

Client Alert

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2015 Year in Review: OPDP and APLB Warning and Untitled Letters

The drought in enforcement by the Office of Prescription Drug Promotion (OPDP) continued in 2015, as OPDP issued a total of only nine enforcement letters. Two of the nine letters were Warning Letters and seven were Untitled Letters. As demonstrated in the chart below, this was a record low for the total number of enforcement letters issued by OPDP in a year.

Year	2015	2014	2013	2012	2011	2010	2009
OPDP Enforcement Letters	9	10	24	28	30	52	38

The primary driver of this decline in OPDP enforcement activity is unclear, but there are a number of potential explanations. FDA is likely still gauging the ramifications of recent First Amendment cases against the Agency, including by Amarin and Pacira in 2015, as well as the potential impact of any additional challenges. Given the current landscape, it would not be surprising if FDA were more careful and deliberate in determining which letters to issue, as well as requiring multiple layers of review for each enforcement letter.

Omission / Minimization of Risk Was Again the Mostly Commonly Cited Violation

Although the volume of letters decreased, OPDP's primary areas of focus remained similar to recent years. Omission and/or minimization of risk information, cited in five of the nine letters, was again the most commonly cited violation.

Omission of material fact and unsubstantiated claim violations were also cited in multiple letters. Although FDA did not use the category "broadening of the indication / promotion of unapproved use" when citing violations in any of the 2015 letters, OPDP cited claims involving broadening of the indication in two letters under the category "lack of adequate directions for use."

Citation	Number of Letters
Minimization/Omission of Risk Information	5
Omission of Material Fact	3
Unsubstantiated Claims	3
Lack of Adequate Directions for Use	2
Misleading Claims	2
Promotion of an Investigational New Drug	1
Inadequate Communication of Indication	1

OPDP continues to rely on a variety of sources to identify potential violations

As in previous years, the violations in the 2015 letters came to OPDP’s attention from a variety of sources, including Form FDA-2253 submissions, OPDP presence and surveillance at medical conferences and promotional exhibits, and routine monitoring of website materials. Complaints to FDA’s Bad Ad Program hotline once again led to an enforcement letter.

Year	2015	2014	2013	2012	2011
Letters Resulting From Bad Ad Referral	1	1	0	3	5

Letters Cited both Digital and Non-Digital Promotion

As indicated in the chart below, the 2015 OPDP enforcement letters addressed claims made in both electronic and traditional media. One letter in 2015 involved claims made in social media.

Electronic Media	Traditional Media
Video segment (Injectafer)	Pharmacology aid (Abilify)
Website (F-18 (FDDNP))	Exhibit banner (Nembutal)
Website (Surfaxin)	Professional zazzle card (EstroGel)
Website (Rapaflo)	Professional sales aid (Tussicaps)
Social media posts (Facebook, Instagram, Twitter) (Diclegis)	

Observations and Important Practical Reminders from the 2015 OPDP Letters:

- **OPDP continues to focus on misleading representations of risk and safety information in enforcement letters.** The majority of the 2015 enforcement letters included allegations of insufficient discussion or presentation of safety and risk information. Listed below are examples from the 2015 letters, serving as practical reminders 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.** In July 2015, OPDP issued a Warning Letter for a sales aid for the cough and allergy drug Tussicaps. OPDP alleged that the four page sales aid included numerous efficacy claims (e.g., “powerful relief,” “sustained relief, “efficacious, safe and proven combination of ingredients”) but failed to include *any* balancing risk information. The bottom of the last page of the sales aid included a statement that the brochure was intended to remain in the sales representative’s possession and that appropriate labeling should accompany the discussion with physicians. OPDP makes clear in this letter that even pieces that are meant as detail aids only and not intended as a leave behind must contain balancing risk information in the piece itself. Reliance on the sales representative’s verbal communication of the safety information or a reference to the full prescribing information (PI) for the safety information is insufficient.
- **Promotional videos must present risk information in the video itself using similar prominence and method to efficacy claims.** In January 2015, OPDP issued an Untitled Letter for the drug Injectafer, indicated for the treatment of iron deficiency anemia in certain adult patients. OPDP objected to a seven minute video that failed to include any mention of risks in the audio portion of the video. Although the risk information was presented in text form at the end of the video, the text displayed for only 30 seconds and was presented in very small font without contrasting background. OPDP stated that this was insufficient presentation of risk information. OPDP also noted that the video discussed risks of other anemia treatments (such as oral iron) but failed to disclose that Injectafer shared many of those same risks, and in some cases, at higher rates. OPDP said that this one-sided presentation of competitor risk information further exacerbated the misleading nature of the video.
- **Promotional exhibit banner containing efficacy claims must contain balancing risk information in the banner itself, and not solely in the surrounding exhibit booth.** In May 2015, OPDP issued an Untitled Letter for an exhibit banner for the drug Nembutal, an anticonvulsant. The exhibit banner was displayed at the American Society of Health-System Pharmacists where it was viewed by two OPDP representatives in attendance. The banner included an efficacy claim for seizure treatment but included no risk information other than the statement “See booth representative for full PI.” OPDP makes clear that it is not enough that the viewer may be able to easily access the risk information (in this case, there may have been risk information available elsewhere in the booth or attendees could have asked the sales rep for the PI).
- **Mere mention of the existence of a boxed warning is insufficient. The specific risks, including the details of a boxed warning, must be disclosed in the piece itself.** In June 2015, OPDP issued an Untitled Letter citing omission of risk information in a professional zazzle card for the drug EstroGel. The card included efficacy claims and some risk information, including a statement that EstroGel may increase the risk of certain cancers, cardiovascular disorders, and dementia. However, the card failed to fully describe the risks articulated in the boxed warning, including more specific information about the types of cancer and cardiovascular disorders. OPDP emphasized that it is insufficient to merely mention that a product has a boxed warning and refer the physician to the PI. The specific risks, including the details of the boxed warning, must be disclosed in the piece itself.
- **OPDP issued one social media-related enforcement letter in 2015 for omission of risk information in promotional statements made on Facebook, Twitter and Instagram.** On August 7, 2015, OPDP issued a Warning Letter for social media posts on Instagram, Facebook, and Twitter by the company’s celebrity spokesperson, Kim Kardashian, regarding the morning sickness drug Diclegis. OPDP alleged that the social media posts were misleading because they presented efficacy claims for Diclegis, but failed to communicate the product’s full indication or any risk information, including a limitation of use that Diclegis has not been studied in women with hyperemesis gravidarum (a severe form of morning sickness). OPDP required corrective advertising as a result of this enforcement letter and Kim Kardashian reposted on Instagram and Facebook with the limitation of use, important safety information, and most common side effects. It is important to note that OPDP has a long history of

sending enforcement letters in response to promotion by celebrity spokespersons. It is likely that OPDP will continue to scrutinize celebrity testimonials like the Kardashian/Diclegis post, particularly when issued over social media, given the exposure created by a celebrity's often substantial social media following. For example, Kim Kardashian's post about Diclegis had over 7,500 comments on Instagram and nearly 400,000 "likes."

- ***OPDP's 2015 enforcement letters included a number of citations for unsubstantiated superiority claims.*** In support of a superiority claim, FDA historically has required data from adequate and well controlled head-to-head trials designed to measure clinical superiority.
 - **Comparative studies in a drug's PI may not always equal adequate substantiation for a superiority claim. The study must meet the substantial evidence standard for that specific claim.** In March 2015, OPDP issued an Untitled Letter for comparative statements made on the website for Surfaxin, a drug indicated to prevent respiratory distress syndrome (RDS) in premature infants at high risk for RDS. The comparative statements implied that Surfaxin, a synthetic surfactant, was superior to animal-derived surfactants. In support of the claims, the website included citations to two publications, which described two clinical studies cited in the Surfaxin PI. Although the studies were in the Surfaxin PI, the studies failed to meet the substantial evidence standard for the specific comparative claim that Surfaxin is superior to animal-based surfactants. The first study was insufficiently powered to make any meaningful efficacy comparison between Surfaxin and the comparator animal-based surfactant. The second study was used in the PI to support the safety of Surfaxin, not its efficacy. OPDP said that neither of these studies was designed to support direct efficacy comparisons between Surfaxin and animal-derived products.
 - **OPDP will carefully scrutinize claims of "treatment evolution" and "market transformation" as potential unsubstantiated superiority claims.**
 - In the March 2015 Untitled Letter for Surfaxin, OPDP cited the claim that Surfaxin is part of a "therapeutic evolution" coupled with the graphic depicting Surfaxin as a human-like robot that had "evolved" from and was superior to the more primitive, animal derived surfactants, depicted as a pig and cow.
 - In the June 2015 Injectafer letter, OPDP cited the statement that Injectafer was "transforming the way iron deficiency anemia is treated," stating that this statement was a superiority claim, and suggesting that Injectafer offered therapeutic and non-therapeutic advantages over all other approved treatments for iron deficiency anemia.
 - This is not the first time that OPDP has taken issue with claims of "market transformation." For example, in the 2013 Natroba Untitled Letter, OPDP cited the company for claims that its lice treatment was "game changing" and represented a new or different approach that was a significant advance over other currently available products. In the 2010 Venofer Untitled Letter, OPDP cited the company for describing its treatment as "first generation" and a class of competitor products as "second generation."
- ***OPDP's 2015 enforcement letters included a variety of claims that the Agency determined were unsubstantiated or misleading.*** Listed below are some examples:
 - **Claims regarding impact on individual symptoms must be supported by studies designed to measure those symptoms.** In May 2015, OPDP issued an Untitled Letter for website claims for the drug Rapaflo, indicated for treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). OPDP cited the claim that Rapaflo "works nights so he can work days" coupled with the picture of a man walking to the bathroom from bed during the night. OPDP found this claim misleading because it suggested that in addition to improving BPH, Rapaflo also improved quality of sleep and work productivity. OPDP emphasized that claims of treatment benefits must be supported by substantial evidence (e.g., adequate and

well-controlled studies using well developed instruments designed to validly and reliably measure those specific individual concepts).

- **Efficacy claims may not be based on components of composite scores.**¹ The company had data from the International Prostate Symptom Score, a composite endpoint that evaluated a variety of BPH symptoms. However, because the study did not measure the impact of Rapaflo on the individual symptoms, such as nocturia, OPDP said that it could not be used to support claims related to those individual symptoms.
- **Patient preference claims must be based on surveys addressing the specific drug.** In the Tussicaps Warning Letter, OPDP took issue with text and images in the sales aid suggesting that patients prefer Tussicaps (because of its capsule format) over liquid cough medications. The data cited in support of this claim was a patient survey by Harris Interactive. OPDP objected because the survey asked questions related to capsule formats generally, but did not specifically evaluate Tussicaps versus liquid cough syrup.
- **OPDP will carefully scrutinize quality of life and general wellness claims for potential overstatement of efficacy.** In the Injectafer Untitled Letter, OPDP cited statements that the Injectafer treatment “really changed [the patient’s] life” and the patient “blossomed like a rose with high-dose IV iron.” OPDP stated that these claims misleadingly implied a broad effect of the drug on various aspects of the patient’s life and general well-being, including *non*-health related aspects of life.
 - OPDP has taken issue with overstatement of efficacy in the form of quality of life claims in a number of letters over the years. These types of claims require careful consideration, particularly when reviewing patient testimonials or patient stories to be used in promotional materials. Testimonials describing the quality of life changes (e.g., travel, retirement, launch of a new business, etc.) that occurred following treatment should be scrutinized before use. FDA has stated that these types of claims may overstate the efficacy of the product “by suggesting that the usual outcome of treatment... is a positive effect on a patient’s interpersonal relationships, physical functioning, work productivity and overall quality of life.”²
- **Carefully assess Mechanism of Action (MOA) claims. Do not state or imply a greater understanding of a drug’s MOA than is known.** In April 2015, OPDP issued an Untitled Letter for claims made in the pharmacology aid for Abilify, indicated for treatment of bipolar disorder and major depressive disorder. OPDP asserted that the claims and images suggested a definitive understanding of Abilify’s MOA. OPDP pointed to language in Abilify’s PI stating that the MOA is unknown. OPDP also objected to the references cited in support of the MOA claims, noting that one was an opinion piece and the other was a general discussion of various antipsychotic medications, including Abilify. OPDP stated that neither provided support for claims that Abilify has been demonstrated to modulate dopamine and serotonin in humans.
- **OPDP issued two citations for “inadequate communication of the indication.” Although OPDP issued no citations in 2015 for broadening of the indication, it appears that OPDP may now be relying on the “inadequate communication of the indication” citation to capture such claims.** The list below includes examples from the 2015 enforcement letters where cited claims involved potential broadening of the indication.
 - **Material facts within the indication (particularly those that narrow the indication) must be disclosed.** In the Nembutal Untitled Letter, OPDP took issue with the statement on the exhibit banner suggesting broad use of Nembutal for severe seizures. OPDP emphasized that Nembutal is not indicated for treatment of all seizures, but is more narrowly indicated for seizure treatment in anesthetic doses, in the emergency control

¹ OPDP articulated its position on composite scores previously in the November 2012 Untitled Letter for the drug Patanase.

² See Incivek Untitled Letter (May 2012).

of certain acute convulsive episodes. OPDP cited the company for failing to include these material facts about Nembupal's indication.

- **Indications should be articulated with precision.** In the Injectafer letter, OPDP objected to statements in the video suggesting use of Injectafer for *any* patient with iron deficiency anemia (IDA). The video described Injectafer as “the first IV iron approved in the U.S. for patients with IDA caused by *any* disease,” and added, “in fact, it’s *also* for patients intolerant to oral iron and it’s *also* approved in adult patients in non-dialysis chronic kidney disease.” OPDP took issue with the “it’s also” language, which suggested a broad indication for IDA. OPDP emphasized that Injectafer’s indication is actually *limited* to those two subsets and is for use only in the second-line.
- **Two drugs with different indications cannot be described as “alternatives.”** In the Surfaxin Untitled Letter, OPDP objected to promotional claims describing Surfaxin as an alternative to animal-derived surfactants. OPDP noted that while Surfaxin was indicated for the *prevention* of RDS, one of the animal-derived surfactants was indicated for *treatment* of RDS. OPDP stated that because Surfaxin and its “alternatives” (as the promotional materials described them) did not have the same indications, they were not actually “alternatives” and the statement created a new intended use for Surfaxin. OPDP noted that inclusion of the full Surfaxin indication in the promotional piece did not mitigate this issue.
- **Images must be consistent with approved patient population.** The Tussicaps Warning Letter serves as a reminder that OPDP carefully scrutinizes images included in promotional pieces, particularly those that depict patients potentially outside of the approved patient population. OPDP is even more likely to scrutinize pediatric images. The Tussicaps sales aid included multiple images of coughing children. OPDP noted that Tussicaps is contraindicated in patients less than six years due to fatal respiratory depression and that the Tussicaps PI includes a warning to use with caution in pediatric patients older than 6 years. OPDP stated that in addition to including images of children who may be outside of the approved patient population, the sales aid failed to adequately communicate the risks of pediatric use.
- **OPDP issued one enforcement letter in 2015 citing promotion of an investigational new drug.**
 - In February 2015, OPDP issued an Untitled Letter to UCLA for materials that promoted the investigational new drug FDDNP. UCLA was the sponsor of clinical investigations of FDDNP for use in brain PET scans. UCLA had partnered with a West Virginia company called Taumark. The promotional materials cited by FDA were found on Taumark’s website. OPDP alleged that the website made numerous safety and efficacy claims for the investigational drug, including for prevention and intervention of traumatic brain injury. OPDP also cited pre-approval safety and efficacy claims, including that treatment with FDDNP was “an easy and safe method.” The website included claims for its use for patients with Alzheimer’s, depression and brain trauma (including images of soldiers, football players and an elderly couple) as well.
 - It is relatively rare to see a letter from OPDP issued to an academic institution rather than to a manufacturer. OPDP states in the letter to UCLA that as part of the issuance of the IND to study an investigational drug, sponsors and investigators must comply with 21 C.F.R. 312.7.³ Even though UCLA was not the entity marketing the investigational drug improperly, FDA held UCLA (the product sponsor) responsible for ensuring that its partner was not improperly marketing the product either. Although the improper claims appeared on Taumark’s website, FDA addressed the enforcement letter only to UCLA.

³ Under 21 C.F.R. 312.7, “a sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug.”

- **Rare Untitled Letter issued by CBER's Advertising and Promotion Labeling Branch (APLB) in 2015.** In March 2015, APLB issued an Untitled Letter for misleading efficacy claims made by a company CEO during a video interview on Lifetime TV's "The Balancing Act" that was posted on the Flublok website. Specifically, APLB asserted that statements made by the CEO on "The Balancing Act" misleadingly implied that Flublok was a high dose vaccine. APLB also noted that the video failed to present any important safety information from the PI.
 - The Flublok letter is reminiscent of the November 2013 Warning Letter for the product Juxtapid. In that instance, FDA took issue with statements made by a company CEO on the CNBC program, "Fast Money." The Agency stated in its letter that the CEO's statements expanded the indication for Juxtapid by suggesting that it could be used for off-label uses and failing to provide any risk information.
 - Taken together, these two letters emphasize the need for careful review of all media statements and executive talking points that discuss specific products. In addition, when executives appear in the media, they should be carefully prepped regarding off-label boundaries, fair balance, omission of risk information, etc.
 - It is also worth noting that the Flublok letter was one of two enforcement letters issued by FDA in 2015 for videos shown on Lifetime TV's "The Balancing Act." OPDP issued an Untitled Letter in January 2015 for a video segment on the "The Balancing Act" for the drug Injextafer.

For your reference, we have prepared a chart that provides: (1) a list of the 2015 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."

2015 OPDP and APLB Warning and Untitled Letters

Warning Letters indicated with * by the Date

OPDP is the Office of Prescription Drug Promotion within the Center for Drug Evaluation and Research (CDER)

APLB is the Advertising and Labeling Branch within the Center for Biologics Evaluation and Research (CBER)

Date with Hyperlink to Letter	Drug and Indications Referenced in Letter	Boxed Warning	Form of Communication	Summary of Alleged Violations
<p>01-29-2015 (Issued by OPDP)</p>	<p>Injectafer® (ferric carboxymaltose injection) For the treatment of iron deficiency anemia (IDA) in adult patients who have intolerance to oral iron or who have had unsatisfactory response to oral iron or who have non-dialysis dependent chronic kidney disease.</p>	<p>No</p>	<p>Video Segment (featuring a blood specialist and a senior director of marketing for the company) Video was shown on the Lifetime TV morning show, “The Balancing Act,” and the Balancing Act website.</p>	<ul style="list-style-type: none"> • Lack of Adequate Directions for Use: <ul style="list-style-type: none"> ○ <i>Broadening of Approved Indication:</i> Although FDA approved Injectafer for only a subset of adult IDA patients, the video segment claimed that Injectafer is “approved in the U.S. for patients with iron deficiency anemia caused by any disease.” OPDP viewed this claim as suggesting a new, unapproved use for Injectafer (i.e., that it could be used to treat all IDA patients, including children). • Minimization of Risk: <ul style="list-style-type: none"> ○ OPDP cited the company for failing to discuss any risks in the audio portion of the video. Risk information in text form was displayed for only approximately 30 seconds (during a seven minute video) and in very small type font without a contrasting background. OPDP also noted that the risk information was displayed at the same time as the audio portion, which distracts the audience from the risk information. ○ OPDP also cited the company for discussing potential risks related to the use of other types of IDA treatments (e.g., blood transfusions and oral iron), but failing to disclose that Injectafer is also associated with many of the same risks (and in some cases, at higher rates than other IDA treatments). • Omission of Material Fact: <ul style="list-style-type: none"> ○ <i>Inaccurate Dosing and Administration Information:</i> The video segment stated that Injectafer is approved “as a high single dose IV iron” (emphasis added). However, Injectafer is approved for administration in two doses, separated by at least 7 days. • Misleading Claims: <ul style="list-style-type: none"> ○ <i>Misleading Quality of Life Claim:</i> OPDP cited the company for misleading quality of life and general well-being claims that suggested that the drug had effects on non-health related aspects of the patient’s life (e.g., Injectafer “really changed her life” and the patient “blossomed like a rose”). ○ <i>Misleading Comparative Claim:</i> OPDP cited the company for comparing Injectafer to iron treatments “in the past,” suggesting that it offered advantages to other approved treatments, when that had not been demonstrated. (e.g., “transforming the way iron deficiency anemia is treated.”)

2015 OPDP and APLB Warning and Untitled Letters

Date with Hyperlink to Letter	Drug and Indications Referenced in Letter	Boxed Warning	Form of Communication	Summary of Alleged Violations
02-20-2015 (Issued by OPDP)	[F-18] FDDNP FDDNP is an investigational new drug for which there is no marketing authorization in the United States.	N/A	Website	<ul style="list-style-type: none"> • Promotion of an Investigational New Drug <ul style="list-style-type: none"> ○ The website described the investigational compound, FDDNP, for use in brain PET scans to diagnose traumatic brain injuries, Alzheimer’s disease, and other neurological conditions. ○ OPDP alleged that the website contained claims that promoted FDDNP as safe or effective for the purpose for which it is being investigated. For example, the website stated that FDDNP had “a high safety profile” with “no reported adverse effects” and that it was the “only available non-invasive method to measure the distribution and level of brain tau.”
03-05-2015 (Issued by OPDP)	Surfaxin® (lucinactant) Intratracheal Suspension Surfaxin is indicated to prevent respiratory distress syndrome (RDS) in premature infants at high risk for RDS.	No	Website	<ul style="list-style-type: none"> • Unsubstantiated Superiority <ul style="list-style-type: none"> ○ The webpage stated that Surfaxin is the “only available synthetic alternative to animal-derived surfactants approved by the FDA” with the phrase “Join the Therapeutic Evolution.” OPDP found these claims misleading because they imply that Surfaxin is the result of a “therapeutic evolution” in this class of drugs and therefore may be safer. OPDP also cited the following: <ul style="list-style-type: none"> ▪ Two clinical studies used to support “direct clinical comparisons” to other surfactants did not constitute substantial evidence. The first study was insufficiently powered to make any meaningful efficacy comparison between Surfaxin and another surfactant. The second study, although cited in the Surfaxin PI, was used to support safety of Surfaxin and did not constitute substantial evidence for a comparative efficacy claim. ▪ The statement “neonatologists and parents share concerns regarding animal-derived medication.” In support of this statement, the website cited to a survey of physicians asking questions such as, “How concerned are you about exposure of your patients to animal proteins?” OPDP noted that because the survey did not include any measures that specifically evaluate Surfaxin against its comparators, the survey cannot support any overt or implied claim that Surfaxin is superior to animal-derived surfactants. • Lack of Adequate Directions for Use <ul style="list-style-type: none"> ○ <i>Broadening of the Indication:</i> OPDP stated that the claim that Surfaxin is the “only available synthetic alternative to animal-derived surfactants” is misleading because it suggests that Surfaxin is an alternative to all available animal-derived surfactants. However, Surfaxin is approved for prevention of RDS while Curosurf, another surfactant, is indicated for treatment of RDS in premature infants. OPDP viewed this claim as creating a new intended use for Surfaxin. OPDP noted that the mere inclusion of the full indication on this webpage does not mitigate the misleading impression from the claim.

2015 OPDP and APLB 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>03-12-2015 (Issued by APLB)</p>	<p>Flublok® (Influenza Vaccine) A vaccine indicated for active immunization against disease caused by influenza virus subtypes A and type B. Flublok is approved for use in persons 18 years of age and older.</p>	<p>No</p>	<p>Video interview with the company CEO on the Lifetime TV morning show, The Balancing Act (also posted on the Flublok website)</p>	<p>APLB issued an Untitled Letter for claims made by the company’s CEO during a video interview on Lifetime TV’s “The Balancing Act” that was posted on the Flublok website.</p> <ul style="list-style-type: none"> • Misleading Efficacy Claim <ul style="list-style-type: none"> ○ APLB cited the claim in the video that the company “is able to put three times more protein in there, so it is also a high dose vaccine. More protein means your body will form more antibodies that will help you fight the flu.” APLB stated that this claim misleadingly implied that the higher antigen content of Flublok translated into greater protection. APLB noted that there was only one licensed high-dose influenza vaccine and no adequate and well-controlled clinical trials meeting the standard of substantial evidence to support a high-dose claim for Flublok. • Omission of Risk Information <ul style="list-style-type: none"> ○ APLB noted that the video presented multiple efficacy claims for Flublok, such as ‘helps you fight the flu,’ but failed to present any important safety information from the PI.
<p>04-17-2015 (Issued by OPDP)</p>	<p>Abilify® (aripiprazole) Tablets Abilify is indicated for the acute treatment of manic and mixed episodes and for maintenance treatment of bipolar I disorder. It is also used as adjunctive therapy to antidepressants for major depressive disorder (MDD).</p>	<p>Yes</p>	<p>Pharmacology Aid</p>	<ul style="list-style-type: none"> • Misleading Claims and Presentations: <ul style="list-style-type: none"> ○ <i>Misleading Claims and Presentations Regarding Mechanism of Action (“MOA”):</i> OPDP alleged a number of misleading claims, including “Abilify . . . modulates both synaptic dopamine and serotonin” and Abilify’s “unique pharmacology sets [it] apart.” OPDP stated that the totality of the claims and presentations suggested a definitive understanding of Abilify’s ability to modulate dopaminergic and serotonergic activity in humans. The claims suggested a greater degree of certainty about Abilify’s mechanism of action than is currently known and misleadingly suggest that Abilify offers clinical advantages over other approved treatments for bipolar disorder or MDD.
<p>05-14-2015 (Issued by OPDP)</p>	<p>Nembutal Sodium Solution (pentobarbital sodium injection, USP) CII Nembutal is an anticonvulsant in the emergency control of certain acute convulsive episodes.</p>	<p>No</p>	<p>Exhibit Banner</p>	<p>The exhibit banner was displayed at an American Society of Health-System Pharmacists Meeting and viewed by two OPDP representatives in attendance.</p> <ul style="list-style-type: none"> • Omission of Risk Information: <ul style="list-style-type: none"> ○ The exhibit banner omitted all risk information, misleadingly suggesting that Nembutal is safer than demonstrated. OPDP found that the statement “See booth representative for full prescribing information” at the bottom of the banner did not mitigate the misleading omission. • Omission of Material Facts: <ul style="list-style-type: none"> ○ The banner also failed to communicate information from the “indications and usage” section of the package insert, specifically that the drug should be used “in anesthetic doses, in the emergency control of certain acute, convulsive episodes.”

2015 OPDP and APLB 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>05-19-2015 (Issued by OPDP)</p>	<p>Rapaflo® (silodosin) Capsule for oral use For the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).</p>	<p>No</p>	<p>Website</p>	<ul style="list-style-type: none"> • Unsubstantiated Claims: <ul style="list-style-type: none"> ○ <i>Unsubstantiated Claims in Text and Images:</i> OPDP cited the claim “works nights so he can work days” accompanied by an image of a man walking to the bathroom from bed in the middle of the night. OPDP found that this claim misleadingly implied that Rapaflo has been shown to improve sleep disturbance and work productivity. The clinical trials for Rapaflo did not measure the impact of individual symptoms, such as nocturia, and did not evaluate the impact of Rapaflo on quality of sleep or work productivity. OPDP emphasized that treatment benefits must be supported by substantial evidence as demonstrated by adequate and well-controlled studies using well-developed instruments that can validly and reliably measure these specific individual concepts.
<p>06-23-2015 (Issued by OPDP)</p>	<p>EstroGel® 0.06% (estradiol gel) for topical use Indicated for the treatment of moderate to severe vasomotor symptoms and vulvar and vaginal atrophy symptoms due to menopause.</p>	<p>Yes</p>	<p>Professional Zazzle Card</p>	<ul style="list-style-type: none"> • Omission of Risk Information: <ul style="list-style-type: none"> ○ OPDP alleged that the Zazzle card was misleading because it included efficacy claims regarding EstroGel, but failed to include important risk information, including the drug’s boxed warning and contraindications. Although the Zazzle card included the statement: “Estrogen therapies increase the risk of certain cancers, cardiovascular disorders, and probable dementia,” the card failed to discuss specific risks related to cancer and cardiovascular disorders in the Boxed Warning.
<p>07-27-2015* (Issued by OPDP)</p>	<p>TussiCaps® (hydrocodone polistirex and chlorpheniramine polistirex) Extended-release Capsules CII Indicated for relief of cough and upper respiratory symptoms associated with allergy or a cold in adults and children 6 years of age and older.</p>	<p>No</p>	<p>Professional sales aid</p>	<ul style="list-style-type: none"> • Omission of Risk Information: <ul style="list-style-type: none"> ○ OPDP alleged that the sales aid was misleading because it included “numerous efficacy claims,” but contained no risk information (including potentially serious and fatal risks) associated with Tussicaps. • Inadequate Communication of Indication: <ul style="list-style-type: none"> ○ OPDP also alleged that the sales aid failed to convey the full approved indication for TussiCaps. The sales aid stated that TussiCaps is used “for the relief of cough and upper respiratory symptoms associated with colds or allergies.” However, OPDP noted that TussiCaps’ indication is limited to use in adults and children 6 years of age and older and TussiCaps is contraindicated for children less than 6 years old. OPDP noted that the omission of age information was particularly misleading in light of an image in the sales aid of a “coughing young child.” • Unsubstantiated Claims: <ul style="list-style-type: none"> ○ <i>Unsubstantiated Patient Preference Claim:</i> OPDP cited the company for claims including “Patient Preferred Capsule” and “73% of adult prescription cough syrup users said they prefer capsules over liquid medication.” OPDP also highlighted an image of a zip bag with liquid medication spilled at the bottom. OPDP alleged that these claims, taken together, misleadingly

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				<p>suggest that patients prefer TussiCaps capsules over liquid formulations. OPDP concluded that the study cited in support of these claims was “insufficient” because it did not “specifically evaluate” whether patients preferred TussiCaps to liquid formulations.</p>
<p>08-7-2015* (Issued by OPDP)</p>	<p>DICLEGIS® (doxylamine succinate and pyridoxine hydrochloride) delayed-release tablets, for oral use Indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.</p>	<p>No</p>	<p>Social media posts on Instagram, Facebook and Twitter by the company’s celebrity spokesperson, Kim Kardashian</p>	<p>The Warning Letter noted that OPDP received the social media posts both from the company via Form FDA 2253 and from a complaint to FDA’s Bad Ad Program.</p> <ul style="list-style-type: none"> • Omission of Risk Information: <ul style="list-style-type: none"> ○ OPDP asserted that the social media posts by the company’s celebrity spokesperson (Kim Kardashian) were misleading because they presented various efficacy claims for Diclegis, but failed to communicate <i>any</i> risk information, including a contraindication for women with a very severe form of morning sickness. • Omission of Material Fact: <ul style="list-style-type: none"> ○ OPDP further alleged that the social media posts were misleading because they failed to provide Diclegis’ full approved indication, including important limitations of use. Specifically, they failed to convey that Diclegis had not been studied in women with hyperemesis gravidarum. <p>OPDP required corrective advertising as a result of this enforcement letter and Kim Kardashian reposted on Instagram and Facebook with the limitation of use, important safety information and most common side effects.</p>