How Vioxx Exposed Conflicts of Interest at the Food and Drug Administration and The New England Journal of Medicine

HARVEY BERMAN[*]

ABSTRACT

This paper analyzes the twelve-month period between August 2000 and August 2001 during which Merck & Co. launched an aggressive marketing campaign for its new anti-inflammatory drug, Vioxx (rofecoxib), published its seminal VIGOR (Vioxx gastrointestinal outcomes research) study in *The New England Journal of Medicine* (NEJM), 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 FDA in February 2001, and, based on internal e-mails within Merck & Co., exposes what Merck & Co. scientists knew about the increased risk of heart attacks attributable to Vioxx. This paper demonstrates the following: 1) that Merck & Co.'s VIGOR study contained critical defects that should have been obvious to a careful editor; 2) that the study did not merit publication; 3) that the *ad hoc* Arthritis Advisory Committee sidestepped its responsibility to acknowledge the increased cardiovascular risk of the drug; and 4) that Merck & Co. knew of these increased risks while actively promoting the drug. Had the outcomes been different at the NEJM 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. . . . [A]nd my doctor prescribed Vioxx for me, and it's as

[*] PhD, MPH. Associate Professor, Department of Pharmacology and Toxicology at the Jacobs School of Medicine and Biomedical Sciences. The author thanks the following readers for their comments on different versions of this manuscript: Jess Alderman, MD, JD, Dennis Bertram, MD, William Scheider, PhD, and Stan Halvorsen, PhD; Nell Aronoff, MLS (Medicine) and Marcia Zubrow, MLS (Law) for assistance in searching different databases; Don Trainor for rendering the artwork in Figure 1; David M. Holmes, MD and Kim Griswold, MD for helpful resources on the practice of family medicine; and the Buffalo campus of the *Romanell Center for Clinical Ethics and the Philosophy of Medicine* for hosting preliminary presentations of this paper.

if 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 & Co. Missing from that presentation was any mention of the measurable risk of fatal heart attacks associated with Vioxx.

Vioxx (rofecoxib), approved by FDA for osteoarthritis treatment and introduced to the market on May 24, 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 (nonsteroidal anti-inflammatory drugs) carried potential for fatal gastrointestinal bleeding.[3] Vioxx, it was thought, could effectively address the effects of inflammation without causing gastrointestinal problems. Describing Vioxx as a miracle drug, Merck & Co. advertised "Everyday Victories" won by ordinary people over debilitating pain.[4] Millions of prescriptions were written for the drug, which earned Merck & Co. more than $2.5 billion annually.[5] As such, it was a surprise when, five and half years after its launch, Merck & Co. signaled on September 30, 2004 that it was voluntarily withdrawing Vioxx from the marketplace, citing an increased risk of myocardial infarctions in patients taking the drug.[6] This worldwide recall of Vioxx[7] was described as "the largest drug withdrawal in history,"[8] made by one of the oldest and most established drug manufacturers in the world.[9]

Since its origins in the seventeenth century, Merck & Co. had prided itself on its safety record, never having to recall a drug in the United States.[10] What went wrong?

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[1] *Larry King Live: What's the Best Way to Combat Arthritis?* (CNN television broadcast Aug. 29, 2000), http://transcripts.cnn.com/TRANSCRIPTS/0008/29/lkl.00.html [https://perma.cc/5LN9-SY96].

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

[3] Ángel Lanas, Patricia Carrera-Lasfuentes, Yolanda Arguedas, Santiago García, Luis Bujanda, Xavier Calvet, Julio Ponce, Ángeles Perez-Aísa, Manuel Castro, Maria Muñoz, Carlos Sostres, Luis A García-Rodríguez, *Risk of Upper and Lower Gastrointestinal Bleeding in Patients Taking Nonsteroidal Anti-Inflammatory Drugs, Antiplatelet Agents, or Anticoagulants*, 13 CLIN. GASTROENTEROL HEPATOL 209–19 (2015).

[4] NESI, *supra* note 2, at 20. "Everyday Victories" was a television commercial for Vioxx featuring Dorothy Hamill.

[5] *Id.* at 11; Peter Juni, Linda Nartey, Stephan Reichenbach, Rebekka Sterchi, Paul A. Dieppe & Matthias Egger, *Risk of Cardiovascular Events and Rofecoxib: Cumulative Meta-Analysis*, 364 LANCET 2021–2029 (2004). *See also* Eric J. Topol, *Failing the Public Health: Rofecoxib, Merck and the FDA*, 351 NEW ENG. J. MED., 1707–09 (2004).

[6] Associated Press, *Merck Announces Withdrawal of Vioxx Painkiller*, N.Y. TIMES, Sept. 30, 2004, https://www.nytimes.com/2004/09/30/business/merck-announces-withdrawal-of-vioxx-painkiller.htm. [https://perma.cc/TU5X-KNUM].

[7] Press Release, Merck, Merck Announces Voluntary Worldwide Withdrawal of VIOXX® (Sept. 30, 2004), https://web.archive.org/web/20120417053059/http://www.merck.com/newsroom/vioxx/pdf/vioxx_press_release_final.pdf [https://perma.cc/L67Y-TQ7E].

[8] NESI, *supra* note 2, at 12; *See also* Bloomberg News, *FDA Report Links Vioxx to 27,785 Heart Attacks, Deaths*, BALTIMORE SUN (Nov. 3, 2004), https://www.baltimoresun.com/news/bs-xpm-2004-11-03-0411030332-story.html [https://perma.cc/T2EB-FX8B].

[9] FRAN HAWTHORNE, THE MERCK DRUGGERNAUT: THE INSIDE STORY OF A PHARMACEUTICAL GIANT 19–49 (John Wiley & Sons 2003).

[10] *Id.* at 14.

Why was Vioxx withdrawn after five-plus years on the market? Its safety profile was published in *The New England Journal of Medicine* (NEJM), one of the most prestigious and venerable medical journals in the world and, if adverse reactions to Vioxx were so prevalent, why had it not been flagged when it underwent editorial review in the *Journal*? Did Merck & Co. know of this cardiovascular risk, and if so, when?[11]

Cardiovascular disease is a leading cause of death in the United States,[12] 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 is an inflammatory disease typically accompanied by cardiovascular disease,[13] is whether Merck & Co. should have *expected* the possibility of myocardial infarctions and been prepared to monitor their incidence.

This paper addresses the approval of Vioxx and the underlying research supporting or opposing that approval through a focus on the VIGOR trial (Vioxx Gastrointestinal Outcomes Research) published in NEJM on November 23, 2000.[14]

Today, there is an extensive cache of data that chronicles the development of Vioxx, its path to approval, and its eventual withdrawal by Merck & Co. In addition to the published VIGOR study, the complete data set on which the VIGOR studies were based is available through FDA, allowing comparison of published and unpublished data. The contents of internal e-mails among Merck & Co. employees as disclosed in Vioxx personal injury litigation are also available.[15] These e-mails allow one 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 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 most prominent and respected pharmaceutical manufacturers and which division of the company—its marketing division or research scientists—controlled when to release a potential blockbuster drug. In a similar vein, one can gauge what FDA understood of the Merck & Co. data and the actions it took to ensure the public's safety. Vioxx drew

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[11] Vioxx (rofecoxib) and Celebrex (celecoxib) are a class of drug known as inhibitors of cyclo-oxygenase 2, or COX-2 inhibitors, sometimes referred to as "coxibs."

[12] Melonie Heron, *Deaths: Leading Causes for 2015*, 66 NAT'L VITAL STAT. REP. 1–76 (2017).

[13] Nicola Goodson, *Coronary Artery Disease and Rheumatoid Arthritis*, 14 CURRENT OPINION IN RHEUMATOLOGY 115 (2002).

[14] Claire Bombardier, Loren Laine, Alise Reicin, Deborah Shapiro, Ruben Burgos-Vargas, Barry Davis, Richard Day, Marcos Bosi Ferraz, Christopher J. Hawkey, Marc C. Hochberg, Tore K. Kvien & Thomas J. Schnitzer, *Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*, 343 NEW ENG. J. MED. 1520 (2000). 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). Fred E. Silverstein, Gerald Faich, Jay L. Goldstein, Lee S. Simon, Theodore Pincus, Andrew Whelton, Robert Makuch, Glenn Eisen, Naurang M. Agrawal, William F. Stenson, Aimee M. Burr, William W. Zhao, Jeffrey D. Kent, James B. Lefkowith, Kenneth M. Verburg & G. Steven Geis, *Gastrointestinal Toxicity with Celecoxib vs Nonsteroidal Anti-Inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis: The CLASS Study: A Randomized Controlled Trial*, 284 J. AM. MED. ASS'N 1247 (2000).

[15] Alex Berenson, *Vioxx Verdict Raises Profile of Texas Lawyer*, N.Y. TIMES (Aug. 22, 2005), https://www.nytimes.com/2005/08/22/business/vioxx-verdict-raises-profile-of-texas-lawyer.html [https://perma.cc/F4EU-MZGZ].

attention by virtue of its publication in NEJM. By examining the VIGOR trial, one can evaluate the integrity of editorial review at NEJM.

I. THE VIGOR TRIAL AND ITS PUBLICATION IN THE NEW ENGLAND JOURNAL OF MEDICINE

The editors at NEJM were lax in their review of VIGOR, and as published in the *Journal*, the VIGOR study suffered from several fatal and misleading flaws. First, the authors of the study referenced the relative risk for gastrointestinal effects of Vioxx relative to naproxen; in contrast, they inverted the expression of relative risk of subjects experiencing a heart attack by comparing naproxen relative to Vioxx, obscuring the magnitude of the cardiovascular events (*See* Equations 1 and 2, below). Second, in providing a single statement of cardiovascular risk within the text, the authors diminished the significance of such cardiovascular events. Third, the authors explained that any increased cardiovascular events were unrelated to action of Vioxx but were related to a theory that naproxen was cardioprotective, offering this without any supporting evidence. Each of these flaws was obvious, and the editors should have noted them and either challenged the authors to provide more information or rejected the study until further information was available.

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 Merck & Co.,[16] 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 also served as the basis for a supplemental New Drug Application (sNDA) through which Merck & Co. requested a label change to delete any reference to adverse gastrointestinal side effects and to extend indications for Vioxx to include rheumatoid arthritis, thereby improving marketing strategies.[17]

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).[18]

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 attending physicians after

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[16] Vioxx was approved for treatment of acute pain, dysmenorrhea, and osteoarthritis on May 20, 1999. U.S. FOOD & DRUG ADMIN., DRUG APPROVAL PACKAGE: VIOXX (ROFECOXIB) TABLETS & SUSPENSION, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-042s007_Vioxx.cfm [https://perma.cc/JXB8-L53Z] (2002). 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.

[17] *See* Scott Gottlieb, *FDA Refuses Companies' Request to Drop Ulcer Warning*, 322 BMJ 385 (2001).

[18] Bombardier et al., *supra* note 14.

endoscopic examination.[19] This triad—bleeding, perforation, and obstruction—is described as a *complicated* gastrointestinal adverse event.[20]

The second endpoint also has three features: *symptomatic* gastroduodenal ulcers, reduced hemoglobin count, and the presence of orthostatic hypotension.[21] Symptomatic ulcers, while more common than upper gastrointestinal complications, are far less serious.[22] Yet these and other symptoms (dyspepsia, abdominal pain, epigastric discomfort, nausea, and heartburn) are typically responsible for patients electing to discontinue treatment.[23] It is important to note that the presence of 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 upper gastrointestinal events and complicated upper gastrointestinal events" than did twice-daily treatment with standard doses of the nonselective COX inhibitor naproxen.[24] Second, the "incidence of complicated upper gastrointestinal bleeding and bleeding from beyond the duodenum was significantly lower among patients who received rofecoxib."[25]

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 (Equation 1).[26] That is, the beneficial gastrointestinal response to rofecoxib with respect to the primary outcome—bleeding, gastrointestinal perforations, or obstruction—was reduced relative to that for naproxen.[27] Based on the analyses of risk and the time-to-event data, FDA reviewers agreed that Merck & Co. scientists had "successfully demonstrated a risk reduction of clinically relevant GI adverse events for [the population taking] rofecoxib compared to [that taking] naproxen."[28]

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

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[19] *Id.* at 1521–22.

[20] *Id.*

[21] *Id.*

[22] U.S. FOOD & DRUG ADMIN., FDA ADVISORY COMMITTEE BRIEFING DOCUMENT: NDA 21-042, S007, VIOXX GASTROINTESTINAL SAFETY (2001), https://web.archive.org/web/20180127041342/https://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_03_med.doc [https://perma.cc/JXB8-L53Z].

[23] Bombardier et al., *supra* note 14, at 1524.

[24] *Id.*

[25] *Id.*

[26] *Id.* at 1522.

[27] U.S. FOOD & DRUG ADMIN, STATISTICAL REVIEWER BRIEFING DOCUMENT FOR THE ADVISORY COMMITTEE, https://web.archive.org/web/20180127041347/https:/www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_04_stats.doc [https://perma.cc/JYM7-XLBP].

[28] FDA ADVISORY COMMITTEE BRIEFING DOCUMENT: NDA 21-042, *supra* note 22, at 11.

However, systemic chronic inflammation predisposes patients with rheumatoid arthritis to an increased risk of cardiovascular disease. Such accompanying cardiovascular comorbidity raises questions of Vioxx safety in patients with rheumatoid arthritis,[29] and would be expected to be front and center in safety studies on patients with rheumatoid arthritis, yet it was not mentioned.

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"[30] (Equation 2). The structure of this statement is peculiar; 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 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 logical/reasonable/discernable explanation for expressing risk in this manner, but it obscures the significance of the finding that heart attacks were almost five times more common in the rofecoxib than in the naproxen group.

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

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" due to a "potent antiplatelet aggregation effect" and rofecoxib, as a COX-2 selective inhibitor, lacked this effect.[31] The VIGOR authors explain the balance of myocardial infarctions in favor of naproxen as being due to its antiplatelet effect rather than the possible pro-thrombotic effects of rofecoxib. As Dr. S. L. Targum, a consultant-scientist at FDA, notes, "[t]his hypothesis is not supported by any prospective placebo-controlled trials with naproxen."[32] Regardless of the underlying mechanism, and with respect to cardiovascular safety, "the results . . . are favorable for naproxen," prompting the conclusion that "naproxen would be the preferred drug."[33]

The data Merck & Co. submitted to FDA for the sNDA but did not include in the published VIGOR study reveals a more alarming safety concern. According to the Kaplan-Meier plot Merck & Co. submitted as part of their sNDA package, reporting the incidence of myocardial infarctions on the y-axis as an explicit function of time on

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[29] Goodson, *supra* note 13.

[30] Bombardier et al., *supra* note 14, at 1523.

[31] *Id.*

[32] Memorandum from Shari L. Targum, Med. Officer, Division of Cardio-Renal Drug Products, U.S. Food & Drug Admin., to Sandra Cook, Project Manager, and Maria L. Villalba, Med. Officer, Div. of Anti-Inflammatory Drug Products, U.S. Food & Drug Admin., Consultation NDA 21-042, S-007 Review of Cardiovascular Safety Database 23 (Feb. 1, 2001), https://web.archive.org/web/20180127041412/https:/www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_06_cardio.doc [https://perma.cc/TND2-5HV4].

[33] *Id.* at 12 (underlining in original).

the x-axis (Figure 1)[34] 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). The incidence of myocardial infarction increased with time in a nonlinear manner, a greater incidence appearing after only three to four months of treatment, and an even sharper deviation beginning at eight months of treatment.[35] That is to say, adverse cardiovascular effects are observed after a relatively short course of treatment with Vioxx.

FIGURE 1: Kaplan-Meier Plot Relating Incidence of Myocardial Infarctions Versus Time of Treatment with Rofecoxib (Vioxx) and Naproxen

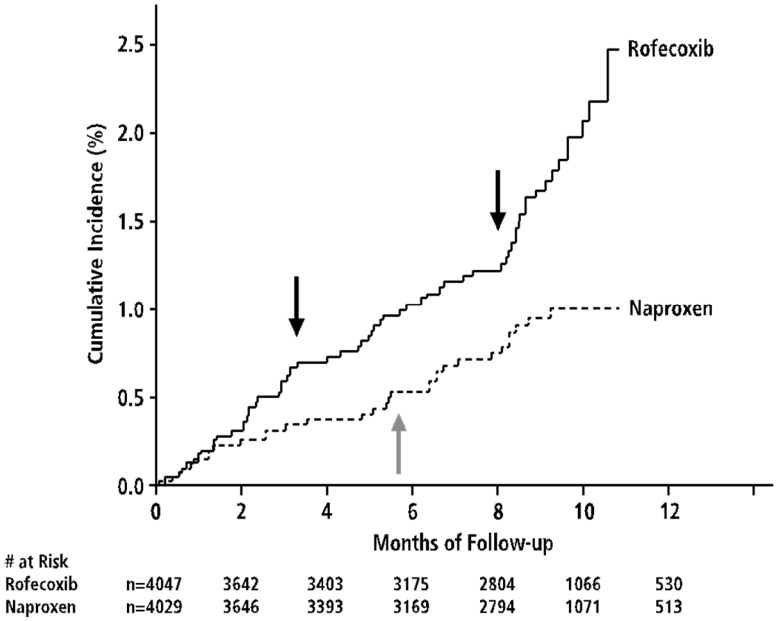

Figure 1. Kaplan-Meier (time-to-event) plot illustrating the cumulative incidence (%) of myocardial infarctions as an explicit function of time over a duration of twelve months in patients with rheumatoid arthritis as reported in the VIGOR study. This figure is taken from Qian Li (supra note 27, at 12). The downward (black) arrows denote times at three- and eight-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.

Also, aspirin use was not permitted in this study. Patients requiring low-dose aspirin for reasons of cardiac health were excluded, as were patients at increased risk of mortality from cardiovascular disease (angina, congestive heart failure, myocardial

[34] FDA ADVISORY COMMITTEE BRIEFING DOCUMENT: NDA 21-042, *supra* note 27, at 12.

[35] *Id.* at 12.

infarction, coronary artery bypass surgery, stroke, and uncontrolled hypertension).[36] Thus, the VIGOR trial demonstrated significantly increased cardiovascular events, even while it excluded those most at risk for these events, patients with rheumatoid arthritis and cardiovascular disease who were most likely to use the drug. Thus, the use of Vioxx within the less homogeneous general population might lead to significantly greater incidence of myocardial infarction and stroke, a public health problem of unimaginable proportions.

To add to these factors, 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, two-times per day), raises concerns of so-called dose-creep, where the patient increases the dose of the analgesic (pain reliever) on the mistaken notion that the drug is safe; this is a potential safety issue. With this as background one can now examine the manuscript as reviewed by NEJM.

II. THE NEW ENGLAND JOURNAL OF MEDICINE PUBLISHES AN "EXPRESSION OF CONCERN"

What can be said about the care exercised in the *Journal's* review of the VIGOR trial and the *Journal's* scientific evaluation prior to publication? First, the inverted expression of cardiovascular risk attributable to Vioxx relative to naproxen (Equation 2) is peculiar, in that it obfuscates the risk of cardiovascular effects of Vioxx. Second, minimal discussion of cardiovascular risks within the middle of the text—providing no more detail and with wording no different from that in the abstract—diminishes the significance of such risks. Third, 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, the presentation of the data, and offering theories without supporting documentation should have been obvious to a careful reviewer or editor. These oddities supported—or at least did not adversely impact—the interests of Merck & Co.

Having published the VIGOR trial in November 2000, the *Journal* eventually published an "expression of concern" in December 2005.[37] This was at a time when litigation was moving from depositions into the trial phase.

As suggested by e-mails at NEJM's editorial offices, the concern was less about apprehension for the public's health than potential criticism against the *Journal* for oversights in its review of the VIGOR trial.[38] The *Journal* feared that its reviewers and editors had not critically questioned the limited description concerning 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, NEJM's editor, Gregory Curfman, acknowledged that "lax editing might have helped the authors make misleading claims in the article."[39] Further, he disclosed that after

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[36] For information on cardiovascular disease, see Ctr. for Disease Control & Prevention, *About Heart Disease*, https://www.cdc.gov/heartdisease/about.htm [https://perma.cc/HV9P-ACLN].

[37] Gregory D. Curfman, Stephen Morrissey & Jeffrey M Drazen, *Expression of Concern: Bombardier et al., "Comparison of upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis,"* 353 NEW ENG. J. MED. 2813 (2005).

[38] David Armstrong, *How The New England Journal Missed Warning Signs on Vioxx.*, WALL ST. J. (May 15, 2006), https://www.wsj.com/articles/SB114765430315252591 [https://perma.cc/W4VS-ZL37].

[39] *Id.*

publication of the VIGOR trial, the *Journal* sold 929,000 reprints of the article, mostly to Merck & Co., earning the *Journal* additional revenue of between $697,000 and $836,000.[40]

In their expression of concern, the editors asserted that they "recently obtained information regarding inaccuracies in 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 which Merck & Co. was aware of but failed to include in the published data.[41] 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 & Co. authors were also aware of them. Accordingly, the editors explain, "certain calculations and conclusions in the article [are] incorrect."[42] In particular, the editors reported the relative risk of 4.25 without the three unreported myocardial infarctions, and a relative risk of 5.00 when those three were 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.[43]

In spite of their 2005 statement, the editors' arguments are not entirely convincing. 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.[44]

Second, the editors criticize the VIGOR authors for including in the 2000 manuscript only "summary percentages, not actual numbers of myocardial infarctions." A careful editorial review would have required the authors to provide precise numbers. The *Journal* had the responsibility and were in a position to request additional data and clarification prior to publication.

III. PROCEEDINGS OF THE *AD HOC* ARTHRITIS ADVISORY COMMITTEE, 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

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[40] *Id.*

[41] Curfman et al., *supra* note 37.

[42] *Id.*

[43] As far as the Merck & Co. authors were concerned, the inclusion of three 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 & Co. authors acknowledged that the Vioxx-treated group demonstrated a significant risk of myocardial infarction. Claire Bombardier, Loren Laine, Ruben Burgos-Vargas, Barry Davis, Richard Day, Marcos Bosi Ferraz, Christopher J. Hawkey, Marc C. Hochberg, Tore K. Kvien, Thomas J. Schnitzer & Arthur Weaver, *Response to Expression of Concern Regarding VIGOR Study*, 354 NEW ENG. J. MED. 1196 (2006).

[44] Curfman et al., *supra* note 37, at 2813.

adulterated or misbranded.[45] 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 & Co. to physicians, patients, *Journal* editors, and the lay press.

Merck & Co.'s principal interest in conducting the VIGOR study and in submitting the sNDA in 2001 was to change 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 *ad hoc* Arthritis Advisory Committee convened by FDA 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) (February 7, 2001)[46] and Vioxx (rofecoxib) (February 8, 2001).[47] In attendance were scientists from FDA (both days),[48] Pfizer's subsidiary G.D. Searle (first day), and Merck & Co. (second day),[49] as well as ten invited consultant-experts, including the Acting Chair, E. Nigel Harris, Dean of the Morehouse School of Medicine.[50] Before each day's meeting, the staff secretary read

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[45] Scott Bass and William McConagha, *FDA Enforcement Powers, in* FOOD AND DRUG LAW AND REGULATION 727–33 (David G. Adams, Richard M. Cooper, Martin J. Hahn & Jonathan S. Kahan eds., 2015); 21 U.S.C. § 351 (2013); Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 352 (2013).

[46] Ctr. for Drug Evaluation and Research, U.S. FOOD & DRUG ADMIN., Transcript of Arthritis Advisory Committee Meeting 1–99 (Feb. 7, 2001), wayback.archive-it.org/7993/20170404100826/https://www.fda.gov/ohrms/dockets/ac/01/transcripts/3677t1_01.pdf/ [https://perma.cc/P6KR-YJYY]; Ctr. for Drug Evaluation and Research, U.S. FOOD & DRUG ADMIN., Transcript of Arthritis Advisory Committee Meeting 100–99 (Feb. 7, 2001) wayback.archive-it.org/7993/20170404100826/https://www.fda.gov/ohrms/dockets/ac/01/transcripts/3677t1_02.pdf/ [https://perma.cc/QTC6-SHV9]; Ctr. for Drug Evaluation and Research, FOOD & DRUG ADMIN., Transcript of Arthritis Advisory Committee Meeting 200–37 (Feb. 7, 2001) wayback.archiverit.org/7993/20170404100826/https://www.fda.gov/ohrms/dockets/ac/01/transcripts/3677t1_03.pdf/ [https://perma.cc/9B82-A8YB].

[47] Ctr. for Drug Evaluation and Research, U.S. FOOD & DRUG ADMIN., Transcript of Arthritis Advisory Committee Meeting 1–99 (Feb. 8, 2001), wayback.archive-it.org/7993/20170404100826/https://www.fda.gov/ohrms/dockets/ac/01/transcripts/3677t2_01.pdf/ [https://perma.cc/47YN-3UBJ]; Ctr. for Drug Evaluation and Research, U.S. FOOD & DRUG ADMIN., Transcript of Arthritis Advisory Committee Meeting 100–99 (Feb. 8, 2001), wayback.archive-it.org/7993/20170404100826/https://www.fda.gov/ohrms/dockets/ac/01/transcripts/3677t2_02.pdf/ [https://perma.cc/2BWR-M4CX]; Ctr. for Drug Evaluation and Research, U.S. FOOD & DRUG ADMIN., Transcript of Arthritis Advisory Committee Meeting 200–37 (Feb. 8, 2001), wayback.archive-it.org/7993/20170404100826/https://www.fda.gov/ohrms/dockets/ac/01/transcripts/3677t2_03.pdf/ [https://perma.cc/A93C-NK6B].

[48] Speakers for FDA were Dr. Lawrence Goldkind, a gastroenterologist; Dr. Shari Targum, a cardiologist; and Dr. Qian Li, a biostatistician.

[49] Representatives from Merck & Co. included Dr. Bonnie Goldman, from its Department of Regulatory Affairs, and she introduced two speakers: Dr. Alan Nies, a clinical pharmacologist, and Dr. Alise Reicin, a research scientist who was part of the VIGOR study. Also, Dr. Goldman described Merck & Co.'s intention in submitting the sNDA to extend the use of Vioxx to patients with rheumatoid arthritis, and that the "highly significant results [on GI safety] merit modification of the product label to reflect a more appropriate presentation of the demonstrated GI safety" of Vioxx. Ctr. for Drug Evaluation and Research, *supra* note 47–48; *see also* Ctr. for Drug Evaluation and Research, U.S. FOOD & DRUG ADMIN., *Arthritis Advisory Committee Proceeding*, 9 (Feb. 8, 2001) (print version).

[50] 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 Cryer, MD. In addition, standing members of the advisory committee were Leigh F. Callahan, MD and

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, M. Michael Wolfe and Allan Sampson."[51] The secretary went on to say that FDA wishes to "disclose for the record that Dr. Steven Nissen, Ileana Pina, H. James Williams and M. Michael Wolfe have interests which do not constitute a financial interest,"[52] "but which could create the appearance of a conflict."[53] Nevertheless, Drs. Nissen, Pina, Williams, and Wolfe were granted permission to participate in the discussion on Vioxx 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."[54] 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 or conflicts. Often, such conflicts of interest 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.[55]

Another consultant, Byron Cryer, 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."[56] In 1997, Dr. Cryer had received a research grant from Merck & Co. to 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 & Co.[57]

Of the ten 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.[58] Of significance, as Harris and Berenson noted in *The New York Times*, those individuals with financial ties to either Merck & Co. or Pfizer voted to approve Vioxx.[59] The conflicts of interest in this case were significant because the

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James H. Williams, MD. Ctr. for Drug Evaluation and Research, *supra* note 46, at 2–3; Ctr. for Drug Evaluation and Research, *supra* note 47, at 2.

[51] *Id.* at 4.

[52] *Id.* at 5.

[53] *Id.* at 5. This statute, 18 U.S.C. § 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," 18 U.S.C. § 208(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," 18 U.S.C. § 208(b)(3).

[54] *FDA Advisory Committees: Financial Conflicts of Interest Overview*, U.S. FOOD & DRUG ADMIN., Slide 9, https://www.fda.gov/media/87421/download [https://perma.cc/FTK3-WZSM] (last accessed Feb. 13, 2021).

[55] *Id.* at Slide 3.

[56] Ctr. for Drug Evaluation and Research, *supra* note 47, at 5.

[57] Ctr. for Drug Evaluation and Research, *supra* note 47, at 4–5.

[58] I indicate that seven individuals—Harrell, Nissen, Pina, Wolfe, Sampson, Williams, Cryer—were identified as having conflicts of interest, but am unable to identify the eighth individual mentioned by Harris and Berenson (2005). *See infra* note 59.

[59] Gardiner Harris & Alex Berenson, *10 Voters on Panel Backing Pain Pills Had Industry Ties*, N.Y. TIMES (Feb. 25, 2005), https://www.nytimes.com/2005/02/25/politics/10-voters-on-panel-backing-pain-pills-had-industry-ties.html [https://perma.cc/66GZ-3JQJ].

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 that 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 primary care physician defined as, among others, an internist or a practitioner of family medicine.[60] Such physicians provide coordinated, long-term care, not merely disease-oriented care, for individuals and families irrespective of age, gender, or disease status, and guide their patients to specialized care when deemed necessary.[61]

As previously stated, the principal questions concerned whether to change the Vioxx label with respect to gastrointestinal and cardiovascular safety, how to advise physicians about supplementing Vioxx with low-dose aspirin, how to balance gastrointestinal benefit and cardiovascular risk, and whether further studies were warranted.[62]

As for gastrointestinal safety, there was uniform agreement that Vioxx was safer on the stomach than traditional NSAIDs.[63] With respect to cardiovascular safety, Alise Reicin, a Merck & Co. 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.[64] Merck & Co. 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.[65] The question, he asked, was whether the differences observed in these hard endpoints reflected a "very low rate in the naproxen group or a

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[60] Barbara Starfield, Leiyu Shi & James Macinko, *Contribution of Primary Care to Health Systems and Health*, 83 THE MILLBANK QUARTERLY 457 (2005). Mark W. Friedberg, Peter S. Hussey & Eric C. Schneider, *Primary Care: A Critical Review of the Evidence on Quality and Costs of Health Care*, 29 HEALTH AFF. 766 (2010).

[61] Starfield et al., *supra* note 59, at 458. Friedberg et al., *supra* note 59, at 757. It is the author's opinion that for FDA to be successful in its mission to protect the public from potential harm, it is vital that the *ad hoc* advisory committees include primary care physicians who, by virtue of their general medical practice, bring a broader perspective to drug evaluation than medical specialists. Primary care physicians have a holistic view of human physiology, are knowledgeable in clinical pharmacology, employ a broad array of drugs that requires them to be familiar with the beneficial and the adverse effects, treat a diversity of individuals and families, are cost conscious, and are likely to cast a skeptical glance toward the optimistic claims of the drug manufacturer. *See supra* note 60; *see also* Julie P. W. Bynum, Chiang-Hua Chang, Andrea Austin, Don Carmichael & Ellen Meara, *Outcomes in Older Adults with Multimorbidity Associated with Predominant Provider of Care Specialty*, 65 J. AM. GERIATRIC SOC'Y 1916 (2017). Derek Hellenberg, Farion R. Williams, Mohan Kubendra & Resmi S. Kaimal, *Strengths and Limitations of a Family Physician*, 7 J. FAMILY MED. & PRIMARY CARE 284 (2018). *Access to Primary Care*, U.S. DEPT. HEALTH & HUMAN SERVS., https://www.healthypeople.gov/2020/topics-objectives/topic/social-determinants-health/interventions-resources/access-to-primary#:~:text=Research [https://perma.cc/VH8Z-V652].

[62] Ctr. for Drug Evaluation and Research, *supra* note 47, at 147.

[63] *Id.* at 106, 186, 188–89.

[64] *Id.* at 56–69.

[65] *Id.* at 152.

very high rate of events in the rofecoxib group."[66] Nissen posited that the 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),[67] describing rates of myocardial infarction among people taking aspirin. The additional data were independent of the review and were 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 & Co. for naproxen, a comparison that was meant to stand as evidence in support of the "hypothesis of a protective effect for naproxen,"[68] suggesting an effect of naproxen similar to 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.[69]

Nissen then raised two questions for which there were no obvious answers. First, 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 & Co. did not conduct.[70] Second, was it possible to "neutralize [the cardiovascular effects] . . . with low dose aspirin?"[71] 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 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.[72] In point of fact, the question of a need for additional studies, as announced by Dr. Harris at the start of the meeting, was 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

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66 *Id.*

67 *Id.* at 151; 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 89 (2001).

68 Ctr. for Drug Evaluation and Research, *supra* note 47, at 153. 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.

69 Ctr. for Drug Evaluation and Research, *supra* note 47, at 155.

70 Contemporaneous with the VIGOR trial, Merck & Co. 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." Robert S. Bresalier, Robert S. Sandler, Hui Quan, James A. Bolognese, Bettina Oxenius, Kevin Horgan, Christopher Lines, Robert Riddell, Dion Morton, Angel Lanas, Marvin A. Konstam & John A. Baron, *Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial*, 352 NEW ENG. J. MED. 1092, 1092 (2005). 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 & Co. was forced to halt this trial when the cardiovascular risks could not be dismissed.

71 Ctr. for Drug Evaluation and Research, *supra* note 47, at 166.

72 *Id.* at 163.

aggressively to an aging and increasingly larger segment of the population vulnerable to its cardiovascular risk.

As for FDA guidance to physicians, Nissen suggested that the committee could say that "this population getting naproxen was associated with a lower cardiovascular event rate than [the group] getting rofecoxib."[73] 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 or excess risk for [Vioxx],"[74] a conclusion that while seemingly acknowledging the possibility of a cardiotoxic effect of Vioxx, downplayed it. The advisory committee, Nissen concluded, could offer no guidance to physicians on whether or not to prescribe aspirin as a cardioprotective adjunct with Vioxx; it was a "matter of clinical judgement . . . . [No] guidance beyond that is possible based upon the data."[75] Yet, it is clear that the Committee discussion plainly acknowledged not only that "there is not a cardioprotective effect for COX-2 inhibitors," but there existed the evident possibility that Vioxx was cardiotoxic, to which Nissen declared that the committee should be "very cautious about how we modify [the label] so that we do not overstate the issue of risk."[76]

The consideration of risk that is centrally enmeshed within three surprising developments of the advisory committee meeting. First, Nissen's comments understated the seriousness of the cardiovascular effects and, surprisingly for a cardiologist, accepted the balance in favor of 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 effects, 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 non-steroidal anti-inflammatory drugs, and that was not the goal of any of the studies that we have seen,"[77] an opinion echoed by Dr. Cryer.[78] 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.[79]

Finally, the Arthritis Advisory Committee in 2001 recommended a wording change on the Vioxx label that acknowledged cardiovascular risk as well as a reduced gastrointestinal harm,[80] a rather limited recommendation in that the advisory committee had available the full compilation of the Merck & Co. data and the accompanying FDA analysis by Drs. Goldkind, Targum, and Li. But in attempting to institute the advisory committee recommendations, FDA met considerable resistance

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[73] *Id.* at 168.

[74] *Id.*

[75] *Id.*

[76] *Id.*

[77] *Id.* at 169–70.

[78] *Id.* at 174.

[79] Gurkipal Singh, appearing in 2004 before a Senate committee investigating the withdrawal of Vioxx, testified that, 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. NESI, *supra* note 2 at 179.

[80] Ctr. for Drug Evaluation and Research, *supra* note 47, at 197–210.

from Merck & Co., who, after debating with FDA over 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 to a lower position on the label.[81] While the committee expressed concern about increased risks of heart attack attributable to Vioxx, as Berenson et al. reported, "none suggested that Vioxx be withdrawn."[82]

IV. AFTER THE ARTHRITIS ADVISORY COMMITTEE MEETING, AUGUST 2001

Six months after the meeting of the a*d hoc* 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 *Journal of the American Medical Association*.[83] The authors searched medical databases to "identify all published, English-language, randomized, double-blind trials of COX-2 inhibitors from January 1998 to February 2001."[84] 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,[85] part of the data that Merck & Co. 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 three months and then further after eight months of treatment. They observe that "the VIGOR trial demonstrated significantly increased risk of cardiovascular event rates with use of rofecoxib [Vioxx] *although the study enrolled patients who did not require aspirin for protection from ischemic events*."[86] As at the *ad hoc* 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)."[87] In addition, they analyzed four aspirin trials, which stated that aspirin reduced all cardiovascular events by 15% and myocardial infarctions by 30%,[88] numbers in line with the effects of naproxen reported by Merck & Co.

Mukherjee et al. recommended caution in considering prescriptions for Vioxx and other COX-2 inhibitors, advice not dissimilar to what was recommended at the

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[81] Gottlieb, *supra* note 17. Alex Berenson, Gardner Harris, Barry Meier &Andrew Pollack, *Despite Warnings, Drug Giant Took Long Path to Vioxx Recall*, N.Y. TIMES (Nov. 14, 2004), https://www.nytimes.com/2004/11/14/business/despite-warnings-drug-giant-took-long-path-to-vioxx-recall.html [https://perma.cc/82PD-TTG8].

[82] Berenson et al., *supra* note 81.

[83] Debabrata Mukherjee, Steven E, Nissen & Eric J. Topol, *Risk of Cardiovascular Events Associated with Selective COX-2 Inhibitors*, 286 J. AM. MED. ASS'N 954 (2001).

[84] *Id.* at 955.

[85] 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. *Id.*

[86] *Id.* at 957 (emphasis added).

[87] *Id.* at 957.

[88] P.S. Sanmuganathan, Parviz Ghahramani, Peter R. Jackson, Erica J. Wallis & L.E. Ramsay, *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 265, 265 (2001).

Arthritis Advisory Committee. But they go further than the Arthritis Advisory Committee in two marked respects. First, 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 "prothrombotic effect seen with rofecoxib," one that "may potentially be dose dependent."[89] They concluded that the data "suggest a potential increase in cardiovascular event rates for presently available COX-2 inhibitors."[90] Second, and more significantly, they "believe that it is mandatory to conduct a trial specifically assessing cardiovascular risk and benefit of these agents."[91] In the absence of such studies, they "urge caution in prescribing these agents to patients at risk for cardiovascular morbidity."[92] All of which is to say that they clearly acknowledged the prothrombotic 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.

Indeed, these recommendations could have been made by the *ad hoc* Arthritis Advisory Committee based on information available at the February 2001 meeting. Had the committee made such recommendations, it is possible that the Merck & Co. 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 of an extra 3.5 years in which the drug was aggressively marketed.

V. WHAT DID MERCK & CO. KNOW ABOUT THE CARDIOVASCULAR EFFECTS OF VIOXX?

The VIGOR authors buried relevant cardiovascular endpoints in the middle of their 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 2, above), obscuring the significance of the cardiovascular risk. Moreover, the VIGOR authors chose to interpret their results supporting never-before-known myocardial benefits of naproxen as an anti-thrombogenic, cardioprotective drug. 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. 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.

Before the VIGOR trial was even considered, as early as 1996, e-mails among unnamed Merck & Co. officials expressed concern about a "substantial chance [of]

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89 Mukherjee et al., *supra* note 83, at 958.

90 *Id.*

91 *Id.* at 958.

92 *Id.*

significantly higher rates" of myocardial infarctions among the group taking Vioxx.[93] In an e-mail of February 25, 1997, a Merck & Co. executive, Briggs Morrison, expressed the view that if Merck & Co. were to proscribe aspirin for patients taking Vioxx, they would "get more thrombotic events," which would, in effect, "kill [the] drug."[94] In response, Alise Reicin, one of the VIGOR authors, 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."[95]

While Merck & Co. refused to publicly acknowledge its doubts about Vioxx, the VIGOR trial confirmed those doubts exactly as expressed in e-mail correspondence to Merck & Co. employees from Ed Scolnick, president of Merck & Co. Research Laboratories. In an e-mail dated March 9, 2000, Scolnick acknowledged that the cardiovascular "events are clearly there" and, moreover, that their nature is "mechanism based as we worried it was."[96] 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 & Co. continued to extol the safety of Vioxx in press releases such as one in which "Merck confirms favorable cardiovascular safety profile of Vioxx."[97]

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[93] The following discussion focuses on internal e-mails from Merck & Co. employees, but also benefits from reporting of Alex Berenson, Gardiner Harris & Barry Meier, *Despite Warnings, Drug Giant Took Long Path to Vioxx Recall*, N.Y. TIMES (Nov. 14, 2004), http://nytimes.com/2004/11/14/business/despite-warnings-drug-giant-took-long-path-to-vioxx-recall.html [https://perma.cc/845F-GKTP]; Anna Wilde Mathews & Barbara Martinez, *E-mails Suggest Merck Knew Vioxx's Dangers at Early Stage*, WALL ST. J. (Nov. 1, 2004), https://www.wsj.com/articles/SB109926864290160719 [https://perma.cc/PN42-TWAK]; NESI, *supra* note 2.

[94] E-mail from Briggs Morrison to Thomas Simon, Elliot Ehrich, Brian Daniels & Alise Reicin (Feb. 25, 1997), https://www.industrydocuments.ucsf.edu/docs/qpww0217 [https://perma.cc/C99J-TCH6] ("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.").

[95] E-mail from Alise Reicin to Thomas Simon, Elliot Ehrich, Brian Daniels & Briggs Morrison (Feb. 25, 1997), https://www.industrydocuments.ucsf.edu/docs/qpww0217 [https://perma.cc/C99J-TCH6].

[96] E-mail from Edward M. Scolnick to Deborah Shapiro, Alise Reicin & Alan Nies (Mar. 9, 2000), https://www.industrydocuments.ucsf.edu/drug/docs/#id=fzgw0217 [https://perma.cc/FB85-485H].

[97] Mathews & Martinez, *supra* note 93. 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. NESI, *supra* note 2, at 194. For a pointed description of Merck & Co. marketing practices see Henry A. Waxman, *The Lessons of Vioxx—Drug Safety and Sales*, 352 NEW ENG. J. MED. 2576, 2577–78 (2005). *See also* Memoranda from Henry A. Waxman to Democratic Members of the Gov't Reform Comm., at 24 (May 5, 2005), https://www.industrydocuments.ucsf.edu/wp-content/uploads/2014/11/waxmanmemo_vioxx.pdf [https://perma.cc/57J9-Z3UJ]. Merck & Co. 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), http://www.dailypress.com/health/sns-ap-vioxx-safety,0,4594516.story [https://perma.cc/9UJS-64U8]. While Merck & Co. pursued talks with the patent department, they continued to promote the cardiovascular safety profile of Vioxx. See E-mail from Alise Reicin to Jonathan A. Tobert (Nov. 28, 2002), https://www.industrydocuments.ucsf.edu/docs/#id=msww0217 [https://perma.cc/MUP3-QAC2]. 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

One damning piece of evidence of Merck & Co.'s knowledge of heart attack risk at the time the VIGOR trial was submitted for publication is found within the metadata stored in Microsoft Word documents. 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."[98]

Merck & Co. had no evidence in support of a cardioprotective effect of naproxen. In an e-mail dated March 13, 2000 to Ed Scolnick and Alan Nies, a clinical pharmacologist at Merck & Co., Alise Reicin, provided a research abstract for "the only study I could find which assessed the potential cardioprotective effects of an NSAID."[99] The abstract, dated 1993, was not about naproxen but flurbiprofen, a chemical derivative of ibuprofen, an NSAID chemically different from naproxen. Later, on January 31, 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 & Co. CEO, and David Anstice, president of Human Health-The Americas, pointing out that:

> there is no way to prove that . . . ALL 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.[100]

However, FDA did allow it to be dismissed, eventually approving the sNDA application. Scolnick's frustration is understandable; as Merck & Co. scientist Briggs Morrison remarked in his appraisal of the data analysis, Merck & Co. was "'fitting the data to a hypothesis' rather than letting the data generate hypotheses."[101] The exercise, he wrote, seemed "wishful thinking, not a critical interpretation of the data."

As early as 2000, Merck & Co. 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."[102] Merck & Co. 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," and that the "implied

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Advisory Committee she described the cardioprotective effect as an indisputable property of naproxen. *See supra* notes 50, 58–69.

[98] Symposium, *Ethics and Professionalism in the Digital Age–A Symposium of the Mercer Law Review*, 60 MERCER L. R., 961 (2009).

[99] E-mail from Alise Reicin to Edward M. Scolnick & Alan S. Nies (Mar. 13, 2003), https://www.industrydocuments.ucsf.edu/docs/#id=xthw0217 [https://perma.cc/CX9U-R2G7].

[100] E-mail from Edward M. Scolnick to Raymond Gilmartin & David W. Anstice (Jan. 31, 2001), https://www.industrydocuments.ucsf.edu/docs/#id=shhw0217 [https://perma.cc/NJC3-MCTK].

[101] E-mail from Briggs Morrison (Aug. 17, 2001), https://www.industrydocuments.ucsf.edu/drug/docs/#id=lnhw0217 [https://perma.cc/ZM5M-8L9M]. 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." *Id.*

[102] Alex Berenson, Gardner Harris, Barry Meier & Andrew Pollack, *Despite Warnings, Drug Giant Took Long Path to Vioxx Recall*, N.Y. TIMES (Nov. 14, 2004), https://www.nytimes.com/2004/11/14/business/despite-warnings-drug-giant-took-long-path-to-vioxx-recall.html [https://perma.cc/EH4Z-DNM2].

message [of such a study] is not favorable,"[103] suggesting a coalescence of marketing and research. Merck & Co., in refusing to conduct a "study solely to determine whether Vioxx might cause heart attacks and strokes," struck a "recurring theme . . . that Vioxx was safe unless proved otherwise."[104]

To demonstrate that Vioxx was not harmful to cardiovascular health, Merck & Co. authored a meta-analysis that appeared in *Circulation*, the flagship organ of the American Heart Association.[105] The stated intention of the study was to "determine whether there was an excess of CV thrombotic events in patients treated with rofecoxib"[106] compared with other NSAIDs. The authors of this meta-analysis reported "no evidence for an excess of CV events for rofecoxib"[107] and concluded more strongly that Vioxx "was not associated with excess CV thrombotic events"[108] relative to other NSAIDs. This further promoted the Merck & Co. theory that any differences between these agents "are likely the result of the [cardioprotective] antiplatelet effects" of naproxen.[109] This meta-analysis was submitted on October 2, 2001 and accepted for publication on October 3, 2001, a day later, raising questions about the quality and depth of review and the intentions of the *Journal*. The publication listed seven authors, five being Merck & Co. employees who participated in VIGOR. The first two authors, M. A. Konstam and M. R. Weir, were associated with academic institutions[110] and were described as the recipients of gift authorship.[111]

VI. IMPLICATIONS FOR PUBLIC SAFETY

The published VIGOR study, the deceit in marketing Vioxx, and the carelessness in the editorial review of the VIGOR trial represent a betrayal of public trust and an abdication of responsibility on the parts of Merck & Co. and NEJM. Merck & Co. 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 & Co.'s marketing division played an outsized role in promoting the

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[103] *Id.*

[104] *Id.*

[105] Marvin A. Konstam, Matthew R. Weir, Alise Reicin, Deborah Shapiro, Rhoda S. Sperling, Eliav Barr & Barry J. Gertz, *Cardiovascular Thrombotic Events in Controlled, Clinical Trials of Rofecoxib*, 104 CIRCULATION 2280 (2001).

[106] *Id.* at 2285.

[107] *Id.* at 2287.

[108] *Id*.

[109] *Id.* at 2280.

[110] According to e-mails, Merck & Co. employee Rhoda Sperling, one of the authors on the paper, sent Konstam and Weir finished manuscripts and asked for their comments, an example of gift authorship. The draft sent to Konstam and Weir was virtually identical to that appearing in *Circulation*. Letter from Rhoda Sperling to Marvin A. Konstam & Matthew Weir (July 12, 2001), https://www.industrydocuments.ucsf.edu/docs/ztww0217 [https://perma.cc/8J9X-VW8Z]. 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*, MEDSCAPE, May 8, 2009, https://www.medscape.com/viewarticle/702606_print [https://perma.cc/9N25-77HX].

[111] Joseph S. Ross, Kevin P. Hill, David S. Egilman & Harlan M. Krumholz, *Guest Authorship and Ghostwriting in Publications Related to Rofecoxib*, 299 J. AM. MED. ASS'N 1800 (2008).

drug. The marketing team applauded the Merck & Co. scientists for their efforts to "defuse the CV risk issue for Vioxx."[112] The marketing division of Merck & Co. conducted its 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.[113] 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,[114] during which Merck & Co. recruited physicians to prescribe Vioxx under the false impression that they were participating in a randomized clinical trial.[115] In internal communications, Merck & Co.'s marketing team was aware that 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."[116] This note demonstrated a callous disregard for a patient's right to informed consent. Furthermore, in a critical analysis of the ADVANTAGE paper, Hill et al. underscored Merck & Co.'s willingness to risk "patient injury for marketing purposes."[117]

At 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 & Co. scientists.[118] Overall, this much is clear: Merck & Co. and the NEJM increased medical risk to the public and compromised the evidence-based practice of medicine.[119] Less clear is a path

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[112] E-mail from Margie McGlynn to Alise Reicin (May 25, 2000), https://www.industrydocuments.ucsf.edu/docs/xgfw0217 [https://perma.cc/L9DQ-6A2H].

[113] Jeffrey R. Lisse, Monica Perlman, Gunnar Johansson, James R. Shoemaker, Joy Schechtman, Carol S. Skalky, Mary E. Dixon, Adam B. Polis, Arthur J. Mollen & Gregory P. Geba, ADVANTAGE Study Group, *Gastrointestinal Tolerability and Effectiveness of Rofecoxib Versus Naproxen in the Treatment of Osteoarthritis: A Randomized, Controlled Trial*, 139 ANNALS OF INTERNAL MED. 539 (2003). ADVANTAGE is an acronym for *Assessment of Differences between Vioxx And Naproxen To Ascertain Gastrointestinal tolerability and Effectiveness*.

[114] Harold C. Sox & Drummond Rennie, *Seeding Trials: Just Say "No,"* 149 ANNALS OF INTERNAL MED. 279 (2008).

[115] Kevin P. Hill, Joseph S. Ross, David S. Egilman & Harlan M. Krumholz, *The ADVANTAGE Seeding Trial: A Review of Internal Documents*, 149 ANNALS OF INTERNAL MED. 251 (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.

[116] E-mail from Rebecca Higbee to Kyra Lindemann, Christine Fanelle & Jan D. Weiner (March 19, 1999), https://www.industrydocumentslibrary.ucsf.edu/drug/docs/tkgw0217 [https://perma.cc/KA5Y-AWXQ].

[117] Hill et al., *supra* note 115, at 256.

[118] Curfman et al., *supra* note 37.

[119] As a practical example of the impact of misleading and false medical claims on evidence-based medicine, see JOHN ABRAMSON, *False and Misleading: The Misrepresentation of Celebrex and Vioxx*, in OVERDOSED AMERICA: THE BROKEN PROMISE OF AMERICAN MEDICINE (HarperCollins 2008). Abramson describes his puzzlement upon receiving a letter sent by Pharmacia, the parent company of Pfizer, the manufacturer of Celebrex (celecoxib), and mandated by 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 Garret A. FitzGerald and Carlo 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 *NEJM*, FitzGerald received grant support from Merck & Co. and he served as a

through which FDA can protect the public from drugs submitted by determined, well-financed pharmaceutical companies.[120]

As a gatekeeper, FDA defines what is allowable in marketing the drugs it approves. However, FDA shares one fault in common with medical journals: both rely on the good faith of drug companies to provide honest and complete information and to 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 and exploited its trust. *Annals of Internal Medicine* was blindsided by Merck & Co.; the evidence indicates that they were victimized by Merck & Co.'s submission of the ADVANTAGE seeding study.

Perhaps there is no infallible mechanism through which FDA can protect the public in all cases from all possible drug interactions.[121] 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 study.[122]

The entire Vioxx chronicle was marked by misrepresentations and obfuscations that lead to death and compromised cardiac health for thousands of patients.[123] The marketing activities of drug companies, the fallibility of journal editors, and the environment in which FDA functions require a healthy skepticism in assessing optimistic claims. Perhaps the best advice in assessing claims made in the medical

consultant to Merck & Co.; Patrono received grant support from Merck & Co. and served as a consultant to Merck & Co. and Pharmacia.

[120] DANIEL P. CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA 665–72, 737 (Princeton University Press, 2010). Carpenter describes Merck & Co. as "perhaps the single most trusted corporate name at FDA in the late twentieth century," *Id.* at 737, and that, having "killed" or abandoned drugs they thought problematic before launch, Merck & Co. had developed credibility for not submitting drugs in which they had little faith, *Id.* at 665–72.

[121] Of interest is testimony by David J. Graham, *Insider: FDA Won't Protect Public*, CBS NEWS (Dec. 7, 2020, 11:03 AM) https://www.cbsnews.com/news/insider-fda-wont-protect-public/ [https://perma.cc/M7KC-CBYN]; *FDA, Merck and Vioxx: Putting Patient Safety First?: Hearing Before the Senate Committee on Finance* (Nov. 18, 2004) (Testimony of David J. Graham) https://www.finance.senate.gov/imo/media/doc/111804dgtest.pdf [https://perma.cc/WJ2T-Y3FE]. Jeanne Lenzer, *FDA Is Incapable of Protecting US Against Another Vioxx*, 329 BMJ 1253 (November 27, 2004).

[122] 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, Mandeep 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*. Allysia Finley, *The Lancet's Politicized Science on Antimalarial Drugs*, WALL ST. J. (June 1, 2020), https://www.wsj.com/articles/the-lancets-politicized-science-on-antimalarial-drugs-11591053222 [https://perma.cc/5JL7-YEXA]; Frank Gannon, *Sullied*, 21 EMBO REPS. Aug. 6, 2020, https://doi.org/10.15252/embr.202051371 [https://perma.cc/4XE3-3A6A].

[123] David J. Graham, David Campen, Rita Hui, Michele Spence, Craig Cheetham, Gerald Levy, Stanford Shoor & Wayne A. Ray, *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 (2005).

literature recalls a 14th Century Chinese proverb: "Be well informed, but always leave room for doubt."[124]

[124] Attributed to the Ko Ku Yao Lun (1388) as cited by DAME JANET MARIA VAUGHAN OBE, DBE, FRS (1899–1993) in the dedication page of her textbook, THE EFFECTS OF IRRADIATION ON THE SKELETON (Clarendon Press) (1973).