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FDA Advertising and Promotion Enforcement Activities: Update

October 17, 2019

Food, Drugs, and Devices

This e-alert is part of a series of e-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 September, the Office of Prescription Drug Promotion (OPDP) posted the following enforcement letters on FDA's website:

- Warning Letter to Galt Pharmaceuticals, LLC re: NDA 018708 DORAL® (quazepam) tablets for oral use C-IV, MA 51 (Sep. 13, 2019) ("Doral Warning Letter")
- Untitled Letter to Kowa Pharmaceuticals America, Inc. re: NDA 022363 LIVALO® (pitavastatin) tablets for oral use, MA 609 (Sep. 24, 2019) ("Livalo Untitled Letter")

Also in September, FDA's Center for Devices and Radiological Health (CDRH) Office of Compliance (OC) posted on FDA's website the following warning letter, issued earlier this year:

- Warning Letter to 21st Century Scientific Inc. re: MARCS-CMS 566834, Bounder VA Power Wheelchair (K901210) (May 13, 2019) ("Bounder VA Warning Letter")

The Doral Warning Letter and the Livalo Untitled Letter are the sixth and seventh enforcement letters OPDP has issued this year. The Bounder VA Warning Letter is the second enforcement letter related to advertising and promotion posted by CDRH OC this year. FDA's Advertising and Promotional Labeling Branch (APLB) in the Office of Compliance and Biologics Quality (OCBQ) has not 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)

Doral Warning Letter (September 2019)

OPDP's warning letter to Galt Pharmaceuticals states that a professional email[1] regarding Doral, a controlled substance indicated for the treatment of insomnia, misbrands Doral under sections 502(a) and 502(n) of the FDCA by making make false or misleading claims and/or representations about the risks and benefits associated with Doral.[2] OPDP's letter states that the alleged violations "are extremely concerning from a public health perspective because they create a misleading impression about the safety and effectiveness of Doral, a drug that is a controlled substance and bears a Boxed Warning due to serious, life-threatening risks from concomitant use with opioids."

OPDP also notes that it "has expressed concerns regarding promotional materials for Doral in a previous [untitled] letter" sent on October 29, 2014 to Sciecure Pharma, Inc., the previous owner of the Doral NDA (the "Sciecure Untitled Letter"). The Sciecure Untitled Letter addresses a professional sales aid "that omitted important risk information, contained unsubstantiated superiority claims, and omitted material facts." The Doral Warning Letter states that "OPDP is concerned that Galt is continuing to promote [Doral] in a similarly violative manner."

<u>False or Misleading Risk Presentation</u>

OPDP alleges the professional email is misleading because it (1) omits certain risk information, and (2) minimizes associated risks of abuse and dependence.

First, OPDP alleges that Galt's professional email is misleading because it includes claims regarding the benefits of using Doral for the treatment of insomnia, but fails to include important risk information. In particular, the professional email "completely omits the warning and precaution regarding benzodiazepine withdrawal syndrome," and "fails to disclose information from the WARNINGS AND PRECAUTIONS" section of the Doral prescribing information (PI) regarding "CNS-Depressant Effects and Daytime Impairment," "Severe Anaphylactic and Anaphylactoid Reactions," "Abnormal Thinking and Behavior Changes," and "Worsening of Depression." OPDP states that the omission of such risk information is not mitigated by the statement, included in the professional email, "For a full list of warnings and precautions, please refer to the full prescribing information." OPDP further alleges that "the email, similar to the professional sales aid at issue in the [Sciecure] Untitled Letter, misleadingly suggests that Doral is safer than has been demonstrated."

Second, OPDP alleges that the professional email "minimize[s] the risks of abuse and dependence associated with Doral and suggest[s] that this C-IV scheduled drug is superior in safety to other prescription and over-the-counter (OTC) products." OPDP points to the following claims included in the professional email under the header, "**Concerned about Abuse potential of sleep medications?**" (emphasis in original; asterisk content below):

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[1] OPDP states the professional email includes an active hyperlink to open the email in a web browser: http://www.doralrx.com/Campaigns/Emails/Doral_Least_Abuse_Potential/ (Last accessed Oct. 15, 2019).
[2] The version of the Doral PI referred to in the Doral Warning Letter is dated August 2017. This is the version of the PI that was in effect when the professional email was disseminated.

- "Doral's relative likelihood of abuse is considerably lower than some of the widely used sleep aids (i.e. Zolpidem & Temazepam)*"
- "Doral was ranked even lower than OTC product Diphenhydramine for relative abuse potential*"
- A figure comparing the "**Relative Likelihood of Abuse**" of 19 drugs, with Quazepam shown as having a score lower than 16 of the drugs depicted
- "**Doral**'s abuse potential is **1/2** of Zolpidem and **1/3** of Temazepam"

OPDP states that such claims give "the overwhelming impression that Doral is superior in safety to other prescription and OTC products." The Agency alleges, however, as it previously stated in the Sciecure Untitled Letter, that "the 'algorithm' [included in the cited reference for these claims and presentation] lacks actual abuse data in human subjects and has not been validated." OPDP further states that this misleading impression is not mitigated by the statement included in the figure:

> *Please see complete prescribing information for detailed information on each product. The above chart is not intended for efficacy comparison. The authors algorithm, while comprehensive, does lack prospective abuse data in human subjects and had not been validated in subsequent research.

OPDP states that the "misleading impression is compounded by the fact that the email fails to disclose Doral's potential for abuse and dependence, including that Doral is classified as a schedule IV controlled substance." The Agency states that "[t]his is alarming as it appears that Galt is intentionally attempting to promote Doral as a non-controlled product that is safer than over-the-counter medication."

<u>False or Misleading Claims About Efficacy</u>

OPDP alleges that the professional email falsely "suggests that Doral is the **only** marketed medication indicated for the treatment of insomnia characterized by" certain symptoms. The Agency cites the following claim (bold emphasis original, underline emphasis by OPDP):

- **"Doral is the <u>only</u> marketed medication for Insomnia that helps with all three important components of sleep:**
  - Difficulty falling asleep
    - Difficulty staying asleep
      - Early morning awakening"

OPDP states that "[t]his claim is false," and that "there are other marketed medications indicated for all three of these components of sleep."

<u>Omission of Material Facts</u>

Finally, OPDP alleges that the professional email "creates a misleading impression about the use of Doral" because it omits material information from the INDICATIONS AND USAGE section of the PI. Specifically, the professional email claims (emphasis original):

- "For your patients with insomnia, Prescribe **Doral** (*Quazepam*) for a complete night's sleep"

- "Doral (Quazepam) is indicated for the treatment of insomnia characterized by difficulty falling asleep, frequent nocturnal awakenings, and/or early morning awakenings."

The professional email omits the following information from the PI:

> Because insomnia is often transient and intermittent, the prolonged administration of DORAL Tablets is generally not necessary or recommended. Since insomnia may be a symptom of several other disorders, the possibility that the complaint may be related to a condition for which there is a more specific treatment should be considered.

OPDP states "[t]hese omissions are particularly concerning from a public health perspective due to the serious health risks associated with Doral that should be considered when prescribing the product."

Livalo Untitled Letter (September 2019)

OPDP's untitled letter to Kowa Pharmaceuticals America states that a direct-to-consumer (DTC) patient testimonial video montage posted on YouTube.com misbrands Livalo, a cholesterol treatment, under sections 502(a) and 502(n) of the FDCA.[3] OPDP alleges the video makes false or misleading claims and/or representations about the risks associated with Livalo. OPDP states:

> This video is concerning from a public health perspective because it creates a misleading impression regarding the side effects a patient may experience as a result of Livalo treatment and deemphasizes the risks associated with taking the drug. . . . The video is especially concerning given that Livalo is associated with a number of serious risks, including the risk of skeletal muscle effects (e.g., myopathy and rhabdomylosis with acute renal failure secondary to myoglobinuria).

<u>False or Misleading Risk Presentations</u>

OPDP alleges that the video misbrands Livalo because it (1) misleadingly suggests that Livalo is safer than its competitors and (2) fails to present risk information with reasonably comparable prominence and readability as benefit information.

First, OPDP alleges that the video "misleadingly suggests that Livalo is safer than its competitors by implying that patients switching to Livalo from other statins will experience a reduction in side effects compared to other statins, or no side effects at all." The Agency cites the following patient testimonials (emphasis original):

> **<u>Debbie D.</u>**
> VOICEOVER (VO) (:04 - :06): "When I did the cholesterol panel, mine was extremely high."
> SUPER: **my** switch to **LIVALO**®
> Debbie D. Switched statins 6 times due to side effects

[3] The version of the Livalo PI referred to in the Livalo Untitled Letter is dated November 2016.

VO (:45 - :48): “After I took LIVALO, I’ve had no pain and my cholesterol levels are down.”
SUPER: **my** switch to **LIVALO**®
Debbie D. Taking LIVALO for 3 years

Donnie W.
VO (:07 - :10): “My doctor recommended I start with a statin. We started with one, we had a lot of side effects.”
SUPER: **my** switch to **LIVALO**®
Donnie W. Switched statins 4 times due to side effects

VO (:31 - :35): “LIVALO definitely made a positive impact in reducing my cholesterol and reduced my side effects.”
SUPER: **my** switch to **LIVALO**®
Donnie W. Taking LIVALO for 8 years

Robert M.
VO (:11 - :19): “The first medication I went on came with a lot of side effects, so I tried other ones after that and it was even worse.”
SUPER: **my** switch to **LIVALO**®
Robert M. Switched statins 3 times due to side effects

VO (:36 - :44): “I wish I was put on LIVALO years ago, because I’m not having the side effects that I was having with the other statins.”
SUPER: **my** switch to **LIVALO**®
Robert M. Taking LIVALO for 4 years

OPDP states that it is not aware of data supporting the suggestion that patients switching to Livalo will experience reduced side effects or no side effects. Moreover, the misleading impression is not mitigated by the onscreen superimposed text (SUPER) stating, “Individual results may vary.” The Agency states that the misleading impression “is especially concerning given that Livalo is associated with serious risks, several of which are the **same** as those associated with other statins” (emphasis by OPDP). As examples, the Agency states that “**all statins**, including Livalo, are associated with the serious risk of skeletal muscle effects” (emphasis by OPDP) and quotes the following from the WARNINGS AND PRECAUTIONS section of Livalo’s PI: “**Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including LIVALO**” (bolded emphasis original, underlined emphasis by OPDP).

Second, OPDP alleges that the video minimizes the risks associated with the use of Livalo by failing to present risk information with reasonably comparable prominence and readability as benefit information. Whereas the “benefit claims ... are presented prominently as part of the patient testimonials, which encompass the majority of the screen throughout the video,” “the risk information is presented as scrolling text relegated to the bottom of the video during these patient testimonials.” OPDP states that the testimonials “compete for the consumers’ attention making it difficult for them to adequately process and comprehend the risk information,” with the “overall effect” of “undermin[ing] the communication of risk information and thereby misleadingly minimiz[ing] the risks associated with the use of Livalo.”

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

Bounder VA Warning Letter (May 2019)

In its letter to 21st Century Scientific Inc. (21st Century), CDRH alleges that product labeling and the product website (http:/www.wheelchairs.com/bseatsys.htm) misbrand the Bounder VA Power Wheelchair (K901210) (Bounder VA) under section 502(o) of the FDCA.[4] CDRH alleges that the labeling and product website misbrand the Bounder VA because a premarket notification (i.e., a "510(k)") was not submitted prior to introducing the device with "significant changes or modifications [that] could significantly affect the safety or effectiveness of the device."

The Bounder VA Power Wheelchair was cleared as a powered wheelchair to provide mobility to individuals restricted to the sitting position. CDRH alleges that 21st Century is "marketing the Bounder Powered Seating Systems as modification options" to the wheelchair. Specifically, the labeling and website position these modification options as "add[ing] device functionality such as lifting the user, tilting the user, and bringing the user to a standing position to allow for various activities and aid in entering and exiting the wheelchair." CDRH also cites a video (linked from the website, http://www.wheelchairs.com/videogallery.html) that "shows the wheelchair being used on rough terrain, sand, and snow." The Agency states that use of the Bounder VA with the above-described safety functions and on such terrains are "significant changes or modifications [that] could significantly affect the safety or effectiveness of the device" as cleared. As a result, the product requires a new 510(k) premarket notification.

The warning letter also states that CDRH discussed these concerns with 21st Century during an inspection in 2018, and that it found the company's justification for not submitting a new 510(k) notification to be inadequate. Specifically, "although [the company's] responses conclude that these seating systems do not add additional risk," the Agency "determined that the modifications ... were significant modifications that require[d 21st Century] to submit a new 510(k) submission."

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[4] The letter also discussed other inspection findings unrelated to the promotion of the Bounder VA.