# THE FINANCIAL AND MARKET IMPACT OF CATASTROPHIC PRODUCT FAILURE: A STUDY OF PRESCRIPTION DRUG WITHDRAWALS

by

QIYU ZHANG

(Under the Direction of SRINIVAS K. REDDY)

## ABSTRACT

On September 30th of 2004, Merck & Co. Inc. made the rather surprising announcement that it was withdrawing Vioxx due to its increased cardiovascular risk. The withdrawal of Vioxx was surely a spectacular example of catastrophic product failure, but by no means unique. In fact, according to the FDA, 14 prescription drugs have been withdrawn from the market since 1996. In these catastrophic product failures, although the immediate financial impact is obvious with the loss of revenue, the spillover impact on other brands of the firm and on competing brands is not clear. This dissertation focuses on the financial and market impact of drug withdrawals in the U.S. market.

In this dissertation, a conceptual framework was developed in order to understand the impact of catastrophic product failures. A comprehensive database were compiled, and used to empirically examine 1) the effect of drug withdrawal on parent company's stock price, 2) the spillover effects of drug withdrawal on the sales of other brands in the parent company's portfolio, 3) the spillover effects on the marketing effectiveness of the parent company's marketing programs, 4) the spillover effects on the sales of competing brands in the therapeutic class, and 5) the spillover effects on the marketing effectiveness of these competing brands.

Using intervention analysis and mixed effect models, the two largest drug withdrawals between 1996 and 2003, namely the Rezulin and the Baycol withdrawals, are thoroughly analyzed. The results from modeling these drug withdrawals provide evidence for 1) significant negative effect of drug withdrawal on the parent company's share price, 2) negative spillover effects on the sales of other brands of the parent company, 3) negative spillover effects on the marketing effectiveness of the parent company, 4) positive spillover effects on the sales of competing brands, and 5) negative spillover effects on the marketing effectiveness of competing brands.

The findings from these two drug withdrawals are verified by replicating the modeling exercise using several additional withdrawn drugs (i.e., Seldane, Posicor, Duract, and Raplon). The results from the replication are generally consistent with those reported in the Rezulin and Baycol withdrawals.

INDEX WORDS: Product Failure, Product Withdrawal, Catastrophic Product Failure, Financial Impact, Market Impact, Spillover Effects, Carryover Effects, Marketing Effectiveness, Prescription Drug Withdrawal, Intervention Analysis, Mixed Effects Models, Pharmaceutical Industry

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To mom and dad whom I love dearly

Mr. Weiming Zhang & Mrs. Shuyi Wen

For

Their love and sacrifice

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# CHAPTER 1

# INTRODUCTION

## Withdrawal of Vioxx

Vioxx[1], a blockbuster pain-relieving drug marketed by Merck & Co. Inc., was initially launched in the United States in 1999, and was then marketed in more than 80 countries. (In some countries, the product was marketed under the trademark CEOXX.) Worldwide sales of Vioxx in 2003 were $2.5 billion. Approximately 20 million Americans took Vioxx (Dow Jones Newswires, November 8, 2004), and more than 100 million prescriptions had been written since its market launch. Vioxx was the second largest drug for Merck before it was pulled from the market (second only to Zocor).

On September 30th of 2004, Merck made the rather surprising announcement that it was effective immediately withdrawing Vioxx from the market based on the results of the new three-year data from a prospective, randomized, placebo-controlled clinical trial called the APPROVe

1 Vioxx (rofecoxib) is a COX-2 selective nonsteroidal anti-inflammatory drug (NSAID). According to the patient information filed with U.S. Food and Drug Administration (FDA), Vioxx is a prescription medicine used to relieve signs and symptoms of arthritis, acute pain in adults, and painful menstrual cycles. From the perspective of clinical pharmacology, Vioxx is also related to the nonselective NSAIDs, such as ibuprofen (best known as its brand name Advil) and naproxen (best known as its brand name Aleve). Generally speaking, COX-2 inhibitors belong to a new generation of NSAID, which selectively inhibit cyclo-oxygenase 2 (COX-2) but not COX-1. The traditional NSAIDs (e.g., Advil and Aleve) inhibit both COX-1 and COX-2. COX-2 inhibitors (e.g., Vioxx, Bextra and Celebrex) exhibit some promising features in gastrointestinal safety. They significantly reduce the risk of development of gastrointestinal perforation, ulcer and bleeding (PUB), typical side effects of non-selective NSAID (e.g., Aleve). The Vioxx Gastrointestinal Clinical Outcomes Research (VIGOR study) shows a significant reduction in PUBs in patients taking Vioxx compared to naproxen (brand name Aleve). Dr. Kweder (2004), director of Office of New Drugs, FDA, calls Vioxx a "tremendous hope of reducing gastrointestinal morbidity and mortality."

(Asenomatous Polyp Prevention on Vioxx) trial[2]. Until one day before the withdrawal, Merck had vehemently denied there was a connection between the use of Vioxx and increased cardiovascular risk (Martinez et. al. 2004), and was aggressively marketing Vioxx directly to consumers.

Vioxx's demise raises questions about Merck's future as a top-tier drug company, whose stock is among the most widely held and is included in the 30-company Dow Jones Industrial Average. Merck's shares plunged about $12, or 27%, to $33 when Vioxx was pulled from the market, and the company lost $26.8 billion from its market capitalization on the day of the Vioxx withdrawal. It was the largest single-day drop in percentage terms for a Dow stock since United Technologies Corp. lost 28% in September 2001. Pfizer shares, however, were up 1.4% on September 30th, 2004. Pfizer, in fact, immediately responded to the withdrawal of Vioxx by mounting marketing campaigns aimed specifically at attracting Vioxx users to Pfizer's own pain medicine Celebrex. Other rivals quickly joined this marketing battle too. Entrants include Johnson & Johnson's Tylenol, Wyeth's Advil, as well as prescription medicine, Boehringer Ingelheim Corp.'s Mobic (Steinberg 2004).

Vioxx accounted for 11% of Merck's global sales in 2003, and its loss was expected to shave around 20% off the company's profit in 2004 (Martinez et al. 2004). Yet, the costs of the Vioxx withdrawal went beyond the loss of revenue. According to the *Wall Street Journal* (October 22, 2004), Merck estimated $491.6 million to account for the costs of customer returns of Vioxx and write-offs of inventory. The company also estimated marketing and administrative

[2] The APPROVe trial began enrollment in 2000. The trial was being monitored by an independent data safety monitoring board (DSMB). In the APPROVe trial, Vioxx was compared to a placebo (sugar-pill). The purpose of the trial was to see if Vioxx 25 mg was effective in preventing the recurrence of colon polyps (it is a rather novel use of the drug). This trial was stopped early because there was an increased risk for serious cardiovascular events, such as heart attacks and strokes, first observed after 18 months of continuous treatment with Vioxx compared with the placebo. The outside panel overseeing Merck's APPROVe trial recommended termination of the trial, and concluded "a statistically significant increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment in the patients taking Vioxx compared to those taking placebo."

costs associated with the withdrawal to be $141.4 million. Wall Street analysts were also concerned about Merck's potential legal liability. Richard Evans, an analyst at Sanford C. Bernstein Research, estimated Merck's legal costs could reach $12 billion (Wall Street Journal November 8, 2004). In December 2004, the same analyst increased the estimation to as much as $38 billion. That estimation assumes that 58,000 heart attacks could be linked to the drug, and that the average settlement would be $659,000 (Forbes December 3rd, 2004). This figure of $38 billion is not a complete exaggeration. Since Wyeth took its drugs, Pondimin and Redux, (better known as Phen-Fen), off the market in 1997, and it has paid $13.6 billion in legal fees and settlements (the biggest amount ever paid by a pharmaceutical company over a withdrawn drug). Only 6 million people took Wyeth's diet drugs, while 20 million Americans took Vioxx[3].

Beyond direct monetary costs, Merck also suffered indirectly from its tarnished image and reputation. If customers (medical professionals and patients) were convinced that Merck had put profit before people[4], the tarnished image might very well translate into the costs of credibility loss. In fact, on August 21st, 2005, a Texas jury found Merck liable for the death of a Vioxx user. The jury awarded the surviving widow $253.4 million, a figure that referred to Merck's 2001 estimate of the additional profit the company expected to make by delaying an FDA warning on Vioxx's heart risks (Berenson 2005). In June 2005, Merck introduced its first marketing campaign in its 114 years history to boost the corporate reputation. This $20 million disclaimer campaign was run across virtually all possible channels, and it had a clear slogan: "Merck. Where Patients Come First." (Elliott 2005)

[3] According to Merck's financial report (2nd quarter 2005), as if June 30th 2005, 'the company has been served or is aware that it has been named as a defendant in approximately 4100 lawsuits, which include about 7500 plaintiff groups alleging personal injuries resulting from the use of VIOXX, and in about 120 putative class actions alleging personal injuries and/or economic loss.'

[4] To see some early evidence of Vioxx's risk before its withdrawal in the medical literature, refer to the Appendix A.

Loss of credibility can affect Merck on two different fronts. On one front, new drug applications from Merck may take longer time to get approved from the U.S. Food and Drug Administration (FDA). In fact, Merck was known for receiving faster approval for its new drugs than any of its competitors. According to Simons and Stipp (2004), between 1995 and 2001, for instance, Merck presented 13 major new drugs to the FDA. All were approved with an average review time of less than 11 months. Vioxx received an accelerated review and got its approval after just 6 months. By contrast, Pfizer's submissions during the same period faced an average review time of more than 24 months. In the pharmaceutical industry, approval time is crucial. A fast approval means additional lifetime on the market before a drug's patent expires, a potential gain worth millions of dollars in sales. Merrill Lynch estimated that Merck gained some $3.3 billion of extra sales between 1995 and 2001 as the consequence of quick approvals. But in the post-Vioxx era, this unique advantage of fast approval may no longer exist. An important drug in Merck's pipeline, Arcoxia (another COX-2 inhibitor) is awaiting the FDA's decision. However, most analysts expect the FDA to require the company to submit a long-term study on safety of Arcoxia before approving it (Hovey 2004).

On the other front, Merck's tarnished corporate reputation may also affect customers' perceptions toward the company and its products (Brown and Dacin 1997). It is possible that medical professionals and patients may have more safety-related concerns towards the remaining products from Merck and thus may have resistance of using Merck products from the company, if possible. In addition, negative media coverage and numerous lawsuits may stimulate a large amount of negative publicity (e.g., putting profits before drug safety), which would create doubts in Merck's social responsibility. Negative associations of corporate social responsibility may in turn influence customers' overall evaluation of the company's products and marketing programs.

In sum, the withdrawal of Vioxx is a recent and spectacular example of a catastrophic product failure. It has influenced the parent company very dramatically and on so many fronts. Some of the damages caused by the withdrawal may be explicit (e.g., loss of Vioxx revenue) and predictable, but some are more implicit and less predictable (e.g., loss of corporate reputation). For marketing researchers, it is pertinent to ask what we have learned about such a catastrophic product failure and the consequential effects on the company as well as on the competitors. For practitioners, it is extremely relevant to understand the different types of impacts caused by a product failure, and the possible means to avoid or to mitigate these impacts. In the next section, I will discuss briefly what we have known about catastrophic product failures and what we have left to learn. Along with this discussion, I explain the motivation and purposes of this dissertation.

**Motivation of Research**

As discussed in the preceding section, a catastrophic product failure affects the parent company and the competitors in many different ways. If there are any higher-level indicators that possibly summarize these influences, responses from the financial markets to the product failure are surely good candidates. Still using the Vioxx example, two facts are worth noting:

1) On November 10$^{th}$ 2004, Merck's stock was trading at about $26 a share. Merck's stock was trading at $45.07 a share before the company pulled Vioxx from the market. These figures suggest that Merck had lost about one third of its market value, or about $27 billion of shareholders' wealth, due to the withdrawal of Vioxx from the market.

2) On November 17$^{th}$ 2004, Standard & Poor's downgraded Merck's credit rating by three notches, from AAA to AA-. A lower credit rating indicates a significantly higher investment risk associated with the company overall.

Such radical responses from the financial markets are by no means unique to the Vioxx withdrawal. On May 20, 2000, Bristol Myers Squibb withdrew its drug Vanlev during the last stage of clinical trials. At the time of withdrawal announcement, the company's stock price fell by 23%, or $30 billion in its market capitalization. In 2000, Johnson & Johnson lost 11% or about $10 billion in the stock market following its decision to pull off its heartburn drug Propulsid from the market (Ahmed, Gardella, and Nanda 2002).

Research in the financial literature suggests that three major causes may lead to dramatic loss in shareholders' equity, namely 1) direct financial loss, 2) potential litigation expenses, and 3) damage to the company's goodwill (Pruitt and Peterson 1986). Direct financial loss includes loss of sales of the withdrawn product and the added expenses of withdrawing the product from market (e.g., writing-offs of inventory and administrative costs). Potential litigation costs involve money paid to lawyers to defend or investigate potential lawsuits filed against the company and, more significantly, settlement costs or liability costs if unfavorable results come from those lawsuits. Loss of goodwill, in marketing terms, typically refers to the dilution of the corporate brand equity and negative corporate associations. Damage to the company's goodwill can negatively affect customer evaluations toward existing products marketed by the withdrawing company (Hersch 1991).

In the context of the Vioxx case, direct financial loss primarily results from loss of future revenues of Vioxx. Before its withdrawal, Vioxx had annual sales of $2.5 billion in year 2003. Share price of Merck before the withdrawal incorporates the net present value (NPV) of future revenues of Vioxx. The NPV is calculated by discounting the projected future revenues of Vioxx over the course of its lifetime, especially over the period with patent protection. This part of

financial loss can be derived rather accurately using the standard net present value method[5]. The other part of direct financial loss involves administrative costs related to recalling the product and writing-off existing inventory. Calculating this type of cost is generally straightforward. These costs are usually disclosed by the company's public financial report. For instance, Merck estimated $491.6 million in writing-off inventory and another $141.4 million in administrative costs associated with the withdrawal. These estimates were in line with real outcomes when the withdrawal process was complete in the second quarter of 2005 (Merck 2005).

Potential litigation expenses are more unpredictable, when compared with direct financial loss. But the company involved in product failures and Wall Street analysts still give estimates for such expenses. For instance, Merck estimated and reserved $675 million for its legal defense. However, Wall Street analysts estimated the figure for potential liability costs related to the Vioxx withdrawal ranging from $4 billion to $20 billion after Merck lost the trial in Texas on August 19, 2005 (Gongloff 2005). Generally, these numbers are estimated by multiplying the number of possible lawsuits with average settlement/liability costs (Simons and Stipp 2004).

Damage to the goodwill of the company appears to be the most intuitive in the context of catastrophic product failures, but it may be the most difficult to precisely measure and quantify. Typically, catastrophic products failures can cause severe consumer harm or even death, which draws substantial attention from the media and consumer-harm lawyers. Negative publicity produced by media coverage and lawsuits may damage the goodwill of the withdrawing company. In the first and well-publicized Vioxx trial in Texas, the plaintiff's lawyer, Mr. Mark Lanier, presented to the jury 1) evidence that Merck's own scientists were worried about Vioxx's

[5] Actual calculation of the NPV can be quite complex with additional considerations of growth in sales, discovery of new uses of the medicine, competition, regulations, changes in the company risk, etc. A vast body of finance literature exists discussing different deviations from the standard NPV formula. Since calculating the NPV of Vioxx is not the focus of this dissertation. No detailed discussion is presented here.

potential cardiovascular risks even two years before the ethical drug's approval, 2) documents indicating that Merck's top scientist was aware of the risk associated with Vioxx in 2000, and 3) marketing programs that train Merck sales representatives to dodge doctors' concerns about Vioxx's heart risks and view these concerns as "obstacles' to be avoided or dismissed. This trial received extensive media coverage. The stock price of Merck dropped 7.7% (or $5 billion dollar in market capitalization) after the announcement of the trial results. Dr. Jerry Avorn, a professor at Harvard Medical School, said the jury's decision to punish Merck reflected their "overall sense of Merck" (Berenson 2005).

An immediate question that follows is how to measure the impact of damage to the company's goodwill? The finance literature has not yet extensively examined this issue in the context of product failures and recalls. Many studies were interested in measuring the impact of product recall/withdrawal announcements on stock price using event analysis (Ahmed, Gardella, and Nanda 2002; Jarrell and Peltzman 1985; Pruitt and Peterson 1986). These studies have been conducted within one industry (e.g., auto industry) or across different industries (e.g., electronics, prescription drugs, toys). But the surprising result was that the share price losses were very large compared with reasonable estimates of the cost to the firm, including direct financial losses and litigation costs. Several studies have found the product recalls in the pharmaceutical industry result in negative cumulative excess stock returns of about twelve times the estimated costs from litigation, product replacement and repair (Marcus, Swidler, and Zivney 1987). Pruitt and Peterson (1986) suggested that an explanation could be a reduction in future product sales attributed to the damage of the corporate reputation. Yet, they treated the impact of loss of goodwill as a catch-all effect. The mechanism through which the effect took place was not understood, and the quantity of the impact was not measured. This is similar to conducting

multiple regression analysis with an important explanatory variable missing from the model. Treating the missing variable as part of the error term can cause considerable biases in model estimates. Marcus, Swidler, and Zivney (1987) offered a different explanation that product recalls would increase systematic risk associated with the company stock return. In other words, investors would use a larger discount rate to calculate the net present value of the company after the product recall. From the perspective of market-based assets, a larger discount rate may correspond to a weakened corporate brand or a damaged corporate brand image (Srivastava, Shervani, and Fahey 1998). However, in the finance literature, what remains to be understood is how the product recalls/withdrawals work to influence the goodwill of the company, how the loss of goodwill will, in turn, affects the parent company, and whether the negative effect will spill over to the parent company's existing products. This dissertation aims to close these gaps by specifically addressing the loss of goodwill effect in the context of catastrophic product failures. The next section will discuss the research questions in detail.

In sum, product withdrawals typically incur substantial equity market losses. Attempting to identify possible explanations for these losses, several studies in the finance literature have examined the link between equity market loss and 1) direct financial losses, 2) potential litigation expenses, and 3) damage to the company's goodwill. The results were surprising: when using direct financial losses and litigation expenses to explain equity market loss, no relationship was found, indicating the significance of the impact of damage to the company's goodwill. Yet, this important component of product withdrawal has not been extensively studied or understood. Current marketing literature (e.g., corporate associations, branding strategies, negative information processing, and the spillover effects of product failure) may provide a useful framework to study and understand the damage to the goodwill effects. This dissertation,

drawing on relevant marketing and finance literature, proposes a conceptual framework to understand the phenomenon of catastrophic product failures, their damage to the goodwill of the company, and the resulting spillover effects on the existing products of the withdrawing company and on the competing products. Along with the conceptual framework, this dissertation also employs analytical models to empirically measure the spillover effects caused by catastrophic product failures using real-life data from the pharmaceutical industry. In the next section, 5 specific research questions of this dissertation are presented and discussed.

**Research Questions**

Consider another recent product failure case. On June 30, 2005, Apple Computer announced its settlement of a class-litigation over the iPod's battery life, agreeing to distribute $50 vouchers to as many as 2 million iPod owners. Plaintiffs claimed the batteries failed to last as long as Apple promised. As part of the settlement, Apple would also extend warranties and issue credits to consumers who had battery problems. This settlement would cost Apple about $100 million ($50 per user and 2 million users). On the day of the announcement, Apple's stock lost 5.19% (down by over $2) or approximately $1.6 billion of its market value. That's over 15 times of the estimated direct financial costs of the settlement (Burgos 2005).

The Apple battery settlement case appears to bear substantial similarity with the Vioxx example discussed earlier. The equity market losses are many times more than direct financial losses, indicating investors' concerns about possible spillover effects on the future sales of existing products from Apple. Yet, there are two significant distinctions between these two product failure cases.

First, the severity of product failure differs across these two examples. Apple iPod's battery problem is correctable, and hence the product continues its market life after problem corrections. In this case, the immediate concerns for the management involve 1) maintaining the replacement products' market share or recovering its lost market share, and 2) defending against negative spillover effects on other products of the company. Vioxx's failure, however, is not correctable in that the withdrawal of the product marks the end of the product's life. It is a termination of the product. In addition, the Vioxx failure may not be containable in the sense that it causes loss of human lives. When such a catastrophic product failure occurs, there is almost nothing that the management can do about the lost product. An important concern on the business side, however, is to ensure negativity caused by the product failure will not spill over to other existing products. In sum, the Apple iPod and Vioxx cases differ in the severity of product failure and in the subsequent implications for the management. There has been little research in the marketing literature to systematically address the implications of catastrophic product failures.

Second, branding strategies of these two companies are substantially different. Apple Computer uses an umbrella branding strategy, letting all products of the company bear the "Apple" brand name. The product brand and the corporate brand are closely correlated. Merck & Co., however, gives each of its products a distinct brand name without a very visible corporate brand name. These two types of branding strategy (i.e., umbrella branding for Apple and house of brands for Merck) give different levels of brand separation between brands in a company's portfolio (Aaker 1996). In the Apple iPod case, shared brand name facilitates spillover of negative associations from the failed product to other products in the company's portfolio. Prior studies in the auto industry have confirmed the spillover effect when a company uses umbrella

branding (Sullivan 1990). For instance, when one car model is found to be problematic, other models that do not have the same problem but share the same brand name from the car maker, also suffer losses in their valuation. In the Vioxx withdrawal, however, the failed brand is not very closely associated with other brands in Merck's brand portfolio, and each product brand from the company stands on its own. Product brands relate to each other only through their associations with the parent company. For instance, Vioxx and Zocor (a cholesterol-lowing drug) were the two largest brands of Merck & Co. in year 2004. Both of them were billion dollar sales blockbuster prescription drugs, but neither of them explicitly carried Merck's corporate name in their brands. They are only associated with each other through a shared parent company. This type of branding strategy keeps the visibility of the corporate brand name low and creates a shielding effect to keep negative information of the failed product from spilling over to other existing brands of the company. Although prior marketing literature has found that branding strategies with different levels of corporate brand visibility (Berens, Riel, and Bruggen 2005; Milberg, Park, and McCarthy 1997) moderate spillover effects, there has been little empirical research done to investigate spillover effects of product failure at high levels of brand separation where the corporate brand is almost invisible in product branding. This dissertation focuses on the spillover effects caused by catastrophic product failures on other brands of the parent company under high level of brand separation. This is an area that the existing marketing and finance literatures have not examined extensively, but has important research and managerial implications.

In the finance literature, "damage to the goodwill" is defined as a negative change in customers' beliefs about the company. Although the notion of damage to the goodwill has not been thoroughly explored in the finance literature, it has received considerable attention in the

marketing literature. This definition of damage to the goodwill is generally consistent with the notion of brand equity dilution in the marketing literature (e.g., Loken and John 1993). Damage to the goodwill effects, by definition, are not readily observable, though such effects may be revealed by field research (Aaker, Fournier, and Brasel 2004) such as in-depth interviews, observations, lab experiments, etc. A possible observable realization of damage to the goodwill is the spillover effect. In the context of this dissertation, spillover effect is defined as the impact of one product failure on the sales and marketing effectiveness of other related products. Specifically, when corporate brand equity is diluted, the resulting damage may influence the sales of existing brands in the portfolio of the parent company. In addition, brand equity dilution may also negatively affect the effectiveness of the withdrawing company's marketing programs. In that sense, the effect of one product failure spills over to other products of the withdrawing company.

Another type of spillover effect has to do with the impact of product failure on competitors. If the spillover effects within the withdrawing company are perceived as vertical, the spillover effects on competitors within a market are horizontal. Figure 1.1 graphically depicts the mechanism of brand separation and the spillover effects caused by a catastrophic product failure on other brands of the company and on competing brands. Separation between existing brands and the parent company mitigate the transfer of negative information furnished by the withdrawn brand. Such shielding effect may moderate the spillover effects of product failure on the parent company. The impact of product failure may also spill over to competing brands within the same market. The direction of such spillover effect is discussed in detail in Chapter 3. In the context of this dissertation, a market is therapeutic class, within which different brand drugs compete with each other.

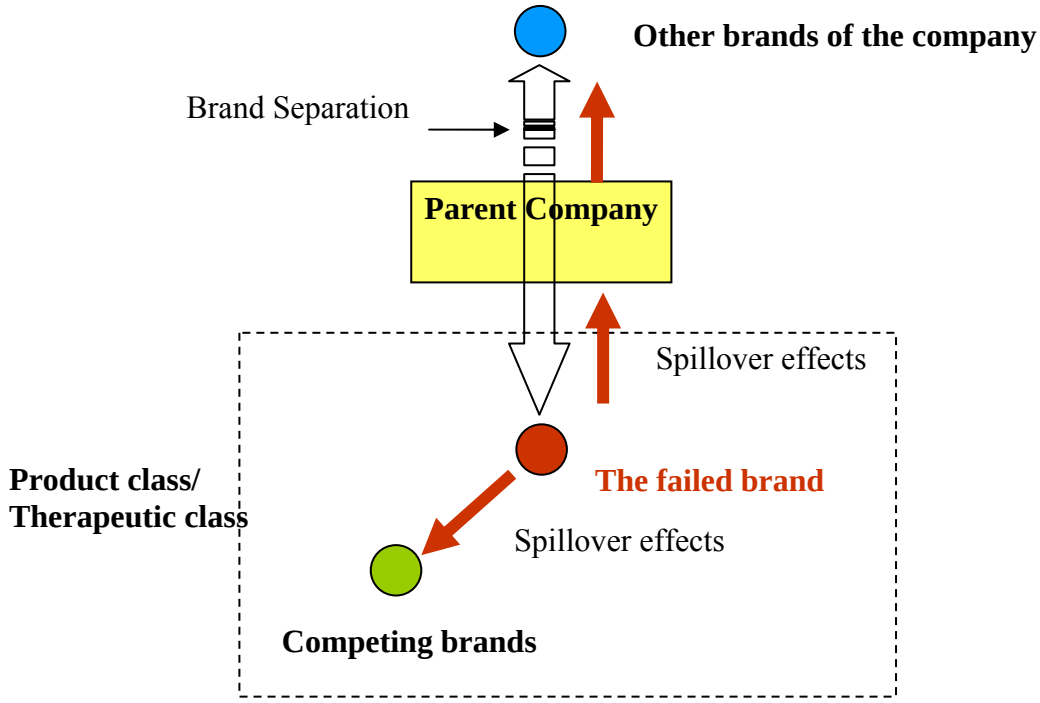


**Figure 1.1 Catastrophic Product Failure and Spillover Effects**

To sum up the preceding discussion, this dissertation attempts to specifically answer the following questions: When a catastrophic product failure occurs, what is the impact 1) on the stock price of the parent company, 2) on the sales of other brands of the parent company, 3) on the effectiveness of marketing programs of the parent company, 4) on the sales of competing brands in the product class where the failure occurs, and 5) on the effectiveness of marketing programs of competing brands? To empirically address the above questions, this study examines product withdrawals occurred in the pharmaceutical industry. This industry, in fact, provides an ideal setting to study catastrophic product failures. In the next section, I introduce the pharmaceutical industry and product failures in the industry.

**Pharmaceutical Industry**

The pharmaceutical industry is an ideal setting to study catastrophic product failures. First, the pharmaceutical industry is gaining increasing importance in the U.S. economy. In 2002, the industry represented about 2.5% of the economy, with the 19 leading drug and research companies generating over $181 billion in sales (Forster and Arndt 2002). In 2004, the pharmaceutical industry had $230 billion sales in the North American market with fast growth from prescription drug usage (IMS 2004). Prescription drugs, being the fastest growing part of the pharmaceutical industry, had an average 17% yearly growth between 1998 and 2002 (Saftlas 2003).

Second, defect-based product withdrawals in the pharmaceutical industry are typically catastrophic. On average, it costs $500 million and takes 15 years to bring one new medicine from the lab to the patient (Pfizer 2005). If one drug completely fails and is withdrawn from the market, it usually has a huge impact on the parent company in terms of loss of revenue, opportunity cost, huge negative publicity, etc., most of which were demonstrated in the recent Vioxx case. On the other hand, the withdrawn drugs cause severe harm to their users, sometimes even loss of lives. For instance, Rezulin, a once-hailed diabetes drug used by about 750,000 Americans, was withdrawn from the market in 2000 after it was linked to at least 63 deaths from liver poisoning (CNN 2000).

Even though drugs and new medications are tested for safety, not all adverse reactions to new drugs can be avoided or anticipated with the current system. Research in medicine (Wood, Stein, and Woosley 1998) indicates that with current system it is not possible to identify all adverse drug reactions (ADRs) before drugs are approved for marketing. Overall, 51% of approved drugs have serious side effects not detected prior to approval by the Federal Food &

Drug Administration (FDA). The major reason why many ADRs cannot be anticipated is because drugs are tested on a limited number of people, during a limited period of time in clinical trials before they are approved. Since individuals vary greatly in their responses to medication, not all the defects of a drug can be revealed from a limited sample of patients within a limited timeframe.

For pharmaceutical companies, there are always possibilities of product withdrawal after a drug's approval and sometimes even after several years' marketing. For example, Vanlev, Bristol-Myers Squibb's superstar for hypertension, was granted an accelerated review by the FDA. However, just one day after its full page ad in the *New York Times*, Bristol-Myers Squibb made a stunning announcement to pull the FDA filing for Vanlev in light of questions about a potentially life-threatening side effect (Barrett 2000). In contrast, the heavily marketed drug, Propulsid by Janssen, was pulled off shelves after some seven years in the market because of its association with 80 deaths. Adverse drug reactions (ADRs) are a serious problem in health care today. Research published in the *Journal of the American Medical Association* estimated that 106,000 Americans die each year due to adverse drug reactions (Lazarou, Pomeranz, and Corey 1998). This figure represents three times the number of people killed by automobile accidents and is the fourth leading cause of death in this country (Sternberg 1998).

Third, the pharmaceutical industry has had several identifiable product withdrawals during the past two decades. According to the FDA, 19 prescription drugs were withdrawn from the market between 1980 and 2001 due to adverse drug reactions. This figure represents about 3% of all the prescription drugs approved during the period (FDA 2001; FDA 2002). Between 2002 and 2005, two more prescription drug withdrawals were added to the list (i.e., Vioxx and Bextra). This dissertation focuses on drug withdrawals between 1996 and 2003, during which 12

drugs were withdrawn from the U.S. market. Table 1.1 summarizes all the safety-based prescription drug withdrawals since 1996 with two most recently withdrawn drugs, Vioxx and Bextra, excluded from the study. Both Vioxx and Bextra are COX-2 inhibitors that are used to treat arthritis pain. The closeness of time of these two withdrawals made their data unavailable at the starting point of this research. In the following section, I summarize this chapter and outline the entire dissertation.

**Table 1.1**
**Prescription Drug Withdrawals between 1996 and 2005**

| Brand | Use | Manufacturer | Year Approval | Year Withdrawal |
|---|---|---|---|---|
| Bextra | Antiarthritics | Pfizer | 2002 | 2005 |
| Vioxx | Antiarthritics | Merck | 1999 | 2004 |
| Raplon | Muscle Relaxant | Akzo Noble | 1999 | 2001 |
| Baycol | Cholesterol-lowering | Bayor | 1997 | 2001 |
| Lotronex | IBS | Glaxo-Wellcome | 2000 | 2000 |
| Propulsid | Heartburn | Janssen (J&J) | 1993 | 2000 |
| Rezulin | Diabetes | Parke-Davis (Pfizer) | 1997 | 2000 |
| Raxar | Antibiotic | Glaxo-Wellcome | 1997 | 1999 |
| Hismanal | Antihistamine | Janssen (J&J) | 1988 | 1999 |
| Seldane | Antihistamine | Aventis | 1985 | 1998 |
| Posicor | Hypertension | Hoffmann-LaRoche | 1997 | 1998 |
| Duract | Analgesic | Wyeth-Ayerst | 1997 | 1998 |
| Redux | Obesity | Wyeth-Ayerst | 1996 | 1997 |
| Pondimin | Obesity | Wyeth-Ayerst | 1973 | 1997 |

*Source: Center for Drug Evaluation and Research, the FDA*

**Outline of Dissertation**

To sum up the preceding discussion, this study examines catastrophic product failures. The focus of this study, in particular, is the spillover effect caused by a prescription drug withdrawal. The spillover effect of drug withdrawal is an important component in the evaluation

of catastrophic product failures. This component, though well acknowledged in prior research, was largely overlooked in quantitative research. This dissertation attempts to fill the gaps in the current literature by specifically examining and modeling the spillover effect of drug withdrawal in a complex industry where product failures are catastrophic and a thorough understanding of the spillover effects is not yet available.

For the withdrawing company, the spillover effect may be realized by the drug withdrawal's impact 1) on the sales of other brands of the parent company, and 2) on the effectiveness of marketing programs of that company. Similarly, for competitors in the same therapeutic class, the spillover effect may be revealed by the drug withdrawal's impact 1) on the sales of the competing brands and 2) on the marketing effectiveness of these brands.

In Chapter 2, I first review relevant literature. To begin the literature review, I propose a scheme to classify different types of product failures. Using the proposed product failure spectrum, I delineate the domain of this study ─ catastrophic product failures. Next, I intend to discuss the notion of brand separation brought about by using different branding strategies. Within the spectrum of brand separation, this dissertation examines spillover effects under the house of brands, where brands in a company's portfolio are deliberately separated from each other and from the parent company. In order to understand the mechanism of the spillover effects of drug withdrawal, I review literature in the following areas: 1) the financial market's responses to product recalls and withdrawals, 2) spillover effects in brand failures, 3) alternative branding strategies to create brand separation, 4) corporate associations, 5) product-harm crisis, and 6) negative information use in decision-making. After reviewing the related literature, I discuss gaps in current knowledge and the contributions of this study to the existing literature.

In Chapter 3, I propose a conceptual framework to understand the impact of drug withdrawal on parent company, as well as on competitors. The theoretical framework to understand the damage to company's goodwill and the subsequent spillover effects due to product failures is primarily based on research in the areas of brand equity dilution and corporate associations.

In Chapter 4, I describe the data compiled for the purposes of this study and the methods I used to analyze the data. In this chapter, I first describe the data and the sources from which the data were collected. Then I provide a description of the key variables used in this study. Following data descriptions, I give an overview of the two statistical methods utilized to answer the research questions in the study. In particular, intervention analysis and mixed effects models are discussed in detail in this chapter. Finally, I conclude the chapter by a summary of the methods used in the dissertation.

In Chapter 5, I present the modeling results from two major drug withdrawals, the Rezulin withdrawal in 2000 and the Baycol withdrawal in 2001. The complete results with regard to these two withdrawals are, in fact, presented over two chapters. Chapter 5 summarizes the impact of drug withdrawal on the parent company including the effect on share price, on the sales of other brands, and on the marketing effectiveness of the withdrawing company. Chapter 6 summarizes the impact of these two withdrawals on competing brands within the same therapeutic class.

In Chapter 7, several drug withdrawals that are appropriate for the modeling exercise are used to replicate the results found in Chapters 5 and 6. This chapter is further divided into two large sections to better present the results. First, three additional withdrawn brands (i.e., Seldane, Posicor, and Raplon) are used to replicate the results for the spillover effects on parent company.

Second, three brands (i.e., Posicor, Raplon, and Duract) are used to replicate the results for the spillover effects on competing brands. The rationales of using these particular brands are also discussed in the chapter.

Lastly, in Chapter 8, I summarize the findings of empirical analysis and draw conclusions primarily based on the results from the Rezulin and Baycol withdrawals. The academic and managerial implications of this study are discussed. Several limitations of this study are acknowledged, which are followed by the directions of future research.

# CHAPTER 2

# RELATED LITERATURE

In this chapter, related literature is reviewed to further the understanding of the spillover effects of product failure. Two classification schemes are discussed in this chapter to delineate the domain of this study. First, a scheme to classify different types of product failures is proposed. According to the proposed product failure spectrum, the domain of this study is catastrophic product failure. Following the spectrum of product failure, the notion of brand separation is discussed. According to the spectrum of brand separation, this dissertation examines spillover effects under the house of brands where brands in a company's portfolio are deliberately separated from each other and from the parent company. The severity of catastrophic product failure and the separation of brand are counter-weighting factors in terms of generating spillover effects in product failure. They add considerable complexities to the conceptual understanding of the spillover effects of drug withdrawal.

In order to understand the mechanism through which the spillover effects of drug withdrawal may occur, I review literature in the following areas: 1) the financial market's responses to product recalls and withdrawals, 2) spillover effects in brand failures, 3) alternative branding strategies to create brand separation, 4) corporate associations, 5) product-harm crisis, and 6) negative information use in decision-making. After completing literature review, I discuss gaps in current knowledge and the position of this study to fill these gaps in the literature.

**Product Failure Spectrum**

Product recall and withdrawal can occur under various conditions. Managers may decide to withdraw a product from the market on a voluntary basis (e.g., insufficient sales, technology innovation, market changes, product life cycle) or on a mandatory basis (e.g., product defects, product harm). In this dissertation, the focus is on defect-based product recall/withdrawal. A distinction is made in this dissertation between product recall and withdrawal. Product recall is defined as an action to call back products for repair or replacement. Within the context of the pharmaceutical industry, Johnson & Johnson's Tylenol contamination crisis in the 80's is an example of product recall. The troubled product, Tylenol (ibuprofen), is still available in the market today. In contrast, product withdrawal is the termination of product's market life. Withdrawn products become permanently unavailable in the market. All the brands listed in Table 1.1 are examples of product withdrawal.

In this dissertation, both product recall and withdrawal start with certain forms of product failure. A product failure occurs when the product is found to be defective or dangerous (Dawar and Pillutla 2000). However, product failures can vary greatly in their impact on the manufacturer as well as in their harm to consumers. This dissertation proposes a preliminary classification scheme for product failures based on the literature in medical crisis management (de Boer 1990; de Boer et. al. 1989). Product failures fall into three categories, namely 1) accident, 2) calamity, and 3) catastrophe. A product failure is an accident when the product defect is minor, correctable, and no extra resources need to be used to contain the problem. A product failure is a calamity when the defects are major, and the resulting product harm may involve casualties. Such product failures are still correctable, and thus only involve product recalls. A product failure is a catastrophe when the defects are disastrous, and cause severe harm

or even death to consumers. These product defects cannot be corrected, and the troubled product needs to be removed from the market permanently. The product's market life is terminated at the point of withdrawal. Figure 2.1 summarizes the product failure classification scheme and offers illustrative examples of each type of product failure.

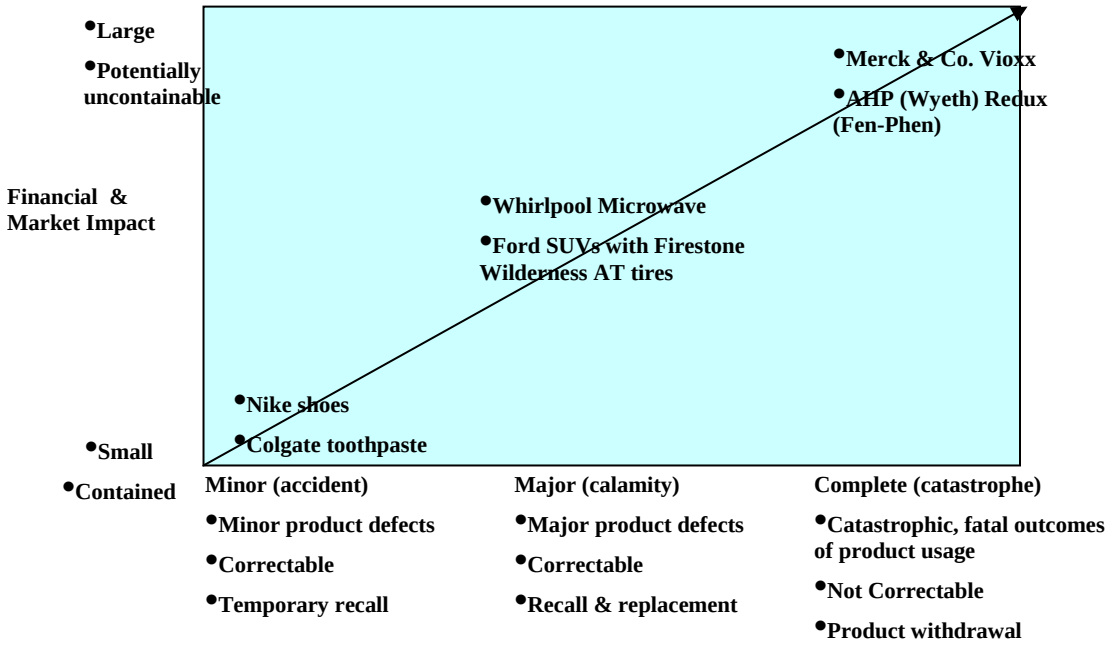


**Figure 2.1 Product Failure Spectrum**

Nike USA Inc. voluntarily recalled about 425,000 pairs of Jordan cross-training shoes in July 2001. These shoes had a thin metal strip on the outside of the heel. The strip could protrude from the shoe and form a sharp edge that could cut consumers. In March 2001, Colgate Palmolive recalled 7,300 cases of toothpaste because of microbial contamination. Product failures like the recall of Nike cross-training shoes or Colgate toothpaste would be considered

minor product defects with minor impact on consumers and a contained small impact on the brand and the parent firm. These failures would be classified as accidents as they would have minor product defects that are correctable and usually the recalls are temporary.

In contrast, Whirlpool recalled about 1.8 million microwave-hood combinations in October 2001, some of which overheated and resulted in several fires and extensive property damages. In August 2001, Ford Motors recalled its sport utility vehicles (SUVs) installed with Firestone Wilderness AT tires. In that quarter of 2001, Ford Motor spent $2.1 billion on replacing 13 million Firestone Wilderness tires on its vehicles (CNN July 18th, 2001). These are major product failures with extensive financial and market effects on the brands and parent firms and severe harm to consumers. The above two examples of product failure are calamities. The defects involved are major and may cause severe harm or death to consumers. These defects are sometimes correctable, but usually demands extra resources in order to correct the problem and/or re-design the recalled product. The failed products are often recalled for a longer period of time.

Product withdrawals such as Merck & Co.'s Vioxx and American Home Product Corporation's (AHP)[6] Redux (often known as Fen-Phen) can be considered as catastrophic product failures. For consumers, these failures can cause severe harm and sometimes even the loss of life. For withdrawing companies, these products have major defects that are not correctable, and need to be withdrawn from the market permanently. The market and financial impacts of such product failures are extensive and profound. Some impacts might last for a long period of time. For instance, when AHP withdrew two of its well-known obesity drugs, Redux and Pondimin, due to their associations with heart valve abnormalities, the two drugs had $132

[6] American Home Product Corporation changed its name to Wyeth on March 11th, 2002 to reflect the company's focus as a pharmaceutical company.

million and $173 million annual sales respectively prior to their withdrawal. The one time cost of the product withdrawal was estimated to be between $200 and $300 million (AHP 1997). According to *Forbes* (December 3rd, 2004), AHP has paid $13.6 billion in legal fees and settlement. As discussed earlier in Chapter 1, this dissertation focuses on examining catastrophic product failures and, in particular, the resulting spillover effects of such failures.

**Brand Separation Spectrum**

Current marketing literature has several taxonomies for categorizing branding strategies, most of which utilize a classification scheme with using only the corporate name at one end and not using the corporate name at all at the other end (Aaker 1996; Laforet and Saunders 1994; Murphy 1987; Olins 1989). Specifically, Olins (1989) suggested a scheme including 3 types of branding strategy: corporate identities only, branded identities without corporate name, and corporate name with a subsidiary name. Murphy (1987) used the notion of 'dominance' to categorize branding strategies into corporate-dominant, brand-dominant, balanced systems and mixed systems. Laforet, and Saunders (1994) used content analysis to examine corporate name usage in product brands. They suggested that, in practice, companies can choose to use one of the following branding strategies: 1) using corporate name prominently in product/service brands, 2) using corporate name combined with another name or 3) not using the corporate name at all. The underlying rationale is that the company and the products/services that the company carries are separate entities. Managers can choose to build and reinforce associations between the corporate brand and product/service brands, or vice versa, by adopting different branding strategies. Aaker (1998) made this point clear by introducing the notion of brand separation.

Using Aaker (1998)'s terminology, there are three branding strategies, namely 1) umbrella branding, 2) endorser branding and 3) product-brand branding (also known as house of brands). These three strategies offer different levels of separation between corporate brand and product/service brands. Ford Motors and Virgin Group are good examples of companies using the umbrella branding strategy. All the products of a company have the same brand name and a monolithic identity. Sony Trinitron and Obsession by C.K. use the endorser branding strategy. These brands share an endorsed identity from the parent corporate brand, but the associations between brands are weaker than those in umbrella branding. Unlike umbrella branding and endorser branding, in the product-brand branding strategy, every product (or a group of similar products) is assigned a unique brand name. Each product has a branded identity and stands alone from the rest in the company's brand portfolio (this branding strategy is also known as house of brands). Each brand in the company has a noticeable identity that is often created intentionally, but its associations with the corporation are typically remote.

When product-brand branding strategy is used, the corporation and the products are separated, which this dissertation refers to as brand separation. Several industries usually use this branding strategy. For instance, in the consumer packaged goods industry, Proctor & Gamble carries many different brands even within one product category. Many brands (e.g., Zest) are well known to consumers, but it is usually difficult for consumers to call to the mind of the parent company that markets the brands. Similarly, the pharmaceutical industry generally uses this branding strategy as well. Nexium, for example, is a popular branded prescription drug to treat heartburn from AstraZeneca, but the corporate brand name is not closely associated with the product. Many consumers who take this medicine may not even know which company manufacturers the prescription drug. One advantage of creating brand separation is to mitigate or

avoid the transfer of negative information from one brand to another. In the context of this dissertation, brand separation may mitigate the spillover effects of product failure on other brands in the company's portfolio. Figure 2.2 graphically represents the brand separation spectrum. This dissertation examines the spillover effects caused by catastrophic product failures under the house of brands.

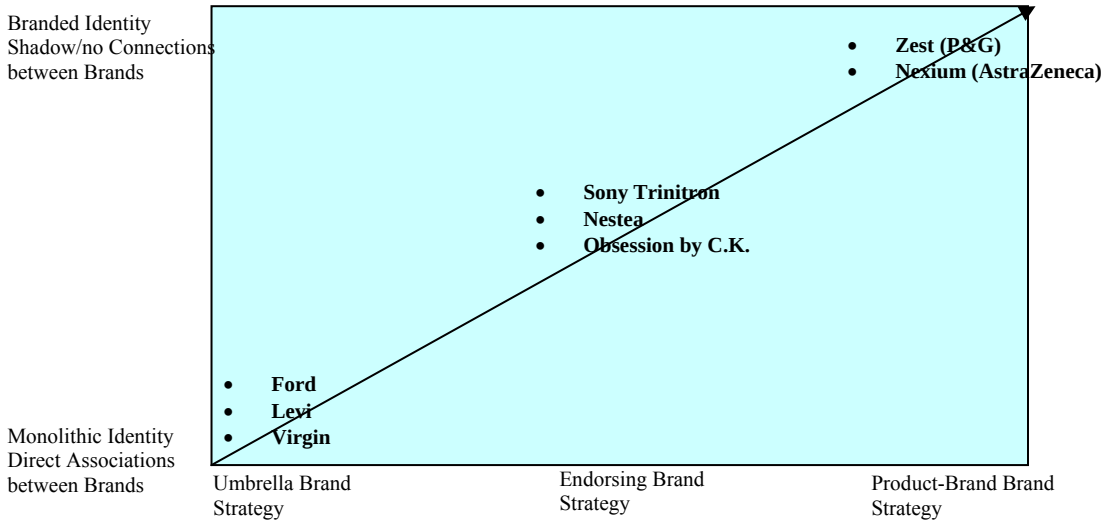


**Figure 2.2**
**Brand Separation Spectrum**

## Literature Review

A summary of the related literature on product/brand failure and its implications are presented in Table 2.1. Related literature has been classified into several streams, which are not necessarily mutually exclusive. Several studies, in fact, can be grouped into multiple streams. The literature is presented in this way due to the lack of a dominant framework that is readily

applicable to address the research questions in this dissertation. The studies listed in Table 2.1 are representative rather than exhaustive.

**Finance Literature on Product Recalls and Withdrawals**

Jarrell and Peltzman's (1985) seminal work on the impact of product recalls on shareholder value represents the opening of an important area in the finance/economics literature. Using data from the pharmaceutical and auto industries, they found that a company's losses in market value after a product recall were many times larger than the direct costs associated with the recall, indicating indirect costs resulted from the damage of the company's goodwill. In addition, they also found evidence that the impact of product recalls spill over to competitors. Hoffer, Pruitt and Reilly (1988) questioned Jarrell and Peltzman's (1985) methodology, and showed that inclusion of data from the auto industry might have biased the findings[7]. Pruitt and Peterson (1986) used data across different industries (excluding the auto industry) and found results similar to those of Jarrell and Peltzman (1985). They suggested that product recalls might damage company reputation, which would negatively affect future corporate sales.

Using data from the pharmaceutical industry, Marcus, Swidler and Zivney (1987) confirmed that the stock market losses were in excess of any reasonable measure of direct costs in product recalls, but suggested that recalls could increase the systematic risk of stock returns of the suffering companies. Ahmed, Gardella, and Nanda (2002) systematically studied drug withdrawals and suggested that the impact of such withdrawals might spill over to the existing products of the withdrawing company and even to the competitors involved in the drug withdrawal.

[7] The auto industry has a high frequency of recalls. In fact, several studies (e.g., Pruitt and Peterson 1986; Davidson and Worrell 1992) have found this industry has more recalls than all other recalls combined across industries.

In sum, these prior studies have confirmed that companies' equity market value losses after product recalls/withdrawals are much larger than the direct costs involved in the actual withdrawals themselves. A possible explanation is that the indirect losses of product recalls (e.g., goodwill loss) have not been measured but are needed in order to fully understand the equity market losses. While acknowledging the need to consider indirect costs, none of the finance studies mentioned above specifically measured the impact of goodwill losses. Jarrell and Peltzman (1985), in fact, stated that goodwill losses had remained something of a "mystery" that warranted future research.

**Spillover Effects in Brand Failures**

Prior research has found evidence of spillover effects in umbrella-branded products. For instance, Sullivan (1990) found that problems associated with Audi 5000's sudden acceleration spilled over to consumer's quality perceptions toward other models that shared the Audi brand. The spillovers were facilitated by the shared umbrella brand name, and were realized by increased depreciation rates in all used Audi cars. She further indicated that negative spillover effects were persistent, and affected Audi even two years after the incident. Erdem (1998) revealed that marketing programs can influence consumers' quality perceptions across product categories in umbrella branding. Specifically, she found a free sample of low quality in one product category can have negative carryover effects on the sales of existing products that belong to other categories but share the same brand name. The findings are consistent with the information economics view of umbrella branding (Wernerfelt 1988). Simonin and Ruth (1998) examined the spillover effects beyond the context of umbrella branding. They posited that, in

brand alliance, consumers' attitudes toward the co-branding efforts can spill over to partnering brands. These effects are moderated by brand familiarity.

In the brand extension literature, research has found negative reciprocal effects on the parent brand when a brand extension produces negative information for various reasons, including lack of fit between the parent brand category and extension product category, inconsistent brand image, etc. Several important studies include Loken and John (1993), John, Loken and Joiner (1998) and Swaminathan, Fox and Reddy (2001). Loken and John (1993) found when brand extension attributes are not consistent with the parent brand, negative reciprocal effects occur on the parent brands. John, Loken and Joiner (1998) further indicated that when negative spillover effects occur, consumer perceptions toward the flagship product are less vulnerable to dilution than perceptions toward the parent brand in general. Swaminathan, Fox and Reddy (2001) identified important moderators for the occurrence of negative reciprocal effects. They suggested that similarity of category and customer prior experience moderate the transfer of the negative information from failed product to parent brand.

In sum, negative information furnished by product failure can transfer to consumers' perceptions toward other products that share the same brand name (e.g., umbrella-branded products or extending an existing brand into another product category). Similar negative spillover effects can also occur in a brand alliance (e.g., co-branding). In these studies, two conditions are usually present for the spillover effects to take place. First, brands share the same brand name. Shared brand name facilitates the transfer of information between different entities (Sullivan 1990). Second, the negative information furnished by the failed brand is considered relevant in the evaluation of other related brands (e.g., the parent brand of the failed extension brand) (Swaminathan, Fox, and Reddy 2001). When brands do not appear to have very visible

associations between them, the transfer of negative information from one brand to another becomes less likely to occur. In the next section, I review the literature on alternative branding strategies and the brand separation they may create to hinder the transfer of information between brands.

**Alternative Branding Strategies**

Aaker (1996) discussed the notion of brand separation in that managers can employ different branding strategies in order to separate brands from the corporation and from each other. Milberg, Park and McCarthy (1997) used lab experiments to demonstrate that "sub-branding"—using a new brand name in conjunction with a family brand (i.e., endorser branding in Aaker's terminology)—separates a brand extension from the parent brand to some degree, thus mitigates negative reciprocal effects on the parent brand, if brand extension fails. They also suggested that if further brand separation is created by using product-brand branding, reciprocal effects of negative information may be avoided. Following a similar strain, Berens, van Riel, and van Bruggen (2005) posited that under the strategy of low corporate brand visibility, what customers know about the corporation (e.g., corporate abilities and corporate social responsibilities) will affect customers' evaluations of products from the company to a lesser degree than it will do under the strategy of high corporate brand visibility. Their experiments showed that when a corporation uses marketing communication with low corporate brand visibility, customers' knowledge about the corporation (positive or negative information) is less likely to be used in product evaluations. Rao, Agarwal, and Dahlhoff (2004) found evidence from the financial market that people react differently to marketing programs under various branding strategies. In particular, they showed that using umbrella branding with the corporate name is more positively

related to the intangible value of the company than using house of brands and mixed brands. Their findings imply that information may carry over to different products more effectively under umbrella branding than alternative branding strategies.

In sum, brand separation created by using alternative branding strategies can have significant moderating effects on the transfer of information between different products in customers' product evaluation. In the context of product failure, when brand separation is high, the transfer of negative information to other brands in the company's portfolio becomes less likely to happen. As a result, the spillover effects of product failure on other brands may be mitigated or avoided. While brand separation may hinder the spillover of information between brands, what customers know about the corporation in general can potentially influence their perceptions toward individual products that the company carries. Research in corporate associations may shed light on the current study, which is reviewed the next section.

**Corporate Associations**

Brown and Dacin (1997) coined the term 'corporate associations' as a label for all the information about a firm that a customer holds. This notion implies that both product level associations and corporate level associations can influence customers' perceptions towards a product. Specifically, two types of corporate associations, those related to the company's expertise in producing its outputs ─ corporate ability (CA), and those related to the company's status and activities with respect to its perceived societal obligations ─ corporate social responsibility (CSR), both influence customer's attitudes towards new products manufactured by that company. Consumers use CA associations to infer missing or partial product attribute information, and use both CA and CSR associations to globally evaluate the company. The

corporate context will, in turn, influence customers' perceptions towards individual products. The notion of corporate associations and its implications in consumer purchase decision making is also documented in the economics literature. Weigelt and Camerer (1988) presented a thorough literature review. In the context of product failure and potential spillover effects of negativity, Klein and Dawar (2004) found that CSR associations not only influence evaluation of new products manufactured by the failed company, but also influence consumers' attributions of the product-harm crisis. They also introduced a boundary condition: consumers need to be CSR-sensitive. Creyer and Ross (1997) also found that consumers' support for the CSR is a key moderator for their willingness to reward CSR. Sen and Bhattacharya (2001), however, found evidence in their experiments that consumers react negatively to negative CSR information regardless of whether they are supportive of any particular CSR issues. Consumers' support for the CSR only moderates their reactions to positive CSR information.

Several studies (e.g., Handelman and Arnold 1999; e.g., Singh et. al. 2005) suggest that relationships between a company and its constituencies are governed by two dimensions: an economic/value dimension and a social/trust dimension. Negative changes in the social/trust dimension can have a deleterious effect on the firm. Trust depletion can also spill over to relationships with other constituencies.

In sum, corporate associations, separate from brand-level associations, can influence consumer's evaluation of the products manufactured by a company. Negative corporate associations in particular negatively influence evaluation of the brands associated with the corporation. But the relationships between corporate associations and customers' product evaluation are moderated by the visibility of corporate brand name, or corporate brand dominance (Berens, Riel, and Bruggen 2005), as discussed in the preceding section. In addition,

there is little empirical evidence for the interaction between corporate and product associations; thus it remains an open question (Brown and Dacin 1997).

**Product-harm Crisis**

Several studies have focused on the management of a product-harm crisis. Siomkos and Kurzbard (1994) found that in a product-harm crisis, a firm is less affected when it has a better reputation, positive external effects (e.g., media reports), and proper responses. In addition, they suggested that under brand separation, damage due to product-harm crisis may be brand specific, as opposed to spilling over to other brands, unless the media makes a link between separate brands. Kabak and Siomkos (1991, and 1992) suggested strategies to introduce a replacement product. For products without replacements, they argued that future sales of other products and stock price should be performance measures of concern. In discussion of the recovery process from the crisis, they suggested using exponential or other functions to approximate the transient process.

Other studies have looked into the processes through which customers process product-harm crisis information. Dawar and Pillutla (2000) investigated the consequences of product-harm crisis on brand equity using field surveys and lab experiments. They found that the interaction of customer expectations and firm responses affect post-crisis brand equity. Folkes and Kotsos (1986) found that prior expectation of product failure explained the discrepancies between buyers and sellers in attribution of product failures. In brand failure studies, Aaker, Fournier and Brasel (2004) found that the impact of brand transgressions is moderated by the type of the relationship between the brand and consumers.

In sum, the impacts of a product-harm crisis on brand equity are complex. These impacts are moderated by many factors, including internal factors (e.g., firm reputation, nature of the crisis, firm responses to the crisis) and external factors (e.g., media coverage, customer types).

**Negative Information Use**

Conventional knowledge suggests that negative information carries more weight in decision making than positive information with the same valence (Fiske 1980). Klein, and Ahluwalia (2005), however, found that negatives may not be more diagnostic than positives in evaluation of presidential candidates. Using motivational explanation, they suggested voters' prior preference moderates the weight of negatives in that only those voters who dislike the candidate may weight the negatives more heavily. Their findings are consistent with the notion of confirmatory bias in prior product-harm research (Handelman and Arnold 1999). Similarly, Ahluwalia, Unnava, and Burnkrant (2001) found negative information about one attribute spills over to other related attributes. But when consumers are committed to the brand, the negative spillover effect is minimized.

A contradictory view is the contrast effects (Brown and Dacin 1997; Sherif and Hovland 1961). Sherif and Hovland (1961) suggested that existing attitudes can distort perceptions and judgments of new objects. In the context of product failures, when a good brand performs badly, it forms a contrast to prior beliefs. The contrast makes the product failure more unacceptable than the same performance from a bad brand.

This contradiction may be attributed to the perceived relevance of negative information. When a piece of negative information is perceived as highly relevant, a contrast is more likely to be formed, and therefore the contrast effects may be dominant. When the negative information is

perceived as less relevant, consumers may rely more on their prior beliefs to process new information and therefore are more likely to ignore incongruent information (i.e., a confirmatory bias).

In sum, in the context of product failure, when the negative information is considered relevant, the negative information may form a contrast bias in that the negative information are more salient and diagnostic in product evaluation. When the negative information is less relevant, it is not more diagnostic than the positive information with same valence.

**Positioning of this Study**

Table 2.2 presents a summary of the positioning of this study with respect to past research in the context of product failure and the spillover effects of product failure. As shown, this study contributes to the current literature by uniquely focusing on catastrophic product failures and their subsequent spillover effects under the high level of brand separation. A set of questions very relevant to managers to academics are examined. In particular, this dissertation attempts to answer the following questions. When a catastrophic product failure occurs, what is its impact 1) on the stock price of the parent company, 2) on the sales of other brands of the parent company, 3) on the effectiveness of marketing programs of the parent company, 4) on the sales of competing brands in the product class where the failure occurs, and 5) on the effectiveness of marketing programs of competing brands?

This dissertation is powerful in that it focuses on catastrophic product failures in the real-world setting. Using a historical approach to systematically examine catastrophic product failures in the pharmaceutical industry enhances the external validity of the findings in comparison to existing knowledge based on the results from lab experiments. This dissertation is unique in that

it attempts to address important real-world problems for which neither the existing finance nor marketing literature readily has an answer. The modeling approaches presented in this study represent a rigorous approach to examine the spillover effects of catastrophic product failures on the suffering company as well as on the competitors.

Based on the literature review, current knowledge offers only limited explanations to the central question, whether a catastrophic product failure will spill over to other brands of the parent company under the high level of brand separation. Although prior finance literature acknowledges the impact of the spillover effects of product failure, the extent to which the spillover effects may influence related brands remains unclear. This study quantifies the magnitude and persistence of the spillover effects of product failure using real world data from the pharmaceutical industry. The spillover effects examined in this dissertation include such effects on both parent companies and competitors. Two forms of the spillover effects—the spillover effects 1) on sales and 2) on marketing effectiveness—are systematically examined. In doing so, this dissertation will provide insights for managers to fully assess the impact of a catastrophic product failure. As discussed earlier, catastrophic product failures usually involves 1) direct revenue loss, 2) litigation expenses, and 3) loss of goodwill. This dissertation focuses on the third component by assessing the magnitude of spillover effects. In the case of product withdrawal, appropriate estimation of the spillover effects is the first step for managers to minimize the negative impact caused by the failure. In sum, this dissertation is among the first to take a very systematic look at the financial and marketing implications of catastrophic product failure. In the next chapter, I provide a conceptual framework to understand the mechanism through which the spillover effects of product failure may take place and possible factors that may moderate these spillover effects.

**Table 2.1**
**Review of Related Academic Literature**

| Research Stream | Study | Study Setting | Important Findings | Notes |
|---|---|---|---|---|
| **Finance Literature on Product Recalls and Withdrawals** | (Pruitt and Peterson 1986) | Empirical study using event analysis | No relation between firm's equity decline and the direct costs of recall is found, indicating the importance of indirect costs such as litigation expenses or a reduction in future corporation sales due to reputation damage. | Data come from various industries. |
| | (Ahmed, Gardella, and Nanda 2002) | Empirical study using event analysis | Find significant market capitalization losses when there are reports of drug withdrawals. Direct competitors, however, gain significant value in the equity market in a five-day post announcement period. | Data from the pharmaceutical industry. |
| | (Marcus, Swidler, and Zivney 1987) | Empirical study using Black-Scholes option pricing model | A drug recall increases the systematic risk of related stock returns. This implies investors use a higher discount rate and offers an explanation to large losses in stock market when a drug withdrawal occurs. | Data from the pharmaceutical industry. |
| | (Jarrell and Peltzman 1985) | Empirical study using event analysis | Stock market losses are far greater than the costs directly emanated from the recall. They concluded that the negative spill over to the firm's 'goodwill'. In addition, the authors suggest that the impact of recalls spill over to competitors. | Data from the pharmaceutical and the auto industry. |

| | | | | |
|---|---|---|---|---|
| | (Hoffer, Pruitt, and Reilly 1988) | Empirical study using event analysis | Find little evidence indicating stock market penalizing auto recalls after revising technical issues on the work of Jarrell, and Peltzman (1985). | Data from the auto industry. |
| | (Davidson and Worrell 1992) | Empirical study using event analysis | Find negative abnormal returns for product recall announcements in stock market. | Data from industries outside of automobile. |
| **Spillover Effects** | (Sullivan 1990) | Empirical study using data from the auto industry | For companies using umbrella branding, information about one product, negative or positive, can spillover to consumer's evaluation of other products with the same brand name. | Product reputation consists of an umbrella brand component and a product-specific component. Spillover effects are facilitated by the shared umbrella brand name. |
| | (Erdem 1998) | Empirical study using panel data from the consumer packaged goods industry | The results indicate the spillover effects of marketing mix (e.g., free sample) on consumers' perceptions toward products in different categories but share the same brand name. | Find evidence of the negative spillover effects when free samples offered are of low quality. |
| | (Simonin and Ruth 1998) | Lab Experiments | Consumer attitudes of brand alliance can spill over to those of partnering brands. Such spillover effects are moderated by brand familiarity. | Each partnering brand in an alliance is not necessarily affected equally in the study. |
| | (Loken and John 1993) | Lab experiments | When brand extension attributes are inconsistent with the family brand beliefs, negative reciprocal effects occur on the | |

| | | | | |
|---|---|---|---|---|
| | | | family brand. Typicality moderates such spillover effects. | |
| | (John, Loken, and Joiner 1998) | Lab experiments | When a brand extension produces negative information, beliefs about flagship products are less vulnerable to dilution than beliefs about the parent brand name in general. | Inconsistent information from line extension negatively affects beliefs about the flagship brand. |
| | (Swaminathan, Fox, and Reddy 2001) | Empirical studies using panel data from consume packaged goods and lab experiments | Negativities generated by unsuccessful brand extensions can spill over to parent brand. Such negative reciprocal effects are moderated by consumer's prior experience with the parent brand. | |
| **Branding Strategies** | (Milberg, Park, and McCarthy 1997) | Lab experiments | Negative information from unsuccessful brand extension can spill over to the family brand. Using a 'sub-branding' (or endorser branding) strategy may mitigate such negative reciprocal effects. | The study suggests that using product-brand branding strategy may avoid potential spillover effects. |
| | (Berens, Riel, and Bruggen 2005) | Lab experiments | Branding strategy is a key moderating variable on the relationship between corporate associations and product evaluations. When firms use low corporate dominance branding, the accessibility of CA associations decreases and thus are more likely to be used in high involvement decisions. | |
| | (Rao, Agarwal, and Dahlhoff 2004) | Empirical studies using financial data | The results reveal that umbrella branding is more positively related to the intangible firm value, compared to house of brands and mixed brands. | The authors collect data for a sample of 113 U.S. firms over a 5 year period. |

| | | | | |
|---|---|---|---|---|
| **Corporate Associations (CA and CSR)** | (Brown and Dacin 1997) | Experiments | CA influences consumers' evaluations of product attributes. Both CA and CSR influence evaluation of the company. | Consumers use CA to infer missing or partial product attribute information. |
| | (Klein and Dawar 2004) | Experiments (manipulating firm's prior CSR) | CSR associations spill over to consumers' attributions in a product-harm crisis when consumers are CSR-sensitive. | CSR is conceptualized as a mediator on consumer attributions of product-harm crisis. |
| | (Sen and Bhattacharya 2001) | Lab experiments | All consumers react negatively to negative CSR information, whereas only those most supportive of the CSR issues react positively to positive CSR information. | |
| | (Creyer and Ross 1997) | Survey (infant formula and athletic shoes) | Among many factors that moderate consumers' willingness to reward CSR, consumers support for CSR is most important. | |
| | (Weigelt and Camerer 1988) | Literature review | Reputation can generate future rent. This is particularly important in the incomplete information settings. | |
| | (Singh et al. 2005) | Historical case studies | Trust-value dynamics governs the healthiness of relationship between a company and its 4 constituencies (consumers, commercial intermediaries, non-commercial intermediaries and regulatory agencies). What happens at one constituencies potentially spills over to influence relationships at other constituencies, and these interconnections collectively influence a firm's effectiveness, | In the case of prescription drugs, value is a drug's efficacy/cost ratio and trust can be viewed as disclosing and controlling known adverse effects. Trust depletion can spillover |

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|---|---|---|---|---|
| | | | even survival, in the marketplace | to relationships with other constituencies. |
| | (Handelman and Arnold 1999) | Lab experiments | Using institutional theory, the authors suggest marketing actions have a social dimension and an economic dimension. Higher level of performative actions and institutional actions will result a consumer's support for the organization. | Negative changes in institutional actions have a notably deleterious effect on firms regardless of their performative actions. |
| **Product-harm Crisis** | (Siomkos and Kurzbard 1994) | Experiments | In a product-harm crisis, a firm is less affected when it has a better reputation, positive external effect and proper responses. | Damage due to product-harm crisis may be brand-specific in consumer packaged goods unless the media brings a link between separate brands. |
| | (Kabak and Siomkos 1991) | Experiments | A replacement product from failed product is more likely to be accepted from firms with better reputation, positive external effects and voluntary efforts to withdraw the troubled product. | |
| | (Kabak and Siomkos 1992) | Suggest using exponential function to approximate the recovery process from product- | For a product recall without replacement, overall company sales and company share price should be the performance measures of concern. Management also needs to minimize spillover effects to the rest of products. | |

| | | | | |
|---|---|---|---|---|
| | | harm crisis. | | |
| | (Dawar and Pillutla 2000) | Field survey and experiments (using soft drink and laptop) | Consumer's perceptions of product-harm crisis are moderated by their prior expectations. There exists a confirmatory bias. | Using the expectations-evidence framework to study product-harm crisis on brand equity. |
| | (Folkes and Kotsos 1986) | Lab experiments | Buyers are more likely to perceive failures as due to defective products and also to blame the product. Sellers are more likely to perceive the failure buyer related. Such discrepancies are due to different sources of consensus information. | |
| | (Aaker, Fournier, and Brasel 2004) | Field study | The impact of brand transgressions is moderated by the types of the relationships between the brand and the consumer. | |
| **Negative Information Use** | (Klein and Ahluwalia 2005) | Empirical study using secondary data from telephone interviews | Negativities may not be more diagnostic than positives in evaluation of presidential candidates. Motivational explanation suggests prior preference moderates the weight of negativities. | |
| | (Ahluwalia, Unnava, and Burnkrant 2001) | Lab experiments | Negative information spills over to attributes (e.g., harmful to fabrics) that are associated with the target attribute (e.g., strong detergent) but not mentioned in message. The spillover effects are moderated by consumer types (i.e., familiar with, like or committed to the brand) | Spillover defined as the extent to which a message influences beliefs related to attributes that are not contained in the message. |

**Table 2.2**
**Positioning of Current Study**

| Representative Studies | Catastrophic Product Failure | Brand Separation | Using Real-world data | Spillover Effects on Brands of the Company | Spillover Effects on Competing Brands | Financial Impact on the Share Price |
|---|---|---|---|---|---|---|
| Pruitt and Peterson (1986) | Yes | Yes | Yes | No | No | Yes |
| Ahmed, Gardella and Nanda (2002) | Yes | Yes | Yes | No | No | Yes |
| Sullivan (1990) | No | No | Yes | Yes | No | No |
| Erdem (1998) | No | No | Yes | Yes | No | No |
| Loken and John (1993) | No | No | No | Yes | No | No |
| Milberg, Park and McCarthy (1997) | No | Yes | No | Yes | No | No |
| Berens, van Riel, and van Bruggen (2005) | No | Yes | No | Yes | No | No |
| Klein and Dawar (2004) | No | No | No | Yes | No | No |
| Siomkos and Kurzbard (1994) | No | No | No | Yes | No | No |
| Present Study | Yes | Yes | Yes | Yes | Yes | Yes |

# CHAPTER 3

# CONCEPTUAL FRAMEWORK

This chapter presents a conceptual framework to systematically examine catastrophic product failures. The conceptual framework is intended to understand 1) the impact of product withdrawal on the share price of the withdrawing company, 2) the spillover effect of product withdrawal on the parent company, and 3) the spillover effects of product withdrawal on the competitors. Prior finance research provides theoretical underpinnings for the impact of product withdrawal on the share price of the parent company. Research in the areas of brand equity dilution and corporate associations helps to understand the possible spillover effects of product withdrawal on the parent company. Studies of product withdrawals and their implications for competition offer insights to understand the spillover effects of product failure on competitors.

Among various impacts of product failure, the spillover effects of product failure on parent company may be the most complex. Brand equity theories suggest that brand-level knowledge and beliefs influence consumers' evaluations and subsequent purchase intentions of a product. When these beliefs undergo a negative change, brand dilution occurs. Brand dilution will negatively affect consumers' evaluation of products that share the same brand name (Loken and John 1993). Such negative effects may be reflected on both the sales and the marketing effectiveness of the diluted brand. Corporate association theories suggest that what customers know about a company influences their beliefs of and attitudes towards the products manufactured by that company (Brown and Dacin 1997). In the context of product withdrawal,

negative information furnished by a withdrawn brand may build negative corporate associations in customers' beliefs and attitudes toward the withdrawing company. These negative associations may dilute corporate brand equity, which in turn may dilute the equity of other brands in the withdrawing company's portfolio. Diluted brand equity may be reflected as a deduction on the brand level sales and the effectiveness of marketing programs.

**Impact of Product Withdrawal on Share Price**

Research in the finance literature has extensively examined the impact of product failure on company's equity market losses (Jarrell and Peltzman 1985; Pruitt and Peterson 1986). Several studies specifically investigate such losses in the context of drug withdrawals (Ahmed, Gardella, and Nanda 2002; Marcus, Swidler, and Zivney 1987). Three major causes that may lead to the losses in the equity market have been identified: 1) direct financial losses, 2) potential litigation expenses, and 3) the damage to the company's goodwill (Pruitt and Peterson 1986).

Direct financial losses include loss of future sales of the withdrawn product and expenses of withdrawing the product from the market (e.g., writing-offs of inventory and administrative costs). Potential litigation expenses involve the money paid to lawyers and potential settlement costs or liability costs if unfavorable results come from lawsuits filed against the company. Loss of goodwill refers to the damage to the corporate reputation and the dilution of corporate brand equity. A negative change in corporate brand equity can potentially influence sales of existing products in the company's brand portfolio, as many Wall Street analysts indicate (Hersch 1991). In addition, dilution in corporate brand equity may have negative impacts on the company's marketing effectiveness (Keller 1993).

Prior research has found extensive evidence that shareholders suffer losses in the stock market due to announcements of product recalls (Davidson and Worrell 1992; Pruitt and Peterson 1986). In the context of prescription drug withdrawals, financial market losses are typically many times greater than direct expenses involved in the withdrawal (Ahmed, Gardella, and Nanda 2002). This study agrees with prior research in that a drug withdrawal will cause a significant drop in the share price of the withdrawing company. However, this dissertation differs from prior studies in that a different modeling approach (i.e., intervention analysis as opposed to event analysis used in most finance studies) is used to quantify stock market losses over time for each incident of drug withdrawal. Compared with event analysis, intervention analysis is more appropriate in this context in that it quantifies the magnitude and persistence of any single product withdrawal. Results from this study provide an empirical validation for prior research.

**Spillover Effects on Parent Company**

As mentioned in the previous section, one consequence of product withdrawal is the damage to the company's goodwill. Pruitt and Peterson (1986) suggested that the damage to the company's goodwill may cause a reduction in the company's future sales, which may be one of the underlying reasons that the stock market penalizes product recalls in excess of the direct losses involved. Kabak and Siomkos (1992) also voiced their concerns in product-harm crisis management. They pointed out that negative publicity generated by product failure may negatively influence the company's sales of other products. In the marketing literature, prior studies suggest that when products share the same brand name, negative information generated by one product (e.g., product failure, inconsistent quality image) can transfer to other products of

the same brand name (Erdem 1998; Sullivan 1990). The transfer of negative information may be reflected as a deduction on the sales of related products. Sullivan (1990) demonstrated that a failure in Audi 5000 negatively affected the valuation of other Audi models through the shared brand name. Similar spillover effects of negative information also find evidence from research conducted in the context of unsuccessful brand extensions (Loken and John 1993; Swaminathan, Fox, and Reddy 2001).

Most of these studies, however, only examine the spillover effects of product failure when related products share the brand name with the troubled product. In the case of product failure under umbrella branding, all brands, including the failed one, share a common brand name. Shared brand name, in effect, facilitates the transfer of information between different products. Similarly, in an unsuccessful brand extension, the failed extension brand may have negative reciprocal effects on the parent brand. A shared brand name makes what happens in an unsuccessful brand extension become relevant in customers' evaluation of the parent brand.

In contrast to those in umbrella branding, brand extension or brand alliance (Simonin and Ruth 1998), when brands do not appear to have very visible connections between them, the transfer of negative information from one brand to another becomes less likely to occur. Milberg, Park and McCarthy (1997) found evidence that using a 'sub-branding' with higher level of brand separation can mitigate negative spillover effects. When brands are completely separate from each other in the house of brands, the only linkage between brands is the shared parent company. Thus, corporate associations may be the only linkages that potentially facilitate the carryover effects of negative information from one product to another in a company's brand portfolio. Brown and Dacin (1997) suggested that corporate associations and brand associations may work separately in influencing customers' attitudes towards a product. Other research indicates that

corporate associations provide organizational associations (Aaker 1996), or secondary associations (Keller 1993) in customers' product evaluations.

Corporate associations, defined as what customers know about the company, primarily include associations of corporate abilities (CA) and corporate social responsibilities (CSR), both of which influence customers' beliefs of and attitudes toward products manufactured by the company (Brown and Dacin 1997). In the context of catastrophic product failure, negative information furnished by consumer harm or even consumer fatalities can add substantial negative associations of both CA and CSR to customers' beliefs and attitudes toward the failing company.

Managing product safety is an important corporate capability in producing its products/services (i.e., CA by definition). Failure in making safe products raises doubts among customers about corporate abilities to manufacturer safe products. In the pharmaceutical industry, product safety is a particularly important product character. In the Vioxx withdrawal, for instance, the failure may raise questions among Merck's customers on the company's ability to manufacture safe medicines, and more importantly, its abilities to disclose and manage product risks. These questions may add negative CA associations to beliefs and attitudes that customers hold toward the company. On the other hand, managing product safety is also considered as an important dimension in a company's CSR actions (Sen and Bhattacharya 2001). If evidence is found by the media or in lawsuits that the company could have avoided consumer harm or could have managed the risks better, negative CSR associations may be added to customers' beliefs and attitudes of that company. As illustrated in several well-publicized Vioxx trials, plaintiff lawyers presented to the jury and eventually the media the evidence that Merck may have mismanaged the risks associated with Vioxx and have put profits before its customers (Berenson 2005). In this ongoing legal battle between Merck and Vioxx users, several plaintiffs have won

the case by proving the wrongful doings of this pharmaceutical giant. The penalties for Merck could go as high as hundreds of millions of dollars for one case. In fact, each of recent Vioxx trials has received extensive attention nationwide (Berenson 2006). Negative changes in corporate associations, let them be changes in CA or CSR, may play a detrimental role in corporate brand equity. Diluted corporate brand equity may, in turn, negatively influence evaluation of each remaining product in the withdrawing company's portfolio.

A key factor moderating the relationship between corporate associations and product evaluation is corporate brand visibility (Berens, Riel, and Bruggen 2005). When the corporate brand has a low visibility, a company's corporate associations (CA and CSR) influence the beliefs and attitudes of that company's products to a lesser degree. In the context of the pharmaceutical industry, corporate brand visibility is usually low in product communications to consumers, but is moderate/high in communications to the medical professionals. Although corporate names are rarely mentioned in direct-to-consumer (DTC) ads for medicines, sales representatives, who bear the company name in their titles and act as the company interface to professionals, are still the most important means to market prescription drugs to the medical professionals.

When a prescription drug is promoted, the parent company sends sales representatives to detail medical professionals about the efficacy and benefits of using the brand drug. Along with the physician detailing, free samples aimed to encourage new prescriptions are usually distributed at doctors' offices to reinforce marketing messages. In the interactions of personal selling, the corporate identities of brand drugs can not be hidden. The visibility of corporate brand for brand drugs, therefore, may be moderate or high depending on the level of marketing promotion each brand drug receives. When a prescription drug withdrawal occurs, the corporate

brand identify of this particular brand is usually visible to medical professionals of various specialties. It may also be visible to consumers because the media and numerous lawsuits may build a linkage between the withdrawn product and the parent company. Following earlier discussion on the implications of negative CA or CSR associations, the negative effects of prescription drug withdrawals may spill over to medical professionals' beliefs and attitudes toward other brand drugs from the withdrawing company. Similar effects may also spill over to consumers' beliefs and attitudes toward the over-the-counter (OTC) drugs of the withdrawing company. But the effects on consumers may be mitigated by the low corporate brand visibility of these OTC drugs to consumers.

In sum, brand equity and corporate association theories suggest the possibility that failure in one product can have spillover effects to other products of the failing company, even when the company uses the house of brand strategy to deliberately separate brands in its portfolio. The spillover effects may be mitigated by brand separation in that negative information does not directly transfer from the failed brand to other brands. Instead, the transfer of negative information affects the corporate brand first, and then spills over to other products of that company through corporate associations. When a large drug withdrawal occurs, it is more likely to have a spillover effect because the withdrawn product may be associated with the parent company more closely than smaller withdrawn drugs do.

Another potential moderating factor of the spillover effects is the level of negativity associated with each product failure. Conceptually, the level of negativity is determined by the severity of product failure and external responses to the failure (e.g., responses from the media and regulatory agencies) (Siomkos and Kurzbard 1994). The higher level of negativity a drug withdrawal associates with, the larger spillover effects of product withdrawal one may expect to

find on other brands of the company. Drawing on the disaster management literature (de Boer 1990), the severity of product failure may be determined by a number of factors, such as the cause of the drug withdrawal, duration of the disaster (life time of the drug), radius of the disaster (number of people affected), number of casualties (number of reported fatalities), and nature of injuries sustained by living victims. Measuring each of these factors and quantifying the level of negativity may be a challenging task and is left to be addressed in future research. Even without measuring these factors specifically, one may expect to find larger drug withdrawal usually associates with higher level of negativity. With some exceptions, large withdrawn drugs usually have a broader user base and therefore may influence more customers at the point of its withdrawal. Larger withdrawn brands typically have been on the market for a longer period of time. In other words, the size of the withdrawn product may be a reasonable surrogate measure for the level of negativity. When a large drug withdrawal occurs, it is likely to generate a higher level of negativity. Therefore, larger drug withdrawals may have a more direct and significant spillover effect on the parent company than smaller drug withdrawals may cause.

Prior studies concerning spillover effects primarily focus on changes in customers' beliefs and attitudes in product evaluation and the subsequent purchase decisions. When the beliefs and attitudes held toward a product undergo negative changes, they negatively influence customers' purchase decisions on related brands. Such negative effects on purchase decisions are usually reflected as deductions on the sales of these related brands (Erdem 1998; Loken and John 1993). Yet, negative changes in beliefs and attitudes of a brand may also influence marketing effectiveness of that brand. According to the conceptualization of customer-based brand equity, positive brand equity gives differential effects of brand knowledge on consumer responses to the marketing of the brand (Keller 1993). In other words, marketing programs from a stronger brand

with high equity will work more effectively on customers than the same programs from a weaker brand. As discussed earlier, a product withdrawal may add negative corporate associations to the beliefs and attitudes that customers hold toward the withdrawing company. These negative changes in corporate associations may dilute the corporate brand equity. The resulting dilution in corporate brand equity may, in turn, negatively affect the effectiveness of marketing programs of the company.

To sum up the above discussion, the spillover effects of product failure may occur on other brands of the failing company, even when the company adopts the house of brands strategy to separate each brand in the company's portfolio. Such spillover effects of product failure may influence the failing company on two different fronts: 1) negative spillover effects on the sales of other brands, and 2) negative effects on the effectiveness of marketing programs. The spillover effects may be moderated by several factors. The corporate brand visibility and the level of negativity are two important factors that may cause variations in the spillover effects of product failure. Larger product withdrawals are usually high on both corporate brand visibility and the level of negativity. Therefore, they are likely to cause more substantial spillover effects on the withdrawing company.

**Spillover Effects on Competing Brands**

Lang and Stulz (1992) suggested that there are two counter-weighting intra-market effects in the context of product withdrawals, namely the contagion effect and the competitive effect. The contagion effect affects the competitors in the same direction as it does the withdrawing company. The competitive effect, in contrast, has an opposite impact on competing brands. In the context of prescription drug withdrawals in the pharmaceutical industry, the

contagion effect occurs when there is a general safety concern for the entire therapeutic class (also known as the clouding effect). For instance, when Merck withdrew Vioxx, other drugs in the same therapeutic class (i.e., Cox-2 inhibitors) might have been negatively affected due to doctors' concerns over the safety of the entire class of Cox-2 inhibitors. As discussed in the introduction chapter, drugs in the same therapeutic class typically have many pharmacological similarities. They share a similar mechanism of actions and may also have similar adverse reactions. In fact, 6 months after the withdrawal of Vioxx, another Cox-2 inhibitor, Bextra (a Pfizer drug) was pulled off the market due to the same safety concerns.

The competitive effect occurs when Vioxx' patients need to find an alternative drug from the same therapeutic class to continue their medication. Brand switching from the withdrawn drug to its competitors in the same therapeutic class (e.g., Vioxx to Celebrex) can, in fact, boost the demand of these competing brands. Increased demand for directly competing brands benefits competitors and embodies the competitive effect in a product withdrawal.

The net outcome of these two opposing effects (i.e., the contagion effect, and the competitive effect) will determine the direction of spillover effects of drug withdrawal on competing brands. Prior research in the finance literature has suggested that in a concentrated market, competitive effect tends to be dominant (Lang and Stulz 1992). Companies will gain their market value when a competitor withdraws a product. In the pharmaceutical industry, therapeutic classes can have different sizes and different levels of concentration. Some classes have only a handful of brands (e.g., Cox-2 inhibitors) whereas some may have many brands (e.g., calcium channel blockers). In most cases, however, the majority of sales in a therapeutic class are concentrated on a few large brand drugs.

When a large brand drug was withdrawn from the market, competitors may benefit from the incident by taking up the market space left by the withdrawn product. Research focused on the pharmaceutical industry has found that after a company is forced to withdraw a product from market, competitors gain market value, providing evidence for the dominance of the competitive effect (Ahmed, Gardella, and Nanda 2002; Dowdell, Govindaraj, and Jain 1992). Ahmed, Gardella, and Nanda (2002) posited that the gain in market value of competitors represents increased demand for close substitutes. Based on these arguments, when a large drug withdrawal occurs, the competitive effect may be dominant for the competition. In other words, the product withdrawal may have positive spillover effects on the sales of competing brands. However, when a small drug withdrawal occurs, there is little market share left for the competitors to take over. Instead, new safety concerns raised by the drug withdrawal may be relevant to the entire therapeutic class. In the case of small drug withdrawal, the contagion effect may be dominant. In this case, a drug withdrawal may have negative spillover effects on the sales of its competing brands.

Due to the competitive effect, a large drug withdrawal may create a positive shift in the demand for its direct competitors. This shift may be reflected as an increase on the sales of competing brands. However, new information about adverse drug reactions furnished by a drug's withdrawal may be considered relevant when medical professionals evaluate similar products in the same therapeutic class. From the perspective of clinical pharmacology, drugs within the same therapeutic class typically share a similar mechanism of actions. Severe side effects found in one member of the class may have a clouding effect on the entire therapeutic class. Doubts or concerns about the safety attributes of other competing brands may add negative associations to these brands. Negative changes in the beliefs and attitudes that medical professionals hold

toward these competing brands, in essence, are detrimental for these brands' equities. Following Keller (1992)'s conceptualization of customer-based brand equity, diluted brand equities, in turn, may negatively affect the effectiveness of marketing programs from these brands.

## Chapter Summary

In this chapter, I have proposed a conceptual framework to aid the understanding of the impacts of prescription drug withdrawal. Specifically, prior studies from the finance literature provide theoretical underpinnings for the negative effect of drug withdrawal on the share price of the withdrawing company. Based on theories from brand equity dilution and corporate associations, a drug withdrawal may incur negative spillover effects on the sales of other brands in the parent's portfolio, and on the effectiveness of marketing programs of the parent company, even when the company deliberately separates its brands. For the spillover effects of drug withdrawal on competing brands, the theories on the competitive effect and the contagion effect suggest the positive spillover effects on the sales of the competing brands when a large drug withdrawal occurs. The theories, however, predict the negative spillover effects on the sales of competing brands when a small drug withdrawal occurs. Customer-based brand equity literature provides the theoretic ground for suggesting the negative spillover effects of drug withdrawal on the marketing effectiveness of competing brands.

The above predictions and propositions are based on a theoretical examination on the phenomenon of prescription drug withdrawal. In the next chapter, I describe the data compiled to empirically examine the spillover effects of catastrophic product failure from the pharmaceutical industry. In addition to the data description, the statistical models used to detect and quantify the spillover effects of drug withdrawals are presented in the chapter as well.

# CHAPTER 4

# METHODS

In this chapter, the data used for this study and the methods utilized to analyze the data are discussed. First, the data and the sources from which the data were collected are described. Following the data description, the key variables used in this study are explained and defined. After variable operationalization, an overview of the statistical models that are used to examine the data is presented. Finally, the models used in this study are fully specified, and they are followed by a summary of the methods employed.

## Data

The data for this study are collected from various sources. The brand level sales and marketing program data come primarily from IMS Health's national sales database. The data collected cover over 2900 brands during the time period from March 1997 to February 2003. The data pertaining to each drug's characteristics (e.g., active ingredients, indications, therapeutic class, patent expiration) come from various databases of the FDA (e.g., Drugs@FDA, and the FDA Orange Book), *Library for IMS National Sales Perspectives*, the National Institutes of Health (NIH), and *Drug Facts and Comparisons*. The company stock price data were compiled from COMPUSTAT through Wharton Research Data Services. Table 4.1 summarizes the data involved in this study and the sources of data collection. Each source of data is briefly introduced next.

**Table 4.1**
**The Data Used in the Study and Sources of Collection**

| Conceptual Variable | Observed Variable | Data Source |
|---|---|---|
| Occurrences of prescription drug withdrawal | Dummy indicators for prescription drug withdrawal | • U.S. Food and Drug Administration (FDA) |
| Financial impact of prescription drug withdrawal | Stock price of the parent company | • COMPUSTAT through Wharton Research Data Services |
| Brand level sales of over 2900 drugs in the U.S. market from 1997 to 2003 | Sales in dollar amount<br>Sales in the number of prescriptions<br>Sales in unit | • IMS Health |
| Brand level marketing programs | # of free samples<br># of professional journal ads<br># of physician contacts | • IMS Health |
| Sets of competing brands involved in drug withdrawals | Drugs in the same therapeutic class | • Drugs@FDA<br>• *Library for National Sales Perspective*<br>• *Drug Facts and Comparisons* |
| Drug characteristics | Drug indications<br>Active ingredients<br>Prescription vs. OTC<br>Patent expiration<br>Availability of therapeutic equivalence<br>Drug approval history | • Drugs@FDA<br>• Orange Book from the FDA<br>• *Drug Facts and Comparisons*<br>• National Institutes of Health (NIH) |

The U.S. Food and Drug Administration (FDA) maintains a list of drugs that were withdrawn from the marketplace after they had been approved by the agency. These drugs were pulled off the market for one or all of the following reasons: 1) unexpected and excessive risk associated with the use of the drug, 2) availability of safer alternatives, 3) difficulty of appropriate drug administration to avoid severe adverse reactions, 4) adverse interactions with other drugs. Essentially, all the past prescription drug withdrawals have involved serious safety

concerns. Typically, these safety concerns were not adequately considered at the time of the drug's initial approval, and therefore were not fully reflected in the drug's label of use. Table 4.2 summarizes the entire list of prescription drug withdrawals occurring between 1996 and 2005, and the reasons associated with each of these withdrawals. The information is available from the FDA's website at http://www.fda.gov.

A few facts are worth noting in the FDA's drug withdrawal list. First, several pharmaceutical companies had multiple drug withdrawals in the specified period. Similarly, several therapeutic classes have had multiple drug withdrawals during that period. Sequential drug withdrawals from one company or one therapeutic class may complicate the modeling exercise, which will be discussed in more detail in Chapter 5. Second, withdrawn drugs had different lifetime. For example, the drug with the longest lifetime, Pondimin, was withdrawn from the market after 24 years' use in the market. In contrast, Lotronex was pulled off the market within a year since its initial approval for marketing. Thirdly, withdrawn drugs also vary greatly in their sizes. For instance, before its withdrawal, Vioxx was a blockbuster drug with over $1 billion annual sales in the U.S. Raxar, in contrast, had only about $1 million sales in the year before its withdrawal. Differences in the withdrawn drugs may cause variation in their impacts on parent companies and competitors.

Financial information used in this study was collected from COMPUSTAT, a commercial service, and a standard source of financial information. Many types of firm level financial information (e.g., stock price, firm size, history of mergers and acquisitions) are readily available through the database maintained by COMPUSTAT. Wharton Research Data Services is an academic research portal that offers access to many commercial databases including the popular

COMPUSTAT. The financial data needed for this study were compiled from COMPUSTAT through Wharton Research Data Services.

A large amount of brand level data was provided by IMS Health. IMS Health is a global leader in collecting pharmaceutical market intelligence. It specializes in compiling proprietary databases in the pharmaceutical industry with 100% coverage of prescription drugs and about 70% coverage of over-the-counter (OTC) drugs. One database involved in this study is called IMS National Sales Perspective, which provides monthly sales data at the brand level for almost all the major drugs in the industry with a timeframe of 6 years.

The IMS updates its database on a rolling basis. Any data older than 6 years are not included in its current electronic database, but are still available in print format. Because of this limitation, when one needs IMS data that dates back more than 6 years from the current time point, or data that has a time coverage longer than 6 years, it is only possible either by merging two available electronic datasets or by inputting additional data manually from IMS data in print format.

Some of the data used in this dissertation are compiled by merging separate datasets according to their timelines; some are amassed by manually inputting the data from printed IMS libraries. I will discuss these issues in greater detail when they become more relevant in the model development section. The rolling data time frame also creates another problem. When data are requested from the IMS at different time points, the data that arrive at different time also have different time windows for their coverage. The data used for this study were collected over a period of half year, a result largely due to the time-consuming process of authorization for releasing the data by the IMS. Table 4.3 summarizes the time frame of each dataset included in this study.

**Table 4.2**
**Prescription Drug Withdrawals and Associated Reasons (1996-2005)**

| Brand | Indicated Use | Manufacturer | Year Approved | Year Withdrawn | Reason of Withdrawal |
|---|---|---|---|---|---|
| Bextra* | Antiarthritics | Pfizer | 2002 | 2005 | Increased cardiovascular risk |
| Vioxx* | Antiarthritics | Merck | 1999 | 2005 | Increased cardiovascular risk |
| Baycol | Cholesterol-lowering | Bayor | 1997 | 2001 | Risk of rhabdomyolysis, severe damage to muscle that is sometimes fatal |
| Raplon | Muscle relaxant | Akzo Nobel (Organon)** | 1999 | 2001 | Risk of bronchospasm, an inability to breathe normally that can lead to permanent injury or death |
| Lotronex | Irritable bowel syndrome | Glaxo-Wellcome | 2000 | 2000 | Risk of intestinal damage resulting from reduced blood flow to the intestine |
| Rezulin | Type II Diabetes | Pfizer (Parke-Davis) | 1997 | 2000 | Risk of liver poisoning which can lead to death |
| Propulsid | Heartburn | Johnson & Johnson (Jassen) | 1993 | 2000 | Risk of fatal heart rhythm abnormalities |
| Raxar | Antibiotic | Glaxo-Wellcome | 1997 | 1999 | Risk of fatal heart rhythm abnormalities |
| Hismanal | Antihistamine | Johnson & Johnson (Jassen) | 1998 | 1999 | Risk of fatal heart rhythm abnormalities when used with other drugs or at too high a dose |
| Duract | Analgesic | Wyeth | 1997 | 1998 | Risk of fatal hepatic failure |
| Posicor | Hypertension | Hoffmann-LaRoche | 1997 | 1998 | Risk of potentially harmful interactions with other drugs; and reduced activity of certain liver enzymes important in helping the body eliminate many other drugs |
| Seldane | Antihistamine | Aventis | 1985 | 1998 | Risk of serious heart problems when used concurrently with certain drugs, including certain antibiotics and antifungals |
| Redux | Obesity | Wyeth | 1996 | 1997 | Risk of heart valve abnormalities |
| Pondimin | Obesity | Wyeth | 1973 | 1997 | Risk of heart valve abnormalities |

* drugs not included in the data for this study

**Table 4.3**
**Time Coverage for the Datasets Involved in this Study**

| | | Measures | Time frame | # of brands included |
|---|---|---|---|---|
| Manufacturer datasets | Sales data | Dollar | Mar_97 – Feb_03 | 2922 |
| | | Unit | May_97 – Feb_03 | 2705 |
| | | Rx | Mar_97 – Feb_03 | 2984 |
| | Marketing program data | Free samples | Oct_96 – Sep_02 | 947 |
| | | Physician contacts | Oct_96 – Sep_02 | 1612 |
| | | Journal ads | Nov_96 – Oct_02 | 639 |
| Class datasets | Sales data | Dollar | Mar_97 – Feb_03 | 287 |
| | | Unit | Mar_97 – Feb_03 | 287 |
| | | Rx | Apr_97 – Mar_03 | 284 |
| | Marketing program data | Free samples | Apr_97- Feb_03 | 109 |
| | | Physician contacts | Mar_97- Feb_03 | 164 |
| | | Journal ads | Mar_97- Feb_03 | 164 |

The data from IMS health are further organized into two separate datasets. One dataset is organized by manufacturers and the other is organized by therapeutic classes. The manufacturer dataset includes all the brands of 12 major pharmaceutical companies, all of which had at least one drug withdrawal between 1980 and 2003. The therapeutic class dataset contains 12 classes. Each of the classes had at least one drug pulled off the market from 1996 to 2003.

The final datasets used for this study cover all drug withdrawals between 1996 and 2003 with over 2900 drugs[8] included in the manufacturer dataset and over 250 drugs included in the therapeutic class dataset. The manufacturer dataset represents about 50% of the entire pharmaceutical industry in the U.S., or about 70% of the top 10 leading pharmaceutical

[8] The figure here reflects the total number of unique drugs in each company's product portfolio. For example, if several divisions of a company manufacture a same drug, this drug is counted only once. As one can see in Table 4.4, the total number of non-unique drugs far exceeds the 2900 figure here.

companies in the U.S.[9] Both the manufacturer dataset and the therapeutic class dataset provide brand-level monthly data covering a period of 72 months from 1997 to 2003. Table 4.4 and Table 4.5 present descriptive information for manufacturers and therapeutic classes included in the final datasets. Numbers in these two tables are both based on the dollar sales datasets and include all products marketed by every division of a company[10]. The therapeutic class codes are provided by the IMS Health, which classifies each and every drug in its database into one or sometimes multiple therapeutic classes. The definition of each therapeutic class provides a good basis for this study to delineate the domain of a market and subsequent competing brands within a market. To cross-verify the appropriateness of the classification system, two more sources were consulted, namely Drugs@FDA and *Drug Facts and Comparisons*.

**Table 4.4**
**Manufacturers Included in the Dataset for this Study**

| Manufacturer | # of Drugs Included |
|---|---|
| Abbott | 502 |
| Akzo | 83 |
| Aventis | 268 |
| Bayer | 248 |
| Bristol-Myers Squibb | 553 |
| GlaxoSmithKline | 646 |
| Hoffmann-La Roche | 137 |
| Johnson & Johnson | 298 |
| Lilly | 137 |
| McNeil | 11 |
| Pfizer | 469 |
| Wyeth | 927 |

[9] Percentages are calculated on the basis of corporate sales in 2003.
[10] If a product is manufactured/marketed by two divisions of the same company, the product is counted twice in the table.

**Table 4.5**
**Therapeutic Classes Included in the Dataset for this Study**

| Therapeutic Class Name | Class Code | # of Drugs Included |
|---|---|---|
| NSAIDs | 02132 | 156 |
| Antihistamines | 14110 | 166 |
| Quinolones | 15180 | 21 |
| Anti-obesity | 18100 | 113 |
| Gi stimulants | 23300 | 48 |
| 5HT3 Receptor antagonist | 23510 | 1 |
| 5HT4 Receptor antagonist | 23520 | 1 |
| Calcium Blockers | 31300 | 155 |
| HMG-COA Reductase Inhibitor | 32110 | 19 |
| Insulin sensitizer | 39230 | 3 |
| Muscle relaxant | 59122 | 32 |

Drugs@FDA is a web-based service maintained by the FDA to provide official information about the FDA approved brand name and generic drugs. It is available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. This service can be used to find labels for approved drug products, generic drug products for a brand name drug product, consumer information on drugs, all drugs with a specific active ingredient, and the approval history of a drug. *Drug Facts and Comparisons* is a yearly handbook organized for pharmacists and physicians by Wolters and Kluwer Health. It includes all the drugs available on the market in a specific year, and organizes these drugs into specific therapeutic classes. Comparing the drug classification systems used by the IMS and *Drug Facts and Comparisons*, the definitions of a therapeutic class are generally consistent. The IMS Health also publishes handbooks each year to accompany the National Sales Perspective database in order to detail the information on data collection and drug classification. The handbooks are also used in this study to systematically identify each drug with its associated therapeutic class.

Within each therapeutic class, different drugs have different chemical formations, but share some similar molecular structures. They can differ in many pharmacological characteristics

such as toxicity, developmentability, solubility, etc. Members of a therapeutic class can not completely substitute each other, but in many circumstances, many brands are simply 'me-too' drugs that have similar efficacy and side effects to other members in the class (Angell 2005). For example, in the therapeutic class of COX-2 inhibitors, Vioxx, Celebrex, and Bextra share a similar mechanism of action to relieve pains, but differ in their risk associated with cardiovascular systems.

The National Institutes of Health hosts an official website to provide consumer information on drugs, food supplements, and herbal products. It is a useful source of easy-to-understand information on drug indications. This source is used to understand the general uses for each drug before any modeling exercises. The website uses the following web address: http://www.nlm.nih.gov/medlineplus/druginformation.html.

**Model Development**

In this section, I describe the statistical models and variable operationalization that are used in the modeling. In general, two statistical modeling approaches, namely intervention analysis and mixed effects models, are considered as appropriate candidates to examine the spillover effects caused by a drug withdrawal. Intervention analysis is a time series method. It is used to model corporate level sales and stock price changes. This method identifies any abnormal changes in a time series caused by an intervention event (i.e., a drug withdrawal in this study). The strength of this method is that it quantifies the magnitude of spillover effects with flexible model specifications to accommodate different variance-covariance structures in a time series. The major weakness of this method is the lack of control of external variables that may in fact have effects on the dependent variable. For instance, when marketing activities are present in

the data, intervention analysis doesn't allow inclusion of a company's own marketing efforts or competitors' marketing efforts into the model. This omission may overlook the impact of marketing activities on product sales. In addition, if the research interest also includes the impact of a drug withdrawal on the effectiveness of marketing, using intervention analysis alone is inadequate.

Mixed effects models can solve the above problems by modeling spillover effects and external effects (e.g., marketing effects) simultaneously. Such models can also easily examine the effects of a drug withdrawal on the marketing effectiveness of the parent company or competing brands. The weakness of mixed effects models, however, is the difficulty of capturing the different shapes of sales curve associated with each brand and specifying a variance-covariance structure that is appropriate for the error term.

Considering the strengths and weaknesses of each type of modeling approach, I used intervention analysis methods to explore the impact of drug withdrawal first. Building on the findings from intervention analysis, it becomes easier to properly specify mixed effects models in order to capture the persistence of spillover effects and the variance-covariance structure in the error term. Findings and conclusions in this study will be primarily based on the results from mixed effects models. Results from intervention analysis are largely exploratory in nature, and are used to guide the modeling exercises used in mixed effects models. I discuss each modeling approach in greater detail in the next section.

**Intervention Analysis**

Sales data or stock price data of a company observed over time are, by nature, a time series. A time series has its own pattern of evolution. This pattern, however, can deviate from its

expected evolutionary path due to an external intervention. For example, stock price may fluctuate due to an important announcement made by the company. An external intervention is an event that is believed to have some impact on the time series. It is typically assumed in the intervention analysis that the intervention event occurs at a specific time, has a known duration, and is of a particular type. The type of intervention refers to the shape of intervention effects, sudden or gradual. These shapes can be represented by a point, a step, an exponential curve, a wave, etc. If assumptions are met, intervention analysis is used to detect any abnormal deviation in a time series due to an intervention event, and to quantify the variation from the time series' otherwise normal pattern. Intervention analysis has been used in a wide range of scientific research. Examples include research on economic policies' effects on air pollution control (Box and Tiao 1975), the impact of the Arab oil embargo on the stock market (Montgomery and Weatherby 1980), the impact of advertising or promotions on sales (Krishnamurthi, Narayan, and Raj 1986; Leonard 2000), the impact of patent infringement on sales forecasting (Mahajan, Sharma, and Wind 1985), among others.

In the current study, the intervention event is defined as a prescription drug withdrawal. The dependent variables are 1) the corporate level sales excluding the sales of the withdrawn product, and 2) the company's share price in the stock market. When a drug withdrawal occurs, this event may have negative effects on the firm-level sales and may cause a deviation in corporate sales from the expected evolutionary pattern (i.e., an evolutionary pattern without the drug withdrawal). Similarly, a drug withdrawal can also generate a significant negative impact on the parent company's share price. The intervention event (i.e., a drug withdrawal) occurs at a specific time and is identifiable through announcements by the FDA. If the intervention analysis model detects a significant deviation in the dependent variable around the time of a drug

withdrawal, the result provides evidence of possible spillover effects. In other words, if the model identifies significant changes in the firm-level sales or the company share price around the time of the drug withdrawal, while allowing for normal variation in the sales and stock price, it gives evidence that the withdrawal has had a significant impact on the company. Accordingly, two dependent variables are used to capture the impact of a drug withdrawal on the parent company: (1) corporate sales and (2) company stock price. The variables used in the intervention analysis for this study are discussed next.

*Corporate sales other than the failed product (Sales):* a sum of sales across all brands other than that of the withdrawn drug. This variable is monthly, and has a time span of 72 months. Only brand drugs are included in the analysis. Sales of generic drugs are excluded.

*Corporate share price (Stock):* company monthly stock price adjusted for dividends and splits to reflect the true market value change regardless of dividend giving and splits of shares. The adjusted data are readily available from COMPUSTAT database.

The intervention analysis models used to examine the company level sales data are specified in 1) and 2).

$$1) \quad Sales_t = \omega_0 X_t + \frac{a_t(1-\sum_i \theta_i B^i)}{(1-\sum_j \varphi_j B^j)(1-B^3)}$$

$$2) \quad \ln(Sales_t) = \omega_0 X_t + \frac{a_t(1-\sum_i \theta_i B^i)}{(1-\sum_j \varphi_j B^j)(1-B^3)}$$

$$X_t = \begin{cases} 1, & t \geq T_{\text{int}} \\ 0, & t < T_{\text{int}} \end{cases}$$

Where

$Sales_t$ is the aggregated company level sales other than those of the withdrawn drug at time $t$.

$X$ is the withdrawal indicator. It is a dummy variable that turns on when a drug withdrawal takes place and stays on. This parameterization of the dummy indicator is equivalent to assuming a step function in modeling the shape of the intervention effect. Without much prior knowledge of persistence or even existence of the spillover effects, assuming a simple but conservative shape of the intervention effect appears to be appropriate.

$\theta_i$ and $\varphi_j$ are moving average parameters and auto-regressive parameters respectively with $i = 1, 2, 3 \ldots$ and $j = 1, 2, 3 \ldots$ $\theta_i$ and $\varphi_j$ are parameters to be estimated. They are determined by the nature of the sales series in the stationary period prior to the intervention event.

$\omega_0$ is the intervention parameter. It captures the postulated spillover effects of drug withdrawal. Significant negative $\omega_0$ provides evidence of the spillover effects of drug withdrawal. The possible spillover effects are represented by a change in the mean of other products' sales after de-trending.

$a_t$ is the white noise term.

$T_{int}$ is the month during which the drug withdrawal occurs.

$B$ is time series back-shift operator. This is a standard notation in time series and it operates in the following fashion:

$Sales_t (1-B) = Sales_t - Sales_{t-1}$

$Sales_t (1-B-B^2) = Sales_t - Sales_{t-1} - Sales_{t-2}$

…

1) and 2) can also be rewritten as 1)* and 2)*:

$$1)^* \quad Sales_t * (1 - \sum_j \varphi_j B^j)(1 - B^3) - a_t(1 - \sum_i \theta_i B^i) = \omega_0 X_t * (1 - \sum_j \varphi_j B^j)(1 - B^3)$$

$$2)^* \quad Ln(Sales_t) * (1 - \sum_j \varphi_j B^j)(1 - B^3) - a_t(1 - \sum_i \theta_i B^i) = \omega_0 X_t * (1 - \sum_j \varphi_j B^j)(1 - B^3)$$

1)* and 2)* can be further simplified to 1)** and 2)**:

$$1)^{**} \quad f(Sales_t) = f'(X)$$

$$2)^{**} \quad f(Ln(Sales_t)) = f'(X)$$

*Where*

$f(Sales_t)$ and $f(Ln(Sales_t))$ are the ARIMA components.

$f'(X)$ is the intervention component.

In intervention analysis, the model specification is largely determined by the pattern of time series evolution. The objective of model fitting is to de-trend the time series and to make it stationary. The above model specification is, in fact, very flexible in that no fixed model structures are assumed. Note that in 1) and 2), there is a $(1-B^3)$ component in the model specification indicating some "seasonality" being present in the sales data every 3 months. This "seasonality" issue is, in fact, found to be attributed to a data reporting issue that IMS Health has with all its sales data. The monthly sales data are reported to the IMS by physicians on a 4-week, 4-week, 5-week basis. Subsequently, there is one month out of every three months that essentially includes data for an additional week, which creates a regular fluctuation in sales data similar to that caused by seasonality. The data reporting problem has also been documented in

other research work using IMS data (Berndt et. al. 1995). The $(1-B^3)$ component is used to account for this data reporting problem.

Similar model specifications are used to analyze the effects of drug withdrawal on the company's stock price with *Stock* as the dependent variable. The models are specified in 3) and 4). In essence, models 3) and 4) are very similar to models 1) and 2), but differ in the exclusion of the $(1-B^3)$ component. A company's share price is not affected by any data reporting problems of IMS, and therefore the omission of the data reporting problem component is expected.

$$3) \quad Stock_t = \omega_0 X_t + \frac{a_t(1-\sum_i \theta_i B^i)}{(1-\sum_j \varphi_j B^j)}$$

$$4) \quad \ln(Stock_t) = \omega_0 X_t + \frac{a_t(1-\sum_i \theta_i B^i)}{(1-\sum_j \varphi_j B^j)}$$

$$X_t = \begin{cases} 1, & T_s \le t \le T_e \\ 0, & otherwise \end{cases}$$

Where

$Stock_t$ is the company's share price in stock market at time $t$.

$X$ is the withdrawal indicator. It is a dummy variable that turns on at $T_s$ and turns off at time $T_e$.

$\theta_i$ and $\varphi_j$ are moving average parameters and auto-regressive parameters respectively with $i = 1, 2, 3 \ldots$ and $j = 1, 2, 3 \ldots$ $\theta_i$ and $\varphi_j$ are parameters to be estimated. They are determined by the nature of the stock price series in the stationary period prior to the intervention event.

$\omega_0$ is the intervention effect estimate on the stock price. In particular, significant $\omega_0$ offers evidence on the impact of the drug withdrawal on the parent company's share prices after allowing normal variation.

$a_t$ is the white noise term.

$B$ is the time series back-shift operator. $Stock_t\ (1\text{-}B) = Stock_t - Stock_{t\text{-}1}$ Multiplying both sides of 3) and 4) by $(1 - \sum_j \varphi_j B^j)$ , they can be simplified to 3)** and 4)**.

$$3)^{**} \quad f(Stock_t) = f'(X)$$

$$4)^{**} \quad f(Ln(Stock_t)) = f'(X)$$

*Where*

$f\ (Stock_t)$ and $f\ (Ln(Stock_t))$ are the ARIMA components.

$f'\ (X)$ is the intervention component.

$T_s$ is the starting month during which the intervention event occurs whereas $T_e$ is the ending month during which the intervention event ends. Together, $T_s$ and $T_e$ define a time window for the effect of drug withdrawal on parent companies' stock prices. The time window used in this study is 3 months. Using a longer time window is possible, but finance literature in a similar context (e.g., event analysis) typically uses a very short time window (e.g., a few days) to avoid introducing additional noises that may affect share prices. Given that the nature of drug withdrawal is usually catastrophic, using a 3 month time window to capture lasting effects appears to be appropriate[11]. More discussion on window selection is included in the next chapter when I fine tune model specification.

[11] Different window lengths are tested in model fitting. Generally, the effect of drug withdrawal on the company's share price is immediate but tails off gradually. In some instances, the information of a drug withdrawal takes effect

The share price data used in the modeling covers a period of 6 years, a length consistent with the sales data used in the study. The 6 year data are selected such that 3 years of data before the drug withdrawal and another 3 years of data after the withdrawal are used to fit models 3) and 4).

**Mixed Effects Models**

Mixed effects models are used as the primary modeling approaches to examine the spillover effects of a drug withdrawal on the sales of other brands of the firm and on those of competing brands. In addition, these models are also employed to examine the spillover effects on the effectiveness of marketing programs of the parent company as well as those of competing brands. The model specifications in this study are similar to those used in prior research conducted to examine the return on investment (ROI) of various marketing programs on brand drug sales (Wittink 2002).

The dependent variable used is the logarithm form of dollar sales at the brand level. Selection of explanatory variables is generally consistent with prior research in similar contexts. Three types of major effects, namely growth effects, marketing effects, and competitive effects, are incorporated in model specifications. Specifically, the growth effects are included by using the first and second order polynomial terms of time. Marketing effects are reflected in modeling by using various marketing variables, including the number of free samples distributed by sales reps (*smp*), the number of ads appearing in professional journals (*jad*), and the number of physician contacts (*con*). The last marketing variable, physician contacts, is a catch-all measure that includes physician detailing, free sample dropping, phone discussion, etc. Another widely

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on the share price even before the official date of withdrawal. Such effects of information leak are quite common in the finance literature. I will discuss the time window selection in more detail in the model fitting section in the next chapter.

used marketing tool in this industry, direct to consumer (DTC) ads, are not included in the modeling of this study due to data unavailability. However, prior research indicates that DTC ads have little impact on prescription drug sales at the brand level (Donohue 2003). The effects of marketing programs are typically not immediate. Yet, the lag in marketing effects has some staying power on the sales of brands in the following periods. Conceptually, the effects of marketing or advertising accumulate over time. Such buildup effects are called the stock of goodwill effects, also known as the carryover effects in the advertising literature. Accordingly, I adjust the marketing variables to account for the stock of goodwill effects. There are different but essentially similar ways to account for the stock of goodwill effects (Gonul et. al. 2001; Narayanan, Desiraju, and Chintagunta 2004). Following Narayanan, Desiraju, and Chintagunta's (2004) parameterization, I use the formulations in 5), 6), and 7) to calculate the cumulative effects of marketing programs (the stock of goodwill effects):

$$5) \quad SMP_{i,j} = SMP_{i,j-1}\theta + \sqrt{smp_{i,j}}$$

$$6) \quad JAD_{i,j} = JAD_{i,j-1}\theta + \sqrt{jad_{i,j}}$$

$$7) \quad CON_{i,j} = CON_{i,j-1}\theta + \sqrt{con_{i,j}}$$

Where

$\theta$ is a discount factor (the carry-over effect factor), and $\theta$ =0.85 in this study.

*i* refers to brand *i*.

*j* refers to *j*th month.

*smp* is the number of free samples distributed by sales reps.

*jad* is the number of ads appearing in professional journals.

*con* is the number of physician contacts.

*SMP* represents the number of free samples after the adjustment for the stock of goodwill[12].

*JAD* represents the number of professional journal ads after the adjustment for the stock of goodwill.

*CON* represents the number of physician contacts after the adjustment for the stock of goodwill.

In this parameterization, I use 85% as the discount/carry-over effect parameter. This number can be estimated in the Nerlove-Arrow (1962) exponential decay goodwill model in simple model settings. Prior research consistently suggests parameters within the range of 0.8 to 0.99. For example, Narayanan, Desiraju, and Chintagunta (2004) used 85% for detailing, and 92% for sampling. Gonul et. al. (2001) used 80% and 99% for both detailing and sampling. I experimented with parameters taking values of 0.85 and 0.95. The final model estimates from different parameter values are very similar. Notice that Gonul et. al. (2001) used a different parameterization, but the underlying rationale of allowing carryover effects of prior marketing efforts is similar to the formulations used in this study. The parameterization suggested by Gonul et. al. (2001) was also experimented in this study, and the results were compared with those obtained using parameterization in 5), 6) and 7). The two parameterizations did not produce differences significant enough to suggest the superiority of one over the other.

The competitive effects are modeled by including competitors' marketing programs as explanatory variables. Identifying the competitors for each drug included in the dataset starts

[12] Because the data in this study is truncated with a uniform starting and ending point, the stock of goodwill effects for period 1 is calculated by using a slightly different formulation. Using *smp* as an example, for period 1, $SMP_{i,1} = smp_{i,1}\theta + \sqrt{smp_{i,1}}$

with tagging each drug with a therapeutic class code. Assigning a therapeutic class code to each drug was achieved by using the drug classification system developed by IMS Health. The IMS electronic datasets used in this dissertation do not include the therapeutic class information for each drug. Instead, the printed library for the National Sales Perspective database provides a complete list of leading brands in the U.S. and their membership in various therapeutic classes. In other words, the library is a reliable source to systematically collect therapeutic class codes for every leading drug in the U.S. market. This was the most comprehensive and systematic classification system available to this study, and this list was used as the basis for compiling competitors' marketing program information. Specifically, the IMS leading drug list includes 1869 brands[13]. These leading brands are qualified with the yearly brand-level sales larger than 5 million dollars in 2003. Among these brands, 903 are included in the datasets compiled for this dissertation. With the therapeutic class information added to most major drugs used for this study, each major drug's competitor set can then be identified. Subsequently, competitors' marketing programs for each drug were calculated by summing up the marketing programs (i.e., *smp, jad,* and *con*) across competitors[14]. After the competitors' marketing program information became available, the same parameterization described in 5), 6), and 7) was used to account for the stock-of-goodwill effects of competitors' marketing programs.

Having introduced the key explanatory variables included in the study, the mixed effects models used to capture spillover effects on the parent company can be expressed by 8).

[13] Note that not all the leading brands are unique. Some large generic drugs are manufactured by several companies and are included in the list several times because each of them has yearly sales larger than $5 million.
[14] Note that the IMS coding system uses 5 digits to define a therapeutic class. The 5 digits are tiered with the first digit defining a very broad category and last digit defining a very narrow sub-category. Using all 5 digits defines a very specific and narrow therapeutic class. Because the data used in this study only capture about 50% of U.S. pharmaceutical industry, using very narrowly defined classes can in fact introduce more noises if a large brand is missing from the dataset. To avoid this problem, the first 3 digits of a therapeutic code are used to define a class. Brands that share the same first 3 digits in their therapeutic class codes are considered as competitors.

$$8)\quad Log(Dollar\_sale_{ij}) = \alpha_i + \beta_i time * brand_i + \beta'_i time^2 * brand_i + \eta_i seasonality * brand_i + \sum_k \lambda_k marketing_{ij} + \sum_k \mu_k c\_marketing_{ij} + \rho_i W * brand_i + \sum_k \xi_k W * marketing + \varepsilon_{ij}$$

Where

$Dollar\_sale_{ij}$ refers to the dollar sales[15] for brand *i* at time *j*

*i* refers to brand *i* ; *j* refers to month *j*

*brand* refers a brand drug used in model fitting. All drugs included in the data are brand drugs. Generic drugs are excluded for the purpose of this study.

*time* refers to a time indicator. *time = 1, 2, 3 ...*

*seasonality* is an indicator for brands that show seasonal fluctuations in their sales. This indicator is a dummy variable that turns on to 1 during seasonally peak months, and turns off during regular months.

$marketing_{ij}$ refers to various marketing programs for brand *i* at time *j*. Marketing programs include *smp, jad* and *con*. When using the data to fit the model, not all the marketing program variables are included in the model due to high multicolinearity between these variables. Discussion on the inclusion of marketing programs is presented in the next chapter. Marketing program variables used in modeling are adjusted for the stock of goodwill effects. These variables are capitalized to indicate the adjustments.

*SMP* refers to the number of free samples (adjusted for stock of goodwill).

[15] The dollar sales used here are adjusted for the data reporting problem discussed earlier. The monthly sales data of IMS were reported by physicians on a 4-4-5 week basis. The first 5 week period in the year is in March, followed by June, September, and December. To rescale the monthly data back for the purpose of this study, I divided the monthly sales data by the number of reporting weeks for that month, and then multiplied by 4.33 in order to retain the same normalization of sales data as in the original IMS data. This rescale approach is suggested in prior research work by Berndt et. al. (1995).

*JAD* refers to the number of professional journal ads (adjusted for stock of goodwill).

*CON* refers to the number of professional journal ads (adjusted for stock of goodwill).

$c\_marketing_{ij}$ refers to various marketing programs from competitors[16]. Similarly, marketing programs from competitors include C_*SMP, C_JAD,* and *C_CON* with each variable adjusted for the stock of goodwill effect.

*W* is the withdrawal indicator. It turns on when the product withdrawal occurs, and stays on.

The interaction terms, *W*brand* and *W*marketing*, are used to capture the spillover effects of drug withdrawal. Significant negative coefficients associated with *W*brand* represents deductions in the sales of other brands. They provide evidence on the spillover effects of drug withdrawal on the sales of other brands of the withdrawing company. Similarly, significant negative coefficients associated with *W*marketing* represents reductions in the effectiveness of marketing programs. They provide evidence on the spillover effects of drug withdrawal on the marketing effectiveness of the withdrawing company.

$\varepsilon$ is the error term. It is self-correlated by time. It is modeled by using an auto-regressive and moving average (ARMA) process that is appropriate for the variance-covariance structure. The exact specification for the ARMA specification is discussed in model fitting in the next chapter.

The above model is used to examine the possible spillover effects caused by a drug withdrawal on other brands in the parent company's portfolio. To capture the spillover effects of drug withdrawal on competing brands in the therapeutic class where the withdrawal occurs, a very similar model specification is used. This specification is expressed in 9).

[16] Competitors are defined as those drugs that belong to similar therapeutic classes but are marketed by companies other than the focal company. Similar drugs within the same company are not categorized as competitors.

$$9)\quad Log(Dollar\_sale_{ij}) = \alpha_i + \beta_i time * brand_i + \beta'_i time^2 * brand_i + \eta_i seasonality * brand_i$$
$$+\sum_k \lambda_k marketing_{ij} * brand + \sum_k \mu_k c\_marketing_{ij} + \rho_i W * brand_i + \sum_k \xi_k marketing * W + \varepsilon_{ij}$$

Where

$Dollar\_sale_{ij}$ refers to the dollar sales[17] for brand $i$ at time $j$

$i$ refers to brand $i$ ; $j$ refers to month $j$

*brand* refers a brand drug used in model fitting. All drugs included in the data are within the same therapeutic class, and hence are direct competitors with each other.

*time* refers to a time indicator. *time = 1, 2, 3 ...*

*seasonality* is an indicator for brands that show seasonal fluctuation in their sales. This indicator is a dummy variable that turns on to 1 during seasonally peak months, and turns off during regular months.

$marketing_{ij}$ refers to various marketing programs for brand $i$ at time $j$. Marketing programs include *smp, jad* and *con*. These marketing programs are adjusted for the stock of good will effects. These variables are capitalized to indicate the adjustments.

*SMP* refers to the number of free samples (adjusted for stock of goodwill).

*JAD* refers to the number of professional journal ads (adjusted for stock of goodwill).

*CON* refers to the number of professional journal ads (adjusted for stock of goodwill).

$c\_marketing_{ij}$ refers to various marketing programs from competitors. Similarly, marketing programs from competitors include *C_SMP, C_CON,* and *C_JAD.*

*W* is the withdrawal indicator. It turns on when the product withdrawal occurs, and stays on.

[17] The dollar sales used here are also adjusted for the data reporting problem discussed earlier.

The interaction terms, *W*brand* and *W*marketing*, are used to capture the spillover effects of drug withdrawal. Significant negative coefficients associated with *W*brand* represents deductions in the sales of competing brands. They provide evidence on the spillover effects of drug withdrawal on the sales of competing brands in the same therapeutic class. Similarly, significant negative coefficients associated with *W*marketing* represents reductions in the effectiveness of marketing programs. They provide evidence on the spillover effects of drug withdrawal on the effectiveness of marketing programs of competing brands.

$\varepsilon$ is the error term. It is self-correlated by time. It is modeled by using an auto-regressive and moving average (ARMA) process that is appropriate for the variance-covariance structure. The exact specification for the ARMA specification is discussed in Chapter 5.

Compared to model 8), model 9) differs by allowing brands to have different marketing effectiveness. This adjustment appears to be appropriate in that 1) brands within a therapeutic class largely come from different companies, and 2) marketing effectiveness can differ significantly across different companies.

**Chapter Summary**

In this chapter, I have provided a review of sources from which the data were collected for this study. The datasets compiled for this study include data from public sources and data from proprietary databases. The data collecting exercise was largely driven by what was needed and what was available to address the focal questions in the study. Following the sources of data collection, I described the data coverage for the past drug withdrawals occurring in the U.S. from 1996 to 2005. The detailed data description was summarized in a series of tables, which include

the time frame for each dataset, the number of observations, the representation of U.S. pharmaceutical industry, etc.

In addition to the data description, I described the key modeling approaches I used to analyze the data. These modeling approaches include intervention analysis and mixed effects models. Intervention analysis is most appropriate to examine the impact of drug withdrawal on the parent company's share price. In addition, intervention analysis was used as the first step to explore the effects of drug withdrawal on the sales of other brands within the parent company's portfolio. Results from intervention analysis provide insights for conducting in-depth analysis using mixed effects models. Built on the knowledge from intervention analysis, the mixed effects models can be specified more appropriately with regards to its variance-covariance structures. Results from the mixed effects models will be used to draw conclusions. For each of the variables used in this study, this chapter provided the definition and operationalization. I will discuss model fitting and model estimates for two large drug withdrawals, namely the Rezulin and the Baycol withdrawals in Chapter 5.

# CHAPTER 5

# IMPACT OF DRUG WITHDRAWAL ON THE PARENT COMPANY

In this chapter, I present the modeling results from two major drug withdrawals, the Rezulin withdrawal in 2000, and the Baycol withdrawal in 2001. The complete results are presented over two chapters. Chapter 5 discusses the impact of drug withdrawals on parent companies, and Chapter 6 discusses the impact of these two withdrawals on their competitors.

Rezulin and Baycol are selected as the focuses of analysis because they are ideal for the purposes of this study. First, the size of brand before its withdrawal was large. Analysis focused on large drug withdrawals may produce more meaningful and relevant results. These two drugs are the largest in size among all the prescription drug withdrawals between1996 and 2003. Both brands had yearly sales around $500 million and large bases of users. The failure of these two brands had huge impacts on many U.S. customers, and generated a significant amount of negative publicity[18]. Relative to the size of the company, both brands were large in terms of share of revenue. Rezulin represented about 5% of the parent company's yearly revenue before its withdrawal; Baycol took an even larger share of about 11%. The withdrawals of these two brands made a significant financial impact on each parent company.

Second, from a technical point of view, the data collected for this study provide the best coverage in terms of the time window to examine these two withdrawals. Within the datasets

[18] A statement from Parke-Davis (Warner-Lambert), Rezulin's manufacturer, indicated the company was facing an environment with "repeated media reports sensationalizing the risks associated with Rezulin therapy." (CNN Health, March 23, 2000). CNN, for example, reported the Rezulin withdrawal with the death certificate and a picture of one victim who died from taking Rezulin

compiled for this study, the Fen-Phen withdrawal (Redux-Pondimin) in 1997 was large and well-publicized. But this withdrawal occurred too early, and the data for this study provide only about half a year coverage before the incident. Such a short time window may not be sufficient to provide reliable model estimates.

Third, several companies had more than one drug withdrawal from 1996 to 2003. Sequential drug withdrawals from one company complicate the research, and the complexity may introduce unnecessary noise. From a modeling perspective, two sequential withdrawals may have interactions; interactions of multiple withdrawals may magnify or diminish the effects of each drug withdrawal. In addition, the interaction effects of sequential withdrawals may also depend on the persistence of the effects caused by each drug withdrawal. When the impact of a single withdrawal is still unclear, incorporating the interactions of multiple withdrawals, and introducing unnecessary complexities, does not seem appealing. Rezulin and Baycol, both of which were the only withdrawals for their parent companies, provide an ideal setting to examine the impact of drug withdrawals on their parent companies.

That said, this chapter is further organized into several sections to clearly present the model fitting results. First, the general backgrounds of the two drugs, including the parent company and the other brands in the parent company's portfolio, are introduced. Following the introduction of the background of each drug withdrawal, I first model the impact of drug withdrawal on the stock price of the parent company. Intervention analysis is most appropriate in this scenario. After examining the effects of drug withdrawal on share price, intervention analysis is employed again as an initial and exploratory step to understand the impact of the drug withdrawal on the sales of other brands of the withdrawing company. This analysis is intended to discover possible spillover effects of drug withdrawal and guide the following modeling exercise.

The mixed effects models are used as the primary modeling tools to investigate the spillover effects on the sales and marketing effectiveness of withdrawing companies. The findings are discussed and summarized at the end of the chapter.

**Rezulin Withdrawal**

Introduced in 1997, Rezulin is the brand name for Troglitazone, a prescription drug manufactured by Parke-Davis (a pharmaceutical arm of Pfizer) for the treatment of type 2 diabetes mellitus. Rezulin was withdrawn from the market in March 2000 due to its associations with liver toxicity, which had caused 69 reported fatalities (FDA News Release, March 2000). A strategically important drug for the parent company, Rezulin was the first drug approved by the FDA in a new therapeutic class, called thiazolidinediones, to increase peripheral glucose intake. Before the introduction of two direct competitors, Avandia (GSK) and Actos (Takeda) in 1999, Rezulin had been the only drug dominating the therapeutic class for about 2 years. It was the second largest selling antidiabetic agent on the market in the first year, and the second largest drug in the company (second only to Lipitor) with yearly sales of $625 million in 1999. Before its withdrawal, Rezulin was taken by approximately 750,000 Americans.

The parent company of Rezulin is identified as Parke-Davis. The choice made here needs more explanation. After a series of mergers and acquisitions, Parke-Davis is now a pharmaceutical arm of Pfizer Pharmaceuticals[19]. But since Rezulin was withdrawn before the merger, only the brands that were originally a part of Parke-Davis' portfolio are included in this study. Table 5.1 lists the top 10 brands of Parke-Davis around the time of the Rezulin withdrawal.

[19] Rezulin was made and marketed by Parke-Davis, the pharmaceutical division of Warner-Lambert. The drug was withdrawn on March 21st, 2000. At that time, Warner-Lambert was being acquired by Pfizer. Warner-Lambert, and Pfizer released a definitive merger agreement dated as of February 6, 2000. The acquisition was completed on June 19th, 2000 (based on Pfizer's annual report, and its corporate information on http://www.Pfizer.com). Before being acquired, Warner-Lambert was a listed company using NYSE trade code WLA.

**Table 5.1**
**Brand Portfolio of Parke-Davis (Pfizer)**

| Brand | Yearly dollar sales[20] (in 000) | Share of revenue | Accumulative share of revenue | Indicated drug uses |
|---|---|---|---|---|
| LIPITOR | 4159160.28 | 0.60 | 0.60 | Lipid-lowing |
| NEURONTIN | 1265853.20 | 0.18 | 0.78 | Epilepsy |
| ACCUPRIL | 550320.70 | 0.08 | 0.86 | Hypertension |
| REZULIN | 353328.21 | 0.05 | 0.91 | Diabetes |
| DILANTIN | 215477.47 | 0.03 | 0.94 | Epilepsy |
| LOESTRIN-FE 1/20-2 | 104170.92 | 0.02 | 0.96 | Birth-control |
| LOESTRIN-FE 1.5/30 | 96263.69 | 0.01 | 0.97 | Birth-control |
| ESTROSTEP FE-28 | 61212.99 | 0.01 | 0.98 | Birth-control |
| NITROSTAT | 28959.68 | 0.00 | 0.99 | Chest pain |
| LOPID | 20510.99 | 0.00 | 0.99 | Lipid-lowing |

**Baycol Withdrawal**

On August 8, 2001, Bayer Pharmaceutical Division withdrew Baycol (cerivastatin) from the U.S. market because of reports of sometimes fatal rhabdomyolysis, a severe muscle adverse reaction from this product. Documents from the FDA indicate that 31 people died of complications of severe muscle breakdown, a rare but well-recognized side effect of many cholesterol-lowering drugs. Reports of severe side effects, including death, are at least 10 times more common for Baycol than for other drugs in the class.

Introduced in January 1998, Baycol was a popular cholesterol-lowering drug. It was used by about 700,000 Americans. Baycol belongs to a popular class of drugs known as "statins," which include lovastatin (Mevacor), pravastatin (Pravachol), simvastatin (Zocor), fluvastatin (Lescol), and atorvastatin (Lipitor). Most drugs within this class are very well known to the

[20] Figures of yearly sales are calculated using a timeframe of 6 months before and after the drug withdrawal. This configuration is intended to identify the largest brands around the time of drug withdrawal.

consumers. Several of them are in fact multi-billion dollar sales blockbuster products. Statins are prescribed to about 12 million Americans each year to treat, and possibly prevent, coronary heart disease.

The parent company of Baycol is Bayer Pharmaceuticals, which is the healthcare division of the German company Bayer AG. Only brand drugs of Bayer are included in the study. Table 5.2 summarizes the top 10 brands of Bayer at the time of the Baycol withdrawal.

**Table 5.2**
**Brand Portfolio of Bayer Pharmaceuticals (Bayer AG)**

| Brand | Yearly dollar sales[21] (in 000) | Share of revenue | Accumulative share of revenue | Indicated drug uses |
|---|---|---|---|---|
| CIPRO | 1161326.57 | 0.52 | 0.52 | Antibiotic |
| ADALAT CC | 317996.93 | 0.14 | 0.66 | Hypertension |
| BAYCOL | 259108.93 | 0.12 | 0.77 | Lipid-lowing |
| AVELOX | 127410.03 | 0.06 | 0.83 | Antibiotic |
| GAMIMUNE N | 114074.28 | 0.05 | 0.88 | Boost immune system |
| CIPRO IV | 99833.78 | 0.04 | 0.92 | Antibiotic |
| TRASYLOL | 94815.31 | 0.04 | 0.97 | Prevention of blood loss in surgeries |
| PRECOSE | 30563.52 | 0.01 | 0.98 | Diabetes |
| NIMOTOP | 25550.68 | 0.01 | 0.99 | Hemorrhage |
| AVELOX ABC PACK | 13043.69 | 0.01 | 1.00 | Antibiotic |

**Modeling Effects of Drug Withdrawal on Stock Price**

In this section, I examine the effects of drug withdrawal on parent company's stock price. The stock price of Pfizer is used to model the impact of the Rezulin withdrawal whereas that of

[21] Figures of yearly sales are calculated by using a timeframe of 6 months before and after the drug withdrawal. This configuration is intended to identify the largest brands of the withdrawing company around the time of drug withdrawal.

Bayer AG is used to capture the impact of the Baycol withdrawal. Using Bayer's stock price for the purpose of this study is rather straightforward, because the parent company of Baycol was Bayer. Using Pfizer's stock price to model the impact of the Rezulin withdrawal, however, warrants some discussion.

At the time of its withdrawal (March 2000), Rezulin's parent company was Parke Davis, which was the pharmaceutical division of Warner-Lambert, a publicly traded company. Warner-Lambert was acquired by Pfizer in February 2000, but the acquisition was complete in June of the same year (Pfizer Annual Report 2000). The NYSE trade code WLA for Warner-Lambert was discontinued after the merger was completed on June 19$^{th}$, 2000. Because the merger and the withdrawal of Rezulin all happened within one year, using stock price of Warner-Lambert doesn't provide sufficient data coverage after the drug withdrawal. Using the adjusted stock price of Pfizer appears to be a more appropriate option in order to capture the financial impact of Rezulin's withdrawal on the share price. The share prices of Pfizer and Bayer are graphically depicted in Figures 5.1 and 5.2 with an arrow pointing to the month during which drug withdrawal occurred.

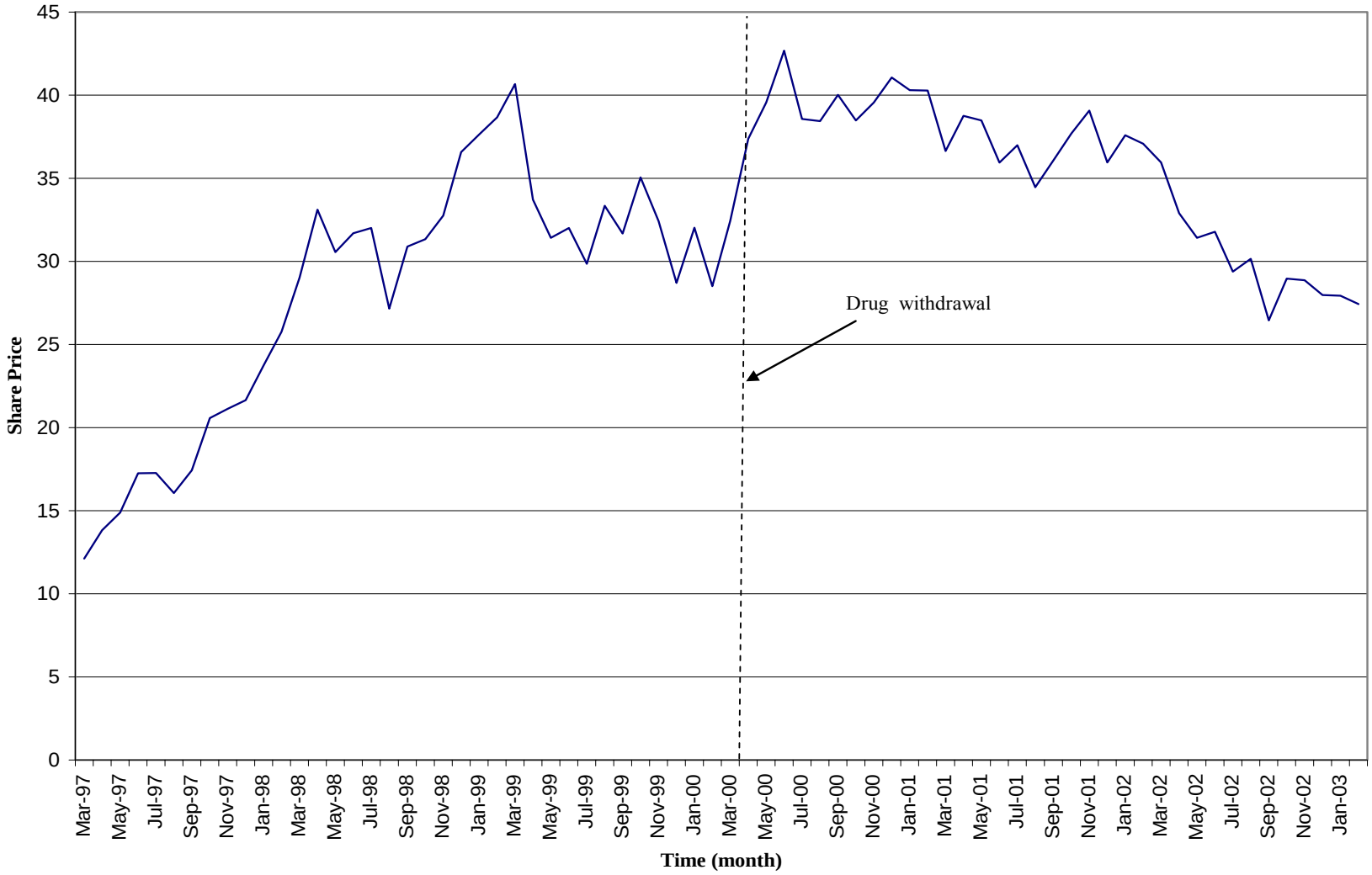


**Figure 5.1**
**Share Price for Pfizer Inc.**

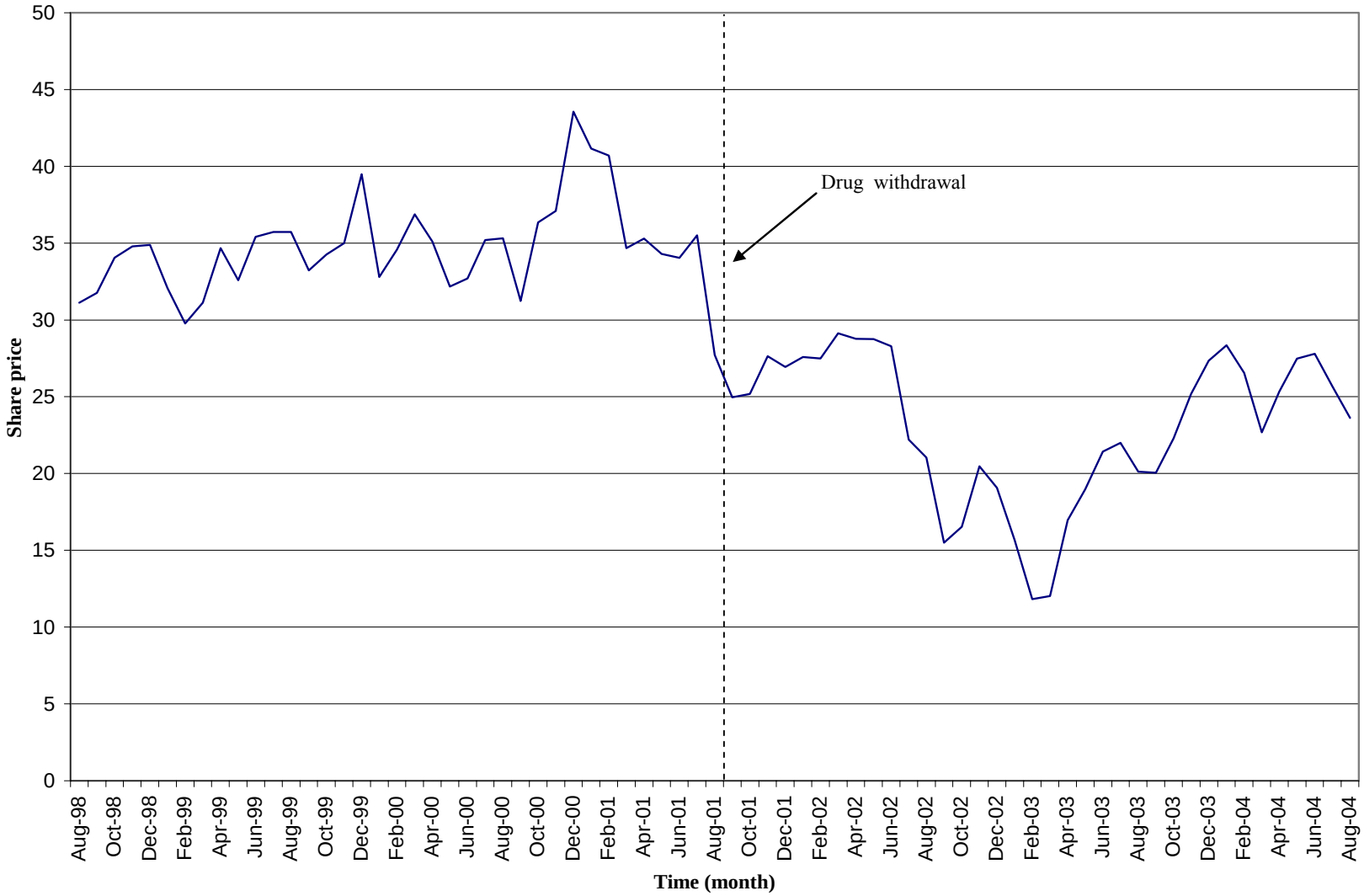


**Figure 5.2**
**Share Price for Bayer AG**

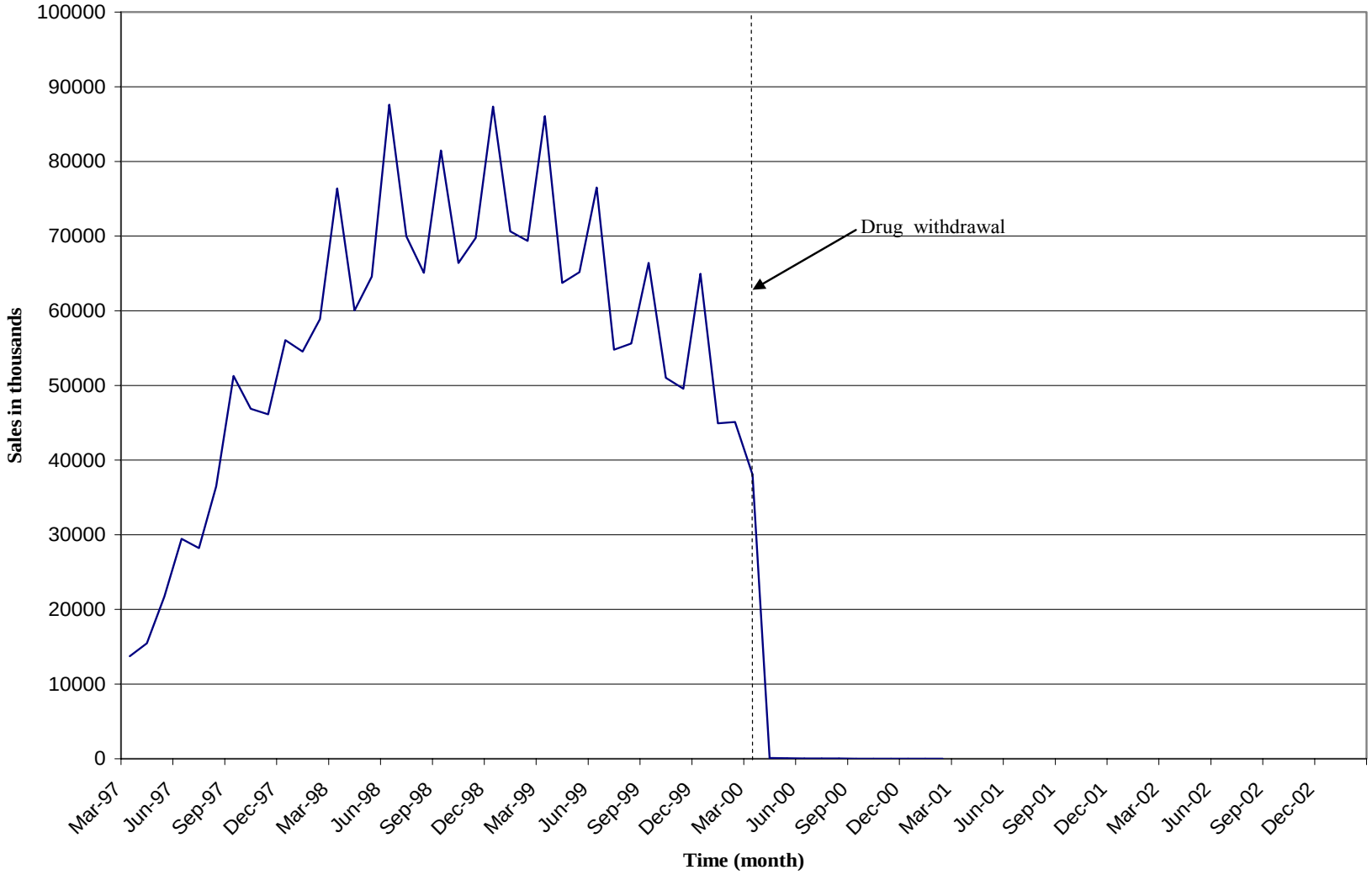


**Figure 5.3**
**Sales of Rezulin (in 1000 dollar)**

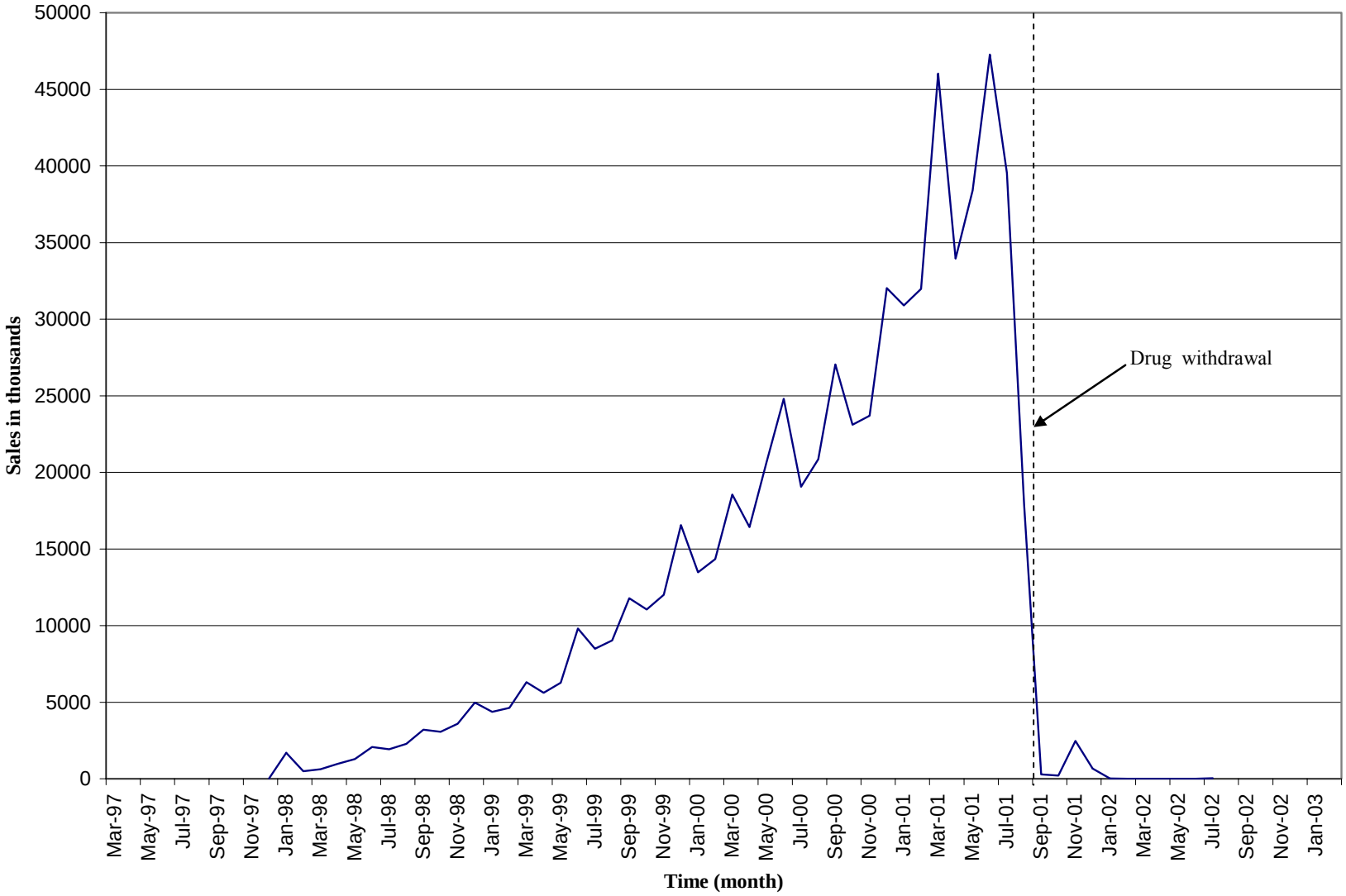


**Figure 5.4**
**Sales of Baycol (in 1000 dollar)**

**The Models**

The selection of an appropriate time window for the intervention event is critical in modeling share prices, and, in many instances, is determined case by case. Using a long time window may introduce noise caused by other events whereas using a short time window may miss the effects that lag behind the event or the effects that occur prior to the event due to information leak. This study used a time window of 3 months[22]. For Rezulin, the time window starts 2 months before the withdrawal and ends in the month of its withdrawal. The 2-month lead in the time window was intended to account for the information leak in the Rezulin case. In other words, when the withdrawal was officially announced, the financial market was not surprised. The information leak is suggested by a premature decline in the sales of Rezulin, which can be observed in Figure 5.3. This visual inspection was verified with secondary research in the FDA's documents. Several months prior to the Rezulin withdrawal, the FDA suggested the possibility of removing the drug from the market given the availability of safer alternatives (Meadows 2002). In contrast, the Baycol withdrawal appears to have much less information leak. The arrival of the announcement to remove the drug was a shock to the financial market, and appeared to be a surprise to doctors as well. Figure 5.2 shows that the sales of Baycol continued to grow rather strongly till the month of withdrawal. In this case, there is little evidence of information leak and no need to starting the intervention window early. Therefore, the time window used in this case starts from the month of withdrawal and lasts for 3 months.

Another important consideration in the model specification of intervention analysis is choosing an appropriate variance-covariance structure. Without much prior knowledge, I experimented with all the combinations of first and second order ARMA model specifications (i.e., AR(1), AR(2), ARMA(1,1), MA(1), and MA(2) ). The best model is chosen among these

[22] Longer time windows (4-6 months) are also tested without finding significant difference in results.

specifications. Table 5.3 summarizes the goodness-of-fit information associated with each of these model specifications.

**Table 5.3**
**Model Fit Information**

| Models | AR(1) | AR(2) | ARMA(1,1) | MA(1) | MA(2) |
|---|---|---|---|---|---|
| Significance of ARMA parameters | yes | yes | yes | no | no |
| Chi-square white noise test (at lag 12) | 23.33** | 18.62** | 19.23** | 777.61*** | 574*** |
| AIC | 335 | 335 | 335 | 613 | 562 |
| SBC | 340 | 342 | 342 | 618 | 569 |

* 10% **5% ***1% significance level

The autocorrelation plots, as well as the parameter estimates suggest a strong auto-regressive (AR) pattern in the time series. Comparing model specifications with different AR components, the SBC and AIC indices both suggest that AR (1) is perhaps the most parsimonious yet adequate model to fit the data. The final model estimates are the results based on using an AR (1) specification. Table 5.4 reports model estimates with AR (1) structure. The complete statistical models are specified in models 3) and 4) in the preceding chapter.

**Results**

Results in Table 5.4 suggest that both drug withdrawals have significant negative effects on the parent companies' share prices. Specifically, Pfizer's share price suffered a $4.3 dollar drop from the event of the Rezulin withdrawal. If the share price is modeled in the logarithm transformation, the results suggest that Pfizer's share price exhibited a roughly 13% drop due to the Rezulin withdrawal. Similarly, Bayer's share price suffered a $5.12 drop from the event of the Baycol withdrawal. In percentage, this was about a 17% drop from what the share price

would have been had Baycol not been withdrawn from the market. These results are expected, given that several negative factors are involved in a drug withdrawal. As discussed in Chapter 3, these factors include the loss of revenue of the withdrawn product, potential litigation liabilities, and negative publicity that may spill over to other products within the company's portfolio. In other words, the negative impact on the share prices is a catch-all phenomenon, in which the possible spillover effects may play a substantial role.

**Table 5.4**
**The Impact of Drug Withdrawal on the Stock Price of the Parent Company**

| | Rezulun Share Price | | Baycol Share Price | |
|---|---|---|---|---|
| | normal | log trans. | normal | log trans. |
| $\omega_0$ intervention estimate | -4.322*** | -0.13** | -5.12*** | -0.17** |
| $\varphi_1$ AR(1) estimate | 0.995*** | 0.99*** | 0.99*** | 0.99*** |

* 10% **5% ***1% significance level

In the next section, intervention analysis models are used again to examine the spillover effects of drug withdrawal on the sales of other brands of the withdrawing companies. As discussed earlier, intervention analysis is employed first to explore the data; the results will be used to guide the specifications of mixed effects models.

**Modeling Effects of Drug Withdrawal on Sales Using Intervention Analysis**

In this section, intervention analysis is used to examine the spillover effects of drug withdrawal on the sales of other brands of the withdrawing company. In the preceding section, the dependent variable used in intervention analysis is the stock price of the withdrawing company. The dependent variable used in this section, however, is the corporate level sales of the

withdrawing company excluding the sales of the withdrawn brand (*Sales*). *Sales,* as defined in Chapter 4, represent aggregate sales of all the brands in the company's portfolio other than those of the withdrawn brand. Intervention analysis in this section is intended to detect any significant changes in the sales of other brands of the withdrawing company around the time of the drug withdrawal. If a drug withdrawal produces significant spillover effects on the sales of other brands in the company's portfolio, such negative effects may be reflected as a deduction in the sales of other brands. More importantly, intervention analysis, as a powerful time series modeling tool, aids to shed light on the autocorrelation structure embedded in the sales data. Insights generated from intervention analysis help to properly specify the variance-covariance structure in the error terms in mixed effects models.

**The Models**

Following the model specifications and variable operationalizations in model 1) and 2) in Chapter 4, different variance-covariance structures can be used to model *Sales.* These different structures are corresponding to different ARMA configurations. Similar to the exercise done in modeling stock price, all the first and second order ARMA models are used in order to find the most appropriate model specification. The goal is to find a model specification that de-trends the time series to a stationary series (white noise), and, at the same time, the specification is parsimonious. Table 5.5 summarizes the goodness-of-fit information of different model specifications using the Rezulin data.

The results in Table 5.5 suggest that structures that include auto-regressive components generally fit the data better than using moving average components alone. Among all the specifications tested, ARMA(1,1) fits the sales data best in that it has the smallest AIC and SBC

values, and it has the best white noise test results. In other words, the model specification adequately captures the trend in the sales series and is parsimonious in using parameters. Based on the above results, the final model specification used to model *Sales* and *ln(Sales)* are models specified in 1) and 2) in Chapter 4 with an ARMA (1,1) structure in the noise component.

**Table 5.5**
**Model Fit Information**

| Models | AR(1) | AR(2) | ARMA(1,1) | MA(1) | MA(2) |
|---|---|---|---|---|---|
| Significance of ARMA parameters | yes | yes | yes | yes | yes |
| Chi-square white noise test (at lag 12) | 34*** | 17.57* | 12.89 | 92.51*** | 25.1*** |
| AIC | 1648 | 1640 | 1628 | 1658 | 1643 |
| SBC | 1652 | 1646 | 1634 | 1662 | 1650 |

**Results**

Table 5.6 presents the key results of modeling *Sales* and *ln(Sales)* using intervention analysis. The sales are aggregate corporate level sales excluding those of the withdrawn brand. The parameters associated with ARMA structures are all significant at 1% level. However, none of the estimates associated with the intervention effects turn out to be significant. Direct interpretations of these results suggest that there were no significant impact caused by a drug withdrawal on the sales of other brands of the withdrawing company. However, these results need to be interpreted rather cautiously. As discussed earlier in Chapter 4, using intervention analysis to examine the spillover effects on the sales of other brands has several major weaknesses. Among them, the lack of control for marketing and competitive effects makes the findings be easily confounded with other uncontrolled factors. In addition, the aggregate sales at

the corporate level neither take into account the sales of new product introductions, nor do they include declines in the sales of mature products. The key takeaways from this modeling exercise, however, are the appropriate structures of variance-covariance to fit the sales series. In using mixed effects models, similar variance-covariance structure is used to account for the auto-correlation in the error terms. The conclusions regarding to the impact of drug withdrawal on the sales of other brands of parent company will be drawn based on the findings of mixed effects models.

**Table 5.6**
**The Impact of Drug Withdrawal on the Sales of Other Brands**

| | Rezulin | | Baycol | |
|---|---|---|---|---|
| | normal | log trans. | normal | log trans. |
| $\omega_0$ intervention estimate | -15431.1 | -0.018 | 2111.1 | -0.018 |
| $\varphi_1$ AR(1) estimate | 0.99*** | 0.99*** | 0.99*** | 0.99*** |
| $\theta_1$ AR(1) estimate | 0.95*** | 0.61*** | 0.94*** | 0.67*** |

* 10% **5% ***1% significance level

**Modeling Effects of Drug Withdrawal on Sales and Marketing Effectiveness**

In this section, the mixed effects models are used to model the spillover effects of drug withdrawal on the sales of other brands in the withdrawing company's portfolio as well as the spillover effects of drug withdrawal on the marketing effectiveness of that company. Mathematical specifications of mixed effects models and relevant variable operationalizations are presented in Chapter 4. These specifications, however, do not complete the modeling exercises. Before fitting models to the data, several issues, including data selection and

marketing variable selection, need further discussion. The following sections first discuss these issues and then present model fitting results.

**The Models**

The model 8) described in Chapter 4 specifies the mixed effects models used to fit the data in this section. Yet, the model specification does not prescribe what data should be used to fit the model. Before presenting the results from model fitting, several issues related to data selection and marketing variable selection are discussed here.

Data selection involves the choice of the number of brands to be included in the dataset to fit the model. In the Parke-Davis case, there are 48 brand drugs in the company's portfolio. However, the top 7 brands represent over 95% of the company revenue, with the remaining brands all smaller than 1% in their respective representation of the company's revenue. Given the purposes of this study, using the largest brands appears to adequately represent the brand portfolio. In fact, including all the 48 brands with many of these brands representing less than 1% of company revenue may introduce unnecessary noises into the results. In the modeling exercise, the selection of data generally used the following guidelines. First, the brands included should represent about 90% of the company's revenue, which guarantees the selected brands well represent the withdrawing company's brand portfolio. Second, if most brands are small in relative size, brands representing less than 1% of the company's revenue are not included. Third, brands introduced after the drug withdrawal are not included.

Marketing variable selection is another issue that relates to the model fitting and warrants discussion in more details. Ideally, all three marketing variables (i.e*., SMP, JAD*, and *CON*) should be included in the model, but the high correlation between these variables does not allow

the inclusion of all three. Based on the entire database, the correlation matrix of the three marketing variables and the inversed correlation matrix are given in Table 5.7. The correlations between *CON* and the other two variables are particularly high, which suggest that using *CON* together with the other two variables may introduce excessive multicollinearatiy. To further examine the multicollinearatiy issue, the inversed correlation matrix was calculated. Results from the inversed correlation matrix clearly indicate that *CON* should not be used in conjunction with *SMP* and *JAD*[23] in order to avoid excessive multicolinearity (Belsley, Kuh, and Welsch 1980). In other words, the choice of marketing variables should be made between *CON* and the pair of *SMP* and *JAD*. Yet, when *SMP* and *JAD* are highly correlated with each other, only one marketing variable should be included in the model.

Based on the above discussion on selecting marketing variables, the selection of marketing variables generally uses the following rules. First, when the correlation between *SMP* and *JAD* is less than 0.7, the pair of *SMP* and *JAD* is preferred over a single variable of *CON*. This is intended to maximize the use of data without introducing excessive multicolinearity between explanatory variables. Second, when the values of correlation between all three variables are greater than 0.7, only one marketing variable can be included in the model (Wooldridge 1999). *CON* is the preferred variable to use. Physician contacts (*con*), as defined, catch various types of marketing activities, including sample dropping, phone discussion, product detailing, etc. If only one marketing variable can be included in the model, using *CON* appears to capture the most important marketing activities in the pharmaceutical industry. Lastly, when there is significant portion of data missing in the marketing variables, the use of marketing variables is largely determined by the availability of data.

[23] The largest value (9.38) in the diagonal of the inversed correlation matrix indicates the variable associated with this value (i.e., *CON*) that should be removed to avoid excessive multicolinearity.

**Table 5.7**
**Correlation between Marketing Variables**

| | Correlation Matrix | | | Inversed Correlation Matrix | | |
|---|---|---|---|---|---|---|
| | SMP | CON | JAD | SMP | CON | JAD |
| SMP | 1 | 0.77 | 0.75 | -0.00039 | 0.00018 | 0.00013 |
| CON | 0.77 | 1 | 0.87 | -10.82 | 9.38 | 0.00046 |
| JAD | 0.75 | 0.87 | 1 | 12.41 | -9.61 | -0.00065 |

Following the guidelines for data selection and marketing variable selection, top 7 brands of Parke-Davis were used to fit the model for Rezulin with two marketing variables, *SMP* and *JAD*, included. The top 7 brands capture more than 90% of the company revenue. Brands with less than 1% of the revenue were not included for the analysis. The correlation between *SMP* and *JAD* is less than 0.7. The inclusion of both measures allows the maximum use of data while avoiding excessive multicolinearity between variables. Table 5.8 provides descriptive information for the data used to fit the Rezulin model, and Table 5.9 provides the correlation matrix between marketing variables.

**Table 5.8**
**Simple Statistics for the Data Used for Rezulin Withdrawal**

| Variable | N | Mean | Std. Dev | Sum | Min | Max |
|---|---|---|---|---|---|---|
| SMP | 497 | 216.60 | 175.12 | 107649.20 | 0.00 | 709.60 |
| JAD | 492 | 33.20 | 31.81 | 16336.84 | 0.00 | 132.52 |
| CON | 497 | 48.93 | 45.28 | 24315.88 | 0.00 | 189.19 |

**Table 5.9**
**Correlation Matrix for Marketing Variables (Rezulin)**

| Variable | SMP | JAD | CON |
|---|---|---|---|
| SMP | 1.00 | 0.55 | 0.88 |
| JAD | 0.55 | 1.00 | 0.79 |
| CON | 0.88 | 0.79 | 1.00 |

Similar to the decisions made to the Rezulin data, top 10 brands are used to fit the model for the Baycol withdrawal. However, only one marketing variable (*CON*) is included in the model. The inclusion of only one marketing variable is based on 1) the high correlation between all three marketing variables, and 2) significant portion of *SMP* data missing (308 vs. 616 in Table 5.10). Table 5.10 and Table 5.11 summarize the key descriptive information for the data used for the Baycol withdrawal.

**Table 5.10**
**Simple Statistics for the Data Used for Baycol Withdrawal**

| Variable | N | Mean | Std. Dev | Sum | Min | Max |
|---|---|---|---|---|---|---|
| SMP | 308 | 270.90 | 229.69 | 83438.31 | 0.00 | 767.96 |
| JAD | 573 | 31.51 | 25.79 | 18054.41 | 0.00 | 89.05 |
| CON | 616 | 32.99 | 39.28 | 20319.34 | 0.00 | 141.66 |

**Table 5.11**
**Correlation Matrix for Marketing Variables (Baycol)**

| Variable | SMP | JAD | CON |
|---|---|---|---|
| SMP | 1.00 | 0.87 | 0.88 |
| JAD | 0.87 | 1.00 | 0.87 |
| CON | 0.88 | 0.87 | 1.00 |

**Results**

Table 5.12 and Table 5.14 summarize the model estimates for the Rezulin and Baycol withdrawals respectively. Estimates associated with time and time squared terms capture various shapes of sales curve at the brand level. Each brand is allowed a unique growth curve over its lifetime. Estimates associated with marketing variables are generally positive, indicating positive returns on marketing programs. Estimates for competitors' marketing programs generally show

negative signs, suggesting that competitors' marketing activities diminish the effects of company's own marketing. Estimates related to the seasonality for a few brands represent the seasonal fluctuation in the sales of these brands. Brands that show seasonality patterns are usually antibiotics or antihistamines.

The key interest in model estimates are those associated with *W*. These estimates are highlighted in bold font. If all the estimates associated with *W*brand* are significantly negative, such results provide evidence of negative impacts of drug withdrawal on the sales of other brands in the parent company. Similarly, if the estimates associated with marketing variables are significantly negative, they represent deductions in the effectiveness of company's marketing programs, which provides evidence of negative spillover effects of drug withdrawal on parent company's marketing effectiveness.

Results from the Rezulin withdrawal modeling indicate that there are no significant spillover effects on the sales of other brands. Results for the marketing effectiveness of the company, however, show a significant deduction after the drug withdrawal. Specifically, the effectiveness of one type of marketing programs, ads in professional journals (*JAD*), suffers a significant drop. To verify the robustness of these model estimates, different sets of brands (e.g., the 4 largest brands or 10 largest brands) are used to fit the model. Results from using top 4 or top 10 brands are very consistent with those in Table 5.12. In other words, selection of data does not alter the model estimates very dramatically.

Table 5.13 summarizes the goodness-of-fit information for different specifications of the Rezulin model. Results from the intervention analysis suggest that the AR(1) or ARMA(1,1) specification may adequately capture the variance-covariance structure in the time series of sales. Both AR(1) and ARMA(1,1) structures are experimented in the mixed effects models in order to

find the best model specification. Goodness-of-fit information from various model specifications is summarized in Table 5.13. Results in Table 5.13 suggest that the AR(1) structure have consistently smaller values in AIC and BIC. The likelihood ratio test also suggests that the AR(1) structure is adequate yet parsimonious in order to model the auto-correlation in the error term[24]. Model estimates in Table 5.12 are, therefore, based on the model specification using the AR(1) structure for the error term. In fact, all the following model estimates are based on the same structure to model the auto-correlation in the error terms.

**Table 5.12**
**Model Estimates for the Rezulin Withdrawal**

| Effect | Brand | Estimate | t-value | p-value |
|---|---|---|---|---|
| Intercept | | 8.694 | 21.786 | 0.000 |
| brand | ACCUPRIL | -2.176 | -1.481 | 0.140 |
| brand | DILANTIN | 0.964 | 3.948 | 0.000 |
| brand | ESTROSTEP FE-28 | -4.184 | -4.971 | 0.000 |
| brand | LIPITOR | 0.454 | 0.920 | 0.359 |
| brand | LOESTRIN-FE 1.5/30 | -2.101 | -2.079 | 0.039 |
| brand | LOESTRIN-FE 1/20-2 | -2.556 | -2.508 | 0.013 |
| brand | NEURONTIN | 0.000 | | |
| time*brand | ACCUPRIL | 0.071 | 3.245 | 0.001 |
| time*brand | DILANTIN | 0.001 | 0.099 | 0.922 |
| time*brand | ESTROSTEP FE-28 | 0.069 | 4.148 | 0.000 |
| time*brand | LIPITOR | -0.057 | -1.302 | 0.195 |
| time*brand | LOESTRIN-FE 1.5/30 | 0.016 | 0.826 | 0.410 |
| time*brand | LOESTRIN-FE 1/20-2 | 0.029 | 1.469 | 0.144 |
| time*brand | NEURONTIN | 0.020 | 1.492 | 0.138 |
| time2*brand | ACCUPRIL | -0.001 | -3.099 | 0.002 |
| time2*brand | DILANTIN | 0.000 | -1.308 | 0.194 |
| time2*brand | ESTROSTEP FE-28 | -0.001 | -3.697 | 0.000 |
| time2*brand | LIPITOR | 0.000 | 0.795 | 0.428 |
| time2*brand | LOESTRIN-FE 1.5/30 | 0.000 | -1.442 | 0.151 |

[24] A statistical test, the likelihood ratio test, can be conducted here to test the appropriateness of model specification. In the likelihood ratio test, the t-value= 0.8 with df=1 (p-value>0.05) indicating that the AR(1) specification is preferred over the ARMA(1,1) specification.

| | | | | |
|---|---|---|---|---|
| time2*brand | LOESTRIN-FE 1/20-2 | 0.000 | -1.776 | 0.078 |
| time2*brand | NEURONTIN | 0.000 | -1.106 | 0.270 |
| SMP | | 0.004 | 1.534 | 0.127 |
| JAD | | 0.024 | 3.616 | 0.000 |
| C_SMP | | 0.002 | 1.264 | 0.208 |
| C_JAD | | -0.004 | -1.423 | 0.158 |
| **w1*brand** | **ACCUPRIL** | **-0.266** | **-0.207** | **0.836** |
| **w1*brand** | **DILANTIN** | **0.038** | **0.385** | **0.701** |
| **w1*brand** | **ESTROSTEP FE-28** | **0.446** | **0.824** | **0.411** |
| **w1*brand** | **LIPITOR** | **1.512** | **0.828** | **0.409** |
| **w1*brand** | **LOESTRIN-FE 1.5/30** | **0.728** | **1.430** | **0.155** |
| **w1*brand** | **LOESTRIN-FE 1/20-2** | **0.678** | **1.222** | **0.223** |
| **w1*brand** | **NEURONTIN** | **0.722** | **0.922** | **0.358** |
| **SMP*w1** | | **0.001** | **0.248** | **0.804** |
| **JAD*w1** | | **-0.017** | **-1.807** | **0.072** |

**Table 5.13**
**Goodness-of-fit for the Model (Rezulin)**

| Measure | AR(1) specification Value | ARMA(1,1) specification Value |
|---|---|---|
| -2 Log Likelihood | -720.56 | -721.30 |
| AIC (smaller is better) | -648.56 | -647.30 |
| AICC (smaller is better) | -642.40 | -640.80 |
| BIC (smaller is better) | -650.51 | -649.30 |

The results from the Baycol withdrawal furnish evidence of significant negative effects of drug withdrawal on the sales of most Bayer brands. 6 out of 9 largest brands of Bayer show a significant decrease in their sales after the withdrawal of Baycol. Sales declines across most brands give evidence of the spillover effects of the drug withdrawal. The results, however, find significant positive changes in the effectiveness of marketing programs after the drug withdrawal. This finding is somewhat surprising, and is consistent if different marketing variables are used.

In other words, the increase in the effectiveness of marketing programs does not depend on the choice of marketing variable. The results are further examined in the discussion section of this chapter in order to provide some explanations.

**Table 5.14**
**Model Estimates for the Baycol Withdrawal**

| Effect | Brand | Estimate | t-value | p-value |
|---|---|---|---|---|
| Intercept | | 7.488 | 30.144 | 0.000 |
| brand | ADALAT CC | 1.151 | 1.686 | 0.095 |
| brand | AVELOX | -14.686 | -4.719 | 0.000 |
| brand | AVELOX ABC PACK | -13.319 | -6.155 | 0.000 |
| brand | CIPRO | -0.925 | -0.446 | 0.657 |
| brand | CIPRO IV | -2.286 | -1.147 | 0.253 |
| brand | GAMIMUNE N | 0.965 | 2.828 | 0.006 |
| brand | NIMOTOP | -1.490 | -2.284 | 0.024 |
| brand | PRECOSE | -0.874 | -1.803 | 0.074 |
| brand | TRASYLOL | 0.000 | | |
| time*brand | ADALAT CC | 0.002 | 0.101 | 0.919 |
| time*brand | AVELOX | 0.445 | 3.498 | 0.001 |
| time*brand | AVELOX ABC PACK | 0.313 | 3.372 | 0.001 |
| time*brand | CIPRO | 0.027 | 1.456 | 0.148 |
| time*brand | CIPRO IV | 0.017 | 1.172 | 0.244 |
| time*brand | GAMIMUNE N | -0.014 | -1.023 | 0.309 |
| time*brand | NIMOTOP | -0.004 | -0.291 | 0.771 |
| time*brand | PRECOSE | -0.013 | -0.546 | 0.586 |
| time*brand | TRASYLOL | 0.027 | 1.922 | 0.057 |
| time2*brand | ADALAT CC | 0.000 | -0.139 | 0.890 |
| time2*brand | AVELOX | -0.004 | -3.470 | 0.001 |
| time2*brand | AVELOX ABC PACK | -0.003 | -3.239 | 0.002 |
| time2*brand | CIPRO | 0.000 | -1.210 | 0.228 |
| time2*brand | CIPRO IV | 0.000 | -1.425 | 0.156 |
| time2*brand | GAMIMUNE N | 0.000 | 2.288 | 0.024 |
| time2*brand | NIMOTOP | 0.000 | 0.338 | 0.736 |
| time2*brand | PRECOSE | 0.000 | -0.582 | 0.562 |
| time2*brand | TRASYLOL | 0.000 | -0.361 | 0.718 |
| season*brand | ADALAT CC | 0.000 | | |
| season*brand | AVELOX | 0.294 | 2.890 | 0.004 |

| | | | | |
|---|---|---|---|---|
| season*brand | AVELOX ABC PACK | 0.377 | 3.721 | 0.000 |
| season*brand | CIPRO | 0.000 | | |
| season*brand | CIPRO IV | 0.000 | | |
| season*brand | GAMIMUNE N | 0.000 | | |
| season*brand | NIMOTOP | 0.000 | | |
| season*brand | PRECOSE | 0.000 | | |
| season*brand | TRASYLOL | 0.000 | | |
| CON | | 0.004 | 0.684 | 0.495 |
| C_CON | | 0.010 | 1.878 | 0.063 |
| **W*brand** | **ADALAT CC** | **-1.355** | **-2.829** | **0.005** |
| **W*brand** | **AVELOX** | **-2.991** | **-2.632** | **0.009** |
| **W*brand** | **AVELOX ABC PACK** | **-0.335** | **-1.368** | **0.172** |
| **W*brand** | **CIPRO** | **-4.490** | **-2.620** | **0.010** |
| **W*brand** | **CIPRO IV** | **-0.711** | **-1.815** | **0.072** |
| **W*brand** | **GAMIMUNE N** | **-0.600** | **-3.017** | **0.003** |
| **W*brand** | **NIMOTOP** | **0.017** | **0.083** | **0.934** |
| **W*brand** | **PRECOSE** | **-0.187** | **-0.710** | **0.479** |
| **W*brand** | **TRASYLOL** | **-0.448** | **-1.946** | **0.053** |
| **CON*W** | | **0.034** | **2.628** | **0.010** |

**Table 5.15**
**Goodness-of-fit for the Model (Baycol)**

| Measure | Value |
|---|---|
| -2 Log Likelihood | -132.82 |
| AIC (smaller is better) | -46.82 |
| AICC (smaller is better) | -39.13 |
| BIC (smaller is better) | -38.34 |

**Summary of Findings and Discussion**

The key findings from the modeling exercise of the Rezulin and Baycol withdrawals are summarized in Table 5.16. With some caveats, the modeling exercise has found evidence of negative spillover effects of drug withdrawal on the sales of other brands and on the marketing effectiveness of the withdrawing company. In one drug withdrawal study, the spillover effects

are reflected directly on the sales of other brands; in the other, the spillover effects are less direct, but are significant on the marketing effectiveness of the withdrawing company.

As discussed in Chapter 3, the size of the withdrawn drug may help to moderate the effects of drug withdrawal and cause variations in the results of different drug withdrawals. Withdrawals of larger brands may make a more direct impact on the sales of other brands whereas withdrawals of smaller brands may only affect marketing effectiveness. Unfortunately, there are no large drug withdrawals readily available in the database to allow replication of the findings. There are, however, a few smaller drug withdrawals in the data that can be used to replicate the findings of the spillover effects on the marketing effectiveness. The results from these replications are presented in Chapter 7.

**Table 5.16**
**Summary of Findings from Mixed Effects Models**

| Brand | Negative Impact on the Sales of Other Brands | Negative Impact on the Marketing Effectiveness |
|---|---|---|
| Rezulin (5% of company revenue) | No | Yes |
| Baycol (11% of company revenue) | Yes | No |

The difference found in the spillover effects of drug withdrawal on the marketing effectiveness of withdrawing companies is closely examined. The positive change in the marketing effectiveness found in the Baycol withdrawal is rather surprising at a first look. A possible explanation for the positive change in the effectiveness of marketing may have to do with the reallocation of marketing programs after the drug withdrawal[25]. Drug withdrawals,

[25] Another possibility is more technical, and may have to do with the data coverage. In the data used, there are 13 months of data following the Baycol withdrawal whereas the data coverage for Rezulin is 30 months following the withdrawal. The relatively short time window after the Baycol withdrawal may not be sufficient to pick up the

especially large ones like the Baycol withdrawal, are catastrophic events for the parent company. Occurrence of such event may bring about changes at many different levels. One such change could be reallocating marketing resources available to the company. Taking a historical approach, the changes in the marketing programs of Parke-Davis and Bayer are closely examined.

As shown in Table 5.17, at the aggregate level, two companies, Bayer and Parke-Davis exhibit a similar pattern of gradually increasing marketing programs over time before and after the drug withdrawal. This similarity does not shed light on the difference with respect to the changes in marketing effectiveness after drug withdrawals.

**Table 5.17**
**# of *CON* (in 000) Before and After the Drug Withdrawal at the Aggregate Level**

| | # of *CON* per brand before the drug withdrawal | # of *CON* per brand after the drug withdrawal | Percentage change |
|---|---|---|---|
| Bayer | 9.97/month | 12.45/month | +24.8% |
| Parke-Davis | 25.5/month | 32/month | +25% |

At the brand level, Bayer's marketing programs show some dramatic changes before and after the drug withdrawal. Marketing programs for several mature drugs (e.g., ADALAT CC, NIMOTOP, and PRECOSE) were almost completely eliminated, which may be attributed to the short of cash flow due to 1) the loss of revenue from an important brand, and 2) fund reserve for potential legal liabilities. Marketing programs for new brands (e.g., AVELOX and AVELOX ABC PACK) were increased significantly, which is not uncommon for new product

effects on the marketing effectiveness. To explore this possibility, Rezulin data was truncated such that only 13 months are included after the withdrawal. Results from modeling the truncated data of Rezulin do not alter the original Rezulin results much. In sum, this suspicion doesn't aid to explain the positive marketing effectiveness change found in the Baycol withdrawal.

introductions. Reducing marketing programs to almost zero for several brands can in fact skew the model estimates. When the sales of these brands were declining at a speed much slower than that of the marketing programs, the model estimates in fact show an increase in marketing effectiveness. In other words, the sharp declines in marketing programs can confound the effects of drug withdrawal on the marketing effectiveness of the withdrawing company. In sum, significant marketing re-allocation occurring at the brand level of Bayer may have confounded the negative spillover effects on marketing effectiveness expected to find. Table 5.18 summarizes the reallocation of marketing programs at the brand level for Bayer and Parke Davis.

**Table 5.18**
**# of *CON* (in 000) Before and After the Drug Withdrawal at the Brand Level**

| | Bayer Brands | | |
|---|---|---|---|
| | # of *CON* per brand before Baycol withdrawal | # of *CON* per brand after Baycol withdrawal | Percentage change |
| ADALAT CC | 10.95 | 0.05 | -99% |
| AVELOX | 39.10 | 55.95 | +43% |
| AVELOX ABC PACK | 0.45 | 1.21 | +169% |
| CIPRO | 42.86 | 54.72 | 27% |
| CIPRO IV | 2.47 | 1.89 | -23% |
| GAMIMUNE N | 0.00 | 0.00 | 0 |
| NIMOTOP | 0.02 | 0.00 | -100% |
| PRECOSE | 6.16 | 0.11 | -98% |
| TRASYLOL | 0.64 | 0.42 | -33% |
| | Parke Davis Brands | | |
| | # of *CON* per brand before Rezulin withdrawal | # of *CON* per brand after Rezulin withdrawal | Percentage change |
| ACCUPRIL | 19.02 | 25.00 | +31% |
| DILANTIN | 0.12 | 0.09 | -25% |
| LIPITOR | 80.68 | 96.26 | +19% |
| NEURONTIN | 6.24 | 6.74 | +8% |

**Chapter Summary**

In this chapter, I have presented results related to the impacts of drug withdrawal on the parent company. Two drug withdrawals are examined closely in this chapter. Results from various modeling exercises are organized by the method employed to examine the problem.

First, the impact of drug withdrawal on the stock price of parent company is modeled by intervention analysis. The results indicate significant negative impact of drug withdrawal on the share price of the withdrawing company. Similar modeling approach is used to explore the impact of drug withdrawal on the aggregate sales of the withdrawing company. The results from the modeling indicate no significant spillover effects on the corporate level sales. This modeling exercise also suggests that using the AR(1) or ARMA (1,1) structure adequately fits the auto-correlation in the data.

Guided by the findings from intervention analysis, mixed effects models are used to model the impact of drug withdrawal on the sales of other brands and on the marketing effectiveness of parent company. The results from mixed effects models are used as the basis for drawing conclusions. These results find evidence of 1) negative spillover effects of drug withdrawal on the sales of other brands of the withdrawing company and 2) negative spillover effects on the marketing effectiveness of that company. These findings are not completely consistent across the two drug withdrawals studied. Some of the findings from mixed effects models are replicated in Chapter 7.

In the next chapter, the mixed effects models specified in model 9) in Chapter 4 are used to quantify the impact of drug withdrawal on the sales of competing brands and the impact on the marketing effectiveness of these competing brands. The results from modeling the Rezulin and Baycol withdrawals are presented in Chapter 6.

# CHAPTER 6

# IMPACT OF DRUG WITHDRAWAL ON COMPETING BRANDS

## The Therapeutic Classes of Rezulin and Baycol

This section summarizes the key descriptive information for the therapeutic classes of Rezulin and Baycol. Rezulin belongs to a therapeutic class called thiazolidinediones used to treat type II diabetes. There were only 3 members in the therapeutic class before the withdrawal of Rezulin. All three drugs were brand drugs. Baycol belongs to a very popular class called statins used to lower cholesterol. Statins are a very large class of drugs. Several brands within the class have yearly sales of over a billion dollars. There were 8 drugs within the class prior to the withdrawal of Baycol. All drugs within this class were brand drugs with one exception—LOVASTATIN, a generic drug that is marketed by multiple generic drug manufacturers. This generic drug is not included in the analysis.

Table 6.1 and Table 6.2 present the dollar size of each drug within the class as well as each drug's relative size to the class. Both Rezulin and Baycol were large brands within the class. Rezulin had about 50% of the market share in the year before its withdrawal; Baycol had about 5% of the market share in the year before its withdrawal[26]. Within each of their erapeutic class, thiazolidinediones and statins respectively, there was only one drug withdrawal between 1996 and 2005. Both withdrawing companies only had one drug withdrawal during the same period.

[26] These market share figures are calculated using the timeframe of 12 months prior to the drug withdrawal. Depending on the timeframe used, the figures for market share are different.

**Table 6.1**
**Brands in the Therapeutic Class of Thiazolidinediones (Rezulin)**

| Brand | Yearly dollar sales (in 000) | Share of revenue | Accumulative share of revenue | Parent company |
|---|---|---|---|---|
| AVANDIA | 558884.80 | 0.41 | 0.41 | GlaxoSmithKline |
| ACTOS | 465415.70 | 0.34 | 0.74 | Takeda (Eli Lily)[27] |
| REZULIN | 353328.20 | 0.26 | 1.00 | Parke Davis |

**Table 6.2**
**Brands in the Therapeutic Class of Statins (Baycol)**

| Brand | Yearly dollar sales (in 000) | Share of revenue | Accumulative share of revenue | Parent company |
|---|---|---|---|---|
| LIPITOR | 5709024.00 | 0.47 | 0.47 | Parke-Davis (Pfizer) |
| ZOCOR | 4038271.00 | 0.33 | 0.79 | Merck |
| PRAVACHOL | 1706670.00 | 0.14 | 0.93 | Bristol-Myers Squibb |
| BAYCOL | 259108.90 | 0.02 | 0.96 | Bayer |
| MEVACOR | 247292.80 | 0.02 | 0.98 | Merck |
| LESCOL | 232530.30 | 0.02 | 0.99 | Novartis |
| LESCOL XL | 53204.88 | 0.00 | 1.00 | Novartis |
| LOVASTATIN | 15954.97 | 0.00 | 1.00 | Generic drug |

**Modeling Effects of Drug Withdrawal on Sales and Marketing Effectiveness**

In this section, I model the spillover effects of drug withdrawal on competing brands. Two types of spillover effects, namely the spillover effects on the sales of competing brands, and the spillover effects on the marketing effectiveness of competing brands are examined using mixed effects models. The model specifications here are similar to the ones used in the preceding

[27] The company within the parentheses is a co-marketer for the drug with the manufacturer.

chapter and are fully described in model 9) in Chapter 4. The data used for modeling are organized by therapeutic class associated with each drug withdrawal.

**The Models**

Model 9) described in Chapter 4 specifies the mixed effects models used to fit the data in this section. Following the variance-covariance specification used in Chapter 5, the AR(1) structure was used to capture the autocorrelation in the error term. Table 6.3 and Table 6.4 summarize the descriptive information for the dataset of Rezulin's therapeutic class. The correlation matrix clearly indicates high correlation among all three marketing variables. Following the marketing variable selection guidelines discussed in the preceding chapter, *CON* was used as the only marketing variable in the model.

**Table 6.3**
**Simple Statistics for the Data Used for Rezulin's Class**

| Variable | N | Mean | Std. Dev | Sum | Min | Max |
|---|---|---|---|---|---|---|
| SMP | 89 | 269.05 | 129.28 | 23945.17 | 3.00 | 436.43 |
| JAD | 89 | 301.59 | 125.91 | 26841.32 | 0.00 | 452.90 |
| CON | 89 | 85.22 | 36.67 | 7584.91 | 2.00 | 135.95 |

**Table 6.4**
**Correlation Matrix for Marketing Variables (Rezulin)**

| Variable | SMP | JAD | CON |
|---|---|---|---|
| SMP | 1.00 | 0.98 | 0.99 |
| JAD | 0.98 | 1.00 | 0.98 |
| CON | 0.99 | 0.98 | 1.00 |

The descriptive information of the dataset associated with the Baycol withdrawal is summarized in Table 6.5 and Table 6.6. Correlation between *SMP* and *JAD* is greater than 0.7, and therefore only *CON* was used in fitting model 9) in Chapter 4[28].

**Table 6.5**
**Simple Statistics for the Data Used for Baycol's Class**

| Variable | N | Mean | Std. Dev | Sum | Min | Max |
|---|---|---|---|---|---|---|
| SMP | 383 | 440.40 | 273.89 | 168672.30 | 0.00 | 1279.73 |
| JAD | 388 | 317.72 | 270.99 | 123276.50 | 0.00 | 1144.74 |
| CON | 388 | 95.74 | 53.04 | 37145.32 | 0.00 | 192.81 |

**Table 6.6**
**Correlation Matrix for Marketing Variables (Baycol)**

| Variable | SMP | JAD | CON |
|---|---|---|---|
| SMP | 1.00 | 0.72 | 0.74 |
| JAD | 0.72 | 1.00 | 0.63 |
| CON | 0.74 | 0.63 | 1.00 |

**Results**

Table 6.7 and Table 6.9 summarize the model estimates for the Rezulin withdrawal and the Baycol withdrawal respectively. Estimates associated with time and time squared terms capture various shapes of sales curve at the brand level. Estimates associated with marketing variables indicate various levels of returns on marketing programs.

The key model estimates are those associated with *W*. Table 6.7 presents the model estimates for the Rezulin withdrawal; Table 6.9 presents the model estimates for the Baycol

[28] Models with *SMP* or *JAD* used as the marketing program measure produce results consistent with the model with *CON*.

withdrawal. The goodness-of-fit information for each model is summarized in Table 6.8 and Table 6.10 respectively.

The modeling exercises for these two withdrawals produced very similar results. Results from Table 6.7 and Table 6.9 provide evidence of significant positive spillover effects on the sales of competing brands, but significant negative spillover effects on the effectiveness of marketing programs of competing brands. These findings are expected from the conceptual framework. Replications of the modeling exercise are presented and discussed in Chapter 7.

**Table 6.7**
**Model Estimates for the Rezulin Withdrawal on Competing Brands**

| Effect | Brand | Estimate | t-value | p-value |
|---|---|---|---|---|
| Intercept | | 7.421 | 1.942 | 0.056 |
| brand | ACTOS | 5.169 | 1.353 | 0.180 |
| brand | AVANDIA | 0.000 | | |
| time*brand | ACTOS | -0.139 | -1.343 | 0.183 |
| time*brand | AVANDIA | 0.075 | 0.431 | 0.668 |
| time2*brand | ACTOS | 0.001 | 0.935 | 0.353 |
| time2*brand | AVANDIA | -0.001 | -0.399 | 0.691 |
| CON*brand | ACTOS | 0.081 | 7.574 | 0.000 |
| CON*brand | AVANDIA | 0.034 | 1.522 | 0.132 |
| C_CON | | -0.010 | -0.794 | 0.429 |
| **W*brand** | **ACTOS** | **1.365** | **4.475** | **0.000** |
| **W*brand** | **AVANDIA** | **1.890** | **4.335** | **0.000** |
| **W*CON** | | **-0.029** | **-4.231** | **0.000** |

**Table 6.8**
**Goodness-of-fit for the Model (Rezulin)**

| Measure | Value |
|---|---|
| -2 Log Likelihood | -98.36 |
| AIC (smaller is better) | -70.36 |
| AICC (smaller is better) | -64.69 |
| BIC (smaller is better) | -88.66 |

**Table 6.9**
**Model Estimates for the Baycol Withdrawal on Competing Brands**

| Effect | Brand | Estimate | t-value | p-value |
|---|---|---|---|---|
| Intercept | | 10.633 | 16.012 | 0.000 |
| brand | LESCOL | -0.797 | -1.579 | 0.117 |
| brand | LESCOL XL | -94.203 | -7.452 | 0.000 |
| brand | LIPITOR | -5.458 | -6.723 | 0.000 |
| brand | MEVACOR | 0.165 | 0.470 | 0.640 |
| brand | PRAVACHOL | -0.489 | -1.097 | 0.276 |
| brand | ZOCOR | 0.000 | | |
| time*brand | LESCOL | 0.042 | 1.717 | 0.089 |
| time*brand | LESCOL XL | 2.773 | 7.081 | 0.000 |
| time*brand | LIPITOR | -0.093 | -3.491 | 0.001 |
| time*brand | MEVACOR | 0.020 | 1.306 | 0.194 |
| time*brand | PRAVACHOL | -0.001 | -0.064 | 0.949 |
| time*brand | ZOCOR | -0.009 | -0.529 | 0.598 |
| time2*brand | LESCOL | -0.001 | -2.389 | 0.018 |
| time2*brand | LESCOL XL | -0.018 | -7.194 | 0.000 |
| time2*brand | LIPITOR | 0.001 | 3.162 | 0.002 |
| time2*brand | MEVACOR | -0.001 | -6.355 | 0.000 |
| time2*brand | PRAVACHOL | 0.000 | 0.394 | 0.695 |
| time2*brand | ZOCOR | 0.000 | 1.448 | 0.151 |
| CON*brand | LESCOL | -0.014 | -1.833 | 0.069 |
| CON*brand | LESCOL XL | -0.225 | -5.261 | 0.000 |
| CON*brand | LIPITOR | 0.054 | 5.539 | 0.000 |
| CON*brand | MEVACOR | -0.031 | -5.929 | 0.000 |
| CON*brand | PRAVACHOL | 0.003 | 0.676 | 0.501 |
| CON*brand | ZOCOR | 0.005 | 1.144 | 0.256 |
| C_ CON | | 0.004 | 0.912 | 0.363 |
| **W*brand** | **LESCOL** | **1.348** | **2.544** | **0.012** |
| **W*brand** | **LESCOL XL** | **1.257** | **4.937** | **0.000** |
| **W*brand** | **LIPITOR** | **3.287** | **2.538** | **0.012** |
| **W*brand** | **MEVACOR** | **0.438** | **3.790** | **0.000** |
| **W*brand** | **PRAVACHOL** | **2.255** | **2.644** | **0.009** |
| **W*brand** | **ZOCOR** | **2.710** | **2.641** | **0.009** |
| **W*CON** | | **-0.018** | **-2.522** | **0.013** |

**Table 6.10**
**Goodness-of-fit for the Model (Baycol)**

| Measure | Value |
|---|---|
| -2 Log Likelihood | -903.74 |
| AIC (smaller is better) | -835.74 |
| AICC (smaller is better) | -829.00 |
| BIC (smaller is better) | -842.82 |

**Summary of Findings**

The key findings from the modeling exercises of the Rezulin and Baycol withdrawal are summarized in Table 6.11. With some caveats, the modeling exercises have found evidence of positive spillover effects of drug withdrawal on the sales of competing brands and negative spillover effects on the marketing effectiveness of competing brands. The results from the two drug withdrawals studies are generally consistent. As discussed in the conceptual framework of the study, the positive spillover effects on the sales of competing brands are, in fact, the net outcomes of two counter-weighting effects, namely the competitive effects and the contagion effects. When the withdrawn brand is large and the market concentration is high, the competitive effects are dominant in that other competitors benefit from the drug withdrawal by taking up the market share left by the withdrawn brand.

For smaller drug withdrawals, the net effects of the competitive effects and contagion effects may be different. Several smaller drug withdrawals in the data are ready to replicate the findings of the spillover effects on competing brands. The results from these replications are presented in Chapter 7.

**Table 6.11**
**Summary of Findings on Competing Brands**

| Brand | Positive Impact on the Sales of Competing Brands | Negative Impact on the Marketing Effectiveness |
|---|---|---|
| Rezulin (25% of class revenue) | Yes | Yes |
| Baycol (2% of class revenue) | Yes | Yes |

**Discussion on Spillover Effects on Marketing Effectiveness**

The modeling exercises for the Rezulin and Baycol withdrawals have found evidence of the negative spillover effects on competitors' effectiveness of marketing programs. It appears that, after a drug withdrawal, the competing brands of this withdrawn drug suffer a reduction in the effectiveness of their marketing programs. One explanation for this finding is brand equity dilution. As discussed in Chapter 3, negative information furnished by a drug withdrawal may be deemed relevant in doctors' evaluation of the withdrawn drug's close competitors. The newly furnished negative information may add negative associations to the attitudes and beliefs that doctors hold toward these close competitors in the same therapeutic class. Negative changes in the attitudes and beliefs of these brands may result in brand equity dilution, which in turn reduce the marketing effectiveness.

Another possibility to explain these findings is the reallocation of marketing programs of competing brands in response to the drug withdrawal. Dramatic reallocation of marketing programs of close competitors may contribute to the reduction in the marketing effectiveness. For instance, competing brands may increase their marketing programs in order to compete for the market share left by the withdrawn drug. If the marketing programs increase at a speed much faster than the actual growth of sales, the effectiveness of marketing decreases. In other words,

competitors could over spend on their marketing programs without gaining expected returns in sales. In contrast, if competitors sharply reduce their marketing programs, such changes may be reflected as an increase in marketing effectiveness in terms of the returns on marketing programs. In sum, sharp reallocation in competitors' marketing programs after a drug withdrawal may confound the spillover effects of the drug withdrawal on these competing drugs' marketing effectiveness.

Table 6.12 examines the reallocation of *CON* at the therapeutic class level after the withdrawals of Rezulin and Baycol[29]. Neither of these two classes has had any dramatic changes in *CON* after the Rezulin or the Baycol withdrawal. The therapeutic class of Rezulin was relatively new and had a moderate increase in marketing programs. The class of Baycol, in contrast, has had a decrease in the marketing programs.

**Table 6.12**
**# of *CON* (in 000) Before and After the Drug Withdrawal at the Class Level**

| | # of *CON* per brand before the drug withdrawal | # of *CON* per brand after the drug withdrawal | Percentage change |
|---|---|---|---|
| Therapeutic Class of Rezulin | 42.89 | 50.03 | 16.65% |
| Therapeutic Class of Bayer | 42.75 | 40.54 | -5.17% |

Table 6.13 breaks down the similar analysis to the brand level. For the therapeutic class of Rezulin, both remaining brands increased their marketing programs moderately after the withdrawal of Rezulin. For the class of Baycol, remaining brands, in fact, changed their

[29] These figures of *CON* are calculated by using all the available data before and after a drug withdrawal.

marketing programs in different directions. Two mature brands, Mevacor and Lescol, reduced their marketing programs quite dramatically (more than 85% of change), which is not uncommon in the pharmaceutical industry. Other brands generally had moderate changes in their marketing programs. Overall, there appears to be little evidence that competitors dramatically adjust their marketing programs to take advantage of the failure of a withdrawn drug.

**Table 6.13**
**# of *CON* (in 000) Before and After the Drug Withdrawal at the Brand Level**

| | Competing Brands of Rezulin | | |
|---|---|---|---|
| | # of *CON* per brand before Rezulin withdrawal | # of *CON* per brand after Rezulin withdrawal | Percentage change |
| ACTOS | 33.13 | 41.97 | 26.71% |
| AVANDIA | 50.70 | 58.06 | 14.51% |
| | **Competing Brands of Baycol** | | |
| | # of *CON* per brand before Baycol withdrawal | # of *CON* per brand after Baycol withdrawal | Percentage change |
| LESCOL | 25.23 | 2.79 | -88.94% |
| LESCOL XL | 14.50 | 19.95 | 37.57% |
| LIPITOR | 86.55 | 99.11 | 14.51% |
| MEVACOR | 2.98 | 0.05 | -98.23% |
| PRAVACHOL | 47.28 | 34.21 | -27.65% |
| ZOCOR | 57.08 | 87.16 | 52.71% |

To visually inspect the changes in marketing programs, Figure 6.1 and 6.2 graphically illustrate changes in *CON* over time for each competitor of Rezulin. Figure 6.3 through 6.8 graphically describe changes in *CON* for the competitors of Baycol[30]. From the plots of the marketing program at the brand level, there is little consistent evidence that other competing

[30] These plots are based on the values of *CON*, which have been adjusted for the stock-of-goodwill effect. Such adjustment in effect smoothes the fluctuations shown in the original physician contact data.

brands in the same therapeutic class change their marketing programs specifically in response to the withdrawal of a failed competitor.

In sum, little evidence has been found that the competitors of a withdrawn drug usually underwent dramatic reallocation of marketing programs in response to the withdrawal. The possible confounding effects from the reallocation of marketing programs may not be very important. The reduction of marketing effectiveness observed in the model estimates may be largely attributed to the theory of the dilution of competing brands' equities.

**Chapter Summary**

In this chapter, I have presented results related to the impacts of drug withdrawal on competing brands. The Rezulin and Baycol withdrawals were examined closely in this chapter. Based on findings from these two drug withdrawals, conclusions were drawn.

Following the modeling exercises in Chapter 5, similar mixed effects models were used to model the impact of drug withdrawal on the sales of competing brands and on the marketing effectiveness of these brands. The results from mixed effects models find evidence of the positive spillover effects on the sales of competing brands in the therapeutic class, and of the negative effects on the marketing effectiveness of these competing brands. These findings are consistent across the two brands studied. Findings from mixed effects models are replicated using more drug withdrawals in Chapter 7.

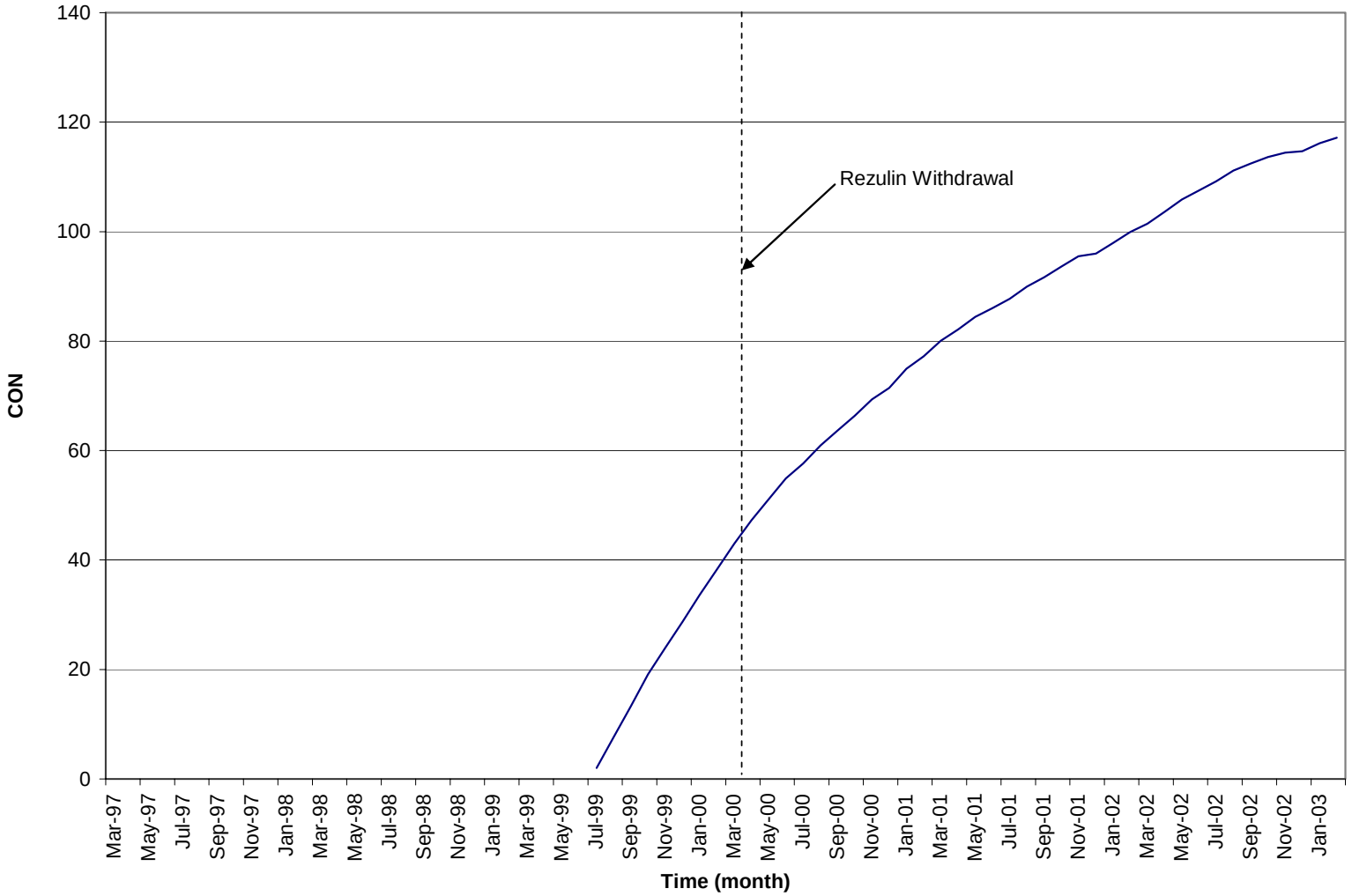


**Figure 6.1**
**Marketing Program Allocation of Actos (competitor of Rezulin)**

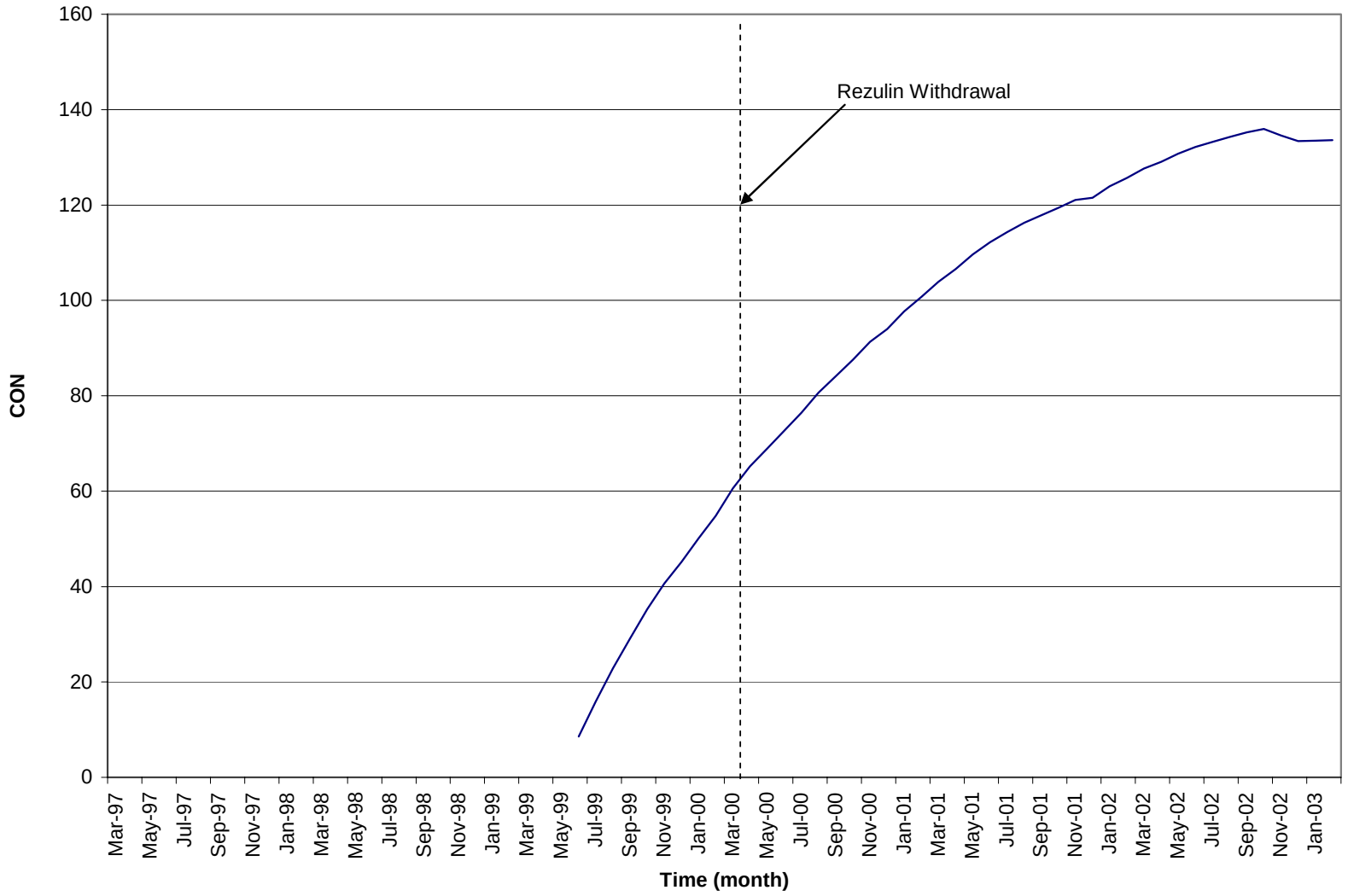


**Figure 6.2**
**Marketing Program Allocation of Avandia (competitor of Rezulin)**

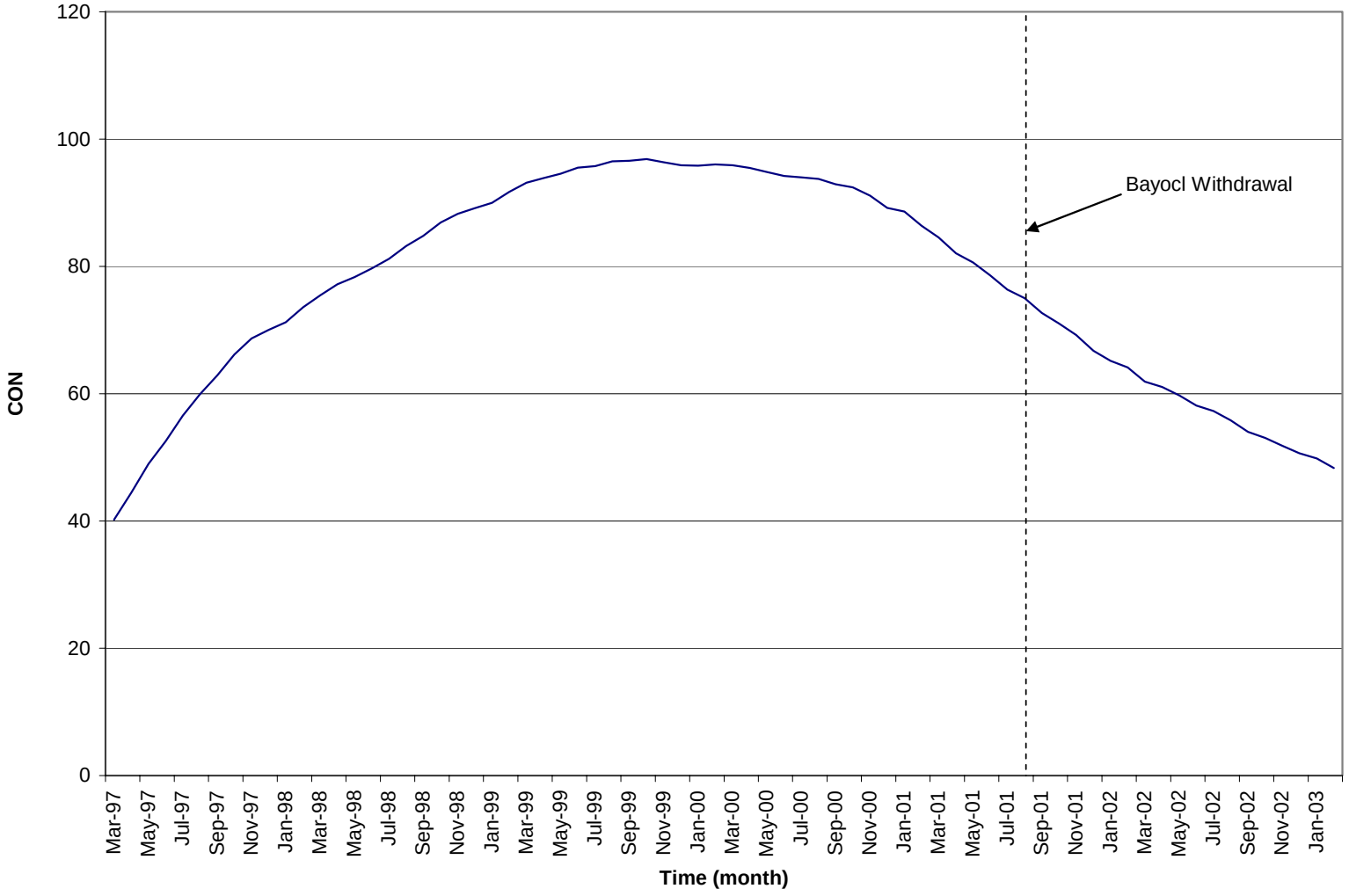


**Figure 6.3**
**Marketing Program Allocation of Lescol (competitor of Baycol)**

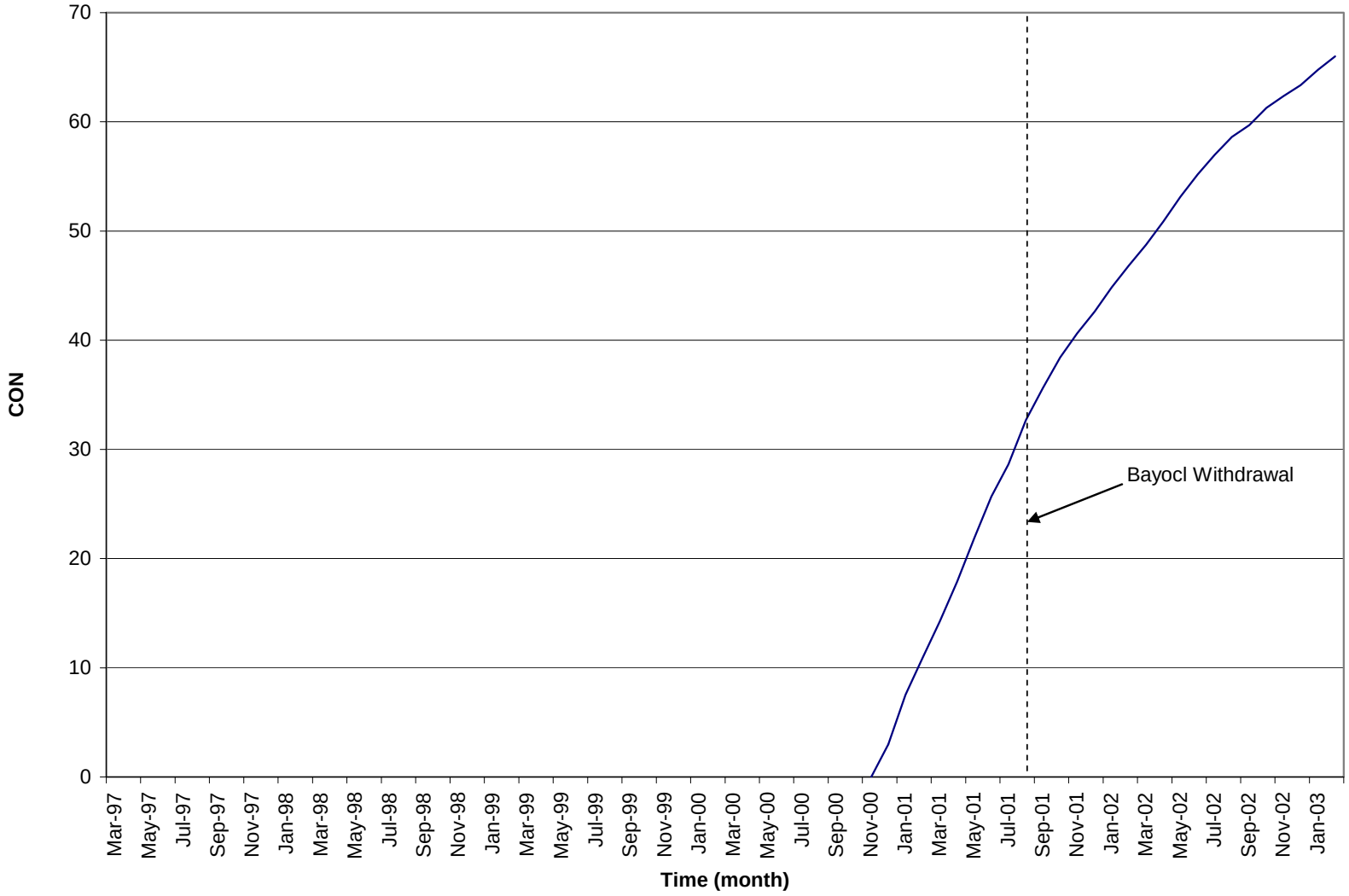


**Figure 6.4**
**Marketing Program Allocation of Lescol XL (competitor of Baycol)**

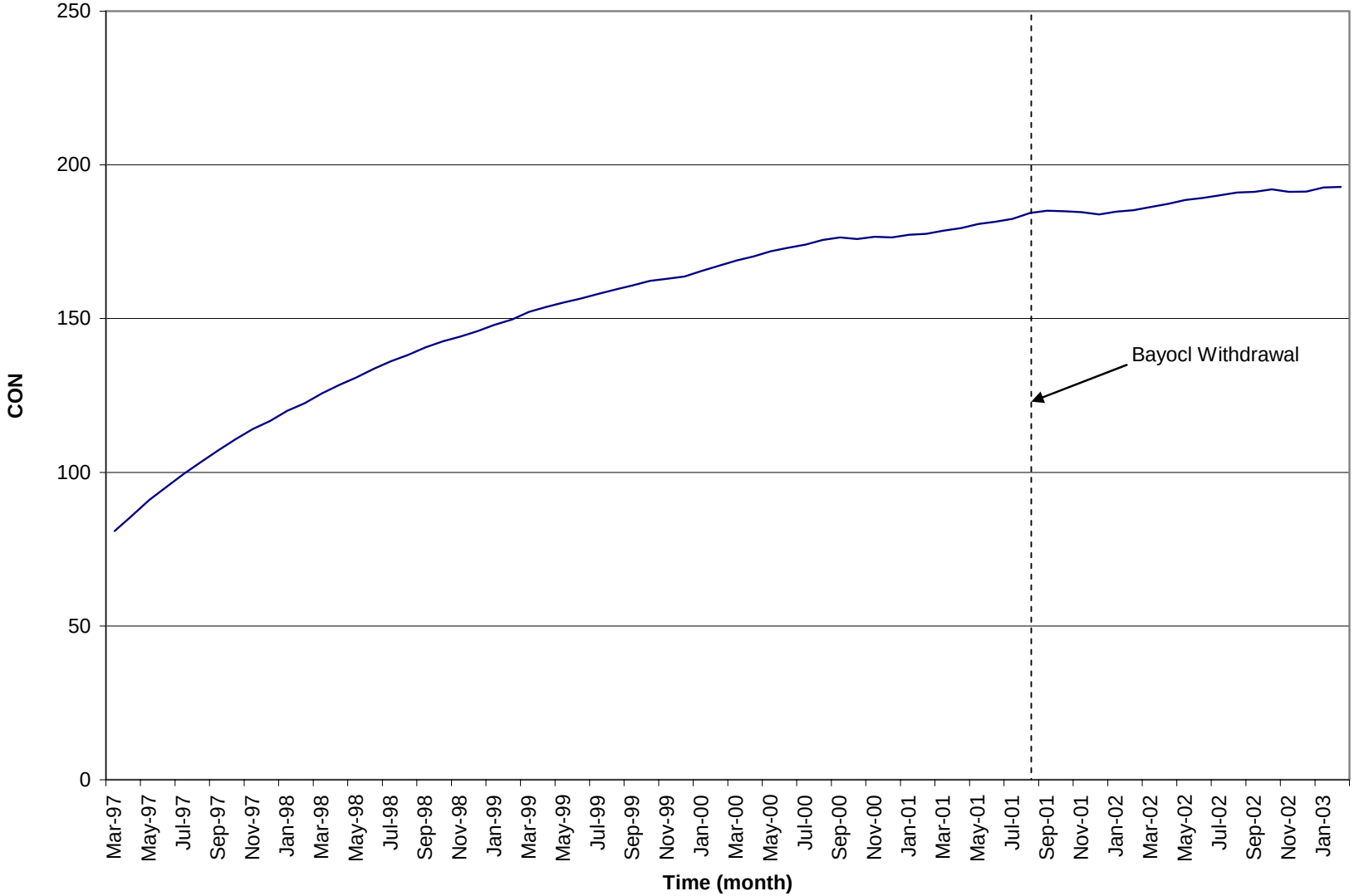


**Figure 6.5**
**Marketing Program Allocation of Lipitor (competitor of Baycol)**

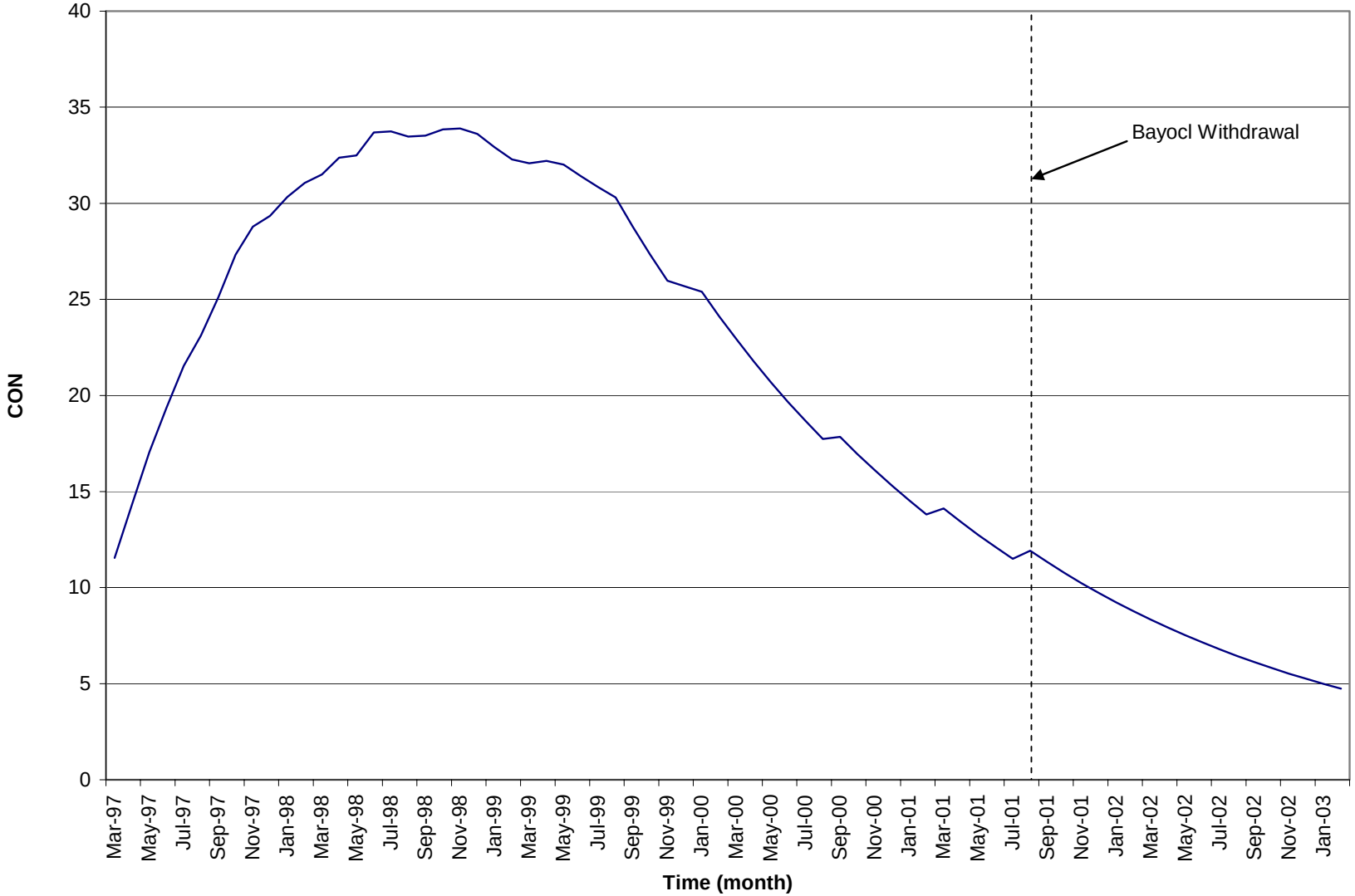


**Figure 6.6**
**Marketing Program Allocation of Mevacor (competitor of Baycol)**

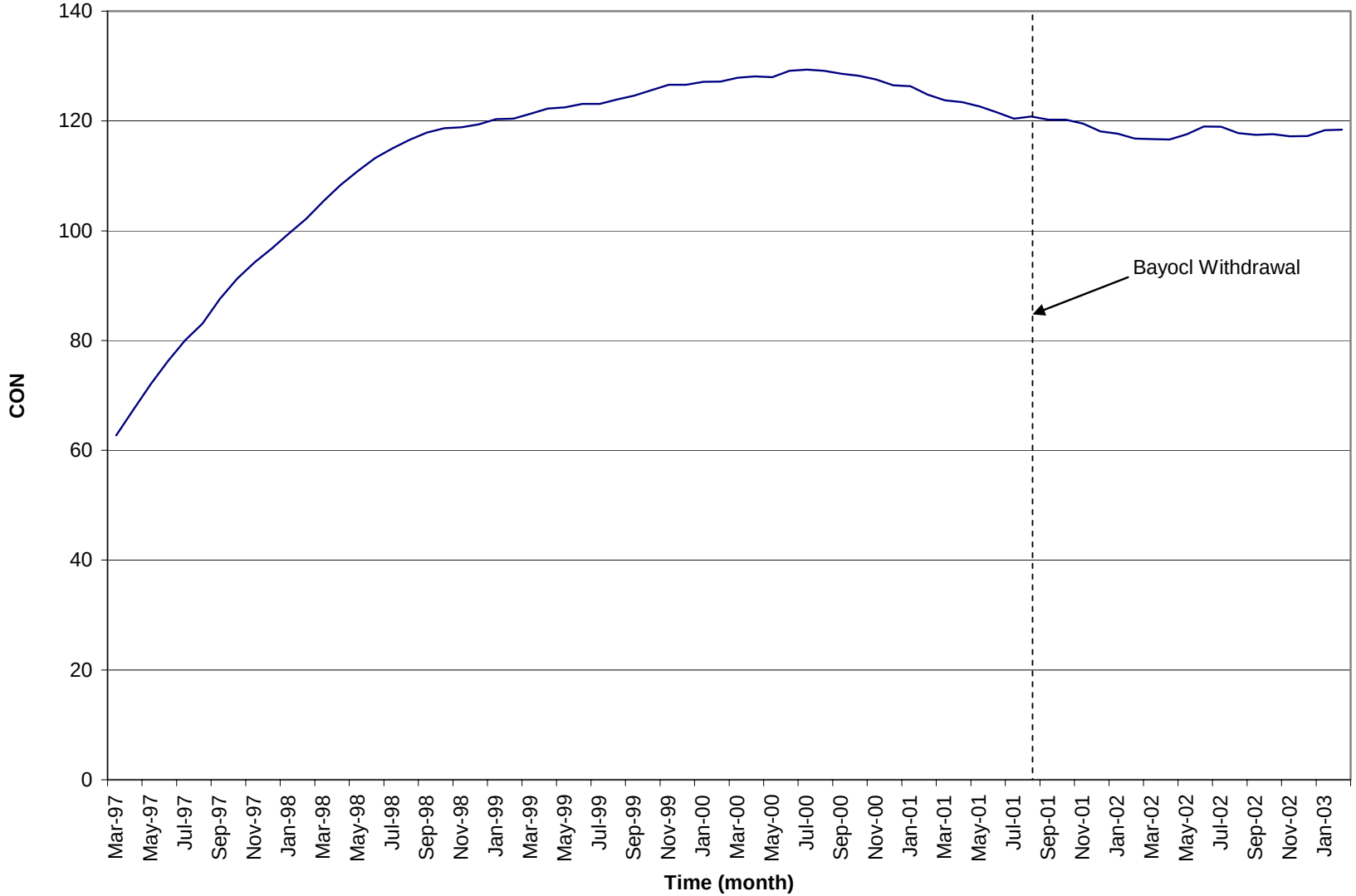


**Figure 6.7**
**Marketing Program Allocation of Pravachol (competitor of Baycol)**

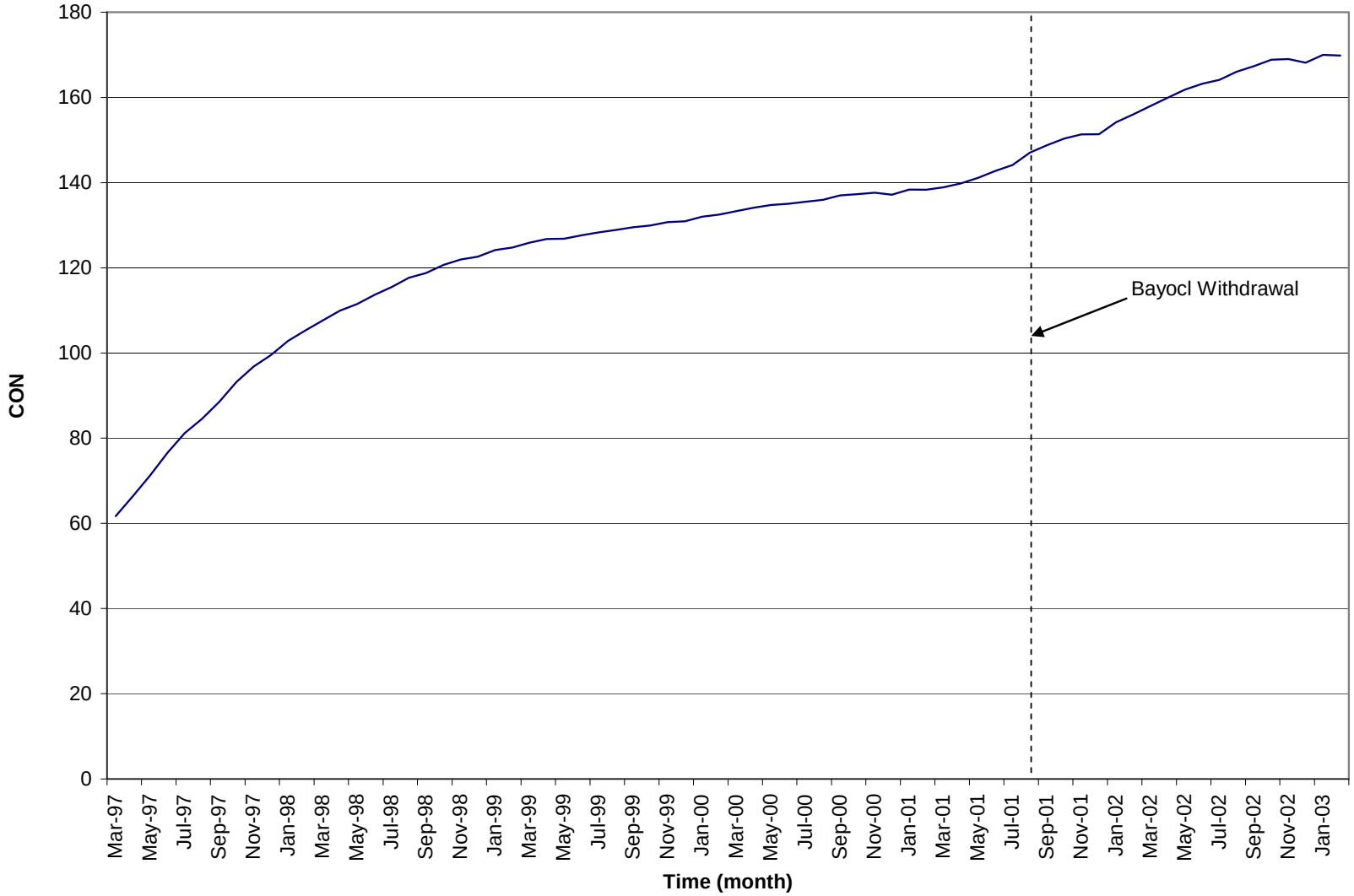


**Figure 6.8**
**Marketing Program Allocation of Zocor (competitor of Baycol)**

# CHAPTER 7

# FURTHER DISCUSSION OF THE FINDINGS

In Chapter 5 and Chapter 6, the results from mixed effects models show evidence of the spillover effects of drug withdrawal on parent companies as well as on competing brands. Specifically, the results indicate that a drug withdrawal has 1) negative effects on the sales of other brands in the parent company's portfolio, 2) negative effects on the marketing effectiveness of the parent company, 3) positive effects on the sales of the competing brands, and 4) negative effects on the marketing effectiveness of competing brands. There are, however, some differences in the results that merit further discussion. For example, the results from the Baycol withdrawal show evidence of negative spillover effects on the sales of other brands, but show no evidence of negative spillover effects on the marketing effectiveness of the parent company. The results from the Rezulin withdrawal, however, only show evidence of negative spillover effects on the marketing effectiveness. These differences in the results, though not completely unexpected, warrant the replication of the modeling exercise using additional drug withdrawals. In this chapter, several drug withdrawals that are appropriate for the modeling exercise are used to replicate the results found in Chapters 5 and 6.

This chapter is divided into several sections to better present the results. First, three additional brands (i.e., Seldane, Posicor, and Raplon) are used to replicate the results of the spillover effects of drug withdrawal on parent companies. Second, three brands (i.e., Posicor, Raplon, and Duract) are used to replicate the results of the spillover effects of drug withdrawal

on competing brands. The rationale for using these brands is discussed in the following section. Findings from the replication are summarized at the end of the chapter.

**Replication of the Modeling Exercise: the Impact on the Parent Company**

The Rezulin withdrawal and the Baycol withdrawal each represent the largest product failure of its respective parent company. These two brands, before their withdrawals, were large both in dollar sales and in their share of the parent company's revenue. Baycol, in particular, represented about 10% of the company revenue around the time of its withdrawal. Rezulin represented about 5%. Among drugs withdrawn between1996 and 2003, there are several withdrawn drugs that are appropriate for the modeling exercise, but these drugs generally are much smaller in size. Excluding sequential drug withdrawals that occurred to any one company, Table 7.1 summarizes the additional drug withdrawals to be modeled in this Chapter. The exclusion of sequential drug withdrawals in this study was discussed at the beginning of Chapter 5. In brief, sequential drug withdrawals involve the interaction effects of these withdrawals. Without prior knowledge of the possible interaction effects (e.g., diminishing interaction effects or intensifying effects[31]) and a good understanding of the persistence of spillover effects, this complication introduces undesirable complexities that may more appropriately be addressed in future research.

The following sections briefly introduce each of these drug withdrawals. Within each section, the parent company of the withdrawn brand is identified, and the largest brands from this company are described for their sizes and indicated uses. Consistent with the modeling exercise done in previous chapters, only the largest brands are used in model fitting. The descriptive

[31] Diminishing interaction effects can occur when customers are less surprised at a second product failure because of the belief that bad companies produce bad products. In contrast, intensifying interaction effects can occur when customers become more intolerant of the negativity accumulated over sequential product failures.

statistics for the data of these largest brands are presented in tables to aid better understanding of the data. The correlation matrix of marketing variables is also presented in tables to justify the selection of marketing variables. Due to high multicolinearity between the three marketing variables included in the data, not all the marketing variables can be used simultaneously. The correlation matrix guides the choice of the appropriate set of marketing variables. The guidelines pertaining to the marketing variable selection are discussed in detail in Chapter 5.

**Table 7.1**
**Brands Used in the Replication for the Spillover Effects on the Parent Company**

| Brand | Parent Company | Size of the Drug (relative to the firm) | Size of drug (yearly $ sales in 000) |
|---|---|---|---|
| Posicor | Roche | 1% | 26,457 |
| Seldane | Aventis | 0.70% | 12,222 |
| Raplon | Organon | 0.50% | 4,184 |

**Seldane Withdrawal**

Seldane was an antihistamine manufactured by Aventis. It is used to treat various symptoms of allergy. The drug was withdrawn from the market in 1998 due to its interactions with other drugs to cause serious heart problems.

In the model fitting, the 15 largest brands are included in order to represent over 90% of the company's revenue. But due to data missing in marketing variables, only 11 brands are in fact used in the model estimation. The correlation between *SMP* and *JAD* is less than 0.7, and thus the pair of SMP and *JAD* is used in the model fitting. The following tables provide in detail the information discussed above.

**Table 7.2**
**The Brand Portfolio of Aventis Pharmaceuticals (Seldane)**

| Brand | Yearly dollar sales[32] (in 000) | Share of revenue | Accumulative share of revenue | Indicated drug uses |
|---|---|---|---|---|
| ALLEGRA | 323937.90 | 0.19 | 0.19 | Antihistamine |
| LOVENOX | 261894.60 | 0.15 | 0.34 | Prevent blood clot forming |
| AZMACORT | 259198.30 | 0.15 | 0.49 | Asthma |
| DDAVP | 147848.90 | 0.09 | 0.58 | Increase urine concentration (used after surgery) |
| TAXOTERE | 106889.70 | 0.06 | 0.64 | Breast cancer |
| NASACORT | 78206.51 | 0.05 | 0.69 | Steroid, nasal stiffness |
| TRENTAL | 77188.31 | 0.04 | 0.73 | Improve blood circulation |
| AMARYL | 55840.76 | 0.03 | 0.76 | Diabetes |
| NASACORT AQ | 54343.45 | 0.03 | 0.79 | Steroid, nasal stiffness |
| CARAFATE | 50213.06 | 0.03 | 0.82 | Ulcers |
| ALLEGRA-D | 48363.94 | 0.03 | 0.85 | Nasal congestion caused by hay fever |
| DIABETA | 38810.66 | 0.02 | 0.87 | Diabetes |
| LASIX | 37837.06 | 0.02 | 0.90 | Reduce swelling & fluid retention; hypertension |
| LOZOL | 27790.16 | 0.02 | 0.91 | Reduce swelling & fluid retention; hypertension |
| RILUTEK | 25435.50 | 0.01 | 0.93 | Lou Gehrig's disease |
| SLO-BID | 23014.60 | 0.01 | 0.94 | Asthma |
| RIFADIN | 16125.79 | 0.01 | 0.95 | Tuberculosis |
| NILANDRON | 12864.21 | 0.01 | 0.96 | Prostate cancer |
| CLOMID | 9418.40 | 0.01 | 0.96 | Ovulatory stimulant |
| NORPRAMIN | 7236.08 | 0.00 | 0.97 | Antidepressant |

[32] Figures of yearly sales are calculated by using a timeframe of 6 months before and after the drug withdrawal. This configuration is intended to identify the largest brands around the time of drug withdrawal and is used consistently for other drug withdrawals.

**Table 7.3**
**Simple Statistics for the Data Used in the Seldane Withdrawal**

| Variable | N | Mean | Std. Dev | Sum | Min | Max |
|---|---|---|---|---|---|---|
| SMP | 1136.00 | 127.33 | 194.45 | 144642.40 | 0.00 | 1067.23 |
| JAD | 909.00 | 35.79 | 30.29 | 32534.79 | 0.00 | 115.21 |
| CON | 1352.00 | 29.14 | 37.47 | 39403.20 | 0.00 | 166.26 |

**Table 7.4**
**Correlation Matrix for Marketing Variables (Seldane)**

| Variable | SMP | JAD | CON |
|---|---|---|---|
| SMP | 1.00 | 0.59 | 0.88 |
| JAD | 0.59 | 1.00 | 0.71 |
| CON | 0.88 | 0.71 | 1.00 |

**Posicor Withdrawal**

Posicor is a hypertension drug manufactured by Hoffmann-La Roche (Roche) Pharmaceuticals. The drug was withdrawn from the market in 1998 due to its harmful interactions with other drugs and its side effect to reduce certain liver enzymes. In the model fitting, the largest 10 brands of Roche are included in order to represent about 90% of the company's revenue. But due to data missing in marketing variables, only 6 largest brands are in fact used in the model estimation. The correlation between *SMP* and *JAD* is less than 0.7, and thus the pair of SMP and *JAD* is used in the model fitting. The following tables provide in detail the information discussed above.

**Table 7.5**
**The Brand Portfolio of Roche Laboratories (Posicor)**

| Brand | Yearly dollar sales (in 000) | Share of revenue | Accumulative share of revenue | Indicated drug uses |
|---|---|---|---|---|
| ROCEPHIN | 573695.30 | 0.19 | 0.19 | Antibiotic |
| ACCUTANE | 404121.30 | 0.14 | 0.33 | Severe acne |
| VERSED | 346639.40 | 0.12 | 0.44 | Anesthetic |
| TICLID | 290877.90 | 0.10 | 0.54 | Prevent blood clustering |
| KYTRIL | 253277.30 | 0.08 | 0.63 | Prevent nausea after chemotherapy |
| CELLCEPT | 149942.70 | 0.05 | 0.68 | Immunosuppressive agents (transplant) |
| CYTOVENE | 99093.35 | 0.03 | 0.71 | Immune system deficiency |
| KLONOPIN | 91528.19 | 0.03 | 0.74 | Antidepressant, seizures |
| FORTOVASE | 84492.81 | 0.03 | 0.77 | HIV |
| INVIRASE | 78836.96 | 0.03 | 0.80 | HIV |

**Table 7.6**
**Simple Statistics for the Data Used in the Posicor Withdrawal**

| Variable | N | Mean | Std. Dev | Sum | Min | Max |
|---|---|---|---|---|---|---|
| SMP | 432.00 | 26.30 | 41.71 | 11362.47 | 0.00 | 155.96 |
| JAD | 698.00 | 27.00 | 21.67 | 18843.51 | 0.00 | 89.98 |
| CON | 707.00 | 14.69 | 20.93 | 10382.63 | 0.00 | 79.50 |

**Table 7.7**
**Correlation Matrix for Marketing Variables (Posicor)**

| Variable | SMP | JAD | CON |
|---|---|---|---|
| SMP | 1.00 | 0.09 | 0.48 |
| JAD | 0.09 | 1.00 | 0.78 |
| CON | 0.48 | 0.78 | 1.00 |

**Raplon Withdrawal**

Raplon is a muscle relaxant manufactured by Organon (a division of Akzo Nobel). The drug was withdrawn from the market in 2001 due to its sometimes fatal damages to muscle. In the model fitting, the largest 5 brands of Organon are included in order to represent over 90% of the company's revenue. But due to data missing in marketing variables, only 4 brands are in fact used in the model estimation. The correlation between *SMP* and *JAD* is less than 0.7, and thus the pair of SMP and *JAD* is used in the model fitting. The following tables provide in detail the information discussed above.

**Table 7.8**
**Brand Portfolio of Organon (Raplon)**

| Brand | Yearly dollar sales (in 000) | Share of revenue | Accumulative share of revenue | Indicated drug uses |
|---|---|---|---|---|
| REMERON | 400658.10 | 0.44 | 0.44 | Antidepressant |
| FOLLISTIM | 129652.10 | 0.14 | 0.59 | Hormone, female fertility |
| ZEMURON | 116386.10 | 0.13 | 0.72 | Muscle relaxant |
| MIRCETTE-28 | 112596.00 | 0.12 | 0.84 | Oral contraceptive |
| DESOGEN-28 | 64359.60 | 0.07 | 0.91 | Oral contraceptive |
| REMERON SOLTAB | 22847.25 | 0.03 | 0.94 | Antidepressant |
| FOLLISTIM/ANTAGON | 18194.88 | 0.02 | 0.96 | Hormone, female |
| ORGARAN | 8837.75 | 0.01 | 0.97 | Prevent blood clots |
| DECA-DURABOLIN | 5616.23 | 0.01 | 0.98 | Hormone, male, build injured tissues |
| RAPLON | 4184.51 | 0.00 | 0.98 | Muscle relaxant |

**Table 7.9**
**Simple Statistics for the Data Used in the Raplon Withdrawal**

| Variable | N | Mean | Std. Dev | Sum | Min | Max |
|---|---|---|---|---|---|---|
| SMP | 255.00 | 115.07 | 71.45 | 29343.01 | 0.00 | 209.12 |
| JAD | 324.00 | 23.71 | 14.28 | 7682.13 | 0.00 | 64.27 |
| CON | 418.00 | 28.34 | 23.62 | 11847.83 | 0.00 | 71.72 |

**Table 7.10**
**Correlation Matrix for Marketing Variables (Raplon)**

| Variable | SMP | JAD | CON |
|---|---|---|---|
| SMP | 1.00 | 0.39 | 0.92 |
| JAD | 0.39 | 1.00 | 0.58 |
| CON | 0.92 | 0.58 | 1.00 |

**Summary of the Results on the Spillover Effects on Parent Companies**

Table 7.11 summarizes the model estimates for all three drug withdrawals (i.e., Seldane, Posicor and Raplon) examined in this section. The fixed effects models used here are the same as the ones used to examine the Rezulin and Baycol withdrawals in Chapter 5. Similar to the model estimates in Chapters 5 and 6, the key interest in these estimates are those associated with *W*. These estimates are highlighted in bold font.

With some caveats, the results from modeling these additional drug withdrawals indicate evidence of significant spillover effects on the effectiveness of marketing programs of parent companies. The results, however, find no evidence of negative spillover effects on the sales of other brands in parent companies' portfolio. Specifically, 2 out of 3 drug withdrawals studied

showed a significant drop in the effectiveness of *SMP*. None of the drug withdrawals studied, however, found evidence of negative spillover effects on the sales of other brands of the parent company. Model estimates associated with negative spillover effects on marketing effectiveness are generally consistent when different sets of brands (e.g., more brands or fewer brands) are used to fit the model. These findings are summarized in Table 7.12, and are discussed in detail next.

In comparison with the findings from the Rezulin and Baycol withdrawals, the results in Table 7.12 are more consistent with the results from the Rezulin withdrawal in that the spillover effects are reflected on the marketing effectiveness, but not on the sales of other brands of the parent company. As discussed earlier in Chapters 3 and 5, these results may not be unexpected. Withdrawals of larger brands appear to have direct impacts on the sales of other brands in the company whereas withdrawals of smaller brands appear to have indirect impacts on the effectiveness of marketing programs. In the data complied for this study, there is no large drug withdrawal that can be used to replicate the findings of the Baycol withdrawal. This is a limitation of this study that may be addressed in future research.

**Table 7.11**
**Model Estimates for Effect of Drug Withdrawals on Parent Companies**

| | Seldane | | | Posicor | | | Raplon | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Effect | brand | Estimate | p-value | brand | Estimate | p-value | brand | Estimate | p-value | |
| Intercept | | 8.802 | 0.000 | | 4.549 | 0.005 | | 14.483 | | 0.000 |
| brand | ALLEGRA | -3.812 | 0.001 | ACCUTANE | 4.687 | 0.001 | DESOGEN-28 | -2.574 | | 0.194 |
| brand | ALLEGRA-D | -2.006 | 0.040 | INVIRASE | 5.631 | 0.000 | FOLLISTIM | -5.095 | | 0.033 |
| brand | AMARYL | -3.482 | 0.000 | KLONOPIN | 4.755 | 0.001 | MIRCETTE-28 | -8.320 | | 0.002 |
| brand | AZMACORT | -0.508 | 0.194 | KYTRIL | 5.141 | 0.001 | REMERON | 0.000 | | |
| brand | CARAFATE | -1.268 | 0.300 | ROCEPHIN | 1.087 | 0.141 | | | | |
| brand | DDAVP | 0.246 | 0.609 | TICLID | 0.000 | | | | | |
| brand | LOVENOX | 0.040 | 0.945 | | | | | | | |
| brand | NASACORT | -1.608 | 0.000 | | | | | | | |
| brand | NASACORT AQ | -2.488 | 0.000 | | | | | | | |
| brand | NILANDRON | -2.662 | 0.000 | | | | | | | |
| brand | TRENTAL | 0.000 | | | | | | | | |
| time*brand | ALLEGRA | 0.040 | 0.002 | ACCUTANE | 0.048 | 0.000 | DESOGEN-28 | -0.049 | | 0.017 |
| time*brand | ALLEGRA-D | 0.115 | 0.000 | INVIRASE | -0.092 | 0.000 | FOLLISTIM | 0.048 | | 0.003 |
| time*brand | AMARYL | 0.049 | 0.000 | KLONOPIN | -0.052 | 0.000 | MIRCETTE-28 | 0.152 | | 0.006 |
| time*brand | AZMACORT | -0.001 | 0.935 | KYTRIL | 0.007 | 0.581 | REMERON | -0.081 | | 0.163 |
| time*brand | CARAFATE | -0.039 | 0.138 | ROCEPHIN | 0.055 | 0.299 | | | | |
| time*brand | DDAVP | 0.000 | 0.974 | TICLID | -0.069 | 0.007 | | | | |
| time*brand | LOVENOX | 0.061 | 0.000 | | | | | | | |
| time*brand | NASACORT | -0.007 | 0.510 | | | | | | | |
| time*brand | NASACORT AQ | 0.033 | 0.001 | | | | | | | |
| time*brand | NILANDRON | 0.009 | 0.339 | | | | | | | |
| time*brand | TRENTAL | -0.063 | 0.000 | | | | | | | |
| time2*brand | ALLEGRA | 0.000 | 0.292 | ACCUTANE | 0.000 | 0.000 | DESOGEN-28 | 0.000 | | 0.254 |
| time2*brand | ALLEGRA-D | -0.001 | 0.000 | INVIRASE | 0.001 | 0.000 | FOLLISTIM | -0.001 | | 0.001 |
| time2*brand | AMARYL | 0.000 | 0.009 | KLONOPIN | 0.000 | 0.001 | MIRCETTE-28 | -0.001 | | 0.001 |
| time2*brand | AZMACORT | 0.000 | 0.472 | KYTRIL | 0.000 | 0.078 | REMERON | 0.001 | | 0.118 |
| time2*brand | CARAFATE | 0.001 | 0.027 | ROCEPHIN | 0.000 | 0.412 | | | | |
| time2*brand | DDAVP | 0.000 | 0.995 | TICLID | 0.000 | 0.119 | | | | |
| time2*brand | LOVENOX | -0.001 | 0.000 | | | | | | | |
| time2*brand | NASACORT | 0.000 | 0.835 | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| time2*brand | NASACORT AQ | 0.000 | 0.295 | | | | | | |
| time2*brand | NILANDRON | 0.000 | 0.124 | | | | | | |
| time2*brand | TRENTAL | 0.000 | 0.013 | | | | | | |
| season*brand | ALLEGRA | 0.136 | 0.000 | ACCUTANE | 0.149 | 0.000 | | | |
| season*brand | ALLEGRA-D | 0.000 | | INVIRASE | 0.000 | | | | |
| season*brand | AMARYL | 0.000 | | KLONOPIN | 0.000 | | | | |
| season*brand | AZMACORT | 0.029 | 0.457 | KYTRIL | 0.000 | | | | |
| season*brand | CARAFATE | 0.000 | | ROCEPHIN | 0.162 | 0.000 | | | |
| season*brand | DDAVP | 0.000 | | TICLID | 0.000 | | | | |
| season*brand | LOVENOX | 0.000 | | | | | | | |
| season*brand | NASACORT | 0.071 | 0.010 | | | | | | |
| season*brand | NASACORT AQ | 0.024 | 0.382 | | | | | | |
| season*brand | NILANDRON | 0.000 | | | | | | | |
| season*brand | TRENTAL | 0.000 | | | | | | | |
| SMP | | 0.006 | 0.034 | | 0.034 | 0.000 | | -0.004 | 0.550 |
| JAD | | 0.004 | 0.430 | | 0.001 | 0.905 | | 0.012 | 0.139 |
| C_SMP | | 0.000 | 0.449 | | 0.001 | 0.108 | | -0.003 | 0.010 |
| C_JAD | | 0.003 | 0.237 | | 0.002 | 0.484 | | 0.005 | 0.247 |
| **W*brand** | **ALLEGRA** | **2.876** | **0.048** | **ACCUTANE** | **-0.081** | **0.665** | **DESOGEN-28** | **-1.763** | **0.139** |
| **W*brand** | **ALLEGRA-D** | **-0.594** | **0.000** | **INVIRASE** | **-0.070** | **0.555** | **FOLLISTIM** | **0.005** | **0.992** |
| **W*brand** | **AMARYL** | **1.210** | **0.045** | **KLONOPIN** | **0.085** | **0.688** | **MIRCETTE-28** | **-1.788** | **0.137** |
| **W*brand** | **AZMACORT** | **0.948** | **0.069** | **KYTRIL** | **0.051** | **0.820** | **REMERON** | **-2.284** | **0.171** |
| **W*brand** | **CARAFATE** | **0.488** | **0.036** | **ROCEPHIN** | **1.200** | **0.047** | | | |
| **W*brand** | **DDAVP** | **0.170** | **0.228** | **TICLID** | **3.967** | **0.000** | | | |
| **W*brand** | **LOVENOX** | **-0.240** | **0.422** | | | | | | |
| **W*brand** | **NASACORT** | **1.056** | **0.039** | | | | | | |
| **W*brand** | **NASACORT AQ** | **0.753** | **0.209** | | | | | | |
| **W*brand** | **NILANDRON** | **0.367** | **0.047** | | | | | | |
| **W*brand** | **TRENTAL** | **0.592** | **0.145** | | | | | | |
| **W*SMP** | | **-0.006** | **0.069** | | **-0.026** | **0.000** | | **0.012** | **0.139** |
| **W*JAD** | | **0.003** | **0.660** | | **0.000** | **0.965** | | **0.001** | **0.962** |

**Table 7.12**
**Summary of Findings of Spillover Effects on Parent Companies**

| Brand | Negative Impact on the Sales of Other Brands | Negative Impact on the Marketing Effectiveness |
|---|---|---|
| Seldane (1% of company revenue) | No | Yes |
| Posicor (0.7% of company revenue) | No | Yes |
| Raplon (0.5% of company revenue) | No | No |

Notice that in Table 7.11, some brands of withdrawing companies appear to have positive changes in their sales after drug withdrawals. These positive changes may have little to do with drug withdrawals. Instead, factors that are not controlled by the modeling exercise may have caused the positive changes in sales. For example, two situations that are unrelated to drug withdrawal may cause the positive estimates of sales after a drug withdrawal. When one blockbuster drug grows strongly at an accelerated rate, such a pattern may be reflected in model estimates as positive changes after the withdrawal. Alternatively, when the decline in sales of a drug flattens out quickly, such a pattern can also be reflected in model estimates as positive changes after the withdrawal. In sum, without a good conceptual understanding that relates these positive changes in sales to drug withdrawals, interpretation of these positive estimates may not be meaningful. These positive estimates of sales after drug withdrawals simply provide no evidence of the negative spillover effects of drug withdrawal on the sales of other brands.

Following the same logic, only when all or most brands consistently show a decrease in sales around the time of drug withdrawal, may there be evidence for the negative spillover effects of drug withdrawal on the sales of other brands. But again, results from mixed effects models provide only evidence, not conclusions. Instead, conclusions are drawn in light of theories and conceptual understandings of the phenomenon, which are discussed in Chapter 3.

**Replication of Modeling: the Impact on Competing Brands**

Similar to the choices made with regard to sequential withdrawals, only single drug withdrawals within a therapeutic class are included in the replication of the modeling exercise. This qualification eliminated two antihistamines for the replication. In addition, two more drug withdrawals are removed from the replication because of the absence of competitors in the therapeutic class. For instance, Lotronex is the only drug in the therapeutic class, called 5HT3 receptor antagonists, which are used to treat a rare disease of irritable bowel movement in women. After its withdrawal, there were no approved drugs in that therapeutic class. Table 7.13 summarizes additional drug withdrawals appropriate to use in the replication. Each of these drug withdrawals is introduced briefly in the following sections.

The description of each drug withdrawal includes 1) the largest brands in the therapeutic class within which the drug withdrawal occurs, 2) descriptive statistics for the data of these largest brands used to fit the model, and 3) the correlation matrix of marketing variables.

**Table 7.13**
**Brands Used in Replication for the Spillover Effects on Competing Brands**

| Brand | Parent Company | Size of the Drug (relative to the therapeutic class) | Size of drug (yearly $ sales in 000) |
|---|---|---|---|
| Posicor | Roche | 0.12% | 26,457 |
| Raplon | Organon (Azko Nobel) | 2% | 4,184 |
| Duract | Wyeth | 3% | 41,273 |

**Posicor Withdrawal**

Before its withdrawal in 1998, Posicor belonged to a therapeutic class called calcium channel blockers. Calcium channel blocking agents affect the movement of calcium into the cells

of the heart and blood vessels. As a result, they relax blood vessels and increase the supply of blood and oxygen to the heart while reducing its workload. The largest 10 brands in the therapeutic class are included in the model fitting. They represent about 90% of the class share. The correlation between *SMP* and *JAD* is greater than 0.7. Therefore, *CON* is used as the single marketing program measure in the model. The following tables provide detailed information discussed above.

**Table 7.14**
**Brands in the Therapeutic Class of Calcium Channel Blocker (Posicor)**

| Brand | Yearly dollar sales (in 000) | Share of revenue | Accumulative share of revenue | Parent company |
|---|---|---|---|---|
| NORVASC | 1360717.00 | 0.28 | 0.28 | Pfizer |
| CARDIZEM CD | 904657.60 | 0.19 | 0.47 | Biovail |
| PROCARDIA XL | 822683.30 | 0.17 | 0.64 | Pfizer |
| ADALAT CC | 421976.00 | 0.09 | 0.73 | Bayer |
| PLENDIL | 159448.80 | 0.03 | 0.76 | AstraZeneca |
| CALAN SR | 158747.80 | 0.03 | 0.79 | Pharmacia |
| TIAZAC | 137925.90 | 0.03 | 0.82 | Forest Laboratories |
| VERELAN | 125456.30 | 0.03 | 0.85 | Schwarz Pharmaceuticals |
| DILACOR XR | 116693.70 | 0.02 | 0.87 | Watson Laboratories |
| COVERA-HS | 96381.69 | 0.02 | 0.89 | Pharmacia |

**Table 7.15**
**Simple Statistics for the Data Used for Posicor's Class**

| Variable | N | Mean | Std. Dev | Sum | Min | Max |
|---|---|---|---|---|---|---|
| SMP | 710.00 | 239.58 | 229.46 | 170102.50 | 1.01 | 1178.50 |
| JAD | 720.00 | 236.26 | 260.29 | 170108.10 | 0.00 | 999.97 |
| CON | 720.00 | 42.84 | 38.42 | 30845.26 | 0.00 | 156.80 |

**Table 7.16**
**Correlation Matrix for Marketing Variables (Posicor)**

| Variable | SMP | JAD | CON |
|---|---|---|---|
| SMP | 1.00 | 0.87 | 0.85 |
| JAD | 0.87 | 1.00 | 0.75 |
| CON | 0.85 | 0.75 | 1.00 |

**Raplon Withdrawal**

Before its withdrawal in 2001, Raplon belonged to a therapeutic class, called nondepolarizing neuromuscular blocking agents, which are used during surgery to relax muscles or in patients who are on mechanical ventilation. In the model fitting, the largest 5 brands in the therapeutic class are included. They represent over 90% of the class share. Due to data missing in marketing variables, only 4 brands are actually used in model estimation. The correlation between *SMP* and *JAD* is greater than 0.7. Therefore, *CON* is used as a single marketing program measure in the model. The following tables provide information discussed above.

**Table 7.17**
**Brands in the Class of Nondepolarizing Neuromuscular Blocker (Raplon)**

| Brand | Yearly dollar sales (in 000) | Share of revenue | Accumulative share of revenue | Parent company |
|---|---|---|---|---|
| ZEMURON | 116386.10 | 0.56 | 0.56 | Organon (Akzo Nobel) |
| NIMBEX | 33653.63 | 0.16 | 0.73 | Abbott |
| VECURONIUM BROMIDE | 17924.25 | 0.09 | 0.81 | Generic drug (multiple manufacturers ) |
| MIVACRON | 14811.20 | 0.07 | 0.88 | Abbott |
| ATRACURIUM BESYLAT | 6300.80 | 0.03 | 0.92 | Generic drug (multiple manufacturers ) |
| RAPLON | 4184.51 | 0.02 | 0.94 | Organon (Akzo Nobel) |

**Table 7.18**
**Simple Statistics for the Data Used for Raplon's Class**

| Variable | N | Mean | Std. Dev | Sum | Min | Max |
|---|---|---|---|---|---|---|
| SMP | 71.00 | 0.51 | 0.56 | 36.41 | 0.00 | 2.00 |
| JAD | 288.00 | 24.51 | 34.61 | 7058.91 | 0.00 | 96.43 |
| CON | 288.00 | 13.84 | 14.69 | 3985.16 | 0.00 | 43.40 |

**Table 7.19**
**Correlation Matrix for Marketing Variables (Raplon)**

| Variable | SMP | JAD | CON |
|---|---|---|---|
| SMP | 1.00 | | -0.13 |
| JAD | | 1.00 | 0.94 |
| CON | -0.13 | 0.94 | 1.00 |

**Duract Withdrawal**

Before its withdrawal in 1998, Duract belonged to a therapeutic class known as nonsteroidal anti-inflammatory drugs (also known as NSAIDs), which are used to relieve some symptoms caused by arthritis, such as inflammation, swelling, stiffness, and joint pain. It was a widely used analgesic. The largest 10 brands in the therapeutic class are included in the model fitting. They represent about 90% of the class share. Due to data missing in marketing variables, only 9 brands are in fact used in model estimation. The correlation between *SMP* and *JAD* is greater than 0.7. Therefore, *CON* is used as the single marketing program measure in the model. The following tables provide detailed information discussed above.

**Table 7.20**
**Brands in the Therapeutic Class of NSAIDs (Duract)**

| Brand | Yearly dollar sales (in 000) | Share of revenue | Accumulative share of revenue | Parent company |
|---|---|---|---|---|
| ULTRAM | 447917.50 | 0.35 | 0.35 | McNeil |
| ADVIL | 211379.30 | 0.17 | 0.52 | Wyeth |
| STADOL NS | 102543.90 | 0.08 | 0.60 | Bristol-Myers Squibb |
| CATAFLAM | 90057.07 | 0.07 | 0.67 | Novartis |
| ALEVE | 58181.34 | 0.05 | 0.72 | Bayer |
| IBUPROFEN | 56651.77 | 0.04 | 0.76 | Generic drug (multiple manufacturers ) |
| DURACT | 41273.99 | 0.03 | 0.79 | Wyeth |
| NAPROXEN SODIUM | 41048.62 | 0.03 | 0.83 | Generic drug (multiple manufacturers ) |
| MOTRIN CHILDS | 40682.30 | 0.03 | 0.86 | McNeil |
| MOTRIN IB | 38855.69 | 0.03 | 0.89 | McNeil |

**Table 7.21**
**Simple Statistics for the Data Used for Duract's Class**

| Variable | N | Mean | Std. Dev | Sum | Min | Max |
|---|---|---|---|---|---|---|
| SMP | 426.00 | 347.68 | 194.50 | 148112.40 | 0.00 | 769.90 |
| JAD | 576.00 | 109.41 | 185.39 | 63021.47 | 0.00 | 1103.26 |
| CON | 576.00 | 27.89 | 24.88 | 16066.25 | 0.00 | 99.50 |

**Table 7.22**
**Correlation Matrix for Marketing Variables (Duract)**

| Variable | SMP | JAD | CON |
|---|---|---|---|
| SMP | 1.00 | 0.64 | 0.78 |
| JAD | 0.64 | 1.00 | 0.63 |
| CON | 0.78 | 0.63 | 1.00 |

**Summary of the Results on the Spillover Effects on Competing Brands**

This section is intended to examine the spillover effects of drug withdrawal on competing brands. Table 7.23 summarizes the model estimates for all three drug withdrawals (i.e., Seldane, Posicor and Raplon). The fixed effects models used with these drug withdrawals are the same as the ones used in Chapter 6. The key interest in model estimates are those associated with *W*. These key estimates are highlighted in bold font.

The results from the modeling exercise indicate evidence of significant negative spillover effects on the sales of competing brands. The results, however, find no evidence of negative spillover effects on the marketing effectiveness of competing brands. Specifically, the results of all 3 drug withdrawals show negative spillover effects on the sales of competing brands, but show no negative spillover effects on the marketing effectiveness of competing brands. The findings from the replication are summarized in Table 7.24.

In comparison with the findings from the Rezulin and Baycol withdrawals, the results in Table 7.24 are not consistent in the spillover effects on the sales of competing brands. The modeling results from the Rezulin and Baycol withdrawals suggest positive spillover effects on the sales of competing brands. The results from the replication using smaller drug withdrawals, however, suggest negative spillover effects on the sales of competing brands. This inconsistency in model estimates is, in fact, expected. According to the conceptual framework in Chapter 3, the spillover effects of drug withdrawal on competing brands are the net effects of two counter-weighting effects, namely the competitive effects and the contagion effects. When the withdrawal brand is large, the competitive effects are dominant in that the competitors benefit from the withdrawal of a drug by taking up the market space left by the withdrawn drug. When the withdrawn drug is small, however, there is not much market space to be taken by competitors,

and the contagion effects become dominant. Contagion effects occur when competing brands suffer along with the withdrawn drug due to the negative information furnished by the failure of the withdrawn drug. When the negative information becomes relevant and is utilized in doctors' evaluation of other drugs in the therapeutic class, the contagion effects, or the clouding effects, may happen. The negative information produced by a withdrawn drug can be quite pertinent to the evaluation of products in the same therapeutic class because members in a therapeutic class typically share a similar mechanism of actions. Such contagion effects are reflected in the model estimates as the deductions in the sales of competing brands in one therapeutic class.

The contagion effects were also observed in the recent Vioxx withdrawal. On the day of Vioxx's withdrawal announcement, Pfizer, the manufacturer of Vioxx's direct competitor Celebrex, enjoyed an increase of 1.4% in its stock price. This increase may be attributed to the anticipation that Pfizer would be able to benefit from the withdrawal of a major competitor. Over time, however, Pfizer's share price dropped along with Merck due to the clouding effects that customers became more cautious about the use of the entire class of drugs.

Although the contagion effects are dominant in the therapeutic class, when smaller drug withdrawals occur, not all the brands within the same therapeutic class are affected equally. The results from the replication indicate that the largest brands in the class suffer the most from a drug withdrawal. This is consistent in all three drug withdrawals studied in this section. Typically, the largest brands are most closely associated with the therapeutic class. When negative information is furnished by the failure of a drug in the class, such information may be more easily utilized in the evaluation of these largest brands given that they are most closely identified with the therapeutic class and the negative information may be more relevant in evaluation. Similarly, in the case of the Raplon withdrawal, Zemuron, a brand that is

manufactured by the same parent company and belongs to the same therapeutic class, suffered the most from the drug withdrawal. Negative information may be most relevant and vivid in the evaluation of brands that belong to the same parent company and the same therapeutic class.

In the Posicor withdrawal, the marketing effectiveness estimate shows a significant positive change after the withdrawal of the drug. This increase in marketing effectiveness after drug withdrawal is unexpected and is examined through the reallocation of marketing programs, similar to the analysis done to the Baycol withdrawal in Chapter 5. Some brands in the therapeutic class show very sudden declines in their uses of marketing programs. Such sudden and sharp changes in marketing programs may skew and confound the expected negative spillover effects on marketing effectiveness. More discussion related to this issue will be provided in the section of limitations.

**Table 7.23**
**Model Estimates for Effects of Drug Withdrawals on Competing Brands**

| | Posicor | | | Duract | | | Raplon | | |
|---|---|---|---|---|---|---|---|---|---|
| Effect | brand | Estimate | p-value | brand | Estimate | p-value | brand | Estimate | p-value |
| Intercept | | 7.898 | 0.000 | | 8.615 | 0.000 | | 8.851 | 0.000 |
| Brand | ADALAT CC | 1.528 | 0.000 | ADVIL | 1.463 | 0.065 | ATRACURIUM BES | -2.166 | 0.000 |
| Brand | CALAN SR | 0.595 | 0.004 | ALEVE | 0.374 | 0.606 | MIVACRON | -1.517 | 0.000 |
| Brand | CARDIZEM CD | 1.710 | 0.000 | CATAFLAM | 0.338 | 0.641 | NIMBEX | -0.897 | 0.039 |
| Brand | COVERA-HS | -1.230 | 0.000 | IBUPROFEN | 0.111 | 0.889 | ZEMURON | 0.000 | |
| Brand | DILACOR XR | 0.197 | 0.368 | MOTRIN CHILDS | -0.312 | 0.658 | | | |
| Brand | NORVASC | 2.866 | 0.000 | MOTRIN IB | -0.386 | 0.593 | | | |
| Brand | PLENDIL | -0.108 | 0.584 | STADOL NS | 0.719 | 0.332 | | | |
| Brand | PROCARDIA XL | 2.523 | 0.000 | ULTRAM | 0.000 | | | | |
| Brand | TIAZAC | -0.358 | 0.301 | | | 0.641 | | | |
| Brand | VERELAN | 0.000 | | | | 0.108 | | | |
| time*brand | ADALAT CC | 0.076 | 0.000 | ADVIL | -0.012 | 0.000 | ATRACURIUM BES | -0.033 | 0.172 |
| time*brand | CALAN SR | -0.025 | 0.000 | ALEVE | 0.029 | 0.811 | MIVACRON | -0.031 | 0.202 |
| time*brand | CARDIZEM CD | -0.044 | 0.000 | CATAFLAM | -0.078 | 0.803 | NIMBEX | 0.004 | 0.885 |
| time*brand | COVERA-HS | 0.020 | 0.060 | IBUPROFEN | -0.003 | 0.472 | ZEMURON | 0.008 | 0.755 |
| time*brand | DILACOR XR | -0.059 | 0.000 | MOTRIN CHILDS | -0.008 | 0.038 | | | |
| time*brand | NORVASC | 0.027 | 0.147 | MOTRIN IB | -0.014 | 0.055 | | | |
| time*brand | PLENDIL | 0.044 | 0.064 | STADOL NS | 0.036 | | | | |
| time*brand | PROCARDIA XL | -0.020 | 0.003 | ULTRAM | -0.083 | | | | |
| time*brand | TIAZAC | 0.050 | 0.000 | | | | | | |
| time*brand | VERELAN | -0.042 | 0.000 | | | | | | |
| time2*brand | ADALAT CC | -0.001 | 0.000 | ADVIL | 0.000 | 0.680 | ATRACURIUM BES | 0.000 | 0.411 |
| time2*brand | CALAN SR | 0.000 | 0.936 | ALEVE | 0.000 | 0.185 | MIVACRON | 0.000 | 0.585 |
| time2*brand | CARDIZEM CD | 0.000 | 0.003 | CATAFLAM | 0.001 | 0.000 | NIMBEX | 0.000 | 0.276 |
| time2*brand | COVERA-HS | 0.000 | 0.504 | IBUPROFEN | 0.000 | 0.370 | ZEMURON | 0.000 | 0.916 |
| time2*brand | DILACOR XR | 0.000 | 0.001 | MOTRIN CHILDS | 0.000 | 0.534 | | | |
| time2*brand | NORVASC | 0.000 | 0.537 | MOTRIN IB | 0.000 | 0.427 | | | |
| time2*brand | PLENDIL | 0.000 | 0.229 | STADOL NS | -0.001 | 0.003 | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| time2*brand | PROCARDIA XL | 0.000 | 0.004 | ULTRAM | 0.001 | 0.080 | | | |
| time2*brand | TIAZAC | 0.000 | 0.005 | | | | | | |
| time2*brand | VERELAN | 0.000 | 0.001 | | | | | | |
| CON*brand | ADALAT CC | -0.024 | 0.000 | ADVIL | 0.001 | 0.968 | ATRACURIUM BES | 0.000 | |
| CON*brand | CALAN SR | -0.056 | 0.068 | ALEVE | -0.030 | 0.066 | MIVACRON | 0.039 | 0.318 |
| CON*brand | CARDIZEM CD | 0.010 | 0.014 | CATAFLAM | 0.035 | 0.005 | NIMBEX | -0.021 | 0.296 |
| CON*brand | COVERA-HS | 0.006 | 0.277 | IBUPROFEN | 0.000 | | ZEMURON | -0.004 | 0.808 |
| CON*brand | DILACOR XR | 0.009 | 0.265 | MOTRIN CHILDS | -0.003 | 0.919 | | | |
| CON*brand | NORVASC | -0.009 | 0.213 | MOTRIN IB | -0.003 | 0.841 | | | |
| CON*brand | PLENDIL | -0.013 | 0.159 | STADOL NS | -0.027 | 0.266 | | | |
| CON*brand | PROCARDIA XL | -0.038 | 0.061 | ULTRAM | 0.039 | 0.020 | | | |
| CON*brand | TIAZAC | -0.008 | 0.331 | | | | | | |
| CON*brand | VERELAN | 0.006 | 0.512 | | | | | | |
| C_CON | | 0.006 | 0.000 | | -0.002 | 0.600 | | 0.010 | 0.402 |
| **W*brand** | **ADALAT CC** | **-0.523** | **0.027** | **ADVIL** | **-0.857** | **0.055** | **ATRACURIUM BES** | **0.155** | **0.258** |
| **W*brand** | **CALAN SR** | **-0.082** | **0.299** | **ALEVE** | **-0.363** | **0.257** | **MIVACRON** | **-0.995** | **0.002** |
| **W*brand** | **CARDIZEM CD** | **-0.393** | **0.096** | **CATAFLAM** | **-0.414** | **0.233** | **NIMBEX** | **-2.539** | **0.003** |
| **W*brand** | **COVERA-HS** | **-0.542** | **0.055** | **IBUPROFEN** | **-0.131** | **0.277** | **ZEMURON** | **-5.500** | **0.002** |
| **W*brand** | **DILACOR XR** | **-0.253** | **0.065** | **MOTRIN CHILDS** | **-0.448** | **0.071** | | | |
| **W*brand** | **NORVASC** | **-0.931** | **0.040** | **MOTRIN IB** | **-0.124** | **0.593** | | | |
| **W*brand** | **PLENDIL** | **-0.264** | **0.112** | **STADOL NS** | **-0.258** | **0.214** | | | |
| **W*brand** | **PROCARDIA XL** | **-0.014** | **0.876** | **ULTRAM** | **-1.012** | **0.225** | | | |
| **W*brand** | **TIAZAC** | **-0.493** | **0.044** | | | | | | |
| **W*brand** | **VERELAN** | **-0.041** | **0.757** | | | | | | |
| **W*CON** | | **0.008** | **0.038** | | **0.014** | **0.196** | | **0.145** | **0.003** |

**Table 7.24**
**Summary of Findings of Spillover Effects on Competing Brands**

| Brand | Negative Impact on the Sales of Competing Brands | Negative Impact on the Marketing Effectiveness |
|---|---|---|
| Duract (3% of class share) | Yes | No |
| Raplon (2% of class share) | Yes | No |
| Posicor (0.5% of class share) | Yes | No |

## Chapter Summary

In this chapter, I have replicated the modeling exercise employed in Chapters 5 and 6 using several additional drug withdrawals. The replication is conducted to verify the findings on the spillover effects of drug withdrawal on parent company as well as on competing brands in the therapeutic class. These additional drug withdrawals are selected because they meet the qualifications for the modeling exercise. The chapter is largely divided into two parts, one of which addresses the spillover effects of drug withdrawal on parent companies and the other deals with the spillover effects on competing brands.

Following the modeling exercise in Chapter 5, the same mixed effects models were used to model the impact of drug withdrawal on the sales of other brands of the parent company and on the marketing effectiveness of that company. The results from mixed effects models found no evidence of the negative spillover effects on the sales of other brands of the withdrawing company, but found evidence of the negative spillover effects on the marketing effectiveness of that company.

Following the modeling exercise in Chapter 6, the same mixed effects models were used to model the impact of drug withdrawal on the sales of the competing brands and on the marketing effectiveness of these brands. The results found evidence of the negative spillover

effects on the sales of competing brands in the same therapeutic class, but found no evidence of the negative spillover effects on the marketing effectiveness of these competing brands.

Overall, the replication of additional drug withdrawals produces largely consistent results with those reported in the Rezulin and Baycol withdrawals. The difference in the spillover effects of drug withdrawal on the sales of competing brands are predicted in the conceptual framework discussed in Chapter 3. This difference is attributed to the different sizes of withdrawn drugs, and the subsequent difference in the net effects of the competitive and contagion effects. The replication exercise provides more validity to the findings and the conclusions in Chapters 5 and 6.

# CHAPTER 8

# CONCLUSIONS

In this chapter, the findings of various modeling exercises are summarized. Following a summary of findings, the theoretical, managerial and methodological contributions of this study are discussed. In particular, the implications of this study for managers are demonstrated through an analysis of the recent Vioxx withdrawal case. Several limitations of this study are acknowledged and the caveats of the findings are discussed. Finally, an agenda for future research is presented.

## Summary of Findings

The objectives of this study are to empirically address 5 research issues related to prescription drug withdrawals: 1) the impact of drug withdrawal on parent companies' stock prices, 2) the spillover effects of drug withdrawal on the sales of other brands in the parent company's portfolio, 3) the spillover effects on the marketing effectiveness of the parent company's marketing programs, 4) the spillover effects on the sales of competing brands in the therapeutic class, and 5) the spillover effects on the marketing effectiveness of these competing brands.

Past research on relating product failures to their financial implications focused on the total effects of product failures on the stock price of these failing companies. These studies found no direct relation between the financial market losses with the loss of revenue due to the product

failure and potential litigation expenses involved (Jarrell and Peltzman 1985; Marcus, Swidler, and Zivney 1987; Pruitt and Peterson 1986). In other words, the equity market loss is much larger than direct revenue loss and litigation expenses combined. This magnifying effects reflected on the loss in the equity market indicate the significance of a third component involved in the losses of product failure, namely the damage to the company's goodwill. The damaged goodwill of a company may in turn negatively affect other products/brands of that company. Such negative spillover effects caused by product failures, though widely acknowledged, have not been thoroughly researched and understood in the finance and marketing literature. This study attempts to fill this gap in the current knowledge, and is specifically focused on examining the spillover effects of catastrophic product failure. Drawing on the relevant literatures of marketing, finance, economics, and crisis management, this research provides conceptual understandings of the phenomenon of product failure in general and the mechanism through which the spillover effects of product failure occur in particular.

This study focuses on catastrophic product failures in the pharmaceutical industry. Research on these catastrophic product failures provides not only important academic implications, but also relevant managerial implications in the areas such as risk control, risk assessment of catastrophic events, etc. Between 1996 and 2003, there are 12 identifiable drug withdrawals in this industry due to excessive safety concerns related to the uses of these drugs. In the current marketing literature, scant research has focused on catastrophic product failures like prescription drug withdrawals, and even fewer studies have looked at the spillover effects of product failure under the house of brands where products/brands are not closely related to each other in the company's portfolio (i.e., brand separation). Research in this important yet complex

setting helps further our understandings of product failure and subsequent spillover effects on the failing company as well as on the competitors.

Data from various sources were complied in order to empirically examine the research issues raised in this study. The datasets from IMS Health consist of monthly sales and marketing program data that cover 12 prescription drug withdrawals from 1996 to 2003. The monthly sales data represent over 50% of the U.S. prescription drug market. The marketing program data include three measures, namely free sampling (*smp*), professional journal advertising (*jad*), and physician contacts (*con*). In addition to the sales and marketing data, drug characteristic data (e.g., drug indications, therapeutic class classification) were collected from the U.S. Food and Drug Administration. Firm level financial data (e.g., stock price, company size, the history of mergers and acquisitions) were compiled from COMPUSTAT. Various statistical methods were utilized to address the research issues. Specifically, intervention analysis was employed to examine the impact of drug withdrawal on the stock price of withdrawing companies. Mixed effects models were used to examine the spillover effects of drug withdrawal on the parent company as well as on the competitors. Two largest drug withdrawals, the Rezulin and the Baycol withdrawals, were analyzed thoroughly as the focuses of this study. Several smaller drug withdrawals were used to replicate the findings from the Rezulin and Baycol withdrawals. The findings related to each of the 5 research issues are described next.

*Effects of drug withdrawal on the parent company's stock price.* The results from intervention analysis in Chapter 5 indicate that drug withdrawals have significant negative impacts on the stock prices of parent companies. The results from the Rezulin and the Baycol withdrawals also suggest that the negative impacts are persistent for a period of at least several months. The negative impacts on stock price tail off gradually over time.

*Spillover effects of drug withdrawal on the sales of other brands in the parent company's portfolio*. The results from the mixed effects models used in Chapter 5 indicate the evidence of negative spillover effects of drug withdrawal on the sales of other brands of the withdrawing company. Such spillover effects, however, were found only in the Baycol withdrawal, which was the largest drug withdrawal in its relative size to the firm among all the drug withdrawals from 1996 to 2003. Unfortunately, there are no drug withdrawals of the similar size that can be used to replicate this finding in the study.

*Spillover effects on the marketing effectiveness of the parent company's marketing programs.* The results from the Rezulin withdrawal clearly provide evidence of negative spillover effects of drug withdrawal on the effectiveness of marketing programs of the withdrawing company. Three additional drug withdrawals were used to replicate the modeling exercise. These drug withdrawals are smaller in size, but meet the qualifications for the modeling exercise. The results from these replications in Chapter 7 indicate the evidence of the negative spillover effects on the effectiveness of marketing programs of these withdrawing companies. The results from the Raplon withdrawal, however, found no significant effects on the sales of other brands as well as on the marketing effectiveness of the parent company. Raplon is the smallest drug withdrawal in this study. As discussed in Chapters 3 and 5, the size of the withdrawn drug may help explain the variations found in the spillover effects of drug withdrawal. The withdrawals of larger brands appear to have direct spillover effects on the sales of other brands of the withdrawing company whereas the withdrawals of smaller brands appear to have indirect spillover effects on the effectiveness of marketing programs of that company. The modeling results pertaining to the spillover effects on parent companies are summarized in Table 8.1.

**Table 8.1**
**The Spillover Effects of Drug Withdrawal on Parent Companies**

| Withdrawn Drug | Relative Size to the Company | Evidence of the Spillover Effects on the Sales of other Brands | Evidence of the Spillover Effects on the Effectiveness of Marketing Programs |
|---|---|---|---|
| Baycol | 12% | Negative | No |
| Rezulin | 5.1% | No | Negative |
| Posicor | 1% | No | Negative |
| Seldane | 0.7% | No | Negative |
| Raplon | 0.5% | No | No |

*Spillover effects on the sales of competing brands in the therapeutic class.* The results from Chapter 6 consistently suggest the positive spillover effects of drug withdrawal on the sales of competing brands. When a drug withdrawal occurs, the competition appears to benefit from the incident by taking up the market space left by the withdrawn drug. The contagion effects do not seem to be dominant in the withdrawals of Rezulin and Baycol. Three smaller drug withdrawals were used to replicate the findings. The results from these additional withdrawals, however, clearly indicate negative spillover effects of drug withdrawal on the sales of competing brands. The difference found in the Rezulin and the Baycol withdrawals and these three smaller withdrawals is expected. The net effects of drug withdrawal on the sales of competitors are determined by two counter-weighting effects, namely the competitive effects and the contagion effects. When the size of a withdrawn drug is large, the competitive effects are dominant and the spillover effects on the sales of competition are positive. In contrast, when the size of a withdrawn drug is small, the contagion effects are dominant, and the subsequent spillover effects on the sales of competition are negative.

When the contagion effects are dominant in smaller drug withdrawals, competing brands suffer along with the withdrawn brand in terms of the losses of sales. Yet, not all the competing brands are affected to the same extent. The results from the replications in Chapter 7 indicate that the largest brands in the therapeutic class suffer the most from a drug withdrawal. Such findings may be attributed to the strong associations of large brands with the therapeutic class. Large brands' close associations with the therapeutic class are likely to make the negative information more relevant and accessible in doctors' evaluation of products. Therefore, negative information furnished by drug withdrawal may be more easily utilized in the evaluation of the largest brands of the same therapeutic class.

*Spillover effects on the marketing effectiveness of competing brands.* The results from modeling the Rezulin and the Baycol withdrawals have found consistent evidence of negative spillover effects on the effectiveness of marketing programs of competing brands. These results, however, were not significant in the replications using smaller withdrawn drugs. The modeling results pertaining to the spillover effects on the competing brands in the therapeutic class are summarized in Table 8.2.

**Table 8.2**
**The Spillover Effects of Drug Withdrawal on Competing Brands**

| Withdrawn Drug | Relative Size to the Therapeutic Class | Evidence of the Spillover Effects on the Sales of other Brands | Evidence of the Spillover Effects on the Effectiveness of Marketing Programs |
|---|---|---|---|
| Rezulin | 26% | Positive | Negative |
| Baycol | 3% | Positive | Negative |
| Duract | 3% | Negative | No |
| Raplon | 2% | Negative | No |
| Posicor | 0.1% | Negative | No |

**Implications of this Study**

There are several theoretical implications of this research. This study is among the first to systematically examine catastrophic product failures. Prior research in the finance literature has largely focused on the impact of product failures on the company's stock price. This study extends the scope of prior research by studying the spillover effects of a product failure on other brands of the parent company as well as on competing brands. The spillover effects of product failure are conceptualized in two forms: the effects on the sales and the effects on the effectiveness of marketing programs.

As discussed in Chapter 2, prior marketing research on the spillover effects of product failure focus almost exclusively on the transfer of negative information to other products/brands that are clearly related to the failing product (Erdem 1998; Sullivan 1990; Swaminathan, Fox, and Reddy 2001). The spillover effects in these studies are facilitated by the shared brand names. Several studies suggest that using branding strategies that weaken the connections between brands can in fact mitigate the spillover effects between brands when product failure occurs (Milberg, Park, and McCarthy 1997). Based on the literature review of product failures and spillover effects, there are gaps in the current marketing knowledge in regard to examining spillover effects of product failure under the house of brands where marketing managers deliberately cut off connections of different brands in the company's portfolio. Our knowledge of whether a catastrophic product failure will spill over and influence other brands of the parent company under the high level of brand separation is limited. This study offers empirical evidence to further our understanding in this under-researched but important area.

This study is unique in that it focuses on catastrophic product failures in the real-world setting. It uses a historical approach to systematically examine several catastrophic product

failures occurring from 1996 to 2003 in the pharmaceutical industry, thus enhances the external validity of the findings in comparison to existing knowledge based largely on the results from lab experiments. This study is powerful in that it attempts to address an important real-world problem for which neither the existing finance literature nor marketing literature readily has an answer.

The modeling methods presented in this study represent a rigorous approach to examine the effects of catastrophic product failures and subsequent spillover effects on the suffering company as well as on the competitors. The modeling exercises quantify the magnitude of spillover effects of product failure. Two forms of the spillover effects, namely the spillover effects on the sales of other brands and the spillover effects on the marketing effectiveness, are modeled simultaneously.

There are several managerial implications of this study. It provides much-needed insights for managers to evaluate and control the risk from catastrophic product failures. In practice, companies employ different strategies reacting to product failures. When a product failure is containable and correctable, the focuses of the management are to reinvigorate the brand and to regain the market share lost (Aaker, Fournier, and Brasel 2004; Siomkos and Kurzbard 1994). In a catastrophic product failure, however, the product is discontinued permanently; the focuses of managers are to protect existing products from negative spillover effects of the failing product and to assess the spillover impact of the product failure. This is particularly important for industries (e.g., the pharmaceutical industry) within which the occurrences of catastrophic product failures, in the long term, are unavoidable, and the subsequent impacts are devastating both on the business and on the customers. To the best of my knowledge, this study is the first to

systematically quantify the spillover effects of prescription drug withdrawals, and is the first to demonstrate the impact of the spillover effects of drug withdrawal on parent companies.

Insights from this study are also intended to help companies to better manage product development risk, and eventually benefit their customers. In the context of the pharmaceutical industry, being the first-to-market is usually an important goal for product development (Angell 2005). This objective partly comes from the first mover advantage, but also has to do with the product's lifetime that is strongly associated with the patent protection. The time spent for product development and clinical trials cuts into the medicine's life under the patent protection. Many major pharmaceutical companies therefore aggressively seek accelerated review status for their new drugs under the FDA's review. The sooner a drug can get through the process of clinical trials and receive the FDA's approval, the longer life the drug can possess under the patent protection. However, hitting the market early may also involve higher risk of product failure. The failure of a product not only wastes upfront investment in the drug, but may also produce lasting spillover effects on the existing products in the company's portfolio. In sum, the thorough understanding of spillover effects of drug withdrawal adds more considerations to the decision of accelerating drug development or drug testing, and may help to justify more cautious strategies in new product development.

**The Vioxx Withdrawal Revisited**

Prior research in the finance literature has indicated the need to quantify the impact of damage to the company's goodwill in the case of product failure (Jarrell and Peltzman 1985). The underlying rationale is that damaged goodwill of the failing company can negatively influence the existing products/brands in that company's portfolio and such spillover effects of

product failure is an important component in the financial valuation of product failure. This study specifically examines the spillover effects of product failure on the parent company. The findings from the study may be used to quantify the spillover effects on the failing company's stock price.

The Vioxx withdrawal is revisited here to illustrate the valuation of the spillover effects caused by the withdrawal. In other words, the following exercise specifically estimates how much the Vioxx withdrawal costs Merck, the withdrawing company, in terms of the spillover effects on the sales of other remaining brands. Such estimation procedure may also be used by managers to assess the impact of product failure specifically attributed to the spillover effects. Without losing much generalizability, a few assumptions are made to make this estimation feasible.

The Vioxx withdrawal was very large both in the dollar size of the drug and in its relative size to the parent company. The spillover effects of such large drug withdrawal may bear more resemblance to those of the Baycol withdrawal. If similar results of the Baycol withdrawal also hold for the Vioxx withdrawal, one can use the findings from the Baycol withdrawal to conduct estimation for Vioxx. In the Baycol withdrawal, the sales of all the remaining brands of Bayer were negatively affected, but not all the brands were influenced equally. For instance, in Table 5.14, Cipro was the brand affected most heavily whereas Trasylol was the brand affected most lightly. In fact, the impact of the Baycol withdrawal on different brands forms a distribution. It appears reasonable to use a value in the middle of that distribution to represent the spillover effects of the Baycol withdrawal. Accordingly, the effect associated with Cipro IV ($W*brand$ = -0.711), a moderately affected brand, was used as the estimated effect of the Vioxx withdrawal on all the remaining brands of Merck.

Specifically, after the withdrawal of Baycol, Cipro IV suffered a 13% loss[33] in its sales in comparison to its otherwise sales without the withdrawal. Using this figure as an estimate for the case of Vioxx withdrawal, it is assumed that the sales of all the Merck brands suffered about 13% loss in comparison to their otherwise sales without experiencing the Vioxx withdrawal.

Several other numbers need to be supplied in order to complete the estimation. The yearly revenue of Merck was found in its 2005 annual report to be 22 billion. The profit margin of the company is assumed to be the industry average, 17%, and the remaining lifetime of Merck's drugs on average is estimated to be 5 years[34]. In addition, the discount rate used for the net present value (NPV) analysis is assumed to be 10%. If Merck's revenue remains constant over the 5 years after the withdrawal of Vioxx, the NPV of the loss of profit due to the spillover effects is estimated to be $2.03 billion. These figures are summarized in Table 8.3. It should be noted that the estimation is rather simplified and many assumptions are made. But the procedure of this estimation is the first step towards more sophisticated estimation exercise.

**Table 8.3**
**Valuation of the Spillover Effects on the Sales of other Brands (Vioxx)**

| Yearly Revenue | Margin | Length of Analysis | Discount Rate Used in the NPV | Spillover Effects on the Sales of Other Brands | Loss of Profit Due to Spillover Effects (NPV) |
|---|---|---|---|---|---|
| 22 billion | 17% | 5 years | 10% | 13% | -2.03 billion |

[33] This figure can be calculated by plugging relevant numbers into the model with all the parameters estimated. The impact of the Baycol withdrawal on the sales of Cipro IV is calculated using the following formula: the predicted sales with the drug withdrawal / the predicted sales without the withdrawal. The impact of the withdrawal varies by time. Generally, the impact is around the 13% range.

[34] The former editor of *The New England Journal of Medicine* estimated that average profit margin in the pharmaceutical industry is about 17% and the effective lifetime of a drug under the patent protection is 8 to 14 years (Angell 2005). Assume all the brands of Merck are in the middle point of their lifetime at the time of the Vioxx withdrawal, 5 years appear to be reasonable to represent remaining lifetime of these brands.

Using similar NPV analysis, the lifetime profit of Vioxx is estimated to be about $4.5 billion, which is considered the largest direct financial loss involved in the Vioxx withdrawal. The litigation expenses are estimated to range from $3 to 38 billion according to different financial analysts (Berenson 2005; Gongloff 2005). The damage to company's goodwill translates into the cost of spillover effects that are estimated in this study to be about $2.03 billion. Table 8.4 summarizes three different types of costs involved in the Vioxx withdrawal and the actual equity market loss of Merck due to the withdrawal. Insight from the table is an attempt to understand dramatic response to drug withdrawal from the stock market, and is the first step to untangle the "mystery of the loss of goodwill" (Jarrell and Peltzman 1985) in the finance literature.

**Table 8.4**
**Different Costs of the Vioxx Withdrawal**

| Direct Financial Loss | Potential Litigation Expenses | Damage to Company's Goodwill/Spillover Effects on Sales of Existing Brands | Equity Market Loss after Vioxx Withdrawal |
|---|---|---|---|
| 4.5 billion | 3-38 billion | 2.03 billion | 26 billion |

## Limitations of this Study

Like any other research, there are several limitations associated with this study. This research attempts to integrate theoretical works and empirical works from various steams of literature. Several key factors influencing drug withdrawal and the spillover effects are considered in the study. There are, however, other factors which could also be relevant (e.g., the media's coverage of product withdrawal, company's responses to the product failure, the causes

of product failure) that have not been included. Each of these factors can be an interesting topic to address in future research.

In modeling the spillover effects of drug withdrawal, the persistence of such effects was not explicitly modeled. Instead, the modeling exercise used the most conservative configuration for the spillover effects, and assumed the spillover effects, if present, should last to the end of timeframe of the data. In other words, the length of the time window for the spillover effects is determined by the timing of the drug withdrawal. If a drug withdrawal occurs early, the withdrawal will have longer time window after the withdrawal whereas a late drug withdrawal will have a shorter time window. Such determination of the time window is not ideal but is intended to conservatively identify the existence of the spillover effects of drug withdrawal. Assuming such time windows after a drug withdrawal may not be sensitive enough to minor spillover effects that were not lasting.

The modeling exercise in this study does not consider the possible recovery process of a withdrawing company. Conceptually, the negative effects from drug withdrawal usually tail off gradually. Companies that suffer from the negative effects of drug withdrawal should recover over time. This recovery process is not reflected in the current modeling exercise.

Only three marketing variables were used in mixed effects models in this study. There is, however, another important marketing variable unavailable in the data of this study. Direct to consumer (DTC) advertising has become increasingly popular among pharmaceutical companies and research has suggested various types of impact of DTC ads (Aikin and Swasy 2003; Menon et. al. 2004). Although empirical research have indicated that DTC ads do not appear to have much impact on prescription drug sales at the brand level (Donohue 2003; Wittink 2002), the inclusion of this important marketing variable may help to reduce biases in model estimates.

More importantly, it is also an interesting research question by itself to examine the impact of drug withdrawal on the effectiveness of DTC ads.

There are some inconsistencies in the spillover effects found in different drug withdrawals. The size of a withdrawn drug may explain some variations in the results. But other moderating factors, as discussed in Chapter 3, including the amount of negativity produced by each drug withdrawal and the level of brand-corporation separation may aid to explain more variations.

**Agenda for Future Research**

This study is the first step towards the understanding of many issues associated with catastrophic product failures (i.e., prescription drug withdrawals in the study) in a very complex industry. Numerous avenues are open for future research.

The findings in this study are all based on non-sequential drug withdrawals. If sequential withdrawals occurred to any one company, these drug withdrawals were not included in the statistical analysis. Similarly, if multiple drugs were withdrawn from any one therapeutic class, these drug withdrawals were not included in the analysis. The exclusion of these sequential drug withdrawals simplified the modeling work and helped to address the research issues in this study. However, it will be of great interest to study the interaction effects of sequential drug withdrawals. Theoretically, both the diminishing interaction effects and the intensifying interaction effects can occur. The diminishing interaction effects can occur when customers are less surprised at a second product failure because of the belief that bad companies produce bad products. In contrast, intensifying interaction effects can occur when customers become more intolerant of the negativity accumulated over sequential product failures. Using an appropriate

modeling approach to incorporate sequential drug withdrawals may produce results with important academic and managerial implications.

Modeling the withdrawing companies' recovery processes from drug withdrawals opens another interesting area for future research. The results from such modeling work will provide knowledge on the persistence and the shape of the spillover effects of drug withdrawal. With such knowledge available, managers will be able to better allocate corporate resources to shield or to offset the negative spillover effects of drug withdrawal.

All the drugs included in the study are prescription-only drugs. Decision-makers for these products are largely medical professionals. The decision-making processes that medical professionals use may be significantly different from the ones that common consumers may use. It will be interesting to replicate the modeling exercise using only the over-the-counter (OTC) brands in order to understand consumers' responses to drug withdrawals.

Product withdrawal is the last step for regulatory agencies to disclose adverse information related to a product to its customers. In practice, the FDA uses various channels to communicate newly found safety problems to doctors and consumers. These channels include using the "dear doctor letters", re-labeling drug uses, adding warning boxes to drug packages, limiting drug distribution, etc. It will be interesting to research the effects of these types of warnings on manufacturing companies and on their competitors.

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# APPENDICES

## A. Evidence of Cardiovascular Risk of Vioxx Prior to APPROVe Trial

Was there sufficient evidence prior to the APPROVe study, based on previous clinical trials, that Vioxx could cause increased risk of cardiovascular events? Professor Peter Juni and his colleagues at Berne Institute in Switzerland think there was. They published a paper in the November 2004 issue of the *Lancet* arguing that a meta-analysis of a number of previous studies, involving about 20,000 total patients, provided statistically irrefutable evidence ─well before the APPROVe study began─ that Vioxx increased this risk. Merck disagrees. Reponses from Merck suggested Juni's study failed to include two favorable studies and was largely driven by data from the VIGOR study (Vioxx Gastrointestinal Outcomes Research study, released in March 2000). Hence, Merck insisted that the pooled analysis "demonstrated a difference in cardiovascular risk between rofecoxib and naproxen but not between rofecoxib and non-naproxen NSAID or placebo."

In a placebo-controlled database derived from 2 follow-up studies with a total of 2142 elderly patients (mean age 75; Vioxx n=1067, placebo n=1075) with a median duration of exposure of approximately 14 months, the number of patients with serious cardiovascular thrombotic events was 21 vs 35 for patients treated with Vioxx 25 mg once daily versus placebo, respectively. In these same 2 placebo-controlled studies, mortality due to cardiovascular thrombotic events was 8 vs 3 for Vioxx versus placebo, respectively. Using the z proportion test, the difference in cardiovascular adverse events between Vioxx and placebo was not significant.

In fact, in the placebo group, there was a higher percentage of patients who reported adverse cardiovascular events.

Based on these facts (the VIGOR trial and the two placebo-controlled studies are published in *New England Journal of Medicine*), Peter Kim, Merck's Research Chief, remarked (Kim 2004) "because there was no difference between the cardiovascular event rates between Vioxx and placebo in these two Alzheimer's trials or between Vioxx and non-naproxen NSAIDS in our previous studies, and because naproxen is known to have anti-platelet aggregation effects similar to aspirin, Merck concluded that the most plausible explanation for the VIGOR results was that naproxen was exerting a cardioprotective effect." In other words, Merck suggested that naproxen could have a beneficial cardiovascular effect, and because of this effect, Vioxx appears relatively more dangerous. Following this logic, Merck contended there was no conclusive evidence back then until a prospective placebo-controlled study (i.e., the APPROVe trial) became available.

In essence, the debate between Merck and Juni (2004) was not just a statistical problem. Merck justified its argument by contending that the statistically significant difference between Vioxx and naproxen did not indicate any detrimental effects of Vioxx. Instead, Merck claimed it was due to the beneficial effects of naproxen. From the statistical point of view, Merck was right that unless a placebo-controlled study was available, no conclusion should be drawn. Yet, research outside of clinical trials might have important implications on this debate.

In response to the VIGOR trial results, Frankish (2002) suggested in the *Lancet* there were two possible explanations for the increased cardiovascular risk, as opposed to the one to which Kim (2004) referred. First, naproxen might be cardio-protective. Second, Vioxx could have deleterious cardiovascular effects (Frankish 2002). He cited a study by FitzGerald

published in *Science* (2002; 296) to suggest there is concern about pro-thrombotic effects of COX-2 inhibitor (including Vioxx).

Does naproxen really have a cardioprotective effect, as Merck contended? In their Lancet article, Ray et al. (2002), using a retrospective cohort analysis, reported that naproxen 1000mg had not shown a protective effect sufficient to explain the difference in the VIGOR study. In addition, they concluded that users of high dose Vioxx were 1.7 times more likely than non-users to have serious heart diseases (Ray et. al. 2002).

Similarly, research in a population-based retrospective cohort study (Mamdani et. al. 2004) suggested that patients on Vioxx and non-selective NSAIDS (including naproxen) had an increased risk for heart failure (1.8 times). This, again, is not in line with Merck's explanation of the VIGOR trial.

In sum, in the medical literature many studies appear to point in one direction, that Vioxx increases the risk of adverse cardiovascular events. It is true that none of these studies were prospective or placebo-controlled, so Merck could argue that none of them were conclusive. However, two key ethical questions remain. First, in face of the mounting evidence of the severe side effects of Vioxx, Merck continued its aggressive direct-to-consumer advertising of this questionable drug. Second, APPROVe is a relatively small trial investigating a novel use for Vioxx. It was not designed or executed with a general safety assessment as its primary goal (Horton 2004). Why take the risk? Did Merck inappropriately downplay the side effect of Vioxx? The Texas jury, which found Merck liable for the death of Mr. Robert C. Ernst, a Vioxx user, clearly thought Merck did downplay the risk and made Merck pay for its failure to protect the consumer.