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2016 End-of-Year Summary of FDA Advertising and Promotion Enforcement Activity

January 9, 2017

Food, Drugs, and Devices

This alert reviews trends emerging from the warning and untitled letters issued in 2016 by the Office of Prescription Drug Promotion (OPDP) of the Center for Drug Evaluation and Research (CDER). No warning or untitled letters concerning promotion were issued this year by the Office of Compliance and Biologics Quality (OCBQ) of the Center for Biologics Evaluation and Research (CBER) or by the Office of Compliance (OC) of the Center for Devices and Radiological Health (CDRH).

We examined the 11 advertising and promotion letters issued by OPDP, and tabulated the most frequently cited allegations, leaving out allegations included in only a few letters.

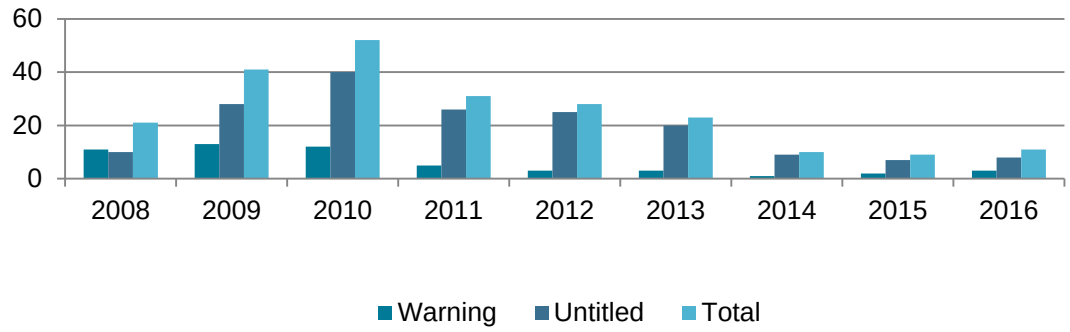
The first half of this alert summarizes our tabulation of all of the letters. The second half of the alert summarizes the individual letters.

Office of Prescription Drug Promotion (OPDP)

I. Enforcement Activity

In 2016, OPDP issued 11 advertising and promotion enforcement letters, two more than the number issued in 2015. This represents a slight uptick in enforcement letters since 2014, and a departure from the downward trend of the past six years.

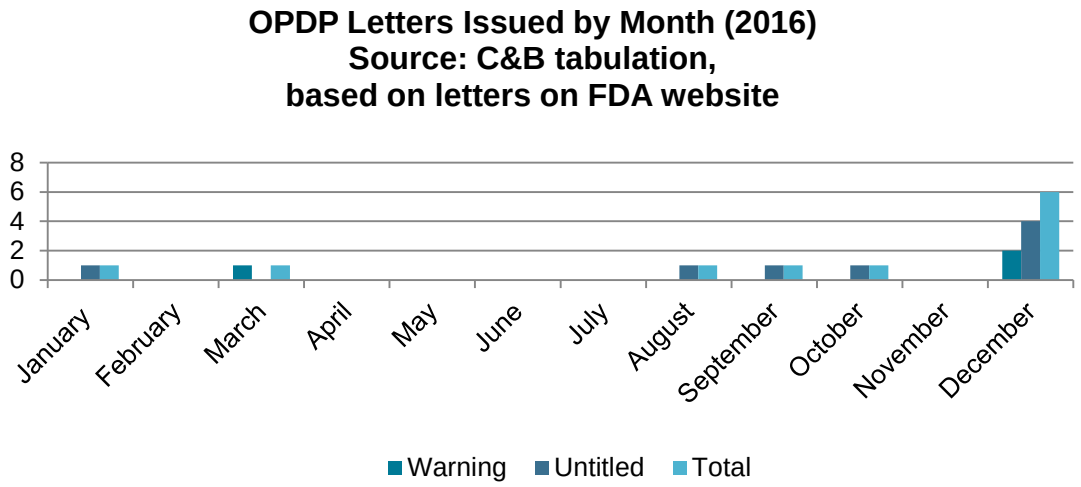
OPDP Warning and Untitled Letters (2008-2016)
Source: C&B tabulation, based on letters on FDA website



In keeping with past practice, OPDP issued more untitled letters than warning letters. Of the 11 letters OPDP issued in 2016, eight were untitled letters. The average number of allegations in each letter was approximately 1.7 (counted by the number of headings in each letter), which is similar to last year's average.[1] This number was a decrease from 2014, in which the average number of allegations per letter was 2.8.

There was a clear trend in the timing of OPDP's enforcement letters: of the 11 letters issued by OPDP, nine were issued in the second half of the year. This trend was driven by OPDP's issuance of six enforcement letters in December (two warning letters and four untitled letters). By contrast, in 2015, the letters were generally distributed evenly throughout the year.[2]

[1] In 2015, the average number of allegations per letter was approximately 1.8.
[2] In 2015, OPDP issued enforcement letters as follows: January (1); February (1); March (1); April (1); May (2); June (1); July (1); August (1).



OPDP has not articulated a reason for its overall decline in enforcement activity, though some have speculated that OPDP might be wary of taking action regarding promotional materials in light of recent First Amendment litigation against the agency. OPDP Director Tom Abrams stated in September that enforcement is still a priority for the office and that issuing warning and untitled letters is only one element of the agency's approach to promoting voluntary compliance. He added that OPDP remains focused on enforcement through other means, such as issuing guidance documents and promoting voluntary compliance by providing advisory comments on draft launch materials and other promotional pieces.[3]

II. Content of Enforcement Letters

A. Approved Products vs. Unapproved Products

In 2016, OPDP sent four letters addressing promotional activity for unapproved products, which amounts to more than one-third of all letters issued.[4] This is an increase from previous years; in 2015, OPDP issued one letter addressing promotional activity of an unapproved product,[5] and in 2014, the office issued no letters related to unapproved products.

B. Promotional Pieces at Issue

Unlike in previous years, there was a relatively even distribution of letters addressing materials directed at health care professionals (HCPs) and patients. In 2016, OPDP sent four letters for

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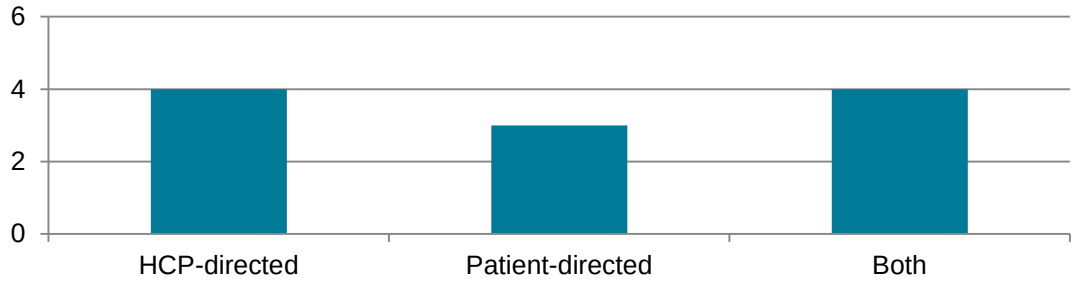
[3] *See* Dana A. Elfin, *FDA Acknowledges Decrease in Rx Promotion Violation Letters*, Bloomberg BNA (September 28, 2016).
[4] Untitled Letter to Celator Pharmaceuticals, Inc. (August 25, 2016); Untitled Letter to DURECT Corporation, Inc. (September 8, 2016); Untitled Letter to Chiasma, Inc. (December 21, 2016); Untitled Letter to Zydus Discovery DMCC (December 21, 2016).
[5] Untitled Letter to Gary W. Small re: [F-18] FDDNP (February 20, 2015), available here.

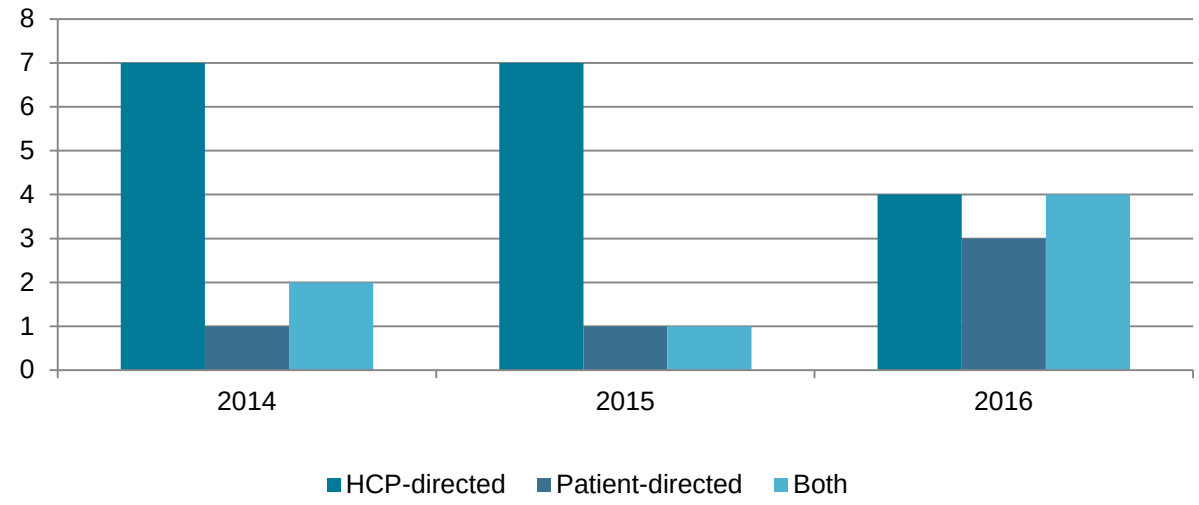
HCP-directed materials, three letters for patient-directed materials, and four letters for materials that potentially targeted both HCPs and patients. Materials that targeted both HCPs and patients typically involved the Internet, including promotional websites and videos posted online (OPDP sent three letters for videos posted on YouTube.com).

Number of Letters by Audience (2016)
Source: C&B tabulation, based on letters on FDA website



By contrast, in 2015, approximately 80 percent of OPDP enforcement letters addressed materials directed at HCPs. There was a similar distribution in 2014, when promotional materials directed at HCPs comprised 70 percent of the materials discussed in OPDP enforcement letters.

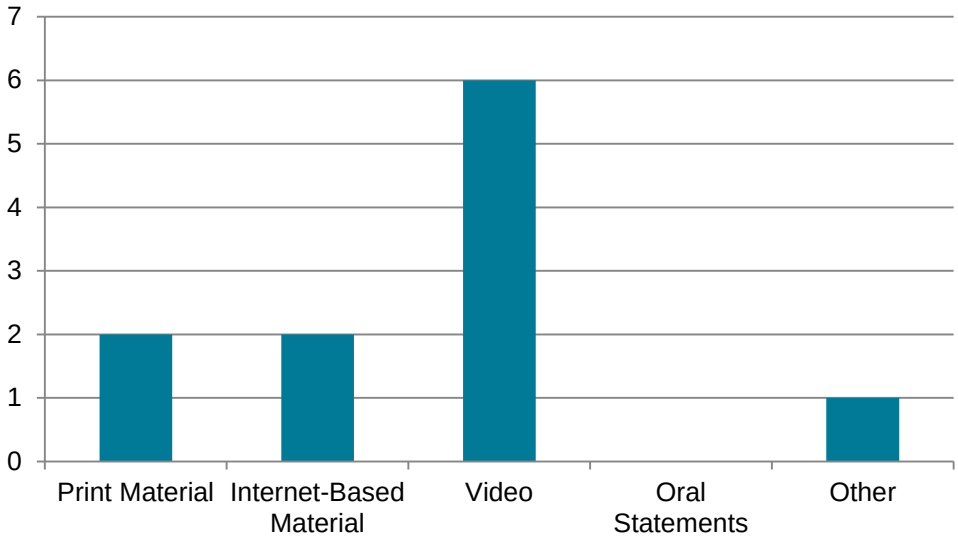
Number of Letters by Audience (2014-2016)
Source: C&B tabulation, based on letters on FDA website



In 2016, OPDP's letters addressed a wide range of promotional pieces, including print materials (e.g., patient vouchers and display panels), Internet-based materials (e.g., websites), and video materials (e.g., television advertisements and videos posted online). This year, videos were the most frequently cited medium (more than 50 percent). By comparison, in 2015, OPDP's letters were more evenly distributed between print (four letters) and Internet materials (four letters).[6] Unlike in previous years, none of the letters addressed oral statements made by company representatives.

Two of the videos addressed in 2016 included footage of key opinion leaders (KOLs) describing the product, likely reflecting an increased use of this tactic by drug manufacturers. In both cases, the statements cited by OPDP seemed to reflect the KOL's personal opinion, but OPDP nevertheless concluded they were violative.

Number of Letters by Type of Promotional Piece Addressed (2016)
Source: C&B tabulation, based on letters on FDA website



C. OPDP's Allegations

OPDP's letters contained allegations similar to those in prior years, focusing primarily on omission of risk information, false or misleading risk presentations, and promotion of investigational drugs.

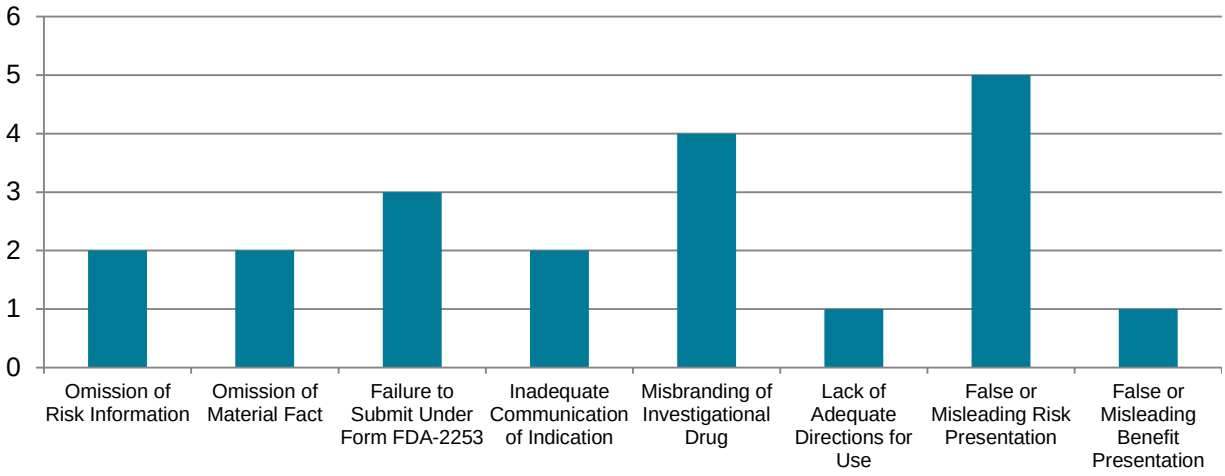
[6] One letter addressed video materials.

In three of these letters, OPDP additionally cited failure to submit under Form FDA-2253 upon first use. FDA regulations require companies to submit any labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement. Each submission must be accompanied by a completed transmittal Form FDA-2253.

Two recipients were also warned for inadequate communication of the indication, and two others for omission of material fact. OPDP criticized one recipient for a "false or misleading benefit presentation" and one for lack of adequate directions for use.

Unlike in previous years, none of the letters issued by OPDP cited unsubstantiated superiority or comparative claims. OPDP also increased its focus on promotion of investigational drugs this year, sending four letters related to that allegation in 2016 (as compared to one letter in 2015).

Number of Letters by Allegation*(2016)
Source: C&B tabulation, based on letters on FDA website



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

1. Omission of Risk Information

Two of the 11 letters issued by OPDP in 2016 contained allegations that the promotional piece at issue omitted risks associated with the drug. Such allegations typically focus on promotional pieces that, according to OPDP, omit all risk information or include risk information but omit a particularly important aspect.

For example, in a March 2016 warning letter to Shionogi, OPDP stated that a patient voucher was "false or misleading" because it omitted important risk information associated with the promoted drug. OPDP noted that, although the voucher included statements such as "Please

refer to the package insert for full prescribing details," such statements were insufficient to mitigate the omission of risk information on the voucher itself.

2. False or Misleading Risk Presentation

Five letters (over 40 percent) addressed promotional materials that contained false or misleading risk information. These types of allegations focus on claims made without supporting evidence, claims that fail to take into consideration all material facts regarding the risk profile of the drug, and claims that are presented in a misleading manner. For example, in December 2016 untitled letters, OPDP criticized two separate television ads (Celgene and Sanofi) that it stated contained "compelling and attention-grabbing visuals" and background music that "compete for the consumers' attention." OPDP doubted that consumers would be able to "adequately process and comprehend risk information" in light of these distracting factors.

FDA has recently completed several studies evaluating how consumers perceive risk information in DTC ads, including a study using eye tracking to assess how patients respond to on-screen "distractions."[7] The Celgene and Sanofi ads could be related to that research.

Interestingly, OPDP includes in this category of allegations "failure to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials." This description seems to overlap with another OPDP category, "Omission of Risk Information." Indeed, in two December 2016 warning letters (Spiraso and United-Guardian), OPDP alleged "False or Misleading Risk Information" due to the recipients' failure "to communicate *any* risk information about the product."

In previous years, OPDP typically categorized allegations of this type as "Minimization of Risk Information" (or "Omission and Minimization of Risk Information"). Recasting these allegations as "False or Misleading Risk Presentation" is noteworthy and perhaps reflects a response to the recent court decisions holding that truthful and non-misleading communications are constitutionally protected.

3. Misbranding of an Investigational Drug

In four untitled letters this year, OPDP contended that the promotional pieces at issue constituted promotion of an investigational drug. These allegations typically focus on suggestions that investigational new drugs are safe and effective for purposes for which they are being investigated.

In three of the four letters, OPDP noted the promotional piece's failure to disclose that the promoted product was an investigational new drug. In one letter to Celator, OPDP found the promotional piece (a panel displayed in an exhibit hall) particularly misleading because it appeared alongside information for approved products. In another letter, to Chiasma, OPDP noted that the video at issue contained a SUPER stating that the product is investigational but added that "no disclaimer" would mitigate the suggestion that the product is safe or effective for the uses described in the video. In two cases (Celator and Zydus), OPDP indicated that use of

[7] 79 Fed. Reg. 30614 (May 28, 2014).

the proprietary name to describe an investigational product contributed to the suggestion that the product has been approved by FDA.

4. Lack of Adequate Directions for Use

One letter (to Supernus) focused on the promotional piece's lack of adequate directions for use. Generally, such allegations concern the lack of information regarding the safety and efficacy of a product for certain uses.

According to OPDP, the video at issue in the Supernus letter suggested that the drug was intended for use in *all* seizure types, when in fact the drug was indicated only for partial seizures. Although the video described the correct indication in scrolling text and a voiceover, OPDP noted that placement of the indication after the main presentation did not negate earlier statements.

Previously OPDP typically categorized similar allegations under the heading "Broadening of Indication." More recently, OPDP began to describe these presentations as lacking adequate directions for use. OPDP has not provided a rationale for the change, but it could be motivated by a desire to tie the alleged violation more closely to the statutory requirement that labeling contain "adequate directions for use."[8]

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 2016 relating to advertising and promotion. This continues a recent downward trend in enforcement letters that began in 2013, when the office issued only three letters total. This was a decrease from previous years. In particular, between 2008 and 2012, OCBQ issued between five and seven letters each year. In 2015, OCBQ posted only one untitled letter, related to an influenza vaccine.[9] Covington discussed the letter in a previous client alert.

CDRH Office of Compliance (OC)

Enforcement Activity

The Office of Compliance (OC) in FDA's CDRH did not post any enforcement letters relating to advertising and promotion on FDA's website in 2016.

Summaries of OPDP Letters

This information below merely summarizes the allegations contained in FDA's enforcement letters. It does not contain any analysis, opinions, characterizations, or conclusions by or of

[8] 21 USC § 502(f).
[9] Untitled Letter to Protein Sciences Corporation re: Flublok (Influenza Vaccine) BLA STN # 125285 (March 12, 2015), available here.

Covington & Burling LLP. As a result, the information presented herein does not necessarily reflect the views of Covington & Burling LLP or any of its clients.

Hospira Untitled Letter (January 2016)

OPDP found that a YouTube.com video promoting Hospira's drug Precedex (dexmedetomidine HCI Injection) was false or misleading because it omitted risks and material facts about the drug.

Omission of Risk Information: The video contained numerous efficacy claims, but failed to include *any* risk information associated with Precedex. Additionally, the video alluded to arousability, but it was presented as a benefit (i.e., how Precedex is "different" from other sedatives), instead of as a warning or precaution, as described in the PI. OPDP found that this omission of risk information created a misleading impression about Precedex's safety.

Omission of Material Fact: The video made representations about the use of Precedex for intensive care unit sedation, but failed to communicate material information about the drug's indications and use. Specifically, Precedex is indicated for the sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting and should not be used continuously for more than 24 hours. FDA alleged that the video omitted material facts by failing to note these limitations.

Failure to Submit Under Form FDA-2253: FDA alleged that a copy of the video was not submitted to OPDP at the time of initial dissemination in violation of 21 CFR 314.81(b)(3)(i).

Shionogi Warning Letter (March 2016)

OPDP contended that a "Patient Co-Pay Assistance Voucher" for Ulesfia (benzyl alcohol) lotion for topical use was false or misleading because it omitted important risk information and omitted material facts.

Omission of Risk Information: The voucher made representations about the efficacy of Ulesfia, including that the drug is "the #1 prescribed banded Rx treatment for head lice," but failed to communicate *any* risk information. OPDP noted that the voucher included statements such as, "For more information, please refer to the package insert for full prescribing details…", but OPDP found that such statements did not mitigate the omission of risk information from the voucher itself.

Omission of Material Facts/Inadequate Communication of Indication: OPDP further alleged that the voucher failed to communicate a limitation of use contained in Ulesfia's indication, namely that it does not have ovocidal activity. In addition, the voucher failed to adequately communicate that Ulesfia is indicated only for patients six months or older. Although the "Dear Pharmacists" section at the bottom of the back page contained information about the indication, OPDP said that this presentation did not "mitigate the misleading impression."

Failure to Submit Under Form FDA-2253: FDA alleged that Shionogi violated 21 CFR 314.81(b)(3)(i) by failing to submit a copy of the voucher to OPDP at the time of initial dissemination.

Celator Untitled Letter (August 2016)

As part of its monitoring and surveillance program, OPDP saw a panel posted by Celator in the main exhibit hall at the American Society for Clinical Oncology Annual Meeting. According to OPDP, the panel promoted Celator's investigational product, CPX-351 (Cytarabine; Daunorubicin) Liposome Injection (CPX-351). OPDP found that the panel suggested that CPX-351 was safe and effective for the purposes for which it was being investigated.

Misbranding of an Investigational Drug: The panel promoted the drug with statements such as "VYXEOS [the intended proprietary name of CPX-351] . . . delivers optimal anti-cancer activity" and "A completed Phase 3 study demonstrated improved survival for VYXEOS compared to '7+3' in newly diagnosed patients with high-risk AML." OPDP alleged that this claim suggested that CPX-351 was effective for treatment of cancer generally and improves survival relative to "7+3" chemotherapy.

OPDP further criticized the "use of a proprietary name without any accompanying identification of the investigational drug product." Finally, OPDP noted that the panel appeared in the main exhibit hall, "alongside approved products" but failed to include information to indicate that CPX-351 was an investigational drug product. For these reasons, OPDP concluded that CPX-351 was misbranded.

DURECT Untitled Letter (September 2016)

OPDP found that website presentations of Remoxy (oxycodone) Extended-Release Capsules (Remoxy ER) suggested that the drug was safe and effective for the purposes for which it was being investigated.

Misbranding of an Investigational Drug: Specifically, OPDP objected to the Durect website's presentation of information about Remoxy ER on a rotating basis with information about other products. OPDP noted that statements about the drug on the page (such that it was "long-acting" and "tamper-resistant") were phrased as established facts, thereby suggesting the drug is safe and effective with the characteristics described.

Clicking on any part of the Remoxy ER presentation on the Durect website linked directly to a specific product webpage devoted to Remoxy ER. The webpage included various "Potential Benefits," including that the formulation of the drug was designed to deter abuse and that it provides "long-term pain control" of "moderate-to-severe chronic pain."

Additionally, nothing in the website's presentation disclosed that the drug was an investigational new drug. Although the Rempoxy ER product webpage stated that the product is "IN DEVELOPMENT" and stated a target action date under the Prescription Drug User Fee Act (PDUFA), OPDP stated that these indirect statements did not adequately convey that the product is unapproved or sufficiently mitigate the impression that Remoxy ER is safe and effective for moderate-to-severe chronic pain and has properties to deter abuse.

Supernus Untitled Letter (October 2016)

OPDP alleged that a "Key Opinion Leader" Spanish-language video for Oxtellar XR (oxcarbazepine) extended-release tablet for oral use (Oxtellar XR) made false or misleading representations about the risks associated with the drug.

Lack of Adequate Directions for Use: OPDP noted that Oxtellar XR is intended to treat only partial seizures in adults and in children six to 17 years of age but that the video used general terms such as "epilepsy" and "convulsive." OPDP found that this presentation misleadingly suggested that Oxtellar XR was approved for treatment of all seizure types. Although the correct indication appeared following the main presentation in scrolling text and a voiceover, OPDP found that this information did not negate the earlier statements.

False or Misleading Risk Presentation: OPDP also found that the video included a false or misleading risk presentation because the opening segment consisted of a presentation of the benefits of Oxtellar XR without disclosure of specific risks. The presentation of risks was "relegated to the end of the video," after the main presentation, where OPDP found it "unlikely to draw the viewer's attention," and was displayed in scrolling text with a voiceover. The video was thus found to misleadingly minimize risks by failing to "convey risk information with a prominence reasonably comparable to the claims of effectiveness."

Celgene Untitled Letter (December 2016)

OPDP found that a Direct-to-Consumer television advertisement for OTEZLA (apremilast) tablets for oral use (Otezla) made false or misleading representations about the risks associated with the drug.

False or Misleading Risk Presentation: The television advertisement at issue had instrumental music playing throughout, including during the major statement of risks. OPDP alleged that a "loud brass interjection" was played over several audio risk disclosures. Moreover, the advertisement included "compelling and attention-grabbing visuals" (e.g., multiple scene changes) and SUPERs during the presentation of risk information. OPDP noted that the visuals were "unrelated to the risk message." OPDP contended that the scene changes and other competing modalities competed for consumers' attention, undermining the communication of the important risk information.

Because the "overall effect" undermined the communication of important risk information, OPDP concluded that the advertisement misleadingly minimized the risks associated with Otezla.

Sanofi-aventis Untitled Letter (December 2016)

OPDP contended that a Direct-to-Consumer television advertisement for TOUJEO (insulin glargine injection) U-300 for subcutaneous use (Toujeo) made false or misleading representations about the risks associated with the drug.

False or Misleading Risk Presentation: The television advertisement at issue communicated risk information through audio and on-screen SUPERs. However, during the presentation of risk information, the advertisement showed fast-paced visuals unrelated to the risk information, frequent scene changes, and "competing modalities" such as background music. OPDP found that these factors would make it challenging for consumers to adequately process and comprehend the risk information. Because the "overall effect" undermined the communication of important risk information, OPDP concluded that the advertisement misleadingly minimized the risks associated with Toujeo.

United-Guardian Warning Letter (December 2016)

OPDP found that a professional email for RENACIDIN (Citric Acid, Glucono delta-lactone, and Magnesium Carbonate) Irrigation Solution made false or misleading claims with regard to the risks and benefits associated with the drug.

False or Misleading Risk Presentation: Because the professional email made multiple claims about Renacidin, but failed to communicate *any* risk information, OPDP found that it was false or misleading. OPDP noted that the statement, "CLICK HERE for complete prescribing information" did not mitigate the omission of risk information from the email itself.

False or Misleading Benefit Presentation: The Renacidin email contained two claims for which OPDP found no support: "Simplifies long-term catheter care" and "Easy 30mL dosing and delivery." OPDP stated that the lack of supporting references for these claims was exacerbated by the email's failure to reveal specific information from the approved PI about how the drug should be dosed and administered.

Spiraso Warning Letter (December 2016)

OPDP contended that a webpage for TUXARIN ER (codeine phosphate and chlorpheniramine maleate) extended release tablets (Tuxarin ER) made false or misleading claims and failed to communicate the full indication for the drug.

False or Misleading Risk Presentation: OPDP found the Tuxarin ER webpage to be false and misleading because it failed to communicate *any* risk information about the drug. Additionally, OPDP considered claims such as "Minimize serious risk of over dosing" and "Current market is dominated by liquids prone to serious risk of dosing errors" to be misleading because they suggested that Tuxarin ER is safer than its competitors based on the difference in dosage formulations and the safety profiles of individual ingredients. No references were cited in support of these claims, and OPDP is unaware of any evidence to support the suggestion that Tuxarin ER is safer than its competitors because of its tablet formulation or because it is not associated with "dosing errors" or "serious safety issues." According to the Warnings and Precautions section of the Tuxarin ER PI, overdose of codeine has been associated with fatal respiratory depression, as well as other several serious safety issues.

Furthermore, similar to the competitors referred to in the webpage, the PI for Tuxarin ER also contains a boxed warning regarding respiratory depression and death in children who received codeine following tonsillectomy and/or adenoidectomy. OPDP stated that "comparing the safety profile of a single ingredient in a combination product to another single ingredient in a competitor combination product . . . is misleading as it fails to take into consideration the overall safety profile of the entire combination product."

Inadequate Communication of Indication: The webpage at issue made claims about the usefulness of Tuxarin ER as an antihistamine but failed to disclose that the drug was not indicated for pediatric patients under 18 years of age. OPDP concluded that the webpage's failure to disclose the limitations of use created "the misleading impression that the drug is approved for use in patients of all ages."

Failure to Submit Under Form FDA-2253: FDA alleged that a copy of the webpage was not submitted to OPDP under cover of Form FDA-2253 at the time of initial dissemination.

Chiasma Untitled Letter (December 2016)

OPDP found that a Chiasma video posted on YouTube.com suggested that octreotide capsules are safe and effective for the purpose for which they are being investigated or otherwise promoted the drug.

Misbranding of an Investigational Drug: Chiasma's video described the use of octreotide capsules in treating acromegaly. It also included presentations in the main audio segment that "the most important result of the trial was that the drug is safe," "effectiveness of the drug was proven in the clinical trials," and "there is no harm no foul by trying a new oral alternative." OPDP objected to the positive and conclusory statements about the safety and effectiveness of octreotide capsules.

OPDP acknowledged that the video included a SUPER that the "Product is an investigational new drug and not available for commercial distribution," which was displayed on the screen for eight seconds at the end of the video. However, OPDP concluded that "no disclaimer . . . would sufficiently mitigate the extensive claims and presentations" made throughout the video.

Zydus Untitled Letter (December 2016)

OPDP found that a Zydus video posted on YouTube.com suggested that Zydus's product, Saroglitazar (brand name "Lipaglyn") is safe and effective for the purposes for which it is being investigated or otherwise promoted the drug.

Misbranding of an Investigational Drug: The video described the use of Saroglitazar in treating patients with diabetic dyslipidemia and hypertriglyceridemia with Type 2 diabetes. In SUPERs, the video claimed that Saroglitazar was "Novel. Superior. Dual Acting" and described the drug as the "World's first dual PPAR-alpha/gamma agonist approved for treating diabetic dyslipidemia." In voiceovers, the video claimed that the treatment was a "novel, first in class therapy that brings in dual lipid and glycemic control in one molecule" and that "Unlike other molecules it does not cause weight gain, edema, cardiac, renal, liver, or muscle toxicity," among other claims.

OPDP found these "broad statements" misleading. Specifically, OPDP contended that the description of Saroglitazar as the "World's first" incorrectly suggested that the drug was approved throughout the world, including the United States. OPDP further objected to the use of the word "Superior" and to claims that Saroglitazar is not associated with the serious risks generally attributed to other molecules with similar mechanisms of action. OPDP noted that the video failed to include any information to indicate Saroglitazar's approval status.

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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