

E-ALERT | Food & Drug

June 27, 2013

SUMMARY OF FDA ADVERTISING AND PROMOTION ENFORCEMENT ACTIVITIES

MAY 2013

This e-alert is part of a series of monthly e-alerts summarizing publicly-available FDA enforcement letters (i.e., warning letters and untitled letters) relating to the advertising and promotion of drugs, medical devices, and biologics.

In May 2013, FDA's Office of Prescription Drug Promotion (OPDP) posted the following enforcement letters on FDA's website¹:

- Untitled letter to CBA Research, Inc. re [redacted] CBT-1 [redacted] Capsule MA #1 (April 25, 2013) ("CBA Untitled Letter")
- Untitled letter to Mobius Therapeutics, LLC re: NDA #022572 Mitosol (mitomycin for solution) MA #15 (May 2, 2013) ("Mobius Untitled Letter")
- Untitled letter to Validus Pharmaceuticals, LLC re: NDA 011961 Marplan (isocarboxazid) tablets MA# 21 (May 6, 2013) ("Validus Untitled Letter")
- Untitled letter to Janssen Biotech Products, L.P. re: NDA # 050718 DOXIL (doxorubicin HCl liposome injection) for Intravneous Infusion MA # 422 (May 22, 2013) ("Janssen Untitled Letter")
- Untitled letter to Sigma-tau Pharmaceuticals, Inc. re: BLA #103411 Oncaspar (pegaspargase) injection, for intramuscular or intravenous use MA #47 (May 22, 2013) ("Sigma-tau Untitled Letter")

The Office of Compliance and Biologics Quality (OCBQ) in FDA's Center for Biologics Evaluation and Research (CBER) posted the following enforcement letter on FDA's website:

- Warning letter to SmartPractice Denmark AS re: BLA STN# 103738/5107 T.R.U.E. Test (Thin-Layer Rapid Use Epicutaneous Patch Test) (May 3, 2013) ("SmartPractice Warning Letter")

The Office of Compliance in FDA's Center for Devices and Radiological Health (CDRH) did not post any enforcement letters relating to advertising and promotion on FDA's website.

This alert merely summarizes the allegations contained in FDA's letters. It does not contain any analysis, opinions, characterizations, or conclusions by or of Covington & Burling LLP. As a result, the information presented herein does not necessarily reflect the views of Covington & Burling LLP or any of its clients.

¹ Only enforcement letters posted to FDA's website in May 2013 are included herein. Letters issued in May but not posted to the website by May 31, 2013 will be summarized in our alerts for the months in which those letters are posted.

LETTERS ISSUED BY OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)

CBA Untitled Letter

CBA's website stated that CBT-1 is being investigated for use as an adjunct to chemotherapy in all cancer types with multidrug resistance. According to OPDP, a new drug application ("NDA") for CBT-1 was submitted, but has not yet been approved. OPDP alleged CBA's website misleadingly promoted CBT-1 as safe and effective for the purposes for which it is being investigated in violation of 21 C.F.R. § 312.7(a). OPDP also alleged CBA's website was false or misleading because it overstated the efficacy of CBT-1 in violation of 21 U.S.C. §§ 352(a), (n).

Promotion of an Investigational New Drug; False or Misleading Promotion: OPDP alleged that the following statements (among others) on CBA's website constituted improper pre-approval promotion of CBT-1 as safe and/or effective for the purposes for which it is being investigated:

- "ADMINISTERED ORALLY Oral delivery of CBT-1 prior to and during the administration of chemotherapy, achieves the required therapeutic concentration necessary to reverse multidrug resistance in the clinical setting."
- "NO SIGNIFICANT OR LASTING TOXIC SIDE EFFECTS CBT-1 demonstrated no significant or lasting side effects in the clinical setting, and had a very favorable adverse event profile."
- "MULTIPLE CANCERS Eight Phase I and II clinical trials, with patients that had failed conventional chemotherapy treatments, showed efficacy of CBT-1 in multiple cancers. Likewise, the targeted mechanism of action multidrug resistance of CBT-1 is found in the vast majority of all late stage human cancer types."
- "HIGH PATIENT BENEFIT IN PHASE I AND PHASE II CLINICAL TRIALS CBT-1 has demonstrated in Phase I and II clinical trials a high rate of patient benefit."

In addition, OPDP alleged that a downloadable presentation on CBA's website was misleading. The presentation contained claims such as the following:

- **"CBT-1 Safety and Efficacy Profile**

Preclinical and Clinical research has consistently demonstrated the potential for CBT-1 to be safe and effective.

The drug is safe, well tolerated, lacks harmful pharmacokinetic interactions when combined with chemotherapeutic agents, has specificity for P-gp and MDR-1, is stable, orally available, and has produced clinically objective responses in heavily pretreated and/or late cancers."²

According to OPDP, the above referenced claims suggested that CBT-1 has the ability to reverse multi-drug resistance in cancer cells and to improve patient outcomes, while reducing toxic side effects and decreasing failures. OPDP alleged that the claims thus implied that CBT-1 is safe and/or effective for its investigational purpose, even though it has not been approved for any use.

OPDP acknowledged that the downloadable presentation included the disclaimer that "research has consistently demonstrated the *potential* for CBT-1 to be safe and effective."³ Nevertheless, OPDP alleged that because this language was followed by "conclusive language that CBT-1 is safe, well tolerated, lacks harmful pharmacokinetic interactions [etc.]," this disclaimer was insufficient. In addition, OPDP stated that "[m]inimal disclaimers that state that an NDA for CBT-1 has been

² Emphasis in presentation.

³ Emphasis added.

submitted to the FDA and is currently under review are not sufficient to mitigate the overwhelming misleading impressions conveyed by the claims on CBA's website. . . ."

Mobius Untitled Letter

Mitosol is an antimetabolite indicated as an adjunct to ab externo glaucoma surgery. OPDP reviewed a professional email for Mitosol solution submitted by Mobius, and alleged that the email was misleading because it omitted the full indication and omitted and minimized risks associated with Mitosol. OPDP also alleged that the email omitted material facts regarding Mitosol's dosage and administration.

Omission and Minimization of Risk Information: OPDP alleged that the following claims (among others) were false or misleading:

- **"Remove the Variables"** with the following words surrounding this text: "Dosing," "Consistency," and "Potency."⁴
- **"Eliminate Your Concerns"** with the following words surrounding this text: "Shelf Life," "Safety," and "Sterility."⁵
- "Assured sterility, potency, and dosing along with closed transfer and qualified disposal reinvents mitomycin for ophthalmology."
- "Mitosol is the only FDA approved ophthalmic formulation of mytomycin."
- "1-877-EYE-MITO."

According to OPDP, the email was misleading because it failed to disclose Mitosol's full approved indication, or any risk information. OPDP contended that a statement ("[p]lease see full prescribing information attached") on the bottom of the email did not mitigate Mobius' allegedly misleading representations. OPDP noted that Mitosol is associated with several risks, including cell death, hypotony, and cataract formation, but "*no* safety concerns associated with the use of the drugs" were discussed.⁶

Omission of Material Facts: OPDP also alleged that the email misleadingly made claims regarding the benefits of Mitosol's dosing, but failed to reveal dosing information that is material to the safe use of the drug. OPDP cited the following text in the email as misleading:

- **"Remove the Variables"** with the following word surrounding this text: "Dosing."
- "Assured Dosing - Yes"

OPDP alleged that Mobius was required to disclose that, according to the approved product label, Mitosol requires reconstitution and that the reconstituted product is then fully saturated on sponges and applied and kept on the treatment area for a total of two minutes. OPDP also contended that the email failed to communicate that Mitosol must be used within one hour of reconstitution.

Validus Untitled Letter

Marplan is indicated for the treatment of depression. OPDP reviewed a healthcare professional webpage for Marplan, and alleged that the webpage was false or misleading because it omitted and

⁴ Emphasis in email.

⁵ Emphasis in email.

⁶ Emphasis supplied by OPDP.

minimized risk information, overstated the efficacy of the drug, and presented unsubstantiated claims.

Omission of Risk Information: OPDP alleged that the webpage omitted serious and potentially fatal risks associated with Marplan. OPDP cited the following examples:

- The webpage included the statement that “**MAO [Monoamine Oxidase]- inhibitors are contraindicated with certain drugs.**”⁷ According to OPDP, this claim was misleading because it failed to disclose the specific drugs and/or drug classes that should not be used in combination with Marplan as stated in the product label. OPDP stated the alleged omission “is particularly concerning because the concomitant use of Marplan with several of these contraindicated drugs . . . can cause serious, and sometimes fatal, adverse reactions.”
- The webpage included the statement that “[p]**otential hypertensive crises may occur with foods that contain tyramine.**”⁸ OPDP alleged that the webpage should have disclosed that foods with high tyramine content are in fact contraindicated, and that hypertensive crises associated with Marplan can be fatal.
- OPDP also alleged that the webpage failed to identify the patient populations in which Marplan is contraindicated and risk information from the WARNINGS TO PHYSICIANS, PRECAUTIONS, and ADVERSE REACTION sections of the product label.

OPDP contended that a statement on the webpage, “[p]**lease see Full Prescribing Information including BOXED WARNINGS . . .**,”⁹ failed to mitigate the alleged omission of the risk information above.

Minimization of Risk: OPDP contended that the webpage misleadingly minimized the risk information provided by prominently presenting efficacy information at the top of the page, using colorful graphics, and large bolded headers, while risk information was included at the bottom of the webpage, below the product logo, tagline, footnotes, and link to references. OPDP stated that because “the product logo, tagline, footnotes, and link to references often signal the end of the piece, the viewer may assume the information placed below are unimportant and unrelated to the main message.”

Overstatement of Efficacy: OPDP alleged that the webpage overstated the efficacy of Marplan, primarily in the following two respects:

- The webpage presented efficacy rates of 41.3% to 68.2% in patients treated with Marplan. According to OPDP, the publication cited in support of these efficacy rates does not support these claims. OPDP alleged that the cited publication describes a literature review and meta-analysis examining the efficacy of several drugs, including Marplan. OPDP stated that the meta-analysis, which was based on a literature review, “may have produced a biased sample of studies since failed or negative clinical trials are not often published in the medical literature.” OPDP also stated that “the clinical studies used to conduct the meta-analyses for [Marplan] were performed in diverse patient populations, with different doses of the drug, and under varying clinical conditions.”
- The webpage cited separate efficacy statistics based on a two-phase clinical study. Phase one was a double-blind, placebo-controlled clinical study, but phase two was an open-label clinical study. According to OPDP, the study did not support efficacy claims because the portion of the

⁷ Emphasis in webpage.

⁸ Emphasis in webpage.

⁹ Emphasis in webpage.

data described in the efficacy claims was collected during the open-label portion of the clinical study. OPDP stated that “an open-label clinical study with no control group do[es] not constitute substantial evidence . . . to support . . . any . . . efficacy claims.”

Unsubstantiated Mechanism of Action Claims: OPDP alleged that a graphic presentation and accompanying text on the webpage misleadingly suggested a greater degree of certainty about Marplan’s mechanism of action than is currently known. The webpage stated that MAO inhibitors “raise the levels of all three of the neurotransmitters in the brain responsible for mood elevation. . .” It also presented a graphic raising the levels of all three key neurotransmitters. OPDP contended that, in contrast, the product label for Marplan states that the mechanism by which MAO inhibitors act as antidepressants is not fully understood.

Sigma-tau Untitled Letter

Oncaspar is indicated as a component of a multi-agent chemotherapeutic regiment for the first line treatment of patients with acute lymphoblastic leukemia (ALL), and as a component of a multi-agent chemotherapeutic regiment for the first line treatment of patients with ALL and hypersensitivity to native forms of L-asparaginase. OPDP reviewed a sales aid disseminated by Sigma-tau, and alleged that the sales aid was false or misleading because it made unsubstantiated superiority claims, minimized risk information, unsubstantiated claims for the product, and omitted material facts.

Unsubstantiated Superiority Claims: OPDP alleged that the following statements (among others) in the sales aid were misleading:

- “Helping Patients Gain the **Full Benefits** of Asparaginase Therapy.”¹⁰ According to OPDP, this and similar statements misleadingly implied that patients would not experience “full benefits” of asparaginase therapy when using treatments other than Oncaspar, including native L-asparaginase and Erwinia asparaginase therapy.
- “Oncaspar: Fewer Doses and **Greater Flexibility** . . . single-dose Oncaspar requires **fewer patient visits**.”¹¹ OPDP contended that the claim that “Oncaspar requires fewer patient visits” was unsupported because the only study cited by Sigma-tau did not consider all of the relevant patient visit scenarios (such as day hospital visits and emergency room use), and therefore, the study was not substantial evidence to support a claim of fewer total visit scenarios.
- “Oncaspar: **Pegylation Enhances Patient Benefits**. . . . Pegylation protects L-asparaginase from enzyme degradation, allowing for sustained plasma concentrations. . . .”¹² OPDP alleged that this and similar statements, which accompanied a chart showing half-life data for Erwinia asparaginase, native L-asparaginase, and Oncaspar misleadingly suggested that Oncaspar was superior in efficacy. OPDP stated that the studies cited by Sigma-tau did not include endpoints assessing asparaginase’s ability to kill leukemic cells, and in fact tended to show that serum asparaginase level did not correlate with serum asparagine depletion. OPDP stated that controlled head-to-head comparative studies would be necessary to support Sigma-tau’s alleged claims of superiority.

Minimization of Risk Information: OPDP alleged that the sales aid minimized risk information by presenting efficacy claims in large, bolded text at the beginning of the aid, but providing the most important risks at the back of the aid in black font, single-spaced bullets. OPDP also claimed that the following statements (among others) misleadingly minimized risk information:

¹⁰ Emphasis supplied by OPDP.

¹¹ Emphasis supplied by OPDP.

¹² Emphasis supplied by OPDP.

- “Local injection-site reactions can be mistaken for clinical allergic reactions.” OPDP alleged that this and similar statements minimized the risks of anaphylaxis by suggesting that hypersensitivity reactions reported on the product label may have been inaccurately attributed to Oncaspar. Further, OPDP stated that the sales aid stated “proper management” of adverse events would allow patients to remain on the therapy, while the approved product label states patients must discontinue Oncaspar if serious allergic reactions occur.
- “No limit on duration of therapy.” OPDP alleged this statement minimized the risks stated in the product label, which states that patients should immediately discontinue treatment if they develop a severe adverse reaction.
- “Oncaspar: Low Rates of Hypersensitivity May Allow Patients to Remain on Therapy.” OPDP alleged that this and similar statements misleadingly framed the important risk of hypersensitivity “as a potential benefit of treatment,” thus minimizing the serious risk of hypersensitivity.
- “When administered via IV, the pain caused by IM injections can be avoided.” OPDP contended that this and similar claims were misleading because they suggested that IV administration of Oncaspar is not associated with any pain or negative consequences, when this is not the case.

Unsubstantiated Claims: OPDP stated that claims such as “[s]ustained asparagine depletion correlates with rapid blast clearance” and “no evidence of M3 bone marrow on day 14” misleadingly implied that Oncaspar has demonstrated efficacy in terms of a blast clearance rate. OPDP contended that the study cited in support of these statements did not include blast clearance or bone marrow blast scores as pre-specified endpoints, and thus, any evaluation of bone marrow blast scores was a post hoc analysis and exploratory analysis.

Omission of Material Fact: OPDP alleged that the front cover of the sales aid, which displayed children and elderly people, along with the heading “**Oncaspar: No Age Restrictions**”¹³ on page seven of the sales aid, misleadingly omitted the fact that studies cited in the Oncaspar product label included only pediatric patients. Further, OPDP stated that the product label states that clinical studies of Oncaspar “did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently than younger subjects.” OPDP acknowledged that this disclaimer was present on the back of the sales aid, but stated that it failed to mitigate the misleading impression made by the information above.

Janssen Untitled Letter

Doxil is indicated, among other things, for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy. According to OPDP, Doxil’s healthcare professional website was misleading because it makes unsubstantiated claims associated with Doxil.

Unsubstantiated Claims: Without pointing to specific statements, OPDP alleged that the website contained claims associating levels of the CA-125 biomarker with clinical responses to Doxil therapy. OPDP stated that these associations were supported by retrospective evaluations of primary data performed in a post-hoc manner, retrospective sub-group analyses, and exploratory studies that cite the sponsor’s data on file. OPDP stated that “[w]hen looking for differences between treatment groups, a study must be prospectively designed to look for these differences, and must be sufficiently powered.”

¹³ Emphasis in sales aid.

LETTER ISSUED BY CBER OFFICE OF COMPLIANCE AND BIOLOGICS QUALITY (OCBQ)

SmartPractice Warning Letter

The T.R.U.E. TEST is an epicutaneous patch test indicated for use as an aid in the diagnosis of allergic contact dermatitis (ACD) in persons 18 years of age and older whose history suggests sensitivity to one or more of the 35 substances included on the T.R.U.E. TEST panels. The FDA-approved product label identifies several risks associated with the T.R.U.E. TEST, including allergic reactions, tape reactions, and burning. The T.R.U.E. TEST is also contraindicated for patients with a history of severe allergic reaction to any of the allergen components or inactive substances of the T.R.U.E. TEST.

Omission of Risk Information: OCBQ reviewed a variety of promotional materials produced by SmartPractice, including reference manuals, newsletters, and press releases, and alleged the materials were misleading because they omitted risk information entirely. According to OCBQ, the cited materials “fail to provide **any** information pertaining to the potential risks associated with the use of T.R.U.E. TEST. . . .”¹⁴

OCBQ also alleged that (1) SmartPractice’s promotional materials were disseminated without a product label, in violation of 21 U.S.C. § 352(f)(1) and (2) SmartPractice failed to submit its promotional materials to FDA at the time of initial dissemination in violation of 21 C.F.R. § 601.12(f)(4).

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¹⁴ Emphasis added.