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COVINGTON & BURLING LLP

E-ALERT | Food & Drug

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SUMMARY OF FDA ADVERTISING AND PROMOTION ENFORCEMENT ACTIVITIES

JUNE 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 June 2012, FDA's Office of Prescription Drug Promotion (OPDP) posted the following enforcement letters on its website:[1]

- Untitled letter to Quintiles, Inc. [U.S. Agent for Swedish Orphan Biovitrum AB] re: Kepivance® (palifermin) For injection, for intravenous use (June 7, 2012) ("Quintiles Untitled Letter")[2]
- Untitled letter to Watson Pharmaceuticals Inc. re: Sodium Ferric Gluconate Complex in Source Injection (June 7, 2012) ("Watson Untitled Letter")

The Office of Compliance in FDA's Center for Devices and Radiological Health (CDRH) posted the following letters on FDA's website:

- Warning letter to Belmont Instrument Corporation re: Belmont Hyperthermia Pump (May 7, 2012) ("Belmont Warning Letter")
- Warning letter to ThermaSolutions Incorporated re: ThermoChem-HT 1000 System (May 7, 2012) ("ThermaSolutions Warning Letter")

During June 2012, the Office of Compliance and Biologics Quality (OCBQ) in FDA's Center for Biologics Evaluation and Research (CBER) did not post any enforcement letters relating to the advertising and promotion of biologics on FDA's website. The letters posted by OPDP and the Office of Complaince at CDRH raise a variety of allegations and conclude that the cited advertising/promotional issues render the subject product misbranded and/or adulterated.

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.

Claims Outside Cleared Use[3]

FDA's letters contain the following allegations under a "Claims Outside Cleared Use" subheading:

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[1] Only enforcement letters posted to FDA's website in June 2012 are included herein. Letters issued in June but not posted to the website by June 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] The letters issued by CDRH does not explicitly use this subheading, but the allegations fit within this category.

Belmont Warning Letter: The Belmont Hyperthermia Pump ("the Pump") is cleared under section 510(k) of the Federal Food, Drug, and Cosmetic Act (FDCA) "to raise the temperature of the thoracic or peritoneal cavity to the desired target temperature by continuously lavaging the cavity with circulating warmed sterile solution, according to a protocol to be selected by the physician." A video posted to Belmont Instrument Corporation's website showed the Pump being used to treat cancer in the appendix and discussed the use of a chemotherapeutic drug as the solution in the Pump. Another Belmont webpage described Hyperthermic Intraperitoneal Chemotherapy (HIPEC)[4] and provided that:

> [T]he HIPEC procedure is a localized approach. . . . Because there is no risk to the unaffected parts of the body, the Chemotherapy dosage can be higher and the results more effective. . . . For more information on the equipment used to circulate the chemotherapy bath, please see the Belmont® Hyperthermia Pump website.

According to CDRH's Office of Compliance, because the Pump is not cleared or approved for the treatment of a specific disease or condition, or for use with heated chemotherapy drugs, these claims rendered the Pump adulterated and misbranded.

ThermaSolutions Warning Letter: ThermaSolutions' ThermoChem-HT 1000 System ("ThermoChem-HT") is cleared under section 510(k) of the FDCA "to raise the core temperature of the peritoneum to the desired target temperature by continuously lavaging the peritoneum with circulated warmed Lactated Ringer's Solution, U.S.P., or another physiologically compatible sterile solution." Several of the company's websites and social media postings made claims regarding the use of ThermoChem-HT with heated chemotherapy drugs to treat cancer, including with HIPEC procedures. For example:

- ThermaSolutions' homepage stated "ThermaSolutions, Inc. is the global leader in hyperthermia medical technology for ovarian, gastric, appendiceal and colorectal cancers . . . . ThermaSolutions manufactures and distributes the ThermoChem HT-1000 and all related disposables."
- On a HIPEC treatment website, a television clip from "Grey's Anatomy" featuring use of the ThermoChem-HT during a HIPEC procedure was posted, along with a caption that stated "[t]he popular show 'Grey's Anatomy' of ABC featured the [HIPEC] procedure with ThermaSolutions' HT-1000 in last year's episode. One of our team members participated in the program to make sure the procedure and equipment was used the way our clients do too . . . ."
- ThermaSolutions' Twitter page stated that the firm "has the first FDA approved medical device for creating hyperthermia in the abdominal cavity — heating and pumping a chemotherapy solution into the region."

CDRH's Office of Compliance found that these claims rendered the ThermoChem-HT adulterated and misbranded because the device is not cleared or approved for the treatment of a specific disease or condition, nor is it cleared or approved for use with heated chemotherapy drugs.

Unsubstantiated Claims

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

Watson Untitled Letter: According to its package insert ("PI") Ferric Gluconate Complex in Sucrose Injection ("sodium ferric gluconate") is indicated for "treatment of iron deficiency anemia in adult

[4] Belmont's website described the HIPEC procedure as follows: "'Intraperitoneal' means that the treatment is delivered to the abdominal cavity. The term 'Hyperthermic Chemotherapy' means that the solution containing chemotherapy is heated to a temperature greater than normal body temperature."

patients and in pediatric patients age 6 years and older undergoing chronic hemodialysis who are receiving supplemental epoetin therapy." OPDP found that a journal ad for sodium ferric gluconate made several unsubstantiated claims.

First, under the heading "Optimized ESA Usage"[5] the journal ad included the claim "[s]odium ferric gluconate complex in sucrose injection showed a mean reduction in ESA requirements by up to 60.2%."[6] According to OPDP, ESA dose requirements can be due to multiple confounding factors, making epoetin dose reduction an invalid endpoint in the assessment of sodium ferric gluconate's efficacy. Additionally, the study cited in support of this claim had unclear endpoints and efficacy parameters, and thus, according to OPDP, did not constitute substantial evidence in support of the claim.

Second, under the heading "Optimized . . . Hospital Spending" the journal ad included the claims "[s]odium ferric gluconate complex in sucrose injection provided significant cost savings when used with ESA therapy" and "$1390 net cost savings per g/dL Hb increase over 12 weeks compared to ESA alone."[7] OPDP found that the reference cited in support of these claims consisted of two separate studies with different designs, and thus could not be considered a continuous 12-week treatment period. Accordingly, the reference did not support a claim that sodium ferric gluconate increases Hb levels when used together with ESAs, as compared to ESA alone over a 12-week period. OPDP concluded it was misleading to base treatment cost savings claims on this premise.

Additionally, according to OPDP, "these statements misleadingly suggest that treatment with sodium ferric gluconate plus ESAs will have a positive impact on **all** aspects of treatment costs . . . compared to treatment with ESAs alone."[8] OPDP found that these "global conclusions about treatment costs" were misleading. The reference cited in support of this claim evaluated drug acquisition costs and costs associated with hospitalizations due to serious adverse events only, and it did not account for other cost aspects (e.g., treatment of mild to moderate adverse events, laboratory monitoring, and drug administration). Finally, although these claims implied a broad, positive impact on treatment costs, the study on which these claims were based analyzed only a specific subgroup of hemodialysis patients. OPDP therefore concluded that the claim misleadingly suggested that "the cost savings is applicable to the general patient population."

Omission of Risk Information

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

Quintiles Untitled Letter: According to its PI, "Kepivance is indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support." A webpage for Kepivance presented the most common serious adverse reaction and common adverse reactions attributed to Kepivance, and it included links to the Prescribing Information and Safety & Tolerability section of the website. Nevertheless, the webpage omitted risk information from the PI regarding the potential for stimulation of tumor growth, the possibility of drug interactions, and the incidences of the most common adverse reactions. According to OPDP, these omissions misleadingly suggested Kepivance is safer than has been demonstrated by substantial evidence or substantial clinical experience.

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[5] "ESA" refers to erythropoiesis-stimulating agents.
[6] Citations omitted.
[7] Citations omitted.
[8] Emphasis in the original.

Misleading Efficacy Claims

FDA's letters contain the following allegations under a "Misleading Efficacy Claims" subheading:

Quintiles Untitled Letter: The webpage for Kepivance made numerous claims and presentations that suggested that treatment with Kepivance in patients with severe oral mucositis improves a patient's ability to eat, drink, swallow, and talk. For example, the webpage stated "**[t]he effect of Kepivance** . . . on mouth and throat soreness **and related functional activities (eating, drinking, swallowing, and talking), was consistent with the clinical findings in that significant improvement was reported**."[9] OPDP found that the references cited in support of these claims did not constitute substantial evidence because "the content validity of the daily diary questionnaire used in the studies has not been established for assessing the underlying concepts (i.e., the impact of severe oral mucositis on eating, drinking, swallowing, and talking)."

Additionally, the webpage contained the claim, "**Kepivance was associated with clinically meaningful and statistically significant improvements** in the requirement for opioid analgesics for oral mucositis; patient-reported mouth and throat soreness **and associated sequelae; and the requirement for [total parenteral nutrition]**."[10] OPDP found that this claim misleadingly suggested Kepivance significantly improves "**all** sequelae of oral mucositis (e.g., decreased patient nutrition, systemic infections, etc.)," when FDA was not aware of substantial evidence or substantial clinical experience that supported this claim. OPDP also concluded that this claim, in addition to others, misleadingly implied that treatment with Kepivance results in a decreased duration of opioid use and a reduction in the need for total parenteral nutrition ("TPN"). According to OPDP, the duration of opioid use and the incidence of TPN use were not pre-specified endpoints in the study cited to support these claims, and thus the reference did not constitute substantial evidence.

Failure to Submit Under Form FDA-2253

FDA's letters contain the following allegation under a "Failure to Submit Under Form FDA-2253" subheading:

Quintiles Untitled Letter: According to OPDP, Quintiles did not submit a copy of the webpage to FDA under cover of Form FDA-2253 at the time of initial dissemination or initial publication, in violation of 21 C.F.R. 601.12(f)(4).

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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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[9] Emphasis added by OPDP.
[10] Emphasis added by OPDP.