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2020 End-of-Year Summary of FDA Advertising and Promotion Enforcement Activity

January 26, 2021

Food, Drugs, and Devices

This e-alert reviews trends emerging from warning letters and untitled letters concerning product advertising and promotion issued in 2020 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), the Office of Product Evaluation and Quality (OPEQ) of the Center for Devices and Radiological Health (CDRH), and the Office of Medical Device and Radiological Health Operations (OMDRHO) in the Office of Regulatory Affairs (ORA). OCBQ did not issue any advertising and promotion enforcement letters in 2020. We examined the seven advertising and promotion letters issued by OPDP, OPEQ, and OMDRHO, and analyzed the most frequently cited allegations. This alert summarizes the letters and other enforcement trends.

Office of Prescription Drug Promotion (OPDP)

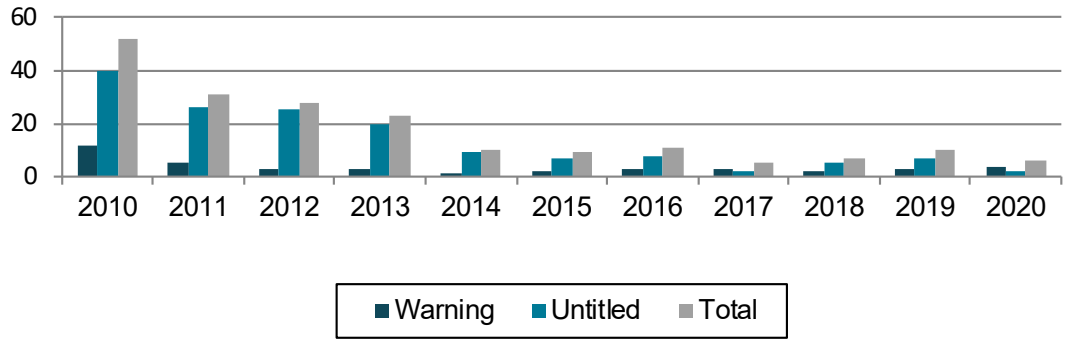
I. Enforcement Activity

In 2020, OPDP issued six enforcement letters relating to the advertising and promotion of prescription drugs, four fewer than it issued in 2019 and one fewer than it issued in 2018. This figure remains consistent with the longer-term trend of OPDP issuing substantially fewer enforcement letters over the course of the past decade. By contrast, OPDP issued 52 letters in 2010.

OPDP has not articulated a reason for its overall decline in enforcement activity. However, the downward trend in enforcement by OPDP likely reflects continued First Amendment pressure on FDA to allow truthful and non-misleading communications about prescription drugs.

In our 2019 alert, we noted that the slight increase in enforcement in 2018 and 2019 might indicate a recalibration of agency policy in a post-*Caronia* world. The slight dip in enforcement letters in 2020, in comparison to recent years, may have been a result of the FDA's focus on addressing the COVID-19 public health emergency.

OPDP Warning and Untitled Letters (2010-2020)*
Source: C&B tabulation, based on letters on FDA website



*In September 2011, FDA announced that the Division of Drug Marketing, Advertising, and Communications (DDMAC) would be reorganized into the Office of Prescription Drug Promotion (OPDP). For ease of reference, this alert refers only to OPDP.

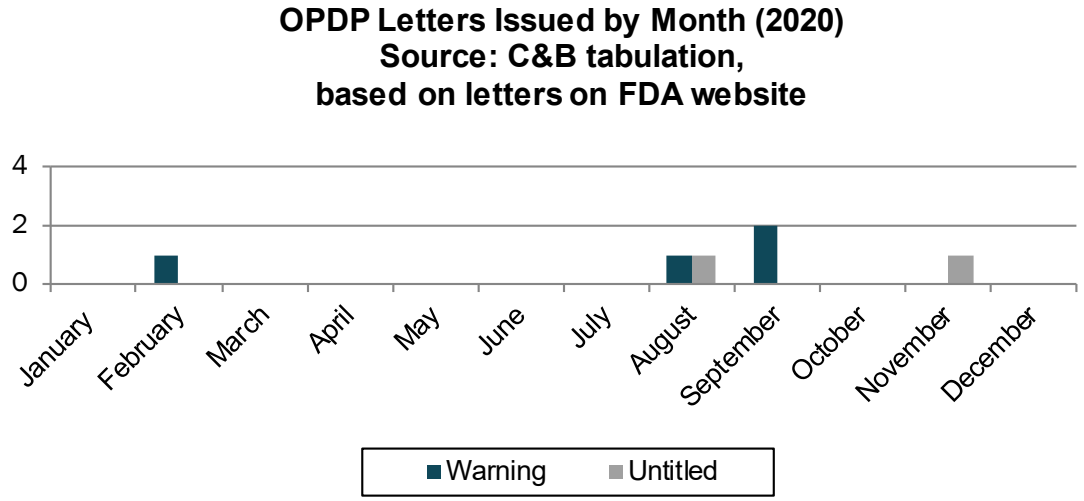
In a departure from historical trends, OPDP relied more heavily on warning letters than untitled letters in 2020. Of the six letters OPDP issued, four were warning letters, and only two were untitled letters.

The average number of allegations increased compared to 2019. Five of the six letters included two allegations, and one letter contained three allegations, for an average of 2.2 allegations per letter (counted by the number of headings in each letter). By contrast, the average number of allegations in each letter was 1.7 in 2019 and 1.1 in 2018.

Four letters, including three warning letters and one untitled letter, related to products with boxed warnings. Notably, the number of letters related to boxed warnings has varied significantly in recent years. In 2019, OPDP cited only one product with a boxed warning, whereas in 2018, all of the letters issued for approved products related to products with boxed warnings.

OPDP's increased use of warning letters, coupled with its emphasis on products with boxed warnings and the higher number of allegations per letter, suggests that OPDP may be focusing its enforcement efforts on violations that pose significant safety risks or have implications on public health. In two letters, OPDP specifically noted that the drug was intended to treat a vulnerable pediatric patient population.

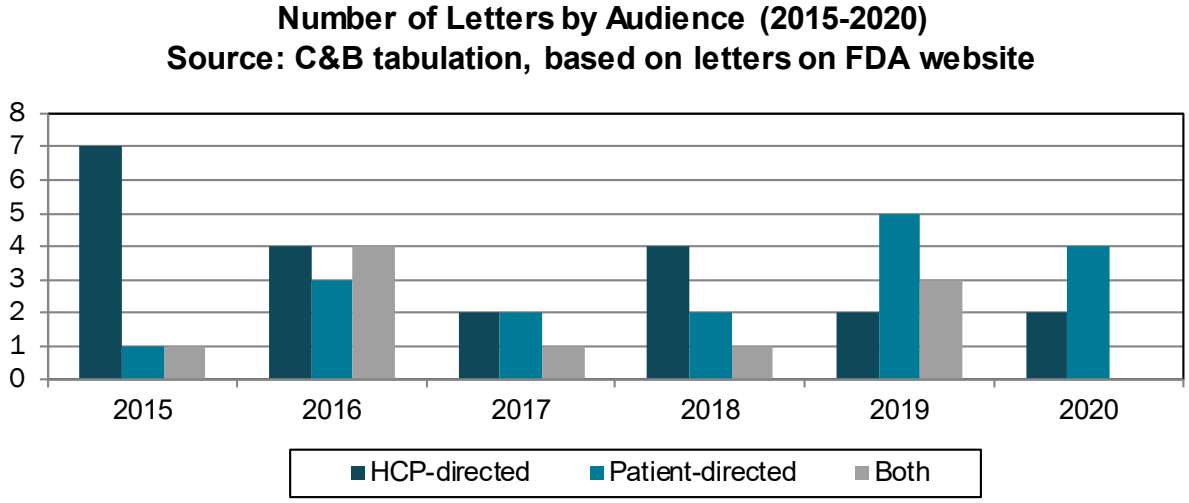
As in years past, OPDP's enforcement letters were clustered in the second half of the year, with one letter issued in February, two letters issued in August and September, and one final letter issued in November. This pattern is similar to that observed in 2019, when seven of ten OPDP enforcement letters were issued in the second half of the year.



II. Content of Enforcement Letters

A. Nature of Promotional Pieces

The majority of OPDP's 2020 enforcement letters addressed materials directed at patients, as opposed to materials intended solely for health care professionals (HCPs). This is consistent with recent trends. As recently as 2015, 80% of OPDP enforcement letters addressed materials directed toward HCPs. However, since then, FDA has turned its attention toward patient communications. In 2019, 80% of letters were directed at least partially at patients.



In 2020, OPDP's letters addressed three types of promotional materials: Internet-based materials (sponsored links and emails), video materials (a direct-to-consumer broadcast television advertisement), and radio materials (a direct-to-consumer radio advertisement). Four of the letters addressed Internet-based materials, and the other two letters addressed video and radio materials, respectively.

Although this scope is consistent with OPDP's increasing focus on Internet-based materials, it is noteworthy for multiple reasons. Whereas OPDP previously devoted significant attention to sponsored links — the office's predecessor once issued 14 such letters in a single day[1] — it had not cited any such material since 2014. This year, OPDP issued two warning letters addressing sponsored links appearing on Google, both of which concerned products with boxed warnings. This year is also the first time since 2005 that OPDP issued a letter related to a radio advertisement.

Additionally, although print materials have made up a declining portion of the overall total letters issued over the past five years, 2020 represents the first year that OPDP issued no letters related to print materials (e.g., print advertisements, brochures, booth displays, and sell sheets). Consistent with recent years, no letters addressed oral statements by company representatives.[2]

OPDP's letter relating to emails sent by the company CEO and a sales representative also is noteworthy. Companies are increasingly evaluating alternative channels for sales representatives to communicate with HCPs, particularly during the pandemic, when in-person meetings are discouraged. In particular, some companies allow, or are considering allowing, sales representatives more freedom to email or text HCPs, including potentially without the use of pre-approved templates. The letter reinforces FDA's view that full safety information is required even in these informal means of interacting with HCPs.

Finally, all of the letters issued in 2020 related to marketed products; none included allegations of preapproval promotion. OPDP issued two letters concerning investigational products in 2019, and one letter each in 2017 and 2018.

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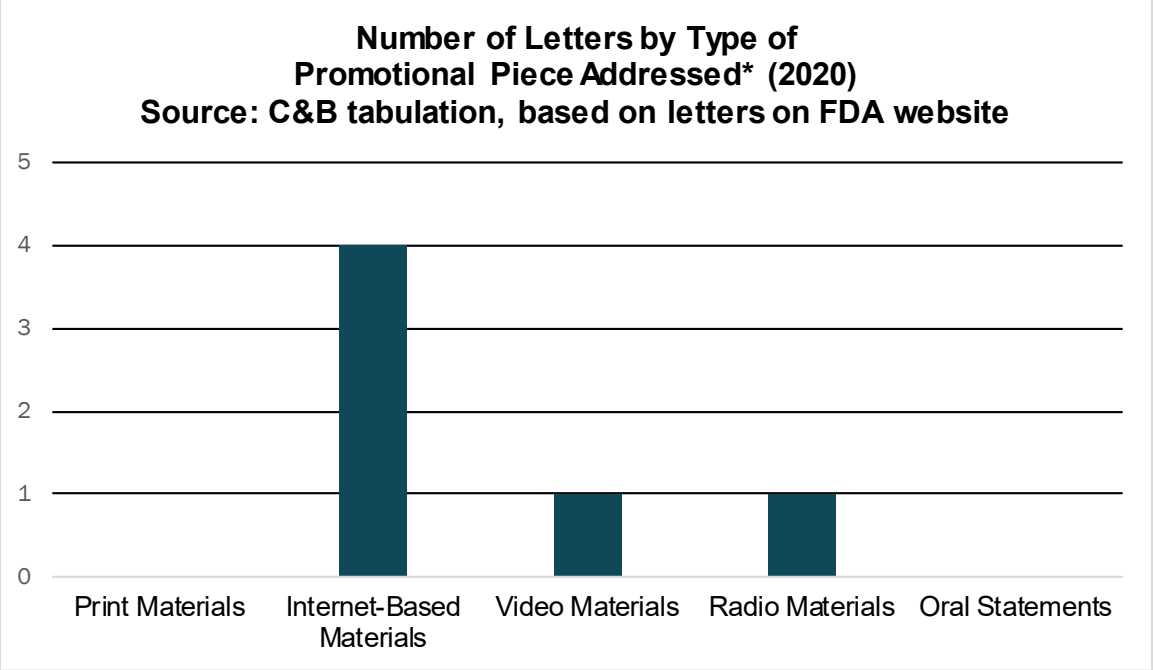
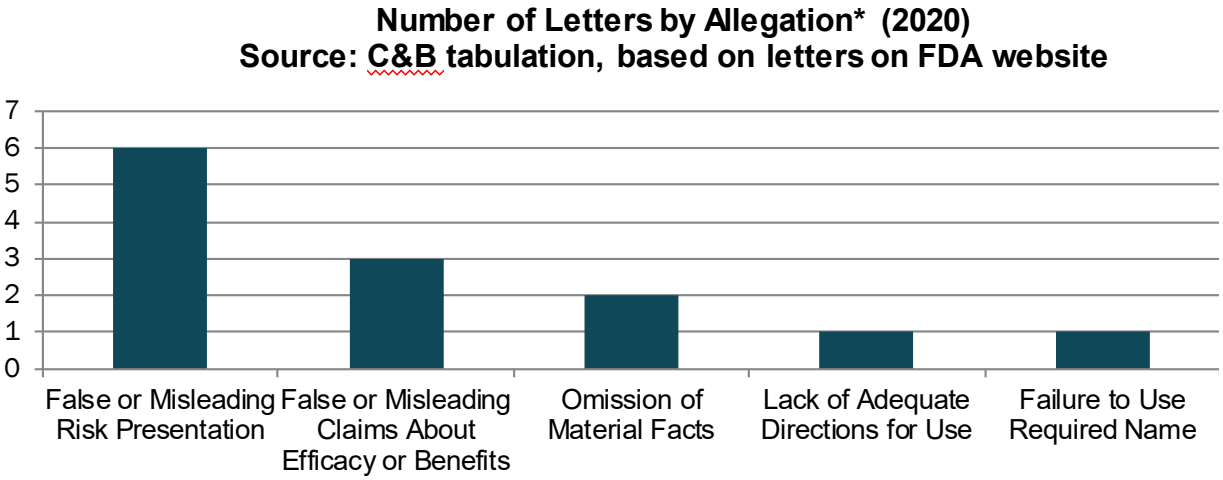
[1] *See* Covington, *2009 End-of-Year Summary of DDMAC and APLB Enforcement Activity* (Jan. 28, 2018), *available at* https://www.cov.com/-/media/files/corporate/publications/2010/01/2009-end-of-year-summary-of-ddmac-and-aplb-enforcement-activity.pdf.

[2] In 2015, 2016, 2017, and 2019, no letters addressed oral statements by company representatives. In 2018, a single letter addressed oral statements.



B. OPDP's Allegations

All six of OPDP's letters contained allegations of false or misleading risk presentation (including one letter that alleged "false or misleading risk and benefit presentations"). Of these letters, three additionally alleged false or misleading claims about efficacy or benefit (including two letters that alleged "false or misleading claims about efficacy" and one that alleged "false or misleading benefit presentation") and two cited omission of material facts (including one letter that alleged "omission of material fact"). Allegations of lack of adequate directions for use and failure to use required established name appeared in one letter each.



*Allegations exceed the total number of enforcement letters issued, as all letters contained more than one allegation. Because OPDP does not use standardized headings in its letters, allegations on the X axis include headings with minor phrasing differences.

1. False or Misleading Risk Presentation

Every letter issued in 2020 alleged that the cited promotional material contained false or misleading risk information. In the past, OPDP typically categorized allegations of this type as "Minimization of Risk Information" or "Omission and Minimization of Risk Information." In 2020, FDA continued to recast these allegations as "False or Misleading Risk Presentation," which may reflect a response to court decisions holding that truthful and non-misleading communications are constitutionally protected. For all six letters, there were one or more additional allegations.

In three warning letters, OPDP alleged that the promotional materials failed to include "any risk information." In one such letter, issued to Nalpropion Pharmaceuticals LLC, OPDP acknowledged that a sponsored link for Contrave (naltrexone hydrochloride and bupropion hydrochloride) included the statement "View Important Safety Info & Boxed Warning," but OPDP added that "this statement does not mitigate the misleading omission of risk information." In another letter, issued to Outlook Pharmaceuticals, Inc., OPDP alleged that a sponsored link included no risk information at all, even though ProCentra (dextroamphetamine sulfate) is a schedule II controlled substance with a boxed warning regarding the potential for abuse and serious consequences associated with misuse, including death. OPDP stated that the sponsored link was "particularly alarming from a public health perspective" because it included statements promoting liquid treatment options and bubblegum flavoring that could appeal to parents.

In the remaining letters, which included one warning letter and two untitled letters, OPDP alleged that promotional materials omitted important risk information, even though some risk information was provided. For example, in a November untitled letter to Azurity Pharmaceuticals, Inc., OPDP alleged that a professional email for Xatmep (methotrexate) included a claim about "easy dose titration" but failed to disclose the warning and precaution regarding the risk of improper dosing. The Xatmep letter also alleged that the email failed to present risk information with reasonably comparable prominence as compared to benefit information. OPDP alleged that Azurity "minimiz[ed]" the boxed warning by including it after the signature block of the email, while providing the benefit claims in the body of the email.

2. False or Misleading Claims About Efficacy or Benefit

In three letters alleging false or misleading risk presentation, including one warning letter and two untitled letters, OPDP contended that the promotional pieces at issue also contained false or misleading claims about efficacy.

The Contrave warning letter alleged that the sponsored link was misleading with respect to efficacy because it failed to disclose relevant information from the indications and usage section of the Prescribing Information (PI) regarding the weight loss product's indication and limitations of use. OPDP stated that broad claims suggested that "patients, no matter their [Body Mass Index] BMI, should expect to achieve the 'average' results presented in the sponsored link," even though Contrave "is not approved for use in patients that do not meet the initial BMI criteria." OPDP also stated that the sponsored link was misleading because it referenced the more favorable co-primary endpoint of percent change from baseline body weight, without disclosing the percentage of patients who achieved a treatment response in comparison to patients who received the placebo.

OPDP's Xatmep untitled letter similarly alleged that the failure to adequately communicate Xatmep's full FDA-approved indication contributed to a misleading impression of the benefits of the drug. OPDP stated that a claim in the email misleadingly suggested that the drug was "approved for use in patients of all ages without consideration for the necessity of other treatments as part of a combination therapy." Xatmep was approved for use in the treatment of pediatric patients with acute lymphoblastic leukemia (ALL) as part of a multi-phase, combination chemotherapy maintenance regimen. OPDP acknowledged that Azurity included the full indication below the signature block of the email, but it stated that doing so did "not mitigate the misleading impression."

In an August untitled letter to Xeris Pharmaceuticals, Inc., OPDP alleged that claims in a direct-to-consumer broadcast television advertisement for Gvoke (glucagon) "misleadingly suggest[ed] that the Gvoke pre-filled syringe can be easily used and individuals can confidently recognize that they have correctly administered the product." OPDP stated that the PI and Instructions for Use for Gvoke describe multiple steps associated with preparing and administering the pre-filled syringe. Additionally, OPDP noted that there is no signal to indicate that the medication was administered correctly.

3. Omission of Material Facts

The Gvoke untitled letter also alleged that the television advertisement omitted material information about the seriousness of hypoglycemia, the circumstances when it is appropriate to administer Gvoke, and the need for administration by others. OPDP stated that, while the advertisement included statements about "early, mild symptoms of hypoglycemia," it did not address "the symptoms of severe hypoglycemia for which Gvoke is indicated." OPDP stated further that the advertisement "fail[ed] to provide any information regarding the circumstances when it is appropriate to administer Gvoke and the need for administration by others."

OPDP's warning letter to Sprout Pharmaceuticals, Inc., regarding a radio advertisement for Addyi (flibanserin), alleged a failure to communicate material information about the product's full FDA-approved indication. OPDP stated that broad claims "suggest[ed] that Addyi is approved for all women 'frustrated by their low libido' when this is not the case."

5. Lack of Adequate Directions for Use

In a warning letter to Nephron Pharmaceuticals Corporation, OPDP alleged that emails sent by the CEO and a company sales representative created a misleading impression that Budesonide Inhalation Suspension, an asthma medication, was safe and effective as a treatment for symptoms associated with COVID-19. OPDP stated that Budesonide is not approved for such use and its labeling does not contain adequate directions for such use. OPDP stated further that these claims and representations "are particularly alarming from a public health perspective because COVID-19 has caused significant morbidity and mortality, and because there is currently no FDA-approved treatment for symptoms associated with COVID-19."

6. Failure to Use Required Name

OPDP's ProCentra letter contended that the sponsored link failed to include the established name of the product (dextroamphetamine sulfate). Under 21 C.F.R. § 201.10(g)(1), "the established name shall be placed in direct conjunction with the proprietary name or designation."

CBER Office of Compliance And Biologics Quality (OCBQ)

Enforcement Activity

FDA's Office of Compliance and Biologics Quality (OCBQ) did not issue any enforcement letters in 2020 relating to advertising and promotion. This lack of enforcement continues a recent downward trend in enforcement letters that began in 2013, when the office issued only three letters total, after issuing between five and seven letters each year between 2008 and 2012. Since 2013, OCBQ has issued only two enforcement letters, one in 2015 and one in 2018.

CDRH Office of Product Evaluation and Quality (OPEQ) and ORA Office of Medical Device and Radiological Health Operations (OMDRHO)

I. Enforcement Activity

ORA's OMDRHO issued one warning letter related to advertising and promotion in 2020, which was co-signed by CDRH's OPEQ. This single letter represented a decline from 2019, when OPEQ and OMDRHO issued a combined eight warning letters, but it remains consistent with the level of enforcement activity in prior years.[3] CDRH's Office of Compliance[4] issued one letter related to advertising and promotion in 2018 and two letters in 2017.

II. Content of Enforcement Letter

A January warning letter alleged that CPAPNEA Medical Supply adulterated and misbranded the Optipillows Expiratory Positive Airway Pressure (EPAP) mask by promoting the product beyond its cleared intended use of alleviating snoring during sleep in adults. Specifically, FDA alleged that the product labeling and statements on the company's website suggested that the device was intended to treat obstructive sleep apnea and that it could be used as a substitute for Continuous Positive Airway Pressure (CPAP) devices. FDA stated that marketing the EPAP device for the treatment of obstructive sleep apnea represented a "major change or modification" that required the submission of a new 510(k) premarket notification. FDA further alleged that statements suggesting the mask could be an effective substitute for CPAP devices and that FDA had cleared EPAP for treating obstructive sleep apnea were false and misleading.

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[3] On December 6, 2019, OPEQ issued a warning letter to Zona Health, Inc., regarding the company's marketing of the Zona Plus, a handheld unit used to perform isometric exercise. Since this letter was not published until March 3, 2020, it was not included in our 2019 end-of-year summary, but it is included in our 2019 tally in this alert.

[4] In March 2019, FDA began implementing a reorganization of CDRH to integrate the center's premarket and postmarket program functions along product lines, rather than according to the stage of the product's life cycle. OPEQ combines the former Office of Compliance, Office of Device Evaluation, Office of Surveillance and Biometrics, and Office of In Vitro Diagnostics and Radiological Health into one super office.

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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