An Updated Review of FDA Warning and Untitled Letters for Clinical Outcome Assessment Claims between 2013 and 2020

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Background

- Clinical outcome assessment (COA) measures are widely used in drug development programs to provide evidence to describe or reflect how a patient feels, functions, or survives.
- In addition to assessing safety, manufacturing, and efficacy of pharmaceuticals, the FDA also oversees the communication of manufacturers to both physicians and patients. The FDA's Office of Prescription Drug Promotions (OPDP) is responsible for review of these promotional materials and will act if these are "false, lacking in fair balance, or otherwise misleading".[1]
- The FDA communicates violations to manufacturers through warning letters (WLs) and untitled letters (ULs). [2,3]
  - WLs: Violations of regulatory significance that **requires** action otherwise it may lead to further enforcement action
  - ULs: Does not meet threshold for regulatory significance but **requests** (rather than requires) a response
- Prior research (Symonds et al., 2014)[4] reported patient-reported outcome (PRO) violations between 2006 and 2012, demonstrating that 19% (41/213) of issued letters contained information about PRO infringements, with the most common being "PRO measure was not fit for purpose".
- Since then, the 21st Century Cures Act (2016) has been signed into law, and along with it, guidance to support patient-focused drug development.

Aims

- This current study aims to update the review by Symonds et al., 2014, to cover the period of 2013-2020 and expands to include infringements across all types of COAs.
- In addition, the aim is to ascertain the frequency and types of COA violations made in US pharmaceutical promotional materials between 2013 and 2020.

Methods

- WLs and ULs issued by the OPDP between January 2013 and December 2020 were sourced from the FDA website.
- The text of each letter was reviewed for COA violations and, if present, their type.
- COA violations were identified as any promotional violation using either patient-reported, observer-reported, clinician-reported, or performance-outcome measures.
- The associated promotional material was retrieved where possible. Details of each letter were noted, e.g., drug product, date of issuance, therapeutic area, etc.
- Violations were classified by their type as following: (1) PRO not fit for purpose; (2) Issue with study design or interpretation of results; (3) Inadequate statistical analysis; and/or (4) No treatment benefit.

REFERENCES:
1. Prescription-drug advertisements. 21 CFR §202.1 (2022).
2. U.S. Food & Drug Administration. About Warning and Close-Out Letters. FDA Website. April 29, 2019. Accessed October 28, 2021. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/about-warning-and-close-out-letters
3. U.S. Food & Drug Administration. Issuance of Untitled Letters. FDA Website. June 6, 2021. Accessed October 28, 2021. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/issuance-untitled-letters
4. Symonds T, Hackford C, Abraham L. A review of FDA warning letters and notices of violation issued for patient reported outcomes promotional claims between 2006 and 2012. Value in Health 2014; 17: 433-437.
5. Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities: Guidance for Industry and Review Staff. June 2018; https://www.fda.gov/media/133620/download

Results

- Between 2013 and 2020, the FDA issued a total of 81 letters (20 WLs and 61 ULs).
- Of the 81 letters, 20 (25%) contained a COA violation (5 WLs and 15 ULs) around efficacy or the broader patient experience elements (**Table 1**).

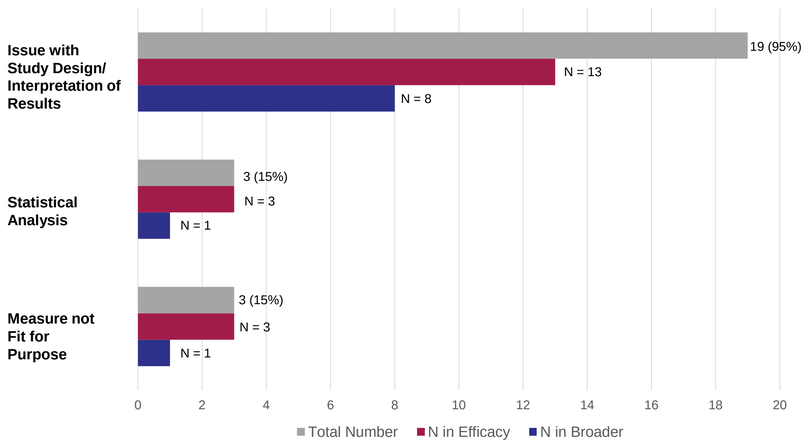
Table 1. Number of WLs and ULs between January 2013 and December 2020

Year	Number of OPDP Letters (WL/UL)	Number (%) of Letters with COA Violations	Number of WLs with COA Violations	Number of ULs with COA Violations
2020	6 (4/2)	2 (33%)	1	1
2019	10 (3/7)	2 (20%)	1	1
2018	7 (2/5)	1 (14%)	0	1
2017	5 (3/2)	0	0	0
2016	11 (3/8)	1 (9%)	1	0
2015	9 (2/7)	3 (33%)	1	2
2014	9 (0/9)	3 (33%)	0	3
2013	24 (3/21)	8 (33%)	1	7
Total	**81 (20/61)**	20 (25%)	**5**	**15**

COA = clinical outcome assessment; OPDP = Office of Prescription Drug Promotions; UL = untitled letter; WL = warning letter

- The most prominent COA violation was around issues with study design or interpretation of results (95%), which included: patient-reported claims in the absence of PRO assessment (63%), insufficient study type to support conclusions (47%), and broadening of claims beyond what was collected in the trial (21%) (**Figure 1**).
- Fewer violations related to statistical analysis issues (15%) and the measure not being fit for purpose (15%) (**Figure 1**).

Figure 1. Frequency of COA Violations by Theme

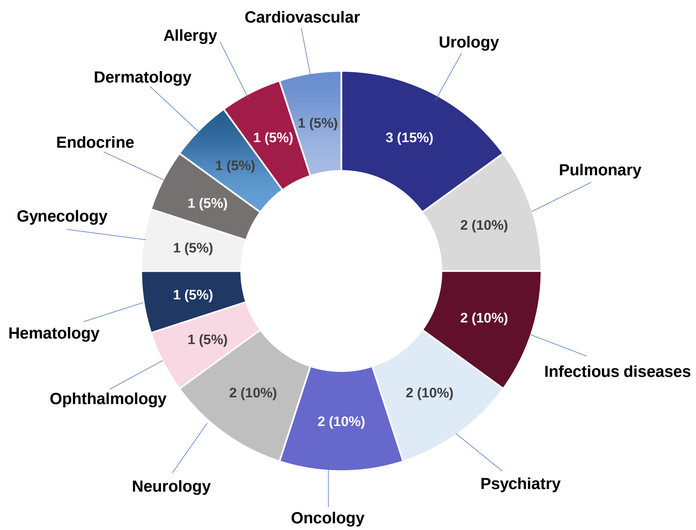


Note: Some letters included multiple violations and for some products, themes overlapped for violation letters across both the efficacy and broader elements. As part of this review, violations were grouped into 1) efficacy-related and 2) broader patient experience outside of efficacy alone (e.g., administration, convenience).

Results

- COA violations were identified across a range of therapeutic areas; the most common area being urology (3 [15%]). The 5 WLs were associated with urology (n = 2), pulmonary (n = 1), cardiovascular (n = 1), and ophthalmology (n = 1) (**Figure 2**).

Figure 2. Frequency of COA WLs or ULs by Therapeutic Area



Conclusions

- Overall, the absolute number of WLs and ULs issued declined from 2006-2012 (213 letters identified) to 2013-2020 (81 letters identified).
- Despite the overall reduction, the 25% identified letters with COA infringements (22% with PRO issues) during this review are still similar to the 19% PRO infringements found in the prior review during the period 2006-2012.
- The most prominent COA violation was related to study design or interpretation of results (95%), predominantly due to patient-reported claims in the absence of PRO assessment (63%).
- The reason for the overall reduction in letters could be due to increased awareness about the FDA expectations regarding promotional statements, which subsequently serves as an enforcement of best practices but, also, new guidance from FDA such as Drug & Device Manufacturer communications with Payers, Formulary Committees, and Similar Entities[5].
- Limitations: Awareness of violations may come from different sources, e.g., competitors, researchers, patients. As this review focused only on those letters captured by the FDA, it may not reflect the number of actual violations as some violations may remain undetected. Additionally, review of other enforcement actions were not included in the review (civil and criminal cases/penalties).

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