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HEALTHCARE AND LIFE SCIENCES
DISPUTES, REGULATORY,
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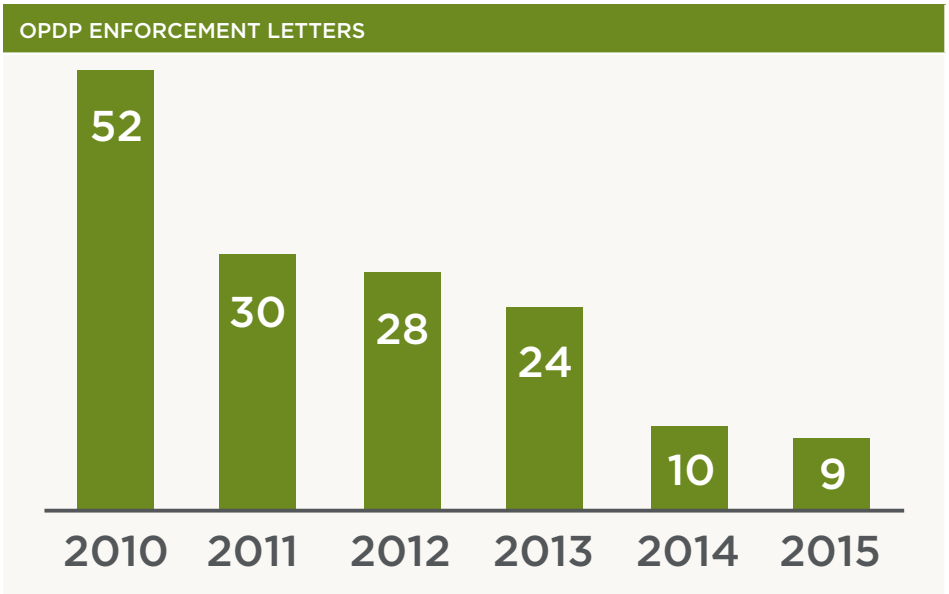
WARNING...?

FDA'S OFFICE OF PRESCRIPTION DRUG PROMOTION ISSUES RECORD LOW NUMBER OF ENFORCEMENT LETTERS IN 2015

The number of enforcement letters from the Food and Drug Administration's Office of Prescription Drug Promotion (OPDP) has steadily declined in recent years, from 52 in 2010 to a record low of nine in 2015. Whether or not this is a good thing seems to be in the eye of the beholder. Consumer rights advocacy group Public Citizen, for example, criticized the Agency for its recent "dismal" performance in issuing Warning Letters and Untitled Letters.[1] Regulatory and compliance professionals looking to keep their company's promotional messages in line with complex, ever-changing regulations may choose a more complimentary word.



One thing that both sides can agree on, however, is that 2015 was a noteworthy year for the OPDP.

The Office's Warning Letter to Duchesnay, Inc. provided FDA with its most blogworthy moment of 2015, courtesy of Kim Kardashian's Instagram endorsement of the company's morning sickness drug, Diclegis.[2] While it didn't produce as many retweets, FDA also took the virtually unprecedented step of rescinding a Warning Letter.[3]

1. http://www.citizen.org/documents/2250.pdf
2. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM457961.pdf
3. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM477250.pdf

OPDP originally issued the Warning to Pacira Pharmaceuticals in September 2014 over a journal advertisement and educational flashcards for the company's local anesthetic product, Exparel. The Agency alleged that the materials—which promoted the product's efficacy in a wider range of surgical locations than had been specifically tested in clinical trials—rendered the product misbranded. Riding a wave of successful challenges to the FDA's enforcement of truthful off-label promotion, Pacira sued the FDA. The company alleged that the Agency had "unilaterally attempt[ed]…to narrow the approved broad indication for Exparel," and that attempts by the FDA to forbid Pacira from sharing truthful and non-misleading information about its product violated the First Amendment. On December 15, 2015, Pacira announced that the company had reached a settlement with the FDA.[4] Under the terms, FDA rescinded the Warning Letter and approved a labelling supplement for Exparel to clarify that the efficacy and safety of the product is not limited to the two specific surgery sites tested in the clinical trials.

The Pacira settlement—which comes on the heels of Amarin Pharma Inc.'s First Amendment victory over FDA in the Southern District of New York in August 2015[5]—suggests that FDA's enforcement of off-label promotion is on shaky ground. However, as the following two Warning Letters and seven Untitled Letters indicate, OPDP remains diligent in its enforcement of numerous types of promotional infractions. *Omission of Risk Information*—by far the most common violation indicated in enforcement letters—should remain a company's priority. *Unsubstantiated Superiority Claims* and *Minimization of Risk* also continually pop-up in FDA's communications.

WARNING LETTERS[6]

July 27, 2015: ECR Pharmaceuticals

Reason: Omission of Risk; Inadequate Communication of Indication; Unsubstantiated Claims

OPDP issued a Warning Letter to ECR, a wholly owned subsidiary of Valeant Pharmaceuticals, over the company's professional sales aid for TussiCaps, a combination product used to treat cold and flu symptoms that also contains a narcotic cough suppressant. OPDP stated that the sales aid did not include any risk information about the product, including that TussiCaps are contraindicated in patients with a known allergy or sensitivity to hydrocodone or chlorpheniramine, and in children less than 6 years of age due to the risk of fatal respiratory depression. Additionally, ECR's materials did not state that Tussicaps are associated with drug abuse and dependence, as is indicated in the product labeling.

August 7, 2015: Duchesnay, Inc.

Reason: Omission of Risk and Omission of Material Fact

OPDP issued a Warning Letter that targeted a short post from celebrity Kim Kardashian's Instagram and Facebook accounts, which promoted her experience using the morning sickness medication Diclegis. OPDP found that the social media testimonials were false or misleading in that they presented efficacy claims but failed to properly communicate any risk information. Notably, the posts included a hyperlink in bold entitled www.DiclegisImportantSafetyInfo.com, which the Agency noted did not mitigate the misleading omission of risk information.

BACKGROUND ON THE OFFICE OF PRESCRIPTION DRUG PROMOTION AND ENFORCEMENT LETTERS

The stated mission of OPDP, formerly the Division of Drug Marketing, Advertising & Communications (DDMAC), is to "protect the public health by ensuring that prescription drug information is truthful, balanced, and accurately communicated." The Office accomplishes this "through comprehensive surveillance, enforcement, and educational programs."

The OPDP keeps track of direct-to-consumer ads and promotion to healthcare professionals through a variety of methods, including: inspecting companies' Form FDA-2253, receiving complaints from industry competitors, monitoring promotional materials at medical conferences, and receiving notifications through the OPDP's "Bad Ad" Program, which encourages doctors to alert the Office of potentially false or misleading ads.

If OPDP finds problematic promotional material, the Agency may then issue "Warning Letters" or less serious "Untitled Letters" to the manufacturers who disseminate the materials. Unlike Untitled Letters, Warning Letters will contain a statement—or warning—including something to the effect of "failure to take prompt corrective action may result in enforcement action, including seizure or injunction, without further notice."

4. http://investor.pacira.com/phoenix.zhtml?c=220759&p=irol-newsArticle&ID=2122491
5. The Amarin Court found that, under the 2012 Second Circuit decision United States v. Caronia, truthful and non-misleading speech may not form the basis of prosecution for misbranding under the Food, Drug and Cosmetic Act. After reviewing the specifics of Amarin's proposed statements about its drug Vascepa, as well as proposed disclaimers, the Court found the speech truthful, and protected under the First Amendment.
6. For the list of Warning Letters and Untitled Letters, including links to the implicated promotional material, see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm432949.htm

UNTITLED LETTERS

January 29, 2015: Luitpold Pharmaceuticals, Inc.

Reason: Lack of Adequate Directions for Use; Minimization of Risk; Omission of Material Fact; Misleading Claims

The first letter of 2015 went to Luitpold Pharmaceuticals over a video segment for an intravenous treatment for iron deficiency anemia called Injectafer. OPDP noticed several issues with the video, including the statement that Injectafer is "for patients with iron deficiency anemia caused by any disease." OPDP noted that FDA actually approved the drug for a more limited group of patients, including patients who cannot tolerate oral iron, or those that suffer from non-dialysis dependent chronic kidney disease. This was not clear from the ad. OPDP also noted that despite the video outlining many risks associated with competing treatments, the audio portion of the ad failed to discuss any of Injectafer's risks. Luitpold instead relied on a small text box of risk information, displayed only briefly. OPDP also noted that because risk information and audio run at the same time, this "distracts the audience" from hearing about the risks. The letter was also critical of the general "feel" of the ad, which suggests that Injectafer "can drastically improve the general well-being of a patient with [iron deficiency anemia] (i.e., Injectafer "really changed her life" and the patient "blossomed like a rose" with Injectafer)."

February 20, 2015: UCLA

Reason: Promoting an Investigational New Drug as Safe and Effective

OPDP addressed a website entitled "Taumark Better Brain Diagnostics," which describes an investigational product, FDDNP, for use in PET scans to diagnose traumatic brain injuries, Alzheimer's, and other neurological conditions. According to OPDP, these are uses that would necessitate a prescription because they require supervision by a physician. OPDP took issue with a number of the claims on the website, and stated: "The website suggests in a promotional context that FDDNP, an investigational new drug, is safe and effective for the purpose for which it is being investigated." Such claims rendered the drug misbranded.

March 3, 2015: Discovery Laboratories, Inc.

Reason: Unsubstantiated Superiority Claims; Lack of Adequate Directions for Use

OPDP found the webpage of Discovery Laboratories Inc. was misleading to consumers because it suggested that the company's synthetic lung drug Surfaxin is superior to and more "evolved" than comparatively "primitive" animal-derived products for respiratory distress syndrome (RDS). OPDP contended that Discovery Labs did not provide adequate support for these superiority claims, nor did it provide a proper explanation of the drug's adverse reactions. Further, the letter states that other claims on the company's website for Surfaxin, including that it is the "only available alternative to animal-derived surfactants approved by the FDA," are misleading because the drug is exclusively approved for the *prevention* of RDS in high-risk infants. Competing drugs like Curosurf, for example, are indicated for the *treatment* of RDS. Again, OPDP noted that Discovery included the Surfaxin's full indication on the webpage, but repeated that the "mere inclusion of the full indication on this webpage does not mitigate the misleading impression that Surfaxin is an alternative to all animal derived surfactants for all uses in RDS."

April 17, 2015: Otsuka Pharmaceuticals

Reason: Misleading Claims and Presentation

Otsuka received an Untitled Letter over a pharmacology aid for their antidepressant and bipolar blockbuster drug, Abilify. The aid showed three light switches at low, medium, and high power to represent how Abilify can modulate a patient's dopamine and serotonin activity. OPDP found "the totality of these claims and presentations misleadingly implies a greater degree of certainty about the mechanism of action of Abilify in humans than is currently known." Furthermore, the aid was "misleading because it implies that Abilify offers advantages over other currently approved treatments for bipolar disorder...when this has not been demonstrated," OPDP stated.

May 14, 2015: Oak Pharmaceuticals, Inc.

Reason: Omission of Risk; Omission of Material Facts

Nembutal Sodium Solution is a short-acting injectable barbiturate used to control seizures. The product's manufacturer, Oak Pharmaceuticals, displayed a large exhibit banner for Nembutal at a specialists meeting where it was viewed by two FDA representatives. The exhibit banner for Nembutal included claims such as "Control the Uncontrollable" and "the control you need when seizures are their worst;" however, it omitted contraindications, warnings, and common adverse reactions associated, stated OPDP. The Office acknowledged that the banner contained the following statement in caps: "See booth representative for full prescribing information and important safety information." This did not mitigate the misleading omission of risk information.

May 19, 2015: Actavis Laboratories

Reason: Unsubstantiated Claims

Actavis received an Untitled Letter from OPDP concerning the homepage of its website for the benign prostatic hyperplasia (BPH) drug, Rapaflo. The webpage contains the statement "BPH symptom relief that works nights so he can work days," and a picture of a man walking to the bathroom from bed at night. The OPDP wrote that because no studies had shown that Rapaflo helps improve quality of sleep and work productivity, the ad made unsubstantiated claims.

June 23, 2015: ASCEND Therapeutics

Reason: Omission of Risk

FDA's letter to ASCEND Therapeutics focused on a "Zazzle card" for the company's EstroGel product, used to treat symptoms of vulvar and vaginal atrophy due to menopause. While the company indicated that "Estrogen therapies increase the risk of certain cancers, cardiovascular disorders, and probable dementia," it failed to disclose material information about the specific risks related to cancers and cardiovascular disorders discussed in the Boxed Warning section of EstroGel's PI, which include endometrial cancer, invasive breast cancer, deep vein thrombosis, pulmonary embolism, stroke, and myocardial infarction. Furthermore, the Zazzle card failed to include any of the conditions for which EstroGel is contraindicated. FDA found that the Zazzle card statement, "See enclosed full Prescribing Information and boxed warning," did not mitigate the omission of these risks.

IMPLICATIONS

While FDA's Office of Prescription Drug Promotion casts a wide net—targeting a large spectrum of therapeutic products, promotional mediums, and intended audiences—a number of common themes surface year after year. The Agency has made known on many occasions that it takes a risk-based approach to enforcement.[7] Promotional materials for pharmaceuticals that have a black box warning, that contain serious contraindications, or that have a high potential for abuse are examples of products that should have their materials screened very carefully, with a focus on including complete and accurate risk information. OPDP reiterates in many of its letters that a prominent hyperlink to risk information, large text directing patients to the product's black box, or similarly clear directives will not suffice. The complete risk information itself must be included in the promotional materials.

Further, OPDP's letters this year confirm that they will take into consideration the totality of a promotional material. If an image suggests a claim of efficacy or superiority not indicated in the products label, OPDP will take this into consideration despite any text in the promotion that may attempt to suggest otherwise.

How should the industry interpret this and what actions should one consider? With the focus on Omission of Risk Information and Minimization of Risk, companies should ensure that their promotional review process and subsequent auditing and monitoring of the use of promotional materials has a similar focus on fair balance and accuracy in safety data included in the materials. Companies should also make sure that any field force monitoring include a focus on the provision of fair balance and accurate safety data in promotional interactions (e.g. sales representative detailing, speaker programs).

The FDA's focus on properly disclosing risk information promises to be a continuous staple in future enforcement actions; however, it is clear from the dearth of enforcement letters that the agency is in a transition mode. Thomas Abrams, Director at OPDP, confirmed this point in a presentation at the CBI Pharmaceutical Compliance Conference in Washington, DC. Abrams stated that "in light of emerging case law involving the First Amendment, FDA is currently engaged in comprehensive review of regulations and guidance documents in an effort to harmonize the fundamental public health interest underlying the FDA's mission and statutory framework along with the interests in disseminating truthful and non-misleading information."[8]

While a number of guidance documents, including guidance on how the industry may communicate about unapproved uses of approved medical products, were promised but not delivered in 2015, we expect the FDA to be busy in 2016.

7. See, for example, OPDP's presentations at the FDLI Conferences from 2014 (Slide 14): http://www.fdli.org/docs/ap2014/abrams_opdp-update_final-compatibility-mode-.pdf?sfvrsn=0; and 2013 (Slide 14): http://www.fdli.org/docs/default-document-library/tom-abrams-slides-policy-updates-fda-1.pdf?sfvrsn=0
8. http://www.policymed.com/2015/05/amarin-v-fda-off-label-first-amendment.html