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Client Alert

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2013 Year in Review: OPDP Warning Letters and Untitled Letters

In 2013, the Center for Drug Evaluation and Research's (CDER) Office of Prescription Drug Promotion (OPDP) issued a total of 24 enforcement letters to pharmaceutical manufacturers, four fewer than in 2012. Of the 24 letters, three were Warning Letters and 21 were Untitled Letters. Roughly 67 percent (16 letters) focused on promotional materials directed at healthcare professionals, and 46 percent (11 letters) related to the promotion of drugs with Boxed Warnings, including two Warning Letters. OPDP did not note that any letters involved complaints submitted to the Bad Ad Program, unlike the three letters specified in 2012 and five letters in 2011. OPDP clearly remained invested in the Bad Ad program, however, launching a continuing medical education ("CME") course in 2013 on how to identify and report violative promotion.

The following were the most cited allegations by OPDP in 2013 along with a comparison to 2012:

Allegation	2013	2012
Omission and/or Minimization of Risk Information	83%	64%
Omission of Material Facts	42%	18%
Unsubstantiated Superiority Claim	38%	32%
Unsubstantiated Claim	38%	29%
Overstatement of Efficacy	21%	43%

As in previous years, the omission/minimization of risk information dominated the enforcement letters. Compared to previous years, the enforcement letters provided more detailed explanations of the rationale for OPDP's objections, especially relating to the presentation of safety and risk information alleged to be false or misleading. These more detailed explanations could reflect, in part, an effort by OPDP to respond to continuing scrutiny of FDA's regulation of drug promotion, particularly truthful speech. In *U.S. v. Caronia*, the Second Circuit found that the prosecution based on truthful speech about off-label uses of FDA-approved drugs violated the First Amendment.[1] Following the *Caronia* decision, OPDP representatives emphasized that the decision would not diminish the Office's enforcement of the prohibitions against misbranding under the

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Federal Food, Drug, and Cosmetic Act because "the First Amendment does not preclude" enforcement based on promotion that is "false or misleading."[2]

Observations and Lessons Learned from 2013 OPDP Letters:

- ***OPDP is focusing on misleading representations relating to the characterization of risk and safety information.*** In 2013, FDA objected to the presentation of risk and safety information in promotional content in the majority of enforcement letters.

    - In a March 4, 2013 Untitled Letter regarding a patient guide for the drug, Cysview, OPDP cited a discussion of hematuria (blood in the urine), finding that the presentation minimized the severity of the adverse event "by describing it in terms that patients may not necessarily equate to hematuria." OPDP explained its reasoning in detail, writing that "the patient guide shows that Cysview is taken up by bladder cells that emit a pink fluorescence when exposed to blue light," and that "the procedure is designed to make areas of concern show pink under observation, so patients may interpret pinkish urine as a byproduct of the Cysview blue light cystoscopy rather than a result of having blood in their urine."

    - In a May 22, 2013 Untitled Letter regarding a sales aid for the drug, Oncaspar, OPDP cited a table showing incidence rates of selected Grade 3 and 4 adverse events, including anaphylaxis and clinical allergic reactions. OPDP objected to the table despite the inclusion of anaphylaxis and allergic reactions because the table suggested that "physicians may mistake injection-site reactions for allergic reactions and that the hypersensitivity reactions reported in the PI and displayed in the table may have been inaccurately attributed to Oncaspar as a result of misclassified injection-site reactions."

    - In a June 6, 2013 Untitled Letter regarding the drug, Xarelto, OPDP objected to a common industry practice of providing risk information on an adjacent page that precedes a direct-to-consumer print ad. OPDP explained that presentation of risks in that manner "without any of the emphasis used with the efficacy claims" made the presentation of risk information "appear to be unconnected to the efficacy claims and therefore unlikely to draw the readers' attention." This enforcement letter underscores the importance of integrating visual elements that bridge the risk and efficacy portions of promotional pieces so that risk information appears in the main body of the pieces.

    - In a July 31, 2013 Untitled Letter regarding webpages and online banner ads for the drug, Naftin, OPDP objected to a claim that the drug had "proven safety for over 20 years." OPDP acknowledged that "[a] formulation containing naftifine hydrochloride was initially approved in 1988 and naftifine hydrochloride is the active ingredient in Naftin," but found the presentation to be misleading because "the current formulation constitutes a different strength and dosage than the 1988 product and does not have a safety profile established based on a 20 year history of use."

    - In a December 9, 2013 Untitled Letter regarding a physician letter for the drug, Lanoxin, OPDP objected to a presentation suggesting that Lanoxin "is superior in safety and efficacy to generic formulations of digoxin and that the generic formulations are not therapeutically equivalent to Lanoxin." OPDP explained, "FDA has reviewed and approved a number of therapeutically equivalent formulations of digoxin tablets and injections and granted an 'AB' or 'AP' rating, so unless and until FDA's determination is changed or reversed, promotion suggesting a lack of equivalence between Lanoxin and products deemed to be therapeutically equivalent are considered to be false or misleading."

- ***Promotional material may contain accurate facts but create a misleading impression from OPDP's perspective.***

  - In a May 22, 2013 Untitled Letter regarding a healthcare practitioner website for the drug, Doxil, OPDP cited claims linking the CA-125 biomarker with clinical responses to Doxil therapy. OPDP recognized that the FDA-approved PI for Doxil included CA-125 in a table of baseline demographic characteristics in pivotal trials, but found that "the pivotal trials did not evaluate changes in CA-125 levels as a measure of response to therapy."

  - In a July 23, 2013 Untitled Letter regarding a sales aid for the drug, Zevalin, OPDP objected to a claim regarding the time-to-progression between study groups. Although the reported time-to-progression data were accurate, OPDP objected to the claim because the sales aid failed to specify that there was no statistically significant difference between the groups.

  - In an October 24, 2013 Untitled Letter regarding a patient brochure for the drug, Brovana, OPDP objected to claims that Brovana would be effective for patients who had not had success with other Chronic Obstructive Pulmonary Disease therapies. OPDP explained that although "trials associated with approval of Brovana did include an active comparator, salmeterol," the studies "were not designed to measure clinical superiority."

  - In a November 18, 2013 Warning Letter regarding an introductory letter for the drug, Ribasphere Ribapak, OPDP objected to claims that use of the drug "will have a positive impact on patient adherence to ribavirin therapy as well as HCV treatment overall, thereby improving rates of sustained viral response (SVR)." OPDP explained that while "some of the claims [were] factually correct," "the overall impression [was] misleading because FDA is not aware of any evidence to suggest that Ribasphere's packaging characteristic or availability in multiple dose strengths will improve patient adherence to ribavirin or HCV treatment overall, leading to improved rates of SVR."

- ***Investor-related communications are not exempt from FDA scrutiny.*** In a November 8, 2013 Warning Letter regarding the drug, Juxtapid, OPDP cited statements made by the manufacturer's CEO during a broadcast interview on CNBC's "Fast Money" talk show. On the show, which discusses stock trading, the CEO made statements suggesting that Juxtapid was safe and effective for use in decreasing the occurrence of cardiovascular events and increasing the lifespan of patients, thereby affecting cardiovascular morbidity and mortality as well as overall mortality. However, Juxtapid is only approved for use as an adjunct therapy and has a specific limitation of use stating that the effect of the drug on cardiovascular morbidity and mortality has not been determined.

- ***Despite the high number of letters citing promotional materials for drugs with Boxed Warnings, OPDP "does not specifically target boxed warning drugs" and instead, relies on a risk-based approach that considers the nature and egregiousness of the violation, its impact on public health, the need for correction, and the company's past behavior.***[3] This approach can be seen in the 2013 Warning Letters, where two of the three companies cited had prior communications with OPDP regarding product promotion. OPDP also has emphasized that it "does not specifically target any type of drug or drug designation" and no drug type or designation is immune from enforcement, *e.g.*, OPDP's July 2013 letter cited a sales aid for an orphan drug product, Zevalin, which is used for the treatment of non-Hodgkin's lymphoma.

- ***Although none of the Warning or Untitled Letters referred to a Bad Ad Program complaint, this program remains an important enforcement initiative for OPDP.*** The absence of references to Bad Ad Program complaints could reflect a lack of complaints resulting in enforcement letters in 2013 or a decision to eliminate

references to Bad Ad Program complaints in the enforcement letters. In any event, OPDP remains invested in the program and educating the public on how to identify and report instances of violative promotion. On October 28, 2013, OPDP Director Tom Abrams announced the launch of a CME Medscape course on the Bad Ad Program for physicians and other healthcare practitioners.[4]

- ***Social media continues to be an area of emerging regulation.*** Unlike in past years, OPDP did not cite promotion on social media platforms in any 2013 Warning or Untitled Letter. OPDP has continued to clarify its stance on such promotion, however, and most recently in the January 2014 draft guidance, "Fulfilling Regulatory Requirements for Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics."[5] According to CDRH's list of New and Revised Draft Guidances planned for Calendar 2014, the Center is planning to release additional social media-related guidances, including: "Internet/Social Media Platforms with Character Space Limitations: Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices," "Internet/Social Media Platforms: Correcting Independent-Third Party Misinformation About Prescription Drugs and Medical Devices," and "Internet/Social Media Advertising and Promotional Labeling of Prescription Drugs and Medical Devices – Use of Links."[6]

For your reference, we have prepared a chart that provides: (1) a list of 2013 OPDP Warning and Untitled Letters; (2) highlights of promotional violations alleged in each letter; and (3) a hypertext link to each letter. The chart is available online in a searchable PDF document **here**.

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[1] *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012). *See also* King & Spalding Client Alert, "Second Circuit Vacates Off-Label Promotion Conviction on First Amendment Grounds in U.S. v. Caronia," Dec. 20, 2012, **http://www.kslaw.com/imageserver/KSPublic/library/publication/ca122012.pdf**.

[2] OPDP Enforcement Actions Webinar, May 16, 2014.

[3] OPDP Enforcement Actions Webinar, Jan. 20, 2014.

[4] Tom Abrams, "FDA and Partners Launch e-Learning Course on Evaluating Drug Promotion," *FDAVoice*, Oct. 28, 2013, **http://blogs.fda.gov/fdavoice/index.php/2013/10/fda-and-partners-launch-e-learning-course-on-evaluating-drug-promotion**.

[5] FDA, "Guidance for Industry: Fulfilling Regulatory Requirements for Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics" (2014), **http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM381352.pdf**.

[6] FDA, "Guidance Agenda: New & Revised Draft Guidances CDER is Planning to Publish During Calendar Year 2014" (2014), **http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM314767.pdf**.