Market Discontinuation of Pharmaceuticals in the United States

Dissertation

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By

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Abstract

The pharmaceutical industry serves societal needs by bringing innovative products and therapies to market. However, innovation does not guarantee market longevity. Consequently, some products are evaluated and considered for market discontinuation. Safety, efficacy, and financial concerns are important considerations when evaluating the reasons for market discontinuation of drugs. In this study, market discontinuation of new molecular entities (NMEs) approved by the FDA from 1980 to 2008 were analyzed. The independent variables considered for the analysis were drug characteristics (route of administration, therapeutic class), sponsor characteristics (sponsor country, sponsor with single NME during study period), drug policy (orphan drug status, accelerated review, priority review and Prescription Drug User Fee Act (PDUFA) enactment).

Data were derived from the FDA, Micromedex, Medline, Lexis-Nexis and Medicaid Drug Utilization Data. A drug was considered discontinued if it was deleted from the FDA's Orange book. Withdrawals of approval were also included in the study. Descriptive statistics, chi-square tests, logistic regression and survival analysis were performed for the study.

A total of 703 NMEs were approved during the study period. In December 31, 2008, 71.8% NMEs remained in the market; 14.4% were discontinued; 5.4%

NMEs had the brand discontinued, but the generic was available; 7.0% had changes in route, dosage form or strength; 0.7% were never marketed and 0.9% were over-the-counter drugs. Safety was the primary reason for withdrawal of 29 (27.4%) NMEs; 4 (3.8%) NMEs had Federal Register determination for not being discontinued for safety or efficacy reasons; 5 NMEs were never marketed (4.7%) and 68 (64.2%) had no reasons stated by the FDA. Compared to other classes anti-infectives were more likely ($p<0.05$) to be discontinued. Analyses of priority review, orphan drug status, and sponsor company's country (US or non-US) with respect to market withdrawal were not significant. Comparisons of pharmaceuticals withdrawn due to safety reasons with therapeutic class and implementation of PDUFA were also not significant.

One in seven NMEs approved during the study period were discontinued from the market. Less than one fourth of the discontinuations were due to safety reasons. Obsolescence and financial reasons are significant contributors to market discontinuations. An ongoing evaluation of NMEs in the market place is important to determine which products provide optimal benefits in terms of efficacy, safety, and value compared to other products overall and other products within the same therapeutic class.

Dedication

Dedicated to Almighty God and my beloved parents

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The pages of this dissertation hold far more than the culmination of my years spent at the Ohio State University. These pages reflect not only my educational journey, but also my relationship with many kind and inspiring people. I cherish each contribution and am grateful to each and every one of those people for all of their support.

This work would not have been possible without the motivation, guidance and challenges presented by my advisers Dr. Sheryl Szeinbach and Dr.Enrique Seoane-Vazquez. They have been strong and supportive throughout my graduate school career. They guided me when needed, but always gave me freedom to pursue independent work. They believed in me, even when I doubted my own ability to accomplish my goals. Their faith in my ability to rise to the occasion and do the necessary work, has carried me through graduate school. They worked with me tirelessly, reviewing my work and offering comments, but always respecting my opinion. Their attention to detail and ability to convert my crude thoughts into dramatically improved, cohesive and concise sentences without losing any of the meaning has always awed me. Without their encouragement and persistent motivation, this dissertation would not have been possible.

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herself with such grace and poise that I would like to emulate some day. I would like to thank her for making the journey through graduate school and my time at OSU as smooth as possible.

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I have to say I have had very little luck with computers over the years, so much so that some would say my laptop may have been possessed. I have Casey Hoerig and Jonathan Gladden to thank for the 24 hour support that they provided for every little technological crisis that I have faced through my graduate years.

I would like to thank my friends who have always been there for me while I was coping with the stresses of graduate school and whose friendship I could always count on through good and bad times. They were not only my social support but my family away from home. I would like to thank Akshata Almad, Katherine Bellebaum, Mohit Bhatia, Sarah Carothers, Elizabeth Chang, Vivek Garg, Parul Gulati, Bushra Liaqat, Srikant Nekkanty, Rajbir Singh and Somnath Sinha for playing a very significant role in not just my education, but also my life.

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CHAPTER I: INTRODUCTION

This chapter provides an overview and foundation for examining market discontinuation of pharmaceuticals. The first section provides background information supporting the selection of factors that are likely to influence drug discontinuations. The second section provides a review of the literature relevant to the rationale for the study and research hypotheses. The third section provides significance of the study and its potential contribution towards streamlining the efforts of the pharmaceutical industry as well as the FDA to minimize drug discontinuations. Section four outlines the conceptual framework for the study and the fifth section states the study's research question, research objectives, and research hypotheses.

1.1 Background

Drug development is a time and cost intensive process not only for the manufacturer but also the FDA. The time frame for drug development ranges between 7 to 9 years and costs approximately U.S. $800 million (J. A. DiMasi, Hansen, & Grabowski, 2003). Despite the immense labor and investment necessary for bringing a drug to the market, pharmaceuticals face an uphill battle to enter the market. The position of a pharmaceutical product remains fragile and uncertain as manufacturers fear discontinuation as they submit a new drug application with the FDA.

Discontinuation of the pharmaceutical implicates multiple parties such as the manufacturing firms, patients, providers and the health authorities. The financial losses resulting from the discontinuation of drugs can present a huge setback for the manufacturer as well as the various stakeholders within the company (Davidson & Worrell, 1992; Pruitt & Peterson, 1986). Moreover, patients are adversely affected if the drug product that provided excellent therapeutic benefits and resulted in positive health outcomes is no longer available in the market (Lechat, 1987). Finally, health authorities are faced with the dilemma of trying to bring safe and efficacious drugs to the market while being charged with liberally granting marketing rights to a drug product upon the passage of the Prescription Drug User Fee Act (PDUFA).

1.2 Problem Statement

Current FDA policies of drug review procedure dates back to early 1960s, shortly after the thalidomide tragedy. In 1962, Drug Amendments for efficacy became a requirement along with the reporting of adverse drug reactions as part of the Kefauver Harris Amendment (Dowling, 1970). During 1980's, the role of animal toxicity data as compared with human side effects became more apparent. For example, most of the early withdrawals were drawn from reports of side effects in animals. Furthermore, the post-market surveillance of drugs were popularized and clinical data was used for considering discontinuation of drugs (O. M. Bakke, Wardell, & Lasagna, 1984; Venning, 1983).

After the revisions to the approval process in response to the thalidomide tragedy, the length of the approval process increased. The review process however became a growing concern for advocates seeking to abridge their access to potentially lifesaving drugs (Burlington, Woodcock, & Zoon, 1999). For example, in 1990s, the activists' demands for anti-retroviral therapy for patients with human immunodeficiency syndrome (HIV) changed the political climate in U.S. (Willman, 2000).

Contrary to the advocate's restless efforts, a number of drugs have been discontinued from the market. In 1987, selective inhibitors of cyclooxygenase-2 (Cox-2 inhibitor) were found to relieve arthritis pain without the gastrointestinal side effects associated with non-steroidal anti-inflammatory (NSAIDs) pain killers.

A little over a decade later, the first Cox-2 inhibitor, rofecoxib,marketed by Merck as Vioxx was approved by FDA. In 2003, the drug reached out to consumers through direct-to-consumer marketing, which resulted in astonishing $6 billion (US) in sales. Despite being a blockbuster product, approximately a year later, Vioxx was withdrawn from the market. The Adenomatous Polyp Prevention on Vioxx (APPROVe) trial, which was designed to compare rofecoxib with a placebo in the prevention of recurrent colorectal polyps, revealed a serious thrombotic events in patients (Baron et al., 2008; Sibbald, 2004).

Another example of a drug withdrawn from the market was Tysabri (i.e. natalizumab), a monoclonal antibody developed to treat patients with relapsing forms of multiple sclerosis (MS). The drug was also used with patients who cannot tolerate or failed to respond to other treatments for MS. Because of its unclear risks when used with other immune modifying drugs, Tysabri was prescribed for monotherapy. The FDA approved Tysabri in November 2004 but its place in the market was short lived when it was withdrawn in February 2005. The drug was withdrawn because three of 3000 patients enrolled in a clinical trial developed progressive multi-focal leukoencephalopathy (PML), a serious viral infection of the brain.

Safety of pharmaceuticals is purported to be the main impetus for discontinuing a drug from the market, especially when clinical implications of drug discontinuations are considered. Clarke and colleagues (Clarke, Deeks, & Shakir, 2006) however, suggests that discontinuations attributed to safety and

efficacy are uncommon, instead commercial reasons by manufacturers were major contributor to drug discontinuations. In addition, financial reasons were also suggested as the driving force behind the drug withdrawals, when a company realizes that the financial viability of the drug fails to exceed the investment of the drug (Lechat, 1987).

More recently, the FDA has been under mounting pressure to expedite the approval procedure for new drugs due to the passing of Prescription Drug User Fee Act (PDUFA). Under the PDUFA, the FDA has streamlined the review process by working closely with drug manufacturers ultimately expediting not only the review process but also increasing the drug approval rate.

There are debates surrounding the implications of PDUFA and the safety of drugs approved under the FDA new review procedure (Wood, 1999). A study conducted by Wood and colleagues suggests since PDUFA went into effect, no differences in the safety of NMEs and the drug approval rate was observed. Examining the safety of new formulation introduced into the market offers inadequate knowledge about how drugs are discontinued by either the FDA or drug manufacturers.

Understanding multiple factors contributing to the discontinuation of drugs would provide greater insight into the dynamics between the FDA and drug manufacturers as well as the need to modernize the drug review procedure.

1.3 Significance

In order to examine various factors attributable to drug discontinuations, identifying New Molecular Entities (NMEs) introduced and generic drugs available in the market are critical. The current study describes the market position of drugs that were approved between 1980 and 2008 to obtain the characteristics of drugs marketed, non-marketed, discontinued, observed change in status (i.e. brand name to over-the-counter status), or changes in dosage, route, strength or form. A study period of 1980 to 2008 was chosen because 1980 marked the introduction of post-market surveillance of drugs in the market.

Most studies in the literature have used data acquired from the industry, examining limited types and classes of drugs. Also New Drug Applications were used to examine discontinuation, but the current study will use NMEs as the unit of analyses because they represent the true new active ingredient introduced to the market. A database of NMEs obtained from the FDA along with their safety and efficacy was created and in doing so, this allowed examination of wider range of drugs approved for the market.

Furthermore, generic drugs in the market were included in the analyses because they served as a proxy for the safety history of the drug, financial success for pharmaceutical companies and commercial viability of entering into the market.

In order to understand whether financial motives played a role behind drug manufacturers discontinuing a drug, current study utilized Medicaid Drug Utilization Data (MDUD). To our knowledge no studies has utilized MDUD and the use of this data is important because at 17%, Medicaid is the single largest payer for drug utilization in the US. Given Medicaid's significant role in drug utilization, a discontinued drug without prior safety and/or efficacy concerns from the FDA would be identified as a drug discontinued by manufacturers due to lack of financial viability.

Drug characteristics such as route of administration as well as therapeutic classification are known to affect the approval timeline and, therefore, were included in the analysis as the lengthening of approval times could potentially affect market status of the drug products.

Sponsor characteristics are expected to affect the drugs marketability not only within the United States but also in countries outside of the US, providing further financial incentive to retain the drug in the market or discontinue the drug.

Finally, the political environment is one of the main factors governing market dynamics. Therefore, it was important to assess the effect of various changes concerning drug policy like the passage of the Orphan Drug Act as well as the PDUFA on market discontinuations.

1.4 Conceptual Framework

The framework for this study is based on the classic Donabedian quality-of-care representation. Donabedian conceptualized the following three dimensions: structure, process and outcome to determine indicators of quality. To understand the complexity of the drug product life cycle, the different stages of the life cycle were categorized into these dimensions. Figure 1 represents the theoretical framework used for this study.

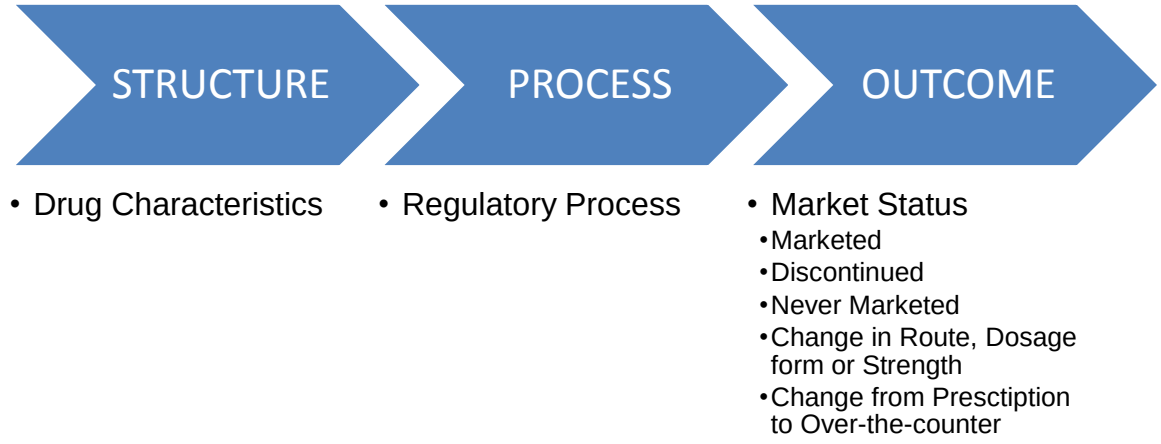

Figure 1.1: Conceptual framework for the study

Within the structural component, the scope of the pharmaceutical industry is described, with particular emphasis on its dynamic and competitive nature giving rise to innovation and diffusion of new drugs within the market. With the continuum of evolution in the drug discovery process and the risks involved in

new drug development, it is important to note the trends that persist in bringing new molecular entities to the market. Additionally, the contrast between the new entrants versus the drugs that are removed from the market will be highlighted.

Pharmaceuticals are one of the most highly regulated industries. Each country has its own regulatory process in place to ensure patient access to safe and effective therapies. A description of the regulatory structure will be provided followed by a chronology of pharmaceutical regulation as well as a justification of the timeline chosen for the study.

Finally, the outcome of interest in the study is the market status of the drug. This section will include a discussion regarding the market status of the drug, the reasons for its discontinuation as well as the impact of drug discontinuations on various stakeholders.

1.5 Model for Market Discontinuation

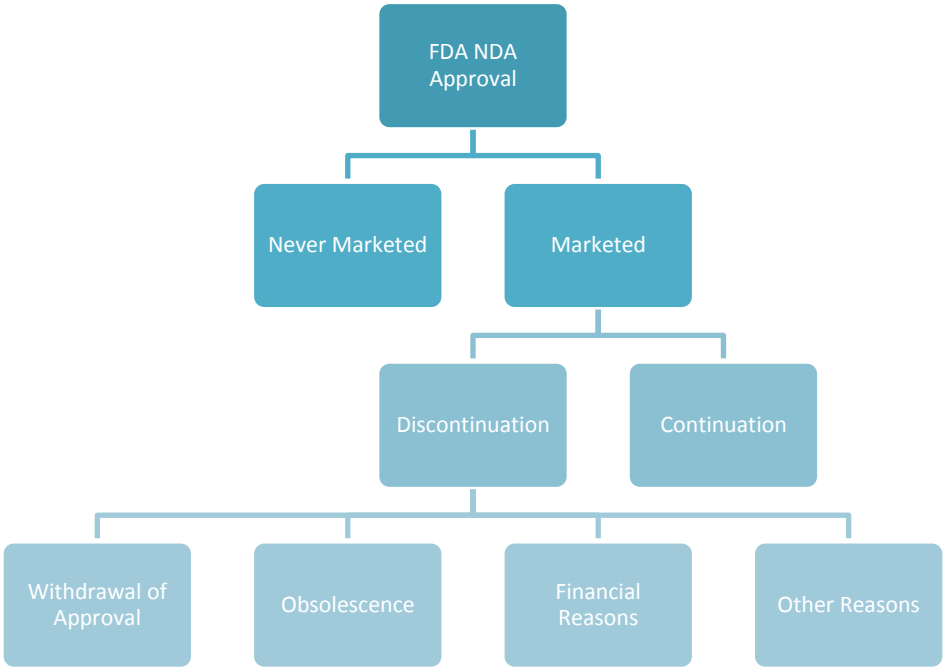

Figure 1.2: Model for Market Discontinuation of Pharmaceuticals

This model illustrates the correspondence between the different events that lead to discontinuations and their driving factors. On top of this figure is the initial step which is the FDA approval of a New Drug Application. Once a drug is approved there may be times when it is never marketed. Drugs that are in the market may either continue to remain in the market or be discontinued. Finally, right at the bottom of this chart are presented some reasons for market discontinuations like: withdrawal of approval which may be for safety or efficacy reasons, obsolescence due to new drugs coming into the market with better risk-benefit profile, financial reasons when there may not be enough incentives to keep a product in the market, or other reasons like market strategy.

1.6 Research Objectives and Hypothesis

Research Question

The purpose of this study is to analyze the market discontinuation of NMEs approved in the U.S. between 1980 and 2008. The study's specific research question is the following: Is the market status of an NME affected by the characteristics of the drug, the characteristics of the sponsor and the regulatory status under which a drug was evaluated and approved?

Research Objectives and Hypotheses

Objective A: Describe the demographic characteristics of the NMEs approved by the FDA between 1980 and 2008 including an analysis of the current market status of the drug (marketed, discontinued, never marketed, changes in route, dosage form, strength, and changes from brand to OTC status) drug characteristics (route of administration, therapeutic classification), sponsor characteristics (country, number of NME approvals) and drug policy (orphan drug status, FDA review type, whether or not user fee applies).

Objective B**:** Determine the reasons for drug market discontinuations.

Hypothesis 1. Safety and efficacy are hypothesized as the main contributors to the explanation of drug market discontinuations

Objective C: Evaluate the effect of drug characteristics (route of administration, therapeutic classification) on Market Discontinuation.

Hypothesis 2. Route of administration as well as therapeutic class are expected to be associated with market discontinuation.

Objective D: Evaluate the effect of sponsor characteristics (country, number of NME approvals) on Market Discontinuation.

Hypothesis 3. Sponsor characteristics are expected to be associated with market discontinuation of pharmaceuticals.

Objective E: Evaluate the effect of drug policy (orphan drug status, FDA review type, whether or not user fee applies) on Market Discontinuation.

Hypothesis 4. Orphan drug designation, FDA accelerated review type, priority review, and the enactment of PDUFA are expected to be associated with market discontinuation.

Objective F: Evaluate the effect of the independent variables or the predictors of Market Discontinuation.

Objective G: Measure the time from approval to Market Discontinuation for drugs discontinued for safety reasons.

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CHAPTER II: LITERATURE REVIEW

The primary responsibility of the pharmaceutical industry is the discovery and development of new chemical entities. The ensuing discussion will focus on the role of pharmaceutical industry investments in research and development as well as an understanding of factors that influence this process.

2.1 STRUCTURE

2.1.1 Evolution of the Drug Discovery Process

Although significant drug discoveries evolve through well-planned efforts during drug development, serendipity also plays a substantial role in drug discovery. Prime examples of the application of serendipity in the origins of drug discovery are digitalis and aspirin. Through the second half of the 20th century previously identified as well as randomly sought molecules were screened in *in vivo* models to identify lead molecules that were subsequently optimized and brought to market. Other drugs such as chlorpromazine, meprobamate and benzodiazepines were the successful consequence of serendipity (Dowling, 1970).

However, fundamental issues limit the efficiency of a method like serendipity. These issues include the lack of molecules with adequate structural diversity, the use of animal models that limited replication of pharmacokinetics *in vivo* as well as the lack of adequate back up molecules that would serve as lead molecules if the current molecule fails. Subsequently, the need for a more rational approach was realized. Carefully conducted *in vitro* assays using animal tissues led to the development of specific and effective agonists and antagonists e.g. β adrenergic receptor blockers and anti-histamines among others. Since this approach allowed for the determination of structure activity relationships, reasons for the failure of molecules were now easily determined (Dowling, 1970).

Today, combinatorial chemistry, (i.e., the ability to rapidly synthesize or produce a large number of molecular entities), is coupled with advanced knowledge of genetics and genomics to help identify more specific lead molecules. From these lead molecules, structural activity relationships can be examined with the purpose to categorize and to indentify promising new drugs.

2.1.2 Risks in New Drug Development

There is no guarantee of a molecules' clinical or commercial success once it has been discovered and approved. Studies focusing on the ratio of compounds synthesized to those marketed show very bleak results. Wardell (Wardell, DiRaddo, & Trimble, 1980) used data from thirty-nine U.S. owned pharmaceutical firms regarding new chemical entities they tested between 1963 and 1976. They demonstrated that 10,000 compounds are synthesized for every compound approved. James (1977), Wardell (Wardell et al., 1980) and Faust (1983) suggested that the ratio may be in the thousands. The most recent estimates are by Halliday *et al*. (Halliday, Walker, & Lumley, 1992) showing that U.S. companies synthesize 6200 compounds for every one approved. It is important to note that economic and regulatory factors play a significant role the in probability that a drug reaches the market. Additionally, economic and regulatory factors could also influence the chance a drug has to sustain within the market place.

This risk is not just limited to chemical compounds but extends to investors such as scientist and managers whose future is dependent on the

success of the drug development process. This risk is even greater for investors as they may have concentrated their assets in one or a few firms with pipelines containing a few risky projects with little or no potential to generate revenue.

Drug development is an intricate and gradual process involving a considerable investment of capital. Numerous studies have focused on the cost and length of the drug discovery process. DiMasi *et al.* (J. A. DiMasi et al., 2003) estimated the average cost of developing a drug using the CSDD survey data of 10 multinational firms. Their data consisted of detailed cost information regarding sixty-eight drugs categorized by the stages of the approval process. The probability of a drug reaching the market was calculated by multiplying the average amount spent in each phase by the probability of reaching that phase. They also used the time spent per phase to estimate the opportunity cost for the drug resulting in an overall drug development cost estimate of $802 million.

Adams and Brantner (C. Adams & Brantner, 2005; C. P. Adams & Brantner, 2006) used a similar methodology, but instead of using the CSDD data, they utilized the Pharmaprojects database. The timeframe considered for the study was 1989 to 2002. Their estimates were slightly higher than the DiMasi study in that the out-of-pocket costs were calculated to be 310 million as compared with 282 million in the DiMasi study. Moreover, after accounting for the opportunity costs, Adams concluded that the cost of new drug development was $868 million and that the DiMasi study results were an underestimation.

2.1.3 The Concept of Innovation

Innovations in the health sciences have resulted in dramatic changes in the ability to treat disease and improve the quality of life. Since the late 1990s pharmaceutical expenditures have outweighed other major constituents of the health care system. This comes as no surprise as the pharmaceutical industry is a major source of health care advancement despite the stringent pricing policies and regulatory environment.

A number of studies have focused on the trends observed among new molecular entities. DiMasi *et al.* (J. A. DiMasi, 2001) gathered data for investigational NCEs from a CSDD survey of pharmaceutical firms within the U.S. Thirty-three parent firms that accounted for 74% of the 691 NCEs approved during 1963 to 1999 in the U.S. A consistent trend of decline in research activity was identified from the late 1980s to the early 1990s with a slight improvement toward 1994. Despite the trends suggesting that the introduction of the Prescription Drug User Fee Act may have improved the efficiency of the approval process, the challenge remains to sustain these drugs in the market.

Bakke *et al.* (O. M. Bakke et al., 1984) conducted a comparative study of drugs that were discontinued in the United States and the United Kingdom for safety reasons. They compared drug introductions and discontinuations during the period when both countries had implemented modern drug regulations. They included older drugs defined as those introduced before 1964 and newer drugs that were introduced after 1964. They concluded that though the number of drug

discontinuations was slightly higher in the UK (20) as compared to the U.S. (14), the number of drug approvals was also higher (drugs marketed per year approx 16 in the U.S. and 21 in the UK), showing that there was not a vast amount of difference between the two countries overall. They also found that drugs discontinued for safety reasons only represented 2% of the new chemical entities introduced. Overall, more stringent drug approval requirements in the U.S. were not markedly superior in the prevention of marketing drugs that were later discontinued for safety reasons.

Bakke *et al.* (O. M. Bakke, Manocchia, De Abajo, & Kaitin, 1995) later compared the number of new chemical entities and new biological entities approved from 1974 through 1993 in the UK, U.S., and Spain that were discontinued for safety reasons. They found that drug discontinuations had increased from the period of 1964 to 1983 (2%) since 3% to 4% of drugs introduced into the market were discontinued in at least one of the countries with the U.S. alone having 10 drugs discontinued. They also classified drugs according to the therapeutic class and found that non-steroidal anti-inflammatory drugs were associated with the highest number of drug discontinuations, followed by vasodilators and antidepressants. In addition, they determined the country of origin to be the location of corporate headquarters at the time of patent issuance and by the ownership of the company during the drugs development. All of the discontinued drugs were discovered and/or developed by European or U.S.

owned companies and U.S. was the found to be the country of origin for about 40% of the drugs that were discontinued.

Studies reveal that the Adverse Event Reporting System (AERS) as a voluntary reporting system is successful, yet suffers from numerous limitations. For example, high rates of undetected post approval risks were associated with low rates of subsequent drug withdrawals. When Lasser *et al.* (Lasser et al., 2002) examined the Physicians' Desk Reference to determine the frequency and timing of discovery of new ADRs described in black box warnings or necessitating withdrawals of the drug from the market from 1975 to 2000, they discovered that out of the 548 new chemical entities approved from 1975 to 1999 there were approximately 2.9% product withdrawals from the market. In addition, out of the 16 drugs withdrawn about one-half were withdrawn within 1.5 years of being in the market. Their findings reemphasized the results of Bakke (O. M. Bakke et al., 1995), and also revealed there was a 20% probability for a drug being withdrawn from the market in 25 years. These findings reinforced the argument that premarketing drug trials were often underpowered to bring drugs to the market and that some drugs were brought to market despite serious ADRs being identified in premarketing drug trials.

Kaitin *et al.* (Kaitin, Richard, & Lasagna, 1987) compared new drugs the new drugs approved in 1985-86 with previous years data from the Center for the Study of Drug Development (CSDD) to assess the trends observed. Data were collected for each new chemical entity, with the exception of vaccines, surgical

products, diagnostic agents, and new salts or esters. The FDA had approved 26 new chemical entities in 1985 and 20 in 1986, resulting in an overall approval of 46 NCEs. This surpassed those NCEs approved in 1981 (22 approvals) and 1982 (21 approvals) with a combined two year approval of 43 drugs. They also demonstrated that 4th quarter approvals had been steadily increasing in the decade between 1975 (0%) to 1985 (73%). Despite these increases, their analysis showed no significant changes in approval rates over time, possibly attributed to FDAs persistently escalating demands for more thorough safety and efficacy data.

2.1.4 Value of Improving Productivity

There is added pressure for pharmaceutical firms to deliver quality pharmaceuticals as the cost of bringing a new drug to the market is on the rise and innovation is on the decline, thus resulting in fewer new molecular entities entering the U.S. market. Rising costs associated with innovation exert additional pressures on firms to retain drugs that do reach the market, as well as rethinking resource allocation strategies for drugs that are currently marketed.

Making the right decisions in the process of drug development could result in significant financial returns. While research and development costs have been on the rise, so have drug development times. By improving the drug development process, investments could be directed toward discovering newer molecules and increasing patient access to more therapies. DiMasi *et al.* (J. A. DiMasi et al., 2003) demonstrated that significant indirect costs savings could be accrued by

decreasing regulatory and drug review times while increasing clinical approval success rate. The cost savings ranged from 129 million to 235 million for decreasing review times and from 221 million to 242 million for increasing the success of drugs approved.

2.2 PROCESS

The life of an NME starts when a drug is discovered. Innovation evolves through a combination of public and private economic resources. Once the NME is discovered, the inventor patents the NME prior to its use in preclinical studies. Current estimates for costs range from 800 to a little less than 900 million to get a drug to the market.

2.2.1 Chronology of Drug Approval Process

The FDA, which is an agency within the United States Department of Health and Human Services, is responsible for protecting the public health by assuring the safety, efficacy and security of drugs. It is estimated to regulate approximately $ 275 billion in drugs alone. Within the FDA the Center for Drug Evaluation and Research (CDER) is the one agency responsible for making sure that safe and effective drugs are available to the public. The CDER regulates over-the-counter as well as prescription drugs, including biologicals and generics.

The gold standard for medical research is considered to be the randomized controlled trial (RCT). There are different ways of classifying clinical trials. According to the National Institutes of Health (NIH) these trials are classified as:

Prevention trials: Refers to trials to find better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vaccines, vitamins, minerals, or lifestyle changes.

Screening trials: Refers to trials which test the best way to detect certain diseases or health conditions.

Diagnostic trials: Refers to trials that are conducted to find better tests or procedures for diagnosing a particular disease or condition. Diagnostic trials usually include people who have signs or symptoms of the disease or condition being studied.

Treatment trials: Refers to trials which test new treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.

Quality of Life trials: Refers to trials that explore ways to improve comfort and quality of life for individuals with a chronic illness.

Compassionate Use trials: A method of providing experimental therapeutics prior to final FDA approval for use in humans. This procedure is used with very sick individuals who have no other treatment options. Often, case-by-case approval must be obtained from the FDA for "compassionate use" of a drug or therapy.

Clinical trials involving new drugs are commonly classified into four phases. The drug usually has to go through all four phases and upon successful completion of Phases I, II, and III, it is approved by the FDA for use in the general population.

Pre-clinical studies

In planning a clinical trial for drug approval the first step is to identify the medication to be tested. But even before launching into the actual trial, companies conduct extensive pre-clinical studies. Preclinical studies are

designed to predict the potential effects of the NME in humans through laboratory investigation and animal testing, and to determine if the NME is safe for use in humans.

Phase 0

Before commencing clinical studies in humans, clinical investigations require previous notification to the FDA and the sponsor of the NME must submit an “investigational new drug application” (IND) to the FDA before starting clinical trials with humans.

Phase I

Phase I trials are the initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness. These trials are usually conducted in-patient clinics to allow for ease of observation of participants which may include healthy participants and/or patients. Typically the group of participants is not very large and ranges from 20 to 50 volunteers.

Phase II

After the safety is established in phase I, these controlled clinical studies are conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks. Phase II trials are performed in slightly larger groups normally ranging from 20 to 300 participants.

These trials are sometimes divided into Phase IIA and Phase IIB, where IIA establishes dosing requirements and IIB determines the efficacy of the drug.

Phase III

Phase III trials usually involve large patient groups ranging from 300 to 3000. At this point the new drug is compared with the current treatment for the condition available in the market. Due to the rigor involved in this step, Phase III trials are the most expensive, time-consuming and difficult trials to design and implement, especially in therapies for chronic medical conditions.

The clinical investigations, consisting of phases I through III, are conducted to determine the NMEs mechanism of action, effective dose range, safety and efficacy to treat the disease intended, and to identify any common adverse reactions. Once these conditions are met, a new drug application (NDA) along with all data and reports generated from the pre-clinical and clinical trials are transmitted via e-submission to the FDA.

Phase IV

Phase IV trial, also referred to as Post-Marketing Surveillance Trial involves the safety surveillance and ongoing technical support of a drug through case-studies, case-reports or adverse event monitoring systems after it receives permission to be sold. Once NDAs are approved, monthly updates for new brand and generic medications are provided in the FDA's Orange Book "Approved Drug Products with Therapeutic Equivalence Evaluations."

The life cycle for the drug approval process takes an average of 12 to 15 years, with post-marketing research performed after the product reaches the market. At this point, any latent side effects that were not expressed during the clinical trial may emerge once the drug is used more extensively in the population. Many similarities exist between phases that comprise the product life cycle for pharmaceuticals and product marketing in general. Of particular interest in this research is what happens to products that fail to maintain their high growth and rate of returns. To justify the removal of these products, several strategies are needed to evaluate their vulnerability to competition, displacement, obsolescence or regulatory interventions.

2.2.2 Chronology of Pharmaceutical Regulation

This study focuses on a certain time frame which was between 1980 and 2008. Prior to and during this time frame, regulations for pharmaceuticals evolved to meet the changing climate for drug distribution and to provide a foundation by which new products were judged to be suitable and safe for use in the general population (O. M. Bakke et al., 1984). Thus, unlike other mainstream products and services, policies that govern the channels for drug distribution support a network that is highly regulated. The current policies for drug review date from 1930s when the Food Drug and Cosmetic Act was passed by congress. Further revisions were made in the early 1960s just after the thalidomide tragedy. Preregistration review for toxicity and for safety data had been practiced for many years, but it was not until 1962 that Drug Amendments

for efficacy became a requirement along with the reporting of adverse drug reactions as part of the Kefauver Harris Amendment. With respect to discontinuations at this time the role of animal toxicity data as compared with human side effects appeared to have shifted. Most of the early withdrawals around the 1970s were related to reports of side effects in animals. After 1970s a number of drugs were discontinued due to tumors found in animal studies. Possibly attributed to better surveillance of adverse events, the 1980s marked the time when all discontinuations were found to be attributed to clinical use in humans.

The principal goal of the health care industry is to improve access to safe and effective drugs. Since the advent of the 1980s drugs were evaluated based on their effect in humans leading to a more conclusive outcome of the drugs prevalence in the market. Our goal was to capture this effect by examining drugs that were approved between 1980 and 2008.

There have been many radical changes in regulatory interventions over time. We chose to highlight the ones that have significantly changed the face of history and are the cornerstones of the regulatory environment today. These include changes that were specific to the development and evolution of the Prescription Drug User Fee Act as it has been debated to impact drug discontinuations. Details of the ensuing regulatory interventions follow (Janssen, 1981):

1938

The Federal Food, Drug, and Cosmetic Act (FDCA) of 1938 was passed by Congress into law on June 24, 1938. The FDCA was considered one of the most important regulatory statues in American History. The new law accommodated provisions that significantly increased federal regulatory authority over drugs. These included stipulations requiring new drugs to be shown safe before marketing, starting a new system of drug regulation. The law also extended the FDA control to cosmetic and therapeutic devices, set safe tolerances for unavoidable poisonous substances, authorized factory inspections, and established standards of identity, quality, and fill-of-container for foods. Despite numerous revisions, this law is still considered the fundamental underpinning of FDA regulation.

During the same time the Wheeler-Lea Act was passed which allowed the Federal Trade Commission to oversee advertising associated with products, including pharmaceuticals, otherwise regulated by FDA.

Further the FDA promulgated the policy in August that sulfanilamide and selected other dangerous drugs must be administered under the direction of a qualified expert, thus launching the requirement for prescription only (non-narcotic) drugs.

1951

Soon after the Durham-Humphrey Amendment was codified into a law that divided drugs into two basic categories: prescription-only and OTC drugs, and

authorized the FDA to classify drugs accordingly. At this time many important drugs could be sold only by prescription from a licensed practitioner making doctors the gate-keepers of prescription medications. Consumers had to pay for the drug as well as a visit to the doctor. These new rules were meant to discourage consumers from trying to self-medicate. Dependence on doctors was further reinforced by making it difficult for patients to gain information, in particular by the labeling and advertising controls in place.

1962

The health care system suffered a tremendous blow when Thalidomide, a new sleeping pill, was the agent that produced specific birth defects in thousands of babies born in Western Europe. The discovery dated back to 1957 when a West German pharmaceutical manufacturer introduced a new sedative, thalidomide, which alleviated the symptoms of morning sickness in women during the first trimester of pregnancy. In 1962, by which time the drug had been sold in forty-six countries, it became clear that thalidomide damaged the fetus, causing stillbirth or, most prevalently, phocomelia (Greek for “seal limb”). Thousands of newborn babies were found to have truncated limbs that resemble flippers. News reports on the role of Dr. Frances Kelsey, FDA medical officer, in keeping the drug off the U.S. market, aroused public support for stronger drug regulation. In response the Kefauver-Harris Drug Amendments were passed to ensure drug efficacy and greater drug safety. For the first time, drug manufacturers were required to prove to FDA the effectiveness of their products before marketing

them. In addition, FDA was given closer control over investigational drug studies, FDA inspectors were granted access to additional company records, and manufacturers had to demonstrate the efficacy of products approved prior to 1962.

1966

It was only logical to begin thoroughly investigating drugs that may have slipped under the existing regulatory surveillance. In 1966 the FDA contracted with the National Academy of Sciences/National Research Council to evaluate the effectiveness of 4,000 drugs that were previously approved on the basis of safety alone between 1938 and 1962.

1968

Further the FDA Bureau of Drug Abuse Control and the Treasury Department's Bureau of Narcotics were transferred to the Department of Justice to form the Bureau of Narcotics and Dangerous Drugs (BNDD), consolidating efforts to police traffic in abused drugs. A reorganization of BNDD in 1973 formed the Drug Enforcement Administration. FDA formed the Drug Efficacy Study Implementation (DESI) to incorporate the recommendations of a National Academy of Sciences investigation of effectiveness of drugs marketed between 1938 and 1962.

1983

By 1983, the research, testing, and development of a new drug could take up to twenty years, a major chunk of which expired in waiting for final FDA

approval of the NDA. Increased awareness of patients desperately waiting for newer treatments gave rise to further changes in regulatory reform. Pharmaceutical companies realized that the costs of obtaining FDA approval were the same whether the projected market was tiny or massive. Naturally the inclination was to pursue the development of large-market therapies and abandon (or “orphaned”) small-market therapies. Thus, FDA regulation seemed to have had negative consequences for people suffering from rare diseases. This gave rise to the Orphan Drug Act which enabled FDA to promote research and marketing of drugs needed for treating rare diseases.

1984

When the U.S. government grants a patent to a drug, other manufacturers are barred from producing a product of the same compound for a specific amount of time. By filing a patent, pharmaceutical firms are granted some degree of monopoly to market the product for a specified time period. The usual life of a patent is seventeen years. When developing a new drug, firms have to be cautious about the possibility that another company may also be working on the same drug and may be filing for a patent. Companies therefore apply for and receive drug patents in advance of final FDA approval to market the drug. By applying for a patent beforehand, some of the time from the patent life is lost in the approval process. This reduces the time the company has to market the drug and recover the investment. When a patent expires, other producers are permitted to replicate the product and to sell it as a “generic drug.” This

competition further reduces a firm's ability to charge the price they would like for the drug.

During the 1970s and 1980s, the duration of FDA requirements continued to grow, reducing the effective patent life. The drug companies therefore experienced not only greater drug development costs and delays, but also shrinking patent protection of products that were eventually approved. Financially this was an unviable option.

In order to be fair, commissions established at this time recommended that patent terms be adjusted to make up for time lost during regulatory review. But this was not accepted by generic drug producers and therefore the reform could not be passed. Thus, a bilateral bill emerged, the 1984 Drug Price Competition and Patent Term Restoration Act, known as the Waxman-Hatch Act. This act served the generic drug producers by removing some arbitrary and absurd constraints on generic drug manufacturers. Prior to the act, it was not sufficient for a generic drug manufacturer to prove that its drug was bioequivalent to an approved drug. Instead, the manufacturer had to submit independent information on safety and efficacy. Thus, the generic drug manufacturer had to repeat many of the clinical trials performed by the original manufacturer, despite the fact that the drugs could be shown to be bioequivalent. As a result of the costs of performing clinical trials, many drugs did not face generic competition even after the relevant patents had expired. The act required the FDA to accept

bioequivalence as sufficient for approval. The procedure for a generic drug approval is called an Abbreviated New Drug Application or ANDA.

Drug Price Competition and Patent Term Restoration expedited the availability of less costly generic drugs by permitting FDA to approve applications to market generic versions of brand-name drugs without repeating the research done to prove them safe and effective. At the same time, the brand-name companies could apply for up to five years additional patent protection for the new medicines they developed to make up for time lost while their products were going through FDA's approval process.

This marked a new phase in the regulatory environment. Though all of the regulations were meant to improve the system by ensuring safe and efficacious drugs reaching the public, many of them had a significant effect of delaying a new molecule entering the market. Access was now a prominent issue being discussed by the media, patients as well as regulatory officials. There was a need to streamline the process so that a balance was achieved between quality and access.

1992

Before 1992, studies demonstrated that on average it took the FDA two and one-half years to review an NDA and sometimes up to eight years. Often, the cause of delay was not the difficulty of the application but merely backlog. Realizing the problem might be attributed to lack of adequate resources, the FDA concluded that the process of approval could be facilitated if they had better

equipment and more workers to review applications. Since congress was unwilling to increase FDA appropriations, the Prescription Drug User Fee Act of 1992 was established. It stated that for a five-year period a mandatory fee of roughly $200,000 to be submitted by a pharmaceutical company along with its application. The FDA hired hundreds of new employees. As a result of the legislation the average processing time reduced substantially. The Prescription Drug User Fee Act required drug and biologics manufacturers to pay fees for product applications and supplements, and other services to supplement FDAs attempts to streamline the process of approval. The act also required FDA to use these funds to hire more reviewers to assess applications.

1997

Because of this evident success, the Modernization Act of 1997, renewed the practice for another five-year period and increased the user fees. Food and Drug Administration Modernization Act reauthorized the Prescription Drug User Fee Act of 1992 and mandated the most wide-ranging reforms in agency practices since 1938. Provisions included measures to accelerate review of devices, advertising unapproved uses of approved drugs and devices, health claims for foods in agreement with published data by a reputable public health source, and development of good guidance practices for agency decision-making.

2.3 PRODUCT EVALUATION

As discussed previously, the environment for pharmaceuticals is highly regulated to ensure that new chemical entities are marketed to the population under the highest standards possible. Once these entities enter the market, they undergo constant scrutiny to assess their impact on society. This is necessary, as the complete safety profile of a drug is not evident until a drug product has remained in the market for a while and is exposed to a sufficiently large and diverse population during the post marketing phase (Anello, 1985; Faich, Dreis, & Tomita, 1998; Gordon & Petrick, 1992; Griffin, 1986). Additionally, other issues like drug misuse or abuse may prevail, lending a drug to cause further harm rather than good (Ronald D. Mann, 1994). Lastly, there is the issue of concomitant use of drugs with alternate therapies that may give rise to drug interactions or adverse drug reactions (Fletcher, 1991; Ronald D Mann, 1992; Sachs & Bortnichak, 1986). These lead to labeling changes, warnings or even drug discontinuations. Due to the afore-mentioned and numerous other reasons that may have an impact on a drug product, drug surveillance became an important constituent of the drug life cycle (Koch-Weser, 1985; Rawlins, 1988; Talbot, 1986).

At this stage, which is also part of drug surveillance, the review process for new products is complex and numerous terms are used to describe how these products are evaluated to determine if they will maintain a presence in the market.

2.3.1 Market Discontinuation

Market discontinuation is regarded as a function of the overall evaluation process to assess product longevity and viability in the market. Drug discontinuation may be defined as approved products that have been discontinued from the market or have had their approvals withdrawn for other than safety or efficacy reasons, subsequent to being discontinued, have never been marketed, are for exportation or are for military use. The pharmaceutical firm's prospect of discontinuing a product from the market may pose considerable consequences such as financial setbacks, loss of good will, and disruptions to drug development. Not only is it in the best interest of a pharmaceutical company to improve fiscal return on an investment but also to meet societal needs for innovative products, thus reinforcing long-term value, building brand loyalty, and maintaining a favorable public image (Ashworth, 1997; Bouvier-Colle, 1994; Burkhart, Sevka, Temple, & Honig, 1997; Kleinke & Gottlieb, 1998; Lynn & Ellis, 1998; Miller, 1990). Considering these implications and their impact on product development, it is vital to characterize and to understand the rationale for market discontinuations. For the purposes of this study, market discontinuation could potentially be triggered by withdrawal of approval by the FDA for safety or efficacy, obsolescence, financial reasons, and other reasons.

2.3.2 Withdrawal of Approval

If the withdrawal criteria have been met, the FDA can withdraw approval of a new drug application (NDA or ANDA). Withdrawal can occur only after an opportunity for a hearing has been granted. Once the hearing is held and decided, the sponsor may file a petition within 60 days in the appropriate U.S. Court of Appeals.[1] After due notice and an opportunity for a hearing is provided to the applicant, the FDA can withdraw approval of an application with respect to any drug if it finds:[2] (1) that clinical or other experience, tests, or other scientific data shows that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the FDA until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the FDA when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) the patent

[1] FDCA Sec. 505(h)
[2] FDCA 505(e), U.S.C. 355(e)

information prescribed for NDAs was not filed within thirty days after the receipt of written notice from the FDA specifying the failure to file such information; (5) that the application contains any untrue statement of a material fact.

The FDA may also, after due notice and opportunity for a hearing to the applicant, withdraw the approval of an application with respect to any drug if the FDA finds:[3] (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or make required reports, or the applicant has refused to permit access to, or copying or verification of, such records; or (2) that on the basis of new information, evaluated together with the evidence when the application was approved, the methods used in, or the facilities and controls used for, the manufacturing, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the FDA specifying the matter complained of; or (3) that on the basis of new information, evaluated together with the evidence when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular way and was not corrected within a reasonable time after receipt of written notice from the FDA specifying the matter of complaint(s).

[3] FDCA 505(e), U.S.C. 355(e)

2.3.3 Withdrawal of Approval of Reference Listed Drug

An ANDA may be withdrawn under the Section 505(e) provisions. However, there are specific provisions dealing with ANDA withdrawal(s). If an ANDA refers to its approved application to a drug the approval of which was withdrawn or suspended for safety issues as determined by the FDA, the approval of the ANDA will also be withdrawn or suspended: (A) for the same period as the withdrawal or suspension of the listed drugs, or (B) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the FDA determines that the withdrawal from sale is not for safety or effectiveness reasons.[4]

2.3.4 Voluntary Withdrawal of listed drugs from the market

In 1986, the FDA initially announced that it would automatically remove from the list all products voluntary withdrawn from the market and put the burden on anyone wishing to rely on those drugs to show that withdrawal was not due to concerns about safety and/or effectiveness. The FDA changed its position and allowed the removal of drugs from the list only after finding that market withdrawal was based on safety or effectiveness concerns.[5] But the FDA refuses to approve an ANDA that refers to a listed drug withdrawn from the market if there has not been a determination about whether such withdrawal was based upon safety and/or effectiveness concerns.[6] Additionally, generic applicants must

[4] FDCA 505 (j)(6)
[5] 21 C.F.R. 314.162(a)(2) (1997)
[6] 21 C.F.R. 314.127(a)(11) (1997)

submit a petition to the FDA to make such determination for the drug seeking generic approval. Then, the FDA determines the reasons for withdrawal of the listed drug if there is already an approved ANDA before approving any ANDA that refers to a listed drug and if anyone who submits a citizen petition asks for such determination.[7]

The discontinuation from the orange book of reference listed drug impedes generic approval of the drug. Somerset Pharmaceuticals had marketed a tablet form of Eldepryl and switched to a capsule form in an effort, according to the company, to avoid “safety” problems with counterfeiting and illegal imports. The FDA rejected the innovator claim and approved generic versions of the tablet form. The fact that the innovator product was a capsule and the generic drug were tablets led the FDA not to rate the generics as AB (interchangeable) in the Orange Book. A judicial challenge to the decision to keep Eldepryl in the list led to a denial of a motion for preliminary injunction.[8]

2.3.5 Recall

Recall means a firm's removal or correction of a marketed product that the Food and Drug Administration considers to be in violation of the laws it administers and against which the agency would initiate legal action, e.g., seizure. Recall does not include a market withdrawal or a stock recovery. Recall classification means the numerical designation, i.e., I, II, or III, assigned by the

[7] 21 C.F.R. 314.161(a) (1997)
[8] *Somerset Pharmaceutical, Inc. v. Shalala*, 973 F. Supp. 443 (D.Del.1997)

Food and Drug Administration to a particular product recall to indicate the relative degree of health hazard presented by the product being recalled.

(1) Class I is a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.

(2) Class II is a situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

(3) Class III is a situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequences.

2.3.6 Revocation

FDA may revoke orphan-drug designation for any drug if the agency finds that:

(1) The request for designation contained an untrue statement of material fact; or

(2) The request for designation omitted material information required by this part; or

(3) FDA subsequently finds that the drug in fact had not been eligible for orphan-drug designation at the time of submission of the request therefore.

(b) For an approved drug, revocation of orphan-drug designation also suspends or withdraws the sponsor's exclusive marketing rights for the drug but not the approval of the drug's marketing application.

(c) Where a drug has been designated as an orphan drug because the prevalence of a disease or condition (or, in the case of vaccines, diagnostic drugs, or preventive drugs, the target population) is under 200,000 in the United States at the time of designation, its designation will not be revoked on the ground that the prevalence of the disease or condition (or the target population) becomes more than 200,000 persons.

2.3.7 Operationalization

For the purpose of our study we used the term Market Discontinuation. We considered a drug to be discontinued from the market if it was deleted from the FDAs Approved Drug Products with Therapeutic Equivalence Evaluations commonly known as the Orange Book. The Orange book is a listing of all the drug products marketed in the U.S.. We also included withdrawals of approval in this category. By withdrawals of approval we mean “drugs that have been taken out of the market due to safety or efficacy concerns.” These withdrawals may be either voluntary or mandated by the FDA.

2.3.8 Reasons for Drug Discontinuation

A. Safety

Friedman *et al.* (Friedman et al., 1999) demonstrated that there was no increase in the number of drugs withdrawn. They evaluated the relationship between the speed of drug reviews and the need to withdraw approved drugs as well as assessed the rate of market withdrawals in the context of historical rates.

It was observed that the number of NDAs submitted as well as those approved post PDUFA increased at the rate of 12% a year. The reason was thought to be the comparatively shorter time of approval and therefore more NDAs were submitted in the U.S. for approval. Also the NMEs withdrawn attributed to safety concerns seemed to have been steadily decreasing since the mid 1980s, allaying the fear that PDUFA may have had negative public health implications.

Rawson and Kaitin (Rawson & Kaitin, 2003) used the Tufts university database as well as the Therapeutic Products Directorate (TDP) of Health Canada to compare new drug approval times in Canada and the USA from 1992 to 2001 as well as information about drugs discontinued for safety reasons. The median approval time in Canada was longer in every drug category than the U.S. but decreased substantially in both countries by the mid-1990s, though the review time in Canada increased subsequently. However, the rate of drugs discontinued for safety reasons was about 2% in Canada and 3.6% in the U.S., which was consistent with previous literature.

Wysowski and Schwartz (Wysowski & Swartz, 2005) discovered that AERS was the primary source of information used by the FDA for identifying post-marketing drug safety problems. They attempted to describe the reports submitted to the database from 1969 to 2002 and provided information associated with regulatory actions that also included information on drugs removed for safety reasons. During the 33 year time frame, more than 75 drug products were removed from the market due to safety reasons, while 11 drugs

had special requirements for prescriptions or restricted distribution programs. Approximately 1% of the drugs that were marketed were found to represent those that were withdrawn or restricted.

B. Financial

Clarke *et al.* (Clarke et al., 2006) viewed evidence used in making withdrawal decisions for drug safety. One of their findings was that withdrawals attributed to safety concerns were fairly uncommon. According to the evidence, commercial reasons were the main cause for products to be withdrawn. Although their sample for this conclusion was the British pharmaceutical market, similar trends may be identified in the U.S. market as well.

Predominant pricing strategies, namely, skimming and penetration pricing have been well established in the literature for consumer products. Pharmaceuticals follow the same pricing strategies dependent on the existing market dynamics. In their paper, Lu and Comanor (Lu & Comanor, 1998) identified several factors governing the pricing of pharmaceuticals from the time of market entry up to eight years in follow up. They demonstrated that a higher therapeutic benefit was the principal cause influencing the pricing of a product. The higher the clinical benefit over preexisting drugs in the market, the higher the launching price of the product. Conversely, products offering little benefit over their predecessors led manufacturers to set low introductory prices. This phenomenon if not reversed over the life cycle of the drug product could result in substantial losses for the firm and eventually lead a product to discontinuation.

As acknowledged by Ahmed *et al.* (Ahmed, Gardella, & Nanda, 2002) , the effects of market withdrawal pose a significant financial threat to the firm and its shareholders. The losses to the firm are increased multifold as compared with a product that may be withdrawn without such reports, especially if the product is linked to reports of adverse drug reactions. Furthermore, these effects are more pronounced when the drug is in advanced phases of the clinical trial as well as when the firm involved is small.

C. Regulatory

During the period following the implementation of PDUFA in 1992 there were a number of concerns raised by critics stemmed by the withdrawal of drugs like fenfluramine, dexfluramine, terfenadine, mibefradil and bromfenac sodium. All of these drugs had severe side effects and public health implications and were withdrawn for safety reasons. It was believed that user fees had relaxed the FDAs vigil. Studies conducted by the GAO and Friedman *et al.* (Friedman et al., 1999) later proved that this was not the case and that the frequency of withdrawals had not changed with the advent of PDUFA.

Berndt *et al.* (Berndt, Gottschalk, Philipson, & Strobeck, 2005)assessed the effect of PDUFA on drug withdrawal rates as the debate for and against PDUFA continued. They also reviewed data on drug approvals and drug approval times and statistically isolated the effects of PDUFA I and PDUFA II by therapeutic class within a multivariate context. They found that though approval times showed an annual decline during PDUFA I (6 – 7%) and PDUFA II (3 –

4%), the proportion of approvals that led to safety withdrawal rates remained constant. Central Nervous System (CNS) and cardiovascular therapeutic classes had the greatest decrease post PDUFA as compared with the pre PDUFA period. It was also observed that anti-neoplastic and anti-infective therapies were approved more rapidly than CNS and cardiovascular drugs probably attributed to urgent, yet unmet needs in oncology.

2.4 OUTCOME

The literature is rife with studies that compare the efficacy and economics of specific treatments versus alternative costs; however, rarely do we consider the value of societal investments for new medical treatments and their long-term benefits. The value created by pharmaceuticals whether realized through increased life expectancy, improved quality of life, or other measures is essential to achieving positive health outcomes in patients. The market status of a drug product has significant implications not only for the patient but also other stakeholders like providers, and regulatory authorities (O M Bakke, 1998; Goyan, 1993; Jefferys, Leakey, Lewis, S, & MD, 1998; McGahn & Block, 1986; Steward & Wibberley, 1980).

2.4.1 Impact of Discontinuations

A. Patients

One of the issues with the health care system is access to life-saving therapies for all. Once a drug reaches the market and is prescribed to patients, it is not desirable for a discontinuation notice to be issued. Patients constantly suffer due to lack of therapies for numerous ailments presently affecting the population ("Hasty approval, more withdrawals," 2005; "Problems with drug withdrawals," 2001). To add to this concern is the possibility of depriving patients of a drug that might provide great health benefit.

Usually an alternative suggested to patients once a drug has been taken out of the market is to switch to another drug in the same class, provided there

are other substitutes available. In situations where there may not be other compounds with comparable efficacy, patients are left to suffer without cure.

B. Pharmaceutical Companies

Ahmed *et al*. (Ahmed et al., 2002) studied the impact of drug withdrawals on firms and their competitors from an economic perspective between 1966 to 1998. They aimed to assess the availability of substitutes for withdrawn drugs as well as understand the comparative withdrawal effects on single versus multiple firms. Their findings, like other studies before, indicated that stockholders of drug producers do suffer significant financial setback at the news of a drug withdrawal. Further they found that the losses for the firm were significantly higher when there were adverse event resulting in a withdrawal rather than just withdrawal announcement. Losses were also found to be higher for a single firm withdrawing a drug versus several firms withdrawing a class of drugs.

The financial losses associated with withdrawal are nothing compared to the combined cost of recuperation of goods and compensation to victims that may be associated with the withdrawal. In addition the firm suffers the loss of reputation and brand loyalty which may take significantly longer to restore as well as the time and opportunity costs associated with the drug withdrawal.

C. FDA

The FDA has been criticized intermittently for either being too cautious thereby reducing access to life saving drugs or being too lax and therefore responsible for exposing patients to less than safe and efficacious therapies.

When the news of a withdrawal or discontinuation hit the media, disapproval is experienced from all sides about the FDA not performing its duties ("Experts Look for Ways to Lessen Impact of Drug Shortages and Discontinuations," 2007; "Problems with drug withdrawals," 2001). In addition, obtaining user fees from drug companies has worsened the situation with some critics saying that the FDA is being swayed by the companies that pay the user fees to make compromises regarding their approval process.

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CHAPTER III: METHODS

This chapter describes the methodology used to conduct this study. The first section addresses the sources of data and data collection. The second section presents the dependent and independent variables used in the study. The third section states the study's research question, research objectives, and research hypotheses. The chapter's fourth section describes the statistical methods used in the study to explain the relationship between the dependent and independent variables. The chapter concludes with a summary.

3.1 Sources of Data

3.1.1 FDA Data Files

3.1.1.1 Freedom of Information Act (FOI) Request to FDA

A Freedom of Information Act (FOI) request was sent to the FDA asking for information pertaining to those NMEs approved during the time period 1980-2008. An Excel data file was sent by the FDA which contained the following information related to all NDA approvals occurring between 1980 and 2008: application type, document number, product number, sponsor, dosage form, route of administration, trade name, drug code, received date, approval type, approved date, discontinued type, discontinued date, withdrawal type, withdrawal date, active ingredient name, potency, therapeutic gain, chemical type, orphan drug code, indication, patent number, patent expiration date, exclusivity code, exclusivity expiration date, and patent use code.

3.1.1.2 Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)

The publication identifies drug products approved on the basis of safety and effectiveness by the FDA under the Federal Food, Drug, and Cosmetic Act (FDCA). Drugs on the market approved only on the basis of safety (covered by the ongoing Drug Efficacy Study Implementation [DESI] review or pre-1938 drugs are not included in this publication. Included were data from the 1st version of the Orange book published in October 1980 through the 27th version in 2007. Information was also extracted from the electronic version of the Orange Book available at the FDA webpage.

The List is composed of four parts: (1) approved prescription drug products with therapeutic equivalence evaluations; (2) approved over-the-counter (OTC) drug products for those drugs that may not be marketed without NDAs or ANDAs because they are not covered under existing OTC monographs; (3) drug products with approval under Section 505 of the Act administered by the Center for Biologics Evaluation and Research; and (4) a cumulative list of approved products that have never been marketed, are for exportation, are for military use, have been discontinued from marketing, or have had their approvals withdrawn for reasons other than safety or efficacy subsequent to being discontinued from

marketing. The list also includes indices of prescription and OTC drug products by trade or established name.

The following data were collected for each NME approved by the FDA in the period of analysis: NDA number, NDA product number, generic name, trade name, NDA sponsor, dosage form, route of administration, orphan drug designation, orphan drug approval, orphan sponsor, classification, and approval date.

3.1.1.3 FDA New and Generic Drug Approvals

This database contains an alphabetical listing of all prescription drugs approved between 1998 and 2008. The database is updated on a daily basis and contains links to labels, approval letters, and reviews.

The following information was extracted from the database and used in this study: product name, company data, application number, and approval date.

3.1.1.4 Subpart H NDA Approvals

This database lists those NDAs approved under the “Subpart H” accelerated approval program.

3.1.1.5 Orphan Drug Designations and Approvals

The database lists those drugs with orphan drug designations and drugs approved under orphan drug status. The database contained the date of designations and the date of approval of the indication/s with orphan designation.

3.1.1.6 Fast-Track Designated Products

This database lists those fast-track designated products approved since 1998.

3.1.2 Other Sources of Data

Several other sources of data were used in the analysis:

3.1.2.1 NDA Sponsors

Information about NDA sponsors, parent company, and country of origin was found in the following databases: LexisNexis (Academic Universe, Business News, Pharmaceutical & Cosmetic News) and FIS online.

3.1.2.2 Clinical Indications

Information about FDA-approved indications for NMEs was found in the Micromedex database (DRUGDEX Drug Evaluations).

3.1.2.3 Discontinuation Data

Information about drug discontinuation was found from various journal articles, governmental web pages, and other documents available on the web (e.g., web pages of pharmaceutical companies and news sites). The Federal Register was used to determine whether a drug was discontinued for safety or efficacy reasons.

3.1.2.4 Drug Utilization Data

Reported State drug utilization information is available for outpatient drugs paid for by State Medicaid agencies since the inception of the Medicaid Drug Rebate Program from the Centers for Medicare and Medicaid Services website. The national summary data is available for each year in a text file format. The file includes the following: National drug code, year, quarter, drug name, units sold, dollar amount in sales.

3.1.2.5 Other Sources of Data

Other sources of data included the following: Merck Index, MediSpan PriceCheck, and selected issues from the journals “Pink Sheet,” “Pharmacy Times,” “Drug Topics,” and “American Druggist,” among others.

3.1.3 Data Management

The study period of 1980 to 2008 was chosen for the analysis. The data for each one of the categories considered in the present study were obtained from the afore-mentioned sources. Data were streamlined based on the inclusion and exclusion criteria.

Market discontinuation and withdrawals of approved drugs were considered for the purpose of the study. A drug was considered to be discontinued if it was no longer listed in the FDAs Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). Discontinuation was determined through a manual search of all the volumes of the Orange Book. The database was updated regularly using the electronic version of the Orange Book available online. Withdrawals of approval were defined as drugs that were no longer marketed due to safety or efficacy concerns. The list of drugs withdrawn for safety reasons was obtained from the Federal Register.

3.1.4 Data Verification

One of the more intuitive approaches of compiling data from different sources is by entering them into a spreadsheet. Moreover, this approach allows for data importation into numerous software packages for statistical analysis. Within the Excel 2007 grid used for the study, each column represented a variable and each row was a NME. Quality control was an important part of the study as it aids in reducing errors in data collection. Additionally, proper verification procedures promoted the strength of the research design.

To minimize errors in data collection two excel spreadsheets were created and the data from the primary sources were entered. Once all of the data were

collected, these two spreadsheets were compared to ensure matching of collected data. In case there were any discrepancies, the information was verified from the primary source and re-entered. Furthermore, the correspondence of the data with the original source was ensured by updating the information collected regularly from the primary data sources.

To combat data coding inaccuracies, we ran frequency distributions of data entered. This approach allowed us to see if our data were outside the acceptable range. For e.g. for the variable Sponsor country, data were coded as U.S. based companies = 1, Non-U.S. based companies/ Other = 0. If our frequency distribution showed a few values of 2, then these values were re-coded. Furthermore, data were checked visually to ensure precision.

3.2 Variables Used in the Analysis

3.2.1 Dependent Variable

The drug market status was the depended variable. The market status has the following values:

3.2.1.1 Marketed

Marketed drugs refer to those products that were approved by the FDA and were marketed within the United States on December 31, 2008.

3.2.1.2 Discontinued

Discontinued drugs refer to those products that were approved by the FDA and that were listed at least once in the Orange Book, but were no longer listed in the electronic Orange Book database, which is updated daily.

3.2.1.3 Never Marketed

Never marketed refers to those drugs that were approved by the FDA for marketing within the U.S., but were never brought to the U.S. market by the manufacturer.

3.2.1.4 Brand Discontinued

This category refers to those products that had the brand name drug discontinued, while the generic drug remained in the market.

3.2.1.5 Change in Route, Dosage form or Strength

This category refers to those products that experienced a change in their route, dosage form or strength while they were being marketed in the U.S..

3.2.1.6 Change from Prescription to OTC

This category refers to those products that were approved by the FDA and experienced a change from a prescription to OTC status.

For the purpose of analysis, the variable market discontinuation was dichotomized to address some of the objectives. The two categories created were –

Not Discontinued was coded as 0 and included the following categories: Marketed, Brands discontinued, Change in route dosage form or strength and Change from prescription to OTC;

Discontinued was coded as 1 and included the following categories: Discontinued and Never marketed.

3.2.2. Independent Variables

The independent variables were classified as drug characteristics, sponsor characteristics, and drug policy.

3.2.2.1 Drug Characteristics

A. Route of Administration

The variable “Route of Administration” represents the method used to administer a drug. This variable has four possible values: oral, injectable, topical, and other, and is represented by three dummy variables. The value “other” is the baseline value. This variable is included in the analysis to account for those changes in drug discontinuation associated with drug route of administration.

B. Therapeutic Classification

The variable “Therapeutic Classification” represents the main clinical indication for a drug using the American Hospital Formulary System classification. This variable has 10 categories: anti-infective, anti-neoplastic, antiretroviral, cardiovascular, central nervous system (CNS), endocrine/hormone, gastointestinal (GI), diagnostic agent, autonomic drugs, blood formation,

coagulation, and thrombosis, electrolytic, caloric, and water balance, enzymes, eye, ear, nose, and throat (EENT) preparations, gold compounds, heavy metal antagonists, hormones and synthetic substitutes, local anesthetics, oxytocics, respiratory tract agents, skin and mucous membrane agents, smooth muscle relaxants, vitamins, and miscellaneous therapeutic agents. This variable is included in the analysis to account for the impact of an NME's clinical indication on drug discontinuation patterns.

3.2.2.2 Sponsor Characteristics

A. Sponsor Country (U.S. vs. Other)

The variable "Sponsor Country (U.S. vs. Other)" represents the nationality of the NME's sponsor at the moment of the first FDA NDA approval. This variable has two values: U.S. and non-U.S. The NME's sponsor can change through company mergers and acquisitions. This variable is included in the analysis to account for those changes associated with the sponsor's nationality. U.S. pharmaceutical companies are assumed to have better access to the FDA and foreign companies could register their NMEs in other countries before they file an NDA in the U.S.

B. Sponsor with a Single NME Approval during the Study Period

The variable “Sponsor with a Single NME Approval during the Study Period” represents those companies having only one NME approval during the study period. This variable has two values: sponsor with a single NME approval and sponsor with multiple NME approvals. This variable is included in the model to account for a company’s experience with NME development and the FDA review process.

3.2.2.3 Drug Policy

A. Orphan Drug

The variable “Orphan Drug” represents those NMEs that were primarily designated as orphan drugs, and this category did not constitute subsequent orphan drug designations. This variable has 2 values: orphan drug and non-orphan drug. A dummy variable is also included that accounts for drugs approved before and after the enactment of the orphan drug program. The variable Orphan Drug is included in the analysis to account for those changes associated with orphan drug status.

B. FDA Accelerated Review

The variable “FDA Accelerated Review” represents those NMEs that have been approved though the “Subpart E,” “Fast Track,” or “Subpart H” review programs. The Subpart E program was established in 1988; the Fast Track program was enacted in 1997; and the Subpart H program was implemented in 1992. This variable has 2 values for each of the three review programs. A dummy variable was also included for each program to account for drugs approved before and after program enactment. The variable FDA Accelerated Review is included in the analysis to account for the impact on drug discontinuations associated with accelerated drug approval.

C. FDA Review Priority

The variable “FDA Review Priority” represents the FDA’s classification of an NME’s therapeutic potential. This variable has two values: standard review and priority review. This variable is included in the analysis to account for those changes associated with FDA review classification.

D. Prescription Drug User Fee

The variable “Prescription Drug User Fee” represents those NMEs approved under the 1992 Prescription Drug User Fee Act. This variable has two values: user fee or no user fee. A dummy variable is included that accounts for drugs approved before and after the enactment of the prescription drug user fee program. The variable Prescription Drug User Fee is included in the analysis to account for those changes in patent life associated with the enactment of the Prescription Drug User Fee Act.

3.3 NME Inclusion and Exclusion Criteria

The unit of analysis of the study was the NME entity. The study included the 703 NMEs approved in the U.S. during the period 1980-2008. The inclusion criteria for subject selection were: (1) to be considered an NME by the FDA, and (2) to be the first NDA approved for an NME. When several NDAs were approved by the FDA for the same NME on the same date, the first product number for the approved NME was chosen.

The study included drugs for use in humans. Those drugs that are meant for animal use were excluded from the analysis.

3.4 Research Objectives and Hypothesis

3.4.1 Research Question

The purpose of this study is to analyze the market discontinuation of NMEs approved in the U.S. between 1980 and 2008. The study's specific research question is the following: Is the market status of an NME affected by the characteristics of the drug, the characteristics of the sponsor and the regulatory status under which a drug was evaluated and approved?

3.4.2 Research Objectives and Hypotheses

Objective A: Describe the demographic characteristics of the NMEs approved by the FDA between 1980 and 2008.

This descriptive analysis included an analysis of the current market status of the drug (marketed, discontinued, never marketed, changes in route, dosage form, strength, and changes from brand to OTC status) drug characteristics (route of administration, therapeutic classification), sponsor characteristics (country, number of NME approvals) and drug policy (orphan drug status, FDA

review type, whether or not user fee applies). Data will be presented at the aggregate level and with respect to therapeutic class.

Objective B**:** Determine the reasons for drug market discontinuations.

The following reasons were considered:

A. Safety and Efficacy

B. Financial reasons

Hypothesis 1. Safety and efficacy are hypothesized as the main contributors to the explanation of drug market discontinuations

For financial reasons the Medicaid Drug Utilization Data were used to evaluate whether being removed from the Medicaid formulary had any effect on drug discontinuations.

Objective C: Evaluate the effect of drug characteristics (route of administration, therapeutic classification) on Market Discontinuation.

Independent variables hypothesized to be associated with market discontinuations were:

1. Route of Administration

    - Oral

    - Injectable

    - Topical

2. Therapeutic Classification

    - Anti-infective

    - Anti-neoplastic

    - Antiretroviral

    - Cardiovascular

    - Central Nervous System (CNS)

    - Endocrine/Hormone

    - Gastrointestinal (GI)

    - Respiratory/Allergy

Hypothesis 2. Route of administration as well as therapeutic class are expected to be associated with market discontinuation.

Objective D: Evaluate the effect of sponsor characteristics (country, number of NME approvals) on Market Discontinuation.

Independent variables hypothesized to be associated with market discontinuations were:

1. Sponsor Country (U.S. vs. Other)
    - U.S.
    - Other
2. Sponsor with a Single NME Approval during the Study Period
    - Single
    - Multiple

Hypothesis 3. Sponsor characteristics are expected to be associated with market discontinuation of pharmaceuticals.

Objective E: Evaluate the effect of drug policy (orphan drug status, FDA review type, whether or not user fee applies) on Market Discontinuation. Independent variables hypothesized to be associated with market discontinuations were:

1. Orphan Drug
    - Orphan Drug Status
2. FDA Accelerated Review
    - Subpart E
    - Subpart H
    - Fast Track
3. FDA Review Priority
    - Priority Review

- Standard Review

4. Prescription Drug User Fee

- Prescription Drug User Fee Enacted

Hypothesis 4. Orphan drug designation, FDA accelerated review type, priority review, and the enactment of PDUFA are expected to be associated with market discontinuation.

Objective F: Evaluate the effect of the independent variables or the predictors of Market Discontinuation.

Objective G: Measure the time from approval to Market Discontinuation for drugs discontinued for safety reasons.

3.5 Statistical Analysis

3.5.1 Statistical Analysis for Objective A

The purpose of Objective A was to describe the demographic characteristics of the NMEs approved between 1980 and 2008. Summary descriptive statistics were computed for both dependent and independent variables. Differences between proportions were tested using chi-square analysis.

3.5.2 Statistical Analysis for Objective B

The purpose of Objective B was to identify the reasons for market discontinuations of NMEs approved between 1980 and 2008. Descriptive statistics were computed for the variables.

To determine whether drugs were discontinued for financial reasons, the dataset was combined with the Medicaid Drug Utilization data to ascertain trends within the Medicaid drug formulary.

According to Intercontinental Marketing Services (IMS) Health about 60 percent of the nation receives healthcare services through managed care plans, amounting to over $100 billion in pharmaceutical product expenditures in 2002. Medicaid prescription drug expenditures grew to $32.2 billion in 2002,

representing more than 18 percent of total prescription sales in the U.S. As Medicaid represents one of the larger drug utilization programs with publicly available data, this database was used for the purpose of our analysis.

The drugs identified as discontinued in our database were tracked within the Medicaid database. Our goal was to map drug utilization trends and our hypothesis for this analysis was that a drug that was discontinued from the Medicaid formulary would be subsequently discontinued from the U.S. market entirely.

3.5.3 Statistical Analysis for Objective C

The purpose of Objective C was to estimate the relationship between drug characteristics and market discontinuations. Differences between proportions were tested using chi-square analysis and Fisher's exact test. Post-hoc analyses were employed to identify the effect of specific therapeutic class on market discontinuations. Specifically, the expected and observed cell counts were assessed and the standardized residuals were obtained to identify the specific levels of the independent variables that demonstrated significant p-values.

3.5.4 Statistical Analysis for Objective D

The purpose of Objective D was to analyze the relationship between sponsor characteristics and market discontinuations. Differences between proportions were tested using chi-square analysis and Fisher's exact test.

3.5.5 Statistical Analysis for Objective E

The purpose of Objective E was to analyze the relationship between drug policy and market discontinuations. Differences between proportions were tested using chi-square analysis.

All analyses were conducted keeping an a priori p-value for statistical significance of 0.05.

3.5.6 Statistical Analysis for Objective F

Objective F focused on the characteristics of drugs to determine their effect on market discontinuation. For the purpose of this objective the dichotomized variable for market discontinuation was used. Since the outcome variable was dichotomous (discontinued drugs = 1, not discontinued drugs = 0), logistic regression was deemed appropriate for the analysis. A logistic regression model was built using Stata® 8.2 software. We used the forward selection procedure to

build the model. We began with the univariate relationship between each predictor from the dataset and the outcome variable market status. The first predictor was safety (drug discontinued for safety reasons = 1; drugs discontinued for other reasons = 0). This formed our univariate model to which the bivariate model was compared to carry out the likelihood ratio test. The Likelihood ratio test was performed for inclusion of a predictor in the model. This test compares a full model containing the variable of interest and a model where only the variable of interest has been eliminated. The following is the formula for the likelihood ratio test:

$$2*(\text{log likelihood of full model}) - 2*(\text{log likelihood of smaller model}) \sim \chi^2 df$$

The variable with the lowest p-value for the likelihood test was added to the model. This p-value indicates how much the predictive power of the model has improved on addition of a particular variable. If there was more than one variable with the lowest p-value then the highest chi-square value was used to add the variable into the model. According to the calculation the variable with the largest chi-square value would be the one that made the full model appreciably different from the reduced model. Forward selection of variables was continued till addition of any of the remaining variables did not significantly improve the predictive power of the model. Odds ratios were calculated for each of the terms in the final model.

The goodness of fit of the model was assessed by looking at the χ^2 value from the Hosmer-Lemeshow test. Our null hypothesis for this test was: Ho: No lack of fit. The discrimination of the model was assessed by creating the ROC curve and calculating the area under the curve. The sensitivity and specificity of the model were also examined.

3.5.7 Statistical Analysis for Objective G

The purpose of Objective G was to measure the time from approval to Market Discontinuation for drugs discontinued for safety reasons. We used Kaplan-Meier survival curves to measure a drugs survival over the study period. Survival was defined as a drug that had not reached the end point or had not been discontinued from the market until the end of the study period. We right censored the drugs that had not reached the endpoint at the time of analysis. Time to event was analyzed using the Kaplan-Meier method including confidence limits for survival rates, the log rank test and the Cox-proportional hazards model. Stata® 8.2 software was used to build the model using the forward selection procedure for including variables in the model.

Before starting the model building process, proportional hazards assumption was tested for all the variables by performing the Schoenfeld Test for proportional hazards assumption. We also tested the assumption graphically. When predictors did not fulfill the assumption we used these time dependent

variables in our model along with their interaction term with the time to event variable.

Each univariate model was run to ascertain which one should be first included in the model. Then each of the other variables was individually added to the univariate Cox proportional hazards model separately, in search of the best bivariate model. The variable whose addition to the model produced the lowest Akaike's Information Criterion value (AIC) was determined to be the best one to be added to the model. The formula used for the AIC is as follows:

$$AIC = -2(\log likelihood) + 2(\#\ parameters\ in\ model)$$

The process was repeated on the remaining variables to generate trivariate and larger models until the AIC value for the model did not decrease any more. Finally survival and hazard function curves were produced for the final model using the statistical software.

There are three assumptions underlying time-to-event analysis. The first is the assumption of proportional hazards, meaning that the ratio of hazard functions must be constant over time. This assumption was checked both mathematically using Schoenfeld residuals and graphically when the final model was determined. The $\chi 2$ statistic was calculated for the final model. If the statistic was found to be less than 0.05, the test indicated that the hazards were significantly different over time and that the assumption of proportional hazards was violated. "Log-log" plots [-ln (-ln (survival)) curves] were plotted for each

variable in the model. If the curve did not appear to be parallel to the horizontal axis, the assumption of proportional hazards was violated.

The second and third assumptions for a proportional hazards model are independence of observations and independence of censoring time from event times respectively. Both these assumptions were validated by examining the design of the study. The third assumption was also tested by observing censoring times on the Nelson-Aalen curve.

Once the model was found and tested for violation of assumptions, practical results were produced. The coefficient for each risk factor was calculated by taking the natural logarithm of the hazard ratio for each risk factor from the software output. In addition we created a table of the different values of the hazard ratio over time for the variable that had a time dependent covariate.

CHAPTER IV: RESULTS

This chapter presents the results of the study. The first section describes the demographic characteristics of NMEs approved by the FDA from January 1st 1980 to December 31st 2008. The next section provides data concerning the main events in the life of the NMEs examined that led to market discontinuation. The chapter's last section describes the relationship between selected dependent and independent variables.

4.1 Results for Objective A: Describe the Demographic Characteristics of NMEs Approved by the FDA between 1980-2008

The total number of NMEs approved by the FDA during the study period was 703.

4.1.1 NDA Approval Year

Table 4.1 displays trends in the number of NMEs approved per year during the period from 1980 to 2008 (Figure 4.1). An average number of 41 NMEs per year were approved during the study period. A higher number of NMEs were approved in the 1990s than in the 1980s (311 vs. 220). There were 172 NMEs approved from 2000 to 2008. Almost one-half (46.79%) of the drugs were approved after 1996.

4.1.2. Drug Characteristics

A. Route of Administration

Frequency statistics related to NME route of administration are displayed in Table 4.2. The oral route was most common; 380 (54%) of the 703 NMEs

approved during the study period utilized an oral route of administration. The injectable route was the second most common route, accounting for 167 NMEs (27%). The topical route was the third most common route, accounting for 33 NMEs (6%). Other routes of administration accounted for 119 NMEs (14%).

B. Therapeutic Classification

Frequency statistics related to NME therapeutic classification are displayed in Table 4.3. Forty-five percent of the 703 NMEs approved during the study period were represented by the anti-infective (121, 17%), CNS (107, 15%), and cardiovascular (93, 13%), classes (see Table 3.3). The remaining classes accounted for 55% of the NMEs approved during the study period. The frequency with which these classes occurred is as follows: anti-neoplastic (60, 8%), diagnostic agent (53, 7%), endocrine/hormone (35, 5%), gastrointestinal (27, 4%), and other (207, 31%).

4.1.3. Sponsor Characteristics

A. Sponsor Country (U.S. vs. Other)

Frequency statistics related to NME sponsor nationality are displayed in Table 4.4. NMEs with multiple sponsors including those from the U.S. included in the U.S. sponsor group. Fifty-seven percent (397) of the 703 NMEs approved during the study period had U.S. sponsors. The remaining NMEs (43%) had non-U.S. sponsors. Sponsors from UK, Switzerland and Germany received 12%, 11%, and 8% of 703 NME approvals, respectively. All other countries accounted for 12% of the NME approvals.

B. Sponsor with a Single NME Approval During the Study Period

Frequency statistics related to number of sponsors with single or multiple NME approvals are displayed in Table 4.5. A total of 111 NME sponsors (16%) received only 1 NME approval from the FDA during the study period. The remaining 592 NME sponsors (84%) received multiple NME approvals during the study period.

4.1.4. Drug Policy

A. Orphan Drug

Tables 4.6-4.7 display frequency statistics related to those 634 NMEs that were approved during the period 1983, when the orphan drug program was enacted, and 2008. Orphan drug status was granted by the FDA to 111 (16%) of these NMEs.

B. FDA Accelerated Review

Tables 4.8-4.9 display frequency statistics related to those NMEs that were approved under the Subpart E accelerated review program during the study period. Twenty-one (4%) of the 483 NMEs approved when the program was applied, were approved under Subpart E accelerated review.

Tables 4.10-4.11 display frequency statistics related to those NMEs that were approved under the Subpart H accelerated review program during the study period. Forty-four (10%) of the 429 NMEs approved between 1992 (when the Subpart H program was first applied) and 2008 were approved under Subpart H accelerated review.

Tables 4.12-4.13 display frequency statistics related to those NMEs that were approved under the Fast Track accelerated review program during the study period. Ten of the NMEs analyzed in the study were approved under Fast Track accelerated review (4% of the 235 drugs approved between 1998, when the Fast Track program was first applied, and 2008).

C. FDA Review Priority

Frequency statistics related to NME review classification are displayed in Table 4.14. Three hundred seven (44%) of the 703 NMEs approved during the study period were approved under priority review classification.

D. Prescription Drug User Fee

Tables 4.15-4.16 display frequency statistics related to those NMEs that were approved under the 1992 Prescription Drug User Fee Act during the study period. Two hundred and six of the NMEs analyzed in the study were approved under the Prescription Drug User Fee Act (57% of the 360 drugs approved between 1993, when the Act was first applied, and 2008).

4.1.5 Market Status of Drugs

Drugs that were marketed during the study period represented 71.8% (506) of all drugs (Table 4.17). There were 5 drugs that never reached the market after FDAs new drug application approval. Of these drugs, 14.4% were discontinued from the market, while 5.4% brands name drugs were discontinued but their generic substitutes remained in the market (Figure 4.2). Another 6.8% of these drugs experienced a change in dosage form, strength, or route, and 0.9% drugs switched from prescription to over-the-counter during this time frame.

4.2. Results for Objective B: Determine the reasons for drug market discontinuations

When evaluating the reasons stated for the discontinuation of the NMEs, five of the drugs identified in the study never reached the market (Table 4.18). Safety reasons accounted for 27.4% of the drugs to be discontinued (Figure 4.3). We found that 64.2% had no stated reason for discontinuation and 3.8% were not discontinued for safety or efficacy reasons.

For each of the drugs that were discontinued for safety concerns, the reasons are provided in Table 4.19.

Three of the drugs that were discontinued were successfully identified within the Medicaid drug utilization database. Graphical representation of the data was provided for a better perspective regarding trends in drug utilization before discontinuation (Figure 4.4 - 4.6).

4.3. Results for Objective C: Evaluate the effect of drug characteristics (route of administration, therapeutic classification) on Market Discontinuation

Since there were less than 5 items per cell for the variable “route of administration” the chi-square test could not be conducted with this variable. When tested for differences in proportions between therapeutic classes, the study revealed that antibiotics were more likely ($p<0.05$) to be discontinued than any other therapeutic class of drugs.

For those NMEs that were currently marketed 68.2% experienced generic competition whereas out of the discontinued NMEs, only 1.9% faced generic competition (Table 4.20). A graphical representation is provided in figure 4.7.

4.4. Results for Objective D: Evaluate the effect of sponsor characteristics (country, number of NME approvals) on Market Discontinuation

Sponsor country (US or non-US) was not significantly associated with market discontinuation ($p<0.05$).

4.5. Results for Objective E: Evaluate the effect of drug policy (orphan drug status, FDA review type, whether or not user fee applies) on Market Discontinuation

Drug policy characteristics (orphan drug status, FDA review type, whether or not user fee applies) were not significantly associated with market discontinuation ($p<0.05$).

4.6. Results for Objective F: Evaluate the effect of all the independent variables or the predictors of Market Discontinuation.

Data were collected on the 703 NMEs. Table 4.21 provides summary statistics of the variables used in this analysis. Table 4.22 summarizes the forward selection procedure for building the regression model. Based on the literature and the chi-square analysis we chose to consider only the oral route among all of the different routes of administration and anti-infective class from all of the therapeutic classes in the dataset for the logistic regression. The main effects model consisted of five predictors of market status: drugs discontinued for safety reasons, user fee enactment, oral route of administration, anti-infectives, and orphan drug enactment. Addition of any other variables showed no significant p-values. The odds ratios for the final model are shown in Table 4.23.

The goodness-of-fit of the model was assessed to determine whether the predicted values are an accurate representation of the observed values in the model. The goodness of fit was assessed using the Hosmer-Lemeshow tests. The p-value for the Hosmer-Lemeshow test was 0.4286 with the cutoff point being 0.05. Based on the test our model fit well.

The discrimination of the model was assessed by calculating the area under the ROC curve (Figure 4.8). The area under the ROC curve was found to be 0.8245. The level of acceptable discrimination is equal to or greater than 0.70. This indicated that our model had a better than chance performance. The

specificity was high 99.33 % (Table 4.24 and 4.25). A graphical representation of the data confirms that sensitivity is low and specificity is very high (Figure 4.9).

The final model is as follows:

$$g(x) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 + \varepsilon_0$$

where β_0 is the y-intercept, β_1 and X_1 are the coefficient and the indicator variable of drugs discontinued for safety reasons, β_2 and X_2 are the coefficient and the indicator variable of user fee enactment, β_3 and X_3 are the coefficient and the indicator variable of oral route of administration, β_4 and X_4 are the coefficient and the indicator variable of antiinfectives, β_5 and X_5 are the coefficient and the indicator variable of orphan drug enactment and is the random error contained within the model.

From the afore-mentioned logit, the probability of having a drug discontinued from the market may be estimated by the following formula:

$$Pr(y=1/x) = \frac{e^{g(xi)}}{1+e^{g(xi)}}$$

We concluded that the odds of a drug being discontinued due to reasons of safety was much higher than those being discontinued for other reasons, keeping all other factors constant. Also after adjusting for other factors the odds of an anti-infective drug being discontinued was more than twice as high as drugs in other classes being discontinued.

4.7. Results for Objective G: Measure the time from approval to Market Discontinuation for drugs discontinued for safety reasons.

We tested each variable individually for the proportional hazards assumption (Table 4.26) before building our model. On the basis of AIC scores, the forward selection procedure (Table 4.27) yielded the most appropriate variables to create the univariate and bivariate models respectively. The final model is presented in Table 4.28.

We did not find any interactions to be significant and hence none were included in the model. The Kaplan-Meier and the Nelson-Aalen curves were plotted for the variables (Figures 4.10 – 4.19).

We tested the proportional hazards assumption for the final model using the global test with the log of the time to event variable. This test yielded a non-significant p-value of 0.09 which indicates the proportional hazards assumption was upheld.

The final model found by Cox proportional hazards calculation is the model with market status and coefficient (β1), (β2), (β3), (β4), (β5) and (β6).

$$\ln[h(t)/h_o(t)] = \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 + \beta_6 X_6$$

where ln [h (t)/ho (t)] is the log of the hazard ratio.

The hazard ratio for drugs that were approved under sub part H was 3.76 indicating that the hazards of time to discontinuation among drugs approved under sub part H were 3.76 times that of drugs not approved under sub part H

adjusting for other factors in the model. So drugs approved under sub part H were more likely to be discontinued.

Also the hazard ratio of time to discontinuation for safety coding was 2.532.53, which indicated that drugs were more likely to be discontinued for safety reasons when adjusting for other variables in the model.

Further the hazard ratios for orphan drug enactment were 2.30 and for those drugs that were approved in the fast track were 2.77.

Finally the hazard ratios for priority review were 0.56 and for the variable sponsor country were 0.66.

In Kaplan-Meier curve for the overall model we see that the estimated probability of a NME being discontinued from the market over a 5 year time period was 25%.

CHAPTER V: DISCUSSION AND CONCLUSIONS

This chapter concludes the dissertation. The first section discusses the findings related to the research objectives described in Chapter I and III. Next, the chapter presents conclusions related to these objectives. Next, implications of the study are discussed. Finally, the chapter notes the study's limitations and suggests areas for future research.

5.1 Discussion of Findings

5.1.1 NME Demographic Characteristics

A. NDA Approval Year

An average number of 41 NMEs per year were approved during the period 1980-2008. A higher number of NMEs were approved in the 1990s than in the 1980s (311 vs. 220). This result is explained in part by the high number of approvals in the years 1996-2008. The reason for higher drug approvals during this time could be the enactment of the PDUFA which sped the approval process. The data show a peak in drug approvals in the years 1996 and 2004 which could be due to the subsequent re-authorization of PDUFA and the streamlining efforts of the FDA to improve the efficiency of the approval process.

Consistent with findings reported in the literature, the number of NMEs approved in recent years has taken a downward turn (Kaitin, DiCerbo, & Lasagna, 1991; Kaitin & Manocchia, 1997; Kaitin, Manocchia, Seibring, & Lasagna, 1994; Kaitin et al., 1987) regarding analyses of NME introductions. This trend could be attributable to investment in more research intensive projects like biotechnology and genetic resulting in a potential improvement in quality of the pharmaceuticals being submitted to the FDA for approval. Alternatively, one

could argue that the increase in approval times as demonstrated by Kaitin and colleagues may retard a drugs entry into the market place.

B. Drug Characteristics

The orally administered drugs were approved the most representing 54% of 703 NMEs introduced since 1980. Forty-five percent of the drugs approved during this period were for CNS, cardiovascular, and anti-infective classes. This is not surprising given the history of substantial R&D investment made in this area by drug manufacturers (Garbowski & Wang, 2006).

Compared to drugs belonging to other therapeutic classes, anti-infectives were much more likely to be discontinued due to drug resistance developed by target microorganisms.

C. Sponsor Characteristics

Previous studies have indicated that multiple sponsors collaborating to submit New Drug Applications may be a strong driver of NMEs entering the market. This finding was obtained from the analysis of data provided by small number of manufacturers and with selected or potentially biased list of drugs in

the market. In addition, analyzing non-comprehensive list of drugs has implications for the length of time to conduct the analysis.

Current study addressed the limitations of past studies by developing a database of drugs from 1980 from the FDA. The analysis of our data revealed that the U.S. continues to lead by innovating and introducing new formularies to the market. U.S. pharmaceutical companies invest more in R&D compared to other manufacturers and our study concurs with the perspective that innovation is strongly correlated with the R&D investments.

This is consistent with the findings by DiMasi et al. (J. DiMasi, Garbowski, & Vernon, 2004) who demonstrated that U.S. firms are leaders in developing first-in-class, biotech and orphan drugs compared with other countries. In order to stay ahead of the competition, R&D investment should remain a high priority for drug manufacturers.

The U.S. as the leader of innovation may be an effort to expedite the FDA review process. Garbowski and Wang reported that US is considered a country of choice for launching new pharmaceuticals (Garbowski & Wang, 2006). This could be another reason behind U.S. firms dominating the introduction of NME into the market.

5.1.2 Market Status of Drugs

About 14% of the drugs were discontinued from 1980 to 2008. Although this is a much higher than the rate reported by previous literature (Friedman et al., 1999; Wood, 1999), one of the reasons for the discrepancy may be the differences in the duration of time period. This study examined all classes of drugs over the course of almost three decades compared to two decades by Wood.

Although the number of drugs withdrawn has increased in recent years, this study suggests that the rate of discontinuation remained consistent despite the passage of PDUFA. This finding is consistent with the findings in the literature irrespective of the differences in the time frame used to conduct the analyses.

5.1.3 Reasons for Market Discontinuations

The results of this study suggest that a large number of drug discontinuation is not necessarily attributable to safety issues. Although safety continue to remain a primary concern for pharmaceutical industries and the health care professional, safety accounted for about one-third of the total number of drug discontinued in the US.

Historically, issues such as adverse physical reactions or drug interactions are unearthed after a drug has entered the market. Recent advancements in electronic surveillance database systems such as MedWatch and AERS allow healthcare professionals to quickly disseminate reports of consequential effects of drugs to other health professionals, health agencies as well as drug manufacturers.

Intercontinental Marketing Service (IMS Health) suggests that 60 percent of the nation receives healthcare services through managed care plans, amounting to over $100 billion (US) in pharmaceutical product expenditures in 2002. Meanwhile, the Medicaid, one of the largest drug utilization programs in the nation observed an astonishing growth of $32.2 billion (US) in drug expenditure (2002). When Medicaid drug utilization data were analyzed, some drugs with high volume of sales were discontinued despite having no prior documentations of safety or efficacy issues with the FDA. Although the total number of drugs discontinued by manufacturers may be small but this finding suggests that an alternative motive exists for discontinuation of drugs. For example, a manufacturing firm may voluntarily choose to discontinue a drug, if the drug is not financially viable for the firm regardless of its safety or efficacy to patients.

5.1.4 Predictors of Market Discontinuation

Logistic regression was used in this study to predict the odds ratio of a drug being discontinued from the market. The model used for the analysis suggests that enactment of PDUFA may reduce the odds of a drug being discontinued from the market. This finding is different from other published studies that reported little or no impact on drugs being discontinued for safety reasons. The differences may be attributable to inclusion of safety and additional factors that could affect discontinuation of drugs in the market. It is also possible that changes in FDA working closely with manufacturers improved the review process, thereby marketing drugs that are safe, efficacious and financially viable for the manufacturers.

The odds of a drug being discontinued due to safety reasons were significantly high but this is expected because safety remains high priority in drug review process.

5.1.5 Time to Discontinuation

The Cox proportional hazards model was used for the study to identify important factors affecting time to drug discontinuation. Subpart H enactment, safety coding, orphan drug enactment, priority review, fast track enactment as

well as sponsor country were found to affect time to discontinuation. With regard to PDUFA enactment, the drugs that were approved pre- and post-PDUFA seemed to have the same probability of survival for the first year. Subsequently, those drugs that were approved before the enactment of PDUFA seemed to survive longer in the market. Although this finding is not in agreement with our logistic regression analysis, the differences in the finding may be due to the absence of unequal follow-up time in the logistic regression model.

Another factor considered was the variable User fee enactment. This identified the drugs that were approved pre- and post-PDUFA and does not indicate a list of drugs that paid user fees for approval versus those that did not.

The Kaplan-Meier survival curve also showed that US sponsored drug products had a higher probability of survival in the market. The US is currently at the fore-front of international research and innovation, with considerable advances in biotech and orphan drugs. These results indicate that not only are the drugs sponsored by US based companies more likely to be marketed, but are better able to acclimatize to the market pressures and societal demands.

5.2 Study Conclusions

Results of this study should be interpreted considering the following: 1) each drug is unique and has its own set of characteristics, and 2) several important changes in pharmaceutical regulation occurred during the study period. More recently there seems to be a downward trend in NME introductions, which is consistent with previous literature regarding analyses of NME introductions. Anti-infectives represented one of the most common therapeutic classes of drugs approved during the study period, and they also represented the most likely class to be discontinued.

Collaborative efforts through multiple sponsorships by US pharmaceutical firms may have attributed to innovating new formularies and improving access to drug to the public. Safety represents an important but one of many facets implicating the discontinuation drugs in the US. Commercial and financial reasons also contribute to drug discontinuations and therefore needs further evaluation.

5.3 Implications of the Study

The PDUFA regulations implemented during the period of the analysis have effectively reduced the length of NME approval. When PDUFA was enacted, the changes within the FDA led to decreasing the length of NDA review time. A reduction in NDA review time is considered by some to affect the review process and ultimately the safety of the new drugs. This study reports the enactment of PDUFA has little or no implications on the safety of drugs compared to pre-PDUFA. The main implication of this study is that attempting to increase the efficiency of the drug approval process may not translate to compromising on safety.

5.4 Limitations of the Study

5.4.1. Subject Selection

Subject selection was limited. The study included only the first NDA of those NMEs selected. When the FDA approved several NDAs for the same NME on the same date, the first product number for the approved NME was chosen.

5.4.2. Clinical Development Time

The inclusion of data concerning NME investigational new drug applications (INDs) would have permitted the estimation of NME time spent in clinical development. While the author's Freedom of Information Act request to the FDA requested such information, the FDA did not provide it. Clinical research information might have explained the resultant market status of the drug not explained by the analysis performed in this study.

5.4.3. Drug Sales

Drug sales were not included as an independent variable in the study. An NME's ranking among the 200 drugs most often prescribed in the U.S. does not reflect that NME's sales and thus does not accurately represent the product's

market size. The inclusion of drug sales as an independent variable might have better explained effects on market status.

5.4.4. Ability to Generalize the Results

The study's results can only be generalized to NMEs fulfilling the study's inclusion criteria. Descriptive analyses were mainly used in our methodology. Additionally we used publicly available data, which limited our study to information from such sources. Thus, our data may not be comprehensive and needs to be considered as such, to avoid misinterpretation of data and results.

5.5 Further Research

Future research could investigate the impact of discontinuations on patients and the medical community. A commercial database may provide more information for conclusive results on financial reasons for drug discontinuations. It would also be interesting to differentiate the effects of obsolescence, and market strategy on drug discontinuations. Other possibilities for future research include the impact of withdrawals on the global market for pharmaceuticals.

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APPENDICES

LIST OF VARIABLES

List of Variables for Dataset

List of Variables used for the Analysis		
Field Name	Type	Description
ApplNo	Numeric	New drug application number assigned to the product
Generic	Alphanumeric	The assigned generic name of the drug
Brand	Alphanumeric	The assigned brand name of the drug
Route	Alphanumeric	The route of administration of the drug
Dosage Form	Alphanumeric	The dosage form under which the drug is marketed
Dosage	Alphanumeric	The dose of the drug
Type Rx-OTC Code	Alphanumeric	Distinguishes whether the drug was prescription or over the counter
Therapeutic Class	Alphanumeric	Identifies the therapeutic classification of the drug according to the American Hospital Formulary System
Sponsor with a Single NME	Numeric	Sponsor country with a single New Molecular Entity approval in the study period
Sponsors Number NME	Numeric	Number of new molecular entity approvals per sponsor country
1st NDA Applicant OB	Alphanumeric	Name of the pharmaceutical firm that was the first new drug applicant as listen in the Orange Book
NDA Sponsor for First NDA (US v non-US)	Numeric	Identifies if the sponsor country for the first NDA was USA or not
Sponsor for the First NDA of an NME Country	Alphanumeric	Identifies the country that sponsored the first NDA

List of Variables used for the Analysis (Contd)		
Field Name	Type	Description
Subpart E	Numeric	Identifies the drugs that were approved under Subpart E
Subpart E Enacted	Numeric	Identifies the drugs that were approved after Subpart E was enacted
Fast Track	Numeric	Identifies the drugs that were approved under Fast track approval
Fast Track Enacted	Numeric	Identifies the drugs that were approved after FDA fast track approval process was enacted
Subpart H	Numeric	Identifies the drugs that were approved under Subpart H
Subpart H Enacted	Numeric	Identifies the drugs that were approved after Subpart H was enacted
Orphan Approvals	Numeric	Identifies the drugs that were approved under the orphan drug category
Orphan Approval Date	Numeric	The date on which the orphan drug approvals took place
Orphan Drug Enacted	Numeric	Identifies the drugs that were apporved after the Orphan drug rule enactment
FDA NDA Review Priority Description	Numeric	Identifies the drugs that were approved as priority review
User Fee Paid	Numeric	Identifies the drugs for which user fees were paid for approval
User Fee Enacted	Numeric	Identifies the drugs that were approved after the Prescription Drug User Fee Act was enacted
NDA Received Date	Numeric	The date on which the New drug application was received
NDA Approved Date	Numeric	The date on which the New drug application was approved by the FDA

List of Variables used for the Analysis (Contd)		
Field Name	Type	Description
Year of First NDA for an NME	Numeric	The year in which the first New drug application was filed for the New molecular entity
ProductMktStatus	Numeric	The market status of the drug
Safety coding	Numeric	Identifies whether the drug was discontinued for safety reasons or not
Discontinued Date	Numeric	The date on which the drug was taken off the market
1st Discountinuation or Withdrawal Date	Numeric	The first discontinuation date for a drug
time to disc	Numeric	The time frame for which a drug remined in the market calculated as the difference between the approval date and the discontinuation date
Disc 1 not 0	Numeric	Identifies whether the drug was discontinued or not
# of Generics	Numeric	Determines the number of generic available for each drug product

List of Variables for the Medicaid Drug Utilization Dataset

List of Variables from the Medicaid Data		
Field Name	Type	Description
State	Numeric	Identifies the assigned state code by Medicaid
NDC	Numeric	Identifies the National Drug Code
Year	Numeric	Identifies the year in which the reimbursement was filed
Qtr	Numeric	Identifies the quarter in which the reimbursement was filed
Name	Alphanumeric	Identifies the generic name of the drug
Unit	Numeric	Identifies the units sold
Dollar	Numeric	Identifies the dollar amount in sales

TABLES

Year	No.	%
1980	12	1.7
1981	28	4
1982	28	4
1983	14	2
1984	24	3.4
1985	29	4.1
1986	20	2.8
1987	21	3
1988	20	2.8
1989	24	3.4
1990	23	3.3
1991	30	4.3
1992	26	3.7
1993	25	3.6
1994	21	3
1995	29	4.1
1996	53	7.5
1997	38	5.4
1998	31	4.4
1999	35	5
2000	27	3.8
2001	24	3.4
2002	17	2.4
2003	21	3
2004	31	4.4
2005	18	2.6
2006	18	2.6
2007	16	2.3
Total	703	100

Table 4.1: NDA Approval Year

Route	No.	%
Buccal	1	0.1
Dental	1	0.1
Im-Iv	2	0.3
Implantation	1	0.1
Inhalation	17	2.4
Inhalation, Intravenous	2	0.3
Injection	167	23.8
Injection, Oral, Rectal	1	0.1
Intramuscular	3	0.4
Intramuscular, Iv (Infusion)	1	0.1
Intraperitoneal	1	0.1
Intrapleural	1	0.1
Intrathecal	3	0.4
Intratracheal	4	0.6
Intravenous	12	1.7
Intravesical	1	0.1
Intravitreal	1	0.1
Iv (Infusion)	13	1.8
Iv (Infusion)-Sc	1	0.1
Nasal	5	0.7
Ophthalmic	25	3.6
Oral	380	54.1
Perfusion, Biliary	1	0.1
Rectal	1	0.1
Subcutaneous	16	2.3
Topical	37	5.3
Transdermal	2	0.3
Vaginal	3	0.4
Total	703	100

Table 4.2: Route of Administration

Year	No.	%
Anti-infective Agents	121	17.2
Central nervous system agents	107	15.2
Cardiovascular drugs	93	13.2
Anti-neoplastic Agents	60	8.5
Diagnostic Agents	53	7.5
Skin and Mucous Membrane Agents	39	5.5
Hormones and Synthetic Substitutes	35	5
Eye, Ear, Nose, and Throat (EENT) Preparations	34	4.8
Miscellaneous Therapeutic Agents	34	4.8
Gastrointestinal drugs	27	3.8
Autonomic Drugs	25	3.6
Blood Formation, Coagulation, and Thrombosis	19	2.7
Electrolytic, Caloric, and Water Balance	15	2.1
Respiratory Tract Agents	8	1.1
Antihistamine Drugs	7	1
Enzymes	5	0.7
Heavy Metal Antagonists	5	0.7
Local Anesthetics	5	0.7
Smooth Muscle Relaxants	4	0.6
Vitamins	3	0.4
Gold Compounds	1	0.1
Oxytocics	1	0.1
Total	703	100

Table 4.3: Therapeutic Class

Country Name	No.	%
USA	397	56.5
UK	82	11.7
Switzerland	76	10.8
Other European Countries	57	8.1
Germany	52	7.4
Japan	18	2.6
Other Countries	5	0.7
France	4	0.6
USA/Japan	4	0.6
Canada	1	0.1
Ireland	1	0.1
Italy	1	0.1
Korea	1	0.1
Netherlands	1	0.1
Sweden	1	0.1
USA/Other European Countries	1	0.1
USA/UK	1	0.1
Total	703	100

Table 4.4: Sponsor Country

Sponsor Country	No.	%
Multiple	592	84.2
Single	111	15.8
Total	703	100

Table 4.5: Sponsor with Single NME Approval

Law Enactment	No.	%
No	69	9.8
Yes	634	90.2
Total	703	100

Table 4.6: Orphan Drug Enacted

Variable	No.	%
NMEs not approved as orphan drugs	592	84.2
NMEs approved as orphan drugs	111	15.8
Total	703	100

Table 4.7: Orphan Drug NMEs

Variable	No.	%
NMEs approved before Subpart E enactment	220	31.3
NMEs approved after Subpart E enactment	483	68.7
Total	703	100

Table 4.8: Subpart E Enacted

Variable	No.	%
NMEs not approved under Subpart E	682	97.0
NMEs approved under Subpart E	21	3.0
Total	703	100

Table 4.9: Subpart E NMEs

Variable	No.	%
NMEs approved before Subpart H enactment	274	39.0
NMEs approved after Subpart H enactment	429	61.0
Total	703	100

Table 4.10: Subpart H Enacted

Variable	No.	%
NMEs not approved under Subpart H	659	93.7
NMEs approved under Subpart H	44	6.3
Total	703	100

Table 4.11: Subpart H NMEs

Variable	No.	%
NMEs approved before Fast track enactment	468	66.6
NMEs approved after Fast track enactment	235	33.4
Total	703	100

Table 4.12: Fast Track Enacted

Variable	No.	%
NMEs not approved under Fast track review	693	98.6
NMEs approved under Fast track review	10	1.4
Total	703	100

Table 4.13: Fast Track NMEs

Variable	No.	%
NMEs not approved under Priority Review description	396	56.3
NMEs approved under Priority Review description	307	43.7
Total	703	100

Table 4.14: Priority Review

Variable	No.	%
NMEs approved before PDUFA enactment	343	48.8
NMEs approved after PDUFA enactment	360	51.2
Total	703	100

Table 4.15: User Fees Enacted

Variable	No.	%
No	376	53.5
Yes	206	29.3
Missing	121	17.2
Total	703	100

Table 4.16: User Fees NMEs

Status	No.	%
Drugs currently in the market	506	71.8
Drugs Discontinued	100	14.4
Never Marketed	5	0.7
Brands Discontinued	38	5.4
Change in route, dosage form or strength	48	6.8
Change to OTS status	6	0.9
Total	703	100

Table 4.17: Market Status of NMEs (N=703)

Reasons	No.	%
Never Marketed	5	4.7
Safety	29	27.4
Not discontinued for safety or efficacy	4	3.8
Reasons not stated	68	64.2
Total	105	100

Table 4.18: Reasons for Discontinuation (N=105)

Generic Name	Brand Name	Therapeutic Class	Reasons for Discontinuation
Alatrofloxacin Mesylate	Trovan	Anti-infective Agents	Serious liver injury
Alosetron Hydrochloride	Lotronex	Gastrointestinal drugs	Increase mortality
Astemizole	Hismanal	Antihistamine Drugs	Drug Interaction
Benoxaprofen	Oraflex	Central nervous system agents	Liver necrosis, photosensitivity, animal caricinogenicity
Bromfenac Sodium	Duract	Central nervous system agents	Hepatic failure, off-label abuse
Cerivastatin Sodium	Baycol	Cardiovascular drugs	Fatal rhabdomyoloysis
Cisapride Monohydrate	Propulsid	Gastrointestinal drugs	Heart rhythm abnormalities
Encainide Hydrochloride	Enkaid	Cardiovascular drugs	Cardiotoxicity and excess mortality
Etretinate	Tegison	Skin and Mucous Membrane Agents	Teratogenicity
Flosequinan	Manoplax	Cardiovascular drugs	Increase mortality
Gatifloxacin	Tequin	Anti-infective Agents	Blood sugar fluctuations, hepatotoxicity
Grepafloxacin Hydrochloride	Raxar	Anti-infective Agents	Cardiovascular reaction
Levomethadyl Acetate Hydrochloride	Orlaam	Central nervous system agents	Cardiovascular adverse events
Mibefradil Dihydrochloride	Posicor	Cardiovascular drugs	Drug Interaction

Table 4.19: Reasons for Safety Discontinuations

Generic Name	Brand Name	Therapeutic Class	Reasons for Discontinuation
Nomifensine Maleate	Merital	Central nervous system agents	Hemolytic, anemia, hepatotoxicity
Pergolide Mesylate	Permax	Central nervous system agents	Serious damage to patients heart valaves
Rapacuronium Bromide	Raplon	Autonomic Drugs	Increased mortality and bronchospasms
Rofecoxib	Vioxx	Central nervous system agents	Cardiovascular adverse events
Sparfloxacin	Zagam	Anti-infective Agents	Cardiovascular adverse events
Suprofen	Suprol/Profenal	Central nervous system agents	Nephrotoxicity
Tegaserod Maleate	Zelnorm	Gastrointestinal drugs	Increased risk of heart attack, stroke and angina
Temafloxacin Hydrochloride	Omniflox	Anti-infective Agents	Increased mortality and liver failure
Terfenadine	Seldane	Antihistamine Drugs	Drug Interactions and cardiovascular toxicity
Trilostane	Modrastane	Hormones and Synthetic Substitutes	Teratogenicity
Troglitazone	Rezulin/Prelay	Hormones and Synthetic Substitutes	Hepatotoxicity
Trovafloxacin Mesylate	Trovan	Anti-infective Agents	Hepatotoxicity
Valdecoxib	Bextra	Central nervous system agents	Cardiovascular adverse events
Zomepirac Sodium	Zomax	Central nervous system agents	Anaphylaxis, renal failure

Table 4.19: Reasons for Safety Discontinuations (Continued)

Status	No.	%
NMEs Marketed	305	100
Generic Entry	208	68.2
No Generic Entry	87	31.8
NMEs Discontinued	105	100
Generic Entry	2	1.9
No Generic Entry	103	98.1

Table 4.20: Generic Entry after Patent and Exclusivity Expiration (N=703)

Variable	Level	No.	%
Oral route of administration	0	323	45.95
	1	380	54.05
Antiinfective class of drug	0	582	82.79
	1	121	17.21
Sponsor country	0	300	42.67
	1	403	57.33
Subpart E enacted	0	220	31.29
	1	483	68.71
Fast track enacted	0	468	66.57
	1	235	33.43
Subpart H enacted	0	274	38.98
	1	429	61.02
Orphan drug enacted	0	69	9.82
	1	634	90.18
Priority Review	0	396	56.33
	1	307	43.67
User Fee enacted	0	343	48.79
	1	360	51.21
Safety code	0	673	95.73
	1	30	4.27
Discontinued	0	597	84.92
	1	106	15.08
* Where 0 = No and 1 = Yes			

Table 4.21: Descriptive Statistics of Variables used for Logistic Regression

OV = Market Status	Step I			Step II		Step III	
	df	χ^2	p-val	χ^2	p-val	χ^2	p-val
Oral route	1	0.82	0.37	10.74	0.00	8.71	0.00
Antiinfective class of drug	1	8.14	0.00	9.03	0.00	8.23	0.00
Sponsor country	1	1.26	0.26	1.24	0.26	0.40	0.52
Subpart E enacted	1	23.1	0.00	28.29	0.00	2.00	0.15
Fast track enacted	1	23.6	0.00	21.62	0.00	0.00	0.95
Subpart H enacted	1	25.5	0.00	37.72	0.00	2.76	0.09
Orphan drug enacted	1	11.8	0.00	16.44	0.00	4.48	0.03
Priority Review	1	0.84	0.36	0.37	0.54	0.50	0.47
User Fee enacted	1	29.2	0.00	41.26	0.00	*******	*******
Safety code	1	109	0.00	******	*******	*******	******

Continued

Table 4.22: Forward Selection Procedure for Creating the Main Effects Regression

OV = Market Status	Step IV		Step V		Step VI	
	χ^2	p-val	χ^2	p-val	χ^2	p-val
Oral route	*******	*******	*******	*******	*******	*******
Antiinfective class of drug	9.42	0.00	*******	*******	*******	*******
Sponsor country	0.80	0.37	0.56	0.45	0.40	0.52
Subpart E enacted	1.47	0.22	1.14	0.28	0.08	0.77
Fast track enacted	0.00	8.99	0.00	0.98	0.00	0.97
Subpart H enacted	2.34	0.12	1.98	0.15	0.81	0.36
Orphan drug enacted	4.68	0.03	4.38	0.03	*******	*******
Priority Review	0.72	0.39	1.25	0.26	1.10	0.29
User Fee enacted	*******	*******	*******	*******	*******	*******
Safety code	*******	*******	*******	********	******	*******

Table 4.22: Forward Selection Procedure for Creating the Main Effects Regression (Continued)

Variable	df	Parameter Estimate	SE	Z	Pr > Z	Odds Ratio	SE
Oral route	1	-0.82163	0.2649	-3.1	0.002	0.4397	0.002
Antiinfective class of drug	1	0.910098	0.292	3.12	0.002	2.4846	0.002
Orphan drug enacted	1	-0.69851	0.3262	-2.14	0.032	0.4973	0.032
User Fee enacted	1	-1.51738	0.3206	-4.73	0	0.2193	0
Safety code	1	6.405773	1.0598	6.04	0	605.33	0

Table 4.23: Final Regression Model

Predicted	Discontinued	Not Discontinued	Total
+ve	32	5	37
-ve	73	593	666
Total	105	598	703

Table 4.24: 2x2 table with probability cut off = 0.5

Criteria	%
Sensitivity	31.13
Specificity	99.33
Positive predictive value	89.19
Negative predictive value	89.04
Correctly classified	89.05

Table 4.25: Predictors from the 2x2 table with probability cut off = 0.5

	χ^2	df	Prob > χ^2
Subpart H enacted	0.1	1	0.7552
Safety code	1.08	1	0.2978
Orphan drug enacted	1.26	1	0.2616
Priority Review	1.23	1	0.2683
Fast track enacted	3.53	1	0.0601
Sponsor country	0.96	1	0.3264

Table 4.26: Test for proportional hazards assumption

Variable	AIC	AIC	AIC	AIC	AIC	AIC	AIC
Oral route	785.3	731.33	721.98	717.15	714.14	710.31	708.56
Anti-infectives	785.9	731.69	721.41	717.15	712.91	709.18	708.28
Sponsor country	779.7	731.57	720.79	716.05	712.49	707.37	********
Subpart E enacted	750.99	730.85	719.64	716.54	712.6	708.8	708.06
Fast track enacted	762.39	727.97	717.46	712.73	708.5	*******	********
Subpart H enacted	730.45	********	********	********	********	********	********
Orphan drug enacted	766.77	724.11	715.37	********	********	********	********
Priority Review	785.98	728.99	718.12	712.28	********	********	********
User Fee enacted	744.81	729.49	721.99	717.24	714.21	709.97	708.22
Safety code	753.36	720.01	********	********	********	********	********

Table 4.27: Tabular summary of the forward selection procedure

Variable	df	z	Pr > z	Hazard Ratio	SE
Subpart H enacted	1	4.19	0	3.7625	1.1892
Safety code	1	3.46	0.001	2.5374	0.6827
Orphan drug enacted	1	2.78	0.005	2.3047	0.6924
Priority Review	1	-2.64	0.008	0.5655	0.1222
Fast track enacted	1	2.76	0.006	2.7732	1.0234
Sponsor country	1	-1.79	0.073	0.662	0.1525

Table 4.28: Results of the Final Model

FIGURES

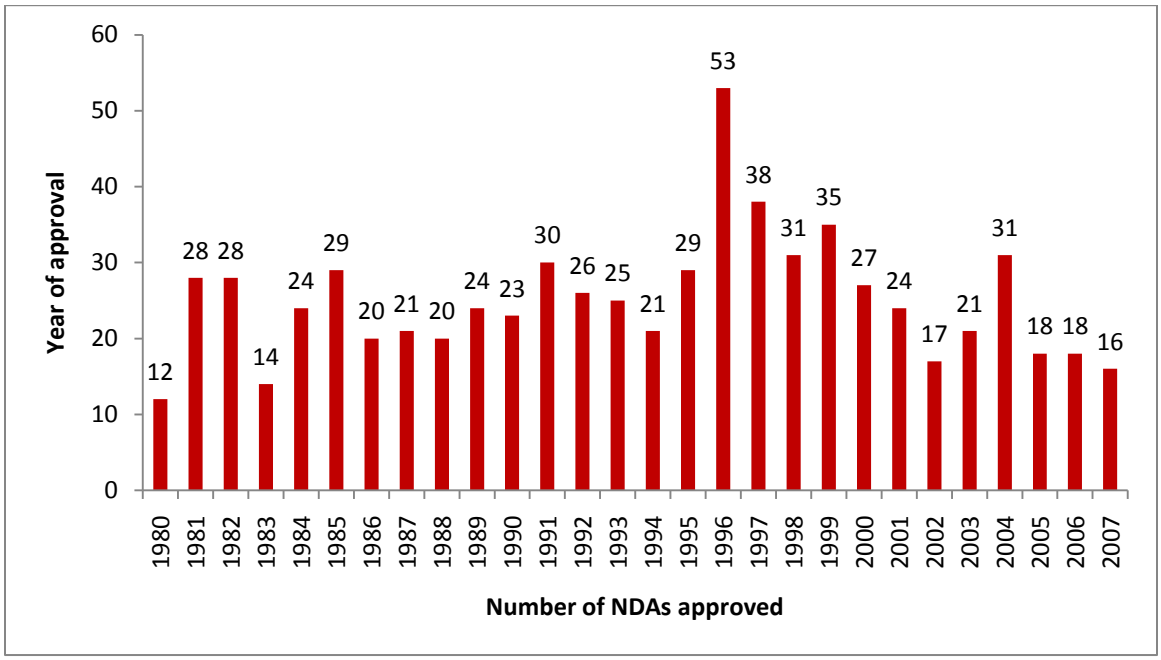


Figure 4.1: New Drug Application Trends (N = 703)

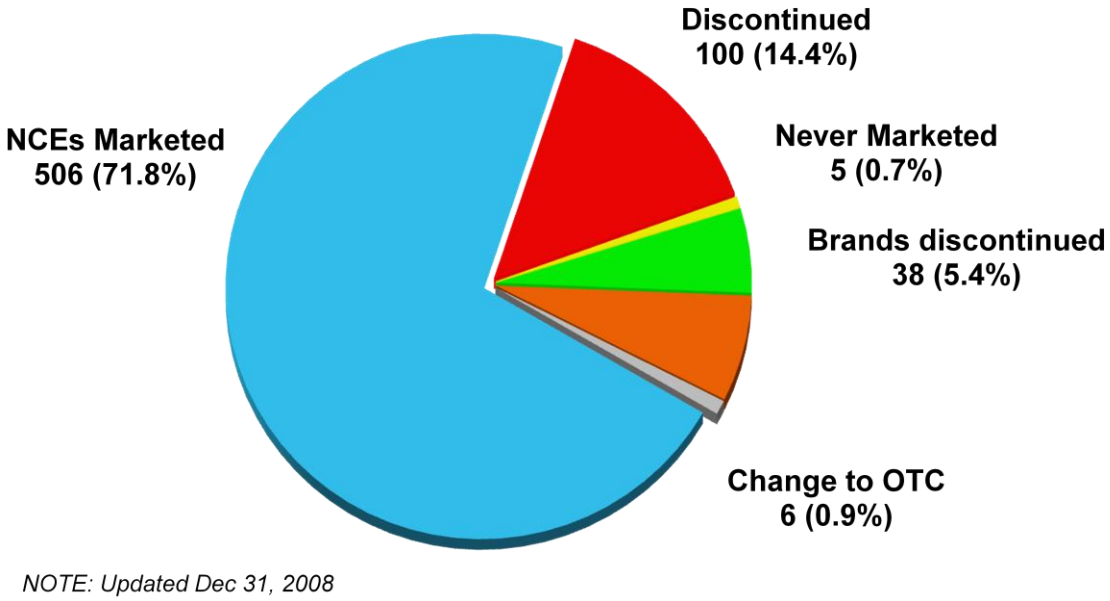


Figure 4.2: Market Status of New Molecular Entities approved by the FDA

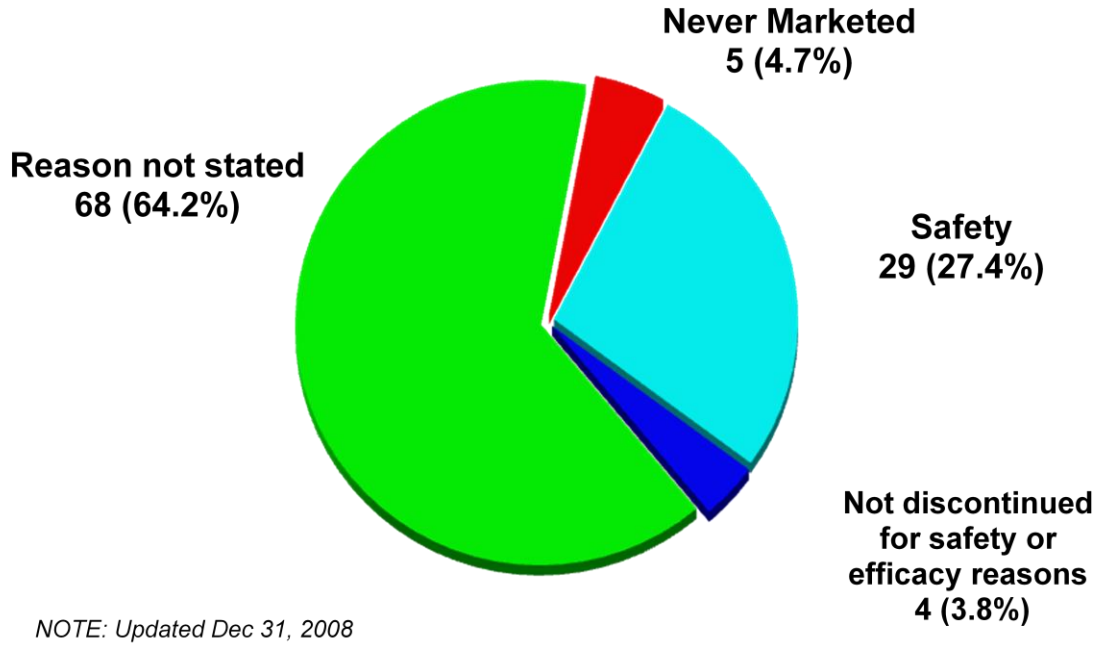
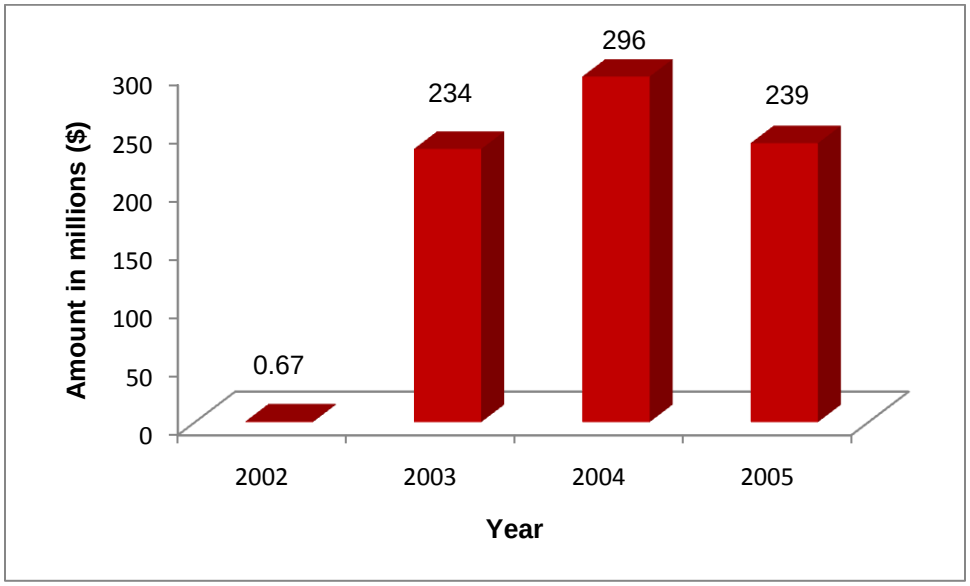
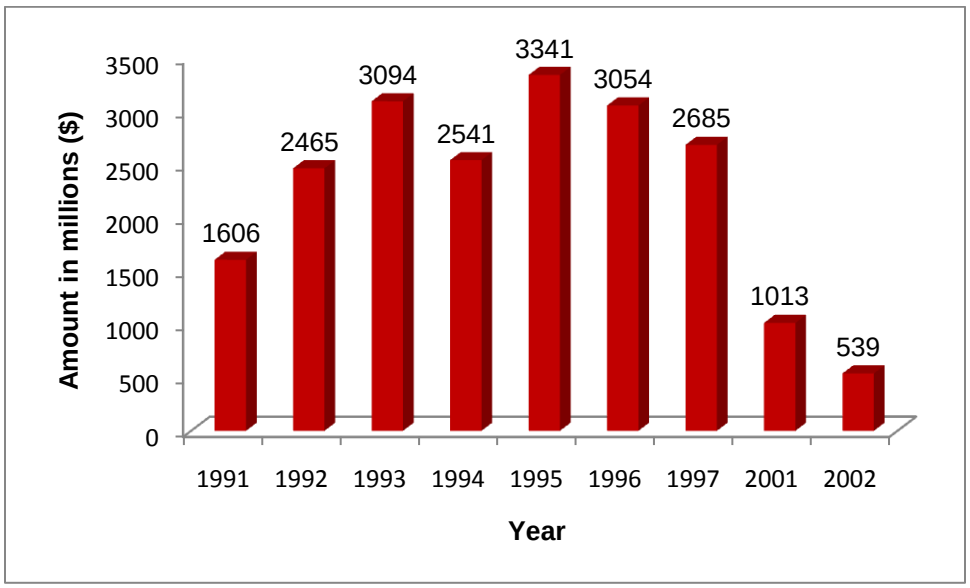


Figure 4.3: Reasons for NME Discontinuation



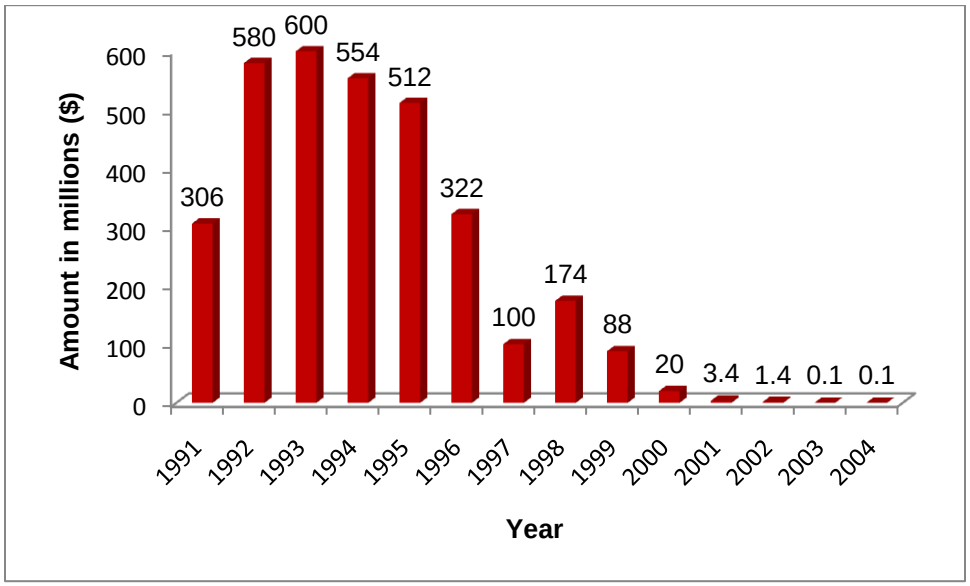
** Pergolide was discontinued in 2007*

Figure 4.4: Trends from Medicaid Drug Utilization Data: Pergolide



** Somatrem was discontinued in 2004*

Figure 4.5: Trends from Medicaid Drug Utilization Data: Somatrem



** Calcitonin was discontinued in 2006*

Figure 4.6: Trends from Medicaid Drug Utilization Data: Calcitonin

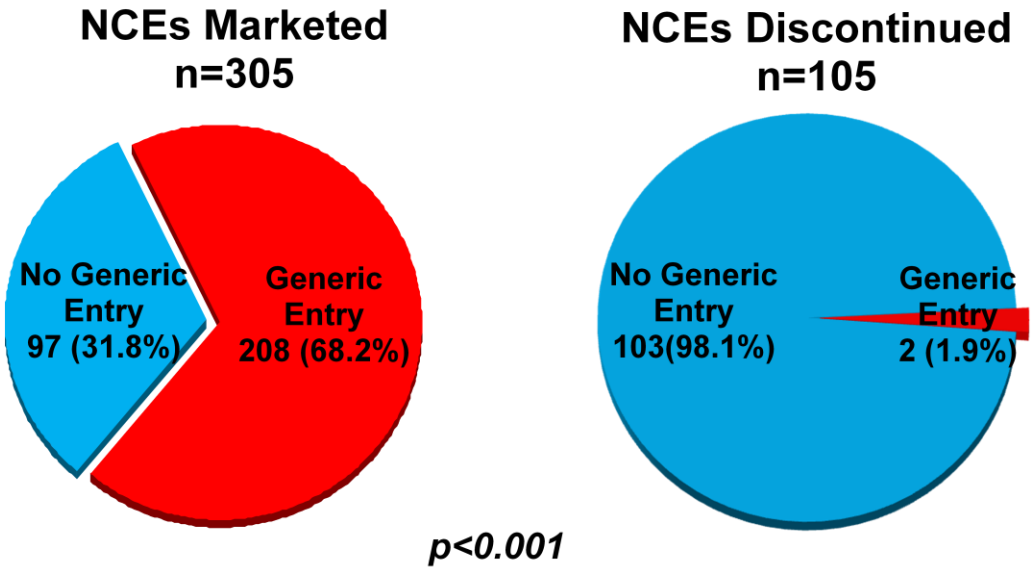


Figure 4.7: Generic Entry after Patent and Exclusivity Expiration (N=703)

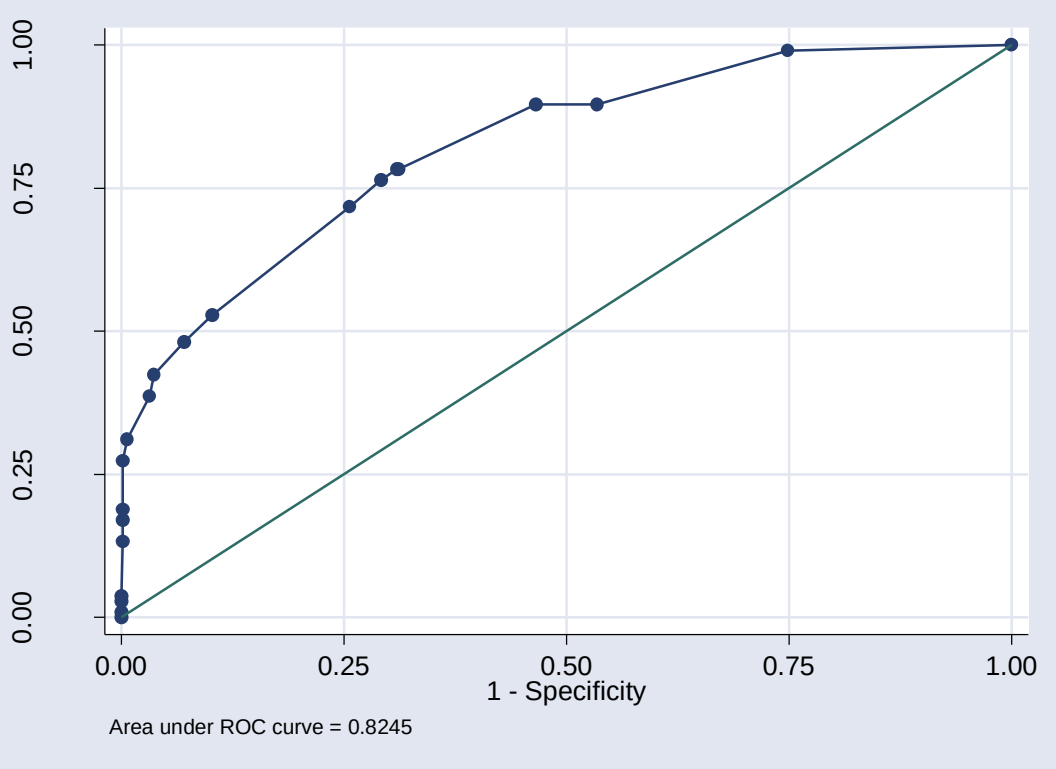


Figure 4.8: ROC Curve

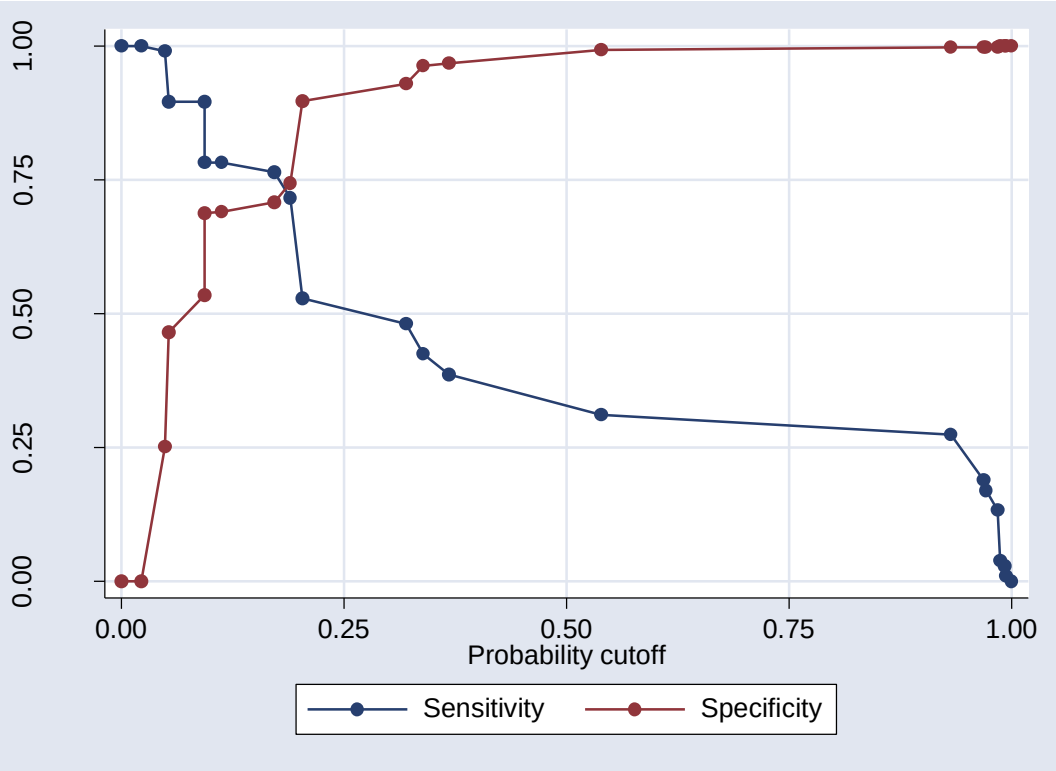


Figure 4.9: Sensitivity and Specificity Plot

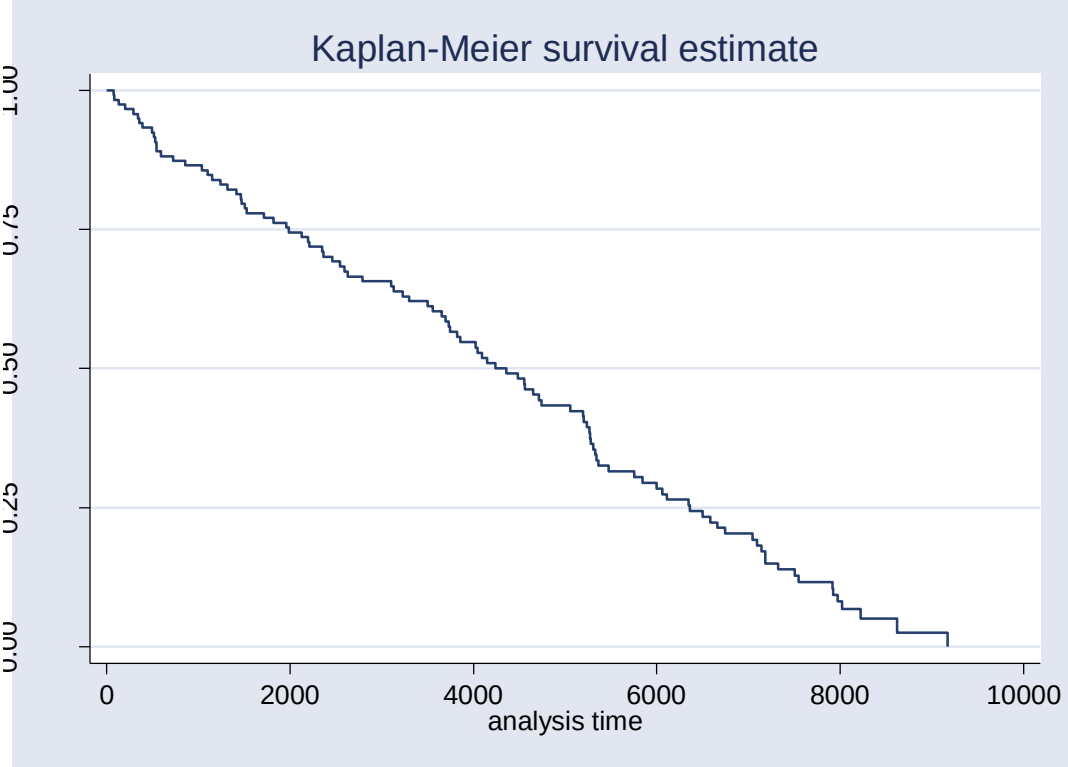


Figure 4.10: Kaplan-Meier Survival Estimate Graph

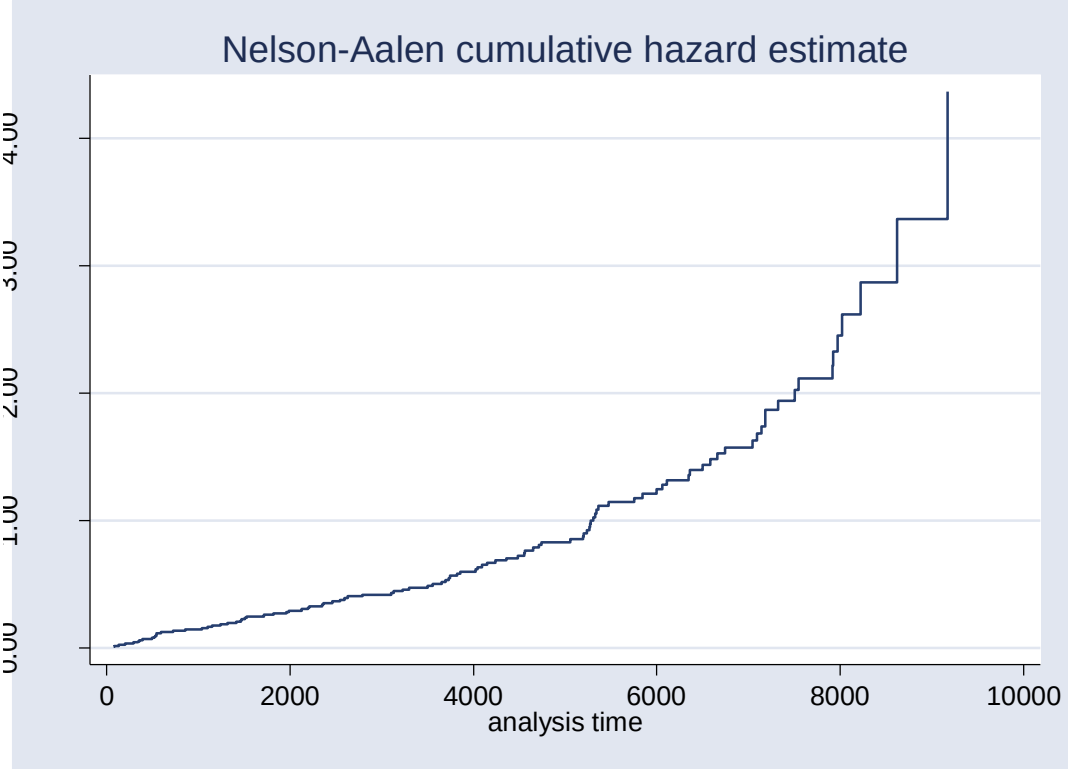


Figure 4.11: Nelson-Aalen Cumulative Hazard Estimate Graph

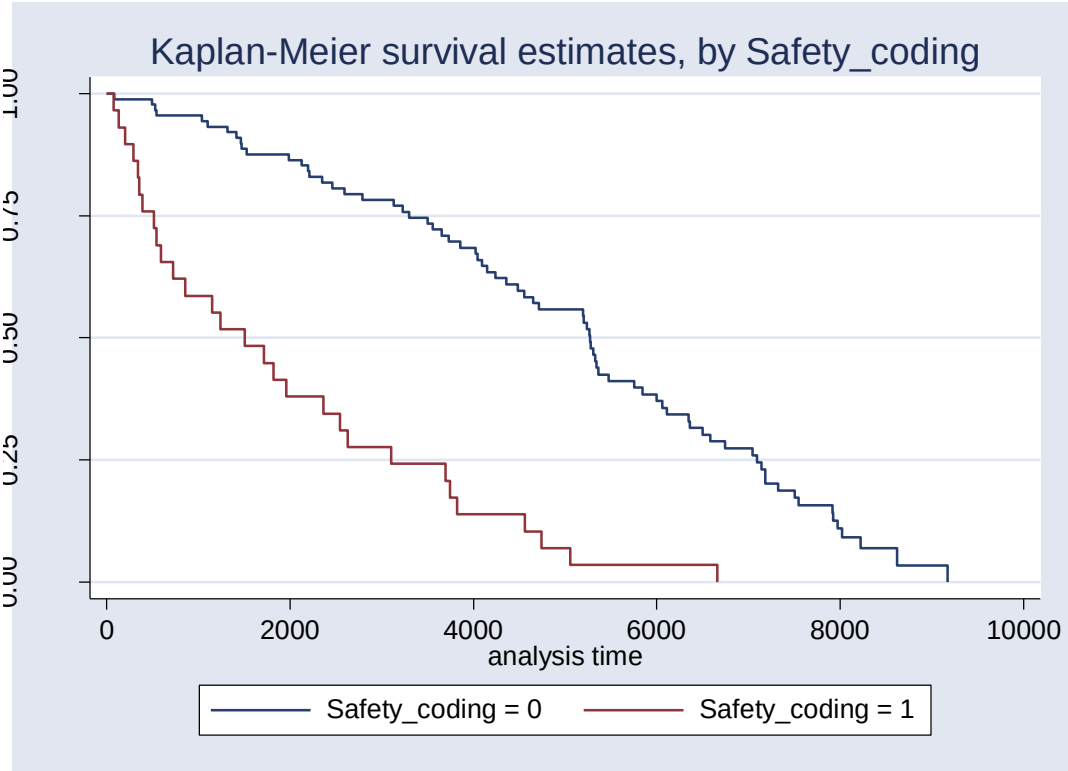


Figure 4.12: Kaplan-Meier Survival Estimate Graph for Drugs Discontinued for Safety Reasons

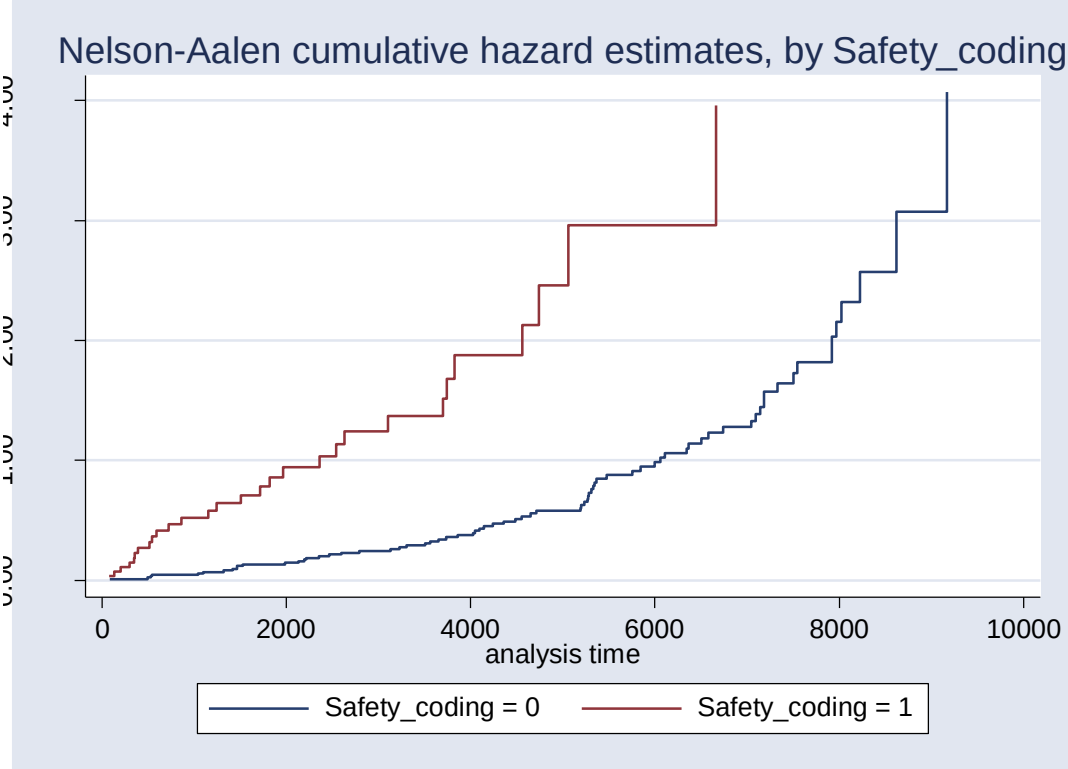


Figure 4.13: Nelson-Aalen Cumulative Hazard Estimate Graph for Drugs Discontinued for Safety Reasons

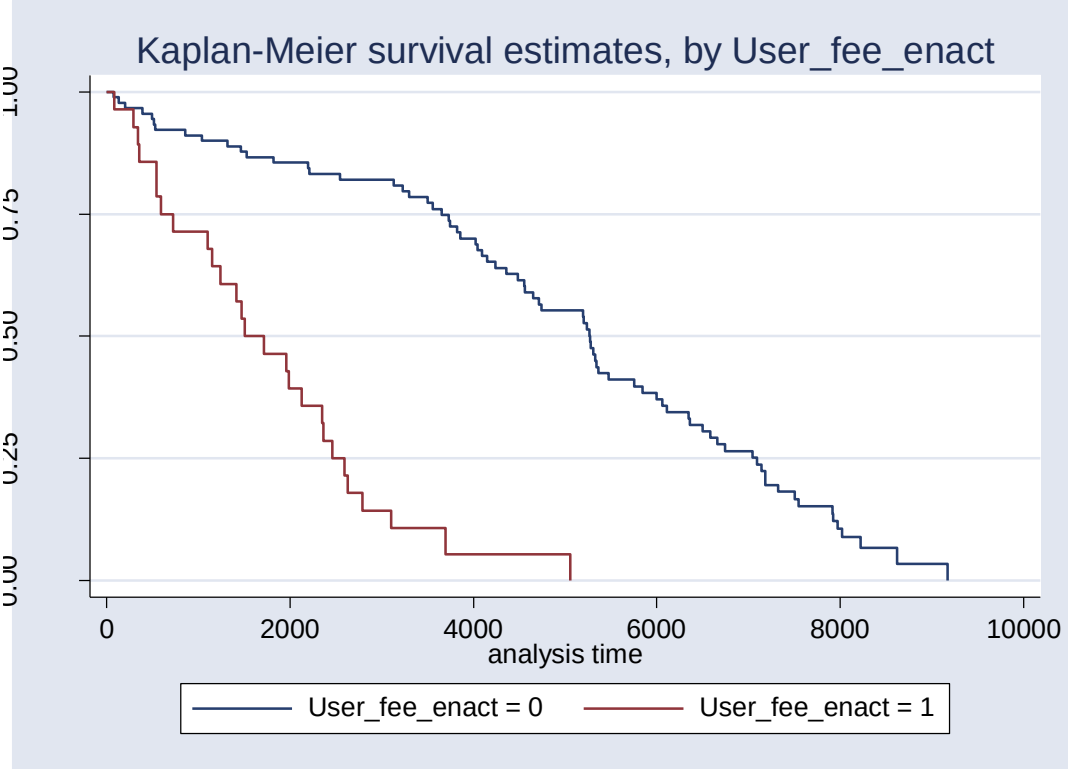


Figure 4.14: Kaplan-Meier Survival Estimate Graph for Drug approved Pre- and Post- PDUFA

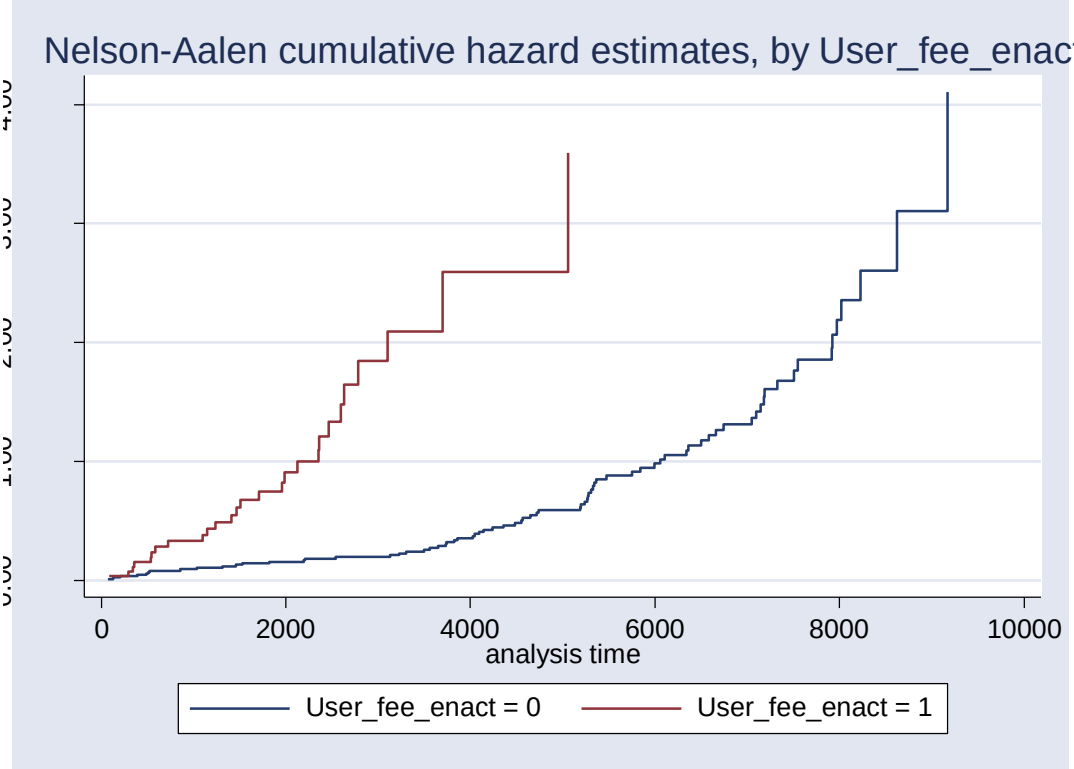


Figure 4.15: Nelson-Aalen Cumulative Hazard Estimate Graph for Drug approved Pre- and Post- PDUFA

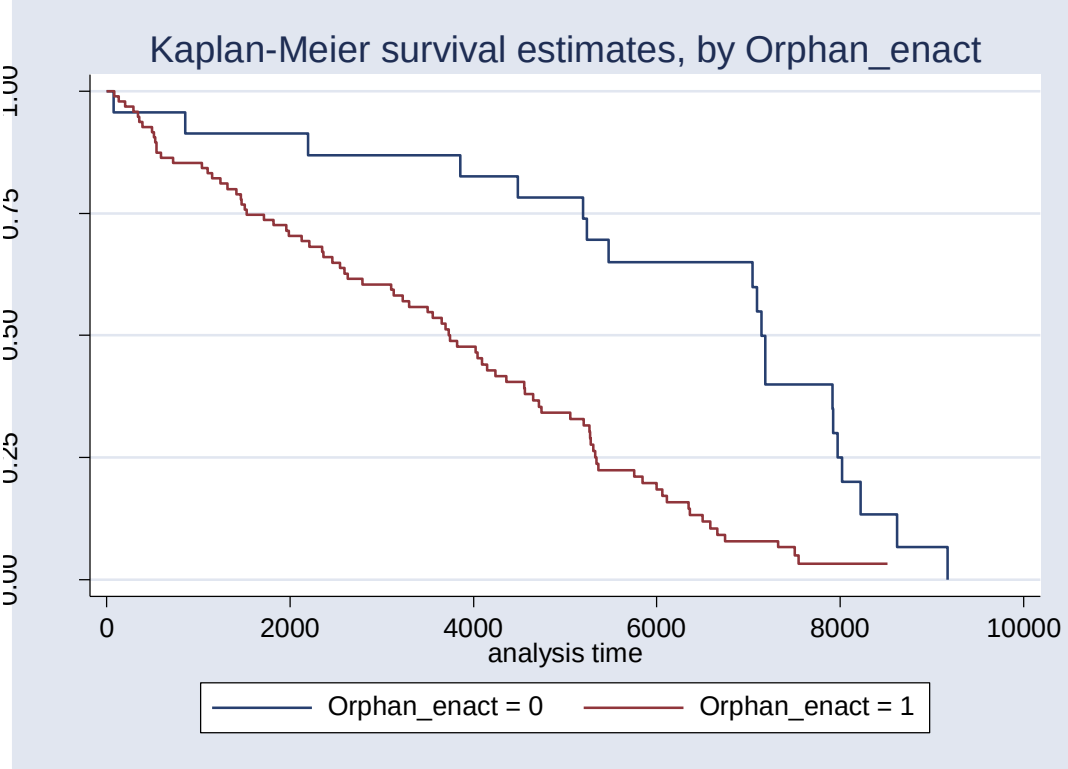


Figure 4.16: Kaplan-Meier Survival Estimate Graph for Drugs approved before and after Orphan Drug Enactment

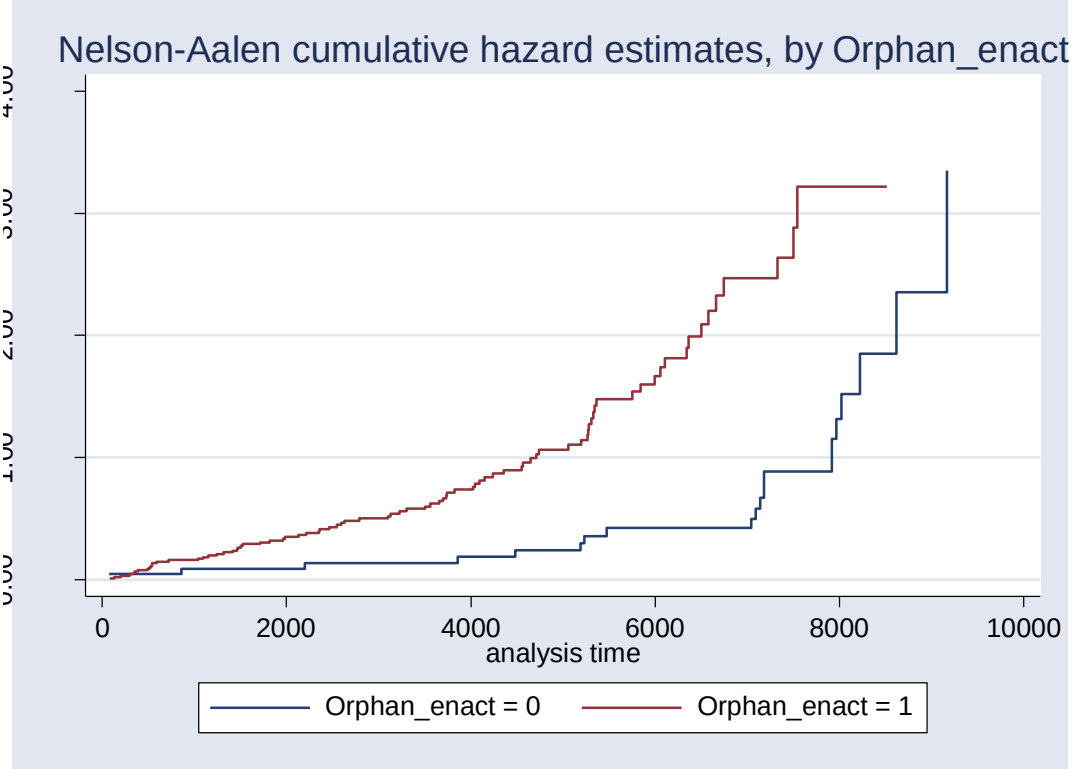


Figure 4.17: Nelson-Aalen Cumulative Hazard Estimate Graph for Drugs approved before and after Orphan Drug Enactment

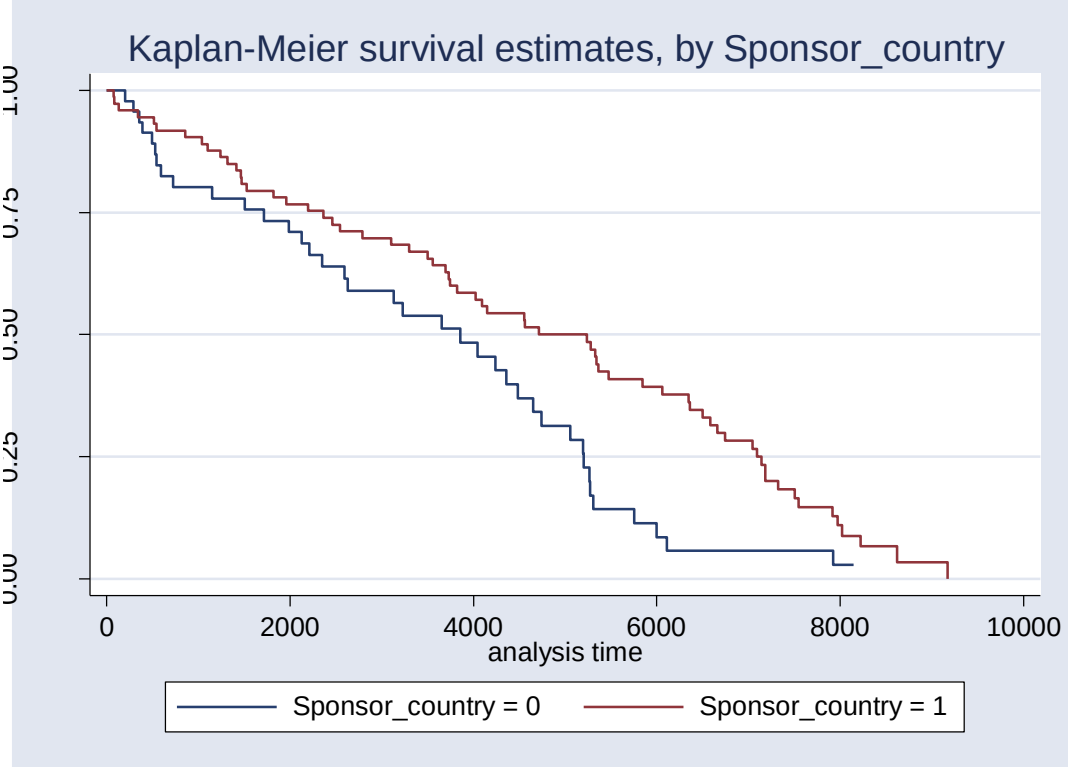


Figure 4.18: Kaplan-Meier Survival Estimate Graph for Sponsor Country

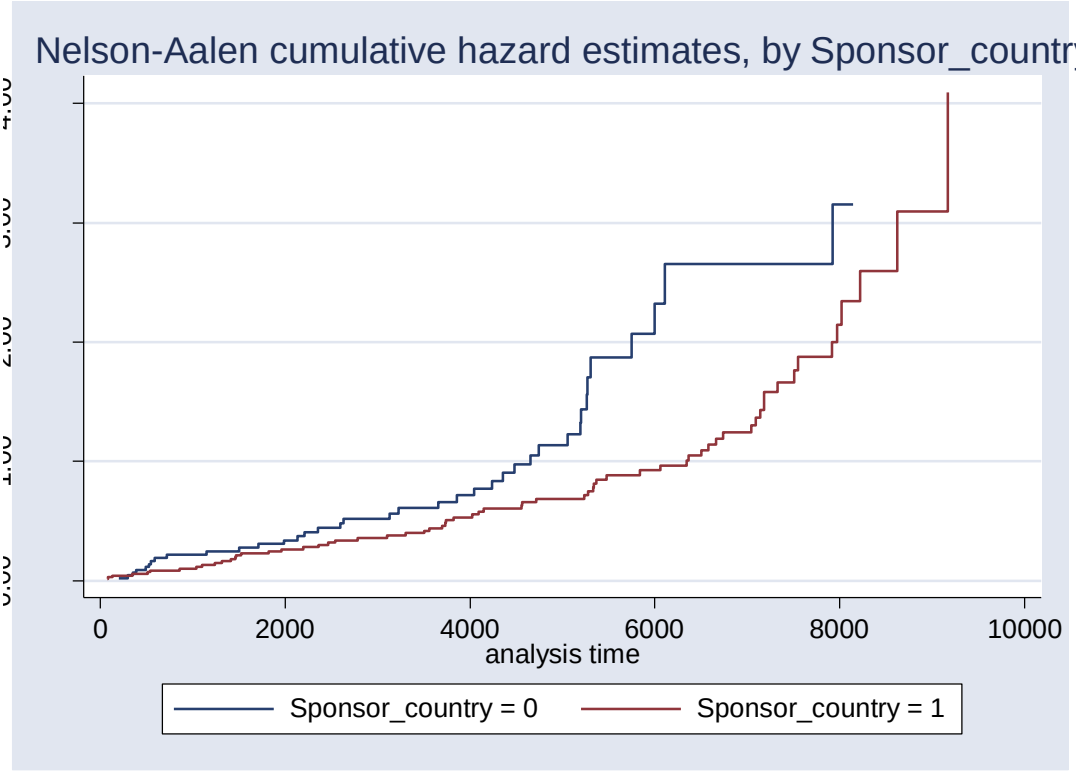


Figure 4.19: Nelson-Aalen Cumulative Hazard Estimate Graph for Sponsor Country

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