

E-ALERT | Food & Drug

July 6, 2010

SUMMARY OF FDA ADVERTISING AND PROMOTION ENFORCEMENT ACTIVITIES

MAY 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 May 2010, FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) posted the following five enforcement letters (one warning, four untitled) on its website:¹

- Warning Letter to Novartis Pharmaceuticals Corporation re: Gleevec® (imatinib mesylate) (Apr. 21, 2010)²
- Untitled Letter to Shire Development, Inc. re: PENTASA® (mesalamine) Controlled-Release Capsules (Apr. 27, 2010)
- Untitled Letter to Shire Development, Inc. re: LIALDA® (mesalamine) Delayed Release Tablets (Apr. 27, 2010)
- Untitled Letter to Genentech, Inc. re: Rituxan® (Rituximab) Injection for Intravenous Use (Apr. 29, 2010)
- Untitled Letter to Amgen, Inc. re: Vectibix® (panitumumab) Solution for Intravenous Infusion (May 13, 2010)

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

- Untitled Letter to Novartis Vaccines and Diagnostics, Inc. re: Menveo [Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM₁₉₇ Conjugate Vaccine] (May 7, 2010)

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

- Warning Letter to St. Jude Medical, Inc. re: the Epicor™ LP Cardiac Ablation System and the Epicor UltraCinch LP Ablation Device (Apr. 23, 2010)³

¹ Only enforcement letters posted to FDA's website in May 2010 are included herein. Letters issued in May but not posted to the website by May 31, 2010 will be summarized in our alerts for the months in which those letters are posted. As of the date of publication of this alert, the following additional letter, issued in May, has been posted on the DDMAC website: Untitled Letter to Eisai Corporation of North America, re: GLIADEL® Wafer (polifeprosan 20 with carmustine implant) (issued May 27, 2010, posted June 17, 2010).

² Dates referenced for the letters are issue dates.

The letters, taken together, make allegations under the following headings: Omission/Minimization of Risk Information; Promotion of Unapproved Use; Unsubstantiated Claims; Broadening of Indication; Overstatement of Efficacy; Omission of Material Facts; Misleading Comparative Claims; Misleading Product Claim Websites; and Failure to Submit. The letters conclude that the cited advertising/promotional issues render the subject products misbranded or adulterated.⁴

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.

Omission/Minimization of Risk Information

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

DDMAC Warning Letter to Novartis Pharmaceuticals Corporation re: Gleevec® (imatinib mesylate) (Apr. 21, 2010) ("Novartis Warning Letter"): Two websites sponsored by Novartis made "prominent claims of effectiveness" for Gleevec in gastrointestinal stromal tumors (GIST) and chronic myeloid leukemia (CML), but omitted material facts about the "considerable risks" associated with the drug. The websites presented data on the efficacy benefits associated with Gleevec, but included "no mention of the serious risks of Gleevec therapy" apart from a brief list of examples of supportive care strategies that can be used to address some of the common and mild side effects (emphasis added by DDMAC).

DDMAC Untitled Letter to Shire Development, Inc. re: LIALDA® (mesalamine) Delayed Release Tablets (Apr. 27, 2010) ("Shire Untitled Letter – Lialda"): An HCP-directed brochure for Lialda failed to include important risk information about the Precautions associated with the drug. Specifically, although the brochure presented some information about material Precautions on page 4, it failed to reveal that patients with pyloric stenosis may have prolonged gastric retention of Lialda, which could delay mesalamine release in the colon. The brochure also failed to reveal that symptoms of acute intolerance syndrome include cramping, acute abdominal pain and bloody diarrhea, and sometimes fever, headache, and rash. Furthermore, the brochure failed to convey that caution should be taken in prescribing this medication to patients with conditions that predispose them to the development of myocarditis or pericarditis. Moreover, the brochure omitted that reports of renal impairment, "including minimal change nephropathy and acute or chronic interstitial nephritis," have been associated with mesalamine medications and pro-drugs of mesalamine, and that it is recommended that all patients have an evaluation of renal function prior to initiation of therapy and periodically while on treatment (emphasis added by DDMAC).

DDMAC Untitled Letter to Genentech, Inc. re: Rituxan® (Rituximab) Injection for Intravenous Use (Apr. 29, 2010) ("Genentech Untitled Letter"): Although table top panels for Rituxan stated, "RITUXAN has also been associated with fatal hepatitis B reactivation with fulminant hepatitis, other serious viral infections, cardiovascular events, renal toxicity, and bowel obstruction and perforation," the panels

³ The caption "Warning Letter" does not actually appear at the top of this letter. However, FDA posted the letter on its warning letter website and St. Jude Medical has referred to it as a warning letter in securities filings.

⁴ Only the medical devices in the Untitled Letter to St. Jude Medical, Inc. re: the Epicor™ LP Cardiac Ablation System and the Epicor UltraCinch LP Ablation Device (Apr. 23, 2010) were found to be adulterated. The other products were found to be misbranded.

omitted material facts regarding related fatalities associated with the use of Rituxan. Furthermore, the table top panels failed to present risk information with a prominence and readability reasonably comparable to the presentation of efficacy information. Specifically, they prominently presented efficacy claims in bulleted format, with colorful, bolded words, colorful charts, plenty of white space, and large font. The risk information presented on the first two panels, however, was “relegated to the bottom of those panels” and presented in single-spaced block paragraph format in small, black font. Additionally, although the first two panels contained a disclosure of adverse reaction information, the most significant risk information associated with Rituxan—the boxed warning—did not appear until the third panel.

DDMAC Untitled Letter to Amgen, Inc. re: Vectibix® (panitumumab) Solution for Intravenous Injection (May 13, 2010) (“Amgen Untitled Letter”): Oral statements made by an Amgen sales representative minimized the risks associated with Vectibix by suggesting that the product has “less infusion reactions” than therapeutic options that are not exclusively human monoclonal antibodies. Vectibix’s package insert (PI) has a Boxed Warning regarding infusion reactions, and severe infusion reactions, including anaphylactic reactions, bronchospasm, and hypotension, occurred in approximately 1% of patients in clinical trials.

OCBQ Untitled Letter to Novartis Vaccines and Diagnostics, Inc. re: Menveo [Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM₁₉₇ Conjugate Vaccine] (May 7, 2010): An audio news release for Menveo failed to present risk information with a prominence reasonably comparable to the presentation of efficacy information. The audio news release presented efficacy claims for the drug in a slow and deliberate manner that was understandable in terms of pacing and articulation. The risk information was presented “in a fast and inarticulate manner” and at a pace that did not allow the audience to hear and process it, thus hindering comprehension of the risks presented. Additionally, FDA’s letter questions whether the risk information was included in digital versions of the audio news release. A heading on the hard copy of the audio news release stated, “free hard copy of the **60 second** audio news release available on CD or as an MP3.” (emphasis added by OCBQ). The efficacy claims lasted approximately 1 minute and 13 seconds, with the risk information following for an additional 46 seconds. If the audio news release with a total play time of 1:59 was being presented as a 60-second presentation, it is “very possible that the risk information [was] actually omitted in its entirety.”

Promotion of Unapproved Use

FDA’s letters contain several allegations under the “Promotion of Unapproved Use” heading. These include:

Novartis Warning Letter: The Novartis-sponsored website, www.gistalliance.com, misleadingly promoted a new intended use for the drug, Gleevec, for which safety and effectiveness have not been established, thereby causing the approved package insert (PI) to lack adequate directions for use. Specifically, the HCP-directed portion of the website contained numerous claims promoting the “neoadjuvant use of Gleevec **before** surgical resection of GIST tumors, a use for which the drug is not indicated.” (emphasis added by DDMAC). The website did not explicitly include the trade name “Gleevec,” but the footnoted references clearly indicated the established name of the drug (imatinib) used in the clinical studies and the text referred readers to the National Comprehensive Cancer Network (NCCN) Treatment Guidelines for GIST tumors, which exclusively recommend the use of imatinib for neoadjuvant GIST therapy. The consumer-directed portion of the website contained similar statements.

Amgen Untitled Letter: Oral statements made by an Amgen representative suggested that Vectibix can be used as a first-line agent when the drug is not approved for such use. Vectibix is “only

approved for use if a patient has disease progression **while on or following a FOLFOX or FOLFIRI regimen.** (emphasis added by DDMAC). It is not approved as a single agent in the first-line setting. Specifically, the sales representative's statement that Vectibix "is **also** for patients who have progressed" implied that Vectibix is intended for use both in patients who have progressed and as a first-line treatment (emphasis added by DDMAC). This, in combination with the representative's suggestion that liver issues and neuropathies are "not as much of an issue" with Vectibix compared to competitor products, FOLFOX or FOLFIRI, and that Vectibix is a "good alternative" to these therapies, misleadingly suggested that Vectibix can be used as a first-line treatment **instead of** a FOLFOX or FOLFIRI regimen to alleviate risk concerns (emphasis added by DDMAC).

CDRH Warning Letter to St. Jude Medical, Inc. re: the Epicor™ LP Cardiac Ablation System and the Epicor UltraCinch LP Ablation Device (Apr. 23, 2010): The website, www.sjmprofessional.com, made claims promoting the Epicor LP Cardiac Ablation System and the Epicor UltraCinch LP Ablation Device for the treatment of atrial fibrillation. The website referenced the "box lesion" and "Maze lesions," which are ablation lesions performed on cardiac tissue during cardiac surgery and specifically intended to disrupt abnormal electrical conduction to isolate the pulmonary veins in an attempt to terminate a patient's atrial fibrillation. These claims constitute the promotion of these medical devices prior to FDA approval of the device for commercial distribution, in violation of 21 C.F.R. § 812.7(a). Additionally, the claims represented that the Epicor UltraCinch LP Ablation Device is safe or effective for purposes for which it has not been approved, in violation of 21 C.F.R. § 812.7(d).

Unsubstantiated Claims

FDA's letters contain several allegations under the "Unsubstantiated Claims" heading. These include:

Novartis Warning Letter: Two websites sponsored by Novartis made numerous dosing-related claims related to Gleevec that were "wholly unsubstantiated, and may even put patients at increased risk for serious adverse events." The likelihood of developing an adverse reaction to Gleevec increases with higher doses. The two websites urged physicians to measure the plasma concentration of tyrosine kinase inhibitor in their patients' blood and use that information to individualize the drug's dosage or schedule, but they failed to reveal any of the serious or potentially dose-related side effects associated with Gleevec. The totality of the presentations on the websites suggested that a lack of response in patients may be due to low plasma levels of Gleevec, and that the dose of Gleevec should be modified (i.e., increased) in the event that plasma concentrations of the drug are found to be "suboptimal." FDA is not aware of substantial evidence or substantial clinical experience to support a correlation between patient outcomes and plasma levels of imatinib. The package insert (PI) for Gleevec "provides very specific dosage recommendations for Gleevec in CML and GIST, with guidelines for monitoring adverse events and specific instructions for **dose reduction or discontinuation** in the event of serious adverse events." (emphasis added by DDMAC). The PI does not contain provisions for plasma level monitoring of Gleevec in patients or increasing the dose of Gleevec based on this information. Furthermore, the fact that these "misleading dosing claims" were presented without any discussion of serious or potentially dose-related side effects, such as neutropenia or thrombocytopenia, is "grossly misleading and greatly minimizes the potential risk to patients of increasing the dose." The websites heavily promoted the "CML and GIST Alliance Blood Level Testing Program," which encourages physicians to test their patients for "suboptimal" plasma levels of imatinib. The associated website dedicated to this testing program made "numerous unsubstantiated claims" about the use of blood tests to optimize outcomes specifically in patients with GIST or CML who are taking imatinib mesylate.

DDMAC Untitled Letter to Shire Development, Inc. re: PENTASA® (mesalamine) Controlled-Release Capsules (Apr. 27, 2010) (“Shire Untitled Letter – Pentasa”): A professional core leave behind for Pentasa made claims implying the superiority of the drug’s delivery system. Specifically, the claims and presentations implied that, as a result of its delivery system (release in the duodenum and release independent of pH), Pentasa offers a clinical advantage over other available treatment options. FDA is not aware of substantial evidence or substantial clinical experience to support this assertion. Additionally, the piece included claims implying that Pentasa significantly improves patients’ quality of life, when this has not been demonstrated by substantial evidence or substantial clinical experience. The study cited as a reference was inadequate because the instruments used to measure “quality of life” in the study included patient responses to single-item questions relating to seven general parameters. A single-item question is not able to provide a complete understanding of a treatment’s effect on a general concept such as “outdoor activities.” Also, the study required patients to recall their average experiences over an eight-week period, and the accuracy/validity of such recall is unknown. Furthermore, the suggestion conveyed by the piece that Pentasa significantly improves patients’ overall quality of life based on these seven parameters is misleading, as other important domains covered under “quality of life,” such as emotional functioning and non-health related aspects of life (e.g., financial stability) were not measured.

Shire Untitled Letter – Lialda: A brochure for Lialda contained a comparative bar graph that showed Lialda doses as numerically superior to Asacol and to placebo for the percentage of patients who achieve “Complete Remission at week 8.” The totality of the presentation misleadingly implied that Lialda is more effective than Asacol. FDA is not aware of “**any** adequate and well-controlled, head-to-head clinical trials comparing these two products.” (emphasis added by DDMAC). The study cited as a reference did not include a pre-specified efficacy analysis for this drug comparison. The exploratory analysis included in the brochure was retrospective and post hoc to the study’s original design, and did not show a statistically significant difference between the treatment effect of Lialda and Asacol. Although the brochure included limiting statements such as, “The study was not designed as a comparative head-to-head trial of Lialda versus Asacol,” these did not mitigate the misleading overall implication that Lialda is better than Asacol. Additionally, the brochure included a graphic representation of Lialda’s Multi Matrix System Technology (MMX), in conjunction with claims suggesting that this delivery system offers a therapeutic advantage over other available treatment options. This has not been demonstrated by substantial evidence or substantial clinical experience. Finally, the brochure included the claim that “**Biopsies from the sigmoid and rectum suggest Lialda with MMX Technology delivered mesalamine throughout the colon.**” The claim was presented in conjunction with graphic images of the colon, showing the time-lapse delivery of Lialda. The totality of the presentation misleadingly suggested that the delayed release technology has been shown to have a clinically relevant effect, based on biopsy data, on “the extent or exposure of the drug on the colon.” The biopsy data from the reference cited to support this presentation did “**not** confirm or deny the extent of delivery of Lialda in the colon or the exposure of the entire colon to the drug product during [the period of time depicted in the time-lapse imagery].” (emphasis added by DDMAC). Therefore, the claim that biopsy data support the delivery of mesalamine throughout the colon is not supported by substantial evidence.

Genentech Untitled Letter: Table top panels for Rituxan misleadingly overstated the efficacy of the product in improving progression-free survival (PFS) and providing benefits across all patient subgroups for the follicular Non-Hodgkin’s Lymphoma (NHL) indication. These claims were not supported by substantial evidence or substantial clinical experience. The references cited in support of the claim contained statistical deficiencies, such as an inadequate statistical analysis plan, failure to specify whether findings were based on independent blinded review, and reliance on exploratory subgroup analyses. Additionally, the table top panels included claims and presentations that overstated the efficacy of Rituxan for the diffuse large B-cell, CD20-positive NHL (DLBCL) indication by suggesting that patients can expect an increase in overall survival beyond the two-year and five-

year overall survival data presented in the package insert (PI). The references cited in support of these claims did not constitute substantial evidence or substantial clinical experience because of statistical deficiencies, such as the fact that the original statistical analysis plan did not provide for statistically valid analyses at seven years of follow-up and the fact that the abstract failed to describe the p-value for its analysis.

Broadening of Indication

FDA's letters contain several allegations under the "Broadening of Indication" heading. These include:

Shire Untitled Letter – Lialda: A brochure for Lialda included the claim, "Nearly 700,000 patients are living with ulcerative colitis (UC)." This claim was misleading in the context of the overall piece because it implied that Lialda is appropriate therapy for all 700,000 patients who may have varying degrees of severity of UC. Lialda is indicated only for "the induction of remission in patients with **active, mild to moderate ulcerative colitis.**" (emphasis added by DDMAC). Although the indication for Lialda was presented on page four of the brochure, this did not mitigate the misleading implication that Lialda is approved to treat a broader patient population.

Shire Untitled Letter – Pentasa: An HCP-directed core leave behind included claims and presentations that focused on the release of Pentasa in the small intestine. The totality of these claims and presentations implied that Pentasa has a therapeutic effect in the small intestine. Pentasa is indicated only for the induction or remission and for the treatment of patients with mildly to moderately active ulcerative colitis. The small intestine is not relevant to this condition, as the large intestine is the site of disease. Other conditions, such as Crohn's disease, do involve the small intestine, but Pentasa is not approved to treat such conditions. The suggestion that Pentasa has a therapeutic effect in the small intestine therefore misleadingly broadened the approved indication of the drug by implying that it is effective in the treatment of conditions affecting the small intestine. Although the piece included the indication for Pentasa in small print on pages 2 and 3, this did not correct the overall misleading impression conveyed by the piece that Pentasa is effective in treating conditions involving the small intestine.

Overstatement of Efficacy

FDA's letters contain the following allegations under the "Overstatement of Efficacy" heading:

Shire Untitled Letter – Lialda: A brochure for Lialda presented numerous claims and presentations that misleadingly overstated the efficacy of the drug. For example, the brochure included multiple claims that implied the induction of "complete remission." The clinical trials published in the articles cited in the brochure as claim support, however, "do **not** provide support for claims of complete remission or total absence of the disease." (emphasis added by DDMAC). Complete remission was not a primary endpoint in these clinical trials. Rather, the trials studied simply "remission," which was defined as an improvement in the Ulcerative Colitis Disease Activity Index (UC-DAI) with specific scores required for some of the four subscore components. The studies did not assess whether patients were completely free of symptoms of ulcerative colitis. In addition, the brochure included claims implying that treatment with Lialda results in mucosal healing, when such as not been demonstrated by substantial evidence or substantial clinical experience. The brochure referenced a post hoc analysis of study data as claim support, but "mucosal healing" was not a pre-specified primary or secondary endpoint in the study. Also, the definition of mucosal healing included in the brochure was not defined in the study protocols submitted to FDA, nor is it discussed in the package insert (PI) or reference article.

Omission of Material Facts

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

Amgen Untitled Letter: An oral statement by an Amgen sales representative, "The PI [package insert] has been updated with *KRAS* information..." was true on its face, but along with the rest of the statement, "...since it is a predictor of response," was misleading because it omitted material information about the impact of *KRAS* mutations on the decision to use Vectibix. Specifically, the PI states: "Retrospective subset analyses of metastatic colorectal cancer trials have not shown a treatment benefit for Vectibix in patients whose tumors had *KRAS* mutations in codon 12 or 13. Use of Vectibix is not recommended for the treatment of colorectal cancer with these mutations." Through the misleading omission of this material information, the oral statement misleadingly suggested that *KRAS* mutations are "a positive predictor of clinical response to Vectibix, when in fact the information added to the PI warns that the use of the drug is **not** recommended in patients with certain *KRAS* mutations due to a lack of treatment benefit." (emphasis added by DDMAC).

Misleading Comparative Claims

FDA's letters contain the following allegations under the "Misleading Comparative Claims" heading:

Amgen Untitled Letter: Oral statements by an Amgen sales representative misleadingly suggested that Vectibix is safer than other products, when this has not been demonstrated by substantial evidence or substantial clinical experience. The suggestion that Vectibix may have "less infusion reactions" because it is a human monoclonal antibody misleadingly suggested that Vectibix is safer than products that are not exclusively human monoclonal antibodies. FDA is not aware of any support for such an implication. Additionally, the Amgen sales representative suggested that liver issues and neuropathies are "not as much of an issue" with Vectibix versus FOLFOX or FOLFIRI. FDA is not aware of any adequate and well-controlled head-to-head trials that substantiate this claim.

Misleading Product Claim Websites

FDA's letters contain the following allegations under the "Misleading Product Claim Websites" heading:

Novartis Warning Letter: Two Novartis-sponsored websites, www.gjstalliance.com and www.cmlalliance.com, effectively promoted Gleevec for the treatment of GIST tumors and CML, respectively, even though the websites did not specifically mention the name of the drug. Specifically, the websites: (i) discussed the use of tyrosine kinase inhibitors (TKIs) for the first-line treatment of GIST and CML, often in conjunction with the Novartis name, when Gleevec is the only TKI indicated for first-line treatment of chronic phase CML and first-line treatment of GIST, as well as the only TKI made by Novartis indicated for both GIST and CML; (ii) contained numerous references to the NCCN Clinical Practice Guidelines in Oncology, which recommend the use of Gleevec exclusively for the first-line treatment of CML and GIST; (iii) were perceptually similar to the Novartis Gleevec product website in terms of color schemes (distinctive orange), design layouts, and other presentation elements; (iv) were clearly marked with the Novartis Oncology name and logo; (v) included a direct link to the Novartis Gleevec product website and a link to a Novartis-sponsored program website discussing Gleevec as a treatment for CML; (vi) were registered to Novartis AG; and (vii) presented data from imatinib clinical studies and provided the corresponding literature references, which include the drug name in the listed publication titles. At least one of the publications recounted pivotal clinical trial data submitted to FDA in support of the approval of

Gleevec in the treatment of adjuvant GIST. Based on this combination of factors, FDA found the websites to be product specific promotions for Gleevec.

Failure to Submit

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

Novartis Warning Letter: Two Novartis-sponsored websites were 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, copies of the websites were not submitted to DDMAC under cover of Form FDA-2253 at the time of their 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:

Ellen Flannery	202.662.5484	eflannery@cov.com
Richard Kingham	202.662.5268	rkingham@cov.com
Peter Safir	202.662.5162	psafir@cov.com
Michael Labson	202.662.5220	mlabson@cov.com
Erika Lietzan	202.662.5165	elietzan@cov.com
Scott Cunningham	202.662.5275	scunningham@cov.com
Scott Danzis	202.662.5209	sdanzis@cov.com
Elizabeth Jungman	202.662.5327	ejungman@cov.com
Stefanie Doeblner	202.662.5271	sdoebler@cov.com
Alissa Jijon	202.662.5341	ajijon@cov.com

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