No. 08-905

In the Supreme Court of the United States

MERCK & CO., INC., ET AL., PETITIONERS

v.

RICHARD REYNOLDS, ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

BRIEF FOR DR. HARLAN M. KRUMHOLZ AND DR. JOSEPH S. ROSS AS AMICI CURIAE IN SUPPORT OF RESPONDENTS

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INTEREST OF AMICI CURIAE

Harlan M. Krumholz, M.D., S.M., is the Harold H. Hines, Jr., Professor of Medicine and Epidemiology and Public Health at Yale University School of Medicine, where he is Director of the Robert Wood Johnson Clinical Scholars Program.[1] He is also the Director of the Yale-New Haven Hospital Center for Outcomes Research and Evaluation. He is the leading international expert in cardiovascular outcomes research, a field of investigation that involves practical research to guide clinical care and health care policy, with a particular focus on outcomes meaningful to patients and populations. Further biographical information on Dr. Krumholz is provided in Appendix A, *infra*.

Dr. Krumholz's research is specifically focused on determining optimal clinical strategies and identifying opportunities for improvement in the prevention, treatment and outcome of cardiovascular disease. Using methods of clinical epidemiology and health services research, he has sought to illuminate the balance of risks, benefits and costs of specific clinical approaches. His research efforts are intended to provide critical information to improve the quality of health care, monitor changes over time, and guide decisions about the allocation of scarce resources. Dr. Krumholz is currently leading initiatives through the

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[1] The parties have consented to the filing of this brief. No counsel for a party authored this brief in whole or in part, and no counsel for a party or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than amicus curiae or their counsel made a monetary contribution to its preparation or submission.

Centers for Medicare & Medicaid Services (CMS) to develop national outcomes measures for public reporting of hospital performance.

Dr. Krumholz is a member of the Association of American Physicians, the American Society for Clinical Investigation, and the Institute of Medicine, each of which recognizes excellence and achievement by electing for membership a small group of nationally recognized experts in medicine. He is also the author of the book *The Expert Guide to Beating Heart Disease: What You Absolutely Must Know.* He has written or co-authored more than 500 articles, reviews, and editorials in medical journals.

Joseph S. Ross, M.D., M.H.S., is an Assistant Professor in the Department of Geriatrics and Palliative Medicine at the Mount Sinai School of Medicine in New York, N.Y., and a staff physician at the James J. Peters VA Medical Center in Bronx, NY, within the HSR&D Research Enhancement Award Program. After completing his postgraduate training in primary care internal medicine, Dr. Ross was a fellow in the Robert Wood Johnson Clinical Scholars program at Yale University, earning a Masters degree in health sciences research. He was awarded a Paul B. Beeson Career Development Award in Aging Research from the National Institute on Aging in 2008. Further biographical information on Dr. Ross is provided in Appendix B, *infra*.

Using health services research methods, Dr. Ross's research focuses on examining factors which affect the use or delivery of recommended ambulatory care services for older adults and other vulnerable populations, evaluating the impact of state and fed-

eral policies on the delivery of appropriate and higher quality care, and issues related to conflicts of interest, medical professionalism, and drug safety. Dr. Ross continues to collaborate with a team of investigators under contract with the Centers for Medicare and Medicaid Services to develop statistical models that are used to measure and publicly report hospital clinical outcomes using administrative data. He has been a peer reviewer for 25 medical journals. Dr. Ross has written or co-authored 52 articles, reviews, and editorials in medical journals.

Drs. Krumholz and Ross were co-authors, along with others, of three articles on Vioxx-related issues in prominent medical journals. See *Guest Authorship and Ghostwriting in Publications Related to Rofecoxib*, 299 J.A.M.A. 1800 (2008); *The ADVANTAGE Seeding Trial: A Review of Internal Documents*, 149 Annals of Internal Medicine 251 (2008); *What Have We Learnt From Vioxx?*, 334 B.M.J. 120 (2007). They have in the past been consultants for plaintiffs in non-securities litigation against Merck relating to Vioxx, and Dr. Krumholz has testified as an expert witness in two such cases.

Amici submit this brief in the hopes that their experience and perspectives will assist the Court in understanding the medical issues underlying this case.

SUMMARY OF ARGUMENT

Respondents in this case allege that Merck made false and misleading statements about Vioxx, a drug it marketed between 1999 and 2004. A large, double-blind clinical trial — the VIGOR study — had shown

that users of Vioxx had a higher rate of heart attacks than patients given naproxen, an older nonsteroidal anti-inflammatory drug (NSAID). There were two major possible explanations for those results — that naproxen had cardiovascular benefits (the "naproxen hypothesis"), or that Vioxx had cardiovascular risks. In an effort to alleviate concerns about Vioxx, Merck advanced the naproxen hypothesis. Respondents claim that Merck's statements advancing the napoxen hypothesis were false and misleading, because Merck itself did not believe them.

The issue before this Court concerns the standards governing whether respondents filed their securities fraud complaint not later than "2 years after the discovery of the facts constituting the violation." 28 U.S.C. 1658(b). Accordingly, this case raises the question of what a reasonable *investor* knew (or, perhaps, should have known) about the validity of the naproxen hypothesis (or the competing hypothesis that Vioxx posed cardiovascular risks) by November 6, 2001, two years before the complaint in this case was filed. This brief addresses the parallel question what a reasonable *medical professional* would have concluded about the cardiovascular benefits of naproxen — or the cardiovascular risks of Vioxx — as of that date.

Vioxx prescriptions in fact increased after the VIGOR study reported a higher rate of heart attacks in the Vioxx group in comparison with the naproxen group, and they continued to increase long after November 6, 2001. This brief focuses on four primary sources of information in the public record that might be thought to have influenced reasonable medical professionals in considering the cardiovascular safety

of Vioxx. The four sources are the VIGOR trial itself, as reported in November 2000; an analysis of VIGOR and other studies in the public record that considered the question whether Vioxx increased, or naproxen decreased, the risk of heart attacks and other adverse vascular events and was published in the *Journal of the American Medical Association* (JAMA) in August 2001; a letter sent by the FDA to Merck in September 2001 warning Merck that its promotional materials and activities for Vioxx had been false and misleading; and an article that first appeared on October 15, 2001, in the online edition of the journal *Circulation* and that considered data on cardiovascular risk from clinical trials of Vioxx that were in Merck's files but generally not available to the public.

Of the four sources, the report of the VIGOR trial raised the question whether naproxen's benefits, or Vioxx's risks, was the predominant cause of the cardiovascular results of that trial, and it advanced the naproxen hypothesis as the answer to that question. The JAMA article, which relied in large part on the VIGOR results, identified the question of the validity of the naproxen hypothesis and the possible cardiovascular risks of Vioxx as one that urgently deserved study. The FDA warning letter rebuked Merck's promotional materials for presenting the VIGOR results — and the naproxen hypothesis — in a one-sided way, but made no recommendations that prescribing patterns should change. Indeed, both sources indicated that the naproxen hypothesis was a reasonable explanation, and the JAMA article elaborated on the reasons supporting and tending to refute both it and the competing theory that Vioxx caused cardiovascular risks. In the end, because

neither source identified any new data in the public record that addressed the question of whether Vioxx conferred an increased cardiovascular risk compared with placebo, neither source would have convinced a reasonable and conscientious doctor that the naproxen hypothesis was false, or that Vioxx posed serious cardiovascular risks.

Finally, the article in *Circulation*, published online on October 15, 2001, did make new data publicly available about the risk of Vioxx compared with placebo. It presented internal and previously unavailable Merck data regarding a number of Vioxx clinical trials. The article in *Circulation* concluded that there was *no* evidence that Vioxx caused more cardiovascular events than either placebo or NSAIDs other than naproxen, and it also supported the theory that naproxen reduced the risk of cardiovascular events. To be sure, data that became public only much later made the risks of Vioxx clear. But as of November 6, 2001, the *Circulation* article provided support for the naproxen hypothesis based on new data not previously available. It would have alleviated — not strengthened — concerns that a reasonable medical professional might have had about Vioxx's cardiovascular safety as of that date.

ARGUMENT

PUBLICLY AVAILABLE INFORMATION AS OF NOVEMBER 6, 2001, WOULD NOT HAVE LED REASONABLE AND CONSCIENTIOUS DOCTORS TO DOUBT THE VALIDITY OF THE NAPROXEN HYPOTHESIS OR TO CEASE PRESCRIBING VIOXX

This securities fraud case concerns the question whether respondents, as investors, had "discover[ed]," 28 U.S.C. 1658(b), enough facts by November 6, 2001, to commence the running of the statute of limitations. The relevant facts concern whether Merck committed fraud in advancing, despite its own lack of belief, the "naproxen hypothesis" — the hypothesis that the greater number of heart attacks in patients given Vioxx as compared with patients given naproxen, another NSAID, predominantly resulted from naproxen's protective effects, rather than Vioxx's cardiovascular harms.

Although this case therefore concerns the facts about the naproxen hypothesis "discover[ed]" by an investor, the inquiry can be informed by considering the parallel *medical* question of what a reasonable medical professional would or could have known about the naproxen hypothesis as of November 6, 2001. Amici address that question by examining the most important documents that were publicly available by that date and that would have been — or that might be thought to have been — relevant to a consideration by a reasonable medical professional of the naproxen hypothesis. A reasonable medical professional examining those sources of information would

have concluded that the naproxen hypothesis as promoted by Merck was supported by evidence, and accordingly such a professional would not have had substantial concerns about the safety of Vioxx and would not have felt it necessary to cease prescribing Vioxx.

A. The VIGOR Trial And Its Report

1, On November 23, 2000, the report of the VIGOR trial was published in the *New England Journal of Medicine*. J.A. 295-318 (originally published as C. Bombardier, L. Laine, A. Reicin et al., *Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*, 343 N. Eng. J. Med. 1520 (2000)). The VIGOR trial was a large (8076 patients with rheumatoid arthritis) double-blind clinical trial that sought to compare the risk of upper gastrointestinal bleeding events in patients treated with Vioxx compared with those treated with naproxen, an older NSAID. From the time of Vioxx's early development, at least some scientists at Merck and consultants to Merck were concerned that Vioxx might adversely affect the ratio of prostacyclin (which promotes blood flow) and thromboxane (which promotes blood clotting), thereby upsetting the normal balance of the two substances and, potentially, increasing the risk of heart attacks or other cardiovascular events related to blood clots. Indeed, presumably for that reason, those with a history of "cerebrovascular events in two years before the study" or "myocardial infarction [*i.e.*, heart attack] or coronary bypass in the year before the study" were excluded from participation. J.A. 296.

The VIGOR publication reported the similar efficacy, or beneficial effect, of Vioxx and naproxen in treating rheumatoid arthritis, J.A. 298, 303, and it reported that Vioxx had better gastrointestinal safety than naproxen, J.A. 303-305. But it also acknowledged that "[t]he incidence of myocardial infarction was lower among patients in the naproxen group than among those in the [Vioxx] group" in the trial. J.A. 296; see J.A. 306, 310. As originally reported, the incidence of heart attacks among the Vioxx group ws 0.4 percent, while it was 0.1 percent among the naproxen group. That rate would translate to 40,000 heart attacks in a population of ten million people similar to those in the study (*i.e.*, with rheumatoid arthritis and no history of heart disease) taking Vioxx, versus 10,000 heart attacks in a similar population of ten million taking naproxen. Cf., *e.g.*, *Plaintiffs Find Payday Elusive in Vioxx Cases*, N.Y. Times, Aug. 21, 2007, at 1 (more than 20 million people in the United States took Vioxx).

The higher rate of heart attacks among the Vioxx group, which was very unlikely to have occurred by chance, could have been the result either of a harmful effect of Vioxx or a beneficial effect of naproxen (or a combination of the two). The data in the VIGOR study, as published, were unable to distinguish between the two possible explanations. Nonetheless, the report discussed in some detail and favorably the theory that naproxen is beneficial (what came to be known as the "naproxen hypothesis"), while it did not discuss the alternative theory that Vioxx was harmful.

For example, the report stated that "the effects of regular use of naproxen may be similar to [the heart-

beneficial effects] of aspirin." J.A. 310. It also noted the mechanism by which naproxen may achieve that beneficial effect, J.A. 310, and that the VIGOR "results are consistent with the theory that naproxen has a coronary protective effect." J.A. 311. The report did add that "[t]he finding that naproxen therapy was associated with a lower rate of myocardial infarction needs further confirmation in larger studies." J.A. 311. That statement itself — with its implication that there was a "finding" that naproxen had a "lower rate" of heart attacks that needed "further" confirmation in studies — strongly promoted the naproxen hypothesis. Indeed, throughout the study, naproxen is treated as the intervention variable when discussing cardiovascular risks (*e.g.*, "[t]he rate of myocardial infarction was significantly lower in the naproxen group than in the [Vioxx] group (0.1 percent vs. 0.4 percent," J.A. 310; see also J.A. 296, 306), while Vioxx was treated as the intervention variable when stating other results (*e.g.*, "The relative risk of confirmed upper gastrointestinal events was 0.4 . . . , whereas the relative risk of bleeding beyond the duodenum was 0.5." J.A. 304). That presentation, too, indicated Merck's promotion of the naproxen hypothesis as an explanation for the higher rate of heart attacks in the subjects randomized to Vioxx.

2. The results of the VIGOR study raised the question whether naproxen had cardiovascular benefits or Vioxx had cardiovascular harms. The language of the report, which was authored at least in part by Merck employees, see J.A. 313, suggested the former as the answer; its publication in the New England Journal of Medicine and its vetting by peer review

would have led readers to have confidence in that conclusion. And Vioxx sales continued to increase after the VIGOR study was published and until at least early 2004. See J.A. 55. Two features of the VIGOR study's design and reporting tended to allay fears about Vioxx and suggested to medical professionals that Vioxx was safe to prescribe.

First, a reasonable and conscientious medical professional would have been aware that Merck was in a uniquely favorable position to assess the safety of Vioxx, due to its extensive and nonpublic research on the drug. Accordingly, Merck's emphasis on, and apparent endorsement of, the naproxen hypothesis would have been accorded substantial weight by a reasonable medical professional. At that time, Merck was one of the most respected companies in the United States.[2]

Second, the VIGOR report used a defective post hoc subgroup analysis that purported to show that any increased risks of Vioxx (or benefits of naproxen) were limited to a small subgroup of the general population. In particular, the study reported results separately for (a) a small subgroup (4% of the total number of patients) with the "highest risk of myocardial infarction" for whom low-dose aspirin would be indicated, and (b) the remaining patients. J.A. 310; see

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[2] For example, in surveys conducted in 1999 and 2000 by *Fortune* magazine, Merck was ranked as the most admired pharmaceutical company in the world. *And the Winners Are . . .*, 142 Fortune (No. 7) 191-198 (Oct. 2, 2000). Earlier, *Fortune* magazine surveys named Merck as the most admired company of any sort in America for a period of seven years in a row, ending in 1993. *America's Most Admired Corporations*, 127 Fortune (No. 3) 44-53 (Feb. 8, 1993).

J.A. 306. The study thus purported to show that the increased number of heart attacks among subjects on Vioxx was entirely attributable to the higher risk aspirin-indicated subgroup, and it thereby tended to minimize any potential risk that Vioxx posed for most patients. See J.A. 310 ("The difference in the rates of myocardial infarction between the [Vioxx] and naproxen groups was not significant among the patients without indications for aspirin therapy."). That result, however, was an artifact of the study's improperly short period for counting heart attacks.[3] As a

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[3] Ordinarily, a trial's end dates should be the same for all effects being counted. The VIGOR study, however, terminated the counting of heart attacks one month before the counting of gastrointestinal events. When the editors of the *New England Journal of Medicine*, in which the VIGOR results had been published, learned that at least two of the authors of the study knew about the additional data long before its publication, they issued an "expression of concern," which explained:

> Lack of inclusion of the three events resulted in an understatement of the difference in risk of myocardial infarction between the rofecoxib and naproxen groups (presented in the article as a reduction in the risk with naproxen but shown [in an accompanying table] as an increase in the risk with rofecoxib). It also resulted in the misleading conclusion that there was a difference in the risk of myocardial infarction between the aspirin indicated and aspirin not indicated groups.

G.D. Curfman, S. Morrisey, J.M. Drazen, *Expression of Concern: Bombardier et al., "Comparison of Upper Gastrointestinal Toxicity of Refoxicob and Naproxen in Patients with Rheumatoid Arthritis," N Eng J Med 2000; 343:1520-8*, 353 N. Eng. J. Med. 2813 (2005). See also *id.* at 2814 (noting that VIGOR authors also knew of "other data on cardiovascular adverse events that we believe would have been relevant to the article" and that "[t]aken together, these inaccuracies and deletions call into question the integrity of the data on adverse cardiovascular events in [the

result, three heart attacks, all of them in the non-aspirin-indicated subgroup, were not counted. Had Merck included the three cases, the subgroup analysis would have shown an increased cardiovascular risk among Vioxx users in *both* subgroups, thus undermining the support in the subgroup analysis for the naproxen hypothesis.

B. The JAMA Article of August 2001

1. In August 22, 2001, the *Journal of the American Medical Association* (JAMA) published an article examining the risk of cardiovascular events posed by Vioxx and a similar drug, Celebrex. D. Mukherjee, S. Nissen, E. Topol, *Risk of Cardiovascular Events Associated with Selective COX-2 Inhibitors*, 286 J. Am. Med. Ass'n 954 (2001). The JAMA article noted the results of the VIGOR trial, and explained that "[t]he results of the VIGOR study can be explained by either a significant prothrombotic [*i.e.*, cardio harmful] effect from [Vioxx] or an antithrombotic [*i.e.*, cardioprotective] effect from naproxen (or conceivably both)." J.A. 326; see also J.A. 327 ("[I]t is difficult to assess whether the difference in cardiovascular event rates in VIGOR was due to a benefit from naproxen or to a prothrombotic effect from [Vioxx]."). The article also noted both an explanation for naproxen's potential benefits ("naproxen . . . resulted in a high level of platelet aggregation inhibition similar to that achieved by aspirin," J.A. 327) and an explanation for the potential cardiovascular risks of drugs like Vioxx ("Administration of selective COX-2 inhibitors [such as Vioxx] 24 hours after ischemic

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VIGOR] article").

preconditioning abolished the cardioprotective effect of late ischemic preconditioning," J.A. 328).

The article went on to discuss potential reasons to believe that Vioxx might pose a risk. The article considered a previous meta-analysis (*i.e.*, a new analysis that combines the data from several previous studies) of trials in which aspirin had been studied in comparison with placebo. The article noted that the rate of cardiovascular events in the Vioxx group in the VIGOR trial was somewhat higher than the rate in the placebo group in the aspirin-placebo trials, suggesting that Vioxx might pose greater risks than placebo. See J.A. 325. That conjecture, however, represented extremely weak evidence from which to draw any conclusions; the article cautioned that "comparison of patient populations in 2 different trials is always problematic," and that the VIGOR patients, unlike the patients in the aspirin-placebo trials, already were being treated for rheumatoid arthritis, which "increases risk of [heart attack], making intertrial comparisons difficult." J.A. 327. The article also examined the results of two smaller trials (labeled as trials 085 and 090 by Merck), which had Vioxx, namubetone (another NSAID), and placebo arms. J.A. 324. Those studies together "did not demonstrate the significant increase in cardiovascular event rate noted in VIGOR," and in that respect they tended to support the naproxen hypothesis. J.A. 329. But their results were of very limited value because they "had smaller sample sizes, used only 25% of the dose of [Vioxx] used in VIGOR, and had few events for meaningful comparison." J.A. 329.

The article noted that "it is useful to consider" that COX-2 inhibitors such as Vioxx may "show less

propensity for gastrointestinal toxicity but greater prothrombotic potential," while aspirin and naproxen have the reverse effects. J.A. 330. But the article noted several "significant limitations" on its analysis. J.A. 330. The authors speculated that their "findings *suggest* a *potential* increase in cardiovascular event rates for the presently available COX-2 inhibitors," and "urge[d] caution in prescribing these agents to patients at risk for cardiovascular morbidity" until "a randomized clinical trial" could be conducted. J.A. 331 (emphasis added). But they noted as well the reverse potential: that cardiovascular conditions have an "inflammatory component" that "may be suppressible by COX-2 inhibitors" such as Vioxx. J.A. 331. While they urged "caution" in prescribing Vioxx for patients at risk — wise advice for any physician in prescribing drugs that could have adverse effects — they did not recommend the drug be suspended or severely limited even for at-risk patients pending a trial that could provide a definitive answer. The article concluded that "[g]iven the remarkable exposure and popularity of this new class of medications, we believe that it is mandatory to conduct a trial specifically assessing cardiovascular risk and benefit of these agents." J.A. 331.

2. The JAMA article, while giving a useful overview of the state of knowledge from publicly available sources, provided no new information that would cause a reasonable medical professional to reject the naproxen hypothesis. Most of the data used in the article had already been published.[4] While the JAMA

[4] The two smaller studies considered in the JAMA article (numbers 085 and 090) had not yet been published, further em-

article continued to pose the question whether Vioxx had cardiovascular risks, or naproxen instead had beneficial cardiovascular effects, its conclusion was only that further study was necessary. The authors of the article were very well-known researchers who themselves perform studies, and their perspectives on the need for further research were credible. But, given the limitations on the data that were publicly available regarding the cardiovascular effects of Vioxx, they were unable to advance the state of knowledge. Reasonable medical professionals would not have altered — and did not alter — their views of Vioxx and its potential risks as a result of the article, as indicated by Vioxx's increasing sales.

C. The FDA Warning Letter

On September 17, 2001, the FDA's Division of Drug Marketing, Advertising and Communication sent Merck a warning letter regarding "promotional activities and materials for the marketing of Vioxx." J.A. 339. The letter stated that Merck's "promotional activities and materials" were "false, lacking in fair balance, or otherwise misleading." J.A. 339. Much of the warning had to do with Merck's promotional activities regarding matters other than Vioxx's car-

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phasizing the preliminary nature of any reported results. They had not yet undergone peer review. To give perspective on how little information was available from those studies, the number of adverse events in the Vioxx group in 085 was 1 and in 090 was 6. And their very short duration (085 lasted only six weeks, J.A. 324) also limited the value of their data for these purposes. As noted above, the JAMA article itself concluded that those studies, though they tended to support the naproxen hypothesis, were of very limited value.

diovascular effects. See J.A. 340 ("minimize the Vioxx/Coumadin (warfarin) drug interaction, omit important risk information, make unsubstantiated superiority claims against other NSAIDs, and promote Vioxx for unapproved uses"); see J.A. 346-351.

The FDA letter did address the fact that the "promotional campaign discounts the fact that in the VIGOR study, patients on Vioxx were observed to have a four to five fold increase in myocardial infarctions" compared with patients on naproxen. J.A. 340. The letter did not, however, add any new information regarding the safety of Vioxx or call for changes in prescribing patterns. Instead, it merely recognized the continued uncertainty. It noted that "the exact reason for the increased rate of [heart attacks] observed in the Vioxx treatment group is unknown," and that the hypothesis that naproxen had cardiovascular benefits "is a possible explanation." J.A. 340 (emphasis added). The FDA's complaint was that the promotional materials "fail[ed] to disclose that your explanation is hypothetical, has not been demonstrated by substantial evidence, and that there is another reasonable explanation, that Vioxx may have pro-thrombotic properties." J.A. 340; see also J.A. 342 ("Although . . . the reason for these differences is not clear, possible explanations include both an ability of naproxen to function as a cardioprotective agent and a pro-thrombotic property of Vioxx.").

The FDA letter detailed specific audio conferences and other promotional activities in which Merck had understated the rate of cardiovascular events suffered by the Vioxx patients in the VIGOR study and had advanced the naproxen hypothesis without not-

ing that it was unproven and that there remained the possibility that Vioxx caused cardiovascular risks. See J.A. 343-344, 345-346. Because "the situation is not at all clear" and "the reason for the difference between Vioxx and naproxen has not been determined," Merck's promotional materials endorsing the naproxen hypothesis without a balanced treatment were misleading. J.A. 344.[5]

The FDA letter thus continued to rely on the scientific findings already in the public record. It rebuked Merck for understating the potentially unfavorable VIGOR results and failing to present the naproxen hypothesis in a sufficiently balanced manner. The letter would have suggested to medical professionals who had been misled by Merck's promotional campaign that the naproxen hypothesis was unproven and that other explanations for the VIGOR results remained possible. The letter did not, however, add anything to public knowledge about the risks posed by Vioxx, and it made quite clear that the naproxen hypothesis retained credibility and, indeed, could even be used in promotional materials, so long as it was presented in a sufficiently balanced way. Nothing in the FDA letter suggested that the naproxen hypothesis was not *more* likely than the competing view that Vioxx posed cardiovascular risks. The letter did not warn doctors about Vioxx or

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[5] The FDA letter did correct the error regarding the underreporting of cardiovascular events in the VIGOR trial and the consequent mistaken claim about the aspirin subgroup. J.A. 345; see note 3, *supra*. While this did remove one support for the naproxen hypothesis, it did not in any way suggest that the competing theory that Vioxx posed cardiovascular risks was correct.

suggest that prescribing patterns should change. The letter would not have caused reasonable medical professionals to conclude that Vioxx in fact posed serious cardiovascular risks or that treatment with Vioxx should be discontinued.

D. The Review of Merck Data Published In *Circulation*

1. The journal *Circulation*, the flagship journal of the American Heart Association, published an article on the cardiovascular safety of Vioxx on October 15, 2001 online (and in print a few weeks later). M.A. Konstam, M.R. Weir, A. Reicin et al., *Cardiovascular Thrombotic Events in Controlled, Clinical Trials of Rofecoxib,* 104 Circulation 2280 (2001). The two leading authors, Drs. Konstam and Weir, had been consultants to Merck, though Merck did not pay them for the article. *Id*. at 2280. Dr. Konstam in particular was Chief of Cardiology at the New England Medical Center and a respected academic leader in the field. The other five co-authors were Merck employees. *Ibid*.

While the article did not itself result from any new clinical trials, it did add to the publicly available medical data about Vioxx, because it considered 23 trials from Merck's internal files that had compared Vioxx to placebo, naproxen, or another nonselective NSAID such as ibuprofen. Most of those trials had not previously been published, and the cardiovascular event data from those trials that had been published had not previously been available to the public.

The comparison of Vioxx with placebo, on which the *Circulation* study added new data, was at the

heart of the controversy. The definitive resolution of the validity of the naproxen hypothesis turned squarely on whether Vioxx, in comparison to placebo, would be associated with cardiovascular risks or would be neutral. If patients given Vioxx and placebo suffered the same level of cardiovascular risks, then the VIGOR findings would likely have turned on the beneficial effects of naproxen — *i.e.*, the naproxen hypothesis would be correct. But if patients given Vioxx suffered more cardiac events in comparison with those given placebo, then the naproxen hypothesis put forward by Merck would be mistaken as a full explanation for the differences observed in the VIGOR study.

2. The article explained that "[t]he primary objective of this analysis was to assess whether [Vioxx] was associated with an excess of [cardiovascular] events," 104 Circulation at 2285 — *i.e.*, the validity of the naproxen hypothesis. The analysis counted cardiovascular events according to what is termed "APTC [Antiplatelet Trialists' Collaboration] standards," which comprise cardiovascular, hemorrhagic, and unknown deaths; nonfatal heart attacks; and nonfatal strokes. *Id*. at 2283. The conclusions of the analysis with respect to the safety of Vioxx were clear: "Most importantly, the results of the [Vioxx] relative to placebo comparison demonstrated a comparable risk of APTC events in both groups," a conclusion that "*[is] most reassuring that there is no evidence for any increased risk of [cardiovascular] thrombotic events with [Vioxx].*" *Id*. at 2285 (emphasis added). The article repeated substantially the same "no evidence" statement twice more. *Id*. at 2280, 2287.

The article's conclusions about naproxen's benefits were only slightly more guarded. The article endorsed the naproxen hypothesis. "The available data indicate that naproxen was different than other NSAIDs and was associated with decreased risk of [cardiovascular] events relative to [Vioxx]." *Id*. at 2285; see *id*. at 2280 ("Differences observed [in the VIGOR study] between [Vioxx] and naproxen are likely the result of the antiplatelet effects of the latter agent."). But the article did, more cautiously, add that "[a]lthough the data are suggestive, neither the VIGOR results nor the current analysis provide sufficient evidence to establish the cardioprotective benefits of naproxen." *Id.* at 2286.

3. The *Circulation* article added to the evidence available to medical professionals on the validity of the naproxen hypothesis, because it was based on data from Merck's files that was previously available only to Merck. Its results unequivocally provided substantial support to Merck's claim that Vioxx did not pose cardiovascular risks, and its results added substantially to the support for the naproxen hypothesis.

Later evidence that became public in 2003-2004 revealed that Vioxx in fact posed serious risks and that the naproxen hypothesis was mistaken. See Resp. Br. 9-10, J.A. 164-165, 174-175, 180. Indeed, Merck withdrew Vioxx from the market in 2004 after an interim analysis of a large randomized trial that studied the impact of Vioxx on reducing risk of colon polyp recurrence, known as the APPROVe trial, revealed that Vioxx in fact increased risk of cardiovascular risk when compared with placebo. J.A. 183-185. But the defects that existed in the *Circulation*

article would not have been apparent in November 2001.[6] As of November 6, 2001, a reasonable medical professional would have concluded that the naproxen hypothesis was likely correct, and that Vioxx did not pose cardiovascular risks sufficient to warrant reducing or ceasing using it to treat indicated conditions.[7]

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[6] One important defect was the authors' use of the APTC standards to identify cardiovascular risk. The APTC standards are appropriate, as the name suggests, for the purpose of testing the net benefit, considering efficacy and safety, of antiplatelet medications. They were not, however, designed for use in measuring the cardiovascular risks of drugs. A better measure would include all nonfatal cardiovascular adverse events (not merely nonfatal heart attacks and nonfatal strokes). It would also include deaths from *all* causes, because cardiovascular deaths are not always identified accurately, especially in clinical trials that were not designed (as the trials examined in the *Circulation* article were not) to examine cardiovascular outcomes. For example, death resulting from a car accident may in fact be caused by a heart attack that triggered the accident, but, especially if the person doing the classification is not specifically alerted to that possibility, the car accident may simply be identified as the cause of death. That is particularly true with Alzheimer's patients, who constituted two of the trials examined and about 25% of the total patients given Vioxx or placebo in Vioxx-placebo trials. See 104 Circulation at 2283 (Table 3). Given their cognitive impairments, Alzheimer's patients may not report symptoms accurately and may not be as thoroughly evaluated when brought for medical attention. It is thus particularly likely that deaths due to cardiovascular events would not be accurately reported in such patients.

[7] Amici, along with several colleagues, have themselves investigated the question of when the greater cardiovascular risk of Vioxx in comparison with placebo could have been known, and their research will be the subject of a forthcoming article in a prominent medical journal to be published prior to November 30, 2009. Due to prepublication embargo restrictions imposed by the journal, amici are unable at this time to provide any further information regarding their forthcoming study.

CONCLUSION

Materials in the public record by November 6, 2001, were insufficient to put a reasonable medical professional on notice that the naproxen hypothesis was flawed.

Respectfully submitted.

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APPENDIX A

Harlan M. Krumholz, MD, SM

Selected Awards and Honors:

1992	Finalist, American Heart Association Young Investigator Award
1996	William Harvey Award for Medical Journalism
1996-1999	Paul Beeson Faculty Scholar
1996-	Fellow, American College of Cardiology
1996-	Fellow, American Heart Association Council on Clinical Cardiology
1999-	Fellow, American College of Physicians-American Society of Internal Medicine
2000	William Coleman Branton Lecture, Mid America Heart Institute
2000-	Elected, American Society for Clinical Investigation
2003	Best Doctors in America
2004-	Elected, Association of American Physicians
2007	Award of Meritorious Achievement, American Heart Association
2007-	Elected, Institute of Medicine of the National Academies of Science
2008-	Elected, Connecticut Academy of Science and Engineering

Selected Recent National Committees:

2004	Scientific Advisory and Coordinating Committee, American Heart Association
2004	Outcomes: Impact from Observational Studies Writing Group from the Dispari-

	ties Conference, American Heart Association
2004	Expert Panel, Division of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention
2004-2006	Standards for Statistical Models Used for Public Reporting of Outcomes Writing Group, American Heart Association
2005	Case Study Development Group of the Committee to Evaluate Measures of Health Benefits for Environmental, Health, and Safety Regulation, Institute of Medicine
2005-2006	Co-Chair, Quality in Cardiovascular Imaging Working Group, American College of Cardiology
2005-2006	Advisory Panel, Gender Differences in Cardiovascular Care Feasibility Study, National Committee for Quality Assurance
2005-2006	Co-Chair, Heart IT Taskforce, American Heart Association
2005-2006	Research Advisory Council, National Committee for Quality Assurance
2005-2008	Acute Coronary Syndromes/Coronary Artery Disease Clinical Data Standards Writing Committee, American College of Cardiology/American Heart Association
2005-	Chair, Cardiac Scientific Advisory Board, UnitedHealthcare
2005-	Quality Strategic Directions Committee, American College of Cardiology

2005-	Chair, Standardizing Ambulatory Care Performance Measures Composite Measures Technical Advisory Panel, National Quality Forum
2005-	Acute Coronary Syndromes Registry Workgroup, American College of Cardiology
2006	Heart Failure and Hypertrophy Working Group, National Heart, Lung, and Blood Institute
2006-2008	Task Force on Practice Guidelines, American College of Cardiology/American Heart Association
2006-2008	Chair, D2B Quality Alliance Steering Committee, American College of Cardiology
2006-	Acute Coronary Syndrome Collaborative Workgroup, American College of Cardiology
2007	Review Panel, 2007 Rippel Scholars Award, Fannie E. Rippel Foundation
2007-	Task Force Reviewer, Guideline for the Management of Patients with Stable Ischemic Heart Disease (SIHD), American College of Cardiology/American Heart Association
2007-	Board of Directors, WikiDoc Foundation
2007-	Liaison to the Peer Review Working Group of the Advisory Committee to the Director, National Institutes of Health
2007-	Advisory Panel to the Cardiovascular Diseases Expert Working Group of the Global Burden of Disease Study, Centers for Disease Control and Prevention

2007-	Blue Ribbon Task Force on Health System Reform, American College of Cardiology
2008-	Clinical Advisory Group, VHA, Inc.
2008-	Methodology for the Selection and Creation of Performance Measures for Quantifying the Quality of Cardiovascular Care Writing Committee, American College of Cardiology/American Heart Association
2008-	Expert Panel on Integrated CVD Risk Reduction in Adults and the Guidelines Implementation Work Group, National Heart, Lung, and Blood Institute
2008-	Committee on Human Rights correspondent, National Academy of Sciences, National Academy of Engineering, and the Institute of Medicine
2008-	Chair, Quality Programs and Products Subcommittee of the Clinical Quality Committee, American College of Cardiology
2009	Science Classification Task Force, American Heart Association
2009-	Scientific Advisory Group, Institute for Healthcare Improvement
2009-	Chair, Steering Committee of the Hospital to Home (H2H) Initiative, American College of Cardiology
2009-	Board of Trustees, American College of Cardiology

Editorial Boards:

1996-1999	Journal Watch: Women's Health (Associate Editor)

1996-2000	Journal Watch for Cardiology (Associate Editor)
1997	American Journal of Medicine
1999-2003	Journal of the American College of Cardiology
2000-2005	American Heart Journal
2000-	Congestive Heart Failure
2000-	Journal Watch for Cardiology (Editor-in-Chief)
2002-	Critical Pathways in Cardiology
2003-	Circulation (Associate Editor)
2003-	American Journal of Managed Care
2003-	Journal of Cardiovascular Medicine, formerly theItalian Heart Journal (International Scientific Board)
2005-	Central European Journal of Medicine
2006-	Current Cardiovascular Risk Reports
2007-	Archives of Medical Science
2007-	JACC: Cardiovascular Imaging (Senior Consulting Editor)
2008-	Circulation: Cardiovascular Quality and Outcomes (Editor)

APPENDIX B

Joseph S. Ross, M.D., M.H.S.

Awards and Honors:

2004-2006	Robert Wood Johnson Clinical Scholars Award
2006	National Institute on Aging Summer Institute Participant
2006	Distinguished Reviewer, Journal of General Internal Medicine
2006-2008	John A. Hartford Center of Excellence Scholar
2008	Exceptional Reviewer, Medical Care
2008	American Heart Association Quality of Care and Outcomes Research Young Investigator Award
2008-2013	Paul B. Beeson Career Development Award in Aging Research
2009	Exceptional Reviewer, Medical Care
2009	Dr. Solomon Silver Award in Clinical Medicine for advances in patient-oriented research, established by the Richard and Hinda Rosenthal Foundation

National Committees:

2007-	Department of Veteran Affairs, Stroke Quality Enhancement Research Initiative (QUERI), Workgroup 3: Stroke Risk Factor Management
2009-	Society of General Internal Medicine, Health Policy Committee, Research Subcommittee

Editorial Boards:

2008- Journal of General Internal Medicine (Role: Advisory)
2009- PLoS ONE (Role: Academic Editor)

Peer Reviewer (Journals):

African Health Sciences
American Heart Journal
American Journal of Managed Care
Archives of General Psychiatry
Archives of Internal Medicine
Arthritis Care and Research
Breast Cancer: Basic and Clinical Research (Open Access)
Circulation
Circulation: Cardiovascular Quality and Outcomes
Diabetes Research and Clinical Practice
Health and Quality of Life Outcomes
Health Affairs
Health Policy
Health Services Research
JAMA
Journal of General Internal Medicine
Journal of Gerontology: Medical Sciences
Journal of Palliative Medicine
Journal of Rural Health
Journal of Urology
Journal of Women's Health
Medical Care
Personalized Medicine
PLoS Medicine
PLoS ONE