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E-ALERT | Food & Drug

April 15, 2013

SUMMARY OF FDA ADVERTISING AND PROMOTION ENFORCEMENT ACTIVITIES

MARCH 2013

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 March 2013, FDA's Office of Prescription Drug Promotion (OPDP) posted the following enforcement letter on FDA's website:[1]

- Untitled letter to Photocure ASA re: Cysview (hexaminolevulinate hydrocloride), for Intravesical Solution MA #14 (March 4, 2013) ("Photocure Untitled Letter")

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

- Untitled Letter to On-line Distributors About Unlawful Marketing of Decorative Contact Lenses (February 28, 2013) ("Contact Lenses Letter")
- Warning Letter to Cynergy, LLC (March 1, 2013) ("Cynergy Letter")
- Warning Letter to Body, Mind & Soul Inc. re: Celluderm (March 13, 2013) ("BM&S Letter")

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.

This alert merely summarizes the allegations contained in FDA's 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.

LETTERS ISSUED BY OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)

Photocure Untitled Letter

Cysview is indicated for use in the cystoscopic detection of non-muscle invasive papillary cancer of the bladder among patients suspected or known to have lesion(s) on the basis of a prior cystoscopy. OPDP reviewed a patient guide for Cysview and alleged that the patient guide is false or misleading

[1] Only enforcement letters posted to FDA's website in March 2013 are included herein. Letters issued in March but not posted to the website by March 31, 2013 will be summarized in our alerts for the months in which those letters are posted.

because it omits and minimizes risk information, and because the patient guide makes unsubstantiated superiority claims.

Omission and Minimization of Risk Information: OPDP raised the following five examples of omission and minimization of risk information within the Cysview patient guide:

1. OPDP noted that the patient guide includes several efficacy claims for Cysview, but fails to disclose that Cysview is contraindicated in patients with gross hematuria.
2. OPDP stated that the following claim in the patient guide misleadingly minimizes the risks of Cysview: "Safety and effectiveness have not been established in patients receiving intravesical chemotherapy or BCG treatment within 3 months of Cysview photodynamic blue light cystoscopy." According to OPDP, this claim is misleading because it "fails to characterize these risks as contraindications, thereby suggesting that the drug is safer than has been demonstrated."
3. OPDP noted that the following claims omit the risk of false fluorescence included in the warnings and precautions section of the approved label:
    - "Under conventional white light, tumors can be virtually invisible and are easily missed. Cysview is taken up faster by malignant cells, causing them to appear first under the blue light, making them easier to see."
    - "How your healthcare professional sees images during a Cysview blue light cystoscopy" (accompanied by side-by-side images of tumors detected by standard white light cystoscopy and compared to vivid fluorescent images detected by Cysview blue light cystoscopy).
4. OPDP stated that the following statements misleadingly diminish the severity of a serious risk of anaphylaxis:
    - "The following adverse reactions have been identified during post-approval use of Cysview. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Cases of anaphylactoid shock, bladder pain, cystitis and abnormal urinalysis have uncommonly been reported."

Specifically, OPDP noted that the above claim downplays the severity of anaphylaxis "**only as a postmarketing adverse event that may be unrelated to the drug.**"[2] The approved labeling states that "[a]naphylaxis, including anaphylactoid shock, has been reported following administration of Cysview." Additionally, OPDP objected to the alleged characterization of "bladder pain" as a risk that has been reported "uncommonly," and only during post-approval use of the drug. OPDP noted that the approved label reports bladder pain as among the most common adverse reactions observed during clinical trials for Cysview. OPDP stated that listing bladder pain as a "common patient complaint" in another section of the patient guide did not mitigate the alleged minimization of risk.

5. OPDP claimed that statements in the patient guide referring to "pinkish tinge to the urine" misleadingly minimize the severity of the adverse event of hematuria. According to OPDP, patients may not necessarily associate hematuria (blood in the urine) with "pinkish tinge to the urine." OPDP also pointed to imagery in the patient guide that illustrates that Cysview is taken up by cancerous bladder cells that emit a pink fluoresce and the fact that the procedure is designed to make areas of concern show pink under observation. OPDP stated that these illustrations would suggest to patients that pinkish urine is a byproduct of Cysview rather than a pink color caused by blood.

[2] Emphasis in original.

Unsubstantiated Superiority Claim: OPDP also stated that the patient guide misleadingly suggests that Cysview blue light cystoscopy is more effective than traditional white light cystoscopy. OPDP pointed to the following statements in the patient guide [3]:

- **"Why would my doctor order a Cysview blue light cystoscopy instead of the conventional cystoscopy procedure?**

  Under certain circumstances, a conventional cystoscopy may provide unclear results. To improve diagnostic accuracy, your healthcare professional may request Cysview blue light cystoscopy.

  Under conventional white light, tumors can be virtually invisible and are easily missed. Cysview is taken up faster by malignant cells, causing them to appear first under the blue light, making them easier to see . . . ."

According to OPDP, suggestions that tumors depicted under traditional white light cystoscopy are "unclear," "virtually invisible," and "easily missed," while tumors under Cysview blue light cystoscopy are "easier to see," with "improve[d] diagnostic accuracy" imply that Cysview blue light cystoscopy is superior to traditional white light cystoscopy "when this is not the case." Further, OPDP noted that conventional white light cystoscopy detects some tumors missed by Cysview blue light cystoscopy, and Cysview's pivotal clinical study only supported the use of Cysview blue light cystoscopy as an adjunct to traditional white light instead of a superior alternative.

LETTERS ISSUED BY CDRH OFFICE OF COMPLIANCE (OC)

Contact Lenses Letter

In an untitled letter issued via e-mail to certain unspecified on-line distributors, CDRH stated that FDA's Office of Criminal Investigations, in coordination with the staff of the Federal Trade Commission (FTC), had reviewed on-line distributors' websites and determined that the websites offer decorative or cosmetic contact lenses for sale without a valid prescription. CDRH reminded the unspecified distributors that under section 520(n) of the Federal Food, Drug, and Cosmetic Act (FDCA), all contact lenses, including non-corrective and decorative or cosmetic contact lenses, are devices under section 201(h) of the FDCA. All contact lenses, including non-corrective and decorative contact lenses, must have in effect either a premarket approval application ("PMA") or a cleared premarket notification ("510(k)"). CDRH stated that the firms should take immediate action to ensure that they are not marketing and distributing decorative or cosmetic contact lenses that have not been approved or cleared by FDA. In addition, CDRH stated that these contact lenses are subject to the Contact Lens Consumers Act, 15 U.S.C. § 7601 et seq., and the Contact Lens Rule, 16 C.F.R. Part 315, which provides that contact lenses may be sold to consumers only in accordance with a valid prescription. Further, CDRH's letter stated that noncompliance could result in enforcement actions, including seizure, injunction, civil monetary penalties, and criminal investigations.

Cynergy Warning Letter

According to CDRH's warning letter to Cynergy, five products marketed by Cynergy, all of which are registered and listed as exempt manual surgical instruments for general use under 21 C.F.R. 878.4800, were adulterated and misbranded. Specifically, CDRH reviewed the company's website and asserted that the intended uses listed on Cynergy's website are not within the scope of the exemption for manual surgical instruments for general use. For example, CDRH pointed to the

[3] Bold emphasis in patient guide, underlined emphasis supplied by OPDP.

following claims made on Cynergy's website (among others) in taking the position that the intended uses for the products exceed the exemption under 21 C.F.R. 878.4800:

- "Medical Dermaroller® therapy triggers angiogenesis and collagenesis by communicating directly with your skin stem cells."
- "In just a few hours your body begins to naturally regenerate and repair the skin."
- "The Home Dermaroller C8 painlessly stimulates your epidermis (uppermost skin layer) to generate thicker, fresher, healthier skin."
- "Enhance delivery and effectiveness of medical grade skincare creams by 200x."
- "Promote continuous skin cell production and collagen induction after a medical Dermaroller® procedure."
- "By using the Home Dermaroller C8® regularly (about 2 to 3 times a week), transitional acne will disappear."
- "Six fine-precision, medical-grade, stainless steel micro-needles are the optimal number for minimal invasive penetration forces and minimal tissue trauma."
- "Proven effective."
- "Stem cell proliferation."

CDRH noted that all of the above intended uses (among others) exceed the limitations described in 21 CFR 878.9(a) and thus are not exempt from premarket notification requirements. According to CDRH, legally-marketed devices classified under 21 C.F.R. 878.4800 consist of either manual or motorized dermabraders indicated for general dermabrasion, scare revision, acne scar revision, and tattoo removal.

In addition, CDRH pointed to statements on Cynergy's website that Cynergy's products have various needle lengths and penetration depths, and that these needles allow for greater skin penetration than other products. According to CDRH, compared to generic devices that abrade the skin, the incorporation and use of needles is a different fundamental scientific technology and thus Cynergy's products exceed the limitations described in 21 CFR 878.9(b) and, accordingly, are not exempt from premarket notification.

Body, Mind & Soul, Inc. (BM&S) Warning Letter

CDRH reviewed BM&S's website and the Operator's Manual and Technology Manual ("Technology Manual") for the Celluderm device, and warned that the Celluderm device is being marketed without required clearance or approval. CDRH noted that the Celluderm device "appears to be a therapeutic massager." According to CDRH, a therapeutic massager as identified by the marketing exemption in 21 C.F.R. 890.5660 is an electrically powered device intended to relieve minor muscle aches and pains. CDRH cited the following statements on BM&S's website and the Technology Manual as exceeding the scope of the exemption for therapeutic massagers:

- "Celluderm System on its own is a highly effective method of stimulating the lymphatic system and reducing congestion . . . drains the fat that has been released into the blood and lymphatic system and attacks the top layer of the fat, breaking up the congestion that contributes to sluggish lymphatic flow."
- ". . . break up fat congestion pulling the breakdown of fats through the softened cell membrane and into the interstitial fluid."

- "Celluderm treatment progressively wears down congestion by manipulating body tissue using a vacuum suction massage."
- "Benefits of Celluderm Treatments [1] Immune System Booster[,] [2] reduces Water Retention and Edema[,] [3] Fibromyalgia Relief[,] [4] Restless Legs Relief[,] [5] Relieves Headaches[,] [and 6] Breast Cyst Reduction."

CDRH thus asserted that these claims establish intended uses for BM&S device that exceed the limitations of exemption described in 21 CFR 890.9. Because the device lacks approval or clearance for such intended uses, CDRH asserted that the device is adulterated and misbranded.

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