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2019 End-of-Year Summary of FDA Advertising and Promotion Enforcement Activity

February 24, 2020

Food, Drugs, and Devices

This e-alert reviews trends emerging from warning letters and untitled letters concerning product advertising and promotion issued in 2019 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)[1] at 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 2019. We examined the 17 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

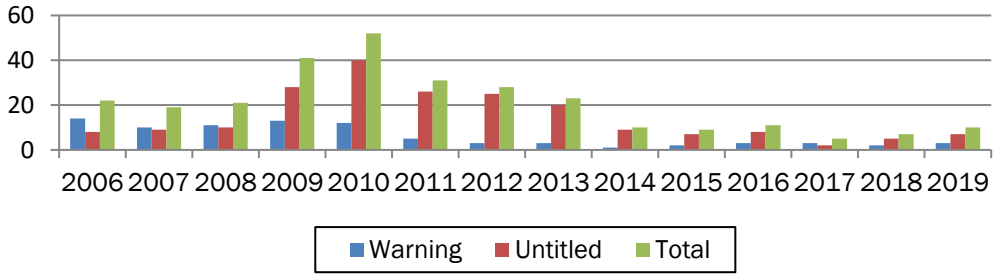
In 2019, OPDP issued ten advertising and promotion enforcement letters, three more than it issued in 2018 and five more than it issued in 2017. This figure represents the second year in a row in which OPDP's enforcement activity has increased. However, it remains consistent with the longer-term trend of OPDP issuing substantially fewer enforcement letters over the course of the past decade. OPDP has not articulated a reason for its overall decline in enforcement activity.

[1] 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.

However, as explained in our end-of-year summary from 2017,[2] the downward trend in enforcement aligns with the timing of significant First Amendment litigation against the agency, most notably the Second Circuit's decision in *United States v. Caronia*.[3] In the seven years prior to *Caronia* (2006-2012), OPDP issued 30.1 enforcement letters, on average, per year, and 52 letters in 2010 alone. In the seven years post-*Caronia* (2013-2019), OPDP has issued an average of 10.6 enforcement letters per year. Even though there were no significant judicial opinions regarding FDA's interpretation of commercial speech rights in 2019, the agency continues to face First Amendment pressure to allow truthful and non-misleading communications about prescription drugs. In this environment of increased suspicion of attempts to regulate advertisers' speech, the ongoing lack of active enforcement by OPDP likely reflects FDA's attempts to balance the commercial speech implications of regulating promotion with the agency's mission to protect the public health.

Nonetheless, the slight increase in enforcement in 2018 and 2019 may indicate a recalibration of agency policy in a post-*Caronia* world. The uptick in enforcement corresponds temporally with the issuance and finalization of two guidance documents on off-label communications.[4]

OPDP Warning and Untitled Letters (2006-2019)*
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), which includes the Division of Direct-to-Consumer Promotion and the Division of Professional Promotion. For ease of reference, this alert refers only to OPDP.

[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").*

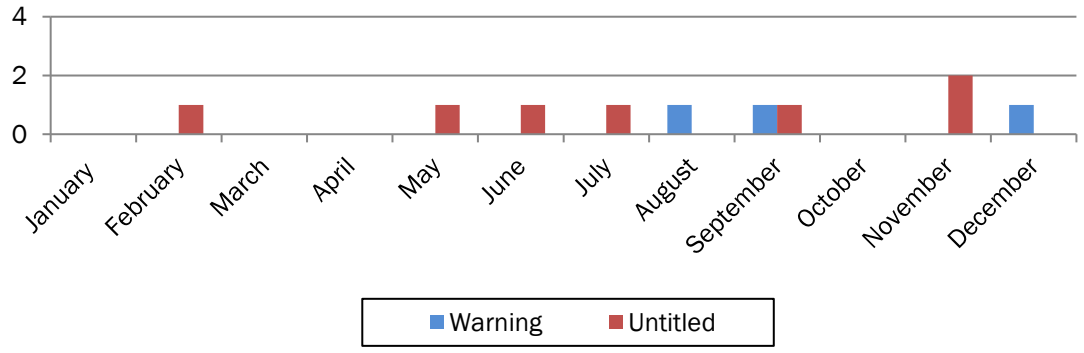
[3] United States v. Caronia, 703 F.3d 149 (2d Cir. 2012).

[4] *See* FDA, Guidance, Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities—Questions and Answers (Final June 2018) (Draft Jan. 2017); FDA, Guidance, Medical Product Communications That Are Consistent With FDA-Required Labeling—Questions and Answers (Final June 2018) (Draft Jan. 2017).

Consistent with historical trends, OPDP relied more heavily on untitled letters than warning letters in 2019. Of the ten letters OPDP issued, seven were untitled letters, and only three were warning letters. The average number of allegations in each letter was 1.7 (counted by the number of headings in each letter). With the exception of 2018, when six of seven letters contained only a single allegation, over the past five years, the average number of allegations per letter has consistently remained between approximately 1.7 and approximately 1.8. By contrast, from 2010 to 2014, the average number of allegations per letter was approximately 2.6.

As in years past, OPDP's enforcement letters were clustered toward the second half of the year, with one letter issued each in February, May, June, July, and August; two letters issued in September and November; and one final letter issued in December. This pattern is similar to that observed in 2018, when four of seven OPDP enforcement letters were issued in the second half of the year. Notably, all three of the 2019 warning letters were issued in the second half of the year.

OPDP Letters Issued by Month (2019)
Source: C&B tabulation,
based on letters on FDA website



II. CONTENT OF ENFORCEMENT LETTERS

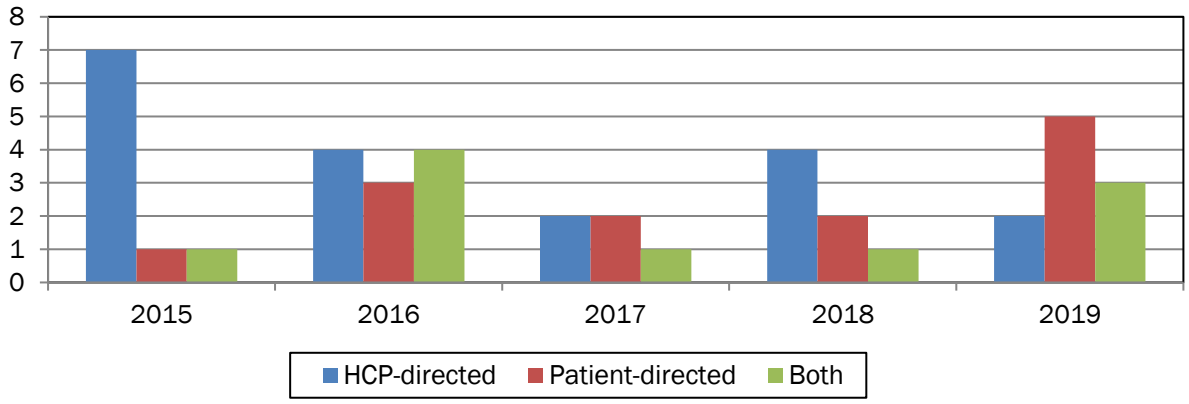
A. Nature of Promotional Pieces

In a departure from past practice, the majority of OPDP's 2019 enforcement letters addressed materials directed at least partially at patients, as opposed to materials intended solely for health care professionals (HCPs). In 2019, OPDP sent five letters based on patient-directed materials, two letters based on materials directed at HCPs, and three letters based on materials

that targeted both[5] HCPs and patients. By contrast, promotional materials directed at HCPs comprised 80% of OPDP enforcement letters in 2015. From 2016 to 2018, there was a more even distribution of letters addressing promotional materials directed at HCPs and patients, though there continued to be slightly more letters addressing promotional materials directed toward HCPs.

FDA's increased emphasis on patient-directed materials corresponds with Department of Justice's (DOJ) recent scrutiny of patient interactions, particularly in the form of False Claims Act (FCA) settlements related to patient support programs. There has been no publically announced coordination between the two agencies, but as companies are increasingly targeting patients directly in connection with their marketing outreach, both agencies are increasingly prioritizing enforcement against improper patient communications.

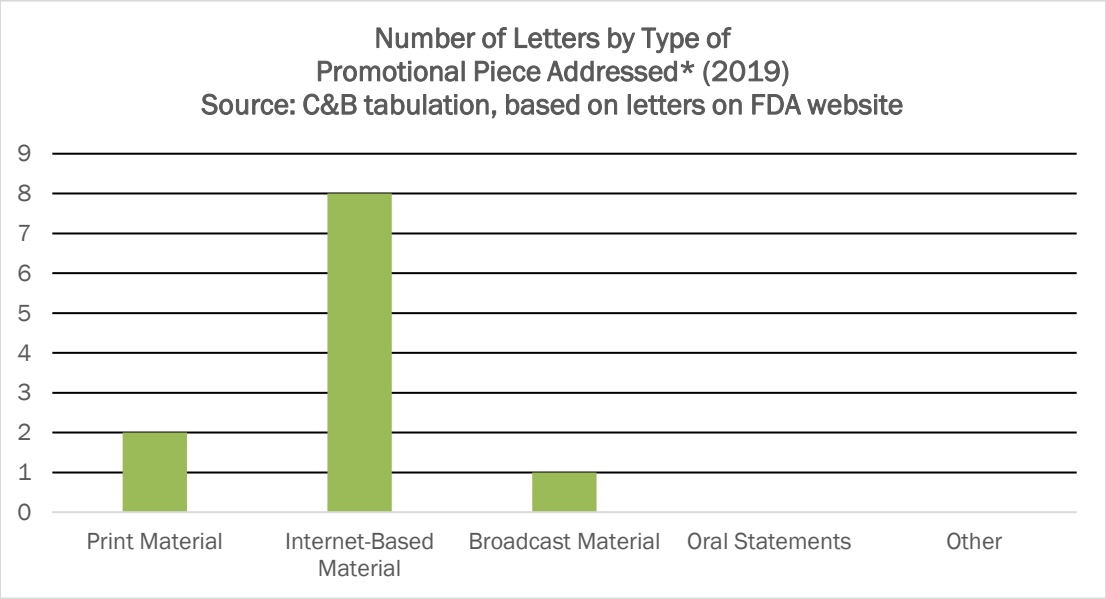
Number of Letters by Audience (2015-2019)
Source: C&B tabulation, based on letters on FDA website



In 2019, OPDP's letters addressed a wide array of promotional pieces, including print advertisements, Internet-based materials (websites, direct-to-consumer videos, online display banners, an online article, and a professional email), and a television advertisement. A majority of these letters (80%) addressed Internet-based materials (seven addressed Internet-based materials only, and one addressed both print and Internet-based materials), and the other two letters addressed print material only and broadcast material only, respectively. This scope is consistent with the three-year trend of OPDP's increasing focus on Internet-based materials, with two of five letters (40%) addressing Internet-based materials in 2017, and four of seven

[5] This includes letters addressing materials on general use websites, such as company corporate websites, which are available to both HCPs and patients and do not otherwise bear any indicia of being intended for only a limited audience.

letters (57%) addressing Internet-based materials in 2018. Consistent with recent years, no letters addressed oral statements by company representatives or other types of materials.[6]



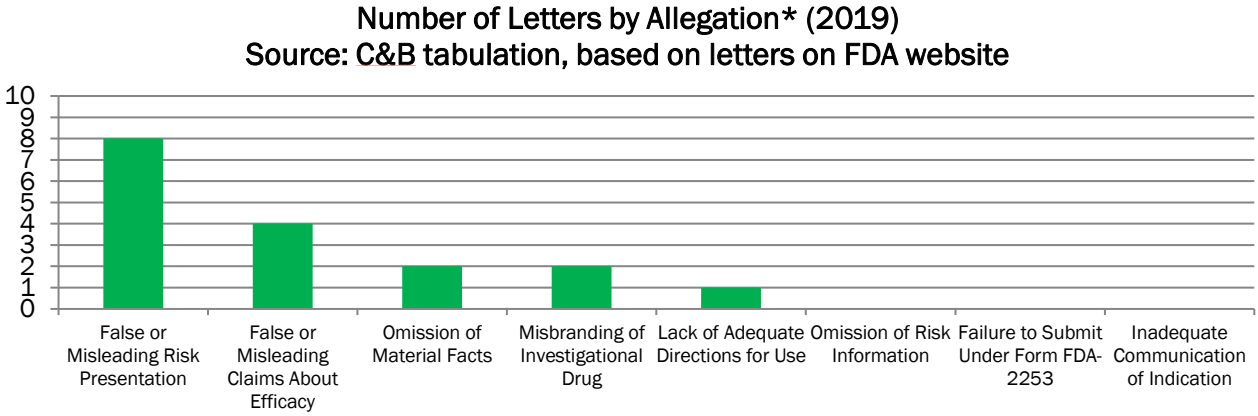
*Number of letters exceeds the total number of enforcement letters issued, as one letter addressed both a print advertisement and online display banners.

B. OPDP's Allegations

Eight out of ten 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, four additionally alleged false or misleading claims about efficacy, two cited omission of

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

material facts, and one alleged lack of adequate directions for use. The remaining two letters alleged misbranding of investigational drugs.



*Allegations exceed the total number of enforcement letters issued, as five 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. For example, of the eight letters alleging "False or Misleading Risk Presentation," five letters included the heading "False or Misleading Risk Presentation," two included the heading "False or Misleading Risk Presentations," and one included the heading "False or Misleading Risk and Benefit Presentations."

1. False or Misleading Risk Presentation

Every letter addressing approved drugs alleged that the cited promotional materials contained false or misleading risk information. As noted in the 2016 and 2017 alerts, in the past, OPDP typically categorized allegations of this type as "Minimization of Risk Information" or "Omission and Minimization of Risk Information." In 2019, 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.[7] In three letters, this allegation was the sole allegation. In five letters, there were one or more additional allegations.

In two letters, OPDP alleged that promotional materials failed to include risk information altogether. These materials included an online banner for Metuchen Pharmaceuticals LLC's Stendra (avanafil) and a portion of Rockwell Medical, Inc.'s website addressing Triferic (ferric pyrophosphate citrate). In other letters, OPDP alleged that the risk information provided was insufficient. For example, in a December warning letter to Alkermes, Inc., concerning a print advertisement for Vivitrol (naltrexone for extended-release injectable suspension), OPDP

[7] *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; Covington, *2016 End-of-Year Summary of FDA Advertising and Promotion Enforcement Activity* (Jan. 9, 2017), *available at* https://www.cov.com/en/news-and-insights/insights/2017/01/2016-end-of-year-summary-of-fda-advertising-and-promotion-enforcement-activity.

alleged that a print advertisement omitted the "serious and potentially fatal risk" of opioid overdose. Although the advertisement directed readers to review additional safety information on subsequent pages, OPDP concluded that this instruction did "not mitigate the misleading omissions of material risk information from the main body of the print ad."

OPDP also alleged that several promotional materials failed to present risk information with reasonably comparable readability and/or prominence as compared to benefit information. For example, in a July untitled letter to CooperSurgical, Inc. regarding a television advertisement for ParaGard (intrauterine copper contraceptive), OPDP alleged that the presentation of the "major statement" of risks via audio and superimposed text (SUPER) was undermined by the simultaneous presentation of fast-paced visuals featuring choreographed dancing to background music and multiple scene changes. The allegations in this letter were nearly identical to those OPDP made in untitled letters to Sanofi-aventis US and Celgene Corporation in December 2016 concerning the use of "compelling and attention-grabbing visuals" and background music that "compete[d] for the consumers' attention" during the presentation of risk information.[8] The ParaGard letter suggests that FDA continues to be particularly concerned about the presentation of risk information in television advertisements.

2. False or Misleading Claims About Efficacy

In four letters alleging false or misleading risk presentation, including two untitled letters and two of the three warning letters issued in 2019, OPDP contended that the promotional pieces at issue also contained false or misleading claims about efficacy.

In two untitled letters, OPDP alleged that promotional materials made efficacy claims not supported by data. In a May untitled letter to VIVUS, Inc., OPDP contended that claims on the consumer website homepage suggested that Qsymia (phentermine and topiramate extended-release capsules) could help patients lose weight three times faster than diet and exercise alone, even though the cited references did not support such a claim. OPDP also stated that the website omitted material information about the relative effect of diet and exercise and selectively represented results data. In a June untitled letter to Aclaris Therapeutics, Inc., OPDP alleged that statements and side-by-side before-and-after images misleadingly represented that the "typical patient" treated with Eskata (hydrogen peroxide topical solution) would experience complete clearance of all treated lesions.

In the August warning letter to Metuchen Pharmaceuticals, OPDP alleged that one of the promotional pieces at issue misleadingly suggested that Stendra was safe and effective for individuals without erectile dysfunction, even though it was indicated only for the treatment of erectile dysfunction. In a September warning letter to Galt Pharmaceuticals, LLC, OPDP alleged that a professional email falsely "suggest[ed] that Doral [was] the only marketed medication indicated for the treatment of insomnia characterized by difficulty falling asleep, frequent nocturnal awakenings, and/or early morning awakenings," even though "there [were] other

[8] *See* Covington, *2016 End-of-Year Summary of FDA Advertising and Promotion Enforcement Activity* (Jan. 9, 2017), *available at* https://www.cov.com/en/news-and-insights/insights/2017/01/2016-end-of-year-summary-of-fda-advertising-and-promotion-enforcement-activity.

marketed medications indicated for all three of these components of sleep."

3. Omission of Material Facts

The Doral (quazepam) warning letter also alleged that the professional email omitted material information from the indications and usage section of the prescribing information (PI). Specifically, OPDP alleged that the email omitted language from the PI stating that "[b]ecause insomnia is often transient and intermittent, the prolonged administration of DORAL Tablets is generally not necessary or recommended" and that "[s]ince insomnia may be a symptom of several other disorders, the possibility that the complaint may be related to a condition for which there is a more specific treatment should be considered." OPDP stated that "[t]hese omissions [were] particularly concerning from a public health perspective due to the serious health risks associated with Doral that should be considered when prescribing the product."

OPDP's untitled Triferic letter from November similarly alleged a failure to communicate material information about the product's full FDA-approved indication and its limitations of use. OPDP stated that broad claims about Triferic's effectiveness "for the majority of dialysis patients" suggested that Triferic was indicated for patients receiving any type of dialysis, even though the labeling made clear that the drug was not intended for patients receiving peritoneal dialysis and had not been studied in patients receiving home hemodialysis.

4. Lack of Adequate Directions for Use

OPDP's Stendra warning letter contended that one of the promotional pieces at issue, the print advertisement, misbranded Stendra by suggesting that it could be used for reducing the risk of heart failure. Stendra was neither approved for such use, nor did its labeling contain adequate directions for such use. OPDP stated that the cited material was "especially concerning from a public health perspective given that the PI contain[ed] a warning and precaution regarding cardiovascular risks, and specifically state[d] that Stendra [was] not recommended for patients with New York Heart Association Class 2 or greater congestive heart failure."

5. Misbranding of an Investigational Drug

Two untitled letters issued this year addressed promotional materials related to investigational drugs. In a February untitled letter to Fabio Almeida, MD, of Phoenix Molecular Imaging Center, OPDP alleged that a webpage hosted an article that misbranded 11C-Acetate by suggesting that it was safe and effective for the purpose for which it was being investigated, or otherwise promoting the drug. FDA's letter did not specify the purpose for which 11C-Acetate was being investigated, but it stated that the webpage "describ[ed] 11C-Acetate as a useful PET scan agent for detecting recurrent prostate cancer," when its "benefit and risk profile . . . [was] . . . not fully known," thereby "creat[ing] a misleading impression regarding the usefulness and regulatory status of this product."

In a November untitled letter to Nascent Biotech, Inc., OPDP alleged that the drug company's website misbranded pritumumab by suggesting that pritumumab had been established as being safe and effective for the use for which it was being investigated, i.e., to treat brain cancer, when its "benefit/risk profile . . . [was] not currently known," thereby "creat[ing] a misleading impression regarding the safety and effectiveness of the product."

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 2019 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

CDRH's OPEQ issued one warning letter related to advertising and promotion in 2019. Additionally, OMDRHO within ORA issued six warning letters related to advertising and promotion, two of which were cosigned by OPEQ.

II. CONTENT OF ENFORCEMENT LETTERS

A. Nature of Promotional Pieces

The seven warning letters focused primarily on websites, but they also addressed other promotional materials, such as brochures, instructional videos, training materials, and software literature.

B. Allegations

The seven letters addressed two types of allegations: (1) that the manufacturer marketed its device beyond the scope of the clearance, approval, or premarket exemption; and/or (2) that the manufacturer marketed its product as "FDA approved" where the product lacked an approved Premarket Approval (PMA) application.

1. Product Promotion Beyond 510(k) Clearance, PMA Approval, or Premarket Exemption

Six letters included allegations that the manufacturers' promotional claims exceeded the scope of the 510(k) clearance or PMA approval, or the limitations of the exemption from premarket review. For example, an OPEQ warning letter addressed to 21st Century Scientific, Inc., alleged that product labeling and website information misbranded the Bounder VA Power Wheelchair. The Bounder VA Power Wheelchair was cleared as a powered wheelchair to provide mobility to individuals restricted to the sitting position. OPEQ alleged that 21st Century was marketing the device with "significant changes or modifications [that] could significantly affect the safety or effectiveness of the device," thereby triggering the requirement for a new 510(k) premarket

notification. These changes included modification options that added device functionality, such as lifting the user, tilting the user, and bringing the user to a standing position.

Similarly, a December warning letter issued jointly by OMDRHO and OPEQ alleged that Vevazz LLC marketed the Contour, an LED light therapy device, for the treatment of "neuropathy, inflammation, and other uses, which constitut[ed] major changes or modifications to its intended uses for which [the] firm lack[ed] clearance or approval." The company marketed the Contour under two separate 510(k) submissions for "non-invasive dermatological aesthetic treatment for the reduction of circumference of hips, waist, and thighs" and for "topical heating for the purpose of elevating tissue temperature for the temporary relief of minor muscle and joint pain, arthritis, stiffness or muscle spasms; the temporary increasing of local blood circulation and/or temporary relaxation of muscle." Not only did FDA allege that the company's claims for the Contour were not supported by the two 510(k) clearances, but the agency also raised serious public health concerns, noting that "patients may use the Contour before or instead of seeking other medical care, which could delay treatment of an underlying injury or disease."

2. Misrepresenting FDA Approval of the Device

Three warning letters included allegations that the manufacturers inappropriately marketed their devices as "FDA approved." For example, in an April warning letter to Surgisil, LLP, FDA stated that the promotional materials for the company's Perma Facial Implant "created an impression of official approval of a device due to clearance of a premarket notification submission." Because the device was 510(k) cleared, and not approved by FDA, the agency requested that the company remove the statement regarding FDA approval from its website.

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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