"Product Liability Litigation: An Issue of Merck and Lawsuits Over Vioxx."

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ABSTRACT

Merck & Co., Inc. pulled Vioxx, a $2.5 billon a year nonsteroidal anti-inflammatory drug, off the shelf in September 2004. The removal followed a study that was published reporting Vioxx increased the risk of cardiovascular events after long-term use. In the years since then, many lawsuits have been filed against Merck. This paper examines the incentive to recall a product and the effects of Merck pulling Vioxx from the shelves. Using the market's expected internal rate of return for Merck, I calculate the expected profits from future Vioxx sales. I then use data on financial effects to show how the market value of Merck reflects their probability of winning legal cases concerning Vioxx.

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I. INTRODUCTION

Merck and Co., Inc. withdrew Vioxx from the market in September 2004 after a study was published stating Vioxx increased the risk of cardiovascular events after long-term use.[1] There were, and still are, many legal cases from Vioxx patients that have been affecting Merck since the drug's removal from the market. This study uses an event-study format to find the market effects of the removal of Vioxx from the shelves. I observe that the market reacted completely and immediately to the announcement of Merck's decision, along with all other news announcements concerning Merck. Because the market reacted efficiently to Merck's decision to remove Vioxx from the market, the change in the market value of Merck will reflect the total damages expected to occur. This information allows the analysis of the withdrawal decision of Merck. With this information it is then possible to calculate the probability of a Merck victory in the courtroom. To do this I will back the total expected costs of the litigation out of the data, in terms of issues brought against Merck.

The decrease in market value to Merck the day they withdrew Vioxx was $26.8 billion at the market close on September 30, 2004. This is not just expected litigation costs, but rather all expected costs from this decision. Merck had to pay direct costs for the recall, including all shipping and notification fees, along with future litigation costs. Furthermore, a large portion of that loss is not due to incurred costs, but the loss of expected profits that were imbedded in the stock price. When Vioxx was withdrawn, Merck still had approximately nine years of patent life left on a drug selling $2.5 billion a year. To accurately find the total expected profits it is necessary to solve the market's expected internal rate of return for Merck.

With this information, this study will analyze the timing of the withdrawal and if it was at a profit-maximizing time for Merck. I will also show how the probability of a successful Merck lawsuit changes as new information becomes available. In section two, I will look at the incentives to withdraw the drug, and what the timing of the withdrawal means. Section three will look at what Vioxx is and has a brief timeline of Merck's history. Section four discusses the data and details an event study that shows the effects of the following events:

Event One – Merck removes Vioxx from the shelf.
Event Two – *The Wall Street Journal* reports that greater heart risk was known by executives.
Event Three – Merck loses part of their patent rights on Fosamax.
Event Four – FDA issues a release supporting Cox-2 inhibitors

In section five, I use an analysis of internal rate of return, along with the information obtained from the Fosamax patent loss, to estimate the loss in expected profits due to the Vioxx withdrawal. Using these events, I show how they explain the change in

[1] Cardiovascular events are: myocardial infarction (heart attack), unstable angina, cardiac thrombus (blood clot), resuscitated cardiac arrest, sudden or unexpected death, ischemic stroke, and transient ischemic attacks (transient stroke).

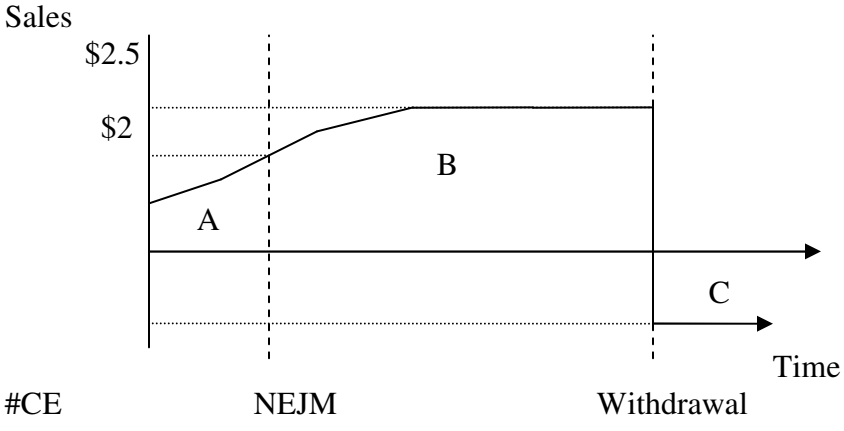
probability of Merck winning lawsuits filed against them concerning the drug Vioxx in section six. The last section concludes.

II. MERCK'S TIMING

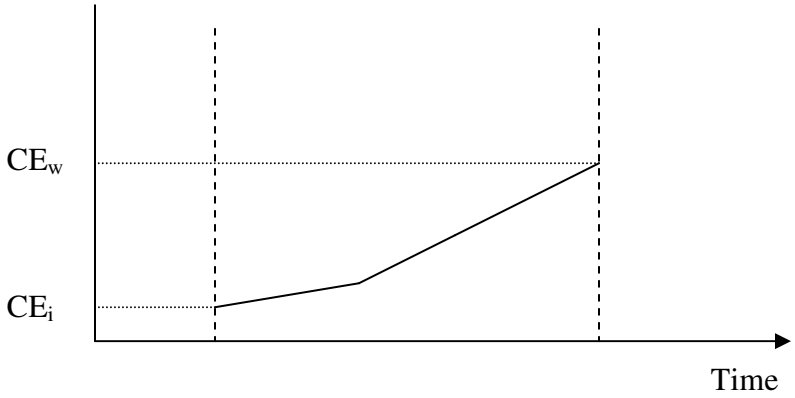
Merck withdrew Vioxx in 2004 when sales were $2.5 billion a year—as opposed to the $2 billion a year sales in 2000. In November of 2000, the *New England Journal of Medicine* published an article stating their VIGOR (Vioxx Gastrointestinal Outcomes Research) study found no significant increase in cardiovascular events, but problems around this article arose. Merck admitted that the data submitted to the journal to be published was correct, but before the study was published, new data (from the same study) arose stating that Vioxx did indeed increase the risk of cardiovascular events. Merck claimed that this information was revealed too late in the process to correct the article. If it was too late to re-write the article, there were still two other options available, they could have withdrawn the article completely or written a rebuttal in the following issue. From this point forward Merck was making the decision to continue selling the drug, or to withdraw/release this information. Merck choose not to publish this information, making the withdrawal of Vioxx a shock to the market on September 30, 2004.

Figure 1, Timing of Withdrawal

1:



2:



In the above charts, NEJM is the date the *New England Journal of Medicine* published results from the VIGOR study, while Withdrawal is September 30, 2004, the date Merck withdrew Vioxx. The top graph (1) shows the yearly sales of Vioxx from the FDA[2] approval date (May 1999) to the withdrawal date (September 2004). After that date, the negative represents the potential loss in brand name capital caused by Merck's actions. The bottom graph (2) shows the expected number of cardiovascular events caused by the use of Vioxx. These cardiovascular events are increasing in time, as more people take the drug and longer usage causes increased risk. The graph shows no risk up to the point of the NEJM article, because up to that point, no risk was known.[3]

Section A, the area below the profit line before the NEJM publication (in part 1 of figure 1), shows the profits that Merck made from selling Vioxx before any knowledge of cardiovascular events (CE) were known. Because CE became known to Merck at the point of the NEJM, Merck had the choice to continue to market the drug or retract the publication and withdraw the drug at that time. When Merck found that Vioxx caused an increase in CE, there were an initial number of people already affected by the drug (CE_i), and the number of events continued to increase until the drug was withdrawn from the market (CE_w). As you can see with part 2 of figure 1, as Merck continues to sell Vioxx, the number of cases of CE continue to increase.

To determine why Merck waited to withdraw Vioxx until 2004, it is necessarily to compare the profits they received by keeping the drug on the market against the costs of doing so. To look at those numbers, I will compare area B's present value, the area of profits between the NEJM and the Withdrawal date, at the time of the withdrawal to area C's present value, the loss in brand name capital after the withdrawal, along with all legal costs incurred, or expected to occur, at the time of the withdrawal. Because quality of a drug is hard to signal, companies try to signal the quality of their product through investments in brand names. Klein and Leffler (1981) argue that a company's investment in brand names and trademarks provide implicit guarantees to consumers of quality products. The idea that brand names are a quality assurance device is supported by Klien, Crawford, and Alchian (1978), Jarrell and Peltzman (1985), Chalk (1986 and 1987), Benjamin and Mitchell (1989) and Mitchell and Maloney (1989). The reason for establishing brand names is that it is not possible for companies to repeatedly fool their consumers about the quality of a product. Although a consumer could be fooled once, they would not be fooled again, and thus the investment in the brand name would be lost. It is this loss in brand name capital that Merck is risking by keeping Vioxx on the market.

[2] FDA is the U. S. Food and Drug Administration, more information about the FDA can be found at FDA.gov.

[3] It is important to note that when drug companies perform statistical analyses, there is a lag between people taking the drug and when they begin to show side effects. An example of the way in which more information becomes available over time is available in appendix A that looks at the increased risks of cardiovascular events found from the VIGOR study (Figure A in Appendix A).

III WHAT IS VIOXX?

Vioxx (rofecoxib) is a prescription medicine that is a Cox-2 (cyclooxygenase-2) selective inhibitor, nonsteroidal anti-inflammatory drug (NSAID). Vioxx is used to relieve the pain and inflammation of osteoarthritis and rheumatoid arthritis in adults. It is also used to manage short-term pain and treat menstrual pain and migraine headaches. The largest competitors to Vioxx are Pfizer's Celebrex and Bextra (Bextra has also been removed from the market) and Schering-Plough's Remicade, an international competitor. The other alternatives to these Cox-2 selective inhibitors (Vioxx, Bextra, Celebrex and Remicade) are nonselective inhibitors, such as naproxen and ibuprofen.[4]

Vioxx was launched in the United States in 1999 and has been marketed in more than 80 countries. In some countries, the product is marketed under the trademark Ceoxx. Worldwide sales of Vioxx were $2.5 billion in 2003. At that time, Vioxx was the third largest seller within Merck, following Zocor and Fosamax. This represented 11 percent of the $22.5 billion of total sales for Merck in 2003.

On September 30, 2004, Merck voluntarily withdrew Vioxx from sale. This came after a three-year study (called APPROVe, Adenomatous Polyp Prevention Vioxx) was done on the drug, concluding that subjects taking 25 mg of Vioxx had a higher chance of cardiovascular events, such as heart attack and stroke, than those taking a placebo. The increased health risks were occurring 18 months after the Vioxx treatment started.[5]

"Merck has always believed that prospective, randomized, controlled clinical trials are the best way to evaluate the safety of medicines. APPROVe is precisely this type of study—and it has provided us with new data on the cardiovascular profile of Vioxx," said Peter S. Kim, Ph.D., president of Merck Research Laboratories. "While the cause of these results is uncertain at this time, they suggest an increased risk of confirmed cardiovascular events beginning after 18 months of continuous therapy. While we recognize that Vioxx benefited many patients, we believe [the removal of Vioxx from the market] is appropriate."[6]

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[4] Examples of these are Advil and Motrin (ibuprofen) and Aleve (naproxen). Note: Tylenol (acetaminophen) is not considered a NSAID. Other Cox-2 selective inhibitors that came later are Merck's Arcoxia and Novartis' Prexige. A detailed explination of Vioxx and Cox-2 inhibitors can be found in Appendix A.

[5] APPROVe was a multi-center, randomized, placebo-controlled, double-blind study to determine the effect of 156 weeks (three years) of treatment with Vioxx on the recurrence of neoplastic polyps of the large bowel in patients with a history of colorectal adenoma.5 The trial enrolled 2,600 patients and compared Vioxx 25 mg to a placebo. The trial began enrollment in 2000.

[6] From the "Statement Issued by Dr. Peter S. Kim at the FDA Advisory Committee Meeting" on February 17, 2005.

Selective Time Line of Merck[7]

May 20, 1999	FDA approves Vioxx. (Closing price of $72.25, which is a one-day increase of 2.48%)
Nov. 23, 2000	VIGOR, which was designed to find the side effects of Vioxx, such as stomach ulcers and bleeding, is published in *The New England Journal of Medicine*.
Apr. 11, 2002	Merck revises the Vioxx label to include precautions about cardiovascular risk cited in the VIGOR trial.[8]
Sept. 30, 2004 – 'Event One'	Merck voluntarily removes Vioxx from the shelves.
Nov. 1, 2004 – 'Event Two'	*The Wall Street Journal* reports that Merck executives were worried in the mid-to-late 1990's that Vioxx would show greater heart risk than cheaper painkillers.
Jan. 28, 2005 – 'Event Three'	The US Court of Appeals in Washington rules that the company will lose its patent on the osteoporosis drug Fosamax by 2008.
Feb 18, 2005 – 'Event Four'	The FDA releases an announcement saying they believe that the Cox-2 inhibitors' benefits outweigh the increased chance of a cardiovascular event caused by the drugs.

IV STUDY SET-UP AND DATA

For this study, I use stock market data on the daily returns for fifteen stocks in the drug industry and two proxies for the market. The proxies used are the Value-Weighted Index (VWI, value weighted stocks from NYSE, AMEX, and NASDAQ stock markets) and the Standard and Poor's 500 index (S&P). The AMEX Pharmaceutical Index (API, ticker DRG) includes the following fifteen stocks, which will be the pharmaceutical stocks analyzed in this paper.

[7] A detailed timeline can be found in Appendix B.

[8] The VIGOR study found that of the 4047 patients taking rofecoxib, 111 had cardiovascular events (2.7%), while of the 4029 patients taking naproxen 50 had cardiovascular events (1.2%). This shows Vioxx has 2.2 times higher chance of having a cardiovascular event then does naproxen. This is a RR (relative risk) of 2.22 and a RD (risk difference) of 44%, found in Mukherjee, Nissen, Topol (2001).

Table 1 – Drugs in the API (AMEX Pharmaceutical Index):

Merck & Co	MRK
Pfizer, Inc	PFE
Johnson & Johnson	JNJ
GlaxoSmithKline plc Adr	GSK
Sanofi-Aventis Ads	SNY
Amgen Inc	AMGN
AstraZeneca Ads	AZN
Abbott Laboratories	ABT

Wyeth	WYE
Lilly (eli)	LLY
Bristol-Myers Squibb	BMY
Schering-Plough	SGP
Teva Pharm Indus Adr	TEVA
Forest Labs	FRX
King Pharmaceuticals	KG

The data is the daily close prices from the CRSP dataset (the Center for Research in Security Prices) and uses daily holding period returns. In 2006, Merck was the seventh largest company by market capitalization in the API, but before the withdrawal, Merck was fifth largest in the API and the second largest in terms of drug sales. This data will be used to find the movement of stock prices as well as movement relative to the market. The market will be represented by the indices VWI and the S&P.

Event Study

Following event-study methodology, I use a zero-one dummy variable to see if there is evidence of abnormal stock movements during a given event window.

$$R_t = \alpha + \beta R_{mt} + \gamma D_t + \varepsilon_t$$

I will be regressing the daily stock price returns on the market returns. R_t is the return to Merck (or the other drug stocks in the API) at time t, and R_{mt} is the market's return at the same date. D_t is a dummy variable that will take the value of one during the event window and zero the rest of the time. This methodology will directly test for any market effects to Merck, or any of the other companies, during the events in this study. Any significant effect on the term γ shows an abnormal return during that event window. Because the γ will be showing the abnormal returns, I will only report the coefficient and t-statistic on these, and not the α and β which show Merck's average movement with the rest of the market.

The null hypothesis on γ is that the stock has no abnormal return over the event window. If γ is statistically different from 0, then the market had a reaction to the event, whereas if γ is not statistically different from 0, the event had no effect on that stock's price. To determine whether all information is captured the day of the event, or is dispersed over a multiple-day period, I use event-study windows both including the event and excluding the event. This is informative because if γ is significant when the event date is included, but not significant when the event day is excluded, it symbolizes that full information was captured the day of the event.

To set this up, I first use a three-day event study. This means that there will be a zero for all dummies, except the three days in question. For table 2, I show the three day window, but I have also used the same methodology using five, seven and ten day windows. The same results are found for all variations of event windows, thus only the three-day windows will be discussed. The three-day study is done four times for each event day. Two of the three-day event studies will include the day of the event, while the other two will not. I will check the reaction of the stock relative to the market both before and after the event, each with the event date and without the event date. The four event-study setups are shown below.

Table 2 -- Event-study format for three-day event studies:[9]

Date																				
20	21	22	23	24	25	26	27	28	29	30	1	2	3	4	5	6	7	8	9	10
September											October									
0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0
Mrkone (Merck event one, three-day dummy including day of event)																				
0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0
Mrkonewoday (Merck event one, three-day dummy without day of event)																				
0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0
Mrkonebef (Merck event one, three-day dummy before the event including event date)																				
0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0
Mrkonebefwoday (Merck event one, three-day dummy before the event without event date)																				

After doing the three-day event study, I also repeat the same process for one and three months before and after the event (none of these studies will include the day of the event). The months after the event will reveal if the company is correcting itself from an 'over/under-reaction' (Hirshleifer 2001), whereas the months before the event will show if any information was acted upon before the announcement was public. I look at these month-long studies with caution, as events in this study tend to occur close in dates causing these longer studies to overlap. I do this for all fifteen stocks; each regressed against both indices using data for one year before and after the event.[10]

Event One

Merck announced that it would remove Vioxx from the shelf September 30, 2004. This was a surprise announcement, as the only publicly available information about Vioxx up

[9] These event studies include data from one year before, to one year after the event. This table is shrunk down to ten days before and ten days after for demonstration purposes only.
[10] All these charts have been complied, please contact author for the regression output.

to this point was the VIGOR study. This study lead to a label change warning about cardiovascular risk. Because the label was changed at the time, and no other information about the drug was released before the withdrawal, the withdrawal announcement was a shock to the market.

The announcement was done after the markets closed September 29, 2004. The first event in this study looks at the effects of Merck's removal of Vioxx from the shelves. To do this, I look at the change from the close of the market on September 29, 2004 (before the announcement) to the close of the market on September 30, 2004. I look at the close because although a lot of information was revealed in the opening price (the opening price on September 30 was $33.40) on September 30, the change in price to the close that day allows investors to react to all information about the removal.

Table 3 -- Event One, the change in price the day Merck removed Vioxx from the shelves, Sept 29, 2004 close to Sept 30, 2004 close.

Market Ticker	Close (9/29/04)	Close (9/30/04)	Percent Change
Merck & Co	45.07	33.00	-26.80%
Pfizer, Inc	30.18	30.60	1.40%
Johnson & Johnson	57.03	56.33	-1.20%
GlaxoSmithKline plc Adr	43.84	43.73	-0.30%
Sanofi-Aventis Ads	36.50	36.61	0.30%
Amgen Inc*	57.99	56.81	-2.00%
AstraZeneca Ads	41.27	41.13	-0.30%
Abbott Laboratories	42.31	42.36	0.10%
Wyeth	37.72	37.40	-0.80%
Lilly (eli)	61.85	60.05	-2.90%
Bristol-Myers Squibb*	23.86	23.67	-0.80%
Schering-Plough	18.50	19.06	3.00%
Teva Pharm Indus Adr*	26.48	25.95	-2.00%
Forest Labs	44.86	44.96	0.20%
King Pharmaceuticals	12.14	11.94	-1.60%
S & P 500	1114.8	1114.58	-0.02%

* - There was a change in shares outstanding during these days (the shares used are from the later date, as the change was expected)

Table 4 -- Event One, the change in market capitalization the day Merck removed Vioxx from the shelves, Sept 29, 2004 close to Sept 30, 2004 close.

Market Ticker	Shares Outstanding In Billions	Market Cap (9/29/04)	Market Cap (9/30/04)	Gain (loss) September 30, 2004 in Billions of Dollars
Merck & Co	2.22	100	73.22	-26.78
Pfizer, Inc	7.55	227.88	231.05	3.17
Johnson & Johnson	2.97	169.27	167.19	-2.08
GlaxoSmithKline plc Adr	2.91**	127.57	127.25	-0.32
Sanofi-Aventis Ads	2.71**	98.92	99.21	0.3
Amgen Inc*	1.27	73.65	72.15	-1.5
AstraZeneca Ads	1.61**	66.44	66.22	-0.23
Abbott Laboratories	1.56	66.05	66.13	0.08
Wyeth	1.33	50.31	49.88	-0.43
Lilly (eli)	1.13	69.93	67.89	-2.04
Bristol-Myers Squibb*	1.95	46.41	46.04	-0.37
Schering-Plough	1.47	27.24	28.06	0.82
Teva Pharm Indus Adr*	0.45	11.91	11.67	-0.24
Forest Labs	0.37	16.61	16.65	0.04
King Pharmaceuticals	0.24	2.93	2.88	-0.05
			Sum:	-29.61

* - There was a change in shares outstanding during these days (the shares used are from the later date, as the change was expected)

** - These stocks are held internationally as ADR,[11] the number used is the shares outstanding listed by Yahoo Finance

Visible from the one-day price changes, the large drop in Merck brought only a small increase in Pfizer and small losses in Johnson & Johnson, Lilly, and Amgen. The largest competitors to Vioxx are Pfizer's Bextra and Celebrex, Schering-Plough's Remicade, and nonselective inhibitors, such as naproxen and ibuprofen. The profits Vioxx previously benefited from are now expected to become profits to the competition. This will occur only if the market believes this is an issue with the Vioxx drug and not all Cox-2 selective inhibitors. If this increased chance of cardiovascular events is thought to be

[11] ADR is the American Depository Reserve.

caused by all Cox-2 drugs, then the market will worry that Pfizer and Schering-Plough will also be battling lawsuits in the near future.[12]

At the time, Merck had 2.2 billion shares outstanding, meaning that the $12.07 overnight loss to the stock price represents a market value loss to Merck of $26.8 billion. That same day, Pfizer had an increase of $3.2 billion and Schering-Plough had an increase of $0.8 billion, while Johnson & Johnson lost $2.1 billion, Lilly lost $2 billion, and Amgen lost $1.5 billion. The net loss to these fifteen stocks that day was $29.6 billion (the overnight loss was $16 billion). This loss represents the total expected loss due to Merck's decision to remove Vioxx from the shelves. The loss to Merck was $26.8 billion, while the difference between Merck's loss and the total drug industry loss was $0.8 billion. So at first thought, the $0.8 billion difference would capture the expected loss to the industry from the effects of the Cox-2 inhibitors. But before exploring that idea, let's first see if indeed the market captured all information that day.

[12] Evidence later revealed that this is an issue as all Cox-2 selective drugs are dealing with similar lawsuits and have had to change their labels to include warnings of heart risk.

Table 5 – Event One, three-day study including event day and without event day: September 30, 2004

Company	Mrkone (Event One With Day)		Mrkonewoday (Event One Without Day)	
	VWI	S&P	VWI	S&P
Merck & Co	-0.081 (7.71)**	-0.081 (7.76)**	0.002 (0.16)	0.001 (0.13)
Pfizer, Inc	0.007 (1.04)	0.007 (1.04)	0.003 (0.43)	0.003 (0.37)
Johnson & Johnson	-0.002 (0.44)	-0.002 (0.49)	0.003 (0.71)	0.003 (0.64)
GlaxoSmithKline plc Adr	-0.007 (1.17)	-0.007 (1.15)	-0.004 (0.63)	-0.004 (0.65)
Sanofi-Aventis Ads	-0.002 (0.22)	-0.002 (0.19)	0.001 (0.11)	0.001 (0.11)
Amgen Inc	-0.009 (1.12)	-0.009 (1.11)	-0.002 (0.26)	-0.002 (0.3)
AstraZeneca Ads	-0.008 (1.02)	-0.008 (1.01)	-0.008 (1.02)	-0.008 (1.04)
Abbott Laboratories	-0.005 (0.86)	-0.005 (0.87)	-0.005 (0.76)	-0.005 (0.81)
Wyeth	0.003 (0.42)	0.003 (0.42)	0.005 (0.61)	0.004 (0.57)
Lilly (eli)	-0.007 (0.89)	-0.007 (0.9)	0.006 (0.83)	0.006 (0.79)
Bristol-Myers Squibb	0.002 (0.38)	0.002 (0.4)	0.003 (0.47)	0.002 (0.43)
Schering-Plough	-0.006 (0.71)	-0.006 (0.71)	-0.015 (1.87)	-0.015 (1.93)
Teva Pharm Indus Adr	-0.006 (0.71)	-0.006 (0.67)	-0.009 (1.03)	-0.009 (1.03)
Forest Labs	0.003 (0.29)	0.003 (0.3)	0.012 (1.05)	0.012 (1.04)
King Pharmaceuticals	0.01 (0.63)	0.01 (0.63)	0.015 (0.96)	0.014 (0.95)

* significant at 5%; ** significant at 1%, Absolute value of t statistics in parentheses

As you can see from the regressions above, Merck is significant when the event day is included, but not significant when the event day is not included. Merck is also the only company that moves statistically different from the market, showing that all information about the withdrawal occurred the day of the event and that Merck is the only company that was significantly affected by the event. The same thing is found when looking at the three days leading up to the event. To do that, I use the same three-day event study looking at the days leading up to the event, along with one and three months before and

after the event (these regressions can be found in Appendix C). This reveals two pieces of information, that the day of the event captured all information and also that there is no evidence of insider trading.

Although Pfizer and Schering-Plough are the two largest competitors, neither company had a significant change in price over the sample period (nor are any companies other than Merck). This shows that their movement is not abnormal from the market movements; therefore, their gains that day were not necessarily due to the Vioxx announcement. This can occur because there are two contradictory pressures on the prices of Vioxx's competitors. One is that they will increase sales making up for Vioxx's lost sales, while the other is the chance that all Cox-2 inhibitors could increase cardiovascular events. Because of this, the price changes expected to Pfizer and Shering-Plough are ambiguous.

Other Events

The same event-study format is used for all four of the events in this study. As the effects of the first event were fully captured the day of the event, the same was found with the other three events as well. The second event occurred while the markets were closed, while the other events all occurred while the market was open. I will compare the one-day price change to see what effect that event had on Merck's market capitalization.

The second event was when the *Wall Street Journal* published an article claiming that Merck executives had knowledge of the increased risk of cardiovascular events well before they withdrew the drug. This event was expected to have a negative effect on Merck because it revealed information that could cause the market to believe that they would lose more lawsuits, so this drop in market value will fully reflect a decrease in the probability of Merck winning cases. This event caused Merck's stock price to decrease by 9.7 percent (or $6.72 billion).

The third event had no direct effects on the lawsuits filed against Vioxx. This event was when Merck lost the last ten years of patent life of Fosamax, their second-largest-selling drug. Teva Pharmaceuticals challenged Merck for patent infringement, and the US Court of Appeals voted that Merck did infringe on the patent. Because of this patent infringement, Merck will lose the rights for an exclusive patent to Fosamax in February 2008, when it was initially set to expire in February 2018. This will not have an effect on the probability of Merck winning cases concerning Vioxx, but will be used as a proxy to estimate the profit loss from Vioxx's expected sales.

Table 6 –all four events, the stock price change when the event occurs:

	Withdraw of Vioxx	*The Wall Street Jorunal* Report	US Court of Appeals ruling	FDA announces support for Cox-2 inhibitors
Event #	One	Two	Three	Four
Date	9/29/2004	10/29/2004	1/27/2005	2/17/2005
	9/30/2004	11/1/2004	1/28/2005	2/18/2005
Company	%Δ	%Δ	%Δ	%Δ
Merck & Co	-26.80%	-9.70%	-10.10%	13.00%
Pfizer, Inc	1.40%	-0.50%	-1.30%	6.90%
Johnson & Johnson	-1.20%	0.10%	0.60%	0.10%
GlaxoSmithKline plc Adr	-0.30%	1.70%	-0.50%	0.90%
Sanofi-Aventis Ads	0.30%	0.10%	-0.10%	2.50%
Amgen Inc	-2.00%	-2.00%	-0.50%	-0.60%
AstraZeneca Ads	-0.30%	0.00%	1.10%	1.70%
Abbott Laboratories	0.10%	0.30%	-0.40%	-0.30%
Wyeth	-0.80%	0.50%	0.70%	1.40%
Lilly (eli)	-2.90%	0.40%	-3.60%	-1.00%
Bristol-Myers Squibb	-0.80%	-0.30%	-2.60%	1.80%
Schering-Plough	3.00%	-2.70%	-0.70%	1.10%
Teva Pharm Indus Adr	-2.00%	-3.30%	2.20%	1.80%
Forest Labs	0.20%	-1.10%	-1.90%	1.50%
King Pharmaceuticals	-1.60%	-2.80%	0.80%	1.70%

The last event (event four) was on February 18, 2005 when a FDA panel voted to allow sales of Cox-2 inhibitors, despite their increased risk of cardiovascular events. This panel voted in favor of Celebrex (31-1), Bextra (17-13), and Vioxx (17-15). This, the fourth event, will have a direct effect on the market's expectations of Merck's ability to win lawsuits as they will now be expected to win more cases since the FDA supports the sale of their drug. Merck increased 13 percent during the day of this announcement.

The second event increased Merck's aggregate amount lost to $33.5 billion, while the FDA panel vote decreased the total amount back to $25.2 billion. Because event three did not have a direct effect on the Vioxx lawsuits, the $7 billion lost that day was not seen as part of the aggregate loss, but rather a reflection of the present discounted value of a Merck Patent loss of ten years.

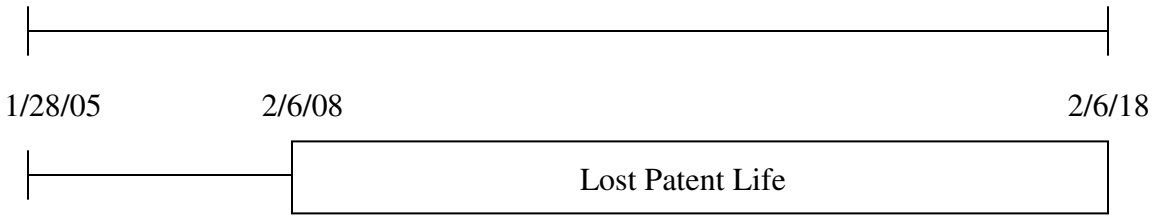
All of the events in the event study show that Merck moves significantly when the event is included, but insignificantly when the event is not included. The coefficients on the dummy variables for events two through four can be requested from the author.

V PATENT LOSS

When Merck withdrew Vioxx from the market in 2004, it was selling $2.5 billion a year world wide. The patent on Vioxx was set to expire on December 24, 2013, giving it approximately nine more years of patent life at the time it was removed from the market. This represents nine years of profits, along with any additional sales that could have been made after the patent expired, that Merck will no longer receive.

The third event in the study showed that the market efficiently reflected the lost value to Merck when the patent of Fosamax[13] was set to expire in February 2008, instead of when it was originally set to expire in February 2018.[14] This decision was made by the US Court of Appeals on January 28, 2005. This natural event will allow the opportunity to examine the value (or return) to a Merck patent.

Figure 2 Fosamax Patent Loss:



The gap between the initial patent life and the new patent life left Merck with a $7 billion loss on January 28, 2005. This means the market value of the last ten years of Merck's patent on Fosamax is $7 billion (b). With the years lost in patent and current sales of the drug, an internal rate of return (IRR) can be calculated. To find the IRR, I solve:

$$\Delta \text{ in Market Cap} = \text{Profits under initial patent} - \text{Profits under new patent}$$
$$\$7\ b = \Sigma^{13}_{0=i} \left(\text{Profits} / (1 + r)^i \right) - \Sigma^{3}_{0=i} \left(\text{Profits} / (1 + r)^i \right) \qquad (1)$$

Where sales will be the sales of the drug expected during that year. In order to solve for r, which will give the IRR, I have to assume what sales were expected to be. In "Safety, Patent Issues Weigh on Big Pharma" published in Forbes by Peter Kang on January 28,

[13] More information about the drug Fosamax can be found in Appendix D.

[14] This is not actually a loss of patent to Merck, but rather a patent that is "…unenforceable due to findings of invalidity. Merck did not lose 10 years of patent term, regarding the one weekly dosing of Fosamax, rather, their patent was held to be invalid over a prior art reference (that means they cannot exclude others from making, selling or using the subject matter of the patent claims…)." Email correspondence from the USPTO (Mary Till) July 13, 2006. More information about the USPTO can be found USPTO.com.

2005, the sales of Fosamax were expected to be $3.6 billion. The sales in 2005 were actually $3.2 billion, but the day the event occurred, the market expectation was $3.6 billion. Although the expected sales are $3.6 billion dollars, the market only reacts to profits from sales. In 2005, Merck's gross margin on sales was 76%. Because the only available measure of profit for Merck, or any of its drugs, is the gross profit margin, this is the proxy that will be used to measure profits. This means that of the $3.6 billion dollars of sales, $2.7 billion is the expected profits:

$$\$7\text{ b} = \Sigma^{13}_{0=i}\ (\ 2.7\text{ b} / (1 + r)^{i}\ ) - \Sigma^{3}_{0=i}\ (\ 2.7\text{ b} / (1 + r)^{i}\ ) \qquad (2)$$

Although Merck will lose the patent rights on Fosamax, this does not mean they will not be able to sell any. This means that they will have some reduced sales of the drug after the patent expires. Many studies have been conducted to examine what happens to the price of a drug when its patent expires. Because price can change in any direction—up, down, or remain constant—it is the remaining market share of the drug that reveals more information. Studies by Grabowski and Vernon (1992) and Caves, Whinston, and Hurwitz (1991) show that in the first year of patent loss a drugs market share will decrease by 20 to 30 percent. The following year's market share falls by 30 to 50 percent, and by the third year out, it will have lost a total of 80 percent of its market share. It is also important to know that the number of generics need to be large (more than 5), for this to occur. But at sales of $3.2 billion in 2005, ranking it in the top 20 for total sales,[15] I feel it safe to say that generics will be entering the market as soon as the patent expires.[16] These additional sales off-patent were to occur after the initial patent loss in 2018, but will now occur after the new patent expire date of 2008.

Thus (simplified because beyond year 15 they will both be discounting 80 percent of the sales and thus will cancel each-other out):

$$\$7\text{ b} = \Sigma^{13}_{0=i}\ (\ 2.7\text{ b} / (1 + r)^{i}\ ) + (\ 2.7\text{ b} * .75 / (1 + r)^{14}\ ) + (\ 2.7\text{ b} * .6 / (1 + r)^{15}\ )) - \Sigma^{3}_{0=i}\ (\ 2.7\text{ b} / (1 + r)^{i}\ ) + (\ 2.7\text{ b} * .75 / (1 + r)^{4}\ ) + (\ 2.7\text{ b} * .6 / (1 + r)^{5} + \Sigma^{15}_{6=i}\ (\ 2.7\text{ b} * .2 / (1 + r)^{i}\ ) \qquad (3)$$

Here I find an IRR of 13.2 percent. Because both Fosamax and Vioxx were in the same stage of sales, having gone through the growth faze and plateaued, along with similar time left on their patent life, this IRR can also be used for Vioxx. This IRR can now be used to estimate Merck's lost profits when Vioxx was withdrawn from the shelves.[17]

[15] This is using the sales of Fosamax in the United States in 2004, Fosamax was 20th with 1.9 billion dollars of sales in 2004 (found at Rxlist.com, $1.9 billion is the Weighted Average Cost times number of prescriptions).

[16] Since then Fosamax has been linked to a very rare jaw disorder that can cause the jaw to shatter. This information was not known at the time of the patent loss thus should have no effect on my estimates.

[17] With Vioxx's sales of $2.5 billion it is safe to assume that it also would have had sufficient generic entry (in 2004 U. S. sales of Vioxx were ranked 37th).

Using the IRR, it is now possible to see what the loss in profits was for Vioxx, which sold $2.5 billion the year before it was removed from the market.[18] The Vioxx patent was set to expire in December of 2013. Merck's gross margin during the last year Vioxx was still sold (2003), was 80 percent, meaning that the $2.5 billion in sales is $2 billion in profits:

$$\Sigma^{9}_{0=i} (2\text{ b} / (1 + .132)^{i}) + (2\text{ b} * .75 / (1 + .132)^{10}) + (2\text{ b} * .6 / (1 + .132)^{11}) + \Sigma^{\infty}_{12=i} (2\text{ b} * .2 / (1 + .132)^{i}) = \$11.5\text{ b} \quad (4)$$

Thus using this approach, the total loss of profits to Merck from the withdrawal of Vioxx is $11.5 billion.[19] But this assumes the market expected Merck to win the fosamax case with certainty. This is not a good assumption, because the case was known before there was a ruling. So there was a positive probability that Merck would lose the case before the ruling came out, so I will check the sensitivity of this IRR.

Sensitivity of Fosamax patent loss

When Merck lost ten patent years from their drug Fosamax, the market cap decreased by $7 billion. This loss is due to their loss in the patent, but the loss in profits may be more than the $7 billion if the expected probability of Merck losing this case was greater than zero. Because of this, I look at the value of the loss in patent for variations in the probability of Merck's victory in this case.

As the expected probability of victory (of the fosamax case) falls, the amount lost due to the expected profits on Fosamax increases:

Probability of Victory * Expected Loss = Change in Market Capitalization
Pr (win) * E (loss) = Δ Mkt. Cap
1 * $7 b = $ 7b

So for the $7 billion loss the day the USPTO ruled against Merck for the loss of ten years of their patent on Fosamax, the expectations of Merck's victory in this case would have had to have been 100 percent. It is reasonable to believe that some investors believed that Merck could lose, so to look at the effects of the probability of victory on the payout, I will change the probability to see how this reflects losses in Merck's market capitalization for this event.

If the expected probability of victory decreased to 90 percent:

Pr (win) * E (loss) = Δ Mkt. Cap
.9 * $7.78 b = $ 7b

[18] It is valuable to note that both these drugs are developed for the same demographics, primarily older people, along with the fact that they both seemed to have hit a plateau in terms of sales.
[19] Vioxx had 9 years and 3 months of patent remaining, the 3 months was controlled for when solving.

This shows that when the expected probability of victory goes down, the expected loss in Merck, due to the lost patent, increases. If the expected probability at the time of the announcement was actually 90 percent, instead of 100 percent, the total loss due to the patent is $7.78 billion. This $7.78 billion would show up as $7 billion at the announcement because part of the adjustment was already made in the expectations of the outcome.

Table 7 – Sensitivity test for Merck's probability of victory on Fosamax patent case:

Expected Probability of Victory	Actual Patent loss Valuation	Change the day of announcement
100%	7.01	7.01
90%	7.78	7.01
80%	8.76	7.01
70%	10.01	7.01
60%	11.68	7.01
50%	14.02	7.01
40%	17.53	7.01
30%	23.37	7.01

The actual loss and change the day of announcement are in billions of dollars

As expected, when the probability of victory falls, the actual amount lost due to the patent loss increases. To see how this changes the IRR and the expected loss in profits to Vioxx, I plug the numbers from table 7 into equation 1 and solve equation 4 to get table 8 (below):

Table 8 – Sensitivity test for Merck's probability of victory on Fosamax patent case:

Expected Probability of Victory	Value of Patent	IRR	Loss to Vioxx
100	7.01	13.24%	11.48
90	7.78	11.87%	12.31
80	8.76	10.38%	13.37
75	9.33	9.6%*	14.01
70	10.01	8.74%	14.80
60	11.68	6.90%	16.94
50	14.02	4.80%	20.70
40	17.53	2.34%	31.26
30	23.37	-0.67%	

* - CAPM estimate of IRR for Merck

Using the CAPM (Sharpe 1964) framework to get that the expected probability of victory was 75 percent and not 100 percent, the loss of profits due to the withdrawal of Vioxx was $14.01 billion. Because the probability is unknown, I will use the CAPM estimate for the loss in profits, giving an IRR of 9.6%.

VI PROBABILITY OF MERCK VICTORY

The market value (MV) of Merck, at any given point in time, is equal to the discounted expected future cash flows (Ç) of the company.

$$MV = \Sigma^{\infty}_{t=0} Ç_t \quad (5)$$

When a recall occurs, there is a direct cost (θ) of the recall. Thus,

$$MV = \Sigma^{\infty}_{t=0} Ç_t - \theta \quad (6)$$

so the direct costs will be taken from the value of the firm. These direct costs, according to Merck's 2005 Annual Report's financial section, will be the costs of recalling the previously sold products ($491.6 million), loss of current inventory ($93.2 million), and the costs to undertake the withdrawal ($141.4 million). This leaves the total direct cost of recall at $726.2 million, which is $552.6 million post tax.[20] The markets estimate of θ the day the announcement is not available, so I will assume the market's estimation was close to the after-tax cost of the recall, or $552.6 million.

The recall will not only entail the direct costs of the recall, but the legal costs of lawsuits that will follow. The first of the legal costs are the fixed legal costs (ρ). Fixed legal costs would be the initial gathering of the data to support their case, along with gathering a legal team to do the proceedings. There will also be a marginal cost of litigation (φ),[21] which will be the lawyer and any other marginal costs representing the firm at each court case, times the number of cases heard (σ).

$$MV = \Sigma^{\infty}_{t=0} Ç_t - \theta - \rho - (\varphi * \sigma) \quad (7)$$

The additional, and arguably largest, cost of the recall will be the expected payout for all cases lost. The expected total payout from litigation will also be encompassed in the market value. This expected total payout will be the payout awarded for any given litigation (ξ) multiplied by the number of cases (δ) and the probability of losing each individual case (γ).[22]

$$E\,[\text{total payout}] = \xi * \delta * \gamma \quad (8)$$

This gives a total market value when the recall occurs:

$$MV = \Sigma^{\infty}_{t=0} Ç_t - \theta - \rho - (\varphi * \sigma) - E\,[\text{total payout}]$$

or

$$MV = \Sigma^{\infty}_{t=0} Ç_t - \theta - \rho - (\varphi * \sigma) - (\xi * \delta * \gamma) \quad (9)$$

[20] From Merck's 2005 annual report.

[21] The cost will be for the litigation for each lawsuit because markets react negatively to companies that settle rather then taking it to court. This and Merck's stated confidence in their ability to win cases causes me to assume that all cases that are filed will go to trial.

[22] The probability of loss is used here because Merck will only have to pay a plaintiff (PL) if Merck loses the case.

Merck also loses its ability to sell Vioxx, both under patent and after patent expiry. This means that the expected profits ($E[\pi]$) will also have to be taken out of the market value.

$$MV = \Sigma^{\infty}_{t=0} Ç_t - \theta - \rho - (\varphi * \sigma) - (\xi * \delta * \gamma) - E[\pi] \qquad (10)$$

To determine the change on the market value I can subtract the market value of the firm after the recall (MV_a) from the market value of the firm before the recall was announced (MV_b). Thus the change in the market value (Δ MV) is:

$$\Delta MV = MV_b - MV_a$$

or

$$\Delta MV = (\Sigma^{\infty}_{t=0} Ç_t) - (\Sigma^{\infty}_{t=0} Ç_t - \theta - \rho - (\varphi * \sigma) - (\xi * \delta * \gamma) - E[\pi])$$

$$= \theta + \rho + (\varphi * \sigma) + (\xi * \delta * \gamma) + E[\pi] \qquad (11)$$

To find the probability of Merck winning cases (ω), I must first find γ then subtract it from one.

$$\omega = 1 - \gamma \qquad (12)$$

The significant change in market value (Δ MV) was \$26.8 billion the day Merck recalled Vioxx. In addition, the direct costs were \$552.6 million (m) and the total loss in profits was \$14.01 billion, based on estimates from the previous patent loss section.

$$\$26.8\ b = 552.6\ m + \rho + (\varphi * \sigma) + (\xi * \delta * \gamma) + \$14.01\ b \qquad (13)$$

Thus,

$$\$12.22\ b = \rho + (\varphi * \sigma) + (\xi * \delta * \gamma)$$

At the time of the withdrawal, it was estimated that Merck would have to face nearly 10,000 cases.

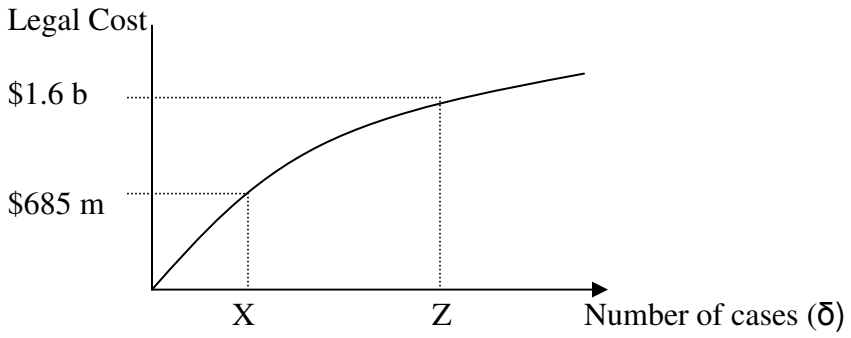
$$\$12.22\ b = \rho + (\varphi * \sigma) + (\gamma * 10{,}000 * \xi) \qquad (14)$$

Merck established approximately \$675 million[23] in reserve to cover the initial and future legal costs over Vioxx. I assume that this is an accurate, and known, estimate at the time of the removal.

As Merck increases the funds to cover the marginal cost of cases, each dollar they increase it covers more cases than it did before.

[23] This was set at the withdraw date, by December 15, 2006 Merck has set aside \$1.6 billion to cover litigation costs and nothing for liability.

Figure 3 Legal Cost Per Case



Where X < (Z – X), showing that as Merck increases the amount set aside for legal costs, doubling the money will cover more than double the cases. The initial legal cost is then $675 million, which will include the legal cost and the marginal cost of the cases they expect to go to trial. This number will grow over time. After the first three cases were heard, this number increased to $685 million, so X = 3, and the total cases heard when Merck increased this number to $1.6 billion was 13 (Z = 13) — ten additional cases for the additional $915 million dollars (Z – X = 10). Because this goes up over time, the average increase in this number over a year is accounted for when solving for the probability of a case after more money is put into this account.

$$\rho + (\varphi * \sigma) = 675 \text{ m}$$

So

$$12.22 \text{ b} = 675 \text{ m} + (\xi * 10{,}000 * \gamma) \qquad (15)$$

or

$$11.54 \text{ b} = (\xi * 10{,}000 * \gamma)$$

It is necessary to determine the expected litigation payout, ξ, to solve this. The first cases heard have large payouts, however payouts tend to fall over time. Also, given that those individuals with the highest risk of cardiovascular events are individuals who are older, the economic value of life will also tend to be lower. Because of these, a good estimate of the litigation cost is $5 million.[24] Thus,

$$11.54 \text{ b} = (5 \text{ m} * 10{,}000 * \gamma) \qquad (16)$$

$$23.1 = \gamma$$

$$\omega = 1 - 23.1 = 76.9$$

[24] I used $5 million as the expected payout. This number can be debated greatly, and it is hard to tell what the expected payout would be per case when this event occurred. I use this number because we have to look at the economic value of life. And although the people taking these drugs are older, thus have a lower economic value of life, juries will also be handing out punitive damages. With these two elements combined, I believe $5m is a good estimate of the average payout expected. However, because I use the relative probability change as each event occurs, this payout will only affect the initial starting point.

Using this information, Merck's probability of loss, for any given case, is 23.1 percent, making the probability that Merck will win a case 76.9 percent.

Because the expected payout per case can vary (see sensitivity test below), I will look at is the relative probability change. Relative probabilities will work, because as long as the expected payout is the same for all cases, the percentage change will capture the relative change in the expected outcome.

After *The Wall Street Journal* announced that Merck executives knew about the increased cardiovascular events in the mid-to-late 1990's their probability of successful litigation decreased by 13.4 percent (or a 13.5% change in the probability) to 63.5 percent. But when the FDA announced its support of Cox-2 inhibitors, despite their increased heart risk, Merck's probability of success increased by 16.7 percent (or a 28.5 percent change) to 79.2 percent.

Figure 4 Expected Probability of Merck Victory

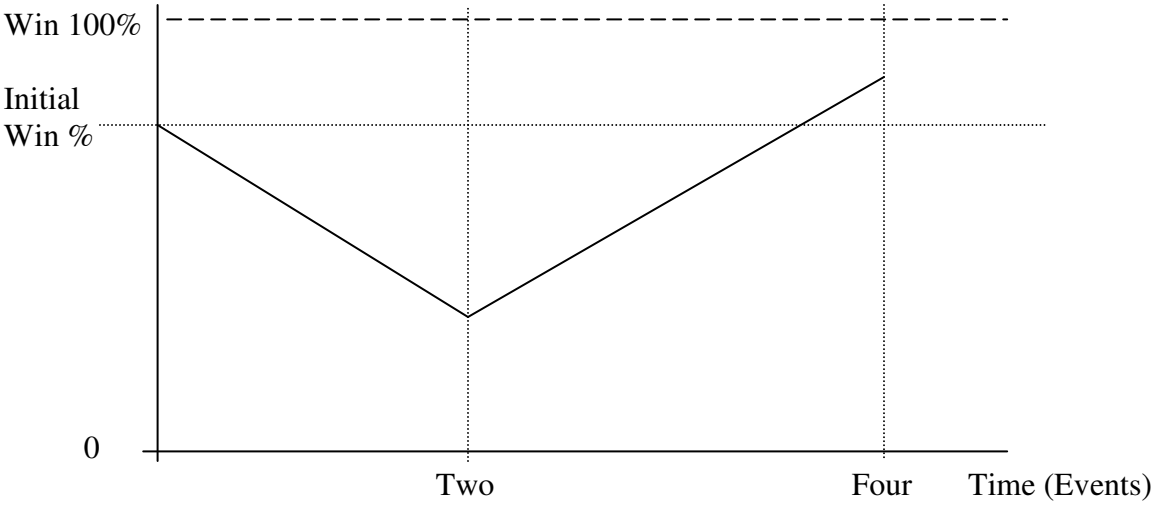


Table 9 – What happens when the assumptions change?

		Sensitivity		
	Baseline	Δ E[π]	Δ Legal Cost	Δ Payout
ω	76.9%	71.9%	78.7%	90.9%
E[π]	$14.01 billion	$11.0 billion	$14.01 billion	$14.01 billion
Legal Cost	$675 million	$675 million	$1.6 billion	$675 million
Payout	$5 million	$5 million	$5 million	$10 million

As you can see from table 9 above, the payout per case has the largest effect on changing the probability outcome.[25] The cases that have been heard are the cases that will most likely have the highest payouts, so I look at these cases as an upper bound estimate. Thus even though the average of the payouts seems high to this point, it makes sense to have

[25] The amount the probability will change can be found below in table 10.

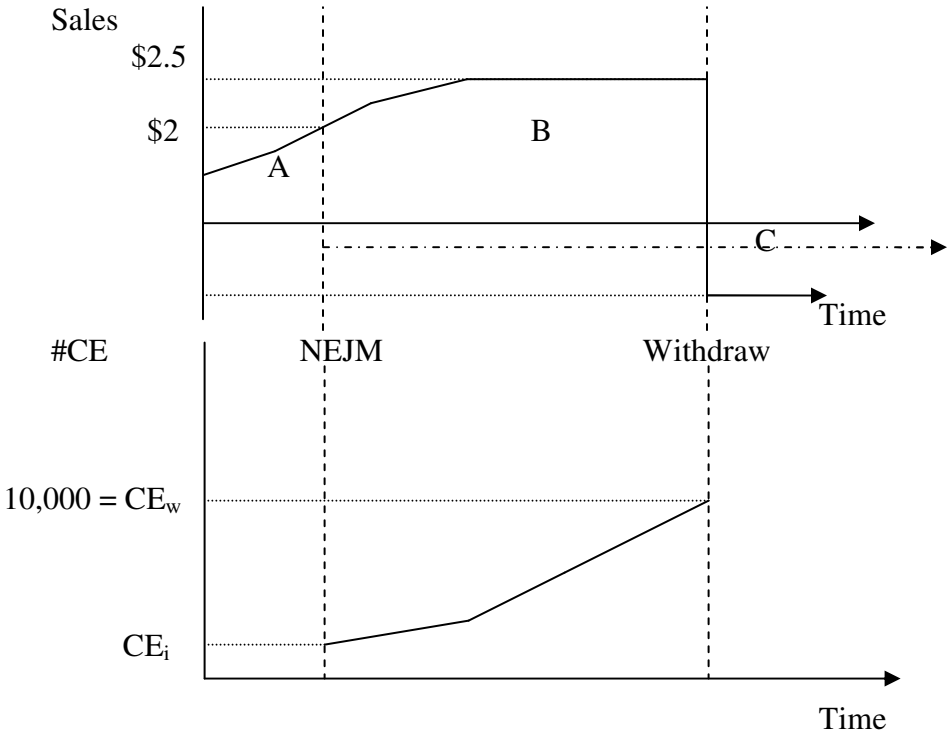
the average expected payout to be lower than that level. For this reason, I also use the relative probability change; this will give an accurate estimate of the change in probability given a starting expected probability.

Table 10 -- Probability outcomes as expected payout changes:

Expected Payout	Probability of Win
$3 million	62%
$5 million	77%
$10 million	88%
$20 million	94%

Should Merck have withdrawn when they did?

Figure 5 Timing of Withdrawal:



Merck lost $26.8 billion from the announcement, and of that $14 billion was a loss in expected profits. This left $12.8 billion dollars as the total cost of cases Merck was expected to face, while Merck was selling $2.5 billion dollars a year of the drug. Because I don't have the ability to adequately separate the $12.8 billion into what is a loss in brand name capital (C) and what are expected litigation costs, I can't find the exact amount of C, but I do know that the $12.8 is the combination of those two. If it was a good idea, than this combination should be smaller then area B. Where, area B is the total amount of sales from Vioxx from late 2000 until late 2004. Using the same

internal rate of return solved for earlier (9.6 percent) to discount forward, the value of sales over that period the day of the withdrawal was $13.1 billion. That $13.1 billion is the amount made in sales, but the actual amount made in profits (using profit margin of 80%) is $10.5 billion. From this information Merck lost more over this time period then they gained in profit, this seems to be (ex-post) a bad idea for Merck to have kept Vioxx on the market. They would have been better off if they would have withdrawn the drug when the NEJM was published.

VII CONCLUSIONS

Using an event-study format, I show that the market reacts immediately, without any evidence of over/under-reaction, to all the events. With that information, I am able to calculate the loss to Merck by looking at their market capitalization change when any particular event occurs. Knowing that the market reacts immediately to information, it is found that when Merck removed Vioxx from the shelves, it had a loss in market value of $26.8 billion. After *The Wall Street Journal* published an article stating that Merck executives knew since the mid-to-late 1990's that Vioxx increases the risk of cardiovascular events, the market value of Merck fell another $6.7 billion. This gave the company a total loss of $33.5 billion. When Merck initially withdrew Vioxx from the shelves, there was an expected probability of 76.9 percent that Merck would win a lawsuit filed against it, but when the information was released by *The Wall Street Journal*, their probability of winning a lawsuit decreased to 63.5 percent. More information was revealed when the FDA announced its support of Cox-2 inhibitors which decreased the total loss of Merck to $25.2 billion, which gave them a 79.2 percent probability of victory.

Although the loss in market capitalization is large, the expected loss to the company is not entirely due to legal issues. When Merck removed Vioxx from the shelves it eliminated its third largest drug from the market, at $2.5 billion a year. So in removing Vioxx from sale, it also took away a large profit-making drug from the company. To find the loss in value to the company due to profit loss, I use the drug Fosamax to find an internal rate of return for the company. I find that the market gives a 9.6 percent internal rate of return to Merck's drugs, allowing an estimation of profit loss from the removal of Vioxx to reach $14.01 billion.

With this information, it is observed how the market reflects the change in the probability of Merck winning cases. I also find that Merck's decision to withdraw in September 2004, rather than 2000, seems to have been, ex-post, the wrong decision. But there are other possible reasons that Merck would have wanted to keep Vioxx on the market. Merck may have known something like this was inevitable, thus they could use this information to acquire companies, through stock purchase, at a stock price that was artificially high. They may have had confidence that they would not have to payout in the lawsuits, and to this date they haven't had to pay out as their cases are still in the appeals process. It has also been announced that Merck is trying to settle all outstanding lawsuits for $4.85 billion. If this goes through, and Merck was anticipating something like this, then this would make the decision to stay on the market the correct one.

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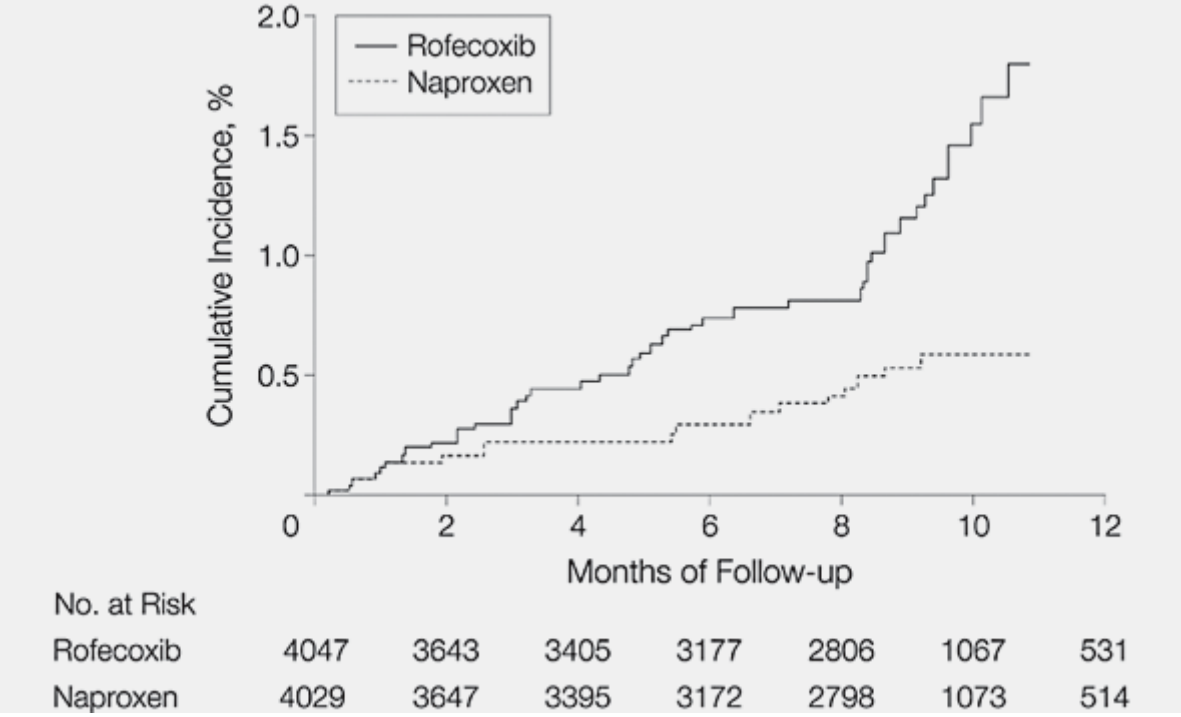
Appendix A

Nonsteroidal anti-inflammatory drugs (NSAIDs) come as both non-selective and selective Cox-2 drugs. A non-selective inhibitor will inhibit both the Cox-1 and the Cox-2 enzymes. Research for these selective drugs began in 1991 when researchers first learned of the two different Cox enzymes. Although both enzymes help produce hormones called prostaglandins, Cox-1 is present throughout the body and Cox-2 is made only under certain conditions. The researchers found that only the prostaglandins made by Cox-2 enzymes lead to inflammation, pain and fever, while Cox-1 primarily makes hormones that help keep the stomach lining intact and the kidneys functioning properly.[26] In the Research News from Pennisi (1998), John Breitner, an epidemiologist at the John Hopkins School of Public Health, said, "the potential long-term adverse consequences are not known," although the Cox-2 inhibitors seemed safe. Breitner notes that because the drugs seem so safe, people are likely to use them at higher doses for much longer than they would aspirin (because of its known risks). Non-selective NSAIDs cause an increased risk of stomach bleeding, ulcers, and potentially fatal stomach and liver damage. The risks non-selective inhibitors present are only found in a small number of people (estimates as low as 2-4 percent of those taking these drugs). For most Americans, ibuprofen or naproxen (non-selective NSAID's) provides the exact same pain relief as Cox-2 inhibitors at a fraction of the cost (naproxen retailed for approximately $0.06 per pill prior to its recall while Vioxx sold for as much as $3.00 per pill).[27]

[26] From "Building a Better Aspirin" Pennisi, Elizabeth 1998
[27] Retail prices from Community Catalyst, where naproxen is a generic while Vioxx still had exclusivity.

Figure A
Time to Cardiovascular Adverse Event in the VIGOR Trial



This figure is from figure 1 in the paper "Risk of Cardiovascular Events Associated With Selective COX-2 Inhibitors" by Mukherjee, Nissen, and Topol published in *Journal of the American Medical Association*, August 22/29, 2001 - Vol 286, No. 8 located on page 956.

Appendix B
Detailed Time-Line

Jan. 2, 1970	Merck's IPO, opening the first day at $112.75.
Nov. 23, 1998	Merck submits NDA (New Drug Application) for approval of Vioxx from the FDA.
Jan. 1999	Merck begins VIGOR (Vioxx Gastrointestinal Outcomes Research), a trial to test the impact of Vioxx. Merck claims "similar" cardiovascular risk among patients taking Vioxx and those on placebo or other pain relievers.
May 20, 1999	FDA approves Vioxx. (Closing price of $72.25, which is a one-day increase of 2.48%)
Feb. 2000	APPROVe (Adenomatous Polyp Prevention Vioxx) begins enrollment for a trial to test the effects of Vioxx on the recurrence of neoplastic polyps of the large bowel in patients.
Nov. 23, 2000	VIGOR, which was designed to find the side effects of Vioxx, such as stomach ulcers and bleeding, is published in *The New England Journal of Medicine*.[28]
May 22, 2001	Merck issues a press release titled "Merck Confirms Favorable Cardiovascular Safety Profile of Vioxx."
Sept. 17, 2001	The FDA sends Merck a "Warning Letter" demanding that Merck discontinue the promotion of Vioxx to doctors for unofficial uses.[29]
Apr. 11, 2002	Merck revises the Vioxx label to include precautions about cardiovascular risk cited in the VIGOR trial.[30]

[28] According to Merck, after the journal's deadline for submission, this study revealed a statistically significant increase in the number of cardiovascular events, heart attacks, and strokes in patients taking Rofecoxib (Vioxx) as compared to those taking Naproxen (the original transcript was submitted in May of 2000). The published article said that there was no increase in cardiovascular events, heart attacks or strokes. The additional information led to an Arthritis Advisory Committee discussion that added safety information to the label of Vioxx in April 2002.

[29] Merck was marketing Vioxx for uses in arthritis treatments that had not been proven to the FDA's satisfaction.

[30] The VIGOR study found that of the 4047 patients taking rofecoxib 111 had cardiovascular events (2.7%), while of the 4029 patients taking naproxen 50 had cardiovascular events (1.2%). This shows Vioxx has 2.2 times higher chance of having a cardiovascular event then does naproxen. This is a RR (relative risk) of 2.22 and a RD (risk difference) of 44%, found in Mukherjee, Nissen, Topol (2001).

Sept. 30, 2004 – 'Event One'	Merck voluntarily removes Vioxx from the shelves after the APPROVe study finds that those patients taking 25 mg of Vioxx for more then eighteen months have an increased risk of suffering a heart attack, stroke, or other cardiovascular event.
Nov. 1, 2004 – 'Event Two'	*The Wall Street Journal* reports that Merck executives were worried in the mid-to-late 1990's that Vioxx would show greater heart risk than cheaper painkillers which are harsh on the stomach but are believed to reduce the risk of heart attacks.
Dec. 23, 2004	The FDA issues a public health advisory urging doctors to carefully weigh the risks in prescribing medications for arthritis and pain, suggesting limited use of Cox-2 inhibitors. (This includes Vioxx)
Jan. 28, 2005 – 'Event Three'	The US Court of Appeals in Washington rules that the company will lose its patent on the osteoporosis drug Fosamax by 2008 (initially set to expire in 2018). This causes Merck's stock to fall ten percent, as this is Merck's second biggest seller, with sales of $3.2 billion in 2004.
Feb 18, 2005 – 'Event Four'	The FDA releases an announcement saying they believe that the Cox-2 inhibitors' benefits outweigh the increased chance of a cardiovascular event caused by the drugs.
April 7, 2005	Pfizer removes Bextra from the market and changes the label of Celebrex after being told to do so from FDA.
Aug. 19, 2005[31]	Merck loses Ernst v Merck case. Merck is found guilty by a jury in the death of Robert Ernst, a Texas man who took the pain killer Vioxx. Robert Ernst's widow is awarded $750,000 in damages, and an additional $24 million for mental anguish and $229 million in punitive damages.[32] Merck argues that Ernst died of clogged

[31] On August 19, 2005, plaintiff Carol Ernst won her lawsuit in the Texas Superior Court in Angleton, Texas (30 miles from Houston). Her lawsuit blamed Vioxx for the 2001 death of her husband, Robert Ernst, a 59-year-old marathon runner and Wal-Mart worker who was taking the arthritis painkiller at the time of his death. Mr. Ernst died of a heart attack, and the verdict held Merck liable for the death. Jurors voted 10-2 in favor of Ernst. The jury awarded more than $250 million in total damages: $24 million for mental anguish and loss of companionship and $229 million in punitive damages; although, Texas state law limits the amount of punitive damages to two million dollars when and if the case is upheld through the appeals process. Ernst's Houston-based lawyer, Mark Lanier, said the punitive-damages figure was based on "the money Merck made and saved by putting off their product label changes."

[32] Texas law limits the punitive damages to two million dollars if this case is upheld through the appeals process.

	arteries, not a Vioxx-induced heart attack. Merck plans to appeal. They also begin to battle 4,200 other state and federal pending lawsuits. (first case)
Nov. 3, 2005	Merck wins Humeston v Merck case. Frederick Humeston from Boise, Idaho, claimed that his heart attack suffered on September 18, 2001 was a result of intermittent use of Vioxx over a two-month period. (second case) On March 13, 2007 the jurors awarded $20 million in compensatory damages, then later said Merck should pay $27.5 million in punitive damages.
Dec. 12, 2005	Mistrial declared in Irvan v Merck in a Houston Texas trial brought by Richard Irvan's widow. Just prior to his death in 2001, Irvin had been taking Vioxx for about a month for back pain. As of Dec. 12, 2005, Merck is facing 7,000 cases over Vioxx.[33] (third case, first federal case)
Feb. 18, 2006	Merck wins Irvan v Merck case. The New Orleans jury finds Merck wasn't responsible for the previous Irvan case that was declared a mistrial in Houston December 12, 2005. (The original case was held in Houston, rather then New Orleans, due to hurricane damage.) Evelyn Irvin Plunkett, widow of Richard 'Dicky' Irvin, alleges his May 2001 heart attack came after taking Vioxx for about a month. (third case)
Apr. 5, 2006	Merck loses McDarby v Merck case, wins Cona v Merck case. John McDarby was awarded damages of $4.5 million, while Merck was absolved Merck in the case of Thomas Cona. (fourth and fifth cases)
Apr 21, 2006	Merck loses Garza v Merck case. A jury in Rio Grande City, Texas orders Merck to pay $32 million for the death of 71-year-old Leonel Garza. On March 8th, 2007 the verdict stands with Merck to pay Garza $7.75 million. (sixth case)

[33] One week before the mistrial, *The New England Journal of Medicine* claimed that Merck-sponsored scientists manipulated the cardiovascular data from a Vioxx study published in November 2000. Editors of the journal accused the study's authors of knowingly omitting the data from the publication's final draft. Merck claims that the heart attacks in questions happened after the journal's deadline for submission and were promptly reported to the FDA. Federal Judge Eldon Fallon declared a mistrial of the case, stating that the jury had not been able to reach a verdict in a timely manner.

Jul. 13, 2006	Merck wins Doherty v Merck case. The New Jersey jury ruled that Vioxx was not a substantial factor in Elaine Doherty's death. (seventh case)
Aug. 2, 2006	Merck wins Grossberg v Merck case. Stewart Grossberg took Vioxx before his heart attack at age 66, on September 18, 2001. "We firmly believed that Vioxx was not the cause of this heart attack because the data do not support that infrequent, sporadic use of Vioxx contributes to heart attacks," said Thomas Yoo, a member of the defense team, in a statement. "At the end of the day, the fact remains that the plaintiff was at high risk for a heart attack regardless of whether he was taking Vioxx." (eighth case)
Aug 17, 2006	Merck loses Barnett v Merck case,[34] and Merck's November win is thrown out. Gerald Barnett was taking Vioxx for 33 moths prior to suffering his hear attack in September 2002 and two years afterwards. He was awarded $51 million in damages, but the judge ruled that the jury's verdict will stand, but the $51 million in compensatory damages were unreasonable. The jury also found that Merck "knowingly misrepresented or failed to disclose" information about Vioxx to the doctors of the 62-year-old, media reports. The same day a New Jersey judge threw out Merck's win from the November Humeston v Merck case. (ninth case)
Sept 26, 2006	Merck wins Smith v Merck case. A New Orleans jury found that Merck did not cause a 2003 hear attack of Robert Smith, 56. Merck's lead trial lawyer, Philip Beck, said "Unfortunately, Mr. Smith would have suffered a heart attack whether he was taking Vioxx or not." (tenth case)
Dec 13, 2006	Merck wins Dedrick v Merck case. "The [New Orleans] jury determined that Merck acted appropriately in the development and marketing of Vioxx, and that Vioxx did not substantially contribute to Mr. Dedrick's heart attack," said Merck's attorney, Phil Beck, of the Chicago law firm Bartlit Beck Herman Palenchar & Scott. (eleventh case)
Dec 16, 2006	Merck wins Albright v Merck case. An Alabama state court jury said that the pain reliever didn't cause Gary

[34] Since this case the judge ruled that the jury's verdict that Merck is liable in the case will stand, but the $51 million in compensatory damages were unreasonable. (8/31/06)

	Albright's March 2001 heart attack. Merck pointed out during the trial that he continued to take Vioxx until September 2004 when the company pulled it from the market. Merck said Albright, now 58, had high blood pressure, diabetes and high cholesterol and was obese, all risk factors for heart disease. (twelfth case)
Jan 18, 2007	A mistrials declared on Appell v Merck and Arrigale v Merck. Los Angeles judge declared two mistrials when the juries couldn't come to a decision on the Scottsdale, AZ man, Lawrence Appell. Appell suffered a heart attack in Dec of 2000 at the age of 51, which he blames on Vioxx. He continued to take Vioxx until it was withdrawn in September 2004. Rudolph Arrigale of Westminster, CA said he used the pain killer for four and a half months before his heart attack in March, 2002 at the age of 72.
Mar 2, 2007	Merck wins Hermans v. Merck, but loses Humeston v. Merck. The Atlantic City jury split their ruling for the Merck cases. The jury split the cases because they believed that Merck gave proper warning before Hermans's Death (September 15, 2002, at age 44), but not before Humeston's death, at age 61, one year earlier.

Appendix C
Three day event study, before September 30, 2004

Table C.1

Company	Mrkonebef (Before Event One With Day)		Mrkonebefwoday (Before Event One Without Day)	
	VWI	S&P	VWI	S&P
Merck & Co	-0.087 (8.37)**	-0.087 (8.38)**	0.008 (0.68)	0.007 (0.68)
Pfizer, Inc	0.008 (1.15)	0.008 (1.23)	0.005 (0.75)	0.005 (0.75)
Johnson & Johnson	-0.003 (0.71)	-0.003 (0.7)	0.002 (0.37)	0.002 (0.36)
GlaxoSmithKline plc Adr	0.005 (0.78)	0.005 (0.83)	0.005 (0.87)	0.005 (0.87)
Sanofi-Aventis Ads	0.01 (1.27)	0.01 (1.32)	0.014 (1.8)	0.014 (1.8)
Amgen Inc	-0.003 (0.4)	-0.003 (0.33)	0.004 (0.45)	0.003 (0.44)
AstraZeneca Ads	-0.008 (1.05)	-0.008 (1.01)	-0.009 (1.18)	-0.009 (1.19)
Abbott Laboratories	-0.003 (0.54)	-0.003 (0.49)	-0.001 (0.19)	-0.001 (0.2)
Wyeth	-0.001 (0.09)	0 (0.04)	-0.001 (0.14)	-0.001 (0.15)
Lilly (eli)	-0.019 (2.53)*	-0.018 (2.49)*	-0.01 (1.42)	-0.011 (1.45)
Bristol-Myers Squibb	-0.001 (0.15)	0 (0.07)	-0.001 (0.26)	-0.002 (0.28)
Schering-Plough	0.005 (0.58)	0.005 (0.64)	-0.005 (0.6)	-0.005 (0.61)
Teva Pharm Indus Adr	-0.009 (1.01)	-0.008 (0.93)	-0.009 (1.03)	-0.009 (1.04)
Forest Labs	0.004 (0.37)	0.005 (0.41)	0 (0.03)	0 (0.02)
King Pharmaceuticals	-0.007 (0.43)	-0.006 (0.41)	-0.005 (0.31)	-0.005 (0.32)

Appendix D
Fosamax

Fosamax (alendronate) is a once–a-week drug used to treat osteoporosis in women after menopause and to reduce the chances of having a hip or spinal fracture. Treatment has been shown to increase the bone mass in both women and men with osteoporosis with as little as three months treatment. Fosamax tablets can be taken as both a treatment and as prevention. Fosamax alters the cycle of bone formation and breakdown in the body, which is called a bisphosphonates.