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FDA Advertising and Promotion Enforcement Activities: Update

March 14, 2019

Food, Drugs, and Devices

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

In February, the Office of Prescription Drug Promotion (OPDP) posted the following untitled letter on FDA's website:

- Untitled Letter to Fabio Almeida, MD, Phoenix Molecular Imaging Center re: Sodium Acetate C-11, MA 1 (Feb. 15, 2019) ("11C-Acetate Untitled Letter")

FDA's Center for Devices and Radiological Health (CDRH) Office of Compliance (OC) issued the following warning letter:

- Warning Letter to Total Thermal Imaging, Inc. re: FDA Reference Number EC180526/E001 Thermography Business Package (Feb. 22, 2019) ("Thermography Warning Letter")

The 11C-Acetate Untitled Letter is the first enforcement letter OPDP has issued this year. The Thermography Warning Letter is the first enforcement letter relating to advertising and promotion issued by CDRH OC this year. FDA's Advertising and Promotional Labeling Branch (APLB) in the Office of Compliance and Biologics Quality (OCBQ) has not yet posted any enforcement letters in 2019.

This alert merely summarizes the allegations contained in FDA's letters. It does not contain any analyses, 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.

Office of Prescription Drug Promotion (OPDP)

11C-Acetate Untitled Letter (February 2019)

OPDP's untitled letter relates to a webpage[1] that hosts an article entitled "Overview of PET/CT Imaging in Recurrent Prostate Cancer-Current and Emerging Techniques." OPDP argues that the article misbrands the investigational drug Sodium Acetate C-11 ("11C-Acetate") under section 502(f)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA). The webpage appears on the website for the Center for Integrative Healing & Wellness @ Civana (www.drfabio.com), which is described as "a modern era clinic for wellness." According to the website, the Center was founded by Dr. Fabio Almeida, and trials of C11-Acetate are being conducted there. According to OPDP, Dr. Almeida is the sponsor and principal investigator for the 11C-Acetate IND.

Misbranding of an Investigational Drug

OPDP alleges the webpage misbrands 11C-Acetate under FDCA section 502(f)(1) by suggesting in a promotional context that the drug is safe and effective for the purpose for which it is being investigated, i.e., as a PET scan agent for detecting recurrent prostate cancer, or otherwise promotes the drug.[2] Under section 502(f)(1), a drug is misbranded unless its labeling bears "adequate directions for use." By regulation, however, an investigational drug is exempt from such requirement if it "complies with section 505(i) [of the FDCA] … and regulations thereunder." 21 CFR 201.115(b). Among these regulations, "[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." 21 CFR 312.7(a). OPDP alleges that the webpage fails to comply with the requirements for this exemption because it makes claims that promote 11C-Acetate as safe and effective for the purpose for which it is being investigated or that otherwise promote the drug when it has not been approved by FDA for any use.

OPDP cites the following claims contained on the website as misbranding 11C-Acetate (emphasis added by FDA):[3]

- "11C-choline and 11C-acetate are lipid metabolism PET agents. **Both of these agents are useful for detecting recurrent disease after a PSA** [prostate-specific antigen] **relapse**."
- "Small direct comparison studies of 11C-acetate and 11C-choline have revealed no clear clinical differences between these agents, although a few studies have **suggested a**

[1] http://www.drfabio.com/imagingblog/2018/1/9/overview-of-petct-imaging-in-recurrent-prostate-cancer-current-and-emerging-techniques (last visited March 8, 2019).
[2] The untitled letter does not specifically identify for what purpose 11C-Acetate is being investigated, but it says that the webpage "describes 11C-Acetate as a useful PET scan agent for detecting recurrent prostate cancer" and then states that the webpage contains "claims and presentations that promote 11C-Acetate as safe and effective for the purpose for which it is being investigated or otherwise promote the drug."
[3] FDA notes that 11C-choline and fluciclovine F 18, which are mentioned in some of the claims, are approved products for PET imaging.

slightly higher detection rate of local recurrences and small pelvic lymph node metastases **with 11C-acetate**."

- "In some patients, the muscle uptake of Axumin [(fluciclovine F 18)] may be so high as to render the study non-diagnostic, despite having properly abstained from physical activity prior to the scan. Additionally, in a small but significant number of patients, interfering urinary excretion is seen. **These factors likely help explain the apparent lower performance of this agent compared to 11C-Acetate and Choline**."
- "The lack of urinary tracer excretion of **11C-Acetate allows visualization** of small and subtle lesions in this region, not typically possible with PSMA [prostate-specific membrane antigen] based agents."
- "So far Axumin [(fluciclovine F 18)] (detection rate 68%, 38% false positive) . . . does not appear to perform nearly as well as Acetate or Choline (88-90% detection rate and <10% false positive rate) . . . **Acetate or Choline remain overall much better choices for imaging**."
- 11C-Acetate "has [been] shown . . . to be a valuable and accurate tool, providing a better understanding of the location and extent of local recurrences and distant disease."

OPDP states that these claims make conclusory statements about the safety and effectiveness of 11C-Acetate. Specifically they "suggest in a promotional context that 11C-Acetate, an investigational new drug, has been shown to be different from or superior to approved therapies for PET imaging, specifically 11-C choline and fluciclovine F 18 . . .." OPDP acknowledges that the webpage states that 11C-Acetate "is available under expanded access clinical trials at multiple institutions," but OPDP alleges that this statement "neither adequately conveys that the product is unapproved, nor sufficiently mitigates impressions conveyed by other presentations . . . that 11C-Acetate is safe and effective for any use." OPDP concludes that the claims create a misleading impression regarding the usefulness and regulatory status of 11C-Acetate, "especially considering the serious nature of disease recurrence and the need for early detection."

Center for Devices and Radiological Health (CDRH) Office of Compliance (OC)

Thermography Warning Letter (February 2019)

In its letter to Total Thermal Imaging, Inc. ("TTI"), CDRH alleges that the company's marketing of its device, called the "Thermography Business Package," as a sole screening device for breast cancer and other diseases violated the FDCA. Because TTI lacked an approved premarket application for this intended use, and because TTI did not submit a premarket notification (commonly referred to as a "510(k)") prior to introducing the device, FDA alleges that the Thermography Business Package was adulterated and misbranded.

According to its website (totalthermalimaging.com), TTI is an "Early Detection & Wellness Center" that offers patient services, physician services, and thermographer certification. CDRH provides the following examples of claims and indications from TTI's website and brochures:

- "Thermal Imaging is intended for early detection of the diagnosis of many disorders including breast cancer, inflammatory breast cancer, pre-stroke, heart disease, deep

vein thrombosis, reflex sympathetic dystrophy/complex regional pain syndrome, back, leg or headache, and even unexplained pain, TMJ, and other disease."

- "You can't prevent or cure breast cancer until it is detected. DON'T WAIT! Schedule an appointment with a certified clinical thermographer today. Start by visiting www.totalthermalimaging.com and find a thermal imaging center near you."
- "Share with your friends & family that there is an alternative to mammography that doesn't involve any patient contact (no pain), will not cause cancer (no radiation), and is far more efficient at detecting cancer."
- "Breast Screening . . . This scan looks for inflammation, lymphatic congestion, hormonal imbalances. Early detection saves lives and breasts!"

FDA states that "telethermographic systems that are intended for use alone in diagnostic screening for detection of breast cancer or other uses have been classified as Class III devices . . . and require approval of a premarket approval application." Because TTI lacked such an approval, CDRH takes the position that the Thermography Business Package was adulterated under Section 501(f)(1)(B) of the FDCA. In addition, because TTI did not submit a 510(k) before introducing a device into commercial distribution, FDA alleges that the device was misbranded under section 505(o) of the FDCA.

CDRH also notes that the Thermography Business Package included a Class I device called the FLIR infrared ("IR") camera as a component. The FLIR IR was cleared by FDA as a "Telethermographic system intended for adjunctive diagnostic screening for detection of breast cancer or other uses." However, CDRH states that "clearance of a component of the Thermography Business Package does not permit the marketing of the Thermography Business Package." In addition, marketing the FLIR IR camera as a component of the Thermography Business Package was a major change or modification to the intended use of the FLIR IR camera that "would not fall under its current clearance" and would require premarket approval.

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