

Client Alert

FDA & Life Sciences Practice Group

January 2015

2014 Year in Review: *OPDP Warning and Untitled Letters*

In 2014, the Center for Drug Evaluation and Research's (CDER) Office of Prescription Drug Promotion (OPDP) issued a total of 10 enforcement letters to pharmaceutical manufacturers. Of the 10 letters, nine were Untitled Letters and only one was a Warning Letter. As demonstrated in the below chart, this was a record low for the total number of enforcement letters issued by OPDP in a year.

Year	2014	2013	2012	2011	2010	2009
OPDP Enforcement Letters	10	24	28	30	52	38

Although the total number of promotion and marketing-related enforcement letters has been decreasing steadily over the last five years, 2014 represented a significant drop with less than half of the letters issued in 2013. One possible explanation for the unusually light year of OPDP enforcement was that OPDP diverted resources typically devoted to surveillance and enforcement actions to the development of guidance documents and other activities. OPDP was involved in the issuance of five draft guidances in 2014 plus a sixth draft guidance in late 2013, an unusually high number. An OPDP representative was also reported earlier this month as indicating that the Office may have devoted increased time last year to core launch promotional compliance reviews as well.¹ Although only time will tell, it is also possible that the slowed pace of enforcement letters may reflect, in part, the continued scrutiny on OPDP's regulation of drug promotion post-*U.S. v Caronia*.²

Most Commonly Cited Allegations

Although the volume of letters issued decreased, OPDP's primary areas of focus remained much the same as in recent years. The following were the most cited allegations by OPDP in 2014 along with a comparison to 2013, 2012 and 2011:

Allegation	2014	2013	2012	2011
Omission and/or Minimization of Risk Information	70%	83%	64%	77%
Omission of Material Facts	60%	42%	18%	17%
Unsubstantiated Superiority Claim	30%	38%	32%	23%
Unsubstantiated Claim	20%	38%	29%	37%
Overstatement of Efficacy	20%	21%	43%	37%

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As in previous years, omission and /or minimization of safety and risk information was the most frequently cited violation in the 2014 OPDP enforcement letters, appearing in 70% of the letters. OPDP continued the trend over the last few years of providing more detailed explanations regarding its objections, particularly when alleging that safety and risk information was false or misleading. This is consistent with OPDP's publicly stated position that *Caronia* does not diminish the Office's enforcement of the prohibitions against misbranding under the Federal Food, Drug and Cosmetic Act because "the First Amendment does not preclude" enforcement based on promotion that is "false or misleading."³

Observations and Important Practical Reminders from 2014 OPDP Letters:

- ***OPDP continues to devote significant resources to the regulation of social media and internet-based communications.*** After not citing promotion on social media platforms in any 2013 enforcement letters, OPDP issued two Untitled Letters involving social media in 2014. Specifically, on June 27, 2014, OPDP issued an Untitled Letter related to promotion of the drug Viread via Google Sponsored Links. On February 24, 2014, OPDP issued an Untitled Letter for promotional claims regarding the drug Tirosint on Facebook. In addition, OPDP issued three social media-related guidance documents in 2014: "Fulfilling Regulatory Requirements for Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics,"⁴ "Internet/Social Media Platforms with Character Space Limitations—Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices,"⁵ and "Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation About Prescription Drugs and Medical Devices."⁶ According to CDER's 2015 Guidance Agenda, OPDP intends to publish another social media guidance in 2015, titled "Internet/Social Media Advertising and Promotional Labeling of Prescription Drugs and Medical Devices – Use of Links to Third-Party Sites."⁷
- ***OPDP continues to focus on misleading representations of risk and safety information in enforcement letters.*** The majority of the 2014 enforcement letters included allegations of insufficient discussion or presentation of safety and risk information. Listed below is one example that serves as a practical reminder regarding OPDP's position on the presentation of risk and safety information in promotional materials:
 - **Promotional pieces containing efficacy claims must include the most serious and frequently occurring risks within the piece itself. It is insufficient to simply reference and attach the full PI.** In a January 24, 2014 Untitled Letter for the drug Tindamax, OPDP cited the company for omitting important risk information from a promotional sales sheet. Although the sales sheet included the Boxed Warning, it failed to include any of the contraindications, other serious warnings and precautions and common adverse reactions associated with use of the drug. OPDP emphasized that a statement to "Please see attached full Prescribing Information, including Boxed Warning" did not mitigate omission of the risk information from the promotional piece itself.
- ***All material information from the "Indications and Usage" section of a drug's approved Prescribing Information must be included in promotional pieces.*** OPDP cited several companies for promotional pieces that failed to reveal important and material information regarding use of the drug.
 - **If a drug's approved indication discusses the need for diagnostic test(s), that material information must be communicated.** In the January 24, 2014 Untitled letter cited above, OPDP also cited the company for omission of material facts in the Tindamax promotional sales sheet. Tindamax is approved to treat trichomoniasis caused by the organism, *Trichomonas vaginalis*. The approved "Indications and Usage" section of the PI specifically states that a diagnostic test should be completed to identify the specific organism affecting the patient. OPDP cited the company for failing to include specific mention of the required diagnostic procedure in the promotional sales sheet. OPDP also noted that the statement that use

of Tindamax “should be reserved for conditions described in the INDICATIONS and USAGE” did not mitigate omission of any specific discussion of the need for the diagnostic test in the sales sheet itself.

- **Similarly, if a drug’s approved indication discusses the need for use of the drug as part of a broader treatment plan, that information must be communicated as well.** In the Tindamax Untitled Letter, OPDP also cited the company for failing to communicate the need (as stated in the “Indications and Usage” Section of the approved PI) to treat sexual partners simultaneously. OPDP expressed a similar concern in its July 7, 2014 Untitled Letter regarding the ADHD drug Kapvay. OPDP took issue with the company’s professional sales script, which failed to communicate the important information from the approved indication that Kapvay is only one element of a comprehensive treatment program for ADHD that includes other measures (i.e., psychological, educational and social).
- **A limitation of use expressed in the approved indication is material information that must be included with the product indication.** On June 9, 2014, OPDP issued an Untitled Letter regarding claims made on the promotional website for Suprenza, a weight loss drug. OPDP cited the company for failing to disclose that there is a minimum initial body mass index (BMI) (as stated in the “Indications and Usage” section of the approved PI) for which treatment with Suprenza is indicated. Similarly, on October 29, 2014, OPDP took issue with a professional sales aid for the insomnia drug, Doral, that failed to communicate the material information from Doral’s approved indication that prolonged administration of Doral is not generally necessary or recommended.
- **Important dosage and administration recommendations from a product’s approved indication must also be included with the general dosing information.** OPDP’s Untitled Letter for Doral also cited the company for omitting important information from the Dosage and Administration Section of the Doral PI. The sales aid stated: “Doral 15 mg @ bedtime” but failed to also include direction to use the lowest effective dose and to begin with an initial dose of 7.5 mg, increasing to 15 mg if necessary for efficacy.
- ***OPDP continues to apply its long-held standard that superiority claims must be supported by data from adequate and well controlled head-to-head trials designed to measure clinical superiority.*** Three of the ten enforcement letters issued by OPDP in 2014 contained allegations regarding unsubstantiated superiority claims. For example, on September 11, 2014, OPDP issued an Untitled Letter regarding the cholesterol drug, Lipofen. OPDP cited the company for claims that misleadingly implied that Lipofen offered clinical advantage over other available fenofibrate products, as a result of its formulation and delivery system. OPDP noted that none of the references cited in support of these claims described clinical trial data comparing Lipofen to other fenofibrate products and emphasized that claims of superiority must be supported by adequate and well-controlled, head-to-head clinical trials.
- ***OPDP re-emphasized that review articles, non-clinical studies, and low-powered studies are not substantial evidence to support claims of efficacy.*** In an October 29, 2014 Untitled Letter, OPDP took issue with superiority claims made in a sales aid for the insomnia drug, Doral. OPDP stated that the sales aid suggested that Doral is a “unique” sleep agent. OPDP noted that the cited references (two review articles, a reference providing an unvalidated algorithm lacking data in human subjects and a clinical study of only nine healthy subjects) failed to meet the standard of substantial evidence.
- ***Several of the 2014 enforcement letters serve as important reminders that OPDP scrutinizes images and visual representations, and not just written text, when reviewing promotional pieces.*** For example, in the Doral Untitled Letter discussed above, OPDP cited the company for making unsubstantiated superiority claims. One of the example violations cited by OPDP in support of this allegation was the image of a single white sheep among a

group of four black sheep in the Doral sales aid. In addition, in a December 15, 2014 Untitled Letter for the anti-seizure drug Aptiom, OPDP again took issue with images included in a print advertisement. Specifically, the ad included an image of a man confined to a dark house surrounded by a fence of EEG brain waves. Further down in the print advertisement, a second image showed the same man walking away from the house with a woman and a dog. OPDP stated that the images (as well as the statement, “seizures can keep patients feeling confined”) misleadingly suggested that Aptiom positively affected patients’ “feelings of confinement” associated with seizures.

- ***Bad Ad Program complaints continue to be a source for OPDP enforcement action.*** OPDP continues to use the Bad Ad Program as a source for enforcement action, as one of the 2014 letters indicated that it was initiated by a complaint submitted to the Bad Ad Program. Although none of the 2013 letters expressly indicated that it was prompted by a Bad Ad Program complaint, the Bad Ad Program was cited in three letters in 2012 and five letters in 2011.

For your reference, we have prepared a chart that provides: (1) a list of 2014 OPDP Warning and Untitled Letters; (2) highlights of promotional violations alleged in each letter; and (3) a hyperlink to each letter. The chart is available online in a searchable PDF document [here](#).

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This alert provides a general summary of recent legal developments. It is not intended to be and should not be relied upon as legal advice. In some jurisdictions, this may be considered “Attorney Advertising.”

¹ Silverman, Ed, “Why has FDA Issued So Few Warning Letters About Drug Marketing,” *WSJ Pharamlot*, January 8, 2015, available at <http://blogs.wsj.com/pharmalot/2015/01/08/why-has-fda-issued-so-few-warning-letters-about-drug-marketing/>.

² In *U.S. v. Caronia*, the Second Circuit found that prosecution based on truthful speech about off-label uses of FDA-approved drugs violated the First Amendment. *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>.

³ OPDP Enforcement Actions Webinar, May 16, 2013.

⁴ FDA, “Draft 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>.

⁵ FDA, “Draft Guidance for Industry: Internet/Social Media Platforms with Character Space Limitations— Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices” (2014), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM401087.pdf>.

⁶ FDA, “Draft Guidance for Industry: Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation About Prescription Drugs and Medical Devices” (2014), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM401079.pdf>.

⁷ FDA, “Guidance Agenda: New and Revised Draft Guidances CDER is Planning to Publish During Calendar Year 2015” (2015), <http://www.fda.gov/downloads/drugs/guidancecomplianceinformation/guidances/ucm417290.pdf>.

2014 OPDP Warning and Untitled Letters

Warning Letters indicated with * by the Date

Date with Hyperlink to Letter	Drug and Indications Referenced in Letter	Boxed Warning	Form of Communication	Summary of Alleged Violations
01-24-2014	<p>Tindamax® For the treatment of trichomoniasis caused by <i>Trichomonas vaginalis</i>, and for bacterial vaginosis (BV) in non-pregnant women.</p>	<p>Yes</p>	<p>Professional Sales Sheet</p>	<ul style="list-style-type: none"> • Omission of Risk Information: <ul style="list-style-type: none"> ○ Sales sheet fails to reveal any of the contraindications for use of Tindamax and the warnings and precautions regarding neurological adverse reactions and blood dysciasias associated with the drug. Also fails to disclose the common adverse reactions associated with the use of Tindamax. ○ By omitting serious and common risks associated with the drug, the sales sheet misleadingly suggests that Tindamax is safer than has been demonstrated. ○ Inclusion of the Boxed Warning and a reference to the full Prescribing Information (PI) does not mitigate the omission of the other risk information. • Broadening of Patient Population or Condition: <ul style="list-style-type: none"> ○ Statements that fail to present the drug’s full approved indication, such as “Tindamax is the one and only treatment for BV...” and images of women of child-bearing age misleadingly broaden Tindamax’s patient population or condition by suggesting that it is approved for the treatment of BV in all women, including those that may be pregnant. ○ These statements and images need to be supported by substantial evidence or substantial clinical evidence. They also provide evidence that Tindamax is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use. • Unsubstantiated Superiority: <ul style="list-style-type: none"> ○ Claims such as Tindamax has “better tolerability – than metronidazole...” suggest that Tindamax is superior to metronidazole. Claims of superiority must be supported by adequate and well-controlled head-to-head trials comparing the two drugs and demonstrating that Tindamax is superior as compared to metronidazole. • Omission of Material Facts: <ul style="list-style-type: none"> ○ Sales sheet misleadingly claims that Tindamax is recommended as a “drug of choice” for BV and trichomoniasis in Treatment Guidelines. However, the sales sheet fails to communicate material information from Tindamax’s full FDA-approved indication for the treatment of trichomoniasis, including important information regarding diagnostic procedures and the need to treat sexual partners simultaneously. ○ Statements referring to the full Prescribing Information (PI), including the Boxed Warning, do not mitigate the misleading omission of important

2014 OPDP Warning and Untitled Letters

Date with Hyperlink to Letter	Drug and Indications Referenced in Letter	Boxed Warning	Form of Communication	Summary of Alleged Violations
				<p>material facts.</p> <ul style="list-style-type: none"> • Unsubstantiated Claim: <ul style="list-style-type: none"> ○ The sales sheet claims “patient-friendly convenience.” This is misleading because overall patient convenience encompasses a variety of factors that need to be supported by substantial evidence. In addition, Tindamax requires multiple tablets to be taken with food and patients must abstain from alcoholic beverages while taking Tindamax for three days afterwards.
<p>02-24-2014</p>	<p>Tirosint As a replacement or supplemental therapy in congenital or acquired hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis.</p>	<p>Yes</p>	<p>Facebook Page</p>	<ul style="list-style-type: none"> • Omission of Risk Information: <ul style="list-style-type: none"> ○ The Facebook page makes representations about the efficacy of Tirosint, but fails to communicate any of the risks associated with its use, including the Boxed Warning. ○ By omitting the most serious and frequently occurring risks associated with Tirosint, the Facebook page misleadingly suggests that Tirosint is safer than has been demonstrated. • Omission of Material Facts: <ul style="list-style-type: none"> ○ The Facebook page fails to provide material information regarding Tirosint’s FDA-approved indication by failing to convey what Tirosint is not indicated for. (i.e., the Facebook page suggests that Tirosint may be used for hypothyroidism, but fails to indicate that Tirosint is specifically not indicated for transient hypothyroidism during the recovery phase of subacute thyroiditis.”)
<p>05-06-2014</p>	<p>Disulfiram As an aid in the management of selected chronic alcohol patients who want to remain in a state of enforced sobriety so that supportive and psychotherapeutic treatment may be applied to the best advantage.</p>	<p>Yes</p>	<p>Professional Sales Aid</p>	<ul style="list-style-type: none"> • Omission of Risk Information: <ul style="list-style-type: none"> ○ Sales aid makes representations about the efficacy of Disulfiram, such as “Product Category: Alcohol antagonist,” but fails to communicate any of the risk information associated with its use, including the most serious and frequently occurring risks. ○ By omitting its risks, the sales aid misleadingly suggests that Disulfiram is safer than has been demonstrated. • Omission of Material Fact: <ul style="list-style-type: none"> ○ The sales aid fails to communicate material information from Disulfiram’s full FDA-approved indication for the management of alcoholism, such as Disulfiram is “not a cure for alcoholism” and “when used alone, without proper motivation and supportive therapy, it is unlikely that it will have any substantive effect on the drinking pattern of the chronic alcoholic.”

2014 OPDP Warning and Untitled Letters

Date with Hyperlink to Letter	Drug and Indications Referenced in Letter	Boxed Warning	Form of Communication	Summary of Alleged Violations
06-09-2014	<p>Suprenza™ For the use as a short-term (a few weeks) adjunct in a regimen of weight reduction.</p>	<p>No</p>	<p>Product Website</p>	<ul style="list-style-type: none"> • Omission of Risk Information: <ul style="list-style-type: none"> ○ The webpage makes numerous efficacy claims for Suprenza, but it omits all of the contraindications and adverse reactions associated with its use, and fails to disclose any of the other warnings and precautions associated with the drug. ○ By omitting serious and frequently occurring risks, the webpage misleadingly suggests that Suprenza is safer than has been demonstrated. ○ A statement included on the webpage providing a link to the full PI does not mitigate the misleading omission of risk information. • Unsubstantiated Efficacy Claims: <ul style="list-style-type: none"> ○ Claims such as “It’s time to take control...and get LEAN,” and an image of a woman squeezing together lettered blocks that spell the word “LEAN,” misleadingly suggest that patients will become lean as a result of therapy with Suprenza. ○ The claims and presentations need substantial evidence or substantial clinical experience to support this implication. ○ The Clinical Studies section of the PI describes only relatively short-term efficacy trials of adult obese patients. These trials found that the magnitude of increased weight loss over placebo is only a fraction of a pound per week. • Omission of Material Fact: <ul style="list-style-type: none"> ○ The Indications and Usage section of the approved PI includes a minimum initial body mass index (BMI) for which treatment with Suprenza is indicated. The Suprenza webpage misleadingly omits this material information regarding the minimum BMI.

2014 OPDP Warning and Untitled Letters

Date with Hyperlink to Letter	Drug and Indications Referenced in Letter	Boxed Warning	Form of Communication	Summary of Alleged Violations
06-27-2014	<p>Viread® For the treatment of chronic hepatitis B in adults and pediatric patients 12 years of age and older.</p>	<p>Yes</p>	<p>Sponsored Link on Google</p>	<ul style="list-style-type: none"> • Lack of Adequate Directions for Use: <ul style="list-style-type: none"> ○ Sponsored link claims Viread is safe and effective for use in the <i>prevention</i> of hepatitis B, but the approved labeling states Viread is safe and effective only for the <i>treatment</i> of hepatitis B. ○ By stating that Viread can prevent hepatitis B, the sponsored link implies a new indication for which it lacks FDA approval • Omission of Risk Information: <ul style="list-style-type: none"> ○ The sponsored link makes representations and/or suggestions about the efficacy of Viread, but fails to communicate any risk information. ○ By omitting all risks, including the Boxed Warning, the sponsored link misleadingly suggests that Viread is safer than has been demonstrated. ○ The sponsored link containing a link to the product’s website does not mitigate the misleading omission of risk information from this promotional material. • Inadequate Presentation of Established Name: <ul style="list-style-type: none"> ○ The sponsored link fails to present the established name for Viread (tenofovir disoproxil fumarate). • Failure to Submit Under Form FDA-2253: <ul style="list-style-type: none"> ○ Companies must 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 is required to be accompanied by a completed transmittal Form FDA-2253. ○ A copy of the Viread sponsored link was not submitted under Form FDA-2253 at the time of initial publication.

2014 OPDP Warning and Untitled Letters

Date with Hyperlink to Letter	Drug and Indications Referenced in Letter	Boxed Warning	Form of Communication	Summary of Alleged Violations
07/07/2014	<p>Kapvay™ For the treatment of attention deficit hyperactivity disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications.</p>	No	Professional telephone script	<ul style="list-style-type: none"> • Omission of Risk Information: <ul style="list-style-type: none"> ○ The script is misleading because it includes efficacy claims for Kapvay, but fails to include important risk information associated with the drug, including the contraindication, all of the warnings and precautions, and common adverse reactions. ○ Inclusion of a general statement about adverse events and the statement “I can email the full prescribing information for Kapvay or you can also access it at the Kapvay website” does not mitigate the omission of important risk information. • Omission of Material Fact: <ul style="list-style-type: none"> ○ The script includes claims that Kapvay is a treatment for ADHD. However, the script fails to communicate other material information about Kapvay’s indication. Specifically, it omits material information from the indication stating that Kapvay is part of a comprehensive treatment program for ADHD that includes other measures (i.e., psychological, educational and social). ○ The script also fails to include important material information regarding dosing. The script indicates that doses should be taken twice a day. However, it fails to provide important information regarding <i>initial</i> dosing (i.e., that dosing should be initiated with one 0.1 mg tablet at bedtime and the daily dosing should be adjusted in increments of 0.1 mg/day at weekly intervals until the desired response is achieved.”
09/11/2014	<p>Lipofen®</p> <ul style="list-style-type: none"> • Adjunctive therapy to diet to reduce elevated low-density lipoprotein cholesterol (LDL-C), total cholesterol (total-c), Triglycerides (TG) and apolipoprotein B (Apo B) and to increase high-density lipoprotein cholesterol (HDL-C) in adult patients with hypercholesterolemia or mixed dyslipidemia. • Adjunctive therapy to diet for treatment of adult patients with severe hypertriglyceridemia. 	No	Email	<ul style="list-style-type: none"> • Unsubstantiated Superiority Claims <ul style="list-style-type: none"> ○ The email contained a number of claims that misleadingly implied that Lipofen offered clinical advantage over other available fenofibrate products, as a result of its formulation and delivery system. Claims included: <ul style="list-style-type: none"> ▪ “All fenofibrates are not created equal.” ▪ “. . . a generic fenofibrate may not be the best option. Only Lipofen offers Lidose® technology, which uses a unique lipid matrix system not available with any other generic or brand-name fenofibrate; avoids dependence on particle formulation; may improve safety and efficacy of the active ingredient in Lipofen...” ▪ “Other fenofibrates are formulated with small particles, which may affect absorption.” ○ None of the references cited as support for the superiority claims describe any clinical data comparing Lipofen to other fenofibrate products. FDA noted that it was not aware of any such head-to-head trials. ○ Claims of superiority must be supported by adequate and well-controlled head-to-head clinical trials.

2014 OPDP Warning and Untitled Letters

Date with Hyperlink to Letter	Drug and Indications Referenced in Letter	Boxed Warning	Form of Communication	Summary of Alleged Violations
09/22/2014*	<p>Exparel® Liposome injection of bupivacaine, an amide-type local anesthetic, indicated for administration into the surgical site to product postsurgical analgesia.</p>	<p>No</p>	<p>Educational Technique Flashcards (administration guides) / Journal Ad</p>	<ul style="list-style-type: none"> • FDA noted in the Warning Letter that the journal ad was submitted to FDA as a complaint to the OPDP Bad Ad Program. • Lack of Adequate Directions for Use <ul style="list-style-type: none"> ○ The administration guides describe specific administration techniques for Exparel in laparoscopic cholecystectomy and open colectomy. These statements suggest that Exparel is safe and effective for use in cholecystectomy and colectomy. ○ However, the Dosing and Administration Section of the Exparel PI provides recommended dosing for bunionectomy and hemorrhoidectomy only. In addition, the Clinical Studies section of the PI specifically states that Exparel has <i>not</i> been demonstrated safe and effective in other procedures beyond bunionectomy and hemorrhoidectomy. ○ Use of disclaimers and disclosures do not mitigate the “overwhelming impression” that Exparel is safe and effective for use in cholecystectomy and colectomy. ○ OPDP also notes that it is concerned with suggestions made in numerous HCP-directed promotional pieces submitted under FDA-form 2253 that Exparel has been demonstrated to be safe and effective in various other surgical procedures (e.g., knee arthroplasty, gastric sleeve, open hysterectomy, lumbar interbody fusion, abdominoplasty, etc.) ○ OPDP states that these materials taken as a whole “suggest an extensive promotional campaign to promote the use of Exparel in surgical procedures other than those for which the drug has been shown to be safe and effective.” • Overstatement of Efficacy <ul style="list-style-type: none"> ○ Claims made in the journal ad misleadingly suggest that Exparel has demonstrated pain control beyond 24 hours. <ul style="list-style-type: none"> ▪ “Patient-Focused Pain Control That Lasts For Up To 72 Hours” ▪ The only single-dose local analgesic to . . . Reduce or eliminate opioids with pain control for up to 3 days.” ○ Neither study cited as support for these claims constitutes substantial evidence to support claims regarding pain control beyond 24 hours. In fact, the Clinical Studies section of the PI specifically states that “Between 24 and 72 hours after study drug administration, there was minimal to no difference between Exparel and placebo treatments on mean pain intensity.” • OPDP noted that due to the seriousness of the violations, the company disseminate corrective messaging to the audiences that received the violative promotional materials.

2014 OPDP Warning and Untitled Letters

Date with Hyperlink to Letter	Drug and Indications Referenced in Letter	Boxed Warning	Form of Communication	Summary of Alleged Violations
10/29/2014	<p>Doral® For the treatment of insomnia characterized by difficulty falling asleep, frequent nocturnal awakenings and/or early morning awakenings.</p>	<p>No</p>	<p>Professional Sales Aid</p>	<ul style="list-style-type: none"> • <i>Omission of Risk Information</i> <ul style="list-style-type: none"> ○ Sales aid contains numerous claims regarding benefits of Doral for insomnia but omits all contraindications and the serious warning and precautions regarding benzodiazepine withdrawal syndrome, the need to evaluate co-morbid diagnoses, severe anaphylactic or anaphylactoid reactions, abnormal thinking and behavior changes, and worsening of depression. <ul style="list-style-type: none"> ▪ OPDP notes that omission of these serious risks is further exacerbated by claims characterizing Doral as having a “favorable safety profile.” ○ The sales aid also omits other material information from the Warnings and Precautions section of the PI, including, among other things, the need to caution patients against driving or engaging in other activities that require mental alertness. ○ The sales aid also presents some of the common adverse reactions (e.g., daytime drowsiness and headache) but completely omits other common adverse reactions associated with the drug (e.g., fatigue, dizziness, dry mouth and dyspepsia). ○ OPDP notes that direction to “Please see accompanying full prescribing information” does not mitigate the omission of risk information. • <i>Unsubstantiated Superiority Claims</i> <ul style="list-style-type: none"> ○ The sales aid also contains numerous statements and images suggesting that Doral is a “unique” sleep agent (e.g., image of a single white sheep among a group of four black sheep and “uniquely selective”). ○ OPDP stated that the totality of the claims and images misleadingly suggests that Doral is safer and more effective than other insomnia products because of a unique mechanism of action. ○ OPDP noted that the cited references (two review articles, a reference providing an unvalidated algorithm lacking data in human subjects and a clinical study of only nine healthy subjects) failed to meet the standard of substantial evidence. • <i>Omission of Material Facts</i> <ul style="list-style-type: none"> ○ The sales aid fails to communicate material information from Doral’s approved indication (e.g., prolonged administration of Doral is not generally necessary or recommended). ○ The sales aid presents an image of a prescription pad with the claim: “Doral 15 mg @ bedtime.” However the sales aid omits important information from the Dosage and Administration Section of the Doral PI (e.g., use the lowest effective dose; recommended initial dose of 7.5 mg with an increase to 15 mg if necessary for efficacy.”) 7 • <u>Failure to Submit Under Form FDA-2253:</u> <ul style="list-style-type: none"> ○ Failure to submit a copy of the Doral sales aid under Form FDA-2253 at the time of initial publication.

2014 OPDP Warning and Untitled Letters

Date with Hyperlink to Letter	Drug and Indications Referenced in Letter	Boxed Warning	Form of Communication	Summary of Alleged Violations
12/15/2014	Aptiom® Adjunctive treatment of partial-onset seizures.	No	Print Advertisement	<ul style="list-style-type: none"> • Overstatement of Efficacy: <ul style="list-style-type: none"> ○ The print advertisement includes the statement “Seizures can keep patients feeling confined. The print advertisement also shows a series of two images. The first image shows a man confined to a dark house surrounded by a fence made of EEG brain waves. The second image shows the same man walking away from the house with a woman and a dog. ○ OPDP stated that the statement and images suggest that Aptiom has benefits on patients’ <i>feelings of confinement</i> associated with seizures. ○ However, the primary endpoints of Aptiom’s clinical studies were standardized seizure frequency. ○ OPDP stated that although Aptiom may reduce seizure frequency, it is not aware of substantial evidence demonstrating any effectiveness of Aptiom on patients’ <i>feelings of confinement</i> associated with seizures.