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FDA Advertising and Promotion Enforcement Activities: Update

September 19, 2018

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 May, the Center for Devices and Radiological Health (CDRH) Office of Compliance (OC) posted the following warning letter on FDA's website:

- Warning Letter to RADLogics, Inc. re: FDA Reference number COR16000016 AlphaPoint Imaging Software (Apr. 5, 2018) ("AlphaPoint Warning Letter")

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

- Untitled Letter to Pfizer Inc. re: NDA 020472 ESTRING® (estradiol vaginal ring) MA 275 (June 19, 2018) ("Estring Untitled Letter")

- Untitled Letter to Arog Pharmaceuticals Inc. re: Crenolanib besylate MA 2 (June 28, 2018) ("Crenolanib Untitled Letter")

In August, OPDP posted the following untitled letter on FDA's website:

- Untitled Letter to ASCEND Therapeutics US, LLC, re: NDA 021166 EstroGel® 0.06% (estradiol gel) for topical use MA 430 (Aug. 16, 2018) ("EstroGel Untitled Letter")

The CDRH letter is the first enforcement letter OC has issued relating to advertising and promotion in 2018, and the OPDP letters are the second, third, and fourth enforcement letters OPDP has issued in 2018. FDA's Advertising and Promotional Labeling Branch in the Office of Compliance and Biologics Quality did not post any enforcement letters relating to advertising and promotion on FDA's website in March, April, May, June, July, or August.

Also in June, the Department of Justice (DOJ) filed a complaint at the request of FDA against Innovative BioDefense, Inc., to prohibit the company from selling Zylast topical antiseptics, which DOJ alleged are unapproved drugs and are misbranded.

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.

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

AlphaPoint Warning Letter (April 2018)

CDRH alleges that AlphaPoint Imaging Software ("AlphaPoint") is misbranded and adulterated because RADLogics is marketing the device for uses outside the scope of its premarket notification, commonly known as a 510(k) clearance. Specifically, FDA alleges that AlphaPoint is misbranded because RADLogics made major changes or modifications to the intended use of the device without obtaining clearance of a new 510(k).

As an initial matter, the agency notes in a footnote that AlphaPoint remains subject to FDA regulation as a device, notwithstanding changes to the law in the 21st Century Cures Act:

> [s]oftware such as AlphaPoint, that is intended for interpretation or analysis of medical image data for the purpose of the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition, was not affected by the amendments to Section 201(h) of the Act made by Section 3060(a) of the 21st Century Cures Act on December 13, 2016, which excluded certain software functions from the definition of device. *See* 21 U.S.C. § 360j(o)(1)(E). Software functions that process or analyze medical images remain devices and continue to be subject to FDA oversight.

AlphaPoint was cleared with indications to allow the "review, analysis and interchange of CT chest images." The cleared indication states that AlphaPoint

> is intended for use with CT Chest images to assist medical professionals in image analysis. It is not intended to be the primary interpretation. . . . The user can review, verify and correct the results of the system and generate a report of findings.

FDA alleges that the RADLogics website (www.radlogics.com) and a YouTube video demonstrate "that AlphaPoint is being marketed as providing computer-assisted detection (CADe) of abnormalities in radiology images." Specifically, the Agency identifies the following claims on the RADLogics website:

- "Detailed, accurate findings for each case are available in a matter of minutes. By the time you sit down to review a case, the preliminary findings are up on the screen. Instead of spending the majority of your time on detection and characterization, you can focus on the critical task of diagnostics and completing your report."

- "The RADLogics Virtual Resident is like having a top resident preparing detailed detection and characterization findings for your review."

- "The RADLogics Virtual Resident is not subject to human variability, minimizing the chances of errors and inconsistencies. For example, if a clinician fails to note that

> contrast media was used in a scan, this will not affect the accuracy of the findings. The RADLogics Virtual Resident analyzes the images and identifies, independently, whether or not a contrast media was used. The software also scans for all of the disease states that are in each scan module. In the case of Chest CT, for example, even if a referring physician has asked the radiologist to look for a rib fracture, the software will identify lung nodules, if present."

FDA also alleges that the YouTube video provides evidence that AlphaPoint is being marketed with CADe functionality. Specifically, FDA states that the video:

- "shows the difference between 'reading a chest CT' and 'Using RADLogics Machine-Learning Virtual Resident'";
- "highlights nodules automatically marked and measured by the AlphaPoint software";
- "suggests the superiority of AlphaPoint's automatic detection capability over that of a human radiologist by calling out an 'Additional Nodule!'"; and
- indicates "that AlphaPoint's automatic detection capability could allow a radiologist to read medical images 3 minutes faster than software without such capability[.]"

FDA states that these claims are not supported by the cleared 510(k). The Agency states that the lack of safety and efficacy data for the CADe functionality "raise[] public health concerns," specifically "the risks for device as advertised are low sensitivity and specificity (*i.e.*, the device has unknown false positive and false negative rates)." FDA states that the RADLogics "promotional materials increase these public health concerns further because they market AlphaPoint as a physician replacement . . ., which leaves the physician to only review the software's findings and provide a diagnosis."

Finally, the Agency's letter refers to prior interactions between the company and FDA. The letter states that RADLogics "indicated an understanding that the AlphaPoint software was not cleared for the intended uses being marketed on [its] website and YouTube video" and "that a new 510(k) was necessary," during a 2016 teleconference. Following the teleconference, RADLogics took down its website and marketing videos, but since that time the company has reactivated its website, updated its YouTube marketing video, and issued a press release that indicates AlphaPoint has automatic diagnostic capabilities. In particular, the press release stated:

> "The solution provides the computational equivalent of a medical resident that traditionally prepares preliminary findings for radiologists in academic medical centers," says Moshe Becker, CEO and co-founder, RADLogics.

FDA cites these materials and activities as evidence that RADLogics continues to market the modified AlphaPoint for a new intended use without 510(k) clearance or approval.

Office of Prescription Drug Promotion (OPDP)

Estring Untitled Letter (June 2018)

OPDP states that Pfizer's direct-to-consumer video posted on michiganmomliving.com, which features paid and trained physician and patient spokespersons, misbrands Estring because it fails to communicate risk information, and it makes false or misleading claims about the efficacy of Estring.

False or Misleading Risk Presentation

OPDP alleges that the video misbrands Estring by creating a misleading impression about the product's safety and efficacy. Although it includes claims and representations about the benefits of Estring, it fails to include any risk information, even though the product bears a boxed warning due to several serious, life-threatening risks, as well as other contraindications and warnings. For example, the package insert (PI) for Estring carries boxed warnings for endometrial cancer, cardiovascular disorders, breast cancer, and probable dementia. The product is contraindicated in women with undiagnosed abnormal genital bleeding; known, suspected, or history of breast cancer; active deep vein thrombosis, pulmonary embolism, or a history of these conditions; known or suspected pregnancy; and other conditions. The PI also carries additional warnings for ovarian cancer, gallbladder disease, hypercalcemia, visual abnormalities, and hereditary angioedema, as well as precautions for other conditions.

OPDP states that the omission of risk information is not mitigated by the physician spokesperson referring women to the website askforthering.com and to their healthcare provider for additional information. OPDP also points out that when the patient spokesperson is directly asked by the interviewer about "side effects," she replies, "I do not experience any side effects. I'm, for me, I was able to just feel relief." OPDP states that "these statements misleadingly suggest that patients using Estring will have similar results and will not experience side effects, further exacerbating the misleading impression created by the omission of risk information." Finally, OPDP highlights that at the end of the interview, when the physician spokesperson is asked, "is there anything we didn't cover in this interview?", the physician spokesperson "declined to take this opportunity to disclose any of the risks of Estring."

False or Misleading Claims about Efficacy

OPDP also alleges that the video misbrands Estring by misleadingly suggesting that patients using Estring will experience instant relief of their symptoms. Specifically, OPDP notes that the patient spokesperson makes the following claim in the video: "I have to say that it was … yea once we came up with the plan and I began using the product it was pretty much an instant relief."

OPDP states that this claim "misleadingly suggests that patients will experience similar results, i.e., instant relief of their symptoms, after initiating treatment with Estring." OPDP states, however, that "the personal experience of an Estring-treated individual such as this spokesperson does not constitute support for the suggestion that patients will experience instant relief of their [vulvar and vaginal atrophy (VVA)] symptoms after starting Estring therapy," and that "FDA is not aware of data to support claims that Estring provides instant relief of moderate to severe symptoms of VVA due to menopause."

Crenolanib Untitled Letter (June 2018)

OPDP states that Arog's booth display at the American Society of Hematology's ("ASH") 59th Annual Meeting and webpage (https://www.arogpharmaceuticals.com/aml), titled "Crenolanib A next-gen tyrosine kinase inhibitor for use in FLT3-mutated AML," misbrand the investigational drug Crenolanib besylate ("Crenolanib") under section 502(f)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA).

Misbranding of an Investigational Drug:

OPDP alleges that the booth display and webpage misbrand Crenolanib 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., treating Acute Myeloid Leukemia ("AML") in general and FMS-like tyrosine kinase-3 ("FLT3") positive AML specifically. Under section 502(f)(1) a drug is misbranded unless its labeling bears "adequate directions for use," but 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 booth display and webpage fail to comply with the requirements for this exemption from FDCA section 502(f)(1) because they make claims that promote Crenolanib 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.

These claims include the following booth display claims:

- Combination Therapy—Future of AML Treatment
    - CRENOLANIB
        - Combinable with chemotherapy at full doses
- Eradicating Activating Mutations
    - CRENOLANIB
        - Potent inhibitor of
            - FLT3
            - PDGFRα
            - PDGFRβ

OPDP states that these claims suggest that Crenolanib has been established as safe and effective in treating AML in general when combined "with chemotherapy at full doses," and states that such a suggestion is "especially concerning given the lack of adequate safety and efficacy data about Crenolanib, as well as the toxicity of current chemotherapy regimens and issues regarding the tolerability of such regimens." OPDP also alleges that the suggestion that Crenolanib is effective at "eradicating activating mutations" like FLT3 "is especially troubling given that FLT3 internal tandem duplication (ITD) mutations are associated with a poor prognosis (i.e., increased likelihood of relapse and decreased overall survival." OPDP notes that the booth display failed to include any information indicating that Crenolanib is an

unapproved investigational new drug, and that the booth appeared in the main exhibit hall at ASH alongside approved products.

OPDP also identifies the following claims from Arog's webpage that it alleges misbrand Crenolanib by suggesting in a promotional context that the drug is safe and effective for the purpose for which it is being investigated.

- Crenolanib
    - A next-gen tyrosine kinase inhibitor for use in FLT3-mutated AML
- Crenolanib, a type I TKI, is a potent inhibitor for FLT3-ITD and secondary KD mutants
- THERE ARE SEVERAL ATTRIBUTES THAT SET CRENOLANIB APART FROM OTHER THERAPEUTIC OPTIONS
    1. Crenolanib, whether delivered by itself or as part of a drug combination, has shown benefit in FLT3 mutant AML.
    2. Patients who progress after treatment with prior TKIs may still remain sensitive to crenolanib.
    3. Crenolanib has favorable pharmacokinetics and does not accumulate with repeated dosing.
    4. Crenolanib is a selective type I TKI that does not inhibit wild-type cKIT.

OPDP alleges that the above claims make conclusory statements about the safety and effectiveness of Crenolanib by stating that the drug is "for use" in FLT3-mutated ALM without including that Crenolanib is an unapproved investigational new drug, and by stating that Crenolanib is a "potent inhibitor for FLT3-ITD and secondary KD mutants," which has not been established. OPDP also states that the claims suggest, in a promotional context, that Crenolanib is different or superior to approved therapies for AML. OPDP states that these claims "may create a misleading impression regarding the usefulness and approval status of this product," and that such claims "are especially concerning given the seriousness of [AML] and the relatively few available treatment options."

EstroGel Untitled Letter (August 2018)

OPDP alleges that Ascend's sell sheet misbrands EstroGel under FDCA section 502(a) by falsely suggesting that EstroGel contains the lowest effective dose of estrogen compared to other estrogen products.

False or Misleading Claims about Efficacy

OPDP states that Ascend's sell sheet misbrands EstroGel because it includes claims that falsely suggest that EstroGel contains the lowest effective dose of estrogen compared to other estrogen products when there are other FDA-approved products with lower doses. OPDP also cites 21 CFR sections 202.1(e)(5) (regarding "true statement[s]" of information) and 202.1(e)(7)(i) (stating that an advertisement may be false, lacking in fair balance, or otherwise misleading if it "[c]ontains favorable information or conclusions from a study that is inadequate in design, scope, or conduct to furnish significant support for such information or conclusions") in its misbranding allegation.

The claims on the sell sheet that OPDP alleges misbrand EstroGel include the following:

- "Provides the lowest, effective dose of transdermal estrogen therapy to help meet your patients' treatment goals[.]"
- "In the 2017 North American Menopause Society (NAMS) Position Statement, NAMS recommends first-line treatment of VMS with the most appropriate, often lowest effective dose, of estrogen therapy consistent with treatment goals[.]"
- "The dose of estradiol in EstroGel has been proven to be the lowest effective dose for the treatment of symptomatic postmenopausal women[.]"

OPDP alleges that the above claims are false or misleading because there are FDA-approved estrogen products, including other transdermal estrogen therapies, with lower doses than EstroGel that are approved for the same indications as EstroGel.

OPDP also alleges that the article cited by the sell sheet for the first and third above-listed claims does not provide support for the claims. OPDP explains that the authors of the article concluded that the lowest dose of EstroGel was "the lowest practical dose *of this estrogen therapy* in the treatment of moderate to severe vasomotor symptoms and vulvar and vaginal atrophy due to menopause" (emphasis added), but that the authors did not compare EstroGel to other FDA-approved formulations of estrogen at any dose. OPDP concludes, therefore, that the studies described in the article are insufficient to support the claims.

Food and Drug Administration (FDA) and the Department of Justice (DOJ)

Zylast Complaint (June 2018)

In June, DOJ filed a complaint in the U.S. District Court for the Central District of California at the request of FDA against Innovative BioDefense, Inc. ("Innovative BioDefense"). The complaint seeks to prohibit the company from selling its Zylast topical antiseptics ("Zylast products") with claims that they are effective against infection by pathogens such as norovirus, rotavirus, flu virus, Methicillin-Resistant Staphylococcus Aureus, and Ebola. The complaint comes three years after FDA and the Federal Trade Commission (FTC) sent a joint warning letter to Innovative BioDefense alleging that the Zylast products were unapproved new drugs and were misbranded.

In the warning letter, FDA and FTC alleged that the Zylast products were unapproved new drugs because claims on the Zylast product labels and on Zylast's website (www.zylast.com) and Facebook and Twitter pages stated intended uses that were not covered by the applicable over-the-counter (OTC) monograph for topical antiseptics. Furthermore, the warning letter stated that Innovative BioDefense's website misbranded Zylast leave-on products by stating on the website, www.zylastdirect.com: "The active ingredient in Zylast, BZT … is considered safe and effective in concentrations 0.1-0.2% by the FDA."

The warning letter noted, however, that

> FDA has not established nor proposed BZT (benzethonium chloride) to be safe and effective at any concentration when used as a leave-on antiseptic such as Zylast XP Antiseptic Lotion. … Additionally, we note that even the rinse-off uses of BZT, which have been evaluated for under the rulemaking, have only been proposed as safe and effective for such uses, so the phrase "is considered" in the above quotation is inaccurate and misleading.

In FDA's press-release regarding the DOJ complaint, Commissioner Scott Gottlieb stated:

> Despite being warned by the FDA about their unproved claims, this company has continued to market their products as a tool for preventing infection from serious disease-related pathogens, without adequate evidence to support these uses . . .. We're concerned that people potentially exposed to pathogens may use these products with a false sense of safety. This may result in infrequent hand washing, or the substitution of these products for protective gloves and clothing or hand washing, which are the principal methods for protecting against the spread of diseases. Today's action reflects the FDA's continued efforts to take appropriate enforcement action against those who market products with inappropriate or unproven claims that could potentially put patients' health at risk.

If you have any questions concerning the material discussed in this client alert, please contact the following members of our Food, Drugs, and Devices practice:

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