed a Biomarker's Qualification program (2008)[4] that is somewhat similar to the DDT guidance in the US.
    - The program provides a formal mechanism for ratifying clinical trial endpoints, including new or existing PROs.
- Despite these somewhat parallel paths, there still appears to be disparity in the use and acceptance of PRO measures in product labeling.
  - Anecdotally, it appears that the EMA is more likely to grant claims in the area of HRQOL (health-related quality of life) or functioning, while the FDA largely limits claims to improvement in signs or symptoms.[5-7]
- However, to our knowledge, a formal comparison of PRO labeling claims for products approved by both the FDA and EMA has yet to be conducted.
- Therefore, the purpose of this review is to compare and contrast product labeling claims for new drug entities or biologic license agents approved by the FDA and EMA in the years 2006–2010.

## METHODS

- The FDA drug approval reports Web site was used to identify new drugs that were approved in the US from January 2006 through December 2010.
  - Only those products classified by CDER as new molecular entities or biological licensing agents were included.
  - Any product containing substances previously marketed with a different brand name or set of indications, as a different dosage form or strength, or as a combination product of previously marketed entities was excluded.
    - This product list then was compared with products identified on the EMA Web site as approved.
- Once approved products in both the US and European Union were identified, drug approval packages (DAPs) and European public assessment reports (EPAR) packages were reviewed.
  - In the US, approved product labels were reviewed, and information was retrieved from the medical review, summary review, cross-discipline team leader review, and other review sections from the DAP, as well as the Indication and Clinical Studies section of the approved product label.
    - The DAPs were located on the FDA Web site Drugs@FDA (www.accessdata.fda.gov).
  - From the EPAR packages, the summary of product characteristics and scientific discussion documents found on the EMA Web site (www.ema.europa.eu) were reviewed.
- Identified PRO labeling claims were grouped into the following types: symptoms, functioning, health-related quality of life (HRQOL), patient global rating (PGR), or "other."

### Statistical Methods

- Statistical analysis consisted of frequencies and cross-tabulations of measured characteristics.
- Calculations were performed using Microsoft Excel 2007.
- For analysis purposes, if a PRO appeared in the DAP or EPAR, it was considered to be an attempt to seek a PRO labeling claim, *despite sponsor intent*, unless specifically noted otherwise.
  - This assumption was made in part due to the proprietary nature of labeling discussions between sponsor and regulatory bodies.

## RESULTS

- As previously reported,[6] a total of 156 new drugs were approved between January 2006 and December 2010.
  - Of these, 33 were generic products and were excluded from analysis, as were 4 new products that were approved but had no data available on the FDA Web site at the time of review.
  - Therefore, this review includes 116 products.
  - A total of 75 of the 116 products reviewed were approved by both the FDA and the EMA.
- Of the 75 products with dual approval, a total of 35 products were granted at least one PRO claim by either of the agencies (Table 1).
  - All 35 products (47%) were granted at least one PRO claim by the EMA.
  - Only 14 products (19%) were granted at least one PRO claim by the FDA.
  - In all instances where the FDA granted a labeling claim, the EMA did as well.
  - About one-third of the products were approved by the EMA first and then by the FDA.
- A total of 70 PRO labeling claims were granted by the FDA (n = 22) and the EMA (n = 48) (Figure 1).
- The EMA granted PRO labeling claims to more products than the FDA (35 vs. 14) between 2006 and 2010 (Table 2).
  - The majority of claims in the US focused on symptoms.
  - Claims granted by the EMA included higher order concepts such as HRQOL and functioning.
- Of the 14 products with PRO claims granted by both the FDA and EMA, only 4 (11%) had exactly the same claim types granted, without deviation.
- Despite discrepancies, some commonalities were identified between FDA- and EMA-approved PRO labels (Table 3).
  - The following claim types were granted by both the FDA and EMA:
    - Symptom claims were granted in 12 of 14 products.
    - Functioning claims were granted in 5 of 14 products.
    - PGR claims were granted in 3 of 14 products.

**Table 1** PRO Claims–FDA as Compared With EMA by Product (2006-2010)

| Product | FDA | US Approval Date | EMA | European Union Approval Date |
|---|---|---|---|---|
| Azilect | Yes | 5/16/2006 | Yes | 2/21/2005 |
| Chantix | Yes | 5/10/2006 | Yes | 9/26/2006 |
| Lucentis | No | 6/30/2006 | Yes | 1/22/2007 |
| Omnaris | Yes | 10/20/2006 | Yes | 3/19/2008 |
| Invega | No | 12/19/2006 | Yes | 3/4/2011 |
| Soliris | Yes | 3/16/2007 | Yes | 6/20/2007 |
| Neupro | No | 5/9/2007 | Yes | 2/15/2006 |
| Torisel | No | 5/30/2007 | Yes | 11/19/2007 |
| Letairis | Yes | 6/15/2007 | Yes | 4/21/2008 |
| Micera | No | 11/14/2007 | Yes | 7/20/2007 |
| Arcalyst | Yes | 2/27/2008 | Yes | 10/23/2009 |
| Cimzia | Yes | 4/22/2008 | Yes | 10/1/2009 |
| Lexiscan | No | 4/10/2008 | Yes | 9/6/2010 |
| Toviaz | Yes | 10/8/2006 | Yes | 4/20/2007 |
| Rapaflo | Yes | 10/8/2008 | Yes | 1/29/2010 |
| Vimpat | Yes | 10/8/2008 | Yes | 8/29/2008 |
| Banzel | Yes | 11/14/2008 | Yes | 1/16/2007 |
| Afinitor | No | 3/30/2009 | Yes | 8/3/2009 |
| Simponi | Yes | 4/24/2009 | Yes | 10/1/2009 |
| Samsca | No | 5/19/2009 | Yes | 8/3/2009 |
| Ilaris | No | 6/17/2009 | Yes | 10/23/2009 |
| Extavia | No | 8/14/2009 | Yes | 5/20/2008 |
| Saphris | No | 8/13/2009 | Yes | 9/1/2010 |
| Stelara | No | 9/25/2009 | Yes | 1/16/2009 |
| Arzerra | No | 10/26/2009 | Yes | 4/19/2010 |
| Votrient | No | 10/19/2009 | Yes | 6/14/2010 |
| Ampyra | Yes | 1/22/2010 | Yes | 7/20/2011 |
| Actemra | Yes | 1/8/2010 | Yes | 1/16/2009 |
| Xiaflex | No | 2/2/2010 | Yes | 2/28/2011 |
| Treanda | No | 3/20/2008 | Yes | 3/19/2010 |
| Vpriv | No | 2/26/2010 | Yes | 8/26/2010 |
| Carbaglu | No | 3/18/2010 | Yes | 1/24/2003 |
| Zortress | No | 4/20/2010 | Yes | 3/08/2009 |
| Lumizyme | No | 5/24/2010 | Yes | 3/29/2006 |
| Jevtana | No | 6/17/2010 | Yes | 3/17/2011 |

**Figure 1** Percentage of Total PRO Claims Granted, by Agency (2006-2010)

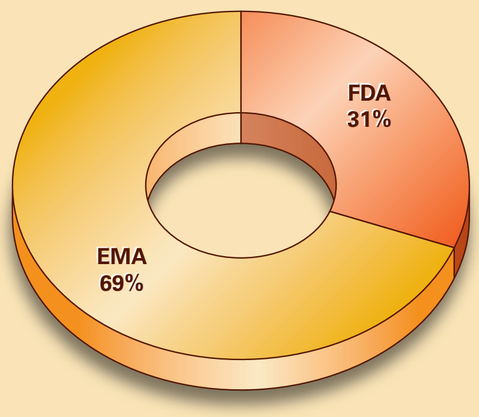


**Table 2** Summary of PRO Labeling Claim Types Granted by the FDA or EMA (2006-2010)

| Type of Claim | FDA Granted Claims (N = 14 products) | | EMA Granted Claims (N = 35 products) | |
|---|---|---|---|---|
| | N | % | N | % |
| Symptoms | 12 | 54% | 19 | 40% |
| Functioning | 5 | 23% | 9 | 19% |
| HRQOL | 2 | 9% | 13 | 27% |
| PGR | 3 | 14% | 5 | 10% |
| Other | 0 | 0 | 2 | 4% |
| Total claims | 22 | 100% | 48 | 100% |

**Table 3** Types of PRO Labeling Claims Approved by the FDA and EMA for the 14 Products With Claims Granted by Both Agencies (2006-2010)

| | EMA | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | PRO Type | Symptom | Function | HRQOL | PGR | Other | None | Total FDA |
| FDA | Symptom | Azilect<br>Chantix<br>Omnaris<br>Soliris<br>Arcalyst<br>Cimzia<br>Toviaz<br>Rapaflo<br>Vimpat<br>Banzel<br>Simponi<br>Actemra | | | | | | 12 |
| | Function | | Azilect<br>Cimzia<br>Simponi<br>Ampyra<br>Actemra | | | | | 5 |
| | HRQOL | | | Soliris<br>Letairis | | | | 2 |
| | PGR | | | | Banzel<br>Simponi<br>Actemra | | | 3 |
| | Other | | | | | | | 0 |
| | None | Letairis | Arcalyst | Azilect<br>Cimzia<br>Simponi<br>Actemra | Toviaz | Cimzia | | 0 |
| **Total EMA** | | **13** | **6** | **6** | **4** | **1** | **0** | **30 (EMA) /22 (FDA)** |

## DISCUSSION

- This review provides the first attempt to compare all PRO claims granted by the FDA and EMA for the same approved products.
- The two agencies appeared to agree on the exact type of labeling less than 12% of the time across approved products. However, upon close inspection, within the 14 products that were common to both agencies, similarities in labeling exist.
  - Although claim language was not exact, the majority of the 14 products (91%) had overlap in their PRO labeling claims. In 12 of 14 products, symptom claims were granted by both agencies with the exception of Letairis, which received a claim for dyspnea by the EMA, and Ampyra, which received a functioning claim by both agencies. Additionally, the EMA granted a claim for improvement in fatigue for Simponi that was not included in US labeling. The differences in these symptoms claims may be due in part to the EMA's acceptance of two PRO measures not currently endorsed by the FDA.
  - In all instances where higher order claims (HRQOL, functioning) were granted by the FDA, they also were granted by the EMA, suggesting that if the evidence to support a claim is deemed sufficient in the US, it is likely to be sufficient for the EMA as well.
- However, distinct differences in PRO labeling claims do exist between the two agencies. As anticipated, the EMA granted more higher order claims (HRQOL and functioning) as compared with the FDA based on the 35 products reviewed with at least one PRO labeling claim from either agency.
  - Reasons for these differences require careful consideration. As noted by Girman and colleagues,[5] regulatory requirements for registration often differ by region, causing sponsors to launch multiple trials with differing endpoints to meet requirements. As such, certain agencies may be predisposed to the acceptance of PRO endpoints, while others do not have this same predilection.
- However, upon careful inspection, outside of differing registration requirements, there still appear to be differences by agency in the acceptance of PRO claims.
- HRQOL claims are approved in greater numbers by the EMA. Azilect, Lucentis, Stelara, and Samsca provide instructive examples where the EMA granted HRQOL or functioning claims based on measures that were rejected by the FDA.
  - The FDA denied an HRQOL claim for Azilect based on the PDQUALIF scale, noting "the sponsor did not make statistically appropriate adjustments for these multiple comparisons."[8] However, the EMA granted a claim of "significant and beneficial effect in quality of life" (as assessed by PDQUALIF scale).
  - The Visual Function Questionnaire (VFQ-25) supported a claim of "patient-reported benefits" for Lucentis by the EMA, while the FDA questioned whether the tool was fit for purpose.
  - Stelara received no PRO claims in the US but did receive endorsement by the EMA for all claims sought, including HRQOL and symptoms (Dermatology Life Quality Index [DLQI], 36-Item Short Form Health Survey [SF-36], itch visual analogue scale).
  - Finally, the EMA granted an HRQOL claim for Samsca based on results from the SF-12, noting "mental scores showed statistically significant and clinically relevant improvements for tolvaptan treatment compared to placebo." However, a Study Endpoints and Label Development (SEALD) review for Samsca indicated "The primary endpoint The SF-12 was developed as a generic health status instrument for the general population and not as a symptom assessment tool or HRQOL tool in patients with hyponatremia."
- Such examples appear to indicate differing levels of evidence are needed to facilitate positive reviews by agency.

## LIMITATIONS

- For the purposes of this analysis, if a sponsor included a PRO in a DAP or EPAR, it was assumed a claim was sought.
  - PROs often are included in clinical trials for reasons outside of labeling,[9] so this assumption may have skewed results.
  - Given the proprietary nature of labeling discussions, the true intent of a sponsor is often unknown to outside observers.
  - The guidance documents (including the EMA reflection paper, FDA PRO guidance, and Biomarker and DDT Qualification programs) are all fairly recent regulatory developments. The impact of these guidance documents on trials planned prior to their release is unknown.
- If a measure was mentioned in the summary of characteristics section of an EPAR package, it was classified as a claim and not limited to treatment benefit.

## CONCLUSIONS

- Based on the products reviewed between 2006 and 2010, the EMA is more likely to grant PRO claims as compared with the FDA and is more likely to grant claims for higher order constructs such as HRQOL and functioning.
- While PRO labeling claims do not demonstrate perfect agreement between agencies on a macro level, acceptance of a PRO claim by the FDA may be predictive of acceptance of the same claim by the EMA.
- Precipitating factors such as therapeutic area, PRO measure, and order of regulatory submission may influence the agreement between agencies.
- Further investigation is warranted to support effective PRO strategies.

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