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E-ALERT | Food & Drug

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SUMMARY OF FDA ADVERTISING AND PROMOTION ENFORCEMENT ACTIVITIES

AUGUST 2010

This e-alert is part of a monthly series of 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 August 2010, FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) posted the following three untitled letters on its website:[1]

- SEROQUEL XR® (quetiapine fumarate) Extended-Release Tablets, AstraZeneca LP (July 29, 2010)[2]
- Tasigna® (nilotinib) Capsules, Novartis Pharmaceuticals Corporation (July 29, 2010)
- Exforge® (amlodipine and valsartan) Tablets, Novartis Pharmaceuticals Corporation (July 30, 2010)

The Office of Compliance and Biologics Quality (OCBQ) in FDA's Center for Biologics Evaluation and Research (CBER) posted the following letters (two untitled, one warning) on its website and on the FDA warning letter website:

- SparVax (Recombinant Protective Antigen (rPA) Anthrax Vaccine), PharmAthene, Inc. (June 11, 2010)
- PROVENGE® (sipuleucel-T), Dendreon Corporation (August 3, 2010)
- Aralast NP [Alpha1-Proteinase Inhibitor (Human)], Baxter Healthcare Corporation (August 3, 2010)

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

- NightForm Infant Positioning Mattress, Blountys LLC (June 23, 2010)
- EnGuard™ Vessel Guard, Replication Medical, Inc. (July 2, 2010)
- ThermoSuit Systems™, Life Recovery Systems HD, LLC (July 28, 2010)
- Corail® Hip System, Depuy Orthopaedics, Inc. (August 19, 2010)

[1] Only enforcement letters posted to FDA's website in August 2010 are included herein. Letters issued in August but not posted to the website by August 31, 2010 will be summarized in our alerts for the months in which those letters are posted.

[2] Dates referenced for the letters are issue dates.

The letters, taken together, make allegations under the following headings: Promotion of Unapproved Products/Uses; Omission/Minimization of Risk Information; Overstatement of Efficacy; Unsubstantiated Superiority/Overstatement of Efficacy; Misleading Claims; Broadening of Indication; Omission of Material Facts; Promotion of an Investigational Product; Use of Outdated Product Labeling; and Failure to Submit. The letters conclude that the cited advertising/promotional issues render the subject products misbranded or, the case of the letters issued by CDRH, adulterated and misbranded.

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

Promotion of Unapproved Products/Uses[3]

FDA's letters contain several allegations that would fit under a "Promotion of Unapproved Products/Uses" subheading. These include:

CDRH warning letter to Blountys LLC re: NightForm Infant Positioning Mattress (June 23, 2010) ("Blountys warning letter"): The product website for the NightForm Infant Positioning Mattress made claims promoting the use of this device "to address the dual risk of SIDS [sudden infant death syndrome] and of sleep-related skull flattening (deformational plagiocephaly)." Although the deformational plagiocephaly claim fit within the scope of this device's 510(k) clearance, promotion of this device for SIDS caused a "significant change" in its intended use, requiring submission of a new 510(k). Because of the SIDS claim, the device is adulterated under section 501(f)(1)(B) of the federal Food, Drug, and Cosmetic Act (FDCA).

CDRH warning letter to Replication Medical, Inc. re: EnGuard™ Vessel Guard (July 2, 2010): A white paper on the company's website and a product brochure for the EnGuard Vessel Guard contained claims suggesting that the product prevents fibroblast penetration, an implication "consistent with adhesion barrier claims because prevention of fibroblast penetration and facilitation of mobilization of necessary tissues, organs, and vessels are equivalent to adhesion barrier functions." This device received clearance "as a cover for vessels following anterior vertebral surgery," but FDA considers the adhesion barrier claims to represent a different intended use for the device—one outside the scope of the 510(k) clearance. Due to the new intended use established by these claims, the product is adulterated under section 501(f)(1)(B) of the FDCA.

CDRH warning letter to Life Recovery Systems HD, LLC re: ThermoSuit Systems™ (July 28, 2010): The company website contained several advertisements from peer-reviewed journals, articles, and video presentations promoting the ThermoSuit system for new intended uses. Specifically, the website promoted the device for the prevention of permanent tissue and neurological damage, for increasing survival rate in cardiac arrest patients, and for limiting damage to the brain and tissues after cardiac arrest. Although the ThermoSuit System has a clearance for temperature reduction in patients where clinically indicated, e.g., in hyperthermic patients, the website claims exceed the scope of the clearance and cause the product to be adulterated under section 501(f)(1)(B) of the FDCA.

[3] The letters issued by CDRH do not explicitly use this subheading, but the promotional allegations therein would fit within this category.

CDRH warning letter to Depuy Orthopaedics, Inc. re: Corail® Hip System[4] (August 19, 2010): The company website contained a brochure that included claims promoting the Corail Hip System for osseointegration or osteointegration. The Corail Hip System has a clearance for total hip arthroplasty "to provide increased patient mobility and reduce pain by replacing the damaged hip joint articulation in patients where there is evidence of sufficient sound bone to seat and support the components." The osseointegration claims, however, represent a "major change or modification" in the intended use of the device, requiring a new premarket notification. Because of these claims, the device is adulterated under section 501(f)(1)(B) of the FDCA.

Omission/Minimization of Risk Information

FDA's letters contain several allegations under an "Omission/Minimization of Risk Information" subheading. These include:

DDMAC untitled letter to AstraZeneca LP re: SEROQUEL XR® (quetiapine fumarate) Extended-Release Tablets (July 29, 2010) ("AstraZeneca untitled letter"): A leave-behind sheet for Seroquel XR omitted material information from a number of risks associated with the product, such as neuroleptic malignant syndrome, hyperglycemia and diabetes mellitus, and the potential for cognitive and motor impairment. For example, although the sheet included a discussion of the risk of tardive dyskinesia, it failed to state that although less common, the syndrome can develop after relatively brief treatment periods at low doses. Although the sheet included information regarding the risk of seizures, it failed to state that the drug should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold.

DDMAC untitled letter to Novartis Pharmaceuticals Corporation re: Tasigna® (nilotinib) Capsules (July 29, 2010) ("Novartis untitled letter – Tasigna"): The health care professional-directed and consumer-directed web pages of the U.S. Tasigna website each contained a "Facebook Share" widget that directed users to a separate web page that included shared content about the product. The posted shared content available from several of the Tasigna product web pages made representations or suggestions about the efficacy of the product, but failed to communicate any risk information. This omission was "particularly concerning" given the fact that Tasigna has a boxed warning and a Risk Evaluation and Mitigation Strategy (REMS). Although the shared content contained a hyperlink to various Tasigna product websites that did contain risk information, the inclusion of such links was insufficient to mitigate the misleading omission of risk information from the shared content itself.

DDMAC untitled letter to Novartis Pharmaceuticals Corporation re: Exforge® (amlodipine and valsartan) Tablets (July 30, 2010) ("Novartis untitled letter – Exforge"): A brochure for Exforge included a description of the boxed warning, certain of the warnings and precautions, and adverse reactions associated with the product, but failed to reveal specific warnings and precautions regarding hepatic impairment and interactions with potassium sparing diuretics, potassium supplements, or salt substitutes containing potassium.

OCBQ untitled letter to Dendreon Corporation re: PROVENGE® (sipuleucel-T) (August 3, 2010) ("Dendreon untitled letter"): An in service kit for Provenge presented a misleading product timeline on a slide entitled, "Is PROVENGE therapy approved for infusion?" The timeline included an entry implying that test results would be complete before the product arrived at the health care provider's office. This is "contrary to the 'Warnings and Precautions' section of the [package insert]," which states that the final sterility test results are not available at the time of infusion.

[4] Although this letter also addressed the TruMatch™ Personalized Solutions system, FDA's allegations regarding that product were not directed at promotional messaging.

Overstatement of Efficacy

FDA's letters contain several allegations under an "Overstatement of Efficacy" subheading. These include:

AstraZeneca untitled letter: A leave-behind sheet for Seroquel XR included claims about the remission rates observed with the product plus an antidepressant versus an antidepressant alone. Such claims "misleadingly suggest[ed]" that patients would achieve "remission" with Seroquel XR plus an antidepressant versus an antidepressant alone, when this has not been demonstrated by substantial evidence or substantial clinical experience. The cited references did not constitute substantial evidence to support "remission claims." First, "remission" was not specified as a primary or key secondary measure in these study protocols. Furthermore, the study length (six weeks) was not long enough to adequately assess "remission." Finally, no regulatory definition or criteria exist regarding "remission" in major depressive disorder. The leave-behind sheet also presented a patient profile that "misleadingly suggest[ed]" that Seroquel XR alleviates the specific symptoms of sadness and loss of interest, when this has not been demonstrated by substantial evidence or substantial clinical experience. According to the package insert, product efficacy was measured using a total score on the Montgomery-Asberg Depression Rating Scale (MADRS), but the clinical trials were not designed to assess the drug's impact on individual depressive symptoms. Inclusion of a footnote stating: "Sadness and loss of interest are select symptoms of MDD based on DSM-IV-TR criteria" did not mitigate the misleading nature of the presentation.

Dendreon untitled letter: A professional detail aid for Provenge included a chart entitled "Kaplan-Meier Survival Rate Estimates," which listed the percentage of patients alive at 12, 24, 36, and 48 months during a clinical trial. The information failed to provide sufficient contextual information for the presented survival rate estimates to convey the limitations of the study. For example, the chart did not include a measure of variability, such as the 95% confidence intervals, when presenting the survival rate estimates.

Unsubstantiated Superiority/Overstatement of Efficacy

FDA's letters contain several allegations under an "Unsubstantiated Superiority/Overstatement of Efficacy" subheading. These include:

Novartis untitled letter – Tasigna: The shared content from the "Facebook Share" widget on one of the consumer-directed web pages for Tasigna made the following claim comparing the efficacy of the drug to other tyrosine kinase inhibitors for the treatment of chronic myeloid leukemia (CML): "Tasigna (nilotinib) 200-mg capsules from Novartis is a next-generation treatment for Ph+ Chronic Myeloid Leukemia in adult patients in chronic or accelerated phase who are resistant to Gleevec." Referring to Tasigna as a "next generation" treatment implied its superiority over other tyrosine kinase inhibitors approved for use in the treatment of Ph+ CML when this advantage has not been demonstrated by substantial evidence or substantial clinical experience. For this reason, the claim also overstated the efficacy of Tasigna.

Novartis untitled letter – Exforge: A brochure for Exforge presented claims guaranteeing that patients would reach the blood pressure goal set by their physicians within 30 days. If not, patients would get their money back. The package insert (PI) presents estimates of the "likelihood" of achieving systolic or diastolic blood pressure control with Exforge, based on baseline systolic or diastolic blood pressure. But as baseline diastolic and systolic blood pressures increase, the probability of achieving one's systolic or diastolic goals decreases. Therefore, although Exforge has been shown to lower blood pressure, the clinical trials do not support claims guaranteeing that patients will reach their goal, regardless of baseline blood pressure. The guarantee claims also "misleadingly

suggest[ed]" that Exforge is more effective than other antihypertensives. Although the PI includes information indicating that Exforge—a combination of amlodipine and valsartan—is superior to its individual components, FDA is not aware of any adequate and well-controlled head-to-head studies supporting the implication that it is more effective than other individual treatments or combination treatments for hypertension and that it "will" lower blood pressure to target levels within at least 30 days.

Misleading Claims[5]

FDA's letters contain the following allegations under a "Misleading Claims" subheading:

OCBQ warning letter to Baxter Healthcare Corporation re: Aralast NP [Alphal-Proteinase Inhibitor (Human)] (August 3, 2010): A physician brochure for Aralast NP contained claims implying that there is an alpha$_1$- antitrypsin (A_1-PI) level that has been demonstrated to have a protective effect even though the clinical benefit of the increased blood levels of A_1-PI at the recommended dose of augmentation therapy has not been established. Furthermore, the inclusion of statements that emphasized a hypothetical threshold misleadingly implied that there is substantial evidence or substantial clinical experience that this threshold is clinically meaningful when FDA is not aware of such evidence.

Blountys warning letter: The NightForm Infant Positioning Mattress is misbranded under section 502(a) of the FDCA in that its labeling—namely the product website—contained misleading claims. These statements "create[d] an impression of official approval of a device due to clearance of a premarket notification submission." Specifically, the website included claims such as: "It has been clinically tested and it is approved by the FDA as a regulated medical device. No other device can claim these medical qualifications." This device was not "approved" by FDA, but rather was determined by be "substantially equivalent."

Broadening of Indication

FDA's letters contain the following allegations under a "Broadening of Indication" subheading:

Novartis untitled letter – Tasigna: In several instances, shared content posted via a "Facebook Share" widget on various web pages of the U.S. Tasigna product website included a very brief statement about what Tasigna treats that "misleadingly broaden[ed] the indication" for the drug. One example is the statement: "Tasigna (nilotinib) is used to treat a type of leukemia called Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML)." This statement implied that the drug is approved to treat all individuals with Ph+ CML, when this is not the case. At the time this shared content was originally disseminated, the drug was approved only as a second-line option after failure or intolerance to prior therapy that included imatinib. Furthermore, Tasigna is approved only for use in patients with Ph+ CML in the chronic or accelerated phases. Although the drug has since been approved for the treatment of adult patients with newly diagnosed Ph+ CML in the chronic phase, the shared content was disseminated prior to the approval of the new indication. Moreover, statements such as the one above broadened even the newly approved indication. Finally, the shared content also failed to disclose other important limitations to Tasigna's use, i.e., that its effectiveness is based on hematologic and cytogenetic response rates and that there are no controlled trials demonstrating a clinical benefit, such as improvement in symptoms or increased survival.

[5] The letters issued by CDRH do not explicitly use this subheading, but the promotional allegations therein would fit within this category.

Omission of Material Facts

FDA's letters contain the following allegations under an "Omission of Material Facts" subheading:

AstraZeneca untitled letter: A leave-behind sheet for Seroquel XR included a claim stating that the drug was proven effective in major depressive disorder as add-on therapy compared to an antidepressant alone. It further specified that: "Primary end point measured at Week 6 with significant improvement in MADRS Total Score as early as Week 1." This presentation failed to disclose that only the 300 mg dosage strength provided a significant improvement in MADRS Total Score at week 1, and it thus "misleadingly impl[ied]" that the 150 mg dosage strength also achieved this effect.

Promotion of an Investigational Product

FDA's letters contain the following allegations under a "Promotion of an Investigational Product" subheading:

OCBQ untitled letter to PharmAthene, Inc. re: SparVax (Recombinant Protective Antigen (rPA) Anthrax Vaccine) (June 11, 2010): A product fact sheet for SparVax contained claims about clinical trials involving the product and product dosage recommendations. Such statements constituted claims promoting either the efficacy or safety of an investigational product, in violation of the prohibition in 21 C.F.R. § 312.7(a) against "represent[ing] in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promot[ing] the drug."

Use of Outdated Product Labeling

FDA's letters contain the following allegations under a "Use of Outdated Product Labeling" subheading:

Novartis untitled letter – Exforge: A promotional brochure for Exforge was disseminated with an outdated version of the package insert (PI), in violation of 21 C.F.R. § 201.100(d). The PI submitted with the promotional piece on Form FDA-2253 was dated April 2007, but the listed dissemination date of the brochure was February 24, 2009. The most current version of the PI as of that date was the July 23, 2008 version, not the April 2007 version.

Failure to Submit

FDA's letters contain the following allegations under a "Failure to Submit" subheading:

Novartis untitled letter – Tasigna: The shared content available through the "Facebook widget" on the Tasigna product website was not submitted to FDA for consideration during the preapproval review period, as required by 21 C.F.R. § 314.550 for Subpart H drugs. Additionally, this content was not submitted to DDMAC under cover of Form FDA-2253 at the time of initial publication, as required by 21 C.F.R. § 314.81(b)(3)(i).

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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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