A Sociotechnical and Ethical Analysis of Responsibility for Merck's Vastly Harmful Arthritis Drug Vioxx

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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Introduction

In 1999, the US Food and Drug Administration (FDA) approved the drug Vioxx (rofecoxib) for use by prescription in the United States. Vioxx is a COX-2-selective nonsteroidal anti-inflammatory drug (NSAID) that was developed by the pharmaceutical company Merck & Co. (hereafter referred to as Merck) mainly to treat arthritis. However, in 2004, Merck voluntarily removed Vioxx from the market after data from APPROVe, a colon-polyp prevention study, showed that Vioxx significantly increased risk of cardiovascular events in patients (*Report*, 2004). This became a point of controversy, as years prior, Merck had misrepresented data from another study called VIGOR that also indicated that Vioxx caused negative cardiovascular health effects to maintain the drug's image as safe (Karha & Topol, 2004; Prakash & Valentine, 2007). 20 million Americans are estimated to have taken Vioxx before Merck removed it from the market, causing an estimated 88,000 heart attacks and 38,000 fatalities (Jüni et al., 2004). For Merck, over a decade of lawsuits and billions of dollars in settlements followed ("Merck Agrees to Pay $830 Million to Settle Vioxx Securities Lawsuit," 2016; *Office of Public Affairs | U.S. Pharmaceutical Company Merck Sharp & Dohme to Pay Nearly One Billion Dollars Over Promotion of Vioxx® | United States Department of Justice*, 2011; Wadman, 2007).

Current literature focuses heavily on the actions of Merck in this case, asserting that Merck's actions were unethical and that the company is at fault for the negative health effects that Vioxx caused. However, this understanding fails to fully analyze the role played by other influential factors and entities in the healthcare disaster of Vioxx. Reevaluating the case of Vioxx in a larger context that considers both the actions of Merck and the influence of factors external to Merck will provide a more comprehensive understanding of how this drug was able to cause

so much harm and could inform a better understanding of how similar occurrences can be avoided in the future.

In this research paper, I argue that in addition to Merck's actions, the FDA, the scientific community, and the pharmaceutical industry are all partially responsible for the adverse health effects that Vioxx imposed on thousands. I do so by utilizing the science, technology, and society (STS) framework of Actor-Network Theory (ANT) and ethical framework of passive responsibility to identify influential actors and the level of passive responsibility that they may or may not possess in the case of Vioxx. Primary sources of information inform my argument, including scholarly articles, press releases, regulatory documentation, direct accounts from scholars, legal documents, etc.

Literature Review

As it is one of the most high-profile and significant controversies in healthcare and pharmaceuticals in the 21st century thus far, there is plenty of scholarly discussion surrounding Merck's development, marketing, and eventual recall of Vioxx. In *What have we learnt from Vioxx?*, a team of researchers and scholars that participated in litigation for some of the legal cases following Vioxx's recall review and discuss the timeline of the case from a scientific and legal perspective. They claim that Merck acted dishonestly many times throughout the research and development of Vioxx, and that the company was aware of the potential risks to cardiovascular health that the drug presented but acted in their own financial interest. They claim that in addition to manipulating the analysis and presentation of the data from their internal studies, Merck ignored an "Expression of Concern" presented by the New England Journal of Medicine about the report they published from their VIGOR study, and that they "selectively

targeted doctors who raised questions about the drug." Looking forward, the authors discuss how regulatory agencies and the scientific community can help to prevent similar cases in the future, but hardly discuss the role they did play in the case of Vioxx or attribute any fault to anything other than Merck (Krumholz et al., 2007). Alexander Lyon comes to very similar conclusions in his analysis of Merck's communication during the Vioxx controversy. He goes into the distorted and internal and external communication of risk of Vioxx by Merck in depth, categorizing the deceptive strategies as neutralization, topical avoidance, and disqualification (Lyon, 2007).

Erin Cavusgil analyzes Vioxx's failure as a case study from an ethical perspective in her article *Merck and Vioxx: An Examination of an Ethical Decision-Making Model*. In it, she asserts that Merck suffered from a lack of "ethical decision-making," acting unethically in 2000 when deciding to market Vioxx. However, she does credit Merck with making the ethical choice in 2004 when removing Vioxx from market. She also briefly asserts that some may think the FDA did not act aggressively enough to prevent, and may be somewhat at fault (Cavusgil, 2007).

In his book *Poison Pills: The Story of the Untold Vioxx Scandal*, Tom Nesi discusses the case as well, focusing specifically on Merck's communication throughout. He asserts that the disaster that occurred was the result of the Merck marketing machine, and that the corporation put safety in the backseat in favor of financial gain (Nesi, 2008). A critic of the book points out that Nesi fails to acknowledge the role that the FDA, academia, and the pressure for a "blockbuster" drug played in the case (Solomon, 2009) .

It is clear that there is a general, prevailing consensus across the literature on the case that Merck acted unethically and is responsible for the failures surrounding Vioxx. Almost all this discussion focuses on Merck's actions throughout the research and development, marketing, and recall phases that Vioxx underwent. These scholars often define Merck's actions as unethical

based on common ethical principles and from a variety of ethical perspectives, such as how many are negatively affected by the actions, the defiance of societal/ethical norms (such as manipulating scientific information), the removal of doctor's and patient's ability to make informed decisions about the healthcare they are providing/receiving, and the attitude motivating these actions.

However, current literature lacks adequate discussion on the role that other entities played in the failure of Vioxx. Many entities are involved in this case, such as the US Food and Drug Administration (FDA), academia (including a variety of scientific journals, the larger pharmaceutical industry and healthcare industrial complex, and economic/intellectual competitors such as the similar drug Celebrex. When mentioned in discussion, it is often very brief, and very rarely are their contributions to the case examined past surface level. These players had influence over the situation, and therefore, there is a need to examine their role/contributions and any subsequent responsibility for the negative consequences that occurred.

Conceptual Framework

My analysis of Vioxx draws upon the science, technology, and society (STS) framework of Actor-Network Theory (ANT) and ethical framework of passive responsibility. This combination of STS and ethical frameworks will allow me to comprehensively examine the roles played by the many different entities involved with Vioxx, including the extent to which each is responsible for the negative health impacts caused by the drug.

Actor-Network Theory (ANT)

ANT regards the various, diverse entities that interact within a sociotechnical system as "actors" in a network and analyzes the dynamics of the network by focusing on the relationships

between actors (Cressman, 2009). Technologies themselves can exist as both a network and an actor. According to ANT, actors are recruited to the network and associated together by a "network builder" for a common purpose, such as developing a treatment for a particular condition, like Rheumatoid Arthritis (Callon, 1984). As it is particularly relevant in this case, I will also be paying attention to "rogue" actors that do not work cooperatively with other actors for the "common goal" of the network, but rather, against them. While the network assembled by Merck/engineers to develop Vioxx had the goal of success for the drug in the market, the eventual failure and recall of the drug implies that many actors acted as rogue actors. ANT defines and examines each of these actors alone and as they interact with one another to understand the system as a whole.

Passive Responsibility

Passive responsibility (in the context of a network of actors, as described by ANT) looks to the past to identify and examine the responsibilities of actors after an undesirable event has occurred in the network, such as Vioxx's negative health impacts on patients. Passive responsibility of an actor includes both accountability and blameworthiness. Accountability is defined as the responsibility of an actor to justify its actions that contributed to the undesirable event. Blameworthiness is defined as the responsibility to be a "target of blame for the consequences of one's actions." To determine the level of blameworthiness an actor is responsible for, four criteria are typically applied: wrong-doing, causal contribution, foreseeability, and freedom of action. For an actor to be guilty of wrong doing, their actions should be able to be defined as "wrong" according to some societal norm or common ethical principle. Causal contribution refers to the degree to which an actor contributed to the negative/undesirable event. To be guilty of causal contribution, the actor needs not be a main

contributor, however, significant causal contribution usually implies that the consequence/event would not have occurred had the actor behaved differently. The last two criteria, foreseeability and freedom of action, involve the liability of the actor. Foreseeability is the ability of the actor to know the potential consequences of their actions, while freedom of action looks at the actors' ability to act independently of any compulsion or manipulation. The extent to which these criteria are met by the actions of an actor determine the level of responsibility that can be placed on the actor for the undesirable event (van de Poel & Royakkers, n.d.).

In the analysis that follows, I begin by defining the network surrounding the Vioxx case according to ANT. This will include identifying the various actors, their level of involvement, and discussing their relationships with one another in respect to Vioxx. Then, I will individually examine each of the significant actors in the context of the network, utilizing the criteria described by passive responsibility to identify the blameworthiness, and thus, responsibility for, the negative health impacts the drug imposed upon thousands of patients. This will allow me to meet the need for a comprehensive analysis of all contributing factors in the case.

Analysis

Defining the Network

When considering the case of Vioxx, it is necessary to consider the full complexity of the relationships and influence occurring between all surrounding factors. Merck can objectively be considered the primary actor within in this case; the company developed Vioxx and was the primary decision-making party throughout the marketing and recall of the drug, including the subsequent litigation (Karha & Topol, 2004; McLean, 2005; *Vioxx Lawsuit | Settlements, Injury Claims & Notable Cases*, 2023). According to ANT, actors within a network can also be

considered networks themselves. This concept applies well to Merck; the various employees, shareholders, committees, and subgroups the company is comprised of constructs an internal network in which relationships are complex and deeply intertwined. However, within the overarching network of the Vioxx case and in relation with other, external actors, Merck often acted as a singular entity. Thus, in this larger context, the analysis of the Vioxx case will involve Merck being treated mainly as a singular entity/actor.

The FDA is another major actor involved in this network. With any drug development, the FDA is responsible for reviewing the development and safety of the drug and approving it for clinical use and marketing (US Food and Drug Administration, n.d.). The regulatory agency is also responsible for overseeing a drug's safety once approved and on the market. This was the case with Vioxx. The FDA approved Vioxx in 1999 (*Drug Approval Package: Vioxx (Rofecoxib) NDA# 021042 & 021052*, n.d.) and was subsequently responsible for the regulatory oversight of the drug on the market until it was recalled in 2004 (Administration (TGA), 2022). Thus, the FDA is a major actor in the case of Vioxx and forms a very direct and complex relationship with Merck.

The global scientific community has established a long-standing culture of accountability and integrity to protect the ability to have confidence in the reliability of scientific research. This includes an expectation of objectivity in research and development (International Science Council, 2008). In order to maintain this expectation, scientific findings are reported and published in academic journals, in which they are peer-reviewed to ensure integrity and accuracy. Although this community can be treated as one actor, it also can be considered a network, made up of a variety of journals and scholars. In the case of Vioxx, the New England Journal of Medicine individually and significantly contributed as an actor in the scientific

community sub-network, as the reports/findings of both the VIGOR and APPROVe studies were published in the journal (Kondro, 2006; Neel, 2005). However, other journals and individual academics also participated in the network, voicing opinions and concerns and publishing other significant data (McLean, 2005). Because of this, the overall scientific/academic community is a significant factor.

As Merck, the center of the network in this case, is a major pharmaceutical company, the pharmaceutical industry and larger healthcare industrial complex undoubtedly has ongoing and significant influence on Merck. Industrial expectations, norms, economic pressure, and more are all imposed upon pharmaceutical companies by the industry and healthcare system (Waxman, 2005a). Thus, the pharmaceutical industry serves as an actor in this network, and possesses a complex relationship with the other actors, mainly Merck. Celebrex is a drug developed by Pfizer Inc. that serves the same purpose as Vioxx and was also being marketed at the time (News, n.d.; *Study*, 2004). Furthermore, at the time, there were studies circulating that supported the claim that Celebrex imposed less of a cardiovascular risk upon patients than Vioxx did (Hudson et al., 2005). As a direct competitor to the central actor, Celebrex/Pfizer is an economic actor within Vioxx's network.

Finally, the network also involved smaller actors, such as patients, physicians, and Merck's investors/stakeholders. Most of these are individuals who were instead victims to the negative health and economic consequences of Merck's Vioxx. Many adverse health events were recorded, investors/stakeholders lost money with the recall of the drug. The harm done is recognized further through numerous lawsuits, from both health and financial sufferers, in the following decade(s) that were either settled or lost by Merck (Jüni et al., 2004; *Merck Moves to*

Settle Shareholder Vioxx Suits, 2010; Waxman, 2005b). Despite their complex relationships with the major actors, are not as influential over the network due to a lack of power.

Merck

The saga of Merck and its actions in the development, marketing, and eventual recall of Vioxx is long and incredibly complex. As the company developing the drug, Merck was in charge of the research and clinical trials testing the safety of the drug, analysis and reporting of the resulting data, and marketing for clinical use (Krumholz et al., 2007; Lyon, 2007). Throughout multiple studies of Vioxx's health effects on patient, Merck distorted and manipulated data to downplay the cardiovascular risks demonstrated in the data. Following the conclusion of the VIGOR study that compared the health effects of Vioxx to naproxen, Merck analyzed and presented the resulting data in a scientifically unusual fashion that made the Vioxx seem safer than it was (Bombardier et al., 2000; Curfman et al., 2005). First, the data used for the study of gastrointestinal study vs. cardiovascular study had different timelines for collection; the cardiovascular data in the report had an end-collection date a month earlier than that of the gastrointestinal data, an unusual inconsistency that affects the reliability of the data. Furthermore, there were 3 heart attacks that occurred in Vioxx patients that were not reported to the FDA with the rest of the VIGOR data (17 were reported, yet 20 occurred). Later, through analysis of Merck's internal communications, it was found that Merck was aware of the 3 additional heart attacks prior to their report which included disclosure of only 17. Finally, the authors of the report chose to present data which showed increased cardiovascular events with Vioxx as a result of cardioprotective activity by naproxen that reduced cardiovascular events in the naproxen group, rather than negative activity by Vioxx (Bombardier et al., 2000; Lyon, 2007;

Presley, n.d.). This claim was met with skepticism from cardiologists and other scientists (Curfman et al., 2005; Karha & Topol, 2004; Mukherjee et al., 2001; Prakash, 2005).

Merck also made immense efforts to market Vioxx as safe despite significant data suggesting otherwise and warnings from the FDA. Merck refused to include a warning recommended by the FDA disclosing that Vioxx increased the risk of heart attack five-fold, and used its own language instead. To market Vioxx to healthcare professionals, Merck utilized a "cardiovascular card" that omitted unfavorable data in order to paint Vioxx as safe (Josefson, 2001; Waxman, 2005a, 2005b). Furthermore, there is evidence that Merck attempted to limit and even silence criticism of Vioxx. An example of this is Dr. Gurkirpal Singh of Stanford University. Singh was recruited by Merck to promote Vioxx, however, upon review of studies such as VIGOR, was concerned about the cardiovascular risks. Reports, documents obtained from Merck's internal communications reveal that upon his expressions of concern, especially when public, Merck was unhappy with the negative light he was shedding on Vioxx and attempted to suppress opportunities for Singh to speak. Later, described in interviews and testimonies given by Singh, he discloses that Merck intimidated and threatened him through meetings, phone, and email communications (Grassley et al., 2004; Prakash, 2005).

First, Merck's actions clearly contributed heavily to the eventual negative health effects of Vioxx on thousands of patients, making the company guilty of causal contribution to a very high degree. People were able to take Vioxx as the direct result of Merck's willingness to bring it to market, and the impact was deepened (more people took it) due to Merck's intense marketing of the drug. It is also easily foreseeable that marketing a drug that has been shown to have significant adverse cardiovascular health effects in clinical trials will lead to significant adverse cardiovascular health effects in patients. Furthermore, Merck had complete freedom in the

decisions made to bring the drug to market and choose marketing strategies. One may argue that there was medical demand and potential financial repercussions that pushed Merck to putting Vioxx on the market. However, there were alternative drugs available that met the medical demand to a degree, and as one of the largest pharmaceutical companies in the world, Merck was not in need of the revenue from Vioxx.

The aforementioned actions by Merck are also "wrong" according to ethical norms. The manipulation of the VIGOR data and non-scientific analysis is an egregious example of scientific misconduct and dishonesty, and goes against many societal norms regarding dishonesty, especially in the scientific community. Marketing efforts and efforts to maintain Vioxx's image as safe also were dishonest, as these efforts downplayed potential negative health impacts while supporting unfounded claims. These actions all include omission and misrepresentation of information. Not only is this behavior dishonest, but it took away patients' and physicians' ability to participate in informed consent and harmed many. For all these reasons, Merck is guilty of wrongdoing. In examination of these actions, and many similar actions by Merck, it is clear that Merck acted unethically and, according to the heavily met criteria of passive responsibility, is largely responsible for the negative health impacts the drug had on patients.

The FDA

In 1999, the FDA approved Vioxx (*Drug Approval Package: Vioxx (Rofecoxib) NDA# 021042 & 021052*, n.d.). In Merck's new drug application for Vioxx, there was no study designed to evaluate cardiovascular risk, and cardiovascular safety was not an "area of concern" in the FDA's medical officer review (Krumholz et al., 2007; US Food and Drug Administration, 1999). After approval of the drug, the FDA issued multiple recommendations and statements of concern to Merck relating to the safety of Vioxx, including concerns about the accuracy of the

VIGOR study data, recommendations for warning labels disclosing cardiovascular risk, and advice against using unapproved marketing materials such as the "cardiovascular card" (Josefson, 2001; Waxman, 2005a). Ultimately, however, Merck voluntarily decided to remove Vioxx from the market in 2004 following results of the APPROVe study (Research, 2018) .

In examining the passive responsibility of FDA in the case of Vioxx, the question is whether the FDA's actions were sufficient, or if the regulatory agency should have done more to prevent the negative health effects that occurred due to Vioxx being allowed on the market. Aside from the initial approval of the drug in 1999, analysis of the FDA focuses more on its lack of action rather than action.

The FDA did not have full freedom of action in the case of Vioxx. First, the FDA cannot mandate a recall of a drug, only request it. Additionally, due to the distorted information provided by Merck to the FDA, the FDA was not informed of the full extent of Vioxx's potential health risks. However, the FDA did have full freedom in the initial approval of the drug. Furthermore, as demonstrated in the recommendations made by the FDA to Merck regarding Vioxx's safety, it is clear that the FDA had some level of foresight into the potential negative health effects of the drug. It is difficult to argue whether the lack of action by a regulatory government agency constitutes wrong-doing. More aggressive action against Merck by the FDA likely would have prevented some of the health impacts, making the FDA guilty of causal contribution, however, the failure to do so is ethically vague and hard to clearly label as "wrong" according to societal norms. Overall, due to the foresight of and causal contribution of the FDA, the regulatory agency does possess significant passive responsibility for the negative health effects of Vioxx. However, this is to a much lesser level than that of Merck.

Academia and the Scientific Community

The New England Journal of Medicine published the results of both the VIGOR and APPROVe studies conducted by Merck (Bombardier et al., 2000; Bresalier et al., 2005). It responded to inaccuracies and misrepresentation of the data from these through issues of statements of concern and requesting corrections (Curfman et al., 2005, 2006).

Like the FDA, the expression of concern from NEJM demonstrates foresight to the potential negative impacts of Vioxx. NEJM also had freedom of action in initially publishing the studies. However, although publishing studies with some inaccuracies and misrepresentation of data is an oversight, NEJM's public attempts to acknowledge these correct any wrongdoing that may be attributed to the journal. Furthermore, the action to publish Merck's studies had a relatively low causal contribution to the actual negative health effects that occurred. Overall, according to the criteria of blameworthiness, the NEJM does possess some level of passive responsibility in the case of Vioxx, but much less than Merck and the FDA.

The rest of the scientific community has the responsibility to hold their peers in science accountable for maintaining scientific integrity, especially as scientific experts are equipped with additional foresight due to their expertise (International Science Council, 2008). However, Merck's actions to silence and intimidate Vioxx critics, especially from a position of power as a major pharmaceutical company, took away freedom of action (Lyon, 2007). Those who did still express concern had a positive causal contribution on the health impacts of Vioxx by exposing some of the risks that Merck was covering up. The greater scientific community does possess the responsibility to maintain a culture of scientific integrity, however, in this case, the passive responsibility that can be assigned to the scientific community for the negative health effects of Vioxx is minimal.

The Pharmaceutical Industry and broader Healthcare Industrial Complex

It is well known that the pharmaceutical industry and healthcare industrial complex place industrial pressure on companies to prioritize financial gain (Josefson, 2002; Maron & Hauser, 2007). This includes the pressure to develop a "blockbuster drug" that has important indications and does very well on the market. Before its removal from the market, Vioxx could be considered a blockbuster drug (Greener, 2005; Nesi, 2008).

The pharmaceutical/healthcare industry, which includes many scientific experts and healthcare professionals, is well aware of the potential negative impacts of creating pressure to prioritize financial gain over safety, and it is commonly accepted as ethically wrong to do so. Additionally, as one of the most profitable and necessary industries in the country, it possesses freedom of choice in how it operates. However, it is hard to quantify the degree to which this perceived external pressure actually motivated Merck to push Vioxx to market, so the causal contribution is not as significant. Thus, the pharmaceutical industry does possess some passive responsibility in the case of Vioxx, but not more so than Merck or the FDA.

Celebrex/Pfizer

Celebrex was a drug developed by Pfizer that was a direct competitor with Vioxx at the time it was on the market (News, n.d.; Prakash, 2005, p. 1; *Study*, 2004). Although the competition with Celebrex likely placed pressure on Merck to push Vioxx to market despite safety concerns, Celebrex/Pfizer did not actually act to place this pressure on Merck. The simple existence of Celebrex was what put pressure on Merck. Therefore, although it is an influential factor, Pfizer does not possess any passive responsibility for the effects of Vioxx, as there was no action taken that influenced Merck to act in a way that Merck is not fully responsible for itself.

Conclusion

Merck's dishonest and unethical actions are the main reason Vioxx became one of the most harmful healthcare disasters this century. However, according to the criteria described by passive responsibility, the FDA, the scientific community, and the pharmaceutical industry all possess some degree of blameworthiness in the case of Vioxx as well. Thus, Merck, although primarily responsible, also shares some of the responsibility for the negative health impacts Vioxx had on thousands with these other, influential actors.

This more comprehensive analysis of Vioxx's development, marketing, and eventual removal from market contributes to a more comprehensive understanding of how the drug was able to be so harmful and can inform the analysis of similar cases in healthcare. Going forward, this understanding can also help to prevent and avoid such a disaster from occurring again, protecting public health.

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References

Administration (TGA), T. G. (2022, May 26). *Vioxx (Rofecoxib) | Therapeutic Goods Administration (TGA)* [Text]. Therapeutic Goods Administration (TGA). https://www.tga.gov.au/news/product-recalls/vioxx-rofecoxib

Bombardier, C., Laine, L., Reicin, A., Shapiro, D., Burgos-Vargas, R., Davis, B., Day, R., Ferraz, M. B., Hawkey, C. J., Hochberg, M. C., Kvien, T. K., & Schnitzer, T. J. (2000). Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis. *New England Journal of Medicine*, *343*(21), 1520–1528. https://doi.org/10.1056/NEJM200011233432103

Bresalier, R. S., Sandler, R. S., Quan, H., Bolognese, J. A., Oxenius, B., Horgan, K., Lines, C., Riddell, R., Morton, D., Lanas, A., Konstam, M. A., & Baron, J. A. (2005). Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial. *New England Journal of Medicine*, *352*(11), 1092–1102. https://doi.org/10.1056/NEJMoa050493

Callon, M. (1984). Some Elements of a Sociology of Translation: Domestication of the Scallops and the Fishermen of St Brieuc Bay. *The Sociological Review*, *32*(1_suppl), 196–233. https://doi.org/10.1111/j.1467-954X.1984.tb00113.x

Cavusgil, E. (2007). Merck and Vioxx: An Examination of an Ethical Decision-Making Model. *Journal of Business Ethics*, *76*(4), 451–461. https://doi.org/10.1007/s10551-006-9302-3

Cressman, D. (2009). *A Brief Overview of Actor-Network Theory: Punctualization, Heterogeneous Engineering & Translation*. Simon Fraser University. https://summit.sfu.ca/item/13593

Curfman, G. D., Morrissey, S., & Drazen, J. M. (2005). Expression of Concern: Bombardier et al., “Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis,” N Engl J Med 2000;343:1520-8. *New England Journal of Medicine*, *353*(26), 2813–2814. https://doi.org/10.1056/NEJMe058314

Curfman, G. D., Morrissey, S., & Drazen, J. M. (2006). Expression of Concern Reaffirmed. *New England Journal of Medicine*, *354*(11), 1193–1193. https://doi.org/10.1056/NEJMe068054

Drug Approval Package: Vioxx (Rofecoxib) NDA# 021042 & 021052. (n.d.). Retrieved March 16, 2024, from https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/021042_52_Vioxx.cfm

Grassley, C., Hatch, O., & Nichols, D. (2004). *FDA, MERCK, AND VIOXX: PUTTING PATIENT SAFETY FIRST?* U.S. GOVERNMENT PRINTING OFFICE.

Greener, M. (2005). Drug safety on trial. *EMBO Reports*, *6*(3), 202–204. https://doi.org/10.1038/sj.embor.7400353

Hudson, M., Richard, H., & Pilote, L. (2005). Differences in outcomes of patients with congestive heart failure prescribed celecoxib, rofecoxib, or non-steroidal anti-inflammatory drugs: Population based study. *BMJ : British Medical Journal*, *330*(7504), 1370.

International Science Council. (2008, October 23). Global scientific community affirms its shared responsibilities for the integrity of science and its role in society. *International Science Council*. https://council.science/current/press/global-scientific-community-affirms-its-shared-responsibilities-for-the-integrity-of-science-and-its-role-in-society/

Josefson, D. (2001). FDA warns Merck over its promotion of rofecoxib. *BMJ : British Medical Journal*, *323*(7316), 767.

Josefson, D. (2002). Drug companies face pressure on profits. *BMJ : British Medical Journal*, *324*(7329), 65.

Jüni, P., Nartey, L., Reichenbach, S., Sterchi, R., Dieppe, P. A., & Egger, M. (2004). Risk of cardiovascular events and rofecoxib: Cumulative meta-analysis. *The Lancet*, *364*(9450), 2021–2029. https://doi.org/10.1016/S0140-6736(04)17514-4

Karha, J., & Topol, E. J. (2004). The sad story of Vioxx, and what we should learn from it. *Cleveland Clinic Journal of Medicine*, *71*(12), 933–934. https://doi.org/10.3949/ccjm.71.12.933

Kondro, W. (2006). Dispute over Vioxx study plays out in New England journal. *CMAJ : Canadian Medical Association Journal*, *174*(10), 1397. https://doi.org/10.1503/cmaj.060433

Krumholz, H. M., Ross, J. S., Presler, A. H., & Egilman, D. S. (2007). What have we learnt from Vioxx? *BMJ : British Medical Journal*, *334*(7585), 120–123. https://doi.org/10.1136/bmj.39024.487720.68

Lyon, A. (2007). "Putting Patients First": Systematically Distorted Communication and Merck's Marketing of Vioxx. *Journal of Applied Communication Research*, *35*(4), 376–398. https://doi.org/10.1080/00909880701611052

Maron, B. J., & Hauser, R. G. (2007). Perspectives on the Failure of Pharmaceutical and Medical Device Industries to Fully Protect Public Health Interests. *The American Journal of Cardiology*, *100*(1), 147–151. https://doi.org/10.1016/j.amjcard.2007.02.072

McLean, T. R. (2005). Discontinuation of Vioxx. *The Lancet*, *365*(9453), 25. https://doi.org/10.1016/S0140-6736(04)17656-3

Merck agrees to pay $830 million to settle Vioxx securities lawsuit. (2016, January 15). *Reuters*. https://www.reuters.com/article/idUSKCN0UT1PW/

Merck moves to settle shareholder Vioxx suits. (2010, February 10). https://www.nbcnews.com/id/wbna35334356

Mukherjee, D., Nissen, S. E., & Topol, E. J. (2001). Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA*, *286*(8), 954–959. https://doi.org/10.1001/jama.286.8.954

Neel, J. (2005, December 8). Medical Journal: Vioxx Paper Flawed. *NPR*. https://www.npr.org/templates/story/story.php?storyId=5045087

Nesi, T. (2008). *Poison Pills: The Untold Story of the Vioxx Drug Scandal*. Macmillan.

News, A. B. C. (n.d.). *For Former Vioxx Users, Celebrex May Be an Option*. ABC News. Retrieved March 16, 2024, from https://abcnews.go.com/Health/story?id=2425435&page=1

Office of Public Affairs | U.S. Pharmaceutical Company Merck Sharp & Dohme to Pay Nearly One Billion Dollars Over Promotion of Vioxx® | United States Department of Justice. (2011, November 22). https://www.justice.gov/opa/pr/us-pharmaceutical-company-merck-sharp-dohme-pay-nearly-one-billion-dollars-over-promotion

Prakash, S. (2005, June 9). Part 1: Documents Suggest Merck Tried to Censor Vioxx Critics. *NPR*. https://www.npr.org/2005/06/09/4696609/part-1-documents-suggest-merck-tried-to-censor-vioxx-critics

Prakash, S., & Valentine, V. (2007, November 10). Timeline: The Rise and Fall of Vioxx. *NPR*. https://www.npr.org/2007/11/10/5470430/timeline-the-rise-and-fall-of-vioxx

Presley, H. (n.d.). *VIOXX AND THE MERCK TEAM EFFORT*.

Report: Vioxx linked to thousands of deaths. (2004, October 6). NBC News. http://www.nbcnews.com/health/health-news/report-vioxx-linked-thousands-deaths-flna1C9445945

Research, C. for D. E. and. (2018). Vioxx (rofecoxib) Questions and Answers. *FDA*. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/vioxx-rofecoxib-questions-and-answers

Solomon, D. H. (2009). Poison pills: *The untold story of the Vioxx drug scandal*. *The Journal of Clinical Investigation*, *119*(3), 427–427. https://doi.org/10.1172/JCI38430

Study: Celebrex Safer Than Vioxx - CBS News. (2004, December 17). https://www.cbsnews.com/news/study-celebrex-safer-than-vioxx/

US Food and Drug Administration. (n.d.). *Food and Drug Administration (FDA) | USAGov*. Retrieved March 16, 2024, from https://www.usa.gov/agencies/food-and-drug-administration

US Food and Drug Administration. (1999). *Medical Officer Review—Vioxx*. https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/021042_52_vioxx_medr_P1.pdf

van de Poel, I., & Royakkers, L. (n.d.). *Ethics, Technology, and Engineering*. 10–13.

Vioxx Lawsuit | Settlements, Injury Claims & Notable Cases. (2023, September 5). Drugwatch.Com. https://www.drugwatch.com/vioxx/lawsuits/

Wadman, M. (2007). Merck settles Vioxx lawsuits for $4.85 billion. *Nature*. https://doi.org/10.1038/450324b

Waxman, H. A. (2005a). The Lessons of Vioxx—Drug Safety and Sales. *New England Journal of Medicine*, *352*(25), 2576–2578. https://doi.org/10.1056/NEJMp058136

Waxman, H. A. (2005b). *Democratic Memo: The Marketing of Vioxx to Physicians*. Congress of the United States. https://www.industrydocuments.ucsf.edu/wp-content/uploads/2014/11/waxmanmemo_vioxx.pdf