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ADVISORY | Food & Drug

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SUMMARY OF FDA ADVERTISING AND PROMOTION ENFORCEMENT ACTIVITIES

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

- Untitled letter to Burzynski Research Institute, Inc. re: Antineoplastons A10 and AS2-1 Injections (October 18, 2012) ("Burzynski Untitled Letter")[2]
- Untitled letter to Cornerstone Therapeutics Inc. re: CUROSURF® (poractant alfa) Intratracheal Suspension (October 31, 2012) ("Cornerstone Untitled Letter")
- Untitled letter to ONY, Inc. re: INFASURF® (calfactant) Intratracheal Suspension (October 31, 2012) ("Ony Untitled Letter")
- Untitled letter to Alcon Research, Ltd. re: PATANASE (olopatadine hydrochloride) Nasal Spray (November 13, 2012) ("Alcon 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 Quanta Systems, S.p.A. re: Quanta Q-Plus (Q-Plus Series) and Light Series Laser models (October 18, 2012) ("Quanta Warning Letter")
- Warning letter to NeuroMed Devices, Inc. re: ViraCalm and OraCalm products (October 22, 2012) ("NeuroMed Warning Letter")
- Warning letter to oBand Centers re: the LapBand gastric banding system (November 2, 2012) ("oBand Warning Letter")
- Warning letter to Tonica Elektronik, A/S re: Magnetic Stimulators (November 6, 2012) ("Tonica Warning Letter")

During November 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 advertising and promotion on FDA's website. These letters raise a variety of allegations and conclude that the cited advertising/promotional issues render the subject product misbranded and/or adulterated.

[1] Only enforcement letters posted to FDA's website in November 2012 are included herein. Letters issued in November but not posted to the website by November 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.

This alert merely summarizes the allegations contained in FDA's letters, presented under the corresponding headings used by the agency in its letters. This alert 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.

Burzynski Untitled Letter

Promotion of an Investigational New Drug: Antineoplastons A10 and AS2-1 Injections ("Antineoplastons" or "ANP") are investigational new drugs. OPDP reviewed websites for The Burzynski Research Institute, Inc. and The Burzynski Clinic and concluded that the websites—and the posted press releases and embedded videos—contained claims that suggested Antineoplastons were "'well tolerated,' 'work[ed] without causing side effects,' and [] demonstrated 'remarkable' results." For example:

- The website stated: "Antineoplastons act as molecular switches, which turn off life processes in abnormal cells and force them to die through apoptosis . . . . They specifically target cancer cells without harming healthy cells."

- The press releases made claims such as: "ANP was well-tolerated with easy [sic] manageable side effects of fatigue, skin rash and electrolyte abnormalities and no chronic toxicities" and "ANP was well tolerated, with just two cases of serious reversible toxicities."

- The embedded videos included statements such as: "[Antineoplastons] play a role on [sic] activating genes that are involved in the cancerous process, and also protecting you with genes that are causing cancer, so in essence, they have been shown to attack cancer cells but protect other cells, so it's the best of both worlds," and "[Antineoplastons] exist normally in our system and that's the reason why the drugs work without causing side effects."

OPDP determined that these claims promoted Antineoplastons as safe and/or effective for the treatment of various types of brain tumors, and otherwise promoted the drugs, in violation of 21 C.F.R. 312.7(a).

Cornerstone Untitled Letter

Curosurf is indicated for the treatment of Respiratory Distress Syndrome (RDS) in premature infants. According to its prescribing information (PI), Curosurf "reduces mortality and pneumothoraces associated with RDS." OPDP reviewed a professional pitch letter that included an attached press release for Curosurf, and concluded that the presentation was false or misleading because it omitted important risk information and presented unsubstantiated superiority claims. Further, OPDP determined that the press release inadequately presented the drug's established name.

Omission of Risk Information: OPDP found that the pitch letter contained several efficacy claims for Curosurf, "but fail[ed] to communicate **any** risk information associated with the use of the drug."[3] Although the press release that accompanied the pitch letter contained an "Important Safety Information" section for Curosurf, OPDP concluded this did not mitigate the pitch letter's misleading suggestion that Curosurf was safer than had been demonstrated.

[3] Emphasis added by OPDP.

Unsubstantiated Superiority Claims: OPDP determined that the pitch letter and press release misleadingly implied that Curosurf is superior to other animal-derived surfactants for reducing the mortality rate associated with RDS. The pitch letter and press release contained claims such as:

- "The study demonstrates that the use of Curosurf® (poractant alfa) Intratracheal Suspension results in lower mortality rates compared to other animal derived surfactants."[4]
- "**New Research Indicates Treating Neonatal Respiratory Distress Syndrome with CUROSURF® Results in Lower Rate of Mortality Compared to Competitive Surfactants**"[5]
- "Overall, CUROSURF treatment for RDS was associated with a significantly reduced likelihood of death compared to Infasurf, and a trend toward reduced mortality when compared with Survanta."

The study referred to in the claims was a retrospective, observational, cohort study that did not include a pre-specified efficacy analysis comparing the three surfactant products. OPDP determined that this study design was insufficient to support the comparative effectiveness claims. Additionally, the analysis relied on data that did not provide precise causes of death, the number of surfactant doses administered, nor any information regarding concomitant treatment with antenatal steroids. Although the press release disclosed some of the limitations of the study design, OPDP concluded that this did not mitigate the otherwise misleading presentation.

Inadequate Presentation of Established Name: The press release for Curosurf featured the drug's proprietary name in the press release's headline. OPDP determined that the press release failed to present the established name (poractant alfa) along with the proprietary name in violation of 21 C.F.R. 201.10(g)(1).

Ony Untitled Letter

Infasurf is indicated for the prevention of RDS in high-risk premature infants and, according to its PI, "for the treatment ('rescue') of premature infants who develop RDS. Infasurf decreases the incidence of RDS, mortality due to RDS, and air leaks associated with RDS." OPDP reviewed a professional website for Infasurf, and a video embedded in the website, and concluded that the webpages and video were false or misleading because they presented unsubstantiated superiority claims, omitted and minimized important risk information, and presented unsubstantiated claims for Infasurf.

Unsubstantiated Superiority Claims: OPDP found that both the webpages and video made unsubstantiated claims regarding Infasurf's superiority as compared to other surfactant products. For example, the webpage included claims such as "Infasurf's greater potency gives the most rapid and biggest initial improvement in respiratory status when treating patients with RDS," and "Infasurf is a pure surfactant that contains only active surfactant unlike our competitors, which contain lung tissue contaminants." Additionally, the video contained numerous comparisons regarding the properties of surfactant products, including concentration, dosing volume, viscosity, and length of treatment effect, among others. OPDP concluded that these claims and presentations misleadingly implied that Infasurf was superior to other available surfactants, when this was not supported by Infasurf's pivotal trials. Specifically, Infasurf's PI described trials comparing Infasurf to Exosurf Neonatal®—which is no longer marketed—and Survanta®—which was not shown to be clinically inferior for treatment or prophylaxis of RDS.

[4] Citation omitted.
[5] Emphasis in original.

Further, the video presented a figure showing "% Inspired Oxygen Concentration" over time for Infasurf and Survanta, and Curosurf and Survanta, and the claim "[a]s this graph highlights, Infasurf has a more vigorous, more rapid, and more sustained acute effect than Survanta or Curosurf." OPDP found this presentation misleading because the cited references did not support the implication that Infasurf was clinically superior to Survanta and Curosurf. Specifically, the first study measured physiologic data that had not been shown to correlate with clinically relevant variables, and the second study did not include Infasurf as a comparator.

Omission and Minimization of Risk Information: The webpages and video discussed the most common adverse reactions reported in clinical trials (cyanosis (65%), airway obstruction (39%), bradycardia (34%), and ETT reflux (21%)). OPDP, however, found the claim misleading because it omitted other significant common adverse reactions associated with Infasurf. OPDP also determined that the risk information was not presented with "a prominence and readability reasonably comparable to the claims of effectiveness." Specifically, the audio portion of the video failed to disclose any of the risks associated with Infasurf. Instead, the video presented the risks in a read-only text format during the last seven seconds of the three-and-a-half minute video. Finally, both the website and the video included claims that Infasurf is "well-tolerated." OPDP concluded that these claims were misleading because they minimized the serious risks associated with Infasurf, such as reflux into the endotracheal tube, airway obstruction, and an increased proportion of patients with intraventricular hemorrhage and periventricular leukomalacia.

Unsubstantiated Claims: The website included the claim: "Lower mortality is the most important benefit of surfactant therapy. **All surfactants** are **equivalent** for that benefit."[6] OPDP determined that this claim was misleading because it implied that Infasurf "has been demonstrated to be 'equivalent' to all other surfactants in terms of the clinical benefit of lowered mortality in patients with RDS," when this had not been demonstrated.

Alcon Untitled Letter

According to its PI, Patanase nasal spray is "an H1 receptor antagonist indicated for the relief of the symptoms of seasonal allergic rhinitis in adults and children 6 years of age and older." OPDP concluded that a professional sales aid for Patanase was misleading because it overstated Patanase's efficacy.

Overstatement of Efficacy: OPDP found the sales aid's presentation misleading because it implied that "Patanase has been shown to be effective in the treatment of the specific symptom of nasal congestion . . . ." OPDP pointed to claims such as "**Congestion relief in 30 minutes**,"[7] and graphics of a woman and child with a cork in each nostril on the front of the sales aid, and the same woman and child without corks on the back of the sales aid along with the tagline "**Unplug with**"[8] and a graphic of two loose corks with the Patanase logo. According to its PI, Patanase's efficacy was assessed via a composite measure of symptoms (the total nasal symptom score (TNSS)), and the individual symptom of nasal congestion was not evaluated. Additionally, the studies cited in support of these claims were conducted in allergen chamber environmental exposure units (EEU). OPDP concluded that these studies did not constitute substantial evidence in support of the claims because the studies were "conducted in controlled settings that do not reflect real world situations."

OPDP also pointed to claims such as "**Patanase® Nasal Spray is the only nasal antihistamine FDA approved to relieve symptoms in 30 minutes**."[9] OPDP stated that this claim implied a guarantee of

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

clinical symptom relief within 30 minutes of administration. The claims were based on findings from the EEU studies, and OPDP explained that the claims misrepresented the onset of clinical symptom relief. Instead of 30 minutes, the pivotal two-week seasonal allergy clinical trials demonstrated an onset of relief within one day of dosing. Finally, OPDP highlighted the claim "**[s]ustained symptom relief, week after week**,"[10] and a graph that suggested relief extended beyond 14 days. OPDP explained that the studies cited in support of these claims were not designed to measure efficacy beyond 14 days, and thus the claim misleadingly overstated Patanase's efficacy.

Quanta Warning Letter

Claims Outside Cleared Use: Quanta Systems, S.p.A. ("Quanta") had obtained 510(k) clearances for the Quanta System Q-Plus T—indicated for cutting, vaporization, and ablation of soft tissue, and the removal of tattoos and benign pigment lesion—and two Light Laser Series devices, indicated for the surgical incision, excision, vaporization, ablation, and coagulation of soft tissue. CDRH found claims in Quanta's marketing material such as "[t]hanks to its higher absorption by water and great penetration into the dermis, it is very effective for non-ablative collagen remodeling," as well as other claims promoting the devices for "skin rejuvenation procedures" and "post scelerotherapy matting." CDRH concluded that promotion of these devices for these uses represented a major change in the intended use of the device, and that the claims rendered the devices adulterated and misbranded.

NeuroMed Warning Letter

NeuroMed Devices, Inc. ("NeuroMed") had obtained clearance for the Neuro Calm Transcutaneous Electrical Nerve Stimulator (TENS) Device for "symptomatic relief and management of chronic, intractable pain, and adjunctive treatment in the management of post-surgical and post-traumatic pain." Model one of the Neuro Calm TENS Device corresponded to NeuroMed's ViraCalm device, and model two corresponded to NeuroMed's OraCalm device; these devices were cleared for prescription use only.

Claims Outside Cleared Use: According to the Warning Letter, CDRH reviewed NeuroMed's website and determined that the company promoted the ViraCalm and OraCalm devices for "treating or allowing someone to overcome herpes," which represented a major change in the intended use of the devices that could affect the devices' safety and effectiveness. Specifically, CDRH pointed to claims such as:

- "The No side Effects Remedy. Stop Herpes right at the outbreak!"
- "Herpes need not hinder your chance to lead a full life. Learn about our breakthrough devices OraCalm® and ViraCalm® lead an enjoyable, healthy life."
- "THUS, USE OF THE NON-INVASIVE DEVICE TO TREAT GENITAL HERPES IN A PREGNANT FEMALE PRIOR TO DELIVERY COULD PREVENT BLINDNESS, BRAIN DAMAGE OR EVEN DEATH OF THE NEWBORN."

According to the Warning Letter, CDRH had previously asked, and NeuroMed had agreed, to revise the names of ViraCalm and OraCalm so as to remove any implied reference to the treatment of herpes. Additionally, CDRH had asked NeuroMed to remove all references to the treatment of oral and genital herpes from the devices' indications for use. CDRH concluded that the claims on NeuroMed's website rendered the ViraCalm and OraCalm devices misbranded and adulterated.

[10] Emphasis in original.

oBand Warning Letter

According to the Warning Letter, oBand Centers ("oBand") marketed the LapBand gastric banding system, which had been approved by FDA for use in weight reduction for certain severely obese adults. The device was approved for prescription use, and could only be sold and distributed upon authorization by a licensed practitioner. CDRH reviewed oBand's website and concluded that claims on the website were misleading because they omitted or minimized material facts about the risks associated with LapBand.

Omission or Minimization of Risk Information: CDRH pointed to the following language on oBand's website:

The incidence of complications for lap band procedures worldwide is extremely low. The rate of complications for specific doctors at specific facilities can vary substantially. Our doctors are among the few nationally recognized lap band specialists who have the best success rates and the lowest complication rates. During your consultation the surgeon will discuss his/her personal success and complication rates and compare them to the worldwide statistics.

According to CDRH, this claim "significantly understates the risks posed by the device, for example by failing to mention the risk of death or serious injury from gastric band surgery (such as damage to the liver, spleen, and major blood vessels . . .)." Additionally, the claim failed to disclose that surgical risks are greater for obese patients and patients who have other underlying medical conditions. CDRH also pointed to a video on oBand's website that included a presentation on LapBand's indications for use, contraindications, warnings and adverse events. This information, however, was not accessible to the viewer because it appeared only briefly and was in "tiny and blurry print, which render[ed] the content illegible."

Tonica Warning Letter

Tonica Elektronik, A/S ("Tonica") manufactures Magnetic Stimulators, which are indicated for stimulation of peripheral nerves for diagnostic purposes. During an inspection of Tonica's facility in Denmark, FDA collected Tonica's catalog entitled "MagPro coils: Versatility in Magnetic Stimulation." CDRH determined that the coils advertised in the catalog promoted unapproved uses, which rendered the devices misbranded and adulterated.

Promotion of Unapproved Use: The catalog advertised four coils having 510(k) clearance: MCF-75, MCF-125, MCF-B65, and Cool-B65. Specifically, the catalog listed "Motor Cortex" as an application of the MCF-75 model, and "Brain tissue" as an application of the MCF-125, MCF-B65, and Cool-B65 models. According to CDRH, these stimulation targets differed from "peripheral nerves"—the cleared indication for use in Tonica's 510(k). Additionally, CDRH explained that the catalog did not distinguish whether these applications were diagnostic or therapeutic in nature. As CDRH explained, "[t]here is a difference between diagnostic and therapeutic intended uses, which may require a new 510(k)."

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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