Warning Label Spin: Further Reflections on What the FDA is Up Against

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By Kalman Applbaum

When modern businesspersons are faced with an obstacle, they do not ask themselves, “How will I overcome this challenge?” Instead they say, “How can I turn this challenge into an opportunity?” This is at heart a marketing philosophy, since it implies not the protection of existing territory, but expansion of it. Marketing is the strategic growth arm of every corporation.

There are large examples and small. In the 1990s, Eli Lilly & Co. faced the challenge of finding a replacement blockbuster for Prozac, which was going off patent. A third of the company’s revenues came from the single drug. The opportunity came from the fact that many people on Prozac weren’t getting better anyway. This spelled “opportunity” for Lilly (and the other atypical antipsychotic marketers) to promote the idea that the reason people weren’t improving on SSRIs was that they had been misdiagnosed with unipolar depression, when in reality they were bipolar!

In Lilly’s detailed Zyprexa marketing plan of 1997 (made available to us at great risk by Dr. David Egilman), the drug reps were instructed: “7 in 10 people with bipolar disorder are initially misdiagnosed… [the] most common misdiagnosis is unipolar depression.” The solution was for Lilly to broaden the definition of bipolar disorder through “condition branding,” then redefine their antipsychotic drug Zyprexa as a “mood stabilizer” (itself a marketing and not a scientific designation) and prophylactic for bipolar disorder. Presto! Prozac’s challenges became Zyprexa’s opportunities. (Required reading: David Healy’s ‘Mania: A Short History of Bipolar Disorder’)

That’s an elaborate example of how a successful expansion strategy was built on the same foundation and using salvaged components of an earlier marketing edifice. A less noticeable form of the application of marketing’s challenge/opportunity orientation is when companies must respond to a direct threat to a brand’s reputation. This is the work of spin. Karl Rove and George Bush (our first MBA president) showed us how to spin weaknesses into strengths. They learned their trade from marketing.

In this post, I illustrate this principle at work in how Merck & Co. answered

the threat of the FDA's demand for a revised warning label on Vioxx in 2001. This was the moment in the brand's history when Merck could no longer suppress the clinical trial data showing that patients on Vioxx were having four times as many heart attacks and twice the rate of other thrombotic events as people taking over-the-counter naproxen. One can only imagine the Merck marketers facing the label changes recommended by the FDA, and asking themselves: How can we turn this threat into an opportunity?

The subject should be of interest to us because of the ongoing debate about pre-emption. Pre-emption refers to when a drug company claims that it cannot be sued for damages caused by its product because the FDA had approved it. Merck successfully used this defense for Vioxx. An important precedent was set last week in the decision against Wyeth in the case of the musician from Vermont who lost her arm as a result of insufficient warning on the drug label (http://www.nytimes.com/2009/03/05/opinion/05thu2.html?ref=todayspaper).

The Vioxx story is familiar to most of us. Vioxx was the reigning heavyweight champion of ethical violations in the drug industry through the early to mid-2000s. It is also one of the most telling examples of FDA failure to convert available safety data to policy. Although the FDA has been given a couple of more teeth since 2001—largely as a result of the Vioxx debacle—it nevertheless remains important to understand how warning labels are put together. What follows is a sampling of how the warning label for Vioxx was reworded in October 2001, after the news about the dangers of the drug finally broke.

As early as 1997, the company was gerrymandering trial subject populations and suppressing data to conceal the drug's tendency to cause heart attacks. Ironically, the damaging truth escaped into the public during an aftermarket study designed to expand use of Vioxx by demonstrating that the drug caused fewer gastrointestinal problems than naproxen. This study was called Vioxx Gastrointestinal Outcomes Research, or VIGOR.

The full story of how serious the findings were and how defiantly Merck went on marketing the drug in the face of these findings is told in many places. The short of it is that even while the inevitable end to Vioxx was in sight, Merck's marketing war machine was in full tilt. Merck continued to report to the public and to doctors that the results of VIGOR were all positive. On 22 May 2001, Merck issued a press release entitled "Merck Confirms Favorable Cardiovascular Safety Profile of Vioxx." On 16 June 2001 they issued a European press release entitled "Vioxx Similar to Placebo and Three Widely Prescribed NSAID's Regarding Cardiovascular

Events." The company maintained its annual half billion dollar budget for promotions to doctors, and another $160 million for direct to consumer advertising. Meanwhile, behind the scenes, Merck prepared to lock horns with the FDA regarding the results of the VIGOR study.

On 15 October 2001, the FDA insisted upon amendments to the Vioxx label. The negotiation over wording in the 39-page document was released during trials filed against Merck (http://dida.library.ucsf.edu/pdf/yjb00a10). Throughout the revision, what is clear is not only Merck's attempt to muffle the alarm bell the FDA was trying to ring, but to further the campaign to protect and sanitize the word environment around the brand name, and to market trust in the company's scientific reputation as expressed through the clinical trial process.

FDA Text 15 October 2001	Merck Revision	Merck explanatory notes in margin
Special Studies Safety Studies The following special studies were conducted to evaluate the comparative safety of VIOXX. [p.7]	Special Studies	Merck proposes to delete new heading 'Safety Studies' Merck proposes to delete sentence since VIGOR was not a general safety study.
No safety information is available regarding the use of VIOXX in patients with advanced kidney disease. Therefore treatment with VIOXX is not recommended for these patients. In post-marketing experience [illegible] renal failure, the need for dialysis and fatalities have been reported in patients with normal as well as impaired renal function. These events may occur after short term therapy. [p. 26]	Treatment with VIOXX is not recommended in patients with advanced renal disease. [p.26]	
VIOXX 50 mg should not be given more than once a day. Chronic use of VIOXX 50 mg daily is not recommended. Use of VIOXX in advanced renal disease is not recommended. Severe renal failure including fatalities and need for dialysis has been reported in post marketing in association with VIOXX. [p. 7] In addition to the CV/thrombotic events, VIOXX 50 mg had a higher incidence of discontinuations due to HTN [hypertension] and edema-related events as well as congestive heart failure events as compared to naproxen. [p. 15]	Use of VIOXX in advanced renal disease is not recommended. [p. 7]	Merck proposes to delete. Hypertension- and edema-related events are adequately covered by NSAID class labeling in this circular. This section is not the appropriate place to discuss CHF [congestive heart failure]. It is addressed in the ADVERSE REACTIONS section. In addition, these adverse experiences were not associated with cardiovascular thrombotic events in the VIGOR study
Study 102/903 (ADVANTAGE study) There were nine cardiac events (5 MI, one unstable angina and 3 sudden deaths) in the VIOXX 25 mg group, compared to 3 cardioserious events (2 unstable angina, one MI) in the naproxen group. [p. 16]	The ADVANTAGE Study… There were nine patients with serious cardiovascular thrombotic events (8 cardiac and 1 cerebrovascular) in the VIOXX 25 mg group, compared to 12 patients with serious cardiovascular thrombotic events (3 cardiac, 7 cerebrovascular and 2 peripheral vascular) in the naproxen group. [p. 16]	Merck proposes revisions as shown. It is more appropriate to include comparison of all cardiovascular thrombotic events as the Agency requested for the VIGOR study.
Vioxx should be used with caution in patients at risk of developing cardiovascular thrombotic events such as those with a history of myocardial infarction and angina and in patients pre-existent hypertension and congestive heart failure. The risk of developing myocardial infarction in the VIGOR study was five fold higher in patients treated with Vioxx 50 mg (0.5%) as compared to patients treated with naproxen (0.1%). (See Special Studies, VIGOR). The finding was consistent in a smaller and shorter study using Vioxx 25 mg but allowed the use of low dose ASA (See Special Studies, ADVANTAGE). Prospective, well-powered, long-term studies required to compare the incidence of serious events in patients taking Vioxx versus NSAID comparators other than naproxen has not been performed. Because of its lack of platelet effect, Vioxx is not a substitute for aspirin for cardiovascular prophylaxis. The impact of Vioxx on the cardiovascular prophylactic benefit ofASA is unknown. (See Special Studies, Platelets: Precautions. Drug Interactions, Aspirin). [p. 25]	The risk of developing a serious cardiovascular thrombotic event in the VIGOR study was significantly different in patients treated with Vioxx 50 mg once daily (twice the highest dose recommended for chronic use in OA [osteoarthritis]) as compared to patients treated with naproxen 500 mg twice daily (common therapeutic dose). This was largely due to the significant difference in the incidents of myocardial infarction between patients taking Vioxx 50 mg once daily (0.5%) and naproxen 5 mg twice daily (0.1%). (See Clinical Studies, Special Studies, VIGOR.) In all other controlled clinical trials, the incidence of all serious cardiovascular thrombotic events including myocardial infarction was similar between Vioxx and placebo and between Vioxx and the non-selective NSAID comparators studied (ibuprofen, diclofenac and nabumetone). The basis for the difference in cardiovascular event rates with Vioxx versus naproxen observed in VIGOR, and the lack of such a difference between Vioxx and placebo or other NSAID	

	comparators in other studies, is not understood. Most active, well-powered, long-term studies specifically designed to compare the incidents of serious CV events in patients taking Vioxx versus NSAID comparators or placebo have not been performed. Because of its lack of platelet effects, Vioxx is not a substitute for aspirin for cardiovascular prophylaxis. While low dose aspirin may be used concomitantly with Vioxx, such concomitant use may result in increased rate of GI ulceration or other complications compared with Vioxx alone. (See Clinical Studies, Special Studies, Use with Aspirin and Platelets. Precautions, Drug Interactions. Aspirin). [p. 28]	
Patients should promptly report signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, unexplained weight gain, edema, chest pain or shortness of breath to their physicians. [p. 30]	Patients should promptly report signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, unexplained weight gain, or edema to their physicians. [p. 30]	
Geriatric use: of the patients who received Vioxx in osteoarthritis clinical trials, 1455 were 65 years of age or older (this included 460 who were 75 years or older). While no substantial differences in effectiveness were observed between these subjects and younger subjects, as with NSAIDs, elderly patients (over 75 years) or those with a prior history of ulcers or UGI bleeding taking Vioxx have a higher risk for developing a GI bleed then patients with neither of these risk factors (see GRI warnings section). Most spontaneous post-marketing works of fatal GRI events have been in the elderly. Most post marketing reports of acute renal failure have also been in the elderly. [p. 34]	Geriatric use: of the patients who received Vioxx in osteoarthritis clinical trials, 1455 were 65 years of age or older (this included 460 who were 75 years or older). No substantial difference is in safety and effectiveness were observed between these subjects and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment in the elderly is not necessary; however, therapy with Vioxx should be initiated at the lowest recommended dose. In one of these studies (a six week, double-blind, randomized clinical trial), Vioxx 12.5 or 25 mg once daily was administered to 174 osteoarthritis patients > 80 years of age. The safety profile in this elderly population was similar to that of younger patients treated with Vioxx. [p. 34]	There are no new data regarding these issues and they are adressed in the WARNINGS, GI Effects and PRECAUTIONS . Renal Effects (as per NSAID class labeling).

Beyond the apparent damage control exercised through the removal of harsh-sounding consequences of taking Vioxx, or even of symptoms that might frighten a patient into quitting the drug (chest pain and shortness of breath), the Merck version reveals subtle alterations in emphasis. Merck's version protects the brand's identity as an autonomous, efficacious medicine. "Treatment with VIOXX is not recommended in patients with advanced renal disease," accentuates Vioxx's identity as a treatment, and not a threat to treatment. Moreover, Vioxx come out feeling like an entity unto itself, a sphere into which outsiders such as doctors, patients and regulators enter on Vioxx's terms. The FDA, by contrast, places control in the hands of an outside expert, who is there to decide whether treatment with Vioxx is appropriate and safe. There is no floating brand autonomy in the declarative litany of the FDA's version: "VIOXX 50 mg should not be given more than once a day. Chronic use of VIOXX 50 mg daily is not recommended. Use of VIOXX in advanced renal disease is not recommended."

Merck saves its declarative sentences for when it wants to shut down thoughts that might lead to doubt: "No substantial difference in safety and effectiveness were observed between these subjects and younger subjects." A reader is discouraged from reading to the end of that sentence, much less to the end of the paragraph. All the information you need is found in the words "no substantial difference."

Elsewhere in the document Merck says, "Cardiovascular Safety in VIGOR: In the VIGOR study there was a significant difference in the incidence of serious cardiovascular thrombotic events between patients

treated with VIOXX 50mg once daily (twice the highest dose recommended for chronic use in OA) and patients treated with naproxen 500mg twice daily (common therapeutic dose)…(See Table 3)" [p. 12].

A hurried reader (especially one who has just been shown the infamous cardiovascular card: http://content.nejm.org/cgi/content/full/352/25/2576) might take this to mean that if you take 40 times the amount of Vioxx than is normally prescribed, bad things might happen. Since that's what naproxen takers are doing, Vioxx must be much safer than naproxen.

Brand-mindedness is evident also in the acronyms give to the clinical studies: The VIGOR, APPROVe (Adenomatous Polyp Prevention On Vioxx), and ADVANTAGE (Assessment of Differences between Vioxx and Naproxen To Ascertain Gastrointestinal Tolerability and Effectiveness) studies were, like their names, marketing and not scientific endeavors. In the Vioxx label of 2001, Merck rewrote the FDA's "Study 102/903 (ADVANTAGE study)" to "The ADVANTAGE Study," to remove the harsh undifferentiated numerical rubric, which would be unflattering for a branded identity.

The foregoing is no substitute for a proper discourse analysis of the labels over time. The organization and length of the labels, the strategic use of Greek versus Germanic rooted words and vice versa, intentional obfuscation through long or passively worded sentences, and other syntactical tactics can form the basis of a proper reading of the role of label language in the marketing of drugs. One can be certain that professional wordsmiths are employed by the company to get the language right. When billions of dollars are at stake, nothing is left to chance. By contrast, the poor FDA has to rely on the layman skills of busy, hapless, unsuspecting bureaucrats.

We ordinarily think of advertising strictly in relation to products—Buy Lux because it smells good! But the work of marketing is to protect the entire biography of a company's products, from the laboratory to the doctor's office to the courts. Its work includes management of image risks associated with brand and company. Merck's eventual decision to take Vioxx off the market can be traced to the marketing motivation of doing so before the drug's bad publicity climbed up the feed tube and poisoned the brand of the mother ship.

Further reading:

Healy, David. Mania: A Short History of Bipolar Disorder. Johns Hopkins University Press (2008).

Hill KP, Ross JS, Egilman DS, Krumholz HM. The ADVANTAGE seeding

trial: a review of internal documents. Ann Intern Med (2008) 149:251-258. Available at: http://www.annals.org/cgi/content/full/149/4/251

Henry A. Waxman. The Lessons of Vioxx — Drug Safety and Sales. NEJM. (2005) 352:2576-2578. Available at: http://content.nejm.org/cgi/content/full/352/25/2576

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