

How Vioxx exposed conflicts of interest at the Food and Drug Administration and

The New England Journal of Medicine

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ABSTRACT

This paper analyzes the 12-month period between August 2000-August 2001 during which Merck-&-Co launched an aggressive marketing campaign for its new anti-inflammatory drug, Vioxx (rofecoxib), published its seminal VIGOR study in the *New England Journal of Medicine*, and applied to FDA to extend the clinical indications of Vioxx to include rheumatoid arthritis. This paper examines the VIGOR study as it was published, analyzes the deliberations of the *ad hoc* Arthritis Advisory Committee convened by the FDA in February 2001 and, based on internal e-mails within Merck, exposes what Merck scientists knew about the increased risk of heart attacks attributable to Vioxx. We demonstrate the following: that Merck's VIGOR study contained critical defects that should have been obvious to a careful editor, that the study did not merit publication, that the *ad hoc* Arthritis Advisory Committee sidestepped its responsibility to acknowledge the increased cardiovascular risk of the drug, and that Merck knew of these increased risks while actively promoting the drug. Had the outcomes been different at the *Journal* or the *ad hoc* Arthritis Advisory Committee, Vioxx would not have been approved, further systematic studies on cardiovascular risk would have been mandated, and thousands of lives might have been spared the risks of fatal and non-fatal heart attacks clearly known but deliberately obscured, misrepresented, and dismissed by each of the participants.

INTRODUCTION

In August 2000, American figure skating star Dorothy Hamill appeared on *Larry King Live* to discuss, among other topics, her battle with rheumatoid arthritis and its effect on her career and personal life. The skater described a new drug she was taking, called Vioxx. As Ms. Hamill said, before taking Vioxx she “felt old ... depressed ... [and] tired all the time ... and my doctor prescribed Vioxx for me, and it’s as I’ve been given a new life, it’s just been amazing.”¹ Although it appeared to be a casual conversation, Hamill’s testimony on *Larry King Live* was, in fact, a tightly scripted, well-rehearsed recitation produced and written by Merck-&-Co, the maker of Vioxx.² The audience had no idea that Hamill’s presence on *Larry King Live* was orchestrated by Merck. Missing from that presentation was any mention of the measurable risk of fatal heart attacks associated with Vioxx.

Vioxx (rofecoxib), approved by FDA for treatment of osteoarthritis and introduced to the market on 24 May 1999, was destined to be a blockbuster drug, an entity that would earn Merck-&-Co and its shareholders billions of dollars. The prevalence of arthritis was increasing among an aging population, and existing NSAIDs carried potential for fatal gastrointestinal bleeding. Vioxx, it was thought, could effectively address the effects of inflammation without causing gastrointestinal problems. Describing Vioxx as a miracle drug, Merck advertised “Everyday Victories” won by ordinary people over debilitating pain. Millions of prescriptions were written for the drug, which earned Merck more than \$3 billion annually.³ As such, it was a surprise when, five and half years after its launch, Merck signaled on 30 September 2004 that it

¹ CNN Transcript - Larry King Live: What’s the Best Way to Combat Arthritis? - August 29, 2000, , <http://transcripts.cnn.com/TRANSCRIPTS/0008/29/lkl.00.html> (last visited Jul 7, 2020).

² THOMAS J. NESI, POISON PILLS : THE UNTOLD STORY OF THE VIOXX DRUG SCANDAL (Thomas Dunne Books 1st ed) 20-26 (2008)

³ Ibid., p. 11. P. Juni, et al., *Risk of cardiovascular events and rofecoxib: cumulative meta-analysis*, 364 LANCET 2021-2029 (2004).

was voluntarily withdrawing Vioxx from the marketplace, citing an increased risk of myocardial infarctions in patients taking the drug.⁴ This was the largest drug withdrawal in history, made by one of the oldest and most established drug manufacturers in the world.⁵

Since its origins in the seventeenth century, Merck had prided itself on its safety record, never having to recall a drug. What went wrong? Why was Vioxx withdrawn after five-plus years on the market? Its safety profile was published in *The New England Journal of Medicine*, one of the most prestigious and oldest medical journals in the world and, if adverse reactions to Vioxx were so prevalent, why was it not flagged when it underwent editorial review in the Journal? Did Merck know of this cardiovascular risk, and if so when?⁶

Cardiovascular disease is a leading cause of death in the United States, so recognizing an event as common as heart attack and asking whether it is attributable to a single drug intervention is less obvious than recognizing a rare event. Perhaps the more appropriate question, considering that rheumatoid arthritis, an inflammatory disease typically accompanied by cardiovascular disease, is whether Merck should have expected the possibility of myocardial infarctions and been prepared to monitor their incidence.

This paper addresses these questions through a focus on the so-called VIGOR trial, short for Vioxx Gastrointestinal Outcomes Research, published in the *New England Journal of*

⁴ Associated Press (September 30, 2004) Merck Announces Withdrawal of Vioxx Painkiller, NEW YORK TIMES, <https://www.nytimes.com/2004/09/30/business/merck-announces-withdrawal-of-vioxx-painkiller.html#:~:text=Pharmaceutical%20giant%20Merck%20%26%20Co.%20is,of%20heart%20attack%20and%20stroke>.

⁵ F. HAWTHORNE, *THE MERCK JUGGERNAUT: THE INSIDE STORY OF A PHARMACEUTICAL GIANT* (John Wiley & Sons) 19-49 (2003)

⁶ Also known as “coxibs.”

Medicine in 23 November 2000.^{7, 8}

There exists today an extensive cache of data with which to chronicle the development of Vioxx, its path to approval, and its eventual withdrawal by Merck. In addition to the published VIGOR study, the complete data set on which the VIGOR studies were based is available through the FDA, allowing comparison of published and unpublished data. Also available are the contents of internal e-mails among Merck employees as disclosed in personal injury litigation related to Vioxx. These e-mails allow us to assess what company officials knew prior to publishing the VIGOR study, how they deliberated prior to presenting their data before FDA advisory panels, and to compare how these deliberations affected their marketing strategy during the time Vioxx was on the market. In short, we have a window on the forthrightness of one of the world's oldest, most prominent, and respected pharmaceutical manufacturers and the basis of their decisions—marketing or science—in releasing a potential blockbuster drug. In a similar vein, we can gauge what the FDA understood of the Merck data and the actions it took with respect to ensuring the public's safety. Vioxx drew attention by virtue of its publication in the *New England Journal of Medicine*. Through examination of the VIGOR trial and the eventual fallout after Vioxx was withdrawn, we are in a position to evaluate the integrity of editorial review at the *New England Journal of Medicine*.

⁷ C. Bombardier, et al., *Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis*. VIGOR Study Group, 343 N ENGL J MED. 1520-1528 (2000).

⁸ It will also be of interest to keep in mind, but discussed here only obliquely, the CLASS study, Celecoxib Long-term Arthritis Safety Study, published only two months earlier in the *Journal of the American Medical Association* by a group from Pfizer concerning their COX-2 inhibitor, Celebrex (celecoxib). F. E. Silverstein, et al., *Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study*, 284 JAMA 1247-1255 (2000).

THE VIGOR TRIAL

The object of the VIGOR trial was not to determine the efficacy of Vioxx, something that had been evaluated two years earlier in a Phase III study conducted by Merck⁹, but to assess its gastrointestinal safety, which would separate the COX-2 inhibitors such as Vioxx from the traditional NSAIDs such as naproxen. The VIGOR trial served also as the basis for a supplemental New Drug Application (sNDA) through which Merck requested a label change to delete any reference to adverse gastrointestinal side-effects, thereby improving marketing strategies.

The VIGOR study was a double-blind, randomized, clinical trial in which 8,076 patients with rheumatoid arthritis were monitored with the aim of comparing the gastrointestinal safety of rofecoxib (50 mg per day), twice the dose approved by FDA for treatment of osteoarthritis, to naproxen (500 mg, two-times per day).¹⁰ Merck submitted this sNDA for the two-fold purpose of extending indications for Vioxx to include rheumatoid arthritis and to remove from the label the routine cautionary statements about stomach bleeds that can occur with NSAIDs.

The adverse gastrointestinal effects of Vioxx were measured according to two separate endpoints. The first endpoint focused on three features: *upper gastrointestinal bleeding*, as identified through endoscopy, an upper gastrointestinal barium x-ray, or the presence of blood in stools; *upper gastrointestinal perforation*, defined as an opening in the stomach or duodenal wall requiring surgical or laparoscopic repair; and *gastric outlet obstruction*, defined as a tight edematous pylorus, or inability to insert an endoscope tip as based on the clinical opinions of

⁹ Vioxx was approved for treatment of acute pain, dysmenorrhea, and osteoarthritis on May 20, 1999 (NDA 21-042). Of note here is that in her promotion of Vioxx, Dorothy Hamill suffered from rheumatoid arthritis, not osteoarthritis. As such, she was prescribed Vioxx off-label.

¹⁰ C. Bombardier, et al., *VIGOR Study Group*.

attending physicians after endoscopic examination. This triad—bleeding, perforation, and obstruction—is described as a *complicated* gastrointestinal adverse event.

This definition of complicated gastrointestinal adverse events is separate from the second endpoint, which also has three features: *symptomatic* gastroduodenal ulcers, reduced hemoglobin count, and the presence of orthostatic hypotension. Symptomatic ulcers, while more common than upper gastrointestinal complications, are far less serious.¹¹ Yet these and other symptoms (dyspepsia, abdominal pain, epigastric discomfort, nausea, and heartburn) are typically responsible for patients electing to discontinue treatment. It is important to note that the presence symptomatic signs does not correlate with development of complicated gastrointestinal symptoms.

The VIGOR study came to two broad conclusions concerning gastrointestinal safety. First, the long-term use of rofecoxib, at twice the maximal dose approved by FDA, led to “significantly lower rates of clinically important gastrointestinal events and complicated upper gastrointestinal events” than did twice-daily treatment with standard doses of the nonselective COX inhibitor naproxen.¹² Second, the “incidence of complicated upper gastrointestinal bleeding and bleeding from beyond the duodenum was significantly lower among patients who received rofecoxib.”¹³

Treatment with rofecoxib was associated with an approximately two-fold reduction in upper gastrointestinal effects (relative risk= 0.5), upper gastrointestinal complications (relative risk= 0.4), and upper (relative risk= 0.4) and lower (relative risk= 0.5) gastrointestinal bleeding.

¹¹ Maria Lourdes Villalba & Lawrence Goldfind, *NDA 21-042, s007, VIOXX Gastrointestinal Safety* Food and Drug Administration (2001), *available at* https://web.archive.org/web/20180127041342/https://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_03_med.doc.

¹² C. Bombardier, et al., *VIGOR Study Group*.

¹³ *Ibid*.

That is, the beneficial gastrointestinal response to rofecoxib relative to naproxen, as represented in the Kaplan-Meier plot provided on the FDA website,¹⁴ demonstrates that the event response for rofecoxib with respect to the primary outcome—bleeding, gastrointestinal perforations, or obstruction—was reduced relative to that for naproxen. Based on the analyses of risk and the time-to-event data, FDA reviewers agreed that Merck scientists had “successfully demonstrated a risk reduction of clinically relevant gastrointestinal adverse events for [the population taking] rofecoxib compared to [that taking] naproxen.”¹⁵

$$\text{Equation 1.} \quad \text{Relative Risk} = \frac{\text{Vioxx}}{\text{Naproxen}} = 0.5$$

Of serious concern is that systemic chronic inflammation predisposes patients with rheumatoid arthritis to an increased risk of cardiovascular disease. Such accompanying cardiovascular co-morbidity raises questions of Vioxx safety in patients with rheumatoid arthritis,¹⁶ and would be expected to be front and center in safety studies on patients with rheumatoid arthritis, yet that was not the case.

Buried in the text of the VIGOR study was the sole statement concerning cardiovascular effects: “Myocardial infarctions were less common in the naproxen group than in the rofecoxib group (0.1 percent vs. 0.4 percent) ... relative risk, 0.2” (Equation 2). The structure of this statement is peculiar in that while the authors reported the risk of adverse gastrointestinal effects of rofecoxib in reference to those elicited by naproxen, which is the usual way of

¹⁴ Qian Li, *Statistical Reviewer Briefing Document for the Advisory Committee*, Food and Drug Administration (2001), available at https://web.archive.org/web/20180127041347/https://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_04_stats.pdf.

¹⁵ Maria Lourdes Villalba & Lawrence Goldfind, *NDA 21-042, s007, VIOXX Gastrointestinal Safety*.

¹⁶ C. S. Crowson, et al., *Rheumatoid arthritis and cardiovascular disease*, 166 AM HEART J (2013). J. M. Hootman & C. G. Helmick, *Projections of US prevalence of arthritis and associated activity limitations*, 54 ARTHRITIS RHEUM (2006).

addressing risk relative to a comparator, they inverted the analysis and reported the risk of the comparator relative to that of the study drug, i.e., *risk of myocardial infarction with naproxen relative to rofecoxib*. There is no explanation for expressing risk in this manner, but it does obscure the significance of the finding. Little additional information or analysis of the cardiovascular risk was presented until the penultimate paragraph, wherein the authors conjectured that the decreased risk associated with naproxen was attributable to “the theory” that naproxen exerted an otherwise unknown “coronary protective effect” and rofecoxib, as a COX-2 selective inhibitor, lacked this effect.¹⁷

$$\text{Equation 2.} \quad \text{Relative Risk} = \frac{\text{Naproxen}}{\text{Vioxx}} = 0.2$$

Restating the conclusion of the VIGOR trial, the risk to a patient of a myocardial infarction is five-fold greater in treatment with rofecoxib than in treatment with naproxen. The data Merck scientists submitted to FDA for the sNDA but chose not to present in the published VIGOR study reveals a more alarming safety concern. According to the Kaplan-Meier plot reporting the incidence of myocardial infarctions on the y-axis as an explicit function of time on the x-axis, Figure 1,¹⁸ the risk of developing a cardiovascular event during treatment with Vioxx was 2.37 times greater than during treatment with naproxen ($p=0.0016$; CI, 1.39, 4.06), and that the incidence of myocardial infarction increased with time in a nonlinear manner, a greater incidence appearing after only 3 to 4 months of treatment, and an even sharper deviation beginning at 8 months of treatment. That is to say, adverse cardiovascular effects are observed after a relatively short course of treatment with Vioxx.

¹⁷ Bombardier, et al., *VIGOR Study Group*.

¹⁸ Qian Li, *Statistical Reviewer Briefing Document for the Advisory Committee*.

Three points are noteworthy. First, and most striking in this supplemental New Drug Application (sNDA), the rates of myocardial infarction in the Vioxx group exceeded the naproxen group by nearly four-fold, which is to say that cardiovascular safety endpoints favored naproxen. The VIGOR authors explain the excess cardiovascular thrombotic events as being due to the “potent anti-platelet aggregation effect of naproxen” rather than to the possible pro-thrombotic effects of rofecoxib.¹⁹ As Dr. S. L. Targum, a consultant-scientist at the FDA, notes, “This hypothesis is not supported by any prospective placebo-controlled trials with naproxen”.²⁰ Regardless of the underlying mechanism, and with respect to cardiovascular safety, “the results ... are favorable for naproxen,” prompting the wry conclusion that “naproxen would be the preferred drug compared to rofecoxib [Vioxx] (underlining in original)”.²¹

Second, the VIGOR authors chose *not* to include the Kaplan-Meier plot (Figure 1) in which the cumulative incidence of cardiovascular thrombotic events for Vioxx diverged from those for naproxen at 3 to 4 months and even more so after 8 months of treatment.

Third, aspirin use was not permitted in this study. Patients requiring low-dose aspirin for reasons of cardiac health were excluded, as were patients with a host of cardiovascular risk factors (angina, congestive heart failure, myocardial infarction, coronary artery bypass surgery, stroke, and uncontrolled hypertension). Thus, the VIGOR trial demonstrated significantly increased cardiovascular events, even while it excluded those most at risk, patients with rheumatoid arthritis and cardiovascular disease who were most likely to use the drug. Thus, the

¹⁹ Maria Lourdes Villalba & Lawrence Goldfind, *NDA 21-042, s007, VIOXX Gastrointestinal Safety*..

²⁰ Shari L. Targum, *Cardiovascular Safety Review of Rofecoxib*, Food and Drug Administration (2001), available at https://web.archive.org/web/20180127041412/https://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_06_cardio.doc.

²¹ Ibid.

use of Vioxx within a less homogeneous population might lead to significantly greater incidence of myocardial infarction and stroke, a public health problem of unimaginable proportions.

With these three points in mind, the study of Vioxx at a single dose (50 mg per day), when the effective dose is not known, and against a single comparator (naproxen, 500 mg, 2 times per day), raises concerns of so-called dose-creep, where the patient increases the dose of the analgesic on the mistaken notion that the drug is safe, thereby unmasking a potential safety issue. With this as background we can now examine the manuscript as reviewed by the *New England Journal of Medicine*.

NEW ENGLAND JOURNAL OF MEDICINE

What can be said with regard to the care exercised in the Journal's review of the VIGOR trial and the Journal's scientific evaluation prior to eventual publication of the results? First, the inverted expression of cardiovascular risk attributable to Vioxx relative to naproxen (Equation 2) strikes the reader as peculiar, in that it obfuscates the risk of cardiovascular effects of Vioxx. Second, placing a minimal discussion of cardiovascular risks within the middle of the text without clarification – providing no more detail and with wording no different from that in the Abstract – clearly diminishes the significance of the risks. Third, and finally, the idea of a “theory” in which naproxen provides a coronary protective effect was offered with no corroborating citations. The style and structure of the narrative text, the presentation of the data, and the offering of theories without supporting documentation, should have been obvious to a careful reviewer or editor. These oddities in all cases supported – or at least did not adversely impact – the interests of Merck & Co.

Expression of concern, 2005. Having published the VIGOR trial in November 2000, the *Journal* eventually published in December 2005 an “expression of concern,” at a time when litigation was moving from depositions into the trial phase.²²

The “expression of concern,” as suggested by e-mails at the editorial offices of the *Journal*, was less about apprehension for the public’s health than potential criticism against the *Journal* for oversights in its review of the VIGOR trial.²³ The *Journal* feared that its reviewers and editors had not critically questioned the diffuse statements about the presence of cardiovascular events, or the coronary protective effect attributed to naproxen, particularly since the VIGOR authors had offered no evidence in support of such an idea. Moreover, the *Journal* editor, Gregory Curfman, disclosed after publication of VIGOR that the journal sold 929,000 reprints of the article, mostly to Merck-&Co, earning the journal between \$697,000 and \$836,000, suggesting that the *Journal* reaped additional financial profit.²⁴

In their expression of concern, the editors asserted that they “recently obtained information regarding inaccuracies in the data” in the published VIGOR trial. They drew attention to a belated finding of three additional myocardial infarctions in the Vioxx group that had been unaccounted for in the 2000 submission to the *Journal*, and cardiac events that Merck-&Co was aware of but failed to include in the published data.²⁵ The editors had become aware of these three additional myocardial infarctions in 2001 but took refuge in the fact that at least two of the Merck authors were aware of them. Accordingly, the editors explain, “certain calculations and conclusions in the article [are] incorrect.”²⁶ In particular, the editors reported the

²² G. D. Curfman, et al., “*Expression of concern: Bombardier et al., “Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis,” N Engl J Med 2000;343:1520-8*” 353 N ENGL J MED 2813-2814 (2005).

²³ David Armstrong, *How the New England Journal missed warning signs on Vioxx.*, THE WALL STREET JOURNAL, May 15, 2006, at A1.

²⁴ *Ibid.*

²⁵ G. D. Curfman, et al., *Expression of concern: Bombardier et al.*

²⁶ *Ibid.*

relative risk of 4.25 without the three additional myocardial infarctions, and a relative risk of 5.00 when those three are included, concluding that the published article resulted in an “understatement of the difference in risk of myocardial infarction between the rofecoxib [Vioxx] and naproxen groups.” In either calculation, risk of cardiovascular events indicates an increased danger of myocardial infarctions, something the editors did not criticize during their review of the VIGOR manuscript. The editors added parenthetically, without irony, that while Merck-&-Co presented their data in the published VIGOR study “as a reduction in the risk with naproxen,” in their expression of concern the editors interpreted the data as presenting an “increase in the risk with rofecoxib.”²⁷

How convincing are the editors’ arguments? First, they ignore obvious deficiencies in their own review of the manuscript, instead relying on the rationalization that “at least two of the [Merck] authors” knew of the three additional cases of myocardial infarction and could have included this information in the original submission.

Second, the editors criticize the VIGOR authors for including in the 2000 manuscript only “summary percentages, not actual numbers of myocardial infarctions,” a risible criticism in that the VIGOR authors said they were basing their calculations only on summary percentages, which would have been obvious in a careful review of the study. The *Journal* had the responsibility to offer such criticism during review of the manuscript, and to request additional data and clarification prior to publication.

²⁷ As far as the Merck-&-Co authors were concerned, the inclusion of 3 additional myocardial infarctions “[did] not suggest a difference in the conclusions” between the published data and the updated data. Yet, in contrast to their contentions in the VIGOR paper, the Merck authors acknowledged that the Vioxx-treated group demonstrated a significant risk of myocardial infarction. C. Bombardier, et al., *Response to expression of concern regarding VIGOR study*, 354 N ENGL J MED. 1196-1199 (2006).

Ad hoc ARTHRITIS ADVISORY COMMITTEE OF FEBRUARY 2001

FDA authority and its powers of enforcement are derived from the Federal Food, Drug, and Cosmetic Act of 1938, providing for enforcement against drugs that are adulterated or misbranded.²⁸ The legal concept of a drug, whether it is adulterated or misbranded, depends in large part on the representations by the drug manufacturer on the label and packaging, including drug contents, putative inert ingredients, indications, adverse effects, and directions for use. While the problems with Vioxx had nothing to do with adulteration and misbranding, they had much to do with how the drug was represented by Merck to physicians, patients, journal editors and the lay press.

Merck's principal interest in conducting the VIGOR study and in submitting the sNDA in 2001 was to determine the allowable wording on the Vioxx label. Another purpose for the sNDA was to expand the indications for use of Vioxx, to include not only osteoarthritis but rheumatoid arthritis as well.

The Arthritis Advisory Committee convened by the FDA, held in February 2001, took up the matter of changing the label, expanding drug indications, and assessing Vioxx safety, and was a linchpin in the lifeline of Vioxx. The meeting took place over two days, and discussed Celebrex (celecoxib) (7 February 2001) and Vioxx (rofecoxib) (8 February 2001).²⁹ In attendance were scientists from the FDA (both days), Pfizer (first day) and Merck (second day),

²⁸ Arthur N. Levine, *FDA enforcement: How it works*, in *A PRACTICAL GUIDE TO FOOD AND DRUG LAW AND REGULATION* (Kenneth R. Piña & Wayne L. Pines eds., 2008). Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §351 (2013). (Adulterated drugs and devices). Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §352 (2013). (Misbranded drugs and devices). Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§351b-e (2013).

²⁹ The transcript of the Arthritis Advisory Committee is archived in three files, available at the following URLs. Pages 1-100: https://wayback.archive-it.org/7993/20170404100859/https://www.fda.gov/ohrms/dockets/ac/01/transcripts/3677t2_01.pdf. Pages 101-200: https://wayback.archive-it.org/7993/20170404100901/https://www.fda.gov/ohrms/dockets/ac/01/transcripts/3677t2_02.pdf. Pages 201-241: https://wayback.archive-it.org/7993/20170404100914/https://www.fda.gov/ohrms/dockets/ac/01/transcripts/3677t2_03.pdf.

and 10 invited consultant-experts, including the Acting Chair, E. Nigel Harris, Dean of the Morehouse School of Medicine.³⁰ Before each day's meeting, the staff secretary read a statement concerning the "issue of conflict of interest with regard to this meeting," adding that "in accordance with 18 United States Code 208(b), full waivers have been granted to Drs. Frank Harrell, Steven Nissen, Ileana Pina, Michael Wolfe and Allan Sampson." The secretary went on to say that FDA wishes to "disclose for the record that Drs. Steven Nissen, Ileana Pina, H. James Williams and M. Michael Wolfe have interests which do not constitute a financial interest within the meaning of 18 United States Code 208(b)³¹, but which could *create the appearance of a conflict* (emphasis added)." To remove such an appearance, the agency granted a further waiver to Drs. Nissen, Pina, Williams and Wolfe because the "agency has determined, notwithstanding these interests, that the interest of the government in their participation outweighs the concern that the integrity of the agency's programs and operations may be questioned." We know from these waivers that the participation of the six individuals engendered a conflict of interest, but we are not privy to the nature of the conflict(s). Often, these involve ownership of stock in excess of a certain worth, or the promise of stock options, speaker fees, consultant fees, or grants to conduct research on a drug company's products.

Another consultant, Byron Cryor, described as a "guest expert," also had "reported interests which we believe should be made public to allow the participants to objectively evaluate his comments." In 1997, Dr. Cryor had received a research grant from Merck to

³⁰ The other consultant experts were Janet Elashoff, PhD; David Wofsy, MD; Steven Nissen, MD; Ileana Pina, MD; M. Michael Wolfe, MD; Allan R. Sampson, MD; Frank E. Harrell, Jr., PhD; and Byron Cryor, MD. In addition, standing members of the advisory committee were Leigh F. Callahan, MD and James H. Williams, MD.

³¹ This statute, 18 U. S. Code § 208 (b), part of the criminal code, allows that penalties will not be exacted against an individual appointed to serve on an advisory committee if he "makes full disclosure of the financial interest" (b)(1) and if the official making the appointment "certifies in writing that the need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved" (b)(3).

conduct a small clinical study on rofecoxib, he had been (it is not clear if he was at the time of the meeting) a paid consultant for work on celecoxib (Celebrex) and rofecoxib (Vioxx), and he had received speaking fees on behalf of a number of drug manufacturers including G.D. Searle, Pfizer and Merck.

Of the 10 invited reviewers, seven had unspecified interests in products from the companies they were about to evaluate, although the nature and degree of the interests were not specified.³² Of significance, as Harris and Berenson noted in the New York Times, those individuals with financial ties to Merck & Co voted to approve Vioxx.³³ The conflicts of interest in this case were significant because the Committee was asked to evaluate not the drug efficacy, which had been evaluated three years earlier, but to determine the drug's safety, requiring an evaluation not just of benefit but of risk, leaving a large margin for subjective bias.

Noteworthy, too, is the advisory committee comprised experts on arthritis (Elashoff and Wofsy), cardiovascular and renal drugs (Nissen and Pina), gastrointestinal drugs (Wolfe), endocrine and metabolic drugs (Sampson), and a biostatistician (Harrell). The committee lacked a physician or a pharmacologist with a holistic or generalist view of medicine and drug therapy, someone to cast a skeptical glance toward the optimistic claims of the drug manufacturer.

The principal questions concerned: whether to change the Vioxx label with respect to gastrointestinal and cardiovascular safety; what to advise physicians about supplementing Vioxx with low-dose aspirin; how to balance gastrointestinal benefit and cardiovascular risk; and whether further studies were warranted.

³² I indicate that seven individuals—Harrell, Nissen, Pina, Wolfe, Sampson, Williams, Cryor—were identified as having conflicts of interest, but am unable to identify the eighth individual mentioned by Harris and Berenson (2005). *Infra* note 33.

³³ Gardiner Harris & Alex Berenson, *10 Voters on Panel Backing Pain Pills Had Industry Ties*, THE NEW YORK TIMES, February 25, 2005. <https://www.nytimes.com/2005/02/25/politics/10-voters-on-panel-backing-pain-pills-had-industry-ties.html>.

As for gastrointestinal safety, there was uniform agreement that Vioxx was safer on the stomach than traditional NSAIDs. With respect to cardiovascular safety, Alise Reicin, a Merck scientist, described the increased incidence of cardiovascular events in the Vioxx-treated group relative to naproxen, claiming that the “risk of sustaining a cardiovascular event on rofecoxib is similar to placebo and to NSAIDs” lacking antiplatelet activity.³⁴ Merck had not previously acknowledged such a result. The Committee ignored the statement and continued its deliberations. Dr. Steven Nissen, Chief of Cardiovascular Medicine at the Cleveland Clinic noted that there was an unequivocal increase in “hard endpoints” of myocardial infarction, cardiovascular death, and stroke. The question, he asked, was whether the differences observed in these hard endpoints reflected a “very low rate in the naproxen group or a very high rate of events in the rofecoxib group.”³⁵ Nissen softened this dichotomy by positing that the naproxen data suggested “at least in part” a protective effect of naproxen, and then proffered data in what was described as a recent journal article (not disclosed),³⁶ describing rates of myocardial infarction among people taking aspirin. This additional data was independent of the review and was not available for prior examination by the other members of the committee. There is also the manner of *how* Nissen presented that data. The rates of myocardial infarction among aspirin users were, according to Nissen, comparable in magnitude to the rates reported by Merck for naproxen, a comparison that was meant to stand as evidence in support of the “hypothesis of a protective effect for naproxen,”^{37, 38} suggesting an effect of naproxen similar to

³⁴ *Supra* note 30, at 56-69.

³⁵ See Arthritis Advisory Committee (2001) p. 152.

³⁶ Collaborative Group of the Primary Prevention Project, *Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice*, 357 LANCET (2001).

³⁷ Arthritis Advisory Committee (2001) p. 157

³⁸ This argument is quite surprising for a medical scientist; that two drugs produce similar effects does not imply that they do so through identical pharmacological mechanisms. Moreover, the data in Figure 1 show the rates of cardiovascular events for both rofecoxib and naproxen did, in fact, increase over the duration of the study. Thus, naproxen was not cardioprotective, but merely produced fewer adverse cardiovascular events compared with Vioxx.

the protective effects known for low-dose aspirin. The Acting Chair, Nigel Harris, cautioned the committee that the aspirin data “did not rise to the level of other data,” that was available to the advisory committee meeting.³⁹

Nissen then raised two questions for which there were no obvious answers. Did Vioxx cause an increased risk of myocardial infarction over placebo? There were no placebo controls, in spite of Reicin’s earlier comments, and this was something that over the ensuing years Merck would refuse to conduct, although the FDA requested such additional data.⁴⁰ Was it possible to “neutralize the [cardiovascular effects] ... with low dose aspirin?”⁴¹ While presenting these as open questions, neither Nissen nor the committee offered any guidance to FDA for mandating that additional studies be conducted. Indeed, Nissen found support for his questions in David Wofsy, a rheumatologist, who proclaimed to uniform agreement that “further studies are always warranted. It is hard to imagine any presentation to this committee that wouldn’t raise important questions” requiring further data. In point of fact, the question of a need for additional studies was raised by Dr. Harris as one of the questions that were part of the Committee’s mandate. Yet, generalizations of the sort raised by Dr. Wofsy diminished the significance of a requirement for further examination. Lost in this discussion was that Vioxx had been – and would be – promoted aggressively to an aging and increasingly larger segment of the population vulnerable to its cardiovascular risk.

What guidance could FDA provide to physicians? Nissen suggested that all “we can say

³⁹ Arthritis Advisory Committee (2001) p. 159.

⁴⁰ Contemporaneous with the VIGOR trial, Merck was sponsoring additional trials on the effect of Vioxx on colon polyps (APPROVe). The APPROVe study, published in 2005 after Vioxx was withdrawn, concluded in this placebo-controlled study, that among “patients with a history of colorectal adenomas the use of rofecoxib [Vioxx] was associated with an increased cardiovascular risk.” Prior to this they relied on the idea that the standard of care dictated that they not employ a placebo arm. It was this trial that demonstrated an unequivocal increase in the number of cardiovascular events in patients taking Vioxx. There was no confusion due to any so-called cardioprotective event of the comparator. Merck was forced to halt this trial when the cardiovascular risks could not be dismissed.

⁴¹ See Arthritis Advisory Committee (2001) p. 166

is that this population getting naproxen was associated with a lower cardiovascular event rate than [the group] getting rofecoxib.”⁴² Nissen proposed that in the absence of any cardioprotective effect of Vioxx, and COX-2 inhibitors as a class, “what we saw was [a] cardioprotective effect of naproxen,” a conclusion that conveniently elided the cardiotoxic effect of Vioxx. The advisory committee, Nissen concluded, could offer no guidance to physicians; it was a “matter of clinical judgement [No] guidance beyond that is possible based upon the data.”⁴³

The problem with Nissen’s comments is that he dismissed the seriousness of the cardiovascular effects and, surprisingly for a cardiologist, accepted the balance in favor of the gastrointestinal safety. Second, the committee members allowed themselves to be hamstrung by a seemingly surmountable technicality: the primary endpoint of the VIGOR study and the sNDA concerned gastrointestinal and not cardiovascular effects. To quote Wofsy, the committee discussion focused “on a question that was not the primary endpoint of the study So, we find ourselves ... talking about whether the label should talk about the cardioprotective effects of nonsteroidal anti-inflammatory drugs, and that was not the goal of any of the studies that we have seen,”⁴⁴ an opinion echoed by Dr. Cryor.⁴⁵ In that the purpose of the advisory committee was the evaluation of drug safety, these statements – that the committee was evaluating gastrointestinal safety and not cardiovascular safety – are incomprehensible.⁴⁶

The outcome of the Arthritis Advisory Committee in 2001 was to recommend a wording change on the Vioxx label that acknowledged cardiovascular risk as well as a reduced

⁴² Arthritis Advisory Committee (2001) p. 172

⁴³ Arthritis Advisory Committee (2001) p. 172-173

⁴⁴ Arthritis Advisory Committee (2001) p. 174

⁴⁵ Arthritis Advisory Committee (2001) p. 178-179

⁴⁶ Gurkupal Singh, appearing in 2004 before a Senate committee investigating the withdrawal of Vioxx, testified with regard to the gastrointestinal safety of the drug, “the tradeoff of 500% increase in heart attacks for a 50% reduction in stomach bleeds did not seem attractive,” a view he had expressed even before his senate testimony. See T.J. NESI, *Supra* note 2, 178-180.

gastrointestinal harm, a rather benign recommendation in that the advisory committee had available to it the full compilation of the Merck & Co data and the accompanying FDA analysis. But in attempting to institute the advisory committee recommendations, FDA met considerable resistance from Merck & Co, who, after haggling with FDA over the wording of the warning label for nearly two years, eventually achieved the label they desired, one in which the cardiovascular effects were subordinate to the gastrointestinal effects, and diminished into a lower position on the label.

After the Arthritis Advisory Committee meeting, August 2001. Six months after the meeting of the Arthritis Advisory committee, Nissen and his colleagues Debabrata Mukherjee and Eric Topol, published a quite different account of the cardiovascular toxicity of Vioxx in the 22/29 August 2001 issue of the *Journal of the American Medical Association*.⁴⁷ This account describes the authors search of the medical databases to “identify all published, English-language, randomized, double-blind trials of COX-2 inhibitors from January 1998 to February 2001.”⁴⁸ Not surprisingly the authors identified the CLASS and VIGOR trials that were the subject of the February meetings, and two other studies, Study 085 and Study 090,⁴⁹ part of the data that Merck submitted in support of its sNDA for Vioxx. In presenting their analysis, the authors included the precise data available to the *Ad hoc* Arthritis Advisory Committee and presented the Kaplan-Meier time-to-event plot (Figure 1), showing the increasing cardiovascular events that occur after 3 months and then further after 8 months of treatment. They observe that “the VIGOR trial demonstrated significantly increased risk of cardiovascular event rates with the use of rofecoxib [Vioxx] *although the study enrolled patients who did not require aspirin for*

⁴⁷ D. Mukherjee, et al., *Risk of cardiovascular events associated with selective COX-2 inhibitors*, 286 JAMA 954-959 (2001).

⁴⁸ Ibid. p. 955

⁴⁹ Study 085 and Study 090 concerned the efficacy and measures of safety of rofecoxib and another NSAID, nabumetone, versus placebo, in patients with knee-joint osteoarthritis.

protection from ischemic events (emphasis added).”⁵⁰ As at the Arthritis Advisory Committee in February, these results, they argue, can arise either from a “significant prothrombic [cardiotoxic] effect from rofecoxib or an antithrombic [protective] effect from naproxen, or conceivably both.” In addition, Mukherjee *et al* analyzed four aspirin trials in which it was reported that aspirin reduced all cardiovascular events by 15% and myocardial infarctions by 30%,⁵¹ numbers in line with the effects of naproxen reported by Merck-&-Co.

Mukherjee *et al* recommended that clinicians be cautious in considering prescriptions for Vioxx and other COX-2 inhibitors, advice not dissimilar to what was recommended at the Arthritis Advisory Committee. But, they go further than the Arthritis Advisory Committee in two marked respects. While noting that administration of COX-2 inhibitors resulted in an increased incidence of hypertension that can increase risk of adverse cardiovascular events, and that rheumatoid arthritis is accompanied by a higher risk of myocardial infarction, the authors noted a “prothrombic effect seen with rofecoxib”, one that “may potentially be dose dependent.” They concluded that the data “suggest a potential increase in cardiovascular event rates for presently available COX-2 inhibitors.” More significantly, they “believe that it is mandatory to conduct a trial specifically assessing cardiovascular risk and benefit of these agents.” In the absence of such studies, they “urge caution in prescribing these agents to patients at risk for cardiovascular morbidity.” All of which is to say that they clearly acknowledged the prothrombic effects of Vioxx and the increased risk of heart attack associated with the drug, and they recommended additional trials to address the cardiovascular risk associated with COX-2 inhibitors, none of which Dr. Nissen had recommended at the *ad hoc* Arthritis Advisory Committee just six months earlier.

⁵⁰ Mukherjee *et al.*, *Risk of cardiovascular events*

⁵¹ P. S. Sanmuganathan, *et al.*, *Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials*, 85 HEART (2001).

Indeed, these recommendations are a remarkable *tour de force*, and could have been made based on information available at the February 2001 meeting. Had Nissen made those recommendations as part of the responsibility of the *ad hoc* Arthritis Advisory Committee, it is possible that the Merck sNDA for Vioxx may not have been approved, and FDA would have been in a position to require more studies regarding cardiovascular safety, something the committee members seemingly ignored, and would have spared the public health of additional 3.5 years of the drug being aggressively marketed.

WHAT DID MERCK KNOW AND WHEN DID IT KNOW IT?

The VIGOR authors buried relevant cardiovascular endpoints in the middle of the paper within a brief narrative, and excluded a Kaplan-Meier time-to-event survival analysis (Figure 1) that demonstrated an increased risk of myocardial infarction in patients taking Vioxx relative to those taking naproxen. In presenting that data, the authors inverted the analytic expression (Equation 1B, above), a seemingly deliberate obscuring of the data. Moreover, the VIGOR authors chose to interpret their results supporting never-before-known myocardial benefits of naproxen as anti-thrombogenic. Finally, by electing to exclude patients with cardiovascular disease, (i.e., by excluding patients taking low-dose aspirin for its blood-thinning, anti-platelet activity) the VIGOR investigators excluded those most at risk for myocardial infarction.

In reiterating these practices, it is fair to ask if these were honest mistakes, unintentional misinterpretations of complex and large data sets, or the result of deliberate decisions in search of favorable conclusions. Were these practices the result of deceitful intentions? It is worth noting, too, that not a single consequence of these actions was injurious in the marketing of Vioxx or its FDA approval. In all cases, the published data favored the interest of the drug sponsor.

The question of whether these actions were innocent mistakes or deliberate actions goes to the heart of whether the published VIGOR trial represented an act of scientific misconduct. In law, fraud comprises multiple, difficult-to-prove but equal components: the *false representation* of fact; the *knowledge* that such representation was false; the *intent* to have another party rely on the false representation; and *damage* incurred as a result of another party having relied on the false representations.⁵²

Did Merck know about the increased myocardial risk associated with the use of Vioxx? Internal e-mails among Merck scientists and executives indicate they did. Before the VIGOR trial was even considered, as early as 1996, e-mails among unnamed Merck officials expressed concern about a “substantial chance [of] significantly higher rates” of myocardial infarctions among the group taking Vioxx.⁵³ In an e-mail of 25 February 1997, a Merck executive, Briggs Morrison, expressed the view that if Merck were to proscribe aspirin for patients taking Vioxx, they would “get more thrombotic events” which would, in effect, “kill [the] drug.”⁵⁴ In response, Alise Reicin suggested a way around the proscription of aspirin: to exclude high-risk patients who presented with existing cardiovascular disease, which “may decrease the CV event rate, so that a difference between the [Vioxx and naproxen] groups would not be evident.”⁵⁵

While Merck refused to publicly acknowledge its doubts about Vioxx, the VIGOR trial confirmed those doubts exactly as anticipated in e-mail correspondence. Ed Scolnick, president

⁵² M.C. LaFOLLETTE, *STEALING INTO PRINT: FRAUD, PLAGIARISM, AND MISCONDUCT IN SCIENTIFIC PUBLISHING* (University of California Press). 41-43; p. 223 (note 42.) (1992)

⁵³ The following discussion focuses on internal e-mails from Merck employees, but also benefits from reporting of A. Berenson, et al., *Despite warnings, drug giant took long path to Vioxx recall*, N Y TIMES WEB (2004), *infra* note 65; AW Mathews & B. Martinez, *E-mails suggest Merck knew Vioxx's dangers at early stage*(2004), available at <http://online.wsj.com/article/0,,SB109926864290160719,00.html>. and Nesi, *Poison Pills*, *Supra* note 2.

⁵⁴ Briggs Morrison to Thomas Simon, et al (February 25, 1997) Vioxx Litigation Documents. <https://www.industrydocuments.ucsf.edu/docs/qpww0217>. (page 2) “I know this has been discussed to death, but [in the] real world is everyone is on it, so why exclude [aspirin] AND without COX-1 inhibition [by aspirin] you will get more thrombotic events and kill the drug.”

⁵⁵ *Ibid.*, 2

of Merck Research Laboratories, in an e-mail dated 9 March 2000, acknowledged that the cardiovascular “events are clearly there” and, moreover, that their nature is “mechanism based as we worried it was.”⁵⁶ Mechanism-based—or class—effects are those for which adverse effects (myocardial infarction and stroke) arise through the precise biological pathway responsible for the beneficial effects (reduced gastrointestinal erosion). While Scolnick and his colleagues were aware of this problem, Merck continued to extol the safety of Vioxx in press releases such as one in which “Merck confirms favorable cardiovascular safety profile of Vioxx.”^{57, 58}

One canny piece of evidence of Merck’s knowledge of heart attack risk at the time the VIGOR trial was submitted for publication is found within the metadata stored in documents produced using Microsoft Word. Within the VIGOR manuscript submitted to the *New England Journal of Medicine*, were “track changes” acknowledging that “Merck had deleted references to heart attack victims before formally submitting the article to the journal.”⁵⁹

⁵⁶ Edward M. Scolnick (March 9, 2000) in Vioxx Litigation Documents, <https://www.industrydocuments.ucsf.edu/drug/docs/#id=fzgw0217>

⁵⁷ Indeed, the marketing of Vioxx continued at full throttle. As Nesi described it, marketing representatives were trained to play “Dodgeball Vioxx” in which they were to evade questions about any incidences of myocardial infarction, claiming that they had not heard such things. For a pointed description of Merck marketing practices see H. A. Waxman, *The Lessons of Vioxx — Drug Safety and Sales*, 352, *NEW ENGLAND JOURNAL OF MEDICINE*, 2576-2578 (.2005). See also H. A. Waxman, *The Marketing of Vioxx to Physicians*, CONGRESS OF THE UNITED STATES, May 5, 2005, available at https://www.industrydocuments.ucsf.edu/wp-content/uploads/2014/11/waxmanmemo_vioxx.pdf.

⁵⁸ Merck was concerned about the “mechanism-based” blood-clotting, or thrombogenic, problems associated with Vioxx as far back as 1999, two years prior to publication of VIGOR. E-mails detailed how, after reviewing the VIGOR data, Ed Scolnick discussed plans to patent a reformulation of Vioxx containing an additional (unspecified) drug that would reduce the tendency for platelets to clot, thereby preventing the thrombogenic mechanism that was undermining Vioxx. Theresa Agovino, *AP: Merck Tried to Alter Vioxx in 2000* (2005), available at <http://www.dailypress.com/health/sns-ap-vioxx-safety.0.4594516.story>. While Merck pursued talks with the patent department, they continued to promote the cardiovascular safety profile of Vioxx. See Alise Reicin, (November 28, 2002) “Cv study design” in VIOXX LITIGATION DOCUMENTS, <https://www.industrydocuments.ucsf.edu/docs/#id=msww0217>. She mentions that Scolnick expressed interest in “evaluating whether Naproxen is in fact a cardioprotective agent,” something they touted two years earlier in the VIGOR publication, and eighteen months earlier in their presentation before the *ad hoc* Arthritis Advisory Committee she described the cardioprotective effect as an indisputable property of naproxen. *Supra* note 29, 56-69.

⁵⁹ Symposium, *Ethics and Professionalism in the Digital Age - A Symposium of the Mercer Law Review*, 60 *MERCER LAW REVIEW*, 961 (2009).

It is worth asking what evidence Merck actually had in support of the protective effect of naproxen, and if Merck genuinely believed such an effect even existed. In an e-mail message dated 13 March 2000 to Ed Scolnick and Alan Nies, a clinical pharmacologist at Merck, Alise Reicin provided a research abstract for “the only study I could find which assessed the potential cardioprotective effect of an NSAID.”⁶⁰ The abstract, dated 1993, was not about naproxen but flurbiprofen, a chemical derivative of ibuprofen, an NSAID chemically different from naproxen. Later, on 31 January 2001, and prior to the *ad hoc* Arthritis Advisory Committee meeting, clearly upset with the data and the naproxen-based explanation, Scolnick sent an e-mail to Raymond Gilmartin, Merck CEO, and David Anstice, president of Human Health-The Americas, pointing out that

*“there is no way to prove that [the difference between Vioxx and naproxen] is due to the benefit of naproxen. IT IS IMPOSSIBLE TO PROVE THIS; IT IS IMPOSSIBLE TO KNOW THIS WITH CERTAINTY The FDA will NEVER allow it to be fully dismissed [caps in original]”.*⁶¹

But the FDA did allow it to be dismissed, eventually approving the application. Scolnick’s frustration is understandable in that, as Merck scientist Briggs Morrison remarked in his appraisal of the data analysis, Merck was “‘fitting the data to a hypothesis’ rather than letting the data generate hypotheses.”⁶² The exercise, he wrote, seemed “wishful thinking, not a critical interpretation of the data.”

⁶⁰ Alise Reicin “Additional Article Request” in VIOXX LITIGATION DOCUMENTS, <https://www.industrydocuments.ucsf.edu/docs/#id=xthw0217>

⁶¹ Edward M. Scolnick (January 31, 2001) in VIOXX LITIGATION DOCUMENTS, <https://www.industrydocuments.ucsf.edu/docs/#id=shhw0217>.

⁶² Briggs Morrison (August 17, 2001) in VIOXX LITIGATION DOCUMENTS, <https://www.industrydocuments.ucsf.edu/drug/docs/#id=lnhw0217>. Morrison in an e-mail thread described the data as “at best [an] hypothesis-generating level of information,” and that such data were pooled from multiple populations “to support a preconceived hypothesis rather than critically review the data to generate hypotheses.”

As early as 2000, Merck discussed conducting a study that directly assessed the cardiovascular safety of Vioxx; however, such a study, they feared, would send the “wrong signal about the company’s confidence in Vioxx.”⁶³ Merck felt that “at present,” [i.e., 2000] while they were in a heated competition with Pfizer’s Celebrex, there was no “compelling marketing need for such a study,” suggesting a coalescence of marketing and research.

To further demonstrate that Vioxx was not harmful to cardiovascular health, Merck produced a meta-analysis that appeared in *Circulation*, the flagship organ of the American Heart Association.⁶⁴ The stated intention of the study was to “determine whether there was an excess of CV thrombotic events in patients treated with rofecoxib” compared with other NSAIDs. The authors of this meta-analysis reported “no evidence for an excess of CV events for rofecoxib” relative to other NSAIDs and, moreover, further promoted the Merck theory that any differences between these agents reflect the “antiplatelet effects” of naproxen. This meta-analysis was submitted on 2 October 2001 and accepted for publication on 3 October 2001, a day later, raising questions about the quality and depth of review and the intentions of the journal. The publication listed 7 authors, the back five being Merck employees who participated in VIGOR. The first two authors, M. A. Konstam and M. R. Weir, were associated with academic institutions⁶⁵ and were described as the recipients of gift authorship.⁶⁶

⁶³ A. Berenson, et al., *Despite warnings, drug giant took long path to Vioxx recall*, N Y TIMES WEB (2004).

⁶⁴ M. A. Konstam, et al., *Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib*, 104 CIRCULATION 2280-2288 (2001).

⁶⁵ According to e-mails, Merck employee Rhoda Sperling, one of the authors on the paper, sent Drs. Konstam and Weir finished manuscripts and asked for their comments, an example of gift authorship. The draft sent to Drs. Konstam and Weir was virtually identical to that appearing in *Circulation*. Rhoda Sperling (July 12, 2001) “Plans for a Rofecoxib CV Meta-Analysis paper,” letters sent to Marvin A. Konstam and Matthew Weir. <https://www.industrydocuments.ucsf.edu/docs/ztww0217>. Dr. Konstam disagrees with claims that that his “role in the *Circulation* paper was insufficient for him to be described as an author.” Lisa Nainggolan, *Konstam Offers New Details on His Role in Vioxx Meta-Analysis* (8 May 2009), available at https://www.medscape.com/viewarticle/702606_print.

⁶⁶ Joseph S Ross et al., *Guest Authorship and Ghostwriting in Publications Related to Rofecoxib*, 299 J. AMER. MED. ASSOC 1800-1812 (2008)

IMPLICATIONS FOR PUBLIC SAFETY

The published VIGOR study, the deceit in marketing of Vioxx, and the carelessness in the editorial review of the VIGOR trial represent a betrayal of the public trust and an abdication of responsibility on the parts of Merck-&Co and the *New England Journal of Medicine*. Merck scientists knew early on that the drug posed a fatal risk to patients, turned a blind eye to unwelcome data, and promoted a theory for which they had neither evidence nor belief, while continuing to extol the safety of the drug.

This behavior cannot be solely attributable to individual research scientists, as it is clear that Merck's marketing division played an outsized role in promoting the drug. Not only did the marketing team applaud the Merck scientists for their efforts to "diffuse the CV risk issue for Vioxx,"⁶⁷ they conducted their own study, the ADVANTAGE trial, published in *Annals of Internal Medicine*, a peer-reviewed journal and the official organ of the American College of Physicians.^{68, 69} Unknown to the editors of the journal, ADVANTAGE was a *seeding trial*, "marketing in the guise of science," as the stunned editors later expressed it,⁷⁰ during which Merck recruited physicians to prescribe Vioxx under the false impression that they were participating in a randomized clinical trial.⁷¹ In internal communications, Merck's marketing team was aware that

⁶⁷ McGlynn, Margie in an e-mail to Alise Reicin. VIGOR Analyst Reports. 2000 May 25. Vioxx Litigation Documents. <https://www.industrydocuments.ucsf.edu/docs/xgfw0217>.

⁶⁸ ADVANTAGE is an acronym for *Assessment of Differences between Vioxx And Naproxen To Ascertain Gastrointestinal tolerability and Effectiveness*.

⁶⁹ Lisse JR, Perlman M, Johansson G, Shoemaker JR, Schechtman J, Skalky CS, et al. ADVANTAGE Study Group. Gastrointestinal tolerability and effectiveness of rofecoxib versus naproxen in the treatment of osteoarthritis: a randomized, controlled trial. 139 ANN INTERN MED. 539-46 (2003). [PMID: 14530224]

⁷⁰ Harold C. Sox & Drummond Rennie, *Seeding Trials: Just Say "No"*, 149 ANN INTERN MED 279-280 (2008).

⁷¹ Harold C. Sox & Drummond Rennie, *Seeding Trials: Just Say "No"*, 149 ANN INTERN MED 279-280 (2008). "Kevin P Hill et al., *The ADVANTAGE Seeding Trial: A Review of Internal Documents*, 149 ANN INTERN MED 251-258 (2008). The purported purpose of the ADVANTAGE study was testing of a research hypothesis concerning, for example, the efficacy, tolerability, and side effects of Vioxx. The real aim of recruiting the unsuspecting physicians was to change their prescribing habits and to convert them to advocating for the new drug.

the ADVANTAGE was not a scientific research study, and chose to hide that fact as implied in the observation: "IT MAY BE A SEEDING STUDY ... LET'S NOT CALL IT THAT" (caps in original).⁷² This note demonstrates a callous disregard for a patient's right to informed consent. Furthermore, in a critical analysis of the ADVANTAGE paper, Hill et al. (2008) underscored Merck's willingness to risk "patient injury for marketing purposes."⁷³

As for the NEJM, having offered no explanation of its lax editorial oversight, the editors were quick—in the face of litigation—to offer an "expression of concern" absolving themselves of responsibility, and placing blame on Merck scientists. Overall, this much is clear: Merck and the NEJM increased medical risk to the public and compromised the evidence-based practice of medicine.⁷⁴ Less clear is a path through which the FDA can protect the public from drug entities submitted by determined, well-financed pharmaceutical companies.⁷⁵

As a gatekeeper, the FDA defines what is allowable in the marketing of drugs it approves. However, the FDA shares one liability in common with medical journals: both are reliant on the good faith of drug companies to provide honest and complete information and to

⁷² <https://www.industrydocumentslibrary.ucsf.edu/drug/docs/tkgw0217>.

⁷³ Hill, et al., *The ADVANTAGE Seeding Trial*, *Supra* note 73 at 256.

⁷⁴ As a practical example of the impact misleading and false medical claims on evidence-based medicine, see JOHN ABRAMSON, *OVERDOSED AMERICA: THE BROKEN PROMISE OF AMERICAN MEDICINE* (HarperCollins, 2008). Chapter 3, "False and Misleading: The misrepresentation of Celebrex and Vioxx." Abramson describes his puzzlement upon receiving a letter sent by Pharmacia, the parent company of Pfizer, the manufacturer of Celebrex (celecoxib), and mandated by the FDA warning physicians about "false and misleading claims" made regarding the safety of Celebrex on the gastrointestinal tract, an increase in bleeding problems associated with its COX-2 inhibitor Celebrex. At the same time reading a review in the Drug Therapy section of the *New England Journal of Medicine*, "The Coxibs, Selective Inhibitors of Cyclooxygenase-2" by G. A FitzGerald and C. Patrono, Abramson noted that the authors claimed otherwise, that coxibs were safe on the gastrointestinal tract, that gastrointestinal bleeding was not a problem and, moreover, nor was there an increased incidence of cardiovascular toxicity. Abramson noted the authors were merely repeating "unsubstantiated claims" and they underplayed the cardiovascular safety of coxibs. As reported in the *Journal*, Fitzgerald reported grant support from Merck and he served as a consultant to Merck; Patrono received grant support from Merck and served as a consultant to Merck and Pharmacia.

⁷⁵ DANIEL P. CARPENTER, *REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA* (Princeton University Press) 665-672; 737 (2010). Carpenter describes Merck as "perhaps the single most trusted corporate name at the FDA in the late twentieth century" (p. 737) and that, having "killed" or abandoned drugs they thought problematic before launch, Merck had developed credibility for not submitting drugs in which they had little faith (p. 665-672).

be forthright in their representations. It falls to medical journals, as both public megaphone and medical authority, to uphold standards of medical practice. Yet, in two of the three cases mentioned here—*NEJM* and *Circulation*—the journals failed the public interest and exploited their trust. *Annals of Internal Medicine*, in contrast, was blindsided by Merck; the evidence indicates that they were victimized by Merck's submission of the ADVANTAGE seeding study.

Perhaps there is no infallible mechanism through which the FDA can protect the public in all cases from all possible drug interactions.⁷⁶ The FDA is destined to function in a business environment in which journals and pharmaceutical manufacturers, each in search of prestige and profit, find the allure of great success irresistible, surrendering to the Circe-like temptation of marketing the next blockbuster drug or publishing the next celebrated, much-talked-about study.^{77, 78}

The entire Vioxx chronicle was marked by misrepresentations and obfuscations that lead to the death and compromised cardiac health for thousands of patients.⁷⁹ The marketing activities of drug companies, the fallibility of journal editors, and the environment in which the FDA functions require a healthy skepticism in assessing optimistic claims of new drugs.

⁷⁶ Of interest is testimony by David J. Graham. Insider: FDA Won't Protect Public, , <https://www.cbsnews.com/news/insider-fda-wont-protect-public/> (last visited Jul 4, 2020). David J. Graham, *Testimony of David J. Graham before the United States Senate* (2004), <https://www.finance.senate.gov/imo/media/doc/111804dgtest.pdf>

⁷⁷ NEJM and the LANCET each published pertinent studies on drugs for combatting COVID-19. It became apparent that the data were not available to outside reviewers nor even to one of the authors. Both journals were quick to retract the papers. Ironically, the lead author, M. R. Mehra, was unable to vouch for the accuracy of the data presented in the retracted papers, an irony in that he is the senior editor at a medical journal, the *Journal of Heart and Lung Transplantation*.

⁷⁸ Allysia Finley, *Opinion / The Lancet's Politicized Science on Antimalarial Drugs*, WALL STREET JOURNAL, June 1, 2020, <https://www.wsj.com/articles/the-lancets-politicized-science-on-antimalarial-drugs-11591053222> (last visited Jul 8, 2020). Frank Gannon, *Opinion / Sullied*, 21, EMBO REPORTS, Aug 6, 2020. 21:e51371 <https://doi.org/10.15252/embr.202051371>.

⁷⁹ David J. Graham, et al., *Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclooxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study*. 365, LANCET, 475-481 (2005).

Perhaps the best advice in assessing claims made in the medical literature recalls a 13th century Chinese proverb: “Be well informed, but leave plenty of room for doubt.”

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FIGURE LEGEND

Figure 1. Kaplan-Meier (time-to-event) plot illustrating the cumulative incidence (%) of myocardial infarctions as an explicit function of time over a duration of 12 months in patients with rheumatoid arthritis as reported in the VIGOR study. This figure is taken from Qian Li (*supra* note 15, p 13). The downward (black) arrows denote times at 3- and 8-months duration of Vioxx (rofecoxib) treatment where the incidence of myocardial infarctions increases in a nonlinear manner. The upward (grey) arrow denotes the time of 5.5 months duration of naproxen treatment where the increase in myocardial infarctions is observed to increase.

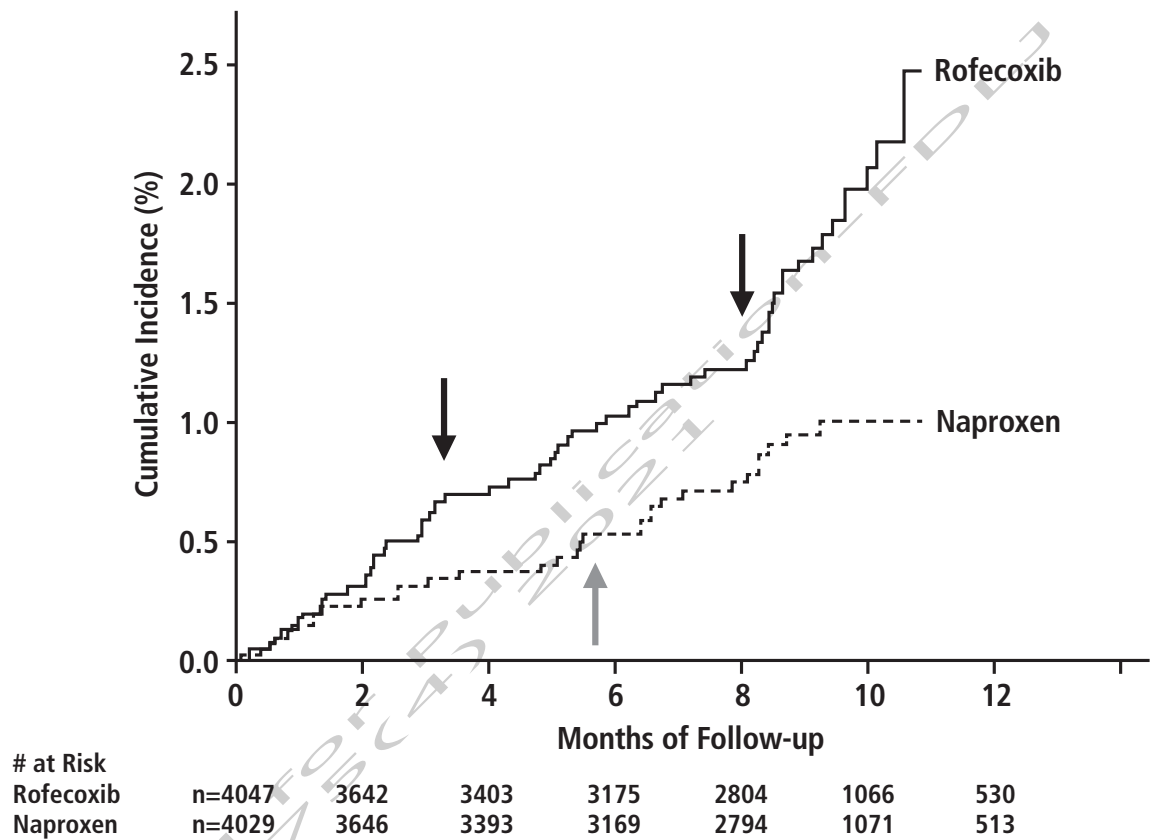
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