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2018 End-of-Year Summary of FDA Advertising and Promotion Enforcement Activity

January 31, 2019

Food, Drug, and Devices

This e-alert reviews trends emerging from warning letters and untitled letters concerning therapeutic product advertising and promotion issued in 2018 by the Office of Prescription Drug Promotion (OPDP) of the Center for Drug Evaluation and Research (CDER), the Advertising and Promotional Labeling Branch (APLB) in the Office of Compliance and Biologics Quality (OCBQ) of the Center for Biologics Evaluation and Research (CBER), and the Office of Compliance (OC) of the Center for Devices and Radiological Health (CDRH). We examined the nine advertising and promotion letters issued by OPDP, OCBQ, and CDRH OC, and tabulated the most frequently cited allegations. This alert summarizes our tabulation of all of the letters and other enforcement trends.[1]

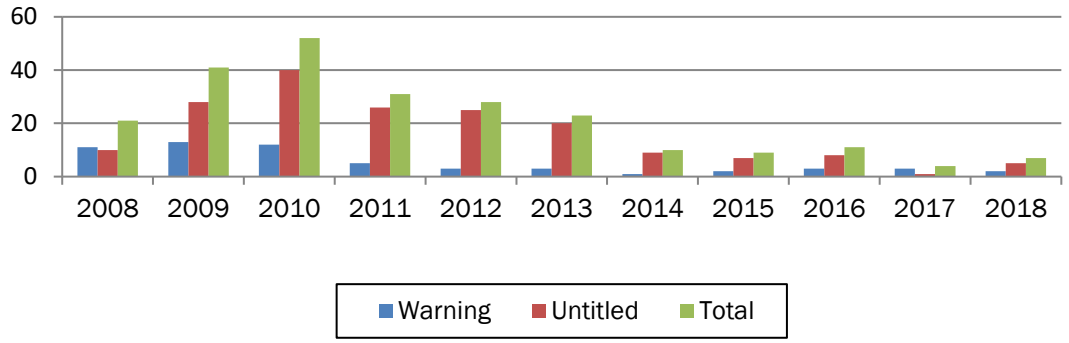
OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)

I. ENFORCEMENT ACTIVITY

In 2018, OPDP issued seven advertising and promotion enforcement letters, three more than the number issued in 2017, but still fewer than the number issued in 2016. Although this represents an increase in enforcement activity by OPDP, it is still consistent with the overall trend of fewer issued enforcement letters since 2010. In contrast, OPDP issued 52 letters in 2010.

[1] At the time of publication, it is unclear whether additional letters may be posted and back-dated to December 2018. In previous years, OPDP has issued multiple letters in December (six in 2016 and two in 2017). The federal government shut down on December 22, 2018, and although it reopened on January 25, 2019, FDA has not posted additional enforcement letters to its website since the shutdown. We will update this alert if additional letters are posted.

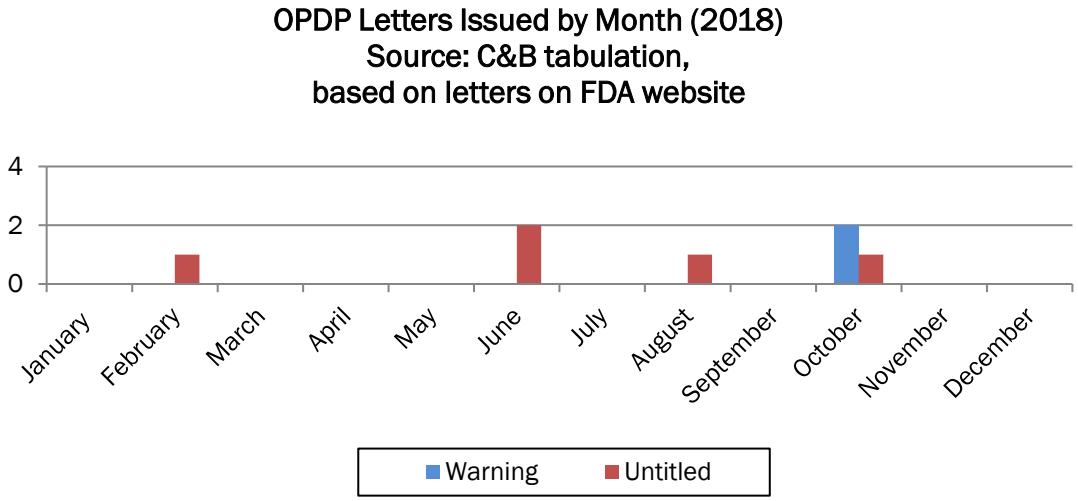
OPDP Warning and Untitled Letters (2008-2018)
Source: C&B tabulation, based on letters on FDA website



In a return to past practice, OPDP issued more untitled letters than warning letters in 2018. Of the seven letters OPDP issued, five were untitled letters, and only two were warning letters. The average number of allegations in each letter was nearly halved compared to 2017, however. Six of the seven letters contained only a single allegation, and only one letter contained two allegations, for an average of 1.14 allegations per letter (counted by the number of headings in each letter).

All of the letters issued for approved products related to products with boxed warnings, perhaps suggesting that OPDP is focusing its enforcement efforts on products that carry more significant risks. Two of the letters came in through FDA's Bad Ad program.

As in years past, OPDP's enforcement letters generally were issued in the second half of the year, with one letter in February, two letters in June, one letter in August, and three letters in October. This is similar to the pattern in 2016 and 2017 in which nine of eleven and three of four of OPDP's enforcement letters were issued in the second half of the year, respectively.



OPDP has not articulated a reason for its overall decline in enforcement activity, but as explained in our 2017 end-of-year summary, the downward trend in enforcement aligns with the timing of significant First Amendment litigation against the agency.[2] Moreover, in the past year, the agency's advertising and promotion enforcement activity has increasingly targeted manufacturers of tobacco products.[3]

II. CONTENT OF ENFORCEMENT LETTERS

A. Approved Products vs. Unapproved Products

In 2016, OPDP sent four letters addressing promotional activity of an unapproved product, a relative spike compared to historical norms. This led some to speculate that unapproved product promotion may be a new area of emphasis for FDA, or a setting in which FDA perceived fewer First Amendment constraints. OPDP's activity in 2017 and 2018 does not support this

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[2] *See* Covington, *2017 End-of-Year Summary of FDA Advertising and Promotion Enforcement Activity* (Jan. 26, 2018), *available at* https://www.cov.com/en/news-and-insights/insights/2018/01/2017-end-of-year-summary-of-fda-advertising-and-promotion-enforcement-activity. *See also* Derrick Gingery, *Advertising Enforcement: US FDA Content to Let Competitors 'Duke It Out,' Woodcock Says*, PINK SHEET (Sept. 23, 2018) (quoting CDER Director Janet Woodcock as stating that FDA is "very wary of wading into the First Amendment" and is focusing on advertising violations "where health and safety might be involved").

[3] *See, e.g.*, FDA, *FDA warns more companies to stop misleading kids with e-liquids that resemble kid-friendly foods as part of Youth Tobacco Prevention Plan*, WWW.FDA.GOV (May 10, 2018), *available at* https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm607327.htm.

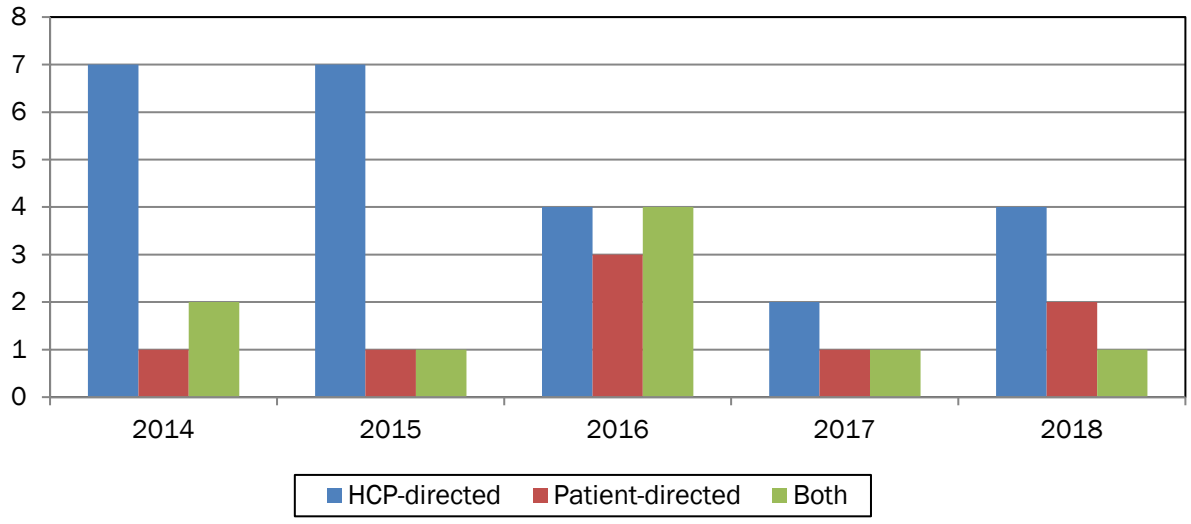
theory, however, as OPDP issued only one letter addressing promotional activity for an unapproved product in 2018 and no such letters in 2017.

B. Nature of Promotional Pieces

Similar to 2017, there generally was an even distribution of letters addressing materials directed at health care professionals (HCPs) and patients. In 2018, OPDP sent four letters based on HCP-directed materials, two letters based on patient-directed materials, and one letter[4] based on materials that targeted both HCPs and patients. Notably, as in years past there were no letters based on payor-directed materials.

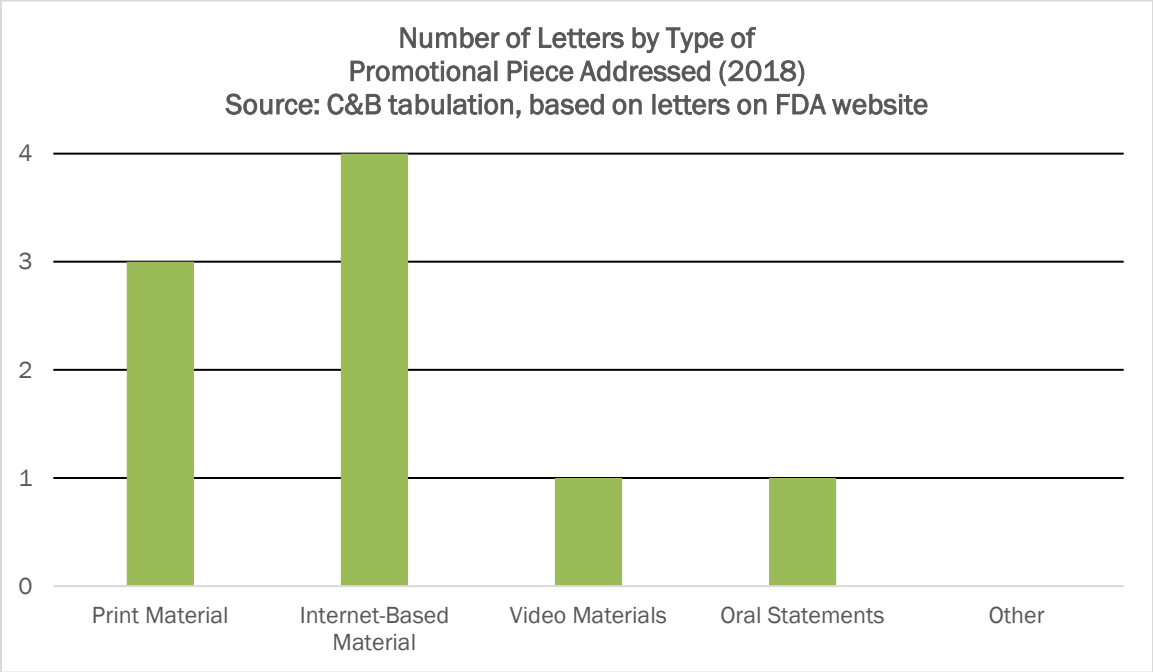
This spread is similar to the trends from 2016 and 2017, when there was also a relatively even distribution of letters addressing materials directed at HCPs and patients. Although there are more letters addressing materials directed toward HCPs than toward patients, the difference is comparatively slight, particularly in view of the small number of letters. By contrast, in 2015, approximately 80% of OPDP enforcement letters addressed materials directed at HCPs. There was a similar distribution in 2014, when promotional materials directed at HCPs comprised 70% of the materials discussed in OPDP enforcement letters.

Number of Letters by Audience (2014-2018)
Source: C&B tabulation, based on letters on FDA website



[4] This includes a letter addressing Vanda Pharmaceuticals Inc.'s corporate website, which would be available to HCPs and patients.

In 2018, OPDP's letters addressed four types of promotional materials: print materials (booth displays and sell sheets), Internet-based materials (websites), video materials (direct-to-consumer Internet video) and oral statements (made by sales representatives). Two letters addressed print materials only; three letters addressed Internet-based materials only (including one letter addressing a direct-to-consumer Internet video); one letter addressed print and Internet-based materials; and one letter addressed oral statements. This was the first time since 2014 that that any of the letters addressed oral statements by company representatives.

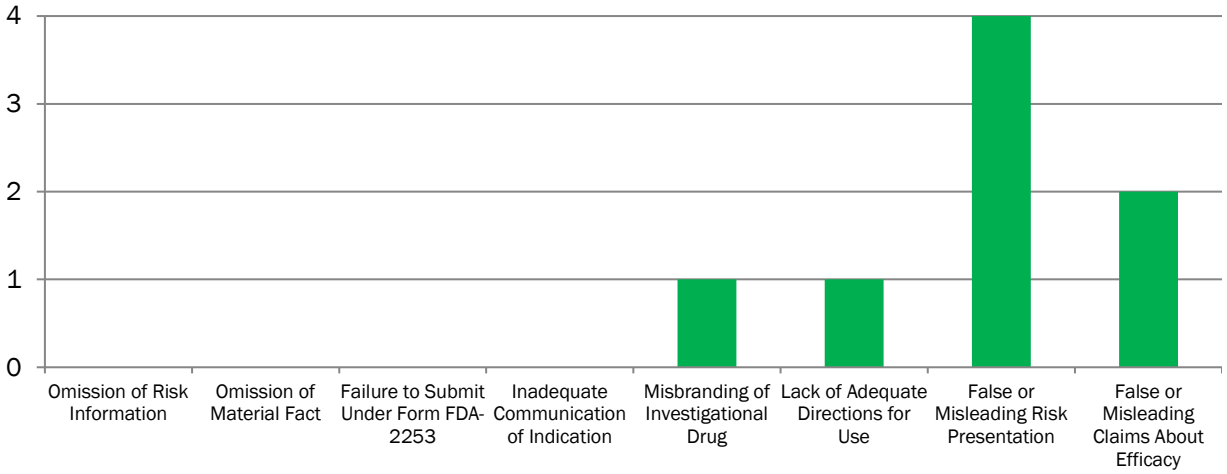


C. OPDP's Allegations

Four out of seven of OPDP's letters contained allegations of false or misleading risk presentation based on the headings in the letters (including one letter that alleged false or misleading "risk and benefit presentations"). Two letters contained allegations of false or

misleading claims about efficacy. One letter alleged misbranding of an investigational drug, and one letter alleged lack of adequate directions for use.

Number of Letters by Allegation* (2018)
Source: C&B tabulation, based on letters on FDA website



*Allegations exceed the total number of enforcement letters issued, as one letter contained more than one allegation.

1. False or Misleading Risk Presentation

Four out of seven letters alleged that promotional materials contained false or misleading risk information.

In two letters, OPDP alleged that the promotional materials contained efficacy claims but failed to communicate any risk information, and in a third letter, OPDP alleged that the promotional material suggested there were no risks associated with the use of the drug. In these three letters, OPDP explained that the misleading impression was not mitigated by directing users toward full prescribing information. Furthermore, these included the only two warning letters issued by OPDP in 2018.

In October, FDA issued two warning letters, one to MannKind Corporation and one to Vanda Pharmaceuticals Inc. In the MannKind letter, OPDP cited a Facebook post that made claims and representations about the drug Afrezza. The agency alleged that the post suggested there were no risks associated with Afrezza's use, despite the accompanying statement, "Please see full Prescribing Information, including boxed WARNING, Medication Guide, and Instructions for Use" with a link to the prescribing information, and a pop-up box (visible when a cursor hovers over the thumbnail of the Afrezza logo in a corner of the post) that includes information regarding acute bronchospasm.

In the Vanda letter, OPDP cited a webpage titled "Products" that stated the indications for which two drugs, Fanapt and Hetlioz, were approved, along with statements that full prescribing information was available at "www.fanapt.com" and "www.hetlioz.com." OPDP acknowledged these statements on the webpage, but it said such statements did not mitigate the omission of risk information from the webpage.

Similarly, in a June untitled letter to Pfizer Inc., OPDP cited a direct-to-consumer video, in which trained and paid physician and patient spokespersons made claims and representations about the benefit of Estring but did not provide risk information. OPDP stated that the omission of risk information was not mitigated by the physician spokesperson referring women to the website "askforthering.com" and to their healthcare provider for additional information.

One untitled letter, issued in February, more specifically alleged false or misleading risk *and* benefit presentations. In that letter, issued to Collegium Pharmaceuticals, Inc., OPDP cited an exhibit booth that displayed abuse-deterrent benefit claims for Xtampza ER on the principal display panel and risk information on a side panel. OPDP stated that presentation of the risk information was "not sufficient to ensure that the claims about abuse deterrent properties are truthful and non-misleading." The principal display panel utilized a blue background and large font size and presented claims at eye-level, whereas the side panel with the risk information was located several feet away from the principal display panel, utilized a much smaller font size and plain white background, and was presented at the bottom of the panel near the floor, partially obstructed from view by a table and chair.

2. False or Misleading Claims About Efficacy

In the June untitled letter to Pfizer, OPDP also cited a patient testimonial in the direct-to-consumer video, where the patient spokesperson claimed she experienced "instant relief." OPDP stated that the claim "misleadingly suggest[ed] that patients will experience similar results, i.e., instant relief of their symptoms," and that FDA was unaware of data to support such a claim.

In an August letter to Ascend Therapeutics US LLC, OPDP cited a sell sheet that suggested EstroGel contained the lowest effective dose of estrogen compared to other estrogen products. OPDP stated that other FDA-approved products contained lower doses of estrogen, however, and that the article cited by the sell sheet did not provide support for the claims for which it was cited.

3. Misbranding of an Investigational Drug

In a June untitled letter to Arog Pharmaceuticals Inc., OPDP alleged that a booth display and webpage misbranded Crenolanib by suggesting in a promotional context that the drug was safe and effective for the purpose for which it was being investigated. OPDP stated that the claims suggested that Crenolanib had been established as safe and effective for the promoted uses and failed to include any information indicating that Crenolanib was an unapproved investigational new drug.

4. Lack of Adequate Directions for Use

In an October untitled letter to Eisai Inc., OPDP alleged that oral statements made by an Eisai sales representative misbranded Fycompa by suggesting the drug was intended for use for which it lacked approval at the time the statements were made, as well as for new uses for which it lacked approval at the time the untitled letter was sent. OPDP acknowledged that Fycompa received approval for some of the indications discussed by the sales representative after the statements were made. It stated, however, that other uses were still unapproved at the time of the untitled letter and that Eisai had not provided data to support the suggested uses.

CBER ADVERTISING AND PROMOTIONAL LABELING BRANCH (APLB), OFFICE OF COMPLIANCE AND BIOLOGICS QUALITY (OCBQ)

ENFORCEMENT ACTIVITY

FDA's APLB in OCBQ issued one untitled letter in 2018 relating to advertising and promotion. This single letter is consistent with a recent downward trend in enforcement letters that began in 2013, when OCBQ issued only three letters total, and last year, when APLB issued no enforcement letters.

The APLB enforcement letter was issued in February 2018 to CSL Behring LLC. APLB alleged that CSL Behring's company website, patient brochure, exhibit panel, and sales aid included misleading efficacy presentations regarding Idelvion. The agency cited 21 CFR 202.1(e)(5), which states that an advertisement does not include a "true statement" of information relating to side effects, contraindications, and effectiveness if, among other things, "[i]t fails to reveal facts material in the light of its representations or material with respect to consequences that may result from the use of the drug as recommended or suggested in the advertisement." APLB stated that the promotional materials, which included claims about the drug accompanied by an image of a man about to engage in heading or kicking a soccer ball while jumping in the air, "misleadingly overpromise the effect that [Idelvion] will have on a hemophilic patient's activities and overall quality-of-life."

CDRH OFFICE OF COMPLIANCE (OC)

ENFORCEMENT ACTIVITY

The Office of Compliance (OC) in FDA's CDRH posted one enforcement letter relating to advertising and promotion in 2018, down from two letters in 2017. In 2015 and 2016 CDRH OC did not post any letters.[5]

In April, CDRH issued a warning letter to RADLogics, Inc., alleging that its AlphaPoint Imaging Software was misbranded because RADLogics marketed the device for uses outside the scope of its premarket notification (commonly referred to as 510(k)). AlphaPoint was cleared with indications to allow the "review, analysis and interchange of CT chest images." FDA stated that RADLogics marketed AlphaPoint on its website and a YouTube video, however, "as providing computer-assisted detection (CADe) of abnormalities in radiology images." FDA alleged that this promoted use was a major change or modification to the intended use of AlphaPoint, and the device was misbranded because RADLogics introduced the device with such intended use without submitting a new premarket notification to FDA under FDCA § 510(k) and 21 CFR § 807.81(a)(3)(ii).

[5] This includes a letter addressing Vanda Pharmaceuticals Inc.'s corporate website, which would be available to HCPs and patients.

If you have any questions concerning the material discussed in this client alert, please contact the following members of our Food, Drugs, and Devices practice:

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