

ONCE DAILY  
**VIOXX**<sup>®</sup>  
(rofecoxib)

# How strong is the case against Merck?



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<sup>1</sup> Merck & Co. Inc., (last visited Dec. 20, 2005), *available at* <http://www.vioxx.com/rofecoxib/vioxx/consumer/index.jsp>

<sup>2</sup> Associated Press, (last visited Dec. 15, 2005), *available at* <http://www.cbsnews.com/stories/2004/11/14/60minutes/main655577.shtml>.

## INTRODUCTION

Suspicious over pharmaceutical ethics in an exclusively profit based industry have surfaced once again. This time is the victim Merck & Co., Inc. (“Merck”) or is it the twenty million Americans who filled their prescriptions for Vioxx? Plaintiff attorney Mark Lainer’s opening statement, in the first publicized trial in Brazoria County Texas state court, described the company’s drug safety policy as “Murky Ethics.” The thousands of personal injury cases filed after Merck’s voluntary withdrawal of Vioxx appear difficult to prove. A large obstacle for plaintiffs is the admissibility of epidemiologic studies, which are required to prove specific causation. Despite considerable obstacles, the sex appeal of these cases is too enticing for the litigation savvy. If plaintiffs can at least get the case to make it to a jury, then the odds are that some will be successful with likely large awards, possibly including punitive damages.

Pharmaceutical companies spend countless hours and resources developing and researching new drugs. While considering America’s health concerns, companies direct most of their attention towards medical problems that have a greater population to market to, or most importantly, ones that will generate the most revenue. Once a drug is initially developed and the corporation believes it to be a profitable venture, trials of drugs begin in the lab and then clinically in order to gain regulatory approval.<sup>3</sup> In order for a drug to be approved for sale in the U.S. the drugs must endure the Food and Drug Administration (“FDA”) three-step approval process.<sup>4</sup>

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<sup>3</sup> Food and Drug Administration, *The New Drug Approval Process: Steps from Test Tube to New Application Review*, available at <http://www.fda.gov/cder/handbook/develop.htm> (last visited Dec. 12, 2005). This clickable diagram explains the process each drug endures in the approval process.

<sup>4</sup> *Id.*

## **FOOD AND DRUG ADMINISTRATION**

The FDA falls under the direction of the Department of Health and Human Services. Overly simplified, the FDA process is one comparing the risks and side effects of a drug to the benefit one receives from taking it. In making these decisions, the FDA takes into account the significance of a targeted health condition, or the status of that condition as a treatable disease.<sup>5</sup> If a product has not received marketing approval (or an exemption) from the agency, then the drug cannot be sold. Even if a company has surmounted the often difficult hurdle of proving that a product serves a therapeutic purpose without posing an undue risk, the FDA's decisions about appropriate labeling may affect how readily patients will be able to use it.<sup>6</sup>

On average, the estimated cost from design to approval in 2000 dollars is \$802 million.<sup>7</sup> The expected cost of developing the average HIV/AIDS drug is \$479 million; however, the expected cost of developing the average rheumatoid arthritis drug is close to double at \$936 million.<sup>8</sup> The difference in cost is attributable to the necessity and speed that AIDS drugs need to get to otherwise terminally ill patients.

## **DIRECT TO CONSUMER MARKETING**

Historically, pharmaceutical companies developed and directed their entire product marketing, promotion, and education to physicians and health care providers responsible for prescribing the manufacturer's products.<sup>9</sup> Realizing the profit potential, drug companies now

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<sup>5</sup> Noah Lars, *Challenges in the Federal Regulation of Pain Management Technologies*, 31 J. L. Med. & Ethics 55 (Spring 2003).

<sup>6</sup> *Id.*

<sup>7</sup> Christopher Adams, *Estimating the Costs of New Drug Development: Is it really \$802m?* (Dec. 2004), available at [http://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=640563#PaperDownload](http://papers.ssrn.com/sol3/papers.cfm?abstract_id=640563#PaperDownload).

<sup>8</sup> *Id.*

<sup>9</sup> Elizabeth Powell-Bullock, *Gaming the Hatch-Waxman System: How Pioneer Drug Makers Exploit the Law to Maintain Monopoly Power in the Prescription Drug Market*, 29 J. Legis. 21, 40 (2002).

provide direct-to-consumer advertising to the public in an effort to increase profits and market share.<sup>10</sup>

Upjohn Co. became the first drug manufacturer to advertise directly to consumers when it advertised for Rogaine, a hair-loss treatment.<sup>11</sup> From 1995 to 1996 drug companies increased advertising directed to consumers by ninety percent.<sup>12</sup> Many ads aimed at consumers were lacking in some manner and did not give the consumer sufficient understanding of the associated risks of using the drug.<sup>13</sup> The massive direct advertising campaign continued in the early 1990's, with marketing directed towards women, instead of their doctors, concerning the Norplant™ birth control system.<sup>14</sup> These recent developments have provoked FDA response.

Merck is one of the five largest pharmaceutical companies in the world.<sup>15</sup> Company sales totaled nearly \$23 billion in 2003.<sup>16</sup> Vioxx was heavily marketed in the U.S. and 80 countries worldwide.<sup>17</sup> The company spent over \$100 million annually in direct-to-consumer advertising on Vioxx alone.<sup>18</sup> The drug became an instant blockbuster with physicians writing over one hundred million prescriptions, twenty million users, and raking in roughly \$2.5 billion in Merck's annual sales.<sup>19</sup>

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<sup>10</sup> *Id.*

<sup>11</sup> *Perez v. Wyeth Laboratories Inc.*, 734 A.2d 1245 (N.J. 1999) *citing* Jon D. Hanson and Douglas A. Kysar, *Taking Behavioralism Seriously: Some Evidence of Marketing Manipulation*, 112 Harv. L. Rev. 1420, 1456 (1999).

<sup>12</sup> *Id.*

<sup>13</sup> Hanson, *supra* note 11.

<sup>14</sup> *In Re Norplant Contraceptive Products Liability Litigation*, 215 F. Supp. 2d 795 (D.C.E.D. Tex. 2002).

<sup>15</sup> *Prescription For Trouble*, ASSOCIATED PRESS, Nov. 14, 2004 *available at* <http://www.cbsnews.com/stories/2004/11/14/60minutes/main655577.shtml>.

<sup>16</sup> *Id.*

<sup>17</sup> Merck & Co. Inc., *Merck Announces Voluntary Worldwide Withdrawal of VIOXX* (Sept 30, 2004), *available at* [http://www.vioxx.com/vioxx/documents/english/vioxx\\_press\\_release.pdf](http://www.vioxx.com/vioxx/documents/english/vioxx_press_release.pdf).

<sup>18</sup> Eric J. Topol, *Good Riddance to a Bad Drug*, N.Y. TIMES, Oct. 2, 2004, at A15.

<sup>19</sup> Dustin R. Marlowe, *Note: A dose of reality for §6(c) of the Restatement (Third) of Torts: Products Liability*, 39 Ga. L. Rev. 1445 (Summer, 2005).

Merck's success with Vioxx paralleled Pfizer's COX-II inhibitors, Celebrex and Bextra.<sup>20</sup> The success of all three drugs was attributable to their apparent ability to satisfy the best of both possible worlds, relieving pain without provoking the risk of stomach or intestinal bleeding inherent to ibuprofen and similar drugs.<sup>21</sup> The cost of a COX-II specific drug is far greater than original non-steroidal anti-inflammatory drugs ("NSAIDs") such as aspirin.<sup>22</sup> Vioxx costs a few dollars a day while aspirin is only a few pennies.<sup>23</sup> Vioxx was not intended to be taken as often (once a day) compared to other NSAIDs (two or more times a day);<sup>24</sup> so while Vioxx is more convenient the greater cost may outweigh the convenience of the dosage.

### **WHAT IS VIOXX?**

Rofecoxib ("Vioxx") received FDA approval in 1999 for sale in the U.S.<sup>25</sup> The drug's intended uses at the time of approval was for reduction of pain and inflammation caused by osteoarthritis, acute pain, and menstrual pain.<sup>26</sup> The drug was subsequently approved to treat rheumatoid arthritis in adults and children.<sup>27</sup> Rheumatoid arthritis is a chronic syndrome characterized by inflammation in the lining of the joints, causing pain, stiffness, warmth, redness,

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<sup>20</sup> Aaron Smith, 'Me-too' drugs can rake in sales: Copycats like Lipitor can make billions, or fail like Vioxx and Bextra. CNN (July, 28, 2005), available at <http://money.cnn.com/2005/07/27/news/fortune500/metoo/index.htm>; See also, Richard A. Epstein, *Pharmaceutical Innovation and Cost: An American Dilemma: Regulatory Paternalism in the Market for Drugs: Lessons from Vioxx and Celebrex*, 5 Yale J. Health Pol'y L. & Ethics 741, 742 (Summer, 2005).

<sup>21</sup> *Id.*

<sup>22</sup> *Id.*

<sup>23</sup> *Id.* The original NSAIDs are not isoform specific and inhibit both COX enzymes which is later explained in greater detail. Some examples include aspirin (Bayer), naproxen (Aleve), and ibuprofen (Advil). To date many (including those listed) of the original NSAIDs are over-the-counter medications ("OTC") which do not require the prescription. All COX-II selective drugs are only obtainable by prescription.

<sup>24</sup> *Id.*

<sup>25</sup> Prescription for Trouble, *supra* note 15.

<sup>26</sup> Marlowe, *supra* note 19.

<sup>27</sup> *Id.*

and swelling, leading to pain and loss of movement.<sup>28</sup> Osteoarthritis, or degenerative joint disease, is characterized by the breakdown of the cartilage that cushions the ends of bones.<sup>29</sup> The cartilage breakdown at the joints causes the bones to rub against each other, leading to pain and loss of movement.<sup>30</sup>

Vioxx is in a class of drugs called NSAIDs.<sup>31</sup> NSAIDs represent peripherally acting analgesics.<sup>32</sup> They work by blocking the production of prostaglandins, which are hormone-like chemicals that are released in the body in response to injury.<sup>33</sup> The prostaglandins are what cause inflammation, redness, swelling, pain, and fever.<sup>34</sup> Reducing the amount of prostaglandins reduces inflammation and its symptoms.<sup>35</sup> In order to inhibit production of prostaglandins, the NSAIDs act by blocking the enzyme cyclooxygenase (“COX”).<sup>36</sup> After further study scientists discovered that the COX enzyme has two isoforms, one associated with inflammation (COX-II) and another thought to protect the lining of the stomach (COX-I).<sup>37</sup> Older NSAIDs blocked both isoforms, which may explain their connection to development of ulcers.<sup>38</sup>

Like other drugs in the same class as Vioxx, the COX-II designation was believed to signify a welcomed measure of specificity. Drugs in this class could work effectively in pain management while being friendlier on the stomach than original NSAIDs.

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<sup>28</sup> Randall W. King and Richard Worthington, *Arthritis, Rheumatoid* (last modified April 8, 2005), available at <http://www.emedicine.com/emerg/topic48.htm>.

<sup>29</sup> Gregory Stacy and Auveek Pat Basu, *Osteoarthritis, Primary* (last modified Nov. 4, 2005), available at <http://www.emedicine.com/radio/topic492.htm>.

<sup>30</sup> *Id.*

<sup>31</sup> Lars, *supra* note 5.

<sup>32</sup> Analgesics relieve pain without causing the loss of consciousness.

<sup>33</sup> Lars, *supra* note 5.

<sup>34</sup> *Id.*

<sup>35</sup> Corinne de Vires, *Cox-II inhibitors versus non-steroidal anti-inflammatory drugs in rheumatoid and osteoarthritis patients: gastrointestinal effects*. STEER 2002; Vol. 2: No. 8 (2001), available at [http://www.wihrd.soton.ac.uk/projx/signpost/steers/STEER\\_2002\(8\).pdf](http://www.wihrd.soton.ac.uk/projx/signpost/steers/STEER_2002(8).pdf). Steer.

<sup>36</sup> *Id.*

<sup>37</sup> *Id.*

<sup>38</sup> Lars, *supra* note 5; Inhibiting COX-I is thought to inhibit the production of mucosa of the inner lining of the stomach and therefore leaves the lining unprotected from irritation leading to ulcers.

## WHAT HAPPENED?

Clinical research began to indicate that there may be an increase in adverse cardiovascular (“CV”) side effects associated with Vioxx. In February 1997, top company scientist, Alise Reicin, wrote an internal email that read “the possibility of increased CV events is of great concern.”<sup>39</sup> She also wrote that the concern of these results may “kill” the drug.<sup>40</sup> Company employees and their consultants published several papers in medical journals rebutting studies reporting Vioxx’s heart attack risk. Merck dismissed these studies, citing poor clinical study design and inadequate data. However, Merck did not engage in research to rebut the allegations.

In February 2001, the FDA consulted its Arthritis Advisory Committee regarding the clinical interpretation and found COX-II inhibitors potentially have a beneficial anti-atherogenic<sup>41</sup> effect by reducing inflammation. Inflammation is also an important contributor to heart attacks and strokes.

On September 17, 2001, the director of the FDA Division of Drug Marketing, Advertising, and Communications, issued a “Warning Letter” to the President and CEO of Merck relating to promotional activities and materials for the marketing of Vioxx.<sup>42</sup> The letter stated that Merck’s promotional campaign discounted the facts of an epidemiological study (VIGOR). The results of this study showed a correlation between patients taking Vioxx and a four to five fold increase in myocardial infarctions<sup>43</sup> compared to patients taking naproxen.<sup>44</sup> A

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<sup>39</sup> Heather Tosoriero, et. al., *Merck Loss Jolts Drug Giant, Industry*, WALL ST. J., Aug. 22, 2005, at A1.

<sup>40</sup> Anna Mathews and Scott Hensley, *Medical Journal Says Merck Study Omitted Data*, WALL ST. J., Dec. 9, 2005, at A6.

<sup>41</sup> Anti-atherogenic properties help to prevent formation of plaques in the arteries.

<sup>42</sup> Thomas W. Abrams, *Warning Letter*, FOOD AND DRUG ADMINISTRATION (Sept. 17, 2005), available at [http://www.judiciary.state.nj.us/mass-tort/forms/vioxx\\_longform\\_exhibb\\_111303.pdf](http://www.judiciary.state.nj.us/mass-tort/forms/vioxx_longform_exhibb_111303.pdf).

<sup>43</sup> Acute myocardial infarction (AMI) is the rapid development of myocardial necrosis (death of heart muscle tissue) caused by a critical imbalance between the oxygen supply and demand of the myocardium. More information available at <http://www.emedicine.com/EMERG/topic327.htm>.

few months later Merck changed product labeling to include the results of this study. However, Merck had such confidence in the ability of Vioxx that the company sought to expand the portfolio of permissible uses by raising the dosage to determine the effectiveness of Vioxx in treating polyps.<sup>45</sup> During this trial Merck discovered an apparent increase in the number of adverse CV occurrences.<sup>46</sup>

On September 30, 2004, Merck announced that it would voluntarily pull Vioxx from the market. Withdrawal occurred before FDA demand. The decision to remove the drug from the market was widely read as a fatal admission of dangerous conduct by a company that should never have launched the drug in the first place. The veritable firestorm of reactions included the anticipated onslaught of ordinary tort actions for personal injuries, congressional investigations, inquiries by the SEC, derivative actions, suits for refunds, internal inquiries and so forth.<sup>47</sup> Merck's shares lost \$12 from \$45.07 to \$33 the day it announced Vioxx's removal, only to stabilize in the \$29-\$33 range thereafter.<sup>48</sup> On November 2, 2004, Merck's stock tumbled 10% after the media reported that the company hid data regarding Vioxx from the FDA.<sup>49</sup>

On a larger scale, one wonders if the drug industry's tolerance for incomplete data is reflective of an industry preference for marketing drugs based on profitability rather than effects. Would the drug companies be so tolerant of incomplete financial data on their drugs? Fingers are being pointed everywhere, hoping to find someone to blame. Dr. David Graham, an FDA scientist, put the blame on the FDA saying the agency overvalues the benefits of the drugs it

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<sup>44</sup> Debabrata Mukherjee, et. al., *Risk of Cardiovascular Events Associated With Selective Cox-2 Inhibitors*, J.A.M.A. 286:8, 954-959, (Aug. 22, 2001). *See also*, Abrams, *supra* note 41.

<sup>45</sup> Polyps are intestinal growths that may become cancerous.

<sup>46</sup> Robert Bresalier, *Cardiovascular Events with Rofecoxib in Colorectal Adenoma Chemoprevention Trial*, NEJM (March 17, 2005), Issue 352, 1092-1102. *See also*, Epstein, *supra* note 20, at 742.

<sup>47</sup> *Id.*

<sup>48</sup> *Id.*

<sup>49</sup> *Id.*

approves and seriously undervalues drug safety.<sup>50</sup> As the CV side effects became increasingly apparent, Merck and the FDA engaged in a tug of war over the label's language.

On December 17, 2004 Pfizer announced that one of two clinical studies on Celebrex, another COX-II, revealed that it presented an elevated risk of heart attacks.<sup>51</sup> There is a strong suspicion as more research is completed that the cardiac events may affect the entire class of COX-II drugs.<sup>52</sup> In 2002, Merck withdrew its FDA application for another COX-II drug the company was developing called Arcoxia.<sup>53</sup> This represented Merck's first application removal in ten years.<sup>54</sup> Pfizer has not removed Celebrex from the market, but has since stopped consumer advertising.<sup>55</sup>

On February 18, 2005, the FDA created an advisory panel to look into concerns related to Vioxx. The panel recommended allowing doctors to prescribe Vioxx provided the product came with a strong warning for special need cases.<sup>56</sup> The panel decided that the arthritis drugs' benefits outweighed the risks of heart problems and strokes but suggested the products carry strong warnings. The FDA is not bound by the panel's findings. At this point Merck has not lobbied the FDA to return the drug to market. Physicians have attempted to explain why there

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<sup>50</sup> See, Philip J. Hilts, PROTECTING AMERICA'S HEALTH: THE FDA; BUSINESS; AND 100 YEARS OF REGULATION. (2003).

<sup>51</sup> FE Silverstein, et. al., *Gastrointestinal toxicity with celcoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study*, JAMA (2000), Vol. 284, Issue 10, 1247-55.

<sup>52</sup> Andrew Pollack, *New Scrutiny of Drugs in Vioxx's Family*, N.Y. TIMES, Oct. 4, 2004, at C1; Rod Winslow, *Heart Risk Is Seen In Class of Drugs For a Host of Ills*, WALL ST. J., Oct. 7, 2005, at B4.

<sup>53</sup> Forbes, *Bad News: Merck Withdraws Arcoxia Application* (March 15, 2005), available at [www.forbes.com/2002/03/15/0315mrk.html](http://www.forbes.com/2002/03/15/0315mrk.html); see also, *In re Merck & Co., Inc.*, 150 S.W.3d 747 (Tex. App. 2004).

<sup>54</sup> *Id.*

<sup>55</sup> Amy Tsao. *Big Changes for Big Pharma* (January 3, 2005). available at [http://www.businessweek.com/bwdaily/dnflash/jan2005/nf2005013\\_7406\\_db037.htm](http://www.businessweek.com/bwdaily/dnflash/jan2005/nf2005013_7406_db037.htm); see also, Epstein, *supra* note 20.

<sup>56</sup> The strongest warning, as here, called a "Black Box Warning," which is of certain size located on the front of the box visible to all users that addresses a specific warning.

may be an increased CV risk with Vioxx.<sup>57</sup> The role of COX enzymes in the body is clearly not fully understood and there is evidence that COX-I has thrombotic effects (helps promote blood clotting). Blocking COX-II and not COX-I could tip the balance in favor of clotting.<sup>58</sup>

On March 1, 2005 the FDA, in response to overwhelming criticism, lobbied congress to be empowered to write warning labels for drugs.<sup>59</sup> This caused a revisit to how the FDA should proceed on matters of withdrawal and recall. Some observers have criticized the agency for approving too many new NSAIDs that offer no particular advantage over existing, and typically less expensive drugs in the class.<sup>60</sup> The FDA usually does not make judgments about comparative efficacy, preferring to leave that task for physicians and patients based on the information supplied in the labeling dictated by agency reviewers.<sup>61</sup> On November 9, 2005, the FDA made a recommendation that all COX-II drugs carry a boxed warning highlighting GI and CV risks.<sup>62</sup>

On December 8, 2005, the *New England Journal of Medicine* released an editorial, published in the December 29<sup>th</sup> edition, stating that editors have uncovered what is believed to be publishing misconduct.<sup>63</sup> Editors allege that authors of the VIGOR study failed to publish the complete findings of patients having adverse CV outcomes.<sup>64</sup> An editor, preparing for

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<sup>57</sup> Yang Chen, et. al., *Role of Prostacyclin in the Cardiovascular Response to Thromboxane A2*, Journal of Science, Vol. 296, pp. 539-541 (Apr. 19, 2002).

<sup>58</sup> Richard Bing and Magdalena, *Why Do Cyclo-Oxygenase-2 Inhibitors Cause Cardiovascular Events?*, J Am Coll Cardiol, Vol. 39 Issue 3, p. 521, 522 (Feb. 6, 2002).

<sup>59</sup> *Drug Safety; FDA wants power to write warning labels on drugs*, CARDIOVASCULAR DEVICE LIABILITY WEEK (March 27, 2005) at 54.

<sup>60</sup> Epstein, *supra* note 20.

<sup>61</sup> Lars, *supra* note 5.

<sup>62</sup> Federal Drug Administration, *COX 2 Selective (includes Bextra, Celebrex, and Vioxx) and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)*, available at <http://www.fda.gov/cder/drug/infopage/COX2/default.htm> (last visited Dec. 12, 2005).

<sup>63</sup> Gregory Curfman, et. al., *Expression of Concern: Bombardier et al., "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," N Engl J Med 2000;343:1520-8.* NEJM (2005) Issue 353, 26.

<sup>64</sup> *Id.*

deposition, discovered a disk in an envelope submitted with the original article.<sup>65</sup> Using a tracing feature in the data entry program, Stephen Morrissey, the journal's managing editor found that the disk contained another version of the study results.<sup>66</sup> This additional data has been explained by the original authors as data which was collected outside of the timeframe of the study design. Even though the non-reported data was not taken during the study timeframe, the authors of the study were seen as misleading the scientific community because they knew that there was additional data which conflicted with their study's results.

### **SUBSEQUENT LITIGATION**

Following Vioxx's withdrawal, an onslaught of lawsuits were filed against Merck. To date over 6,500 lawsuits have been filed and the number is growing rapidly.<sup>67</sup> Federal courts have assigned these cases to Multi-District Litigation<sup>68</sup>. Two widely publicized trials in State court have already been completed; *Ernst v. Merck* in Brazoria County, Texas, and *Humeston v. Merck* in Atlantic County Superior Court, New Jersey. Analysts have estimated Merck's potential liability exposure somewhere between four and thirty billion dollars.<sup>69</sup>

Robert Ernst, a 57 year-old marathon runner and Wal-Mart employee, died suddenly after taking Vioxx for eight months to ease pain in his hands.<sup>70</sup> The medical examiner put in her autopsy report that Earnst died of an arrhythmia;<sup>71</sup> however, at trial, she stated the cause of death

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<sup>65</sup> *Id.*

<sup>66</sup> Mathews, *supra* note 40.

<sup>67</sup> David Brown, *Journal Questions Data in Vioxx Study: 3 Heart Attacks Not Mentioned*, WASH. POST, Dec. 9, 2005, at A2.

<sup>68</sup> The shareholder cases have been designated in New Jersey as MDL 1658 – In re Merck & Co., Inc., Securities, Derivative & “ERISA” Litigation; the product liability lawsuits have been designated MDL 1657 – In re VIOXX Product Liability Litigation.

<sup>69</sup> Associated Press, *Newbury woman files Vioxx lawsuit*, THE UNION LEADER (Manchester, NH) March 24, 2005, at B3.

<sup>70</sup> Nora L. Toohar, *Vioxx Goes On Trial*, LAWYERS WEEKLY, 2005 LWUSA 437, 460, Aug. 1, 2005 at 1, 24.

<sup>71</sup> Arrhythmias are disorders of the heart's regular rhythmic beating.

was a heart attack. There is no medical or scientific evidence indicating that taking Vioxx is associated with arrhythmias. In addition, the court allowed experts to testify from merely their own expertise and admitted the evidence on adverse CV events for 18 month use, while the plaintiff had only used the drug for eight.<sup>72</sup> Despite the lack of evidence, on Aug 19, 2005, the jury delivered a \$253.5 million dollar verdict against Merck in a 10-2 decision.<sup>73</sup> Texas law limits the amount of punitive damages that are recoverable to two million dollars.<sup>74</sup> After caps on respective damages the total award will be reduced to \$26 million.<sup>75</sup> Following the verdict, interviews with the jurors revealed that the jurors apparently did not heavily weigh the evidence; they focused more on sending a message to drug companies regarding their deceptive acts.<sup>76</sup>

Following the Texas trial Merck released a statement on August 20, 2005, which argued the verdict was not based on reliable science and that Merck continues to act in the best interests of their patients.<sup>77</sup> The statement also made clear that Merck plans to continue its strategy of vigorously defending individual Vioxx lawsuits.<sup>78</sup>

Fortunately for Merck, the jury sided 8-1 with the company in the second publicized state court trial in Atlantic City Superior Court of New Jersey.<sup>79</sup> In that case, Mike Humeston suffered a heart attack after taking 25mg of Vioxx for pain in his knee from an injury he had received during his U.S. Marine service.<sup>80</sup> Because the cause of death was not in dispute, this case was arguably more indicative of a sample of the lawsuits filed. However, since Mr.

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<sup>72</sup> Tooher, *supra* note 68.

<sup>73</sup> *Id.*

<sup>74</sup> Heather Win Tesoriero, et al., *Merck Loss Jolts Drug Giant, Industry*, WALL ST. J., Aug. 22, 2005, at A1.

<sup>75</sup> *Id.*

<sup>76</sup> Kristen Hayes, *Vioxx Jurors Sought to Send a Message*, ASSOCIATED PRESS (Aug. 19, 2005), available at <http://www.abcnews.go.com/US/LegalCenter/wireStory?id=1053407>.

<sup>77</sup> Associated Press, *Merck Wins New Jersey VIOXX® Product Case* (Nov. 3, 2005), available at <http://www.vioxx.com/rofecoxib/vioxx/consumer/index.jsp>.

<sup>78</sup> Barbara Martinez, *Facing Vioxx Trials, Merck Pledges To Fight Each Case*, WALL ST. J., April 22, 2005, at A1.

<sup>79</sup> Lisa Brennen, *Merck Wins Big in New Jersey Vioxx Trial* (Nov. 4, 2005), available at <http://www.law.com/jsp/article.jsp?id=1131012312488>.

<sup>80</sup> Associated Press, *Major Victory for Merck in N.J. Trial* (Nov. 3, 2005), available at <http://msnbc.msn.com/id/9910674>.

Humeston had taken Vioxx for less than three months, it was difficult to relate any of the negative studies which have all been trials of at least nine months or longer.<sup>81</sup> There has not been any negative short-term data collected, likely because the human body is very resilient to short-term, low-level toxicity.

### **CLINICAL RESEARCH**

The research results have received different interpretations throughout both the medical and pharmaceutical field. One interpretation of the epidemiological data suggests a relationship between Vioxx and patients suffering adverse CV events. Others cite that the data is inaccurate because the CV results were not collected as part of the study's intended design. All CV data collected comes from secondary findings<sup>82</sup> from studies designed for a different purpose. However, plaintiffs will attempt to use these findings in order to imply that Merck had knowledge of an increased risk of adverse CV outcomes. The use of these studies as admissible evidence will center on the reliability of the data, the intended design timeframe, and how long the patient took Vioxx.

### ORIGINAL DATABASE

The original FDA safety database on Vioxx included approximately 5000 patients and did not show an increased risk of heart attack or stroke.<sup>83</sup> The reliability of studies for examining gastrointestinal ("GI") adverse effects was generally limited. Many studies were inadequately powered to detect differences in frequency of separate adverse GI events. Most studies

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<sup>81</sup> *Id.*

<sup>82</sup> A secondary finding is additional data collected during a study's intended timeframe regarding a category or class that was not part of the specific study design, but was collected contemporaneously with the clinical trial period.

<sup>83</sup> FDA, *Vioxx Questions and Answers* (created Sept. 30, 2004), available at <http://www.fda.gov/cder/drug/infopage/vioxx/vioxxQA.htm>. (last visited Feb 10, 2006). See also, Epstein, *supra* note 20.

examined short term effect, which suggested that COX-II inhibitors are associated with a slightly lower risk of GI toxicity compared with NSAIDs.<sup>84</sup>

### VIGOR

In March 2000, Merck funded a GI safety study entitled “Vioxx Gastrointestinal Outcomes Research” (“VIGOR”).<sup>85</sup> The VIGOR trial was a double blind, randomized, stratified, parallel group trial of 8076 patients designed to compare the occurrence of GI toxicity with Vioxx 25mg and 50mg per day or naproxen<sup>86</sup> 1000mg per day during long term treatment for patients with rheumatoid arthritis. Aspirin use was not permitted in the study. As a secondary finding, patients taking Vioxx had an overall increase in adverse CV events throughout the 18 month study compared to placebo. The study initially published in the *New England Journal of Medicine* showed Vioxx has a 4.25 times the relative risk of heart attack compared to naproxen. (Vioxx 17/2315 = 0.0073 vs. Naproxen 4/2316 = 0.0017).<sup>87</sup> This study was submitted to the FDA.<sup>88</sup> The additional data recently uncovered shows additional heart attacks which would increase the relative risk of Vioxx to five times that of patients taking naproxen (Vioxx 20/2698 = 0.0074 vs. Naproxen 4/2699 = 0.00148).<sup>89</sup> None of the adverse CV events in the study were fatal.<sup>90</sup> In May 2000, after VIGOR publication, Merck’s top research and marketing executives declined to perform a more extensive study focused on Vioxx’s CV risks, arguing that the VIGOR data was unreliable.<sup>91</sup>

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<sup>84</sup> Corinne de Vires, *supra* note 35.

<sup>85</sup> Mukherjee, *supra* note 44.

<sup>86</sup> Naproxen is commonly known by trade name as Aleve.

<sup>87</sup> Claire Bombardier, et. al., *Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*, NEJM (2000), Issue 343, 1520-1528.

<sup>88</sup> *Id.* This data is depicted in tables on page 46.

<sup>89</sup> Curfman, *supra* note 63.

<sup>90</sup> *Id.*

<sup>91</sup> Epstein, *supra* note 20.

## APPROVe

Subsequently, Merck undertook a different large, randomized trial of 2,586 patients in an attempt to expand the permissible uses of the drug approved to include treatment of colon polyps.<sup>92</sup> The study, termed APPROVe, revealed that 3.6% of subjects taking Vioxx had adverse CV events compared to 2.0% in the placebo group.<sup>93</sup> This data prompted Merck to voluntarily remove the drug from the market.<sup>94</sup> Removal of the drug also came from pressure of FDA scientists, such as David Graham, who interpreted the study to say Vioxx had caused between 88,000 and 139,000 heart attacks. Out of that number, he suggested that 40% of those were fatal.<sup>95</sup>

## CLASS

Pfizer Inc. performed a six-month study comparing the cardiovascular effects of its drug Celebrex to Vioxx.<sup>96</sup> The study was called CLASS (Celecoxib Arthritis Safety Study).<sup>97</sup> The study found a decrease in GI complications by 10-20 per 1000, but an increase in adverse CV events by 3 per 1000.<sup>98</sup> In percentages, Vioxx decreased GI bleeding by 1-2% while increasing CV events by approximately 0.3% when compared to placebo.<sup>99</sup> Patients showed a greater increase in hypertension rates<sup>100</sup> with Vioxx than Celebrex when compared to placebo.<sup>101</sup> The

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<sup>92</sup> A polyp is a small growth of tissue shaped like the head or stalk of a mushroom. Two types of polyps developed in the wall of the colon. They are either hyperplastic (harmless) or adenomatous (precursor to cancer); *see also*, <http://www.emedicine.com/radio/topic185.htm>.

<sup>93</sup> Bresalier, *supra* note 46.

<sup>94</sup> Topol, *supra* note 18; *see also*, Epstein, *supra* note 20.

<sup>95</sup> Douglas C. Nelson, *Insurance Brokerage Giant Exposed by Consumer Fraud Charges*, 17 Loy. Consumer L. Rev. 237 (2005).

<sup>96</sup> Silverstein, *supra* note 51.

<sup>97</sup> *Id.*

<sup>98</sup> *Id.*

<sup>99</sup> *Id.*

<sup>100</sup> Hypertension is a blood pressure above the normal range.

<sup>101</sup> Silverstein, *supra* note 51.

placebo control data came largely from patient populations with substantial CV risk, which is why most were not given the COX-II's in the first place.<sup>102</sup>

#### OTHER STUDIES

Other research revealed discrete clinical differences between the two COX-II inhibitors which suggest that the effect of the drugs on the cardiovascular system should be viewed separately rather than as a single class of drugs.<sup>103</sup> Subsequent studies have also revealed a deficiency in what was originally believed to be one of the greatest benefits of the COX-II inhibitors. Scientists believed COX-II drugs were associated with a reduction in GI bleeding; however, that reduction may have been grossly exaggerated.<sup>104</sup> A British study of two randomized controlled trials which followed patients for a year or more found that there was no significant difference in frequency of perforation, ulceration or bleeding between NSAIDs and the COX-II inhibitors rofecoxib or etodolac.<sup>105</sup>

#### **PRODUCT LIABILITY LAW**

The law of product liability has developed in tort through *Greenman v. Yuba Power Products, Inc.*<sup>106</sup> Strict liability was assigned to a manufacturer of a defective product on the market even though both privity of contract and notice of breach of warranty were lacking.<sup>107</sup> Strict liability does not rest on a consensual foundation, but on one created by law. In *Greenman*, the court held that no notice was needed for a breach of express warranty regarding

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<sup>102</sup> *Id.*

<sup>103</sup> University of Pennsylvania Health System Public Affairs, *Penn Epidemiological Study Shows Difference in Cardiovascular events Between Vioxx and Celebrex* (last visited Nov. 29, 2005), available at <http://www.upenn.edu/researchatpenn/article.php?894&hlt>.

<sup>104</sup> Corinne de Vires, *supra* note 35.

<sup>105</sup> *Id.*

<sup>106</sup> *Greenman v. Yuba Power Products, Inc.*, 337 P.2d 897 (Cal. 1963).

<sup>107</sup> *Id.*

representations made in a brochure.<sup>108</sup> Thus, strict liability in tort for products was born judicially as a policy for the economic and social needs for consumer protection. This policy also alleviated some of the limitations in the negligence and warranty remedies.

Subsequently, the *Greenman* strict liability principle was incorporated in §402A of the Restatement (Second) of Torts which has been adopted in the majority of jurisdictions. Federal courts will apply state law to the claims because these claims fall under diversity jurisdiction. The publication of the Restatement (Second) of Torts, drafters have been working on the Third edition. In 1998, a draft version of the Restatement (Third) of Torts was released which focuses on product liability in much greater detail, but its provisions are not yet officially enacted into state legislation. Even though no state has adopted the specific provisions of the third edition, the courts use it as a guide to interpret existing law.

To establish a successful claim under §402A the plaintiff must establish, (1) the product had a defect, (2) the product was defective when it left the hands of defendant, and (3) that the product defect proximately caused the plaintiff's harm.<sup>109</sup> A product may be defective because of a defect in manufacture, design, or a failure to adequately warn the consumer of a hazard involved in the foreseeable use of the product.<sup>110</sup>

A defective condition is one not contemplated by the ultimate consumer which would be unreasonably dangerous to him.<sup>111</sup> A defective product is one that is "unreasonably dangerous."<sup>112</sup> This means it must be dangerous to an extent beyond that which would be contemplated by the ordinary consumer who purchases it, with the ordinary knowledge common

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<sup>108</sup> *Id.*

<sup>109</sup> Restatement (Second) of Torts §402A, AMERICAN LAW INSTITUTE (1965).

<sup>110</sup> *Id.*

<sup>111</sup> Restatement (Second) of Torts, §402A(G)AMERICAN LAW INSTITUTE (1965).

<sup>112</sup> §402A, *supra* note 109.

to the community as to its characteristics.<sup>113</sup> For example, sugar would not be not be considered unreasonably dangerous to a diabetic.

A defect in the manufacture of a product exists if the product differs from the manufacturer's intended design.<sup>114</sup> The harmful incident a plaintiff suffers must be of a kind that ordinarily occurs as a result of a product defect.<sup>115</sup> Common examples of manufacturing defects are products that are physically flawed, damaged, or incorrectly assembled. The Vioxx litigation does not concern a “bad batch” or contaminated product associated with a manufacturing type of defect. Here, claims for product defect include defective design and defective warning.

The essential elements of a claim based upon an alleged design defect are: the defendant was the manufacturer or supplier of a product; the product was defective in design; the defect in design existed when it left the defendant's possession; the defect in design was a cause of injury to the plaintiff; and the plaintiff's injury resulted from a use of the product that was reasonably foreseeable by the defendant.<sup>116</sup> Different jurisdictions, and even inconsistencies within a jurisdiction, use two common tests to determine whether a product is defective in design.

A product has a defective warning if the use of the product in a manner that is reasonably foreseeable by the seller involves a substantial danger that would not be readily recognized by the ordinary user of the product and the manufacturer knows or should have known of the danger, but fails to give any or adequate warning of such danger.<sup>117</sup> The duty to provide adequate warning to the user extends to those risks which are known or knowable in light of the

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<sup>113</sup> §402A(i), *supra* note 109; *see also*, Cronin v. J.B.E. Olson Corp, 501 P.2d 1153 (Cal. 1972).

<sup>114</sup> *Id.*

<sup>115</sup> *Id.*

<sup>116</sup> Restatement (Third) of Torts §6, AMERICAN LAW INSTITUTE (1998).

<sup>117</sup> *Id.*

generally recognized and prevailing best scientific and medical knowledge at the time of manufacture and distribution.<sup>118</sup>

Specific attention is directed toward prescription drugs in products liability law. Restatement (Second) of Torts §402A, comment k (“comment k”) takes special notice of unavoidably unsafe products and recognizes that because of the high social utility, some products are incapable of being made safe for intended and ordinary use.<sup>119</sup>

A manufacturer may also be liable in tort under other theories of recovery. Those related to the Vioxx litigation include misrepresentation or fraud, and breach of express or implied warranty. We will now explore each of these theories, their strengths and weaknesses, as applied to the Vioxx litigation.

There is no question that Vioxx is a product.<sup>120</sup> In addition, there is no dispute as to whether Merck is in the business of selling or otherwise distributing. And since Merck is the sole manufacturer of Vioxx, we will assume that the consumers were actually given the drug distributed by the sole manufacturer. There is no question Merck manufactured, designed, packaged, marketed, sold or distributed Vioxx. There will also be an assumption each user took their medication as directed by their prescribing physician.

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<sup>118</sup> *Id.*

<sup>119</sup> §402A, *supra* note 109, at *comment k*. Unavoidably unsafe products: There are some products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use. These are especially common in the field of drugs. An outstanding example is the vaccine for the Pasteur treatment of rabies, which not uncommonly leads to very serious and damaging consequences when it is injected. Since the disease itself invariably leads to a dreadful death, both the marketing and the use of the vaccine are fully justified, notwithstanding the unavoidable high degree of risk which they involve. Such a product, properly prepared, and accompanied by proper directions and warning, is not defective, nor is it unreasonably dangerous. The same is true of many other drugs, vaccines, and the like, many of which for this very reason cannot legally be sold except to physicians, or under the prescription of a physician. It is also true in particular of many new or experimental drugs as to which, because of lack of time and opportunity for sufficient medical experience, there can be no assurance of safety, or perhaps even of purity of ingredients, but such experience as there is justifies the marketing and use of the drug notwithstanding a medically recognizable risk. The seller of such products, again with the qualification that they are properly prepared and marketed, and proper warning is given, where the situation calls for it, is not to be held to strict liability for unfortunate consequences attending their use, merely because he has undertaken to supply the public with an apparently useful and desirable product, attended with a known but apparently reasonable risk.

<sup>120</sup> Restatement (Third) of Torts §19, AMERICAN LAW INSTITUTE (1998).

## ADMISSIBILITY OF CLINICAL RESEARCH

Merck consistently argues that the studies are unreliable due to their design. Reliability is a relative term. Something can be highly reliable or it may only be vaguely reliable. What are the factors that show us whether it is reliable enough to give to the jury?

This revisits one of the greatest disconnects between law and medicine. Just as you would not want your medical malpractice attorney practicing medicine on you, most Judges are not medically literate enough to understand the reliability of these scientific studies. This is the same reason physicians argue for medical courts overseen by a panel of physicians similar to specialized courts in other areas such as bankruptcy.<sup>121</sup>

If it is so difficult to understand whether the research is reliable, one suggestion is to let the jury decide. However, having unsophisticated juries decide whether the data is reliable, which experts on both sides contradict, does not alleviate any problems and effectively allows plaintiffs to play the courtroom lottery. In the cases already tried to verdict, allowing for the introduction of this evidence has only produced what could be expected, inconsistent results that do not properly instruct the market on how to act or the company to insure against. This has been a result of differing rules and interpretations in diverse jurisdiction. Some state courts differently interpret or do not apply the principles laid out in the *Daubert* Trilogy, which is followed in a majority of jurisdictions.<sup>122</sup>

All clinical data that parties wish to introduce will undergo a *Daubert* hearing on admissibility as the court operates in its “gate-keeping” function.<sup>123</sup> The admissibility of evidence will likely have different outcomes that varies depending on where a case was filed.

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<sup>121</sup> Maggie Fox, *Fear of Lawsuits Hurts Medical Care, Survey Shows*, REUTERS (April 17, 2002), available at <http://newt.acrisoft.com/index.php?src=news&prid=280&category=Articles>.

<sup>122</sup> This commonly refers to the following three cases; *Daubert v. Merrell Dow Pharmaceuticals*, 509 U.S. 579 113; *GE v. Joiner*, 522 U.S. 135; *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137.

<sup>123</sup> *Daubert*, *supra* note 122.

The state and federal rules of evidence often differ drastically.<sup>124</sup> An expert may rely on information that is not itself admissible.<sup>125</sup> It would not seem difficult then to be able to find experts willing to use some or all of the studies, in addition to their own medical experience<sup>126</sup> to formulate an opinion that Vioxx caused patients taking it to have a heart attack or stroke.

Under the older *Frye* test,<sup>127</sup> evidence of scientific theory or technique is inadmissible unless it has gained the general acceptance in the community or the particular field to which it belongs. Under the current *Daubert* standard, the trial court judge needs to make sure that scientific testimony or other specialized knowledge is relevant and reliable.<sup>128</sup> In order to determine reliability of the evidence the judge may consider: whether the theory can and has been tested; whether it has been subject to peer review; whether the theory or methodology employed is generally accepted in the relevant scientific community; and the known or expected rate of error.<sup>129</sup>

The difficulty with the Vioxx data is the expected rates of error of secondary findings and the acceptance of those in the scientific community. The gold standard<sup>130</sup> in the scientific community for a reliable epidemiological study is a double blind placebo controlled study designed to study a certain effect. The research showing increased CV would also have to correlate to the milligrams taken by the patient. If the study used patients taking Vioxx at 50mg and the injured patient only used Vioxx at 25mg, the correlation between the two would not be

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<sup>124</sup> FED. EVID. R. 703 (2005).

<sup>125</sup> *Id.* See also, FED EVID. R. 702 (2005).

<sup>126</sup> *Khumo Tire, supra* note 114. Expert testimony based solely on the experience of the expert with out more would not be admissible.

<sup>127</sup> *Frye v. United States*, 293 F. 1013 (D.C. App. 1926).

<sup>128</sup> *Daubert, supra* note 122.

<sup>129</sup> *Rider v. Sandoz Pharmaceutical Corp.* 295 F.3d 1194 (11<sup>th</sup> Cir. 2002).

<sup>130</sup> The gold standard refers to the ideal scientific standard; however it is difficult to attain and is not necessarily indicative of the standard in the community.

scientifically reliable. The VIGOR study followed patients for 18 months so it would not be on point for those who took Vioxx for a lesser time period.

Further, Merck argued that Vioxx itself did not cause the heart attacks but that Naproxen was somehow preventing them, which makes the two products dissimilar comparisons in head-to-head trials.<sup>131</sup> The CLASS study was the only one designed to study CV events. In the publication of the CLASS findings comparing CV effects of Vioxx to Celebrex, the author disclaims the reliability of the data comparing Vioxx to placebo because it is a secondary finding.<sup>132</sup> The other research also discovered CV risk only through secondary findings. Plaintiffs have also pointed to a study conducted in 1998 that had secondary results indicating Vioxx caused heart problems in dogs, but this may not show a similar reaction in humans.

It appears that each piece of evidence individually should not pass *Daubert* standards. However, judges may decide after reviewing the studies that collectively they are reliable enough to be admissible.

### **THE COX-II DESIGN**

For most products, there are two common assessments to determine if a product is defective in design. Under the first test, called the Consumer-Expectation-Test, a product is defective in design if it fails to perform as safely as an ordinary consumer would expect when used in an intended or reasonably foreseeable manner.<sup>133</sup> This is the impression reasonably received by a consumer through representations or other communications made to him about the

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<sup>131</sup> Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, *Joint Meeting of the Arthritis Advisory Committee and The Drug Safety and Risk Management Advisory Committee*, Vol. 2 (Feb. 17, 2005), transcript available at <http://0-www.fda.gov.lilac.une.edu/ohrms/dockets/ac/05/transcripts/2005-4090T2.doc>.

<sup>132</sup> See note 82, *supra*..

<sup>133</sup> 402A(i), *supra* note 102; *see also*, *Heaton v. Ford Motor Co.*, 435 P.2d 806 (Or. 1967).

product through various means such as: advertising, appearance of product, or other ways in which product projects an image on the mind of the consumer, including impressions created by widespread social agreement about the products function.<sup>134</sup>

It is quite easy to satisfy this test because often this is the sole purpose of filing the litigation in the first place. Here, users would argue that after taking the appropriately prescribed amount to cure their pain they suffered a heart attack. No ordinary person would expect to have a heart attack as a result from taking their pain medication. However, ordinary patients do expect drugs to have at least some side effects.

The second and most prominent test is the Risk-Utility-Test which determines if there is a risk of danger inherent in the design which outweighs the benefits of that design.<sup>135</sup> When making this determination, the trier of fact considers: the gravity of the danger posed by the design; the frequency of harm; the likelihood that such danger would cause damage, the mechanical feasibility of a safer alternate design at the time of manufacture, the financial cost of an improved design, and the adverse consequences to the product and the consumer that would result from an alternate design.<sup>136</sup>

Here, the danger of heart attack or stroke is extremely grave, but according to the studies the frequency of these events is only marginally increased compared to naproxen (0.17% to 0.73%).<sup>137</sup> The likelihood is different depending on how high a CV risk the patient had to begin with. The only properly designed CV effect study only compared the drug to Celebrex. This may indicate the feasibility of a safer design, but no one understands how or why. Different people weighing these factors may place different emphasis on what they believe to be important

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<sup>134</sup> *Id.* See also, *Brown v. Raymond Corp.* 432 F.3d 640 (6<sup>th</sup> Cir. 2005).

<sup>135</sup> Restatement (Second) of Torts §520, AMERICAN LAW INSTITUTE (1965).

<sup>136</sup> *Id.* See also, *Caballero v. Concord*, 956 F.2d 204. (9<sup>th</sup> Cir. Cal. 1992).

<sup>137</sup> *Bombardier, supra* note 87.

factors. It appears relatively clear that medical science hasn't evolved enough to understand just how the COX enzymes work. It would be difficult to argue with any medical certainty since scientists do not understand exactly how Celebrex and Vioxx differ from each other besides their chemical structures. Because of this ambiguity, it would seem for now that after weighing the factors under this test, the purported benefits of the drug outweigh the risk; thus, no design defect.

However, neither traditional risk verses benefit nor consumer expectation analyses apply in the majority of jurisdictions for prescription drugs.<sup>138</sup> The majority of jurisdictions follow the holding in *Brown v. Superior Court*, whereby pharmaceutical drugs are automatically analyzed using comment k.<sup>139</sup> There is no requirement that the drug be determined unavoidably dangerous in order to be measured by comment k.<sup>140</sup> The test provides that when a drug does not provide any net benefits to any class of patients or when reasonable, informed health-care providers would not prescribe it to any class of patients, then the design of the product is defective and the manufacturer should be subject to liability for harm caused.<sup>141</sup> The issue is whether, objectively viewed, reasonable providers, knowing the foreseeable risks and benefits of the drug, would prescribe it for any class of patient.<sup>142</sup> The majority follow this test because the foreseeability of risk of harm is more complex in the case of prescription drugs.<sup>143</sup>

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<sup>138</sup> *Brown v. Superior Court of the City and County of San Francisco*, 1061 751 P.2d at 477, 478 (Cal. 1998) overruling *Kearl v. Lederle Laboratories*, (1985) This effectively changed the analysis for prescription drugs where the judge no longer must first ascertain if product falls under unavoidably dangerous exception. The court in *Brown* court noted that the test adopted in *Kearl* was too confusing because of its analysis between useful and harmful drugs which lead to inconsistent conclusions about the same drug.

<sup>139</sup> *Id.*

<sup>140</sup> *Id.*

<sup>141</sup> §402(a), *supra* note 109, at *comment k*. See also, *Hill v. Searle Laboratories, Div. Of Searle Pharmaceuticals, Inc.*, 884 F.2d 1064 (U.S. App. 8<sup>th</sup> Cir. 1989).

<sup>142</sup> *Brown*, *supra* note 138.

<sup>143</sup> Restatement (Third) Torts, §2 AMERICAN LAW INSTITUTE (1998) at *comment m*.

Prescription drugs are necessary to alleviate pain and suffering or to sustain life. They are distinct from other products, such as construction machinery, which are used to make work easier or provide pleasure.<sup>144</sup> The delay involved in withholding a drug from the market until scientific skill and knowledge advanced to the point at which additional dangerous side effects would be revealed, when added to the delay required for approval from the FDA, would not serve the public welfare.<sup>145</sup>

The comment k test is the most difficult test to prove. After Merck removed Vioxx from the market, patients complained that it was the only drug effective to help them with pain management. Patients cited that if there was an associated CV risk they had an open willingness to confront it.<sup>146</sup> The drug still provides great benefits to the entire classes taking the drug, although providing less of a benefit for those with high CV risk. Doctors still prescribed the drug after the research and editorials were published in medical literature. Also, there is no research which indicates increased CV risk for short-term use. However, if Merck representatives had not downplayed the risk associated with Vioxx, physicians may have not prescribed the drug because of the wide range of available alternatives. Even assuming Vioxx was not intended to be prescribed to some classes, the data does not indicate that if Vioxx does cause heart attacks it would not benefit any class at all.

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<sup>144</sup> *Brown, supra* note 138.

<sup>145</sup> *Id.* There is an underlying assumption that the reference to serious side effects is applied with restraint.

<sup>146</sup> John Wilen, *A hometown CEO*, THE INTELLIGENCER (Philadelphia, PA), (May 8, 2005), available at <http://www.phillyburbs.com/pb-dyn/news/147-05082005-486484.html>.

## DID MERCK PROVIDE ADEQUATE WARNING?

The issue of warning is acute in drug cases because of the extensive federal regulation of warnings.<sup>147</sup> The majority of courts also follow comment k when determining whether the manufacturer provided an adequate warning.<sup>148</sup> One cited reason is that in the case of new or experimental drugs there can often be no assurance of safety or purity.<sup>149</sup> The comment k rule is that manufacturers are not strictly liable for injuries caused by a prescription drug so long as the drug was properly prepared and accompanied by warnings of its dangerous propensities that were either known or reasonably scientifically knowledgeable at the time of distribution.<sup>150</sup> If a manufacturer satisfies those elements the product is considered not defective or unreasonably dangerous.<sup>151</sup> The burden is on the plaintiff to prove by preponderance that adequate warnings were not provided.<sup>152</sup> The adequacy and sufficiency of the manufacturers warning is determined under the objective reasonableness standard.<sup>153</sup> The question becomes would a reasonable person in the same or similar circumstances have been adequately warned.

Putting a warning on a product may increase the manufacturer's exposure to liability because the manufacturer may not then say it did not owe the consumer a duty to warn.<sup>154</sup> By not placing a warning on a product, the issue becomes a question of fact for jury of whether Merck owed a duty to the consumer. However since all prescription drugs require warnings, Merck may not follow this logic.<sup>155</sup>

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<sup>147</sup> Walsh, *The Conflicting Objectives of Federal and State Tort Law Drug Regulation*, 41 Food Drug Cosm. L. J. 171 (1986).

<sup>148</sup> *Brown*, *supra* note 138.

<sup>149</sup> §402(A) *supra* note 109, at *comment k*.

<sup>150</sup> *Id.*

<sup>151</sup> *Id.*

<sup>152</sup> §2, *supra* note 143, at *comment o*.

<sup>153</sup> Restatement (Third) of Torts §2(c), AMERICAN LAW INSTITUTE (1998).

<sup>154</sup> *May v. Dafoe*, 611 P.2d 1275 (1980).

<sup>155</sup> Federal Food, Drug, and Cosmetic labeling act, 15 U.S.C.S. §1331 et seq. (2005).

## LEARNED INTERMEDIARIES

A manufacturer may be excused from warning each user if it properly warns the prescribing physician of the medication's dangers.<sup>156</sup> In this case, Merck engaged in direct-to-consumer marketing which may also require the company to adequately directly warn consumers. The Restatement (Third) of Torts has left this issue to developing case law, depending on whether a state's products liability law legislates the boundaries of the learned intermediary doctrine.<sup>157</sup> One court has determined that factors to consider include the amount spent on advertising and how aggressive the company was in advertising to the public.<sup>158</sup> Other courts have held that if the advertisements inform patients to consult with a physician, then the doctrine applies.<sup>159</sup>

For the majority, comment k limits the duty of drug manufacturers to only provide adequate warnings to learned intermediaries.<sup>160</sup> Strict liability applies when prescription drug manufacturers fail to adequately warn physicians of the dangers associated with its product.<sup>161</sup> Under normal circumstances, prescribing health care providers are in the best position to reduce risks of harm to a patient in accordance with instructions or warnings.<sup>162</sup> Those professionals know what type of patient they are giving the prescription to, what types of risks that person carries, what other medicines they are taking, what other ailments they have, and minimally assess the level of sophistication of the patient's capability to use the product correctly.

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<sup>156</sup> Porterfield v. Ethicon, Inc. 183 F.3d 464, 467, 468 (5<sup>th</sup> Cir. 1999).

<sup>157</sup> Restatement (Third) of Torts §6, AMERICAN LAW INSTITUTE (1998) at *comment e.*; *Perez*, *supra* note 11.

<sup>158</sup> *Perez*, *supra* note 11.

<sup>159</sup> *Presto v. Sandoz*, 487 S.E.2d 70 (Ga. Ct. App. 1997) rejecting plaintiff's claim that brochure given to child's guardian owed a duty to warn them directly because the brochure advised consultation with a physician.

<sup>160</sup> §6, *supra* note 157.

<sup>161</sup> *Carlin v. Superior Ct.*, 920 P.2d 1347 (Cal. 1996); *see also*, *Feldman v. Lederle Labs*, 479 A.2d 374 (N.J. 1984).

<sup>162</sup> §6, *supra* note 157.

The learned intermediary doctrine does not necessarily bar all failure to warn claims against drug manufacturers. It does not shield drug manufacturers from liability if the warnings they provided to physicians do not permit the physicians to adequately advise their patients.<sup>163</sup>

Pharmaceutical companies and their representatives must reasonably instruct doctors of the dangers of their product. “Dear Doctor” letters, which warn doctors of newly discovered risks or side effects of a product, have been held to be an inadequate way to appropriately warn.<sup>164</sup> Merck issued one of these letters in April 2002 informing doctors of the marketing and labeling changed to address the VIGOR study.<sup>165</sup>

What Merck arguably failed to do was adequately represent the findings of the study to physicians. This applies to the case of an injured patient relying on the warnings conveyed to him through his doctor about Vioxx. Patients often visit a doctor’s office, request medication, and must completely rely on the physician’s statements. The learned intermediary doctrine does not preclude the plaintiffs from seeking damages, because Merck sales representatives made representations regarding the safety and efficacy of its product which were not true. According to the FDA warning letter, Merck’s representatives allegedly were not appropriately warning physicians about the seriousness of the CV risk. However, if the data was unreliable as Merck believed and still believes it to be, then they did not fail to warn the doctors.

#### STATE OF THE ART KNOWLEDGE

A product manufacturer is not strictly liable for failure to warn of dangers that the manufacturer neither knew nor could have known given the state of the art knowledge at the time

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<sup>163</sup> *In re Meridia Prods. Liab. Litig.*, 328 F. Supp. 2d 791 (N.D. Ohio).

<sup>164</sup> *Sterling Drug, Inc. v. Yarrow*, 408 F.2d 978 (8<sup>th</sup> Cir. 1969).

<sup>165</sup> New Jersey State Court, (last visited Dec. 20, 2005), *available at* [http://www.judiciary.state.nj.us/mass-tort/forms/vioxx\\_longform\\_exhibd\\_111303.pdf](http://www.judiciary.state.nj.us/mass-tort/forms/vioxx_longform_exhibd_111303.pdf).

the product was manufactured.<sup>166</sup> The manufacturer's duty is confined to a situation in which the seller has knowledge or should have known of the danger.<sup>167</sup> Therefore, a manufacturer has no duty to warn of unknown risks. Termed the "state of the art defense," it is not an affirmative defense because it relates to one of the fundamental elements of the claim. The court in *Brown* and the Restatement (Third) of Torts have adopted Professor Wade's view that a manufacturer's actual or constructive knowledge should be measured from the time the drug is distributed.<sup>168</sup> However, there is still a small minority of jurisdictions that reject this view and measure actual or constructive knowledge known at the time of trial.<sup>169</sup> When courts follow the later approach, an unavoidable risk on manufacturers is created because one cannot insure against an unknowable risk.

Once evidence is introduced by plaintiffs that the defendant knew or should have know of the danger, then the burden shifts to the defendant to prove that information was not reasonably obtainable or available and that the defendant lacked constructive knowledge. Constructive knowledge is knowledge which is obtainable by the application of reasonable, developed human skill and foresight.<sup>170</sup> The burden on the defendant is a matter of policy since it was the defendant who released the product into the stream of commerce.

Many courts find that if a risk is beginning to be known and there is a difference in opinion, but the manufacturer reasonably decides not to warn consumers and harm still occurs,

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<sup>166</sup>§402A, *supra* note 102, at *comment j*. A manufacturer's duty is continued to warn to a situation in which the seller has knowledge or by the application of reasonable, developed human skill and foresight should have knowledge of the danger.

<sup>167</sup> *Id.*

<sup>168</sup> *Brown*, *supra* note 138, *citing* Wade, *The Effect in Product Liability of Knowledge Unavailable Prior to Marketing*, 58 N.Y.U.L.Rev. 734, 753, 754 (1983); *see also*, §2, *supra* note 143, at *comment i*. The basic duty to warn is measured from the time of sale. A manufacturer must warn users when feasible and reasonably necessary.

<sup>169</sup> *Brown*, *supra* note 138.

<sup>170</sup> *Bashesda v. Johns-Mansville Products*, 447 A.2d 539 (N.J. 1982). The defendant must have actual or constructive knowledge of the harm.

then the product is unreasonably dangerous.<sup>171</sup> This is because knowable harm can be avoided through reasonable diligence in discovering the risk. For Vioxx, it is questionable when anything became knowable or even if it ever has. Because the results of the studies are secondary findings, a question arises as to whether pharmaceutical companies must research every potentially harmful yet unreliable finding that is produced. The answer is of course not; however, the data's reliability increases when it continues to yield the same results.

One reason Merck did not perform additional studies specifically designed toward CV safety is that conducting an additional or specific study indicates that the manufacturer believes there is a problem with their product.<sup>172</sup> The company argues that it did test for CV safety before the drug went to market.<sup>173</sup> If the results were detrimental they would surely be used against them. Physicians and patients would not widely use a product that is under review by the manufacturer for causing heart attacks and strokes. It was financially not in their best interest. This reason is in addition to the obvious one that if a risk did exist it would not be in the shareholder's interest to find out. Plaintiffs will say that Merck continued to deny the ill health effects associated with Vioxx while at the same time reaping profits obtained through non-disclosure and concealment.

In addition to the duty to warn at the time of sale, many states require manufacturers to fulfill a post-sale duty to warn of dangers when they become aware of new risks and should reasonably warn the users.<sup>174</sup> As may happen with any new drug product, serious side effects associated with analgesics may become evident only after approval and widespread use. Even though Merck may not have known or have been able to know of CV risks at the drug's

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<sup>171</sup> Anderson v. Owens-Corning Fiberglass Corp. 810 P.2d 549 (Cal. 1991).

<sup>172</sup> Fed. Evid. R. 407 This would likely not constitute a Subsequent Remedial measure and would be admissible for the purpose of knowledge or notice.

<sup>173</sup> Heather Tesoriero, *Merck Seeks to Prove it Tested Vioxx for Impact on Clotting*, WALL ST. J., Oct. 7, 2005, at B4.

<sup>174</sup> Restatement (Third) of Torts §10, AMERICAN LAW INSTITUTE (1998).

inception, the company must warn users if they subsequently find out or should have found out patients are suffering heart attacks from use of Vioxx. Merck has warned post sale. After receiving the FDA warning letter in 2002, Merck changed Vioxx's labeling to include findings of the VIGOR study results as well as precautions against hypertension and those patients with CV risk.<sup>175</sup>

At some point between the drug's inception at Merck's labs and when the product was removed, the company believed the concern was great enough to remove the drug from market. It would obviously take a large concern to remove a drug which generated \$2.3 billion a year from the market. Plaintiffs will try to use this to impeach Merck's credibility and play to juror's emotions by stating that the publicly-traded corporation has loyalty only to its shareholders. They can argue that Merck ignored the possible increased CV risk and continuing to market its product only to later find subsequent studies only supported the conclusion that the risk exists. Merck will argue that at no point has there been enough reliable data showing increased CV risk. As Merck saw it, the weight of the imperfect studies eventually shifted the weight of the unreliable studies to give an indication that the reoccurrence of the secondary results were not merely random chance.

Merck representatives argued that the VIGOR study showing increased heart attack and stroke risk was flawed because the data was a secondary finding of a study directed for another purpose. If this is true, then why did Merck voluntarily remove the product from the market after their own study indicated the increase risk also as a secondary finding? Why was Merck's study reliable enough to take Vioxx off the market and others were not?

One idea is that Merck decided that their own study made the weight of all available data reach a evidentiary threshold that they should be aware that there may be a CV problem. It

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<sup>175</sup> Food and Drug Administration, *supra* note 3.

would not matter that Merck's own study was not a study designed for CV effects, merely that the weight of several imperfect studies have reached a level to indicate a probable outcome. Also, Merck's study was conducted with a large population which also increased the reliability of any secondary finding. Again the issue rests on the reliability and admissibility of these studies, which is later discussed in further detail.

#### HEEDING PRESUMPTION

In order for an injured party to recover, the patient would have had to read and followed any additional warning. Assuming the warning was inadequate, discerning whether someone would have still taken Vioxx if given the proper warning is difficult to do. This is especially true if the patient died as a result of taking the medication. It is not appropriate to view this retrospectively because it is obvious that if the patient knew they were going to die they never would have taken the drug. The Restatement (Second) of Torts takes this quandary into consideration and presumes that the consumer heeded the warning.<sup>176</sup> Evidence may be offered to rebut such testimony, which is often done at trial.

This is effectively accomplished by impeaching someone for smoking despite strong labeling or taking other prescriptions with similar or more significant risks. Also, the warning was changed in 2002 to incorporate the concerns of the VIGOR study. If the claimant took the drug after 2002 and read the warning, then they would have already taken the drug with some warning of CV risks even if the VIGOR data was underrepresented. If the patient never read the product insert, then it shows the probability of them heeding the warning is highly unlikely.

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<sup>176</sup> §402A, *supra* note 109, at *comment j*.

## EXPRESS WARRANTY

Breach of express warranty occurs when products fail to conform to a promise made by a seller to the buyer regarding statements (oral or written) at or before time of sale.<sup>177</sup> The statements may be packaged with the goods at time of sale or even directed to the public at large.<sup>178</sup> The representation from the seller must become some basis of the bargain; in other words, the buyer must rely upon the seller's statements.<sup>179</sup>

The proposed amendments to the Uniform Commercial Code ("UCC") specifically attend to information provided in packaging and advertising, holding those responsible for such statements to conform to the affirmations of fact within.<sup>180</sup>

After 2002, the Vioxx package insert warned of CV risks.<sup>181</sup> If the product was taken between 1999 and 2002, then there may be some type of implication that the drug is safe. However, because there were no affirmative representations, it does not amount to a promise. Any statements given during Merck's multi-million dollar a year advertising campaign likely did not warn of CV effects. Again, as long as there were not any affirmative statements in the ads regarding CV risk then they are not express warranties.

It appears from the FDA warning letter directed to Merck that their sales representatives were making express warranties about the product that were not true. Those representatives during presentations not only downplayed VIGOR results, they also stated the drug was safe for other uses which were not FDA approved and the CV safety of the drug was perfectly fine.

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<sup>177</sup> Uniform Commercial Code §2-313, Express Warranties By affirmation, Promise, Description, Sample.

<sup>178</sup> *Baxter v. Ford* 12 P.2d 409 (Wash. 1932).

<sup>179</sup> *Cipollone v. Liggett Group Inc.*, 893 F.2d 541 (3d Cir. 1990); *Yarusso v. Int'l Sports Marketing*, 1999 WL 463531 (Del Super. Ct. 1999).

<sup>180</sup> Uniform Commercial Code §2-313A, Obligation to Remote Purchaser Created by Record Packaged with or Accompanying Goods; §2-313B, Obligation to Remote Purchaser Created by Communication to the public (Proposed Final Draft, 2003).

<sup>181</sup> New Jersey State Court (last visited Dec. 20, 2005), *available at* [http://www.judiciary.state.nj.us/mass-tort/forms/vioxx\\_longform\\_exhibc\\_111303.pdf](http://www.judiciary.state.nj.us/mass-tort/forms/vioxx_longform_exhibc_111303.pdf); *see also*, [http://www.judiciary.state.nj.us/mass-tort/forms/vioxx\\_longform\\_exhibe\\_111303.pdf](http://www.judiciary.state.nj.us/mass-tort/forms/vioxx_longform_exhibe_111303.pdf).

Although medical professionals had access to the same studies published in the journals, it is not the standard of care for them to be current with nonstandard practices.

From the known facts, Merck's representatives did not make any express warranty that adverse CV events would never result from use of Vioxx. Any representation that the drug was CV safe is still correct because if adverse CV events do occur it effects such a small percent of the population.

### **IMPLIED WARRANTY**

There is a general societal assumption that a product is safe and effective when it is put on the market. Vioxx was approved for the earlier stated uses and is assumed fit for those purposes. A product must be reasonably fit for the ordinary purposes for which it is used.<sup>182</sup>

The advertisements to the public and promotion to physicians were an implicit indication that the drug was safe and effective for its intended uses. In this case, one would expect when ingesting Vioxx that it would be effective in relieving pain; a drug that caused patients to have heart attacks would not be fit for much of anything. However, comment k specifically addresses this issue in prescription drug cases stating that adverse reactions are unavoidable in prescription drugs.<sup>183</sup> Not everyone that took Vioxx suffered an adverse CV event; only 0.73% of participants using Vioxx did during the VIGOR study. Since adverse CV events occur in such a small minority of users it would seem that Vioxx would not be unfit for its intended purpose.

Another implied warranty may be made regarding the heavy marketing of COX-II inhibitors as reducing stomach bleeding. Some of the new studies show that this is not true, and if any GI benefit is associated it is marginal at best. This may have induced some patients with

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<sup>182</sup> Uniform Commercial Code §2-314(2)(c).

<sup>183</sup> §402A, *supra* note 109 at *comment k*.

higher risk for GI bleeding to use this medication when the risk of traditional NSAIDs was too great. This would only concern those plaintiffs who suffered GI injury. They would not have to prove they would not have had a GI injury from another NSAID because they likely would not have taken any COX drug at all because of their risk. It would not matter when or if Merck knew that the drug did not provide this benefit. It merely matters that the drug did not conform to the implied representation. However, there is no reliable information to this effect and both the original and updated package insert expressly warns of an associated GI risk

### **MISREPRESENTATION**

Returning to the FDA warning letter, Merck should not have been as careless in downplaying the CV dangers of Vioxx. The sales representatives allegedly continued to market Vioxx by downplaying the risk. Misrepresentation<sup>184</sup> occurs when the seller makes a fraudulent, negligent, or innocent misrepresentation of material fact concerning the character or quality of its product which caused justifiable reliance and someone is physically harmed as a result of that misrepresentation.<sup>185</sup> Those responsible are strictly liable in tort without proving any actual defect in the product.<sup>186</sup> Did Merck know or should it have known otherwise when making their statements?

According to the FDA warning letter, Merck sales representatives misinformed physicians about the proven abilities of the drug in addition to downplaying any CV risk. The letter stated, “Additionally, your claim in the press release that Vioxx has a ‘favorable cardiovascular safety profile,’ is simply incomprehensible, given the rate of MI and serious CV

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<sup>184</sup> Restatement (Second) of Torts §§ 311, 310, AMERICAN LAW INSTITUTE (1965).

<sup>185</sup> Restatement (Third) of Torts §9, AMERICAN LAW INSTITUTE (1998).

<sup>186</sup> Restatement (Second) of Torts §402B, AMERICAN LAW INSTITUTE (1965).

events compared to naproxen.”<sup>187</sup> If such allegations are true, physicians were likely induced to prescribe Vioxx to patients. The patients then justifiably relied on the advice of their prescribing physician to take the medication. However, the statements Merck’s sales representatives must actually be false or substantially misleading. Merck would only be able to make representations on the safety of their product if they had reliable data which did not show an increase in CV events, but Merck argues that they did test CV safety prior to the drug’s approval.<sup>188</sup>

The scientists clearly knew data was omitted when submitted to the FDA. Merck will argue it is not a misrepresentation. The study was not designed or promoted to show CV effects. In addition the data left out was given to editors after they wrote the article, but before it was submitted to the FDA. The additional data was taken outside the timeframe of the study design. Scientists often continue to collect data for additional months so that it may show a reason to design a study for a longer length. Since the patients that are studied do not all start and stop on the same date, researchers are often still studying a patient past the studies timeframe while others have not yet finished. This is where the extra data has come from.

The FDA warning letter issued to Merck informed them that their sales representatives were bolstering the ability and effectiveness of Vioxx for unapproved uses and downplaying the drug’s associated risks. If sales representatives were affirmatively representing that the drug was perfectly cardiovascularly safe, the representatives would not have exercised reasonable care in the accuracy of any data they gave. There is no reliable data either way. Just because there is no reliable data saying Vioxx causes heart attacks does not mean company representatives can misrepresent that the drug does not without evidence. However, it would hardly promote

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<sup>187</sup> Barbara Martinez, *Vioxx Lawsuits May Focus on FDA Warning in 2001*, WALL ST. J., Oct 5, 2004, at B1.

<sup>188</sup> Tesoriero, *supra* note 74.

justifiable reliance because the data only changed the CV risk from 4.25 to five times placebo.<sup>189</sup> This only showed a slightly greater statistical, but no true clinical, difference. The data on the disk merely will be usable for Merck's credibility, making the company appear to be covering up other data because they did not show the three additional CV events in the additional 383 persons studied outside of the study's timeframe. Any argument that when Merck's scientists made additional public statements and published articles that it believed its product was safe and that the data showing otherwise was a misrepresentation is incorrect.

### CAUSATION

Another fundamental element to a successful products liability claim is causation. The damages must be a proximate result from a defect or failure to warn. Causation is the causal connection between a defective product and the user's harm.<sup>190</sup> Causation in fact occurs when but for the defect or failure to give adequate warning the harm would not have occurred.<sup>191</sup> The defect must also be the producing cause of the harm which is the extent that public policy allows liability to extend.<sup>192</sup> In analyzing one must find that the product could actually cause this type of injury; and if so, whether the product caused that type of harm in this situation. It is often necessary for an injured party to produce expert testimony to prove the specific cause of the injuries.

In the case of Vioxx, a plaintiff must show a casual nexus between taking Vioxx and the adverse CV event the plaintiff suffered. Epidemiological studies, case reports of injuries, animal

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<sup>189</sup> Curfman, *supra* note 63.

<sup>190</sup> Restatement (Third) of Torts §15, AMERICAN LAW INSTITUTE (1998).

<sup>191</sup> Restatement (Third) of Torts §26, AMERICAN LAW INSTITUTE (1998).

<sup>192</sup> Public Policy limits design and defect warnings to those risks that are foreseeable; Restatement (Second) of Torts §341, AMERICAN LAW INSTITUTE (1965). Public Policy limits design and defect warnings to those risks that are foreseeable.

studies, and FDA statements, if admissible, may be used as evidence to this effect.<sup>193</sup> One alone may not satisfy the plaintiff's burden, but it may be satisfied collectively.<sup>194</sup>

Because the plaintiffs have the burden of proof for causation, without it Merck will obtain summary judgment or directed verdict. This element is often easily satisfied where patients suffer from signature diseases. In those cases it is more obvious why a patient is suffering from such disease.

Because there are no studies or other evidence linking Vioxx to anaphylactic shock, summary judgment was granted to Merck in one Ohio case where the plaintiff died from sudden anaphylactic shock after taking samples of Vioxx.<sup>195</sup> The ruling was upheld on the issue that there was no evidence that the plaintiff's death was caused by the lack of warnings.<sup>196</sup>

The problem with these Vioxx cases is different; here, the injury that is produced, adverse CV events, are normally occurring phenomena. With the current science, we are medically incapable of making an exact determination whether a CV event was caused by Vioxx or another contributing factor(s). So while there may arguably be an increase in occurrence, a determination as to which CV events were natural and which were due to Vioxx are beyond medical science. There is no medically discoverable difference between someone who dies of a Vioxx heart attack or stroke and someone who dies from one due to other causes.

Additionally, the epidemiological studies indicate the injury only affects a small percentage or fractional percentage of the users. Merck's experts will point to plaintiff's medical records and any indication of other factors which may have contributed to an adverse CV event. There are dozens of contributing factors to one suffering an adverse CV event; stress in a

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<sup>193</sup> *Rider, supra* note 122.

<sup>194</sup> *Id.*

<sup>195</sup> *Kennedy v. Streibel*, 2003 Ohio 7241; 2003 Ohio App. LEXIS 6556 (2003).

<sup>196</sup> *Id.*

patient's work and family life or whether they drink coffee or other caffeinated beverages could have contributed to heart problems.

Expert testimony does not meet the plaintiff's burden by merely stating problem X causes Y effect. In order for there to be sufficient causation evidence they must say Y effect here occurred as a result of X problem. The plaintiff's expert will have difficulties ruling out other possibilities on cross-examination, but if proper testimony was elicited then the issue will go to jury.

The adverse CV effect alleged in Vioxx litigation appears strikingly similar to the ephedra litigation. In those cases, plaintiffs alleged that ephedra caused increased heart attacks and strokes.<sup>197</sup> However, there was no scientific evidence as to what caused any individual heart attack. The only evidence was that overall there is an increased incidence of these CV events.<sup>198</sup>

The most noteworthy irregularity between Vioxx trials will be whether the jurisdiction advocates the application of probability theory of proof process.<sup>199</sup> Aside from the differences in conceptual and analytic application, fundamental arguments surround whether courts should use (1) probabilistic techniques to determine the likelihood of the facts supporting a defendant's guilt or liability and (2) whether or not the plaintiff's burden is satisfied when that probability exceeds a threshold value.<sup>200</sup> Individual judges also have different interpretations on the relationship between probability and proof. Each judge carries his or her own personal views on whether integrating mathematics into the fact-finding process of a legal trial outweigh the benefits.

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<sup>197</sup> *In re Ephedra Prod. Liab. Litig.*, 393 F. Supp. 2d 181, 2005 U.S. Dist. LEXIS 20259 (S.D.N.Y. 2005).

<sup>198</sup> *Id.*

<sup>199</sup> Neil B. Cohen, *Confidence in Probability: Burdens of Persuasion in a World of Imperfect Knowledge*. 60 N.Y.U.L.Rev. 385 (1985)

<sup>200</sup> *Id.*

Proponents of probabilistic decision-making believe that statistics may be used to meet the preponderance of the evidence standard employed in civil litigation.<sup>201</sup> The standard is the burden of demonstrating that the likelihood of the defendant's liability is greater than the likelihood of his innocence; in other terms the probability supporting the defendant's liability exceeds 0.5 or 50%.<sup>202</sup> Generally, probability of a given outcome in some activity is calculated by measuring the frequency with which that outcome occurs.<sup>203</sup> Alone, the frequency rate of injury is insufficient to determine the probability of causation that Vioxx was more likely than not to have caused the plaintiff's heart attack.<sup>204</sup> In order to illustrate this common misapplication, consider the hypothetical case of a High School baseball game where 1000 people come to view the game.<sup>205</sup> If 499 people pay the \$3 for a ticket and the other 501 attend by gate-crashing, then in a legal action against any one spectator according to the 0.501 probability, the action would be successful against any spectator.<sup>206</sup>

There is continuing theoretical debate on whether to find some defendants liable for those torts which they did not commit or having individual plaintiffs fail to recover for actual harm.<sup>207</sup> The answer is often different depending on the goal or the court in a particular case, i.e. to deter conduct or allow companies to insure against ascertainable loss. Some theorists even suggest allowing discounted recoveries to reflect scientific uncertainty.<sup>208</sup>

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<sup>201</sup> Sander Greenland, James M. Robins, *Epidemiology, Justice, and the Probability of Causation* (2000) 40 JURMETRICS 321.

<sup>202</sup> Steve Gold, *Causation in Toxic Torts: Burdens of Proof, Standards of Persuasion, and Statistical Evidence*. 96 Yale L.J. 376 (1986).

<sup>203</sup> *Id.*

<sup>204</sup> Cohen, *supra* note 199, at 391.

<sup>205</sup> *Id.*

<sup>206</sup> *Id.*

<sup>207</sup> Gold, *supra* note 202.

<sup>208</sup> *Id.*

A bare probability should lead the legal system to decline to act by holding for the defendant.<sup>209</sup> In *Smith v. Rapid Transit* the court held, “merely that mathematically the chances are in favor of a proposition is not enough to establish it by a preponderance of the evidence; there must be actual belief from evidence that the proposition is more probably true.”<sup>210</sup> The scientific data alone is not sufficient for a directed verdict or summary judgment, and no matter how strong the data is in either direction, it must be submitted to the trier of fact to make the determination of liability. Harvard Law Professor Laurence Tribe has argued in support of the actual belief requirement stating, “Moral qualms about imposing civil liability under conditions of uncertainty should respond to the actual risk of verdict error, not its overtness.”<sup>211</sup> “Because people readily perceive the risk of verdict error, they become uneasy if the legal system relies on such evidence to change the status quo by holding for the plaintiff.”<sup>212</sup>

In addition to the flawed nature of the statistical theories, courts are often guilty of misapplication of statistics.<sup>213</sup> The risk ratio, also known as relative risk, may be defined as the risk of disease in a population segment exposed to a particular substance, divided by the risk of the disease in the rest of the population.<sup>214</sup> The risk ratio represents how much more likely an exposed person is to contract the disease than an unexposed person.<sup>215</sup> A comparison is made

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<sup>209</sup> Daniel Shaviro, *Statistical-Probability Evidence and the Appearance of Justice*, 103 Harv. L. Rev. 530 (1989).

<sup>210</sup> *Smith v. Rapid Transit*, 58 N.E. 2d 754 (Mass. 1945) In *Smith*, a bus forced the plaintiff off the road and into a parked car. Evidence that the sole owner and operator of all public buses on a particular street, absent any other evidence, was insufficient for a directed verdict that the defendant actually was the owner of the bus. The court found that the bus could have been operated by a private or charter carrier in the city. The infamous blue bus hypothetical which evolved from the case is slightly different, which reads as follows: a woman is hit by a bus crossing the street, in a wrongful death action against the bussing company the only evidence presented is that 80% of all blue busses in that city are owned and operated by the defendant. Is this evidence alone sufficient to prove the defendant’s liability? *See also*, Porter Sargent v. Massachusetts Accident Company, 29 N.E.2d 825 (Mass. 1940).

<sup>211</sup> Shaviro, *supra* note 209.

<sup>212</sup> *Id.*

<sup>213</sup> Greenland and Robins, *supra* note 201.

<sup>214</sup> *Id.* ((Number of persons\* with heart attacks taking Vioxx / total number of people taking Vioxx) / (Number of persons not taking Vioxx with heart attacks / total number of people not taking Vioxx)). \*Number of persons = persons in the study.

<sup>215</sup> *Id.*

between the proportion of persons with the disease in a group of people exposed versus the proportion of persons with the disease in the group not exposed. The risk ratio does not equal or even approximate the probability of causation.<sup>216</sup> There is a clear distinction between the excess incidence caused by an exposure (attributable fraction) and the probability that the exposure caused an individual's disease (the "probability of causation").<sup>217</sup> Many epidemiologists and health physicists serving as expert consultants and witnesses continue to equate attributable fractions with the probability of causation.<sup>218</sup>

In epidemiology, risk is quantitative. Due to generalized error rates from sample size, study bias, and error due to chance, resulting data simply represents a close approximation of the actual risk.<sup>219</sup> The subjective probability derived by a legal fact-finder is more accurately described as an estimate based on a sample of information rather than a true value derived from an analysis of all possible information.<sup>220</sup> Risk ratios less than three can be generated entirely by factors such as study bias and lack of precision.<sup>221</sup> A large risk ratio signifies a strong association, which is highly indicative, although not determinative, of a casual relationship. Some courts have viewed risk ratios greater than one as capable of proving causation.<sup>222</sup> In *Oxendine v. Merrell Dow Pharmaceuticals, Inc.*,<sup>223</sup> testimony based on an epidemiological study with a risk ratio between 1.3 and 1.8 and other data was found to be sufficient.<sup>224</sup> Although any

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<sup>216</sup> Sander Greenland, James M. Robins, *Conceptual Problems in the Definition and Interpretation of Attributable Fractions*, 128 AM J. EPIDEMIOLOGY 1185 (1988).

<sup>217</sup> Greenland and Robins, *supra* note 201.

<sup>218</sup> Linda A. Bailey et al, Reference Guide on Epidemiology, in Reference Manual on Scientific Evidence 168-169 (Federal Judicial Center ed., 1994); Noel Weiss, *General Concepts of Epidemiology, Modern Scientific Evidence: The Law and Science of Expert Testimony*, 321.

<sup>219</sup> Michael D. Green, Expert witnesses and sufficiency of Evidence in Toxic Substances Litigation: The Legacy of Agent Orange and Bendectin Litigation. 86 Nw. U.L. Rev. 643 (1992).

<sup>220</sup> *Id.*

<sup>221</sup> Ernst L. Wyder, Guidelines to the Epidemiology of Weak Associations, 16 Preventative Med. 139 (1987).

<sup>222</sup> *Id.*

<sup>223</sup> *Oxendine v. Merrell Dow Pharmaceuticals*, 506 A.2d 1100 (D.C. App. 1986).

<sup>224</sup> Michael D. Green, *Legal Theory: Expert Witnesses and Sufficiency of Evidence in Toxic Substances Litigation: The Legacy of Agent Orange and Bendectin Litigation*. 86 Nw. U.L. Rev. 643 (1992).

risk ratio greater than one logically would support the notion of a casual relationship, any risk ratio less than three generally indicates a weak association.<sup>225</sup>

One oversight with this measurement is the fact that the risk is viewed in statistical differences; in other words, it fails to address true clinical differences. For example, a scientific study revealing that there is a clear increase in the number of patients acquiring a particular disease is attributable to a certain drug, but where the particular disease affects a significant population of people. Note that the more common the disease, the lower the risk ratio (i.e. the increase in denominator value). Analogically speaking, five pebbles in an empty bucket looks much different than adding five to an already half-full bucket even though the increase was the same.

## **DEFENSES**

Assuming that a plaintiff was able to bring a successful claim against the manufacturer, those seeking recovery would still have face any affirmative defenses. Comparative fault is a defense to strict liability.<sup>226</sup> It is negligence on the part of a plaintiff which combining with the product defect or failure to warn contributes as a cause in bringing about the injury.<sup>227</sup> Comparative fault on the part of plaintiff does not bar recovery by the plaintiff against the defendant, but the total amount of damages to which plaintiff would otherwise be entitled shall be reduced by the percentage that plaintiff's comparative fault contributed as a cause to plaintiff's injury.<sup>228</sup>

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<sup>225</sup> Melissa Moore Thompson, *Casual Inference in Epidemiology: Implications for Toxic Tort Litigation*, 71 N.C.L. Rev. 247, 251, 252 (1992).

<sup>226</sup> Apportionment of Responsibility, Restatement (Third) of Torts §17, AMERICAN LAW INSTITUTE (1998).

<sup>227</sup> *Id.*

<sup>228</sup> *Id.*

The facts in the case of Vioxx assume Merck will not be able to use comparative fault if its product was properly taken as prescribed. Any other outside medical factors which may have contributed to the heart attack are relevant to proving causation and not comparative fault. These are outside factors that do not amount to negligence on the part of the user.

## **OUTLOOK**

It appears that plaintiffs will encounter significant obstacles to their claims. There are no solid portions to any part of the claims. The largest hurdle to any claim is the reliability of the scientific studies and expert testimony. Again, that will largely depend on what jurisdiction or whether the case is in federal or state court. The issue of causation here is almost impossible to prove, but if the plaintiffs survive summary judgment, then statistically if enough cases are tried some will be successful. For future litigation, plaintiffs in federal court will also confront the requirement of a unanimous verdict.

These cases appear to be duds, but that is not stopping plaintiffs from attempting to reap the large judgments of the few winnable cases. If Merck is successful in defending say 90% of their lawsuits, but they are mostly tried, the company will have to face financial difficulties. The cost of defending some suits may cost more than settling. The few cases that win will surely be enough to fuel the well organized plaintiff's bar to continue in the fight since the likely payouts would be significant.

## VIGOR

**Table 1. Data on Myocardial Infarctions Omitting the Three Events.\***

Study Group	Person-Years of Exposure	No. of Myocardial Infarctions	Relative Risk	95% CI
Total				
Rofecoxib	2315	17	4.25	1.39 to 17.37
Naproxen	2316	4		
Aspirin indicated				
Rofecoxib	95	8	∞	1.65 to ∞
Naproxen	92	0		
Aspirin not indicated				
Rofecoxib	2220	9	2.25	0.63 to 10.02
Naproxen	2224	4		

\* The numbers of person-years of exposure as of February 10, 2000, have been estimated. Relative risks were estimated by Poisson regression; confidence intervals were calculated by the exact method.

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**Table 2. Data on Myocardial Infarctions Including the Three Events.\***

Study Group	Person-Years of Exposure	No. of Myocardial Infarctions	Relative Risk	95% CI
Total				
Rofecoxib	2698	20	5.00	1.68 to 20.13
Naproxen	2699	4		
Aspirin indicated				
Rofecoxib	105	8	∞	1.66 to ∞
Naproxen	102	0		
Aspirin not indicated				
Rofecoxib	2593	12	3.00	0.91 to 12.78
Naproxen	2597	4		

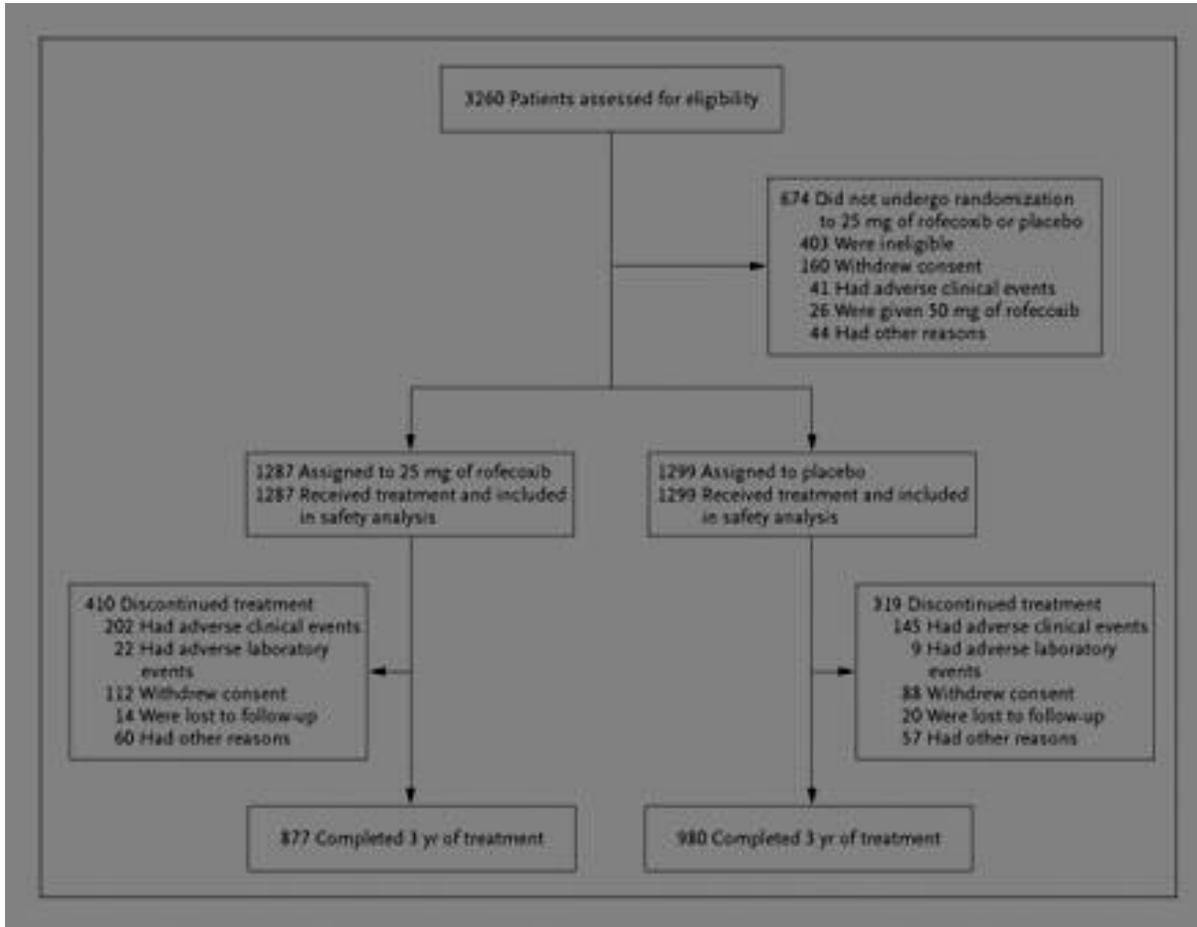
\* Relative risks were estimated by Poisson regression; confidence intervals were calculated by the exact method.

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<sup>229</sup> Curfman, *supra* note 63, at 2813.

<sup>230</sup> *Id.*

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<sup>231</sup> Bresalier, *supra* note 46, at 1094.

**Table 3. Summary of Rates and Relative Risks of Confirmed Serious Thrombotic Events and the APTC End Point.\***

Adverse Event	Rofecoxib Group				Placebo Group				Difference in Rate (95% CI)	Relative Risk (95% CI)
	No. at Risk	No. of Events	No. of Patient-yr at Risk	Rate/100 Patient-yr	No. at Risk	No. of Events	No. of Patient-yr at Risk	Rate/100 Patient-yr		
<b>Confirmed event</b>										
Overall	1287	46	3059	1.50	1299	26	3327	0.78	0.72 (0.19 to 1.25)	1.92 (1.19 to 3.11)
Month 0–18	1287	22	1656	1.33	1299	20	1765	1.13	0.20 (–0.55 to 0.94)	1.18 (0.64 to 2.15)
Month 19–36	989	24	1403	1.71	1079	6	1561	0.38	1.33 (0.58 to 2.08)	4.45 (1.77 to 13.32)
<b>APTC end point</b>										
Overall	1287	34	3070	1.11	1299	18	3334	0.54	0.57 (0.12 to 1.02)	2.06 (1.16 to 3.64)
Month 0–18	1287	14	1658	0.84	1299	12	1769	0.68	0.17 (–0.42 to 0.75)	1.25 (0.58 to 2.69)
Month 19–36	994	20	1412	1.42	1083	6	1565	0.38	1.03 (0.34 to 1.73)	3.69 (1.43 to 11.24)

\* CI denotes confidence interval, and APTC Antiplatelet Trialists' Collaboration.

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**Table 4. Incidence of Nonadjudicated Cardiovascular Adverse Events.\***

Adverse Event†	Rofecoxib Group (N=1287)		Placebo Group (N=1299)		Hazard Ratio (95% CI)
	No. of Patients (%)	Rate/100 Patient-yr	No. of Patients (%)	Rate/100 Patient-yr	
Hypertension	377 (29.3)	14.9	219 (16.9)	7.3	2.02 (1.71–2.38)
Serious event	11		1		
Edema	111 (8.6)	3.8	76 (5.9)	2.4	1.57 (1.17–2.10)
Serious event	3		0		
Congestive heart failure, pulmonary edema, or cardiac failure	17 (1.3)	0.6	4 (0.3)	0.1	4.61 (1.50–18.83)
Serious event	12		2		

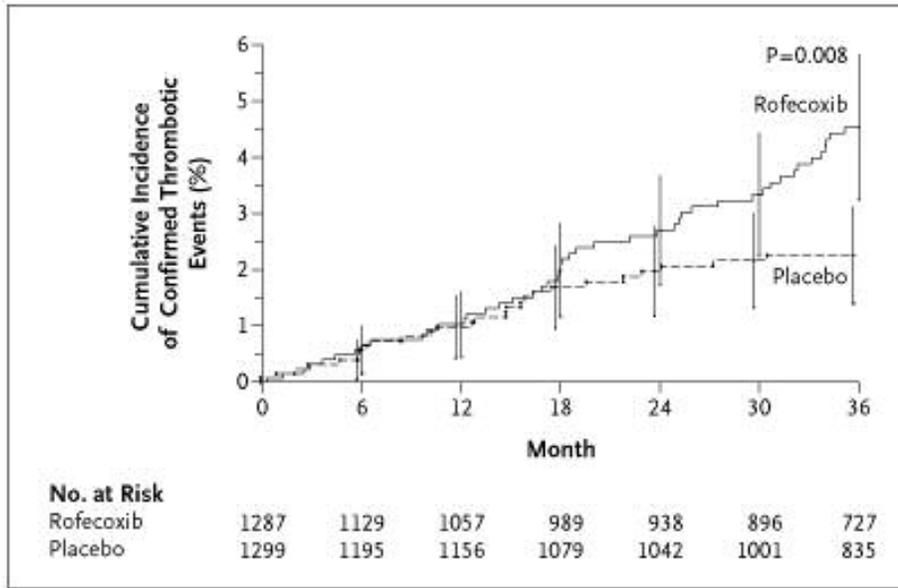
\* The total duration of follow-up was 3059 patient-years in the rofecoxib group and 3327 patient-years in the placebo group. Although a patient may have had two or more clinical adverse events, the patient was counted once within a category. The same patient may appear in different categories. CI denotes confidence interval.

† A serious event was defined as one that was life-threatening, resulted in (or prolonged) hospitalization, or caused permanent disability.

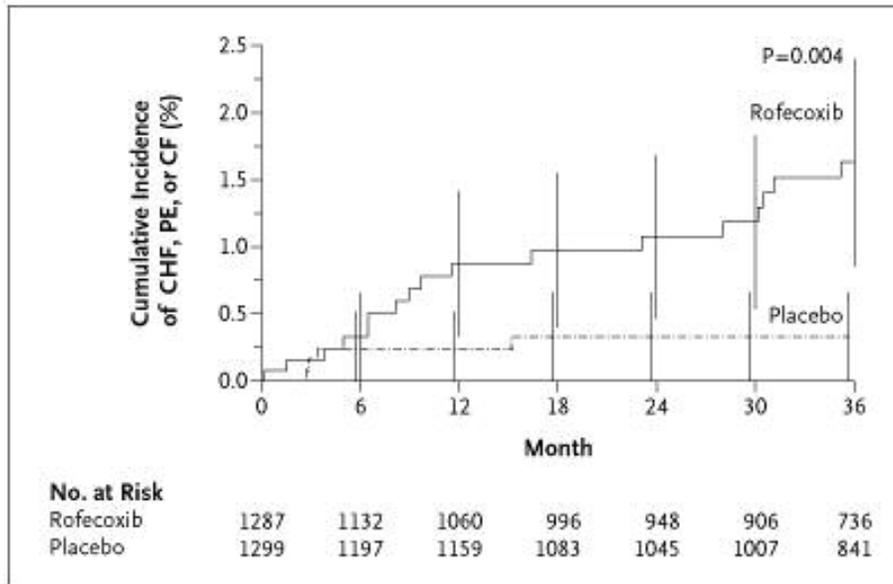
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<sup>232</sup> *Id.*

<sup>233</sup> *Id.*



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<sup>234</sup> *Id.*

<sup>235</sup> *Id.*