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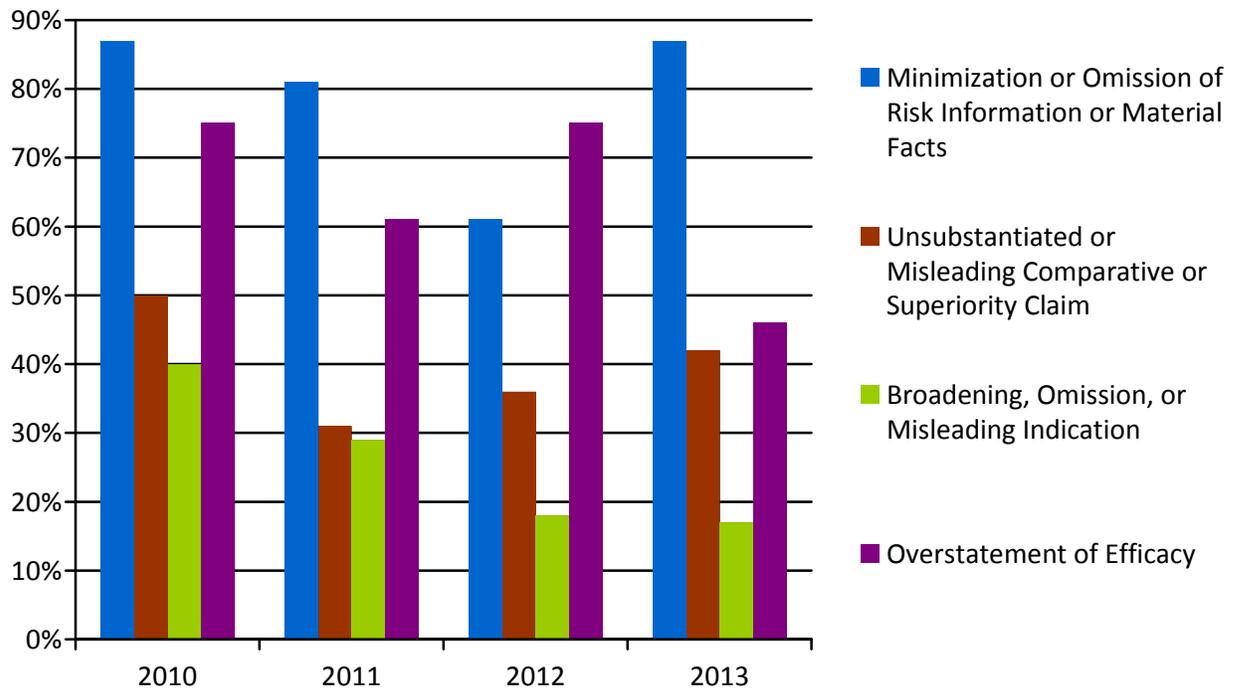
FDA's Office of Prescription Drug Promotion (OPDP) Enforcement: A Summary of 2013 Warning and Untitled Letters

Jennifer A. Romanski, J.D.
Director, Regulatory and Compliance Services

Kim C. Capone
Senior Regulatory Analyst



FDA’s Office of Prescription Drug Promotion (OPDP) issued a total of 24 enforcement letters to pharmaceutical manufacturers in 2013, 3 Warning Letters and 21 Untitled Letters. This is comparable to the 21 enforcement letters issued by OPDP in 2012. With respect to the types of violations, OPDP focused more on “Omission of Material Facts” this past year than it did in 2012. A comparison of the most frequently cited violations for the last few years is listed below.



Within these broader categories, the following areas of non-compliance were noted:

Minimization or Omission of Risk Information or Material Facts	
Failure to include risk information	46%
Failure to include warning(s)	46%
Failure to include precaution(s)	46%
Lack of or inadequate fair balance	29%
Inadequate prominence or visibility of risk information	29%
Failure to include contraindication(s)	25%
Misleading or unsubstantiated safety claim	25%
Failure to include full indication or limitations to indication	25%
Failure to include adverse event(s)	17%
Failure to include most frequent, important or serious risk information	17%
Failure to include risk information in main body of promotional material	8%
Failure to include information from a boxed warning	4%

Misleading or Unsubstantiated Efficacy Claim(s)	
Claim not based on adequate, well-controlled studies	42%
Misleading or unsubstantiated claim regarding efficacy or benefits of drug	33%
Claim based on post-hoc analysis	21%
Claim not based on pre-defined study endpoints	21%
Claim based on retrospective data	17%
Claim based on open-label study	8%
Misleading presentation or use of images or graphic matter	8%
Misleading or unsubstantiated claim regarding patient compliance	8%
Claim based on mechanism of action	4%
Misleading or unsubstantiated claim implying “cure” for ailment or resolution of symptoms	4%
Misleading presentation or use of medical, clinical or statistical data	4%
Misleading or unsubstantiated “quality of life” claim	4%
Misleading or Unsubstantiated Comparative Claim(s)	
Misleading or unsubstantiated superiority claim	38%
Claim not based on adequate, well-controlled head-to-head studies	29%
Misleading or unsubstantiated claim that drug is “easier to use” or “more convenient”	13%
Generic superiority claim	4%
Misleading or unsubstantiated claim that drug is “unique,” “different,” or “only”	4%
Misleading or unsubstantiated claim that drug is “new” or “first”	4%
Misleading or unsubstantiated patient preference claim	4%
Broadening, Misinformation or Inadequate Communication of Indication, Use or Administration	
Broadening of disease state / conditions	13%
Broadening of patient population	13%
Misinformation regarding dosing or administration	8%
Failure to adequately communicate indication or limitations to indication	4%

Of the 24 letters issued in 2013, 6 identified violations concerning website promotion, 5 identified violative direct-to-consumer promotion involving patient brochures and print advertisements, 2 identified violative sales aids and 2 identified violative direct mailers. The remaining letters identified violations concerning a videotape, print invitation, announcement letter, email, detailer, professional letter, intro letter, and oral statements. Approximately half of the letters addressed materials directed at healthcare professionals, and half addressed consumer-directed materials.

WEBSITE PROMOTION

The most common types of promotional material cited by OPDP in 2013 were websites and webpages. Referenced violations included minimization of risk information, misleading efficacy claims, unsubstantiated comparative claims, and promotion of unapproved uses.

Untitled Letter to CBA Research, Inc. (April 25, 2013)

OPDP issued an Untitled Letter to CBA Research, Inc. regarding its website for CBT-1 (tetrandrine), a drug under investigation for use as an adjunct to chemotherapy in all cancer types with multidrug resistance (MDR). The Untitled Letter cited multiple claims presented on CBA's website that make positive and definite conclusions about CBT-1, such as its ability to reverse multi-drug resistance in cancer cells and to improve patient outcomes, while reducing the toxic side effects of chemotherapy and decreasing treatment failures. According to OPDP, these claims suggest that CBT-1, an investigational new drug, is safe and/or effective for use as an adjunct to chemotherapy when it has not been approved for this or any use.

Untitled Letter to Validus Pharmaceuticals, Inc. (May 6, 2013)

OPDP issued an Untitled Letter to Validus Pharmaceuticals, Inc. for its healthcare professional webpage for Marplan (isocarboxazid) tablets. OPDP found that the webpage fails to present risk information with a prominence and readability reasonably comparable to the presentation of efficacy information. By presenting efficacy information at the top of the page, using colorful graphics and large bolded headers, and limiting risk information to the bottom of the page, OPDP claimed the webpage minimizes the risks of the drug. OPDP also noted that the webpage fails to include drug contraindications, and neglects to disclose that hypertensive crises associated with Marplan treatment can be fatal and blood pressure should be monitored closely in treated patients. The webpage also makes misleading representations that overstate the effectiveness of Marplan in the treatment of depression, per OPDP, citing studies that do not constitute substantial evidence or substantial clinical experience.

Untitled Letter to Janssen Biotech Products, L.P. (May 22, 2013)

OPDP's Untitled Letter to Janssen Biotech Products, L.P. found Janssen's website for its ovarian cancer drug Doxil (doxorubicin HCl liposome injection) to be misleading because it makes unsubstantiated claims associated with Doxil and cites retrospective and exploratory studies to support the claims. OPDP pointed out that retrospective studies and institutional chart reviews do not constitute substantial evidence or substantial clinical experience.

Untitled Letter to Merz Pharmaceuticals, LLC (July 31, 2013)

OPDP issued an Untitled Letter to Merz Pharmaceuticals, LLC for its webpage and banners for Naftin (naftifine hydrochloride) Cream, 2%. The Untitled Letter stated that the promotional pieces include unsubstantiated efficacy claims and comparative claims, and omit and minimize risk information. According to the Untitled Letter, the banners include the indication for Naftin Cream, 2%, and several other efficacy claims, such as "Twice as Strong Half as Long," and "Once a day for 2 weeks," but fail to include any risk information. In addition, per OPDP, the webpage suggests that Naftin is superior to other anti-fungal treatments based on its two-week treatment period when there are other prescription products available that have a recommended treatment length of two weeks or less. Merz also makes the claim "Proven safety established from naftifine hydrochloride for over 20 years." While acknowledging that naftifine hydrochloride was initially approved in 1988, Naftin's formulation, according to OPDP, "constitutes a different strength and dosage approved in 2012 that does not have a safety profile established based on a 20-year history of use."

Untitled Letter to US WorldMeds, LLC (November 8, 2013)

OPDP issued an Untitled Letter to US WorldMeds, LLC regarding its webpage “About Revonto,” part of a website for Revonto (dantrolene sodium) for injection. According to OPDP, the webpage contains claims that suggest that Revonto is superior to other treatments for malignant hyperthermia, which is not supported by substantial evidence. OPDP also found that the presentation fails to convey the important risk information with a prominence and readability reasonably comparable to the claims of effectiveness in the piece.

Untitled Letter to Pernix Therapeutics Holdings, Inc. (December 20, 2013)

OPDP issued an Untitled Letter to Pernix Therapeutics Holdings, Inc. for its webpage for Cedax (ceftibuten capsules and ceftibuten for oral suspension). According to the Untitled Letter, the webpage contains several efficacy claims for Cedax, but fails to communicate any risk information associated with the use of the drug. In addition, the webpage associates the efficacy claims with images of children who are clearly under 12 years of age, but omits material facts about the instructions for use of the product in that population.

PATIENT-DIRECTED AND DIRECT-TO-CONSUMER PROMOTION

OPDP has continued to enforce promotional regulations as they pertain to consumer and patient-directed pieces. Violations cited in 2013 include omission of material facts, minimization of risk information, overstatement of efficacy, broadening or inadequate communication of use or indication, misleading comparative claims, and promotion of an unapproved use.

Untitled Letter to Alcon Research, Ltd. (February 5, 2013)

OPDP issued an Untitled Letter to Alcon Research, Ltd. regarding its patient education brochure for Pataday (olopatadine hydrochloride ophthalmic solution) 0.2%. In the Untitled Letter, OPDP stated that the patient education brochure misleadingly omits material facts regarding the Warning and Precaution instructing patients to wait ten minutes after using Pataday before inserting soft contact lenses. Further, OPDP stated that the claims in the brochure misleadingly suggest that Pataday has demonstrated efficacy in treating all “allergy eye symptoms,” improves “overall eye health,” prevents “eye damage,” and can positively impact eye comfort, when, per OPDP, this is not the case. The Untitled Letter explained that Pataday is only approved for the treatment of “ocular itching associated with allergic conjunctivitis.” OPDP further stated that the claims misleadingly imply that all patients who use Pataday will experience “zero-itch” and be symptom-free (i.e., “not give those itchy eyes a second thought”) when this was not demonstrated by substantial evidence or substantial clinical experience.

Untitled Letter to ParaPRO, LLC (February 21, 2013)

OPDP issued an Untitled Letter to ParaPRO, LLC for its video news release for Natroba (spinosad) topical suspension, 0.9%, a topical treatment of head lice infestation in patients 4 years of age and older. According to the Untitled Letter, OPDP found the video news release to be misleading because it presents efficacy claims for Natroba, but fails to communicate any

risks associated with its use, presents an unsubstantiated superiority claim, and inadequately communicates the full indication for the drug. The video news release claims that Natroba “could be a game changing medication in the war against head lice; one that doesn’t require nit combing to be effective.” According to OPDP, this claim misleadingly implies that Natroba represents a new or different approach in the treatment of head lice, and superiority over other currently available products, when this has not been demonstrated by substantial evidence or substantial clinical experience. OPDP noted that while Natroba does not require nit combing to be effective, there are several other prescription products available for the treatment of head lice infestation that also do not require nit combing to be effective.

Untitled Letter to Photocure ASA (March 4, 2013)

OPDP issued an Untitled Letter to Photocure ASA regarding its patient guide for Cysview (hexaminolevulinate hydrochloride), for Intravesical Solution. According to the Untitled Letter, the patient guide is false or misleading because it omits and minimizes risk information, and makes unsubstantiated superiority claims for Cysview. In addition, according to OPDP, the patient guide makes claims that misleadingly suggest that Cysview blue light cystoscopy is more effective than traditional white light cystoscopy, which is not supported by substantial evidence or substantial clinical experience.

Untitled Letter to Johnson & Johnson International, Inc. (June 6, 2013)

OPDP issued an Untitled Letter to Johnson & Johnson International, Inc. regarding its direct-to-consumer print advertisement for Xarelto (rivaroxaban) tablets. Xarelto is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. According to the Untitled Letter, the print ad presents various efficacy claims for Xarelto in large, bolded and/or colorful text and graphics. For example, one bolded efficacy claim states: “XARELTO® is the first and only once-a-day prescription blood thinner for patients with AFib not caused by a heart valve problem, that is proven to reduce the risk of stroke—without routine blood monitoring.” The risk information, however, is presented on the preceding adjacent page with no emphasis on color, borders, layout, or graphics. Therefore, the overall presentation, according to OPDP, misleadingly minimizes the risks associated with Xarelto because it fails to communicate this information with a prominence and readability reasonably comparable to the efficacy claims.

Warning Letter to Acorda Therapeutics, Inc. (July 25, 2013)

Acorda Therapeutics, Inc. received a Warning Letter for its direct-to-consumer print ad for Ampyra (dalfampridine). According to the Warning Letter, the print ad entirely omits risk information, including contraindications, warnings and precautions, and the most frequently reported adverse events for Ampyra. Additionally, OPDP had previously expressed concerns regarding violative promotional activities to Acorda. In a June 21, 2012 Untitled Letter, OPDP cited an Ampyra video segment for minimization of risk information and overstatement of efficacy.

Untitled Letter to Sunovion Pharmaceuticals (October 24, 2013)

OPDP issued an Untitled Letter to Sunovion Pharmaceuticals regarding its patient brochures for Brovana (arformoterol tartrate) Inhalation Solution. The totality of the claims and presentations, along with the headline claim, “With the right COPD medicine, you may get back to daily living”, suggests that Brovana is clinically superior to other available COPD therapies, per OPDP. In addition, OPDP noted that the overall effect of the presentation undermines the communication of important risk information, minimizing the risks associated with Brovana, and misleadingly suggests that Brovana is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Warning Letter to Aegerion Pharmaceuticals, Inc. (November 8, 2013)

OPDP issued a Warning Letter to Aegerion Pharmaceuticals, Inc. for oral statements made by its Chief Executive Officer during broadcast interviews on CNBC’s television show, “Fast Money.” The statements made were regarding Juxtapid (Iomitapide) capsules, which is indicated as an adjunct to a low-fat diet and other lipid lowering treatments to reduce certain kinds of cholesterol in patients with homozygous familial hypercholesterolemia (HoFH). One statement suggested that treatment with Juxtapid prevents heart attacks and extends the lives of patients with HoFH. A second statement asserted, “these patients are going to die of a cardiac event, either a stroke or a heart attack, if we don’t have them on therapy.” These statements and others, according to OPDP, “provide evidence that Juxtapid is intended for new uses for which it lacks approval, and for which its labeling does not provide adequate directions for use.”

OTHER HCP-DIRECTED PIECES

Untitled Letter to Teva Neuroscience, Inc. (April 8, 2013)

OPDP issued an Untitled Letter to Teva Neuroscience, Inc. regarding its article detailer for Clozapine Tablets USP. According to OPDP, Teva cited an unsubstantiated study in the detailer to support the efficacy claims presented, therefore rendering the presentation misleading. The Untitled Letter stated that the studies cited in the article detailer are not well-controlled head-to-head clinical trials, and, therefore, the claims are not supported by substantial evidence or substantial clinical experience. Further, OPDP noted that numerous efficacy claims are presented throughout the article detailer using colorful pictures and graphics, and large bolded headers, but the majority of risk information is presented in smaller print on the back page of the article detailer. The overall effect of this presentation, as stated by OPDP, undermines the communication of important risk information, minimizes the risks associated with clozapine, and misleadingly suggests that clozapine is safer than has been demonstrated.

Untitled Letter to Mobius Therapeutics, LLC (May 2, 2013)

Mobius Therapeutics, LLC received an Untitled Letter for its email regarding Mitosol (mitomycin for solution). According to OPDP, the company’s email makes representations about Mitosol’s safety, effectiveness, and use, including claims such as “Remove the Variables” and “Eliminate Your Concerns,” but fails to disclose Mitosol’s full approved indication or any risk information associated with the drug. OPDP explained that these claims significantly minimize the risks associated with Mitosol, and suggest there are no safety concerns associated with the drug. In

addition, per OPDP, the email fails to reveal important material facts regarding the dosing and administration of Mitosol.

Untitled Letter to Sigma-tau Pharmaceuticals (May 22, 2013)

OPDP issued an Untitled Letter to Sigma-tau Pharmaceuticals for its sales aid for the chemotherapy drug Oncaspar (pegaspargase) injection. According to the Untitled Letter, the sales aid was discovered by an OPDP representative at the company's promotional exhibit booth at a chemotherapy conference. The Untitled Letter explained that the sales aid presents efficacy data with large bolded headlines and colorful graphics on the first seven pages of the 10-page sales aid. The safety information, however, starts on page eight, with the most important risk information on page 10. OPDP concluded that risk information is not presented with a prominence and readability reasonably comparable to the efficacy information. In addition, the sales aid presents numerous superiority claims about Oncaspar that, according to OPDP, are not supported by substantial evidence.

Untitled Letter to Spectrum Pharmaceuticals (July 23, 2013)

OPDP's Untitled Letter to Spectrum Pharmaceuticals cited the sales aid for its drug Zevalin (ibritumomab tiuxetan) Injection for Intravenous Use. OPDP explained that the sales aid uses imagery that suggests that Zevalin can precisely target lymphoma cells without targeting healthy cells, thereby implying that the drug is safer than has been demonstrated by substantial evidence or substantial clinical experience. OPDP also found that the sales aid overstates the efficacy of Zevalin by implying that the drug has demonstrated efficacy in terms of overall survival when used after first line treatment, when this is not the case. The sales aid also contains claims of enhanced efficacy with "earlier treatment" with Zevalin, and enhanced complete response rates for patients who had a response after first-line induction therapy. According to the Untitled Letter, studies cited to support the efficacy claims are based on post-hoc and retrospective analyses, which do not constitute substantial evidence.

Untitled Letter to Daiichi Sankyo (November 5, 2013)

Daiichi Sankyo received an Untitled Letter regarding its direct mailer for Benicar (olmesartan medoxomil) and Benicar HCT (olmesartan medoxomil/hydrochlorothiazide). The direct mailer contains claims that, according to OPDP, imply that Benicar and Benicar HCT demonstrated efficacy by reducing high blood pressure in "challenging patients," which is not supported by substantial evidence or substantial clinical experience. The Untitled Letter explained that the references in support of the claims describe an open-label, uncontrolled trial, and excluded patients with severe hypertension and uncontrolled blood pressure during the run-in phase of the study.

Untitled Letter to Duchesnay (November 12, 2013)

OPDP issued an Untitled Letter to Duchesnay for its announcement letter for Diclegis (doxylamine succinate and pyridoxine hydrochloride). According to OPDP, the announcement letter fails to mention any risk information, including warnings, contraindications, and precautions. The Untitled Letter also noted that Duchesnay failed to present the established name of the drug in direct conjunction with the proprietary name.

Warning Letter to Kadmon (November 18, 2013)

Kadmon's Intro Letter for Ribasphere RibaPak (ribavirin, USP) was the subject of a Warning Letter for containing unsubstantiated efficacy claims and failing to include any risk information in the body of the letter, per OPDP. OPDP also claimed that the Intro Letter omitted material facts, including information about combination therapy use in clinical trials, parameters relevant to the study, and the drug's limitations with respect to safety and efficacy. OPDP identified as "unsubstantiated efficacy claims" statements that use of the drug will result in improved rates of sustained viral response (SVR) and patient adherence. The Warning Letter stated that there is no substantial evidence to back up the "improved" SVR claim.

Untitled Letter to Amgen, Inc. (November 19, 2013)

OPDP issued an Untitled Letter to Amgen, Inc. for its direct mailer for Aranesp (darbepoetin alfa). According to the Untitled Letter, the direct mailer omits multiple warnings and precautions for Aranesp, misleadingly suggesting that the drug is safer than has been demonstrated. OPDP also noted that the direct mailer presents claims such as "For chemotherapy-induced anemia (CIA) in metastatic patients with Hb<10 g/dL" and "Stabilize the fall." According to OPDP, the totality of the claims and presentations misleadingly suggests that Aranesp is useful to treat chemotherapy-induced anemia in any patient with metastatic cancer whose hemoglobin is falling, or has fallen below 10g/dL. This, per OPDP, implies use in a broader range of patients, which has not been demonstrated by substantial evidence or substantial clinical experience. OPDP also cited Amgen for omitting important dosing information from the direct mailer.

Untitled Letter to Amarin Pharmaceuticals (December 16, 2013)

OPDP issued an Untitled Letter to Amarin Pharmaceuticals regarding its webex print invitation for Vascepa (icosapent ethyl). OPDP claimed that the invitation is misleading because it presents efficacy claims for Vascepa but fails to communicate any of the risks associated with its use. Although the print invitation includes the statement, "*Please see the accompanying full Prescribing Information for VASCEPA,*" OPDP noted that this does not mitigate the misleading omission of risk information.

Untitled Letter to Covis Pharmaceuticals (December 19, 2013)

OPDP issued an Untitled letter to Covis Pharmaceuticals regarding a physician letter for Lanoxin (digoxin). According to the Untitled Letter, the physician letter fails to include important risk information associated with the drug. It also, per OPDP, suggests that Lanoxin is superior to generic formulations of digoxin, and includes claims that broaden the indication for the drug. The Untitled Letter also explained that the piece provides evidence that Lanoxin is intended for a new use for which it lacks approval.

Untitled Letter to DaraBiosciences, Inc. (December 20, 2013)

OPDP issued an Untitled Letter to DaraBiosciences, Inc. for a violative sales aid regarding its cancer drug Soltamox (tamoxifen citrate). According to the Untitled Letter, the selected portions of the drug's approved prescribing information regarding dosage and administration

included in the sales aid render it misleading. OPDP explained that the sales aid notes the drug's effectiveness in treating "patients with breast cancer," but does not clarify which kinds of breast cancer because it fails to include the full approved indications (e.g., metastatic breast cancer, adjuvant treatment of node-positive and node-negative breast cancer, ductal carcinoma in-situ). OPDP also noted that the sales aid cites several risks associated with the drug, including the boxed warning, but then refers the reader to the background section of the PI for a more complete list. According to OPDP, this implies the drug is safer than has been shown.

LOOKING AHEAD

It is noteworthy that a substantial portion of OPDP enforcement letters in 2013 are related to website promotion, as 2014 will undoubtedly be an important year for FDA and social media. Under the FDA Safety and Innovation Act, FDA is required to publish its social media guidance by July 2014. FDA issued a long awaited Draft Guidance on January 14, 2014, "Fulfilling Regulatory Requirements for Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics," and its Guidance Document agenda for the year includes the following: "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."

OPDP's body of letters have continually demonstrated, however, that regulatory requirements will be enforced, regardless of medium. Indeed, OPDP's first letter of 2014, an Untitled Letter to Mission Pharmacal regarding Tindamax (tinidazole), concerned a professional sell sheet. OPDP explained that the sell sheet is misleading because it omits risk information and material facts, makes unsubstantiated superiority and efficacy claims, and implies that the drug is useful in a broader range of patients or conditions than has been substantiated, suggesting that Tindamax is intended for a new use for which it lacks approval.

A key take-away, then, is similar to prior years: Industry efforts to create promotional presentations that are on-label, adequately substantiated, and fairly balanced are of utmost importance. We trust that 2014 enforcement by OPDP will continue to accentuate this message.