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E-ALERT | Food & Drug

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SUMMARY OF FDA ADVERTISING AND PROMOTION ENFORCEMENT ACTIVITIES

APRIL 2012

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, biologics, and medical devices. In April 2012, FDA's Office of Prescription Drug Promotion (OPDP) posted the following enforcement letters on its website:[1]

- Untitled letter to Ferring Pharmaceuticals Inc. re: Firmagon® (degarelix for injection) for subcutaneous administration (March 30, 2012) ("Ferring Untitled Letter")[2]
- Untitled letter to The Medicines Company re: Angiomax® (bivalirudin) For Injection (April 13, 2012) ("The Medicines Company Untitled Letter")
- Untitled letter to Meda Pharmaceuticals Inc. re: ASTEPRO® (azelastine hydrochloride) Nasal Spray 0.15% (April 26, 2012) ("Meda Untitled Letter")

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

- Warning letter to Octapharma USA, Inc. re: Octagam® [Immune Globulin Intravenous (Human) 5%] (April 10, 2012) ("Octapharma Warning Letter")
- Warning letter to Thomas E. Young, LLC re: Young Medical Spa stem cell product (April 20, 2012) ("Young Warning Letter")[3]

During April 2012, the Office of Compliance in FDA's Center for Devices and Radiological Health (CDRH) did not post any enforcement letters relating to the advertising and promotion of medical devices. The letters posted by OPDP and OCBQ raise a variety of allegations and conclude that the cited advertising/promotional issues render the subject product misbranded and/or result in the unlawful marketing of an unapproved drug.

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.

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[1] Only enforcement letters posted to FDA's website in April 2012 are included herein. Letters issued in April but not posted to the website by April 30, 2012 will be summarized in our alerts for the months in which those letters are posted.

[2] The dates referenced for the letters are the issue dates.

[3] OCBQ did not provide a specific name for Thomas E. Young, LLC's biologic product. For ease of reference, the subject biologic will be referred to as "Young Medical Spa stem cell product" throughout this alert.

Promotion of an Unapproved Use[4]

FDA's letters contain the following allegations under a "Promotion of an Unapproved Use" subheading:

Ferring Untitled Letter: Firmagon is a GnRH receptor antagonist indicated for treatment of patients with advanced prostate cancer. A sales aid entitled "Electronic Sales Aid, Short Version (iPad MVA)" made statements, such as "USE FIRMAGON FIRST" and "USE FIRMAGON® (degarelix for injection) FIRST IN 3 PATIENT TYPES." These claims were accompanied by descriptions of hypothetical patients, including "Joe," who plans to "start hormone therapy prior to receiving radiation therapy in the coming months, and wants a rapid reduction in testosterone levels," and "Gregory," who is "[c]onsidering hormone therapy due to rising [prostate specific antigen (PSA)] levels, even after curative attempt." According to OPDP, the sales aid misleadingly suggested new "intended uses" for Firmagon as a neoadjuvant therapy (i.e., prior to radiation therapy) and as a treatment for rising PSA. OPDP's letter acknowledges that Firmagon's indication for prostate cancer is general, but concludes that "Firmagon is indicated for treatment of **advanced** prostate cancer,"[5] and the drug has not been evaluated or approved by FDA as a neoadjuvant therapy or as a treatment for patients with rising PSA.

Young Warning Letter: Upon inspection of Young Medical Spa establishments, FDA determined that these establishments recover and process adipose tissue (aka lipoaspirate) from donors for autologous use. The Young Medical Spa stem cell product is injected into specific areas of the body, such as joints and breasts. OCBQ found that Young Medical Spa's website, and a brochure collected during the inspection, promoted injections of Young Medical Spa's stem cell product for Natural Breast Augmentation (NBA). Specifically, Young Medical Spa's website stated:

> "Fat is gently removed from body areas, such as the abdomen and waist, using standard tumescent liposuction techniques. The fat is then processed in our state-of-the-art lab which is the only one of its kind in the area. The lab extracts the regenerative and stem cells from the fat cells . . . . The stem cell mixture is examined for viability and is then combined with other fat cells that were removed from your body at the beginning of the procedure. This results in a stem cell enriched fat sample which is then injected into your breasts for a smooth and natural volume increase . . . . By adding stem cells to the harvested fat it helps to increase new blood vessel formation that is needed to feed the fat after transfer and helps to tighten the skin over the breast."

According to FDA, the Young Medical Spa stem cell product does not qualify for regulation solely under section 361 of the Public Health Service Act and therefore is both a drug and a biological product. Because the Young Medical Spa stem cell product is not the subject of an approved biologics license application (BLA), and the company does not have an IND application in effect, OCBQ concluded that the Young Medical Spa stem cell product violated the Food, Drug, and Cosmetic Act and the Public Health Service Act.

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[4] The Young Warning Letter issued by OCBQ does not explicitly use this subheading, but the allegations fit within this category.

[5] Emphasis added by OPDP.

Overstatement of Efficacy

FDA's letters contain the following allegations under an "Overstatement of Efficacy" subheading:

Ferring Untitled Letter: OPDP found that several claims in the Firmagon sales aid overstated the efficacy of the drug. First, OPDP concluded that claims such as "**Firmagon** reduces PSA levels by more than **60% in just 2 weeks**,"[6] and "[p]atients treated with LHRH agonists experienced an 18% overall reduction in 2 weeks," misleadingly suggested that the speed of PSA reduction is clinically meaningful for advanced prostate cancer patients. These claims were presented in conjunction with a bar graph entitled "Rapid PSA reduction," which showed that patients taking Firmagon had a faster reduction in PSA levels at 14 and 28 days after initiation of therapy compared to leuprolide. According to OPDP, FDA was not aware of sufficient evidence to establish a link between the speed of PSA decline and clinical benefit. Although the graph included a disclaimer that "no evidence has shown that the rapidity of PSA decline is related to a clinical benefit," OPDP determined that this statement did not mitigate the misleading impression created by the sales aid's claims.

Second, OPDP found that claims, such as "Firmagon patients were less likely to experience a PSA recurrence in 1 year," misleadingly suggested that the reduction in risk of PSA recurrence is clinically meaningful, or associated with improved survival or disease control. OPDP explained that the reference cited in support of these claims was "an exploratory subgroup analysis of the pivotal study," and that there is neither substantial evidence nor substantial clinical experience to support these efficacy claims.

Meda Untitled Letter: ASTEPRO 0.15% is indicated for "the relief of the symptoms of seasonal and perennial allergic rhinitis in patients 12 years of age and older." A professional telephone script ("script") for ASTEPRO included the claim: "Also, ASTEPRO 0.15% **rapidly** relieves allergic rhinitis symptoms, **including nasal congestion**, without an added decongestant **within 30 to 45 minutes**!"[7] According to OPDP, the clinical studies used for the approval of ASTEPRO 0.15% evaluated a composite measure of symptoms only, and did not specifically evaluate efficacy for the symptom of nasal congestion. Thus, according to OPDP, this claim misleadingly implied that ASTEPRO effectively treats the specific symptom of nasal congestion. Additionally, OPDP concluded that the claim misleadingly implied that the clinical symptoms of allergic rhinitis will be relieved "rapidly" (i.e., within 30 to 45 minutes after administration of the drug), even though there is neither substantial evidence nor substantial clinical experience to support this claim.

Omission of Risk Information

FDA's letters contain the following allegations under an "Omission of Risk Information" subheading:

Meda Untitled Letter: OPDP found that although the professional telephone script included efficacy claims regarding ASTEPRO 0.15%, it entirely omitted all risk information associated with the use of the drug. OPDP acknowledged that the script included instructions "indicating that if an adverse event 'is mentioned' the sales representative should 'follow the appropriate procedures,'" but concluded that this was insufficient to mitigate the script's misleading presentation.

The Medicines Company Untitled Letter: OPDP determined that a professional booth panel for Angiomax omitted important risk information about the drug. Although the booth panel included the drug's contraindications, part of the warning regarding bleeding events, and some adverse events, OPDP explained that the booth panel omitted the warnings listed in the prescribing information ("PI") regarding coronary artery brachytherpay, and failed to convey "that the most common adverse event

[6] Emphasis in original.
[7] Emphasis added by OPDP.

associated with Angiomax was bleeding, which was experienced in 28% of patients." Further, regarding the risk of bleeding events, the booth panel failed to include the following language from the WARNING AND PRECAUTIONS section:

> "Although most bleeding associated with the use of Angiomax in [percutaneous coronary intervention]/[percutaneous transluminal coronary angioplasty] occurs at the site of arterial puncture, **hemorrhage can occur at any site. . . . Angiomax should be used with caution in patients with disease states associated with an increased risk of bleeding.**"[8]

According to OPDP, these omissions misleadingly overstated Angiomax's safety profile.

Octapharma Warning Letter: Octagam's FDA-approved PI has a boxed warning that states:

> "Renal dysfunction, acute renal failure, osmotic nephrosis, and death may be associated with Immune Globulin Intravenous (Human) (IGIV) products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. Octagam 5% does not contain sucrose. Administer IGIV products at the minimum concentration available and the minimum infusion rate practicable."

The Advertising and Promotional Labeling Branch (APLB) in CBER found that Octapharma's journal advertisements, printed in the BDI Pharma Product Catalogue and *BioSupply Trends Quarterly*, failed to provide any information pertaining to the risk of acute renal dysfunction and renal failure associated with the use of Octagam. Further, the journal advertisements omitted Octagam's boxed warning, contraindications, warning and precautions, and adverse reactions. APLB concluded that these omissions of risk information rendered the advertisements false and misleading.

Unsubstantiated Superiority Claims

FDA's letters contain the following allegations under an "Unsubstantiated Superiority Claims" subheading:

The Medicines Company Untitled Letter: According to its PI, Angiomax is indicated for use as an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA), and, with provisional used of glycoprotein IIb/IIIa inhibitor (GPI) as listed in the REPLACE-2 trial, in patients undergoing percutaneous coronary intervention (PCI). Angiomax is also indicated for patients with, or at risk of, heparin induced thrombocytopenia (HIT) or heparin induced thrombocytopenia and thrombosis syndrome (HITTS) undergoing PCI. For these indications, Angiomax is intended for use with aspirin and has been studied only in patients receiving concomitant aspirin. Angiomax's PI indicates that the safety and effectiveness of the drug have not been established in patients with acute coronary syndromes who are not undergoing PTCA or PCI.

OPDP concluded that Angiomax's booth panel misleadingly implied that Angiomax is more effective than heparin, with or without GPI, for patients with stable angina, unstable angina, NSTEMI, and STEMI, who are undergoing PCI. The booth panel included the following claims:

- "ANGIOMAX: documented **victories** across a broad spectrum of patients from stable to STEMI"[9]
- "Data-Driven ***victories***"[10]

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[8] Emphasis added by OPDP.
[9] Emphasis added by OPDP.
[10] Bolded emphasis added by OPDP.

- "Unsurpassed ischemic efficacy throughout the risk spectrum
  - Demonstrated unsurpassed ischemic efficacy and reduced bleeding vs heparin with or without glycoprotein (GP) IIb/IIIa inhibitor"[11]

A graphic showing an increased risk of ischemic complications as stable angina progressed to unstable angina to NSTEMI to STEMI—and an arrow indicating that as the risk increased, the ability of heparin to penetrate the thrombus decreased—accompanied these claims. In support of the above claims, the booth panel cited numerous references. OPDP concluded that these references did not constitute substantial evidence of superiority because the referenced-trials: (1) made *ex vivo* findings that did not correlate with claims of clinical benefits; (2) were non-inferiority trials and not head-to-head studies; (3) were confounded by the administration of other anti-thrombin agents; (4) included patients undergoing PTCA, not PCI; or (5) were review articles that did not mention Angiomax.

Failure to Submit Post-Marketing Report at the Time of Dissemination

FDA's letters contain the following allegations under a "Failure to Submit Post-Marketing Report at the Time of Dissemination" subheading:

Octapharma Warning Letter: According to APLB, Octapharma failed to submit a copy of the journal advertisements printed in the BDI Pharma Product Catalog and *BioSupply Trends Quarterly* at the time of the advertisements' initial dissemination, in violation of 21 C.F.R. 601.12(f)(4).

Failure to Fulfill "Adequate Provision" Requirement

FDA's letters contain the following allegations under a "Failure to Fulfill 'Adequate Provision' Requirement" subheading:

Meda Untitled Letter: According to OPDP, Meda's professional telephone script failed to present a brief summary of information relating to side effects and contraindications of ASTEPRO 0.15%, or make adequate provision for dissemination of the approved or permitted package labeling in connection with the script, in violation of 21 C.F.R. 202.1(e)(1).

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If you have any questions concerning the material discussed in this client alert, please contact the following members of our Food & Drug practice group:

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[11] Emphasis in original.