INFLUENCING PHYSICIAN PRESCRIBING BEHAVIOR: DIRECT-TO-CONSUMER ADVERTISING AND THE DEMAND FOR ME-TOO DRUGS

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by

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ABSTRACT OF DISSERTATION

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ABSTRACT

This study examines the variables that may influence physicians' choices of medication for their patients and the effect of the entry of me-too drugs on the market of breakthrough and generic drugs. Using the 2006 National Ambulatory Medical Care Survey (NAMCS), drugs belonging to the drug classes statin, cardioselective beta blockers, proton pump inhibitors and selective serotonin reuptake inhibitors were classified as generic, breakthrough and me-too drugs and analyzed separately. This study uses the discrete choice model of demand in analyzing the relationship between physician prescribing behavior and patient, physician and drug characteristics. This study found age, sex, race, ethnicity and number of current medication influence physicians' prescribing behavior. Some physicians tend to prescribe one type of drug over the other. The study also found an indication of moral hazard. Price, direct-to–consumer advertising and certain characteristics of drugs that may indicate quality affect the likelihood of a drug to be prescribed.

The findings on the effect of direct-to-consumer advertising expenditure of me-too drugs on the market share of generic drugs and breakthrough drugs give empirical support to the proposed policy of approving new drugs on the basis of their efficacy against existing drugs in the market. With direct-to-consumer advertising, the findings of this study suggest that me-too drugs may reduce the market share of breakthrough drugs and generic drugs. It implies an increase on prescription drug spending but with little associated quality gain. The study validates previous findings that me-too drugs compete with breakthrough drugs and reduce incentives to invest in research.

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Table of Contents

FIGURES

TABLES

1. GENERAL INTRODUCTION

Me-too drugs are new drugs that are not generic drugs, but nevertheless "duplicate the actions of existing drugs and offer little or no therapeutic gain" (Rogawski, 2006:23). Data from the U.S. Food and Drug Administration (FDA) show that from 1990 to 2006, 77% of the 1,135 unique drugs approved by the FDA "appears to have therapeutic qualities similar to those of one or more already marketed drugs" (CDER, 2004, 2007). Pharmaceutical companies invest more resources in producing and selling these drugs than in developing drugs with significant medical advancement (Angell, 2004; Goozner, 2004).

Given the increase of me-too drugs in the pharmaceutical market, this study examines the factors that may influence physician prescribing behavior in prescribing a generic, breakthrough or me-too drug to a patient. Previous studies (Hellerstein, 1994, 1998) used the 1989 NAMCS data to examine the importance of physicians in prescription decision and the factors that influenced them to prescribe branded or generic drugs. This research adds to existing studies by expanding the physicians' choice of prescribing breakthrough, me-too, generic me-too and generic drugs to their patients. In addition, the influence of patients' increased awareness of drugs through direct-to-consumer advertising on physician's prescribing behavior is examined. The increased role of patients in selecting their medication is examined through the relationship between direct-to-consumer (DTC) advertising and physicians' prescribing behavior.

This study uses the 2006 National Ambulatory Medical Care Survey (NAMCS), a cross-sectional consumer-level data. Drugs belonging to the drug classes statin, cardioselective beta

blockers, proton pump inhibitors and selective serotonin reuptake inhibitors were analyzed separately. The 2006 National Ambulatory Medical Care Survey (NAMCS) is an annual national level survey of office-based physicians who are primarily engaged in direct patient care. Information about patient visits and physician prescribed medication are available. The 2006 expenditures on direct-to-consumer advertising are incorporated in the model to examine the relationship between DTC advertising and the demand for prescription drugs. Since direct-to-consumer advertising is the patients' primary source of information about particular drugs, it may serve as a proxy to estimate the role of patients in physician prescribing behavior. The DTC data were from TNS Media Intelligence, a leading provider of direct-to-consumer advertising expenditure and occurrence data. Price data are from Consumer Reports Best Buy Drugs publication of Consumers Union (Consumers Union, 2006a, 2006b, 2007a, 2007b).

Additionally, this study examines the effect of me-too drugs on the market share of breakthrough drugs and generic drugs. Me-too drugs compete with breakthrough drugs when introduced during patent exclusivity (J. A. DiMasi, 2000; Lee, 2004; Lu & Comanor, 1998). The period of marketing exclusivity for breakthrough drugs have fallen overtime from a median of 10.2 in the 1970s to 1.2 years in the late 1990s (Joseph A. DiMasi & Paquette, 2004). This will have negative implications on research and development of new drugs as the monopoly profit which serves as incentives for research and development is reduced.

When me-too drugs enter the market after patent expiration, it may increase industry profit of branded prescription drugs but may compete with generic drugs. This implies an increase on prescription drug spending but with little associated quality gain. The entry of new drugs in the

market in the 1990s is a major driver of drug-spending growth (Danzon & Pauly, 2002). The Center for Medicare and Medicaid Services estimated that spending for prescription drugs grew at an average annual rate of 14.5 percent from 1997 to 2002 reaching a total spending of $162 billion in 2002. Drug spending grew faster than spending for any other kind of medical goods and services. Prescription drug spending was the third-largest category of personal health care expenditures, after hospital and physician services in 1999 (Baker, 2004).

This research answers the following questions:

1. What factors influence the physician's choice to prescribe breakthrough, me-too, generic or generic me-too drug?

   - What characteristics of an individual will increase the likelihood that he or she will be prescribed a breakthrough, me-too, generic or generic me-too drug?

   - What physician characteristics will increase the likelihood of prescribing a patient with breakthrough, me-too, generic or generic me-too drug?

   - What drug characteristics will increase the likelihood of prescribing a patient with breakthrough, me-too, generic or generic me-too drug?

2. What is the relationship between direct-to-consumer advertising and prescribing physician's choice of drugs?

3. What is the effect of direct-to-consumer advertising and price of me-too drugs on the market share of generic drugs and breakthrough drugs?

This study includes patient characteristics (patient's age, gender, ethnicity and number of medication) and physician characteristics (specialization, region of practice and primary source of income) without any predicted effect on the physician decision to prescribe a specific type of prescription drug. This study tests the hypothesis that an increase in price will decrease the likelihood that a drug is prescribed. This study also hypothesizes that the increase in the length of time the drug has been in the market increases the likelihood that a drug is prescribed. Theory on physician prescribing behavior suggests that physicians tend to prescribe established drugs thus creating a positive relationship between length of time in the market and likelihood of prescribing older drugs. The hypothesis that direct-to-consumer advertising increases the likelihood of a drug from being prescribed is also tested. This research also tests whether a patient's generous insurance coverage increases the likelihood of being prescribed a more expensive drug like me-too drug than a generic drug. Furthermore, this study also tests whether the price, length of time in the market and direct-to-consumer advertising of me-too drugs have negative effects on the market share of generic and breakthrough drugs.

The outcomes of this research on the influence of direct-to-consumer advertising on physician prescribing behavior and the demand for prescription drugs will inform policies governing the pharmaceutical industry. The primary instrument in informing patients about drugs is pharmaceutical advertising. In the United States, prescription drug advertising increased from US$11.4 billion in 1996 to US$29.9 billion in 2005. During the same period, direct-to consumer advertising more than tripled (Donohue, Cevasco, & Rosenthal, 2007).

Current law requires pharmaceutical companies to disclose efficacy and risks of prescription drugs in these promotional materials but none of these contain information on their price or relative cost effectiveness with other drugs. With the role of direct-to-consumer advertising in shaping the demand for pharmaceuticals and the wide array of medication that the physicians and patients can choose from, it is important that doctors and patients get accurate information about the drugs' relative cost-effectiveness to be able to make an informed decision.

This study will give empirical support to the case of approving new drugs on the basis of their efficacy against existing drugs. It will also have implications on existing policies on direct-to-consumer (DTC) advertising of pharmaceuticals which is the primary mechanism to get information about prescription drugs to consumers. This paper proceeds by providing an overview of the policy dynamics that shaped the pharmaceutical industry using an interbranch perspective. This is followed by a chapter analyzing physician prescribing behavior and the factors that may affect it. The third chapter presents the effect of direct-to-consumer advertising on the demand for prescription drugs. The paper concludes with policy recommendations based on the findings of the study.

2. POLICY DYNAMICS IN THE PHARMACEUTICAL INDUSTRY: AN INTERBRANCH PERSPECTIVE

2.1 INTRODUCTION

The policymaking process relating to the pharmaceutical industry exemplifies the dynamism of American policymaking. An interbranch perspective is applied in analyzing how policies are formed through the interaction of the different stakeholders in the pharmaceutical industry. This process looks at the dynamic between the different policymaking institutions – the executive, legislative and the judiciary – and the interplay between federal, state, and local governments. From this view, policy making emanates not from a single branch of government, but rather, the interaction of its many branches (Miller & Barnes, 2004). This captures how the interactions of these institutions result in policies that govern a very important industry compared to the traditional approach of policy analysis that looks at policy making through specific institutions or political actors. This paper will use a historical approach in presenting significant policies on availability and accessibility of prescription drugs until 2010. An overview of laws and policies are presented, together with the strategic response of the policy players and the movement of the arena of policy conflict in the different levels of government in recent years.

2.2 BACKGROUND

The pharmaceutical industry is one of the most highly regulated industries in the United States (L. G. Thomas, 1989) . Two issues that are critical in regulating the industry are ensuring that the right drugs to treat diseases are available and that everyone has access to these drugs. However,

the extent to which government should regulate the pharmaceutical industry has been an ongoing debate among policy experts and researchers.

The state of the availability and accessibility of prescription drugs in the United States raises a number of controversies. The average monthly prices for a 30-day supply of 96 prescription drugs frequently used by Medicare and non-Medicare enrollees increased by 24.5 percent from 2000 to 2004 (United States Government Accountability Office, 2005). The Center for Medicare and Medicaid Services estimated that spending for prescription drugs grew at an average annual rate of 14.5 percent from 1997 to 2002 reaching a total spending of $162 billion in 2002. Drug spending grew faster than spending for any other kind of medical goods and services. Prescription drug spending was the third-largest category of personal health care expenditures, after hospital and physician services in 1999 (Baker, 2004).

With respect to research and development, the Congressional Budget Office (CBO) reported that despite the tripling of industry and federal government spending on health-related research and development since the 1990s, "the number of innovative new drugs approved by the Food and Drug Administration each year has not shown a comparable upward trend." There is no study to show the new drugs are better quality than older drugs to make up for the decrease in the number of drugs approved by the FDA. Furthermore, "a growing share of the industry's R&D output has consisted of incremental improvements to existing drugs rather than new molecular entities" (Congressional Budget Office, 2006:4). On the other hand, "the range of illnesses for which drug therapies exist has never been broader, and technological advances have yielded new drug

treatments of increasing sophistication, convenience, and effectiveness" (Congressional Budget Office, 2006:4).

The federal government has adopted a market driven policy to ensure availability of prescription drugs. It provides public funds to academic and research institutions to conduct research and grants property rights over their output to encourage them to establish partnerships with pharmaceutical companies to manufacture drugs for commercial use.

The federal government also provides pharmaceutical companies with tax incentives and grants sole power to manufacture and market their products to encourage them to invest more in research and development. They are free to decide which drugs to develop and to set their prices. The only regulation requirement is for the Food and Drug Administration (FDA) to approve the products they sell to the public.

This study will focus on the two main policy areas of the pharmaceutical industry: the policies that govern the availability of prescription drugs and the policies that ensure the accessibility of such drugs. Under the policies governing availability of prescription drugs are the rules on research, approval of new and generic drugs and marketing of prescription drugs. Under the accessibility of prescription drugs include substitution laws, insurance coverage, (re)importation and price control.

2.3 SUPPLY SIDE POLICIES: ENSURING THE AVAILABILITY OF PRESCRIPTION DRUGS

2.3.1. RESEARCH INCENTIVES AND PATENT LAWS

Like many other industries in the U.S., the pharmaceutical industry was founded on solid legal ground. The Constitution empowered Congress to promote science by granting exclusive rights to authors and inventors over their works for a limited time. This provision became the basis for the enactment of patent laws in the United States. Since the Patent Act of 1790, industries like the pharmaceutical industry enjoyed monopolies over their own work to encourage them to invest further in research and development.

In the 1980s, with the initiative of the Carter administration and the support of many industries, a market-oriented incentive driven economy became the primary scaffold of many US policies (Hemphill, 1997). There are federal laws that provide incentives to improve the competitiveness of small research firms (National Small Business Association, 2003). The Small Business Innovation Development Act of 1982 requires 10 federal agencies to set aside 2.5% of their R& D budget as a grant to small businesses and to provide additional grant for the development and commercialization of promising products. The same law was reauthorized for another 7 years until year 2000 through Small Business Research and Development Enhancement Act of 1992 and was reauthorized again until 2008 by the Small Business Innovation Research Program Reauthorization Act of 2000. Congress has not reauthorized the law but the programs funded by the law are extended until September 30, 2011 (Office of Extramural Research, 2011).

There are also different tax incentives that pharmaceutical and research and development companies can apply for. Companies can file claims under Net Operating Loss Deduction (Title 26.

Subtitle A. Chapter 1, Subchapter B. Part VI. § 172). Local governments also provide incentives for R&D in the form of tax credits.

But there are specific laws that helped strengthen the pharmaceutical industry. The Bayh-Dole Act of 1980 and Stevenson-Wydler Technology Innovation Act of 1980 govern the rules on patents for projects associated with federal research and development activities (Schacht, 2000). The Bayh-Dole Act provided government funding for research and encouraged the transfer of scientific knowledge, discoveries and technologies from academic institutions to businesses with commercial interests. Small biotech companies proliferates around major academic research institutions and often carry out the initial phases of drug development, hoping for lucrative deals with big drug companies that can market the new drugs (Angell, 2004). The Stevenson-Wydler Act of 1980 governs the transfer of intellectual property rights of researches in government owned laboratories, industry, and academia to outside parties.

The Orphan Drug Act of 1983 was enacted to encourage the development of drugs to treat rare diseases. Drugs are considered orphaned if the potential market is too small to generate attractive profit to firms, the drug is not patentable or because liability concerns arise because of the nature of the target population (Hollon, 1999). The law provides exclusive marketing rights of orphan products for 7 years, 50 percent tax credit of the cost of conducting human clinical testing, and research grants for clinical testing of new therapies to treat orphan diseases. Within a decade of the enactment of the law, orphaned drugs rose from 10 to 513, 87 of which were approved by FDA for marketing (Hollon, 1999).

Effective patent life is shorter for pharmaceutical products because patents are obtained before drugs are approved for marketing. The Drug Price Competition and Patent Restoration Act of 1984 also known as the Hatch-Waxman Act extended the marketing exclusivity of pioneering companies for drugs that are already in the pipeline. The extension is five years maximum in addition to the 20 years exclusivity granted upon the issuance of patent. The remaining patent life of a prescription drug after FDA approval, however, should not exceed fourteen years under the law. Delays because of lack of due diligence by the pioneer drug manufacturer during the FDA review process will also reduce the restored patent term accordingly (Chen, 2007). Effective patent life for new drugs range from 10 to 15 years (Congressional Budget Office, 2004; Public Citizen's Congress Watch, 2001).

Extending Patent Life

Most of the favorable laws and regulations of the pharmaceutical industry is attributed to the lobbying muscle of the pharmaceutical industry. According to a study by the Center for Public Integrity, the pharmaceutical industry spent $612 million to lobby for important bills and has employed around 3,000 professional lobbyists from 1998 to 2005. This is hundred folds more than any other organized interest (Ismail, 2005). But aside from lobbying in Congress, the pharmaceutical industry has utilized the courts to shape the policies governing the industry, mostly to extend patents of their drugs and undermine the impact of generic competition.

The Food and Drug Authority (FDA) has found itself in hot seat in one of the industry's strategy to extend patent life. The FDA's regulatory processes in approving new drugs allegedly

take 12 to 15 years. This is usually blamed for consuming the patent life of prescription drugs. It is also blamed for the high prices of prescription drugs because the pharmaceutical companies need to recover losses brought about by the delay (Pilon, 2004). Angell (2004) explained that while it is true that the total time from the beginning of preclinical testing of a candidate drug to its coming on the market takes several years, "the time for FDA review accounts for only… about sixteen months in 2002 and getting shorter." She also claimed that in special cases, approval time can be cut to weeks. Still, media is saturated with claims that the FDA is so inefficient prompting calls for its abolition (Friedman, 1999). The pharmaceutical industry's continued assault on the FDA's alleged bureaucratic inefficiency by the pharmaceutical industry helped produce laws that extended the patent life of drugs.

President Reagan took interest on the issue of patent term restoration to compensate pharmaceutical companies for loss in patent time due to regulatory review. An intellectual property committee was set up under the Cabinet Council on Commerce and Trade, which recommended patent restoration (Mossinghoff, 1999). This proposal turned into a bill, and after going through the legislative mill, became the Drug Price Competition and Patent Restoration Act in 1984 (Mossinghoff, 1999). The law (otherwise called the Hatch-Waxman Act) granted pioneer drug manufacturers extension of their intellectual property rights on their drugs while simultaneously expediting generic drug approval process (Burgess & Lucas, 2005; Karki, 2005). It extended the average effective patent life of drugs to 11.8 years (Public Citizen's Congress Watch, 2001). The Prescription Drug User Fee Act of 1992, the Uruguay Round Agreements Act of 1994, and the Food and Drug Modernization Act of 1997 added 4.4 to 5.9 years of effective patent life which now averages 13.9 to 15.4 years (Public Citizen's Congress Watch, 2001).

2.3.2. REGULATION ON SAFETY AND EFFICACY

The first federal drug regulation law was the 1906 Pure Food and Drugs Act. It mandated the Bureau of Chemistry in the Department of Agriculture to prohibit interstate commerce of adulterated and misbranded food and drugs. This Bureau became the Food and Drug Administration in 1930 (Meadows, 2006).

In 1938, the Food, Drug and Cosmetic Act was enacted providing the Food and Drug Administration the power to ensure the safety of prescription drugs. It required the pre-market approval of all new drugs and proper labeling to include directions for safe use. The enactment of the law was triggered by the sale of elixir sulfanilamide which targeted pediatric patients. The solvent in the untested product was highly toxic that resulted to the death of over 100 people, mostly children (Bureau of Food and Drugs).

The Kefauver-Harris Drug Amendment of 1962 requires pharmaceutical companies to show that their drugs are sufficiently effective and safe. The enactment of the law was triggered by the attempt to prevent the sale of Thalidomide in the US market, a sleeping pill which was proven to cause birth defects among children in Western Europe. Prior to 1962, drugs can be marketed even without proof of its efficacy (Fox, 2005). The law also required the FDA to approve the marketing application before the drug could be marketed (Meadows, 2006).

To date, the FDA only requires new drugs to prove their efficacy against a placebo and not against medications that are already in the market (Angell, 2004; Furberg, Herrington, & Psaty,

1999). This process ignores the possibility that new drugs can actually be less effective than the drugs that are already in the market today.

2.3.3. Approval Process of New Drugs

The development of new drugs starts with screening and discovery phase where compounds are tested to see if they will interact with a target. A potential drug is then evaluated for toxicity and tests on animals (Cook, 1998). The screening and discovery phase and preclinical testing was estimated to run for about two to four years based on the experience with drugs developed between 1980-1992 (Joseph A. DiMasi, Seibring, & Lasagna, 1994). The next step is to submit an investigational new drug application to FDA to begin testing the new drug with human subjects. The clinical trials have three phases. Phase I is the determination of safe dosage levels and toxicity with humans. The sample for phase I clinical trials are usually comprised of fewer than 100 healthy individuals. Phase II is the testing for both safety and efficacy. The drug is tested to 50 to 200 individuals with the disease that the drug is designed to target. Phase III involves testing the drug to thousands of individuals to see if the benefit of the drug is statistically significant (Cook, 1998).

After the clinical trials, the pharmaceutical company then submits a New Drug Application (NDA) to the FDA. The evidence from the clinical trials are used to prove that "the new drug is safe and effective in its proposed use(s) and the benefits of the drug outweigh the risks; the proposed labeling is appropriate; the methods used in manufacturing the drug and the controls used to

maintain the drug's quality are adequate to preserve the drug's identity strength, quality and purity" (Center for Drug Evaluation and Research, 2007).

The FDA classifies application of new drug for standard or priority review. Standard review is granted to drugs that "appears to have therapeutic qualities similar to those of one or more already marketed drugs" in contrast to priority review which is granted to drugs which present "significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease" (CDER, 2004). In 2004, the median time for approval of priority applications is around six months while the approval of standard applications takes around 10 months (Food and Drug Administration, 2004). This is a huge decline from 27 months to approve standard application in 1993. The approval of priority application has fluctuated around six months since 1997 (United States Government Accountability Office, 2002a). The Prescription Drug User Fee Act, which authorizes FDA to collect fees from companies that produces human drug and biological products, is responsible for expediting the approval process of new drugs (United States Government Accountability Office, 2002a). It was enacted in 1992 and was renewed by Congress in 1997, 2002 and 2007. These fees are estimated to amount to $205,000 in 1997 (Cook, 1998). Pharmaceutical firms are also required to pay annual fees for their manufacturing establishments and the drugs they currently have on the markets (Cook, 1998; "Federal Food, Drug, and Cosmetic Act of 1938," 1938).

Overall, based on the data in the 1980s and 1990s, drug development from screening and discovery, clinical trials to approval of FDA for marketing takes about eight to nine years (Cook, 1998; Joseph A. DiMasi et al., 1994). Despite criticism on the length of time it takes FDA to approve

application for new drugs, a study showed that more important drugs are developed and approved at a shorter time compared to less important drugs (Dranove & Meltzer, 1994).

Me-too Drugs

In the past two decades, the pharmaceutical industry began producing drugs which have only marginal new benefits for conditions for which treatments are already available (Shtilerman, 2006a). These drugs, usually known as "me too" drugs, are copycats of highly profitable patented drugs. "Once the first breakthrough discovery is made of a new pharmacological activity for a new molecule, subsequent years saw the emergence of a host of new molecules or 'me-too' drugs from the same chemical class and possessing the same pharmacological profile" (Nair, 2003). Me-too drugs have similar chemical structure or mechanism of action with a drug that is already in the market which usually referred to as the breakthrough drug (Joseph A. DiMasi & Paquette, 2004). The breakthrough drug and me-too drugs are assumed to belong to the same class and may have the same therapeutic activity or class effect. Because patent is based on specific chemical structure and not on mechanism, many drugs in the market are "functionally similar"(Cook, 1998). This allowed the marketing of me-too drugs as substitute of proven drugs in the same class (Furberg & Pitt, 2001:1456-1457).

The Hatch-Waxman Act extended the patent of branded drugs to three years for improvements of existing products that requires additional research. This provision resulted in the reformulations of existing products like the delayed-release and extended-release versions of already marketed drugs (Levy, 1999). The development of these drugs usually cost about one-

fourth of the cost to develop new molecular entities especially if clinical trials are no longer required (Congressional Budget Office, 2006). These reformulated drugs will have longer patent life (greater than the three year extension provided by the Hatch-Waxman Act) if new patent is obtained (Reiffen & Ward, 2005a).

Reforming the Approval of New Drugs

The soaring prices of prescription drugs and the boom in me-too drugs production motivated many experts to call for reforms in the approval of new drugs in the United States. Consumer organizations, insurance and health care provider groups even Republican Senators like Bill Frist support the use of independent studies of comparative effectiveness of prescription drugs (Marwick, 2004). An example of this is the Australian model which requires pharmaceutical companies to prove the cost effectiveness of their drugs relative to those drugs already in the market before they are included in the list of drugs funded by the Australian Pharmaceutical Benefit Scheme. Australia has the most comprehensive pharmacoeconomic regulation and is the first to implement this regulation in 1995 (Kulp, Greiner, & Schulenburg, 2003). Similar regulations are in place in Canada, Japan and the United Kingdom, among other countries (Chokshi, Avorn, & Kesselheim, 2010).

There were many attempts to legislate the use of independent research to compare clinical efficacy of prescription drugs. Among the members of Congress who supported this initiative and had filed related legislation include Representatives Thomas H. Allen (D-ME) and Jo Ann H. Emerson (R-MO) and Senator Hillary Rodham Clinton (D-NY) (Office of Legislative and Policy

Analysis, undated). The Food and Drug Modernization Act of 1997 mandated the Agency for Healthcare Research and Quality (AHRQ) to conduct research on comparative effectiveness and safety of drugs, biological products, and devices. The Healthcare Research and Quality Act of 1999 expanded the mandate of AHRQ to 1) conduct state-of-the-art research, 2) provide objective clinical information to clinicians, patients, pharmacists, and others, and 3) improve the quality of health care while reducing costs by focusing on appropriate use of these products and prevention of adverse events (Office of Legislative and Policy Analysis, undated).

All initiatives on independent comparative research of prescription drugs during the 108th Congress were related to (Office of Legislative and Policy Analysis, undated):

> "comparing prescription drugs that account for high levels of expenditures or use by individuals in federally funded health programs with other drugs and treatments used for the same disease or condition. The goal of the research would have been to develop valid scientific evidence regarding the comparative effectiveness, cost-effectiveness, and, where appropriate, comparative safety of those drugs."

None of the legislative initiatives survived the legislative mill. Then Senator Hillary Clinton attempted to insert similar provisions in the Medicare Prescription Drug Improvement, and Modernization Act of 2003 but the amendment failed (Office of Legislative and Policy Analysis, undated). These initiatives have been thwarted by the strong lobbying of the pharmaceutical industry. The industry argued that "attempts to determine equivalence between older and most likely cheaper drugs, would discourage manufacturers from developing new and possibly better products, even though they were likely to be more expensive" (Marwick, 2004).

The Center for Medicare and Medicaid supported comparative research on effectiveness of prescription drugs to be part of the Medicare Prescription Drug Improvement, and Modernization Act of 2003 (MMA). The law authorized $50 million for the Agency for Healthcare Research and Quality (AHRQ) to conduct comparative clinical effectiveness studies (Office of Legislative and Policy Analysis, undated). But the funding for the proposed comparative effectiveness studies were eliminated in the President's budget for 2004-2005. The law also stated that comparison for functional efficiency of prescription drugs are a responsibility of the FDA and not the CMMS (Marwick, 2004).

However, despite the defeats in legislation of comparative effectiveness studies, the private sector has taken the initiative to adopt the requirement of proof of comparative effectiveness for inclusion of prescription drugs in formularies. Many refer to this requirement as the "fourth hurdle in drug development."

> If one considers the demonstration of safety, efficacy, and benefit–risk management as the three hurdles that must currently be overcome to secure registration of a new product, one can think of product reimbursement (i.e., persuading someone to pay a fair price for a product) as a critical fourth hurdle to successful commercialization (Honig, 2011).

In 2000, the Academy of Managed Care Pharmacy (AMCP) first issued its formulary guidelines advising health plans to formally request drug companies to submit a standardized dossier containing detailed information including the cost effectiveness of the prescription drug compared to alternative therapies. The AMCP is a trade group representing most health plans in the

United States. Countries like Australia, Canada and the United Kingdom used similar drug dossier in deciding on reimbursement and pricing of prescription drugs. Although AMCP gave its members the flexibility on how to implement the guidelines, about 65% of the health plans started implementing the formulary guideline in 2004 (Cohen, 2004).

The federal government has invested modest amount in comparative effectiveness studies until 2009 when Congress allocated $1.1 billion for comparative effectiveness research trough the economic stimulus law of President Obama (Chokshi et al., 2010). In 2010, President Obama signed the Patient Protection and Affordable Care Act. It created the Patient-Centered Outcomes Research Institute, a quasi-government enterprise mandated to fund comparative effectiveness research. The funds for the Institute will come from the Medicare program and contribution of private insurers (Iglehart, 2010). The legislation is a result of compromise between the different stakeholders in the health care industry. This is reflected by the critical features of the law. It created a public-private nonprofit enterprise to address concerns about burgeoning bureaucracy, government control and the encroachment of government on private rights. The composition of the board reflects the accommodation of different interest groups. The board of the Institute has twenty-one slots for representatives from consumers, hospitals, industry, nurses, payers, physicians, researchers, surgeons and two government agencies: the Agency for Healthcare Research and Quality (AHRQ) and the National Institutes of Health (NIH). As Iglehart (2010) discussed, the comparative effectiveness research agenda will be set by private stakeholders and not the government or purely science-minded researchers. Iglehart (2010) in his article, also explained the politics behind the passage of the law. With support coming from AARP, the American Federation of Labor-Congress of Industrial Organizations (AFL-CIO), the Center for

American Progress, Consumers Union, the National Partneship for Women and Families and the Pacific Business Group of Health, other organizations like PhRMA and individual pharmaceutical companies eventually supported the passage of the law when their agenda have been included in the legislation. They want to make sure that "research findings were transparent, that the administrative agency was an enterprise that operated independently of government, and that its members were represented on the board." In the end, after all the negotiations and compromises, "the research entity does not make coverage decisions and the studies conducted do not include coverage recommendations or clinical practice guidelines" (Iglehart, 2010:1759).

This piece of legislation mirrors the classic divide between the Democrats and the Republicans. Prior to this legislation, there are a handful of Republicans who are supportive of comparative effectiveness research. This includes Sen. John McCain and former House Speaker Newt Gingrich of Georgia and Gail Wilensky, Health Affairs' adviser on this thematic issue and a former administrator of Medicare and Medicaid who also served as White House health policy adviser to President George H.W. Bush (Iglehart, 2010). But with this initiative, the Republicans, including conservative institutions and radio pundits, started associating the legislation to government rationing and control. The voting pattern shows a clear divide in the Senate, where all the Democrats and independents voted in favor of the legislation and all the Republicans voted against it (60-39).

2.3.4. Approval of Generic Drugs

A generic drug is assumed to be an identical, or bioequivalent drug to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and

intended use (Food and Drug Administration). Of the 11,487 drugs listed in the FDA's Orange Book[1], 8,730 have generic counterparts (Generic Pharmaceutical Association, undated citing FDA Med Ad News).

The most significant piece of legislation that facilitated generic competition is the Hatch-Waxman Act of 1984. This law shortened the approval process of generic drugs to facilitate their entry in the market after the patent of the branded drug expires. The law reduced the average delay between patent expiration and generic entry from more than three years to less than three months for top-selling drugs and increased competition between innovator and generic firms (Cook, 1998). Competition between generic drugs also increased with the passage of the law. The price of generic drug is about 60% of the brand name drug when there are about one to 10 firms producing a particular generic drug. The price can fall to less than half of the brand-name price when there are more than 10 manufacturers (Cook, 1998).

Prior to the enactment of the Hatch-Waxman Act, generic drug manufacturers are required to conduct safety and efficacy tests similar to what are required of the original branded drug manufacturers. Generic drug manufacturers can only proceed with the testing only after the patent of the branded drug has expired because clinical testing beforehand is considered patent infringement (Chen, 2007). With the law, generic drug manufacturers submit abbreviated new drug applications (ANDA) for approval to produce the generic version of off-patent drugs. The abbreviated new drug applications are not required to conduct preclinical (animal) and clinical (human) trials to establish safety and effectiveness since these have been established already with

[1] Orange book is a listing of drug products approved by the Food and Drug Administration.

the approval of the innovator drug product. Instead, ANDA requires bioequivalence, chemistry/ microbiology and labeling reviews.

The bioequivalence review process establishes that the proposed generic drug is bioequivalent to the innovator drug on the basis that both the rate and extent of absorption of the active ingredient of the generic drug fall within established parameters when compared to that of the reference listed drug. This may or may not require human testing. The chemistry/microbiology review process provides assurance that the generic drug will be manufactured in a reproducible manner under controlled conditions. The generic company's manufacturing procedures, raw material specifications and controls, sterilization process, container and closure systems, and accelerated and room temperature stability data are reviewed to assure that the drug will perform in an acceptable manner. The labeling review process ensures that the proposed generic drug labeling (package insert, container, package label and patient information) is identical to that of the reference listed drug except for differences due to changes in the manufacturer, distributor, pending exclusivity issues, or other characteristics inherent to the generic drug product (Food and Drug Administration). The law also allowed the generic manufacturers to conduct bioequivalence test even prior to patent expiration of the branded drug. The law insulated ANDA-related clinical research from patent infringement liability (Chen, 2007).

When pioneer firms submit NDAs, they are also required to submit a list of patents relevant to the drugs to the FDA. These patents are published in the Orange Book (Food and Drug Administration, 2009). The generic firms' subsequent ANDAs are then required to issue any of the

four certifications to each of the patent listed in the Orange Book ("21 U.S.C. § 355(j)(2)(A)(vii) ", 2000):

(I) that such patent information has not been filed,

(II) that such patent has expired,

(III) of the date on which such patent will expire, or

(IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted.

Paragraph IV certification has been the most controversial since the generic firm is seeking entry prior to patent expiration (Chen, 2007). Generic firms who submit paragraph IV certification must inform the pioneer firm which in turn has 45 days upon receipt of the notification to file a patent infringement lawsuit ("21 U.S.C. § 355(j)(5)(B)(iii) (Supp. III).", 2003; Chen, 2007). If litigation is not pursued by the pioneer firm, the FDA has to immediately approve the ANDA assuming all other regulatory requirements have been satisfied (*Generic Pharmaceuticals: Marketplace Access and Consumer Issues: Prepared Statement of Timothy J. Muris, Chairman, Federal Trade Commission*, 2002). Litigation, on the other hand, automatically triggers a thirty-month stay in which the FDA cannot approve the ANDA until the patent expiration, a final resolution of the patent litigation in favor of the generic firm or expiration of the thirty-month period, whichever comes first ("21 U.S.C. § 355(j)(5)(B)(iii) (Supp. III).", 2003; Chen, 2007).

The first generic drug manufacturer to file an ANDA with a paragraph IV certification is awarded with a 180 day marketing exclusivity among generic products as an additional incentive for generic drug manufacturers to enter the market (Frank, 2007). During this period, the FDA

cannot approve other competitors' ANDA (*Generic Pharmaceuticals: Marketplace Access and Consumer Issues: Prepared Statement of Timothy J. Muris, Chairman, Federal Trade Commission*, 2002). The 180-day period is triggered on the first commercial marketing of the generic drug product or the date of a court decision declaring the patent invalid or not infringed, whichever is sooner (*Generic Pharmaceuticals: Marketplace Access and Consumer Issues: Prepared Statement of Timothy J. Muris, Chairman, Federal Trade Commission*, 2002).

2.3.5. REDUCING THE IMPACT OF GENERIC COMPETITION

Estimates in the early 1990s showed that a year of delayed competition from generic drug competitors would increase the profit of a branded drug with $110 million domestic annual sales by about 12 million (Cook, 1998; H. Grabowski & Vernon, 1994). Aside from challenging laws and policies, the industry has developed sophisticated strategies to slow down the erosion of its market share and reduce the impact of generic competition. These strategies include colluding with generic companies to forestall the entry of generic drugs, extending and creating new patents to protect branded drugs whose patents are about to expire and producing authorized or branded generics to compete with generics.

Collusion between Brand and Generic Companies

One strategy to forestall generic entry is to engage in anticompetitive settlement agreements between pioneer and generic drug firms which the Federal Trade Commission referred to as the "first generation litigation." Under these collusive arrangements, the generic firm, who is challenging the branded drug's patent under Paragraph IV certification, accepts a substantial

monetary payments in exchange for its potential profit if it enters the market (Chen, 2007). This collusive act delays the entry of the first generic competitor and with it the triggering of the 180-day exclusivity (*Generic Pharmaceuticals: Marketplace Access and Consumer Issues: Prepared Statement of Timothy J. Muris, Chairman, Federal Trade Commission*, 2002). This enables the pioneer firm to block all subsequent generic competitors, whose market entry depends on the expiration of 180-day exclusivity which has been put off indefinitely (Chen, 2007). This collusive act extended the patent life of the branded pharmaceutical (Rubin & Rubin, 2003).

The two most known cases of brand/generic collusion are the Abbott Laboratories and Geneva Pharmaceuticals, Inc. relating to Abbott's branded drug Hytrin[2] and Hoechst Marion Roussel and Andrx Corp. relating to Hoechst's branded drug Cardizem CD[3]. Both generic drug companies received enormous amount of money to delay the entry of the generic versions of the drugs and to use the 180-day exclusivity to block the entry by other generic competitors (*Generic Pharmaceuticals: Marketplace Access and Consumer Issues: Prepared Statement of Timothy J. Muris, Chairman, Federal Trade Commission*, 2002). The 11 month delay also resulted in huge losses in Medicaid in 28 states and an additional $700 million in sales to Aventis[4] ("In re Cardizem CD Antitrust Litig.," 2002).

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[2] Abbott paid Geneva Pharmaceuticals $45M/month until a district court makes a judgement on the patent infringement dispute. See http://www.ftc.gov/os/2000/05/abbottgenevaanalysis.htm

[3] Hoechst (HMR) allegedly paid Andrx $10M per quarter beginning in July 1998 and additional $60M per year from July 1998 to the conclusion of the lawsuit if Andrx prevailed. See http://www.ftc.gov/opa/2001/04/hoechst.shtm

[4] Aventis acquired Hoechst Marion Roussel in 2000.

To address both cases and avoid similar cases in the future, the Federal Trade Commission issued consent orders prohibiting the drug companies from entering into agreements in which a generic drug company, that is first ANDA filer with respect to a particular drug, agrees not to enter the market or transfer its 180-day marketing exclusivity rights.[5] Companies were required to notify in advance the FTC and to seek court approval for interim settlement of patent infringement action that provide for payments to the generic not to enter the market. FTC also required advance notice before drug companies could enter into similar agreements in non-litigation contexts (*Generic Pharmaceuticals: Marketplace Access and Consumer Issues: Prepared Statement of Timothy J. Muris, Chairman, Federal Trade Commission*, 2002).

To eliminate the collusive act of pharmaceutical companies, Congress enacted the Medicare Prescription Drug Improvement, and Modernization Act of 2003. Title XI of the Act requires branded and generic drug firms to notify the FTC and Department of Justice within 10 days of any agreements involving the 180-day exclusivity period. Furthermore, Paragraph IV sets time limitations for which generic firms must take advantage of their exclusivity period or loose the reward (Chen, 2007; Greene, 2005).

Evergreening

Some patent holders were able to delay the entry of generic competitors through multiple thirty-month stay by filing additional new patents to those listed in the Orange Book after the approval of the NDA but before the approval of the generic drug application (Federal Trade

[5] The consent orders are available at http://www.ftc.gov/os/2000/03/abbott.do.htm, http://www.ftc.gov/os/2000/03/genevad&o.htm, http://www.ftc.gov/os/2001/05/hoechstdo.htm

Commission, 2002). This strategy is referred to as "evergreening." Evergreening exploits the 30-month stay provision of the Hatch-Waxman Act. By filing new patents, generic drug companies would need to file additional Paragraph IV certification for each of the new patent which will trigger successive 30-month stays and delay generic competition (Chen, 2007).

The cases of Bristol Myers with its drug Buspar and Biovail's Tiazac are examples of attempt by pharmaceutical companies to delay the entry of generic competitors through fraudulent patent filings with the FDA (*Generic Pharmaceuticals: Marketplace Access and Consumer Issues: Prepared Statement of Timothy J. Muris, Chairman, Federal Trade Commission*, 2002).

This strategy resulted in both the branded pharmaceutical company suing the generic drug company for violating some patent and the generic drug company suing to invalidate extra patents (Herper, 2002). The pharmaceutical industry itself has propelled a specialized field of the legal profession that mainly focuses on patent litigation.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 addressed this problem by mandating only one thirty-month stay to patent holders, limiting Paragraph IV certification to patents listed in the Orange Book and allowing generic firms to file counter lawsuits against fake patents (Chen, 2007; Federal Trade Commission, 2002; Greene, 2005).

Branded/Authorized Generic

The introduction of branded generics to discourage the entry of generic competitors started in the early 1990s (Wagh, Patel, & Baheti, 2010). Some companies of prescription drugs whose patents were about to expire introduced or issued authorization for the introduction of the generic

version of the drugs prior to patent expiration (Reiffen & Ward, 2005a). The production of branded generics includes the creation of a specific division within the innovator company to produce the generic drugs, acquisition of generic competitor, or through a contractual agreement with another firm to market the drug while the innovator company manufactures the generic version (Reiffen & Ward, 2005a). Branded generics are chemically identical to the pioneer drug as opposed to the ANDA generic version which is a bioequivalent version of the pioneer drug (Federal Trade Commission, 2009).

In 1994, eight of the fifteen largest generic drug companies were subsidiaries of branded pharmaceutical companies. Some companies eventually sold their generic subsidiaries after realizing that this venture is not very profitable. In 1998, at least 13 brand name manufacturers have a generic subsidiary or division (Cook, 1998). Since 2003, 121 authorized generics entered the market, in which 64% were launched by generic companies and the remaining were launched by subsidiaries (Wagh et al., 2010).

The entry of branded generics has an effect on competition, consumer welfare and profit. Since branded generics can enter the market even before the patent expires, other potential entrants are discouraged from entering the market resulting less competition, higher equilibrium price for generic drugs and higher profit for branded drugs (Hollis, 2003; Reiffen & Ward, 2005a). Branded generics undermine the economic value of the 180 day marketing exclusivity awarded to generic firms that are first to get their ANDA approved. Producers of branded generics have three advantages over an independent generic firm: (1) the branded company has production experience which lowers the costs in producing the drug as opposed to an independent firm; (2) the branded

company does not need to apply for ANDA as long as the generic drug is produced on the same production lines as the branded drug; and (3) there are no legal obstacles for the entry of the branded generic even prior to patent expiration because it is introduced by the patent holder (Reiffen & Ward, 2005a). On the other hand Berndt et al. (2007) presented in their study that consumers benefit from authorized generic through lower short-run prices. They argued that long term price and competition are less likely to be affected by authorized generic and the potential cost to consumers of a slight delay in generic entry is likely to be small.

Two court cases have questioned the legality of the entry of authorized generics during the 180 day marketing exclusivity of the first ANDA filer. In *Teva Pharmaceutical Industries v. Crawford*, the court affirmed the legality of Pfizer's authorized generic version of gabapentin concluding that there is no statutory basis in the Hatch- Waxman act that can prevent the marketing of authorized generics during a 180-day marketing exclusivity period of the ANDA filer ("Teva Pharmaceuticals Industries Ltd. v Crawford," 2005). Similarly, in *Mylan Pharmaceuticals v. FDA,* the Fourth Circuit arrived at a similar conclusion that the Hatch-Waxman Act does not prohibit the marketing of authorized generics (Chen, 2007).

According to an FTC report, consumers benefit from competition between authorized generic and ANDA generic during the 180-day marketing exclusivity period. The retail prices and the whole sale prices are on average lower (4.5 and 6.5 percent respectively), relative to the pre-generic brand prices, when an authorized generic compete with one ANDA generic during the exclusivity period than when there is no competition. The report also explained that the revenues of a sole ANDA generic company during the 180-day exclusivity period drop by 47% to 51% on the

average because of the entry of authorized generic. The revenue effect is significantly larger than the price effect for consumers. The authorized generic typically obtains a significant share of the market because it is chemically identical to the branded drug, a much closer substitute than the ANDA generic. As a result of this market dynamic, about one-quarter of the final patent settlements between pioneer firms and first-filer generics reviewed by the FTC between FY2004-2008 contained (1) explicit agreement by the pioneer firm not to launch an authorized generic to compete with the first-filer ANDA generic; and (2) an agreement by the first-filer to defer its entry past the settlement date by on average 34.7 months. Consumers are harmed by this practice because the overall prescription drug cost will remain high with the delay of generic drug entry. The consumers will also lose the price discounts from competition between authorized generic and ANDA generic during the 180-day marketing exclusivity (Federal Trade Commission, 2009). Finding normative and doctrinal support from the Hatch-Waxman Act and the patent law regimes, Chen (2007) concluded that authorized generics constitute predatory behavior in which the intent and operation are anti-competitive and should be prohibited.

2.3.6. MARKETING OF PRESCRIPTION DRUGS

In 2008, the U.S. pharmaceutical industry spent around $18 billion dollars on advertising and promotion (IMS Health, 2008). This includes direct-to-consumer advertising, detailing and advertising in professional journals. But if we include spending on continuing medical education (CME), travel and lucrative honoraria to medical professionals, marketing expenditure directed to medical professionals alone could reach up to $25 billion each year (Donohue et al., 2007).

Pharmaceutical detailing is one of the most aggressive marketing strategies of the pharmaceutical industry. This involves regular visits from medical sales representatives which provide free meals, gifts and drug samples. The industry employed 87,892 detailers in 2001; a ratio of 1 medical sales representative for every 5 physicians (Chin, 2002). Industry spending on lunches for doctors is estimated at roughly $1 billion a year (Saul, 2006). Around 94% of physicians have accepted some form of gifts from the pharmaceutical industry (Campbell, 2007).

Spending on direct-to-consumer (DTC) advertising of prescription drugs has tripled in recent years. It has been the fastest growing marketing expense of the industry (Goozner, 2004:230). Between 1996 and 2005, spending on DTC advertising increased by 330% (Donohue et al., 2007). Pharmaceutical companies spent $4.4 billion on DTC advertising in 2008 (IMS Health, 2008). Overall, this is only a small portion (15.7%) of the industry's marketing expenditure. But if drug samples are excluded in the 2000 marketing expenditure of the industry, DTC advertising would account for 32% of the expenditure (National Institute of Health Care Management, 2001). Pharmaceutical companies promote their products directly to consumers through advertisements in magazines, newspapers, and consumer brochures; on the internet; and on radio and television (United States Government Accountability Office, 2002b). Television advertising accounted for more than half (57%) of prescription drugs' DTC expenditure (National Institute of Health Care Management, 2001).

Marketing Regulation in the United States

The United States is one of two countries that allows direct-to-consumer advertising (Vastag, 2005). Direct-to-consumer advertising of pharmaceuticals has been practiced in the

United States for over 30 years until in 1982 when the FDA requested a voluntary suspension of advertisements until it can formulate guidelines to regulate the advertisements. The Federal Food, Drug and Cosmetic Act also known as Wheeler Lea Act of 1938 gave the jurisdiction to regulate advertising of prescription drugs to the Federal Trade Commission until the 1962 Kafauver-Harris amendments to the Federal Food, Drug and Cosmetic Act (FFDCA) transferred the authority to FDA (Donohue, 2006). The FFDCA empowers the FDA to regulate the promotion of prescription drugs, including the content of DTC advertisements. The act sets general standards for FDA's regulation of prescription drug advertising directed to consumers and physicians.

Direct-to-consumer advertising existed until 1982 when the FDA called for a voluntary moratorium on mass media advertisement (Donohue, 2006). In 1985, the FDA issued a regulation requiring advertisement to include the generic name of the product, the risk, side effects and contra-indication and adequate provision on where to obtain full FDA-approved prescribing information (D. Bradford & Kleit, 2006; Calfee, Winston, & Stempski, 2002). Advertisement can discuss an illness or condition and encourage consumers to see a physician for treatment without mentioning any brand or it can advertise a brand without mentioning any illness (Calfee et al., 2002). However, these requirements presented a natural barrier to direct-to-consumer advertising on television and radio because it is impossible to present all the requirements in a short television commercial so direct-to-consumer advertising used the print media instead (Donohue, 2006).

The regulation was amended in August 1997 (D. Bradford & Kleit, 2006). The current guidelines on implementing the act require that advertisements present accurate information and fairly represent both the benefits and the risks of the advertised drug (United States Government

Accountability Office, 2002b). The name of the drug and its clinical benefits can now appear in the same advertisement given adequate provision on risk, side effects, contra-indication and complete information on where to find additional resources (toll free numbers, web address or a reference to a complete print advertisement) (D. Bradford & Kleit, 2006).

The FDA does not have the authority, however, to require the approval of promotional materials before airing them and most of the time can only take action when false or misleading claims about prescription drugs were already made (Kessler, Rose, Temple, Schapiro, & Griffin, 1994:1351 ; Vastag, 2005). It issues regulatory letters to pharmaceutical companies to call their attention regarding violations of drug-advertising regulations. Pharmaceutical companies that receive regulatory letters have invariably ceased dissemination of the misleading advertisement. However, FDA's oversight has not prevented some pharmaceutical companies from disseminating new misleading advertisements for the same drug. FDA has a limited ability to monitor and assess the compliance of pharmaceutical companies because FDA cannot verify that it receives all advertisements that have been disseminated (United States Government Accountability Office, 2002b, 2006). FDA has no power to penalize or sanction drug companies that run misleading advertisements (Vastag, 2005).

The FDA reviews only a sample of the DTC advertisements submitted by the pharmaceutical companies. According to the review of the GAO, FDA only has informal criteria in prioritizing materials for review. Therefore, there is no guarantee that the agency is in fact reviewing the materials that has the most critical impact on public health (United States Government Accountability Office, 2006).

FDA's oversight powers was affected by a change in its procedures for reviewing draft regulatory letters that was directed by the Department of Health and Human Services (DHHS) on January 2002. The DHHS required that all FDA regulatory letters be reviewed by FDA's Office of Chief Counsel before they are sent out. This change resulted in the delay of some regulatory letters. Some were sent out after the advertising campaigns had already run its course (United States Government Accountability Office, 2002b). Because of this change in policy, FDA took an average of four months to issue a regulatory letter, compared with an average of two weeks before this policy change (United States Government Accountability Office, 2006).

Donohue et al. (2007) further explained that the number of FDA staff in charge of reviewing DTC advertising remain stable while DTC has grown substantially. This is further supported by the fact that the proportion of broadcast advertisements that were reviewed by FDA before airing went down from 64% in 1999 to only 32% in 2004. The number of letters sent by the FDA to pharmaceutical companies declined from 142 in 1997 to only 21 in 2006 and this might be some indication of the FDA's weakened capacity to enforce advertising regulation (Donohue et al., 2007).

The pharmaceutical industry has recently come under serious criticisms because of misleading advertisements. Such is the case of Vioxx and Celebrex. These are Cox-2 inhibitors that were approved by the FDA for arthritis pain. These drugs were marketed as super aspirins even if they are no better than over-the-counter aspirin, ibuprofen or prescription naproxen (Goozner, 2004). Vioxx was the most heavily advertised drug in 2000 (National Institute of Health Care Management, 2001). Misleading results from industry sponsored clinical trials appeared recurrently in medical journals to make a case that it is better than traditional non-steroidal anti-

inflammatory drugs (NSAIDs). It turned out that patients using Vioxx developed serious heart problems at three times the rate of patients on the traditional NSAID Naproxen and Celebrex is equally likely as traditional NSAIDs in causing ulcer-related complications (Goozner, 2004). Vioxx, while being the top selling drug for arthritis, reportedly caused serious heart problems to 140,000 and is facing more than 6,000 lawsuits in the United States (Vastag, 2005; Zwillich, 2005).

As a response, then Senate Majority leader Bill Frist asked the pharmaceutical industry for a voluntary two-year moratorium on direct-to-consumer advertising from the day it was introduced in the market (Smith, 2005). Historical data shows that advertising campaigns starts within a year after the FDA approval of the prescription drug (Donohue et al., 2007). Pfizer voluntarily agreed to hold direct-to-consumer advertising until after six months of sale while Bristol-Myers Squibb extended that to a year. On August, 2005, the Pharmaceutical Research and Manufacturers of America issued voluntary guiding principles on direct-to-consumer advertisement for the industry. The PhRMA guidelines encourage pharmaceutical companies to spend appropriate time educating health professionals about new medication before advertising directly to consumers.[6] The organization also advised member companies to submit all new DTC television ads to the FDA before they are released for broadcast.

However, despite all the voluntary regulations that were put in place after the Vioxx-Celebrex incident, another television advertisement has come under scrutiny for misleading the public. The television advertisements for Lipitor with Dr. Robert Jarvik as its spokeman were

[6] PhRMA recommends that "appropriate time" be determined based on the relative importance of informing patients of the availability of a new medicine, the complexity of the risk-benefit profile of that new medicine and health care professionals' knowledge of the condition being treated.

launch in January 2006. One ad depicted the doctor as an accomplished rower when fact a body double was used in the ad and the doctor does not row at all. Congressional legislators also questioned Dr. Jarvik's credentials for endorsing the prescription drug. Pfizer decided to end the ads in 2008 (Saul, 2008). In response, PhRMA revised its guidelines again to include disclosures if actors are being used to act as health care professionals, if the health care professionals endorsing the product received compensation for the appearance or if a celebrity endorser has actually used the product and the ad is accurately reflecting the "opinions, findings, beliefs or experience" of the person endorsing the product. The revised version, which took effect on March, 2009 is available in the organization's website (Pharmaceutical Research and Manufacturers of America, 2008).

Because of the growing concern with prescription drugs, the FDA and the Department of Health and Human Resource (DHHS) asked the Institute of Medicine to assess the U.S. drug safety system. One of the recommendations include setting limits on advertising of new medications (Committee on the Assessment of the US Drug Safety System, 2006).

At the state level, concern about the impact of prescription drug advertising motivated state legislatures to proposed bills or passed laws that affect pharmaceutical marketing. The National Conference of State Legislatures (NCSL) summarizes the proposed bills and laws in their website (Hanson, 2009). The nature of bills and legislation ranges from setting limits on detailing and gifts to medical practitioners, disclosure of marketing expenditures of pharmaceutical companies, prohibition of sale of pharmaceutical information for pharmaceutical marketing and adoption of code of conduct for marketing prescription drugs. As of June 2009, ten states have laws or resolutions that touched on pharmaceutical marketing. These laws are summarized in Annex A.

The marketing strategies of the pharmaceutical industry are obvious source of conflict of interests for health care professionals that might compromise the welfare of patients. In 1998, the American Medical Association updated a set of voluntary guidelines on accepting gifts from the industry (American Medical Association, 1998). PhRMA also issued a similar voluntary code of ethics on interaction with healthcare professionals in 2002. This was updated in 2009 (PhRMA, 2009). In 2006, experts from the Institute of Medicine as a Profession (IMAP) and the American Board of Internal Medicine Foundation published a paper in the Journal of the American Medical Association (JAMA) calling on Academic Medical Centers to take on the challenge of addressing these conflict of interests (Brennan et al., 2006). From 2006 to 2007, more than a dozen academic medical institutions responded and implemented more stringent measures on accepting gifts, consulting and research grant awards, travel assistance, drug samples, continuing medical education, funds for travel, speakers bureaus and ghostwriting for pharmaceutical companies (The Prescription Project, 2007).

Because of the growing call to limit the influence of pharmaceutical marketing, some members of Congress responded by proposing the Physician Payments Sunshine Act 2007 which "would require drug and medical device manufacturers with more than $100 million in annual revenue to report all gifts over the amount of $25 given to physicians, clinicians and other prescribers, which would be registered in a national and publicly accessible online database." Provisions of this proposed legislation were included in the Patient Protection and Affordable Care Act of 2009 which was signed into law by President Obama in 2010 (The Prescription Project, 2010).

2.4 DISCUSSION

The policies governing the availability of prescription drugs are constantly churning in the policy arena. It shows the shift in the policy making venue from the legislative to the executive and sometimes to the judiciary. It also shows the shift in policy formulation at the state levels when policies are not moving at the federal level. It shows the glaring difference between the policy paradigms of Republicans and Democrats. Initiatives of private organizations complement and sometimes even outpace government in adopting policies.

There are four different policies on availability of prescription drugs. These are a) policies on incentives, patents and generic competition, b) policies on approval of prescription drugs, and c) policies on marketing of prescription drugs.

Early policies on pharmaceuticals leaned heavily towards developing the industry and providing the industry with incentives to grow and expand. This was coupled with policies facilitating the entry of generic drugs in the market. But beginning in 2000, the policy formulation on patents and entry of generic prescription shifted to the courts. Pharmaceutical companies challenge the limits of the laws by engaging in strategies that would maximize the patent life of prescription drugs and limit drug competition. Some of the issues about patents were addressed by the Medicare Modernization Act of 2003. But the Courts remain to be the primary venue in shaping the policies on patent life of prescription drugs. This is evidenced by the booming industry of patent lawyers.

There is an obvious hesitation among Republicans to adopt stringent federal regulation in approving prescription drugs. The standard in the US for the approval of prescription drugs is its effectiveness compared to a placebo. However, policies in other countries like Australia, Canada and the UK have been towards comparative effectiveness of prescription drugs and the use of these studies in designing prescription formulary. There have been proposals to adopt similar policies in the US as a response to increasing cost of prescription drugs. There was clear political support for these policies from the health advocates and the Democrats. The Food and Drug Modernization Act of 1997 that mandated the Agency for Healthcare Research and Quality (AHRQ) to conduct research on comparative effectiveness and safety of drugs, biological products, and devices and the Healthcare Research and Quality Act of 1999 were policies adopted during President Clinton's time.

However, the little interest from the Republicans and the strong lobby of the pharmaceutical industry were enough to counter initiatives to push for stronger policies on comparative effectiveness of prescription drugs. With support from the Center for Medicare and Medicaid, funding was appropriated for comparative effectiveness study through the Medicare Modernization Act of 2003 but this funding was eliminated in the President's budget for 2004-2005. Despite these hurdles, the Academy of Managed Care Pharmacy issued its own guidelines on the use of comparative effectiveness studies to guide the formularies. When the Democrats won the presidency in 2009, budget allocation for comparative effectiveness research was included in the economic stimulus law of President Obama. The interest of the different stakeholders including the AARP, AFL-CIO and the PhRMA among others aligned in support of the Patient Protection and Affordable Care Act (PPAC) that created the Patient-Centered Outcomes Research Institute. The Institute was mandated to fund comparative-research studies. There was a clear divide between

the political parties in Congress, with the Democrats supporting and the Republicans opposing the legislation.

Beginning in the late 1990s to the 2000s, discussions on the negative consequences of pharmaceutical marketing intensified. Aside from the issues related to direct-to-consumer advertising, experts took notice on the conflict of interest created by the interaction of the pharmaceutical industry to healthcare professionals.

Except for the two main laws on marketing, the Food, Drug and Cosmetic Act and Kefauver-Harris Amendment, regulation on advertising of prescription drugs fall mainly on the limited regulatory power of the executive branch, specifically to the FDA. The Republican leadership in the executive and the legislative refused to adopt stringent measures to regulate the marketing activities of the pharmaceutical industry. In 2005, Sen. Bill Frist called for a voluntary moratorium on direct-to-consumer marketing. The overwhelming paradigm at that time was to "self-regulate." PhRMA, the organization that represents the pharmaceutical industry, issued its own guidelines on advertising in 2005. These guidelines were amended in 2008. On conflict of interest, AMA issued its voluntary ethical guideline in 1998. PhRMA has its own voluntary code of conduct that was adopted in 2002 and updated in 2009.

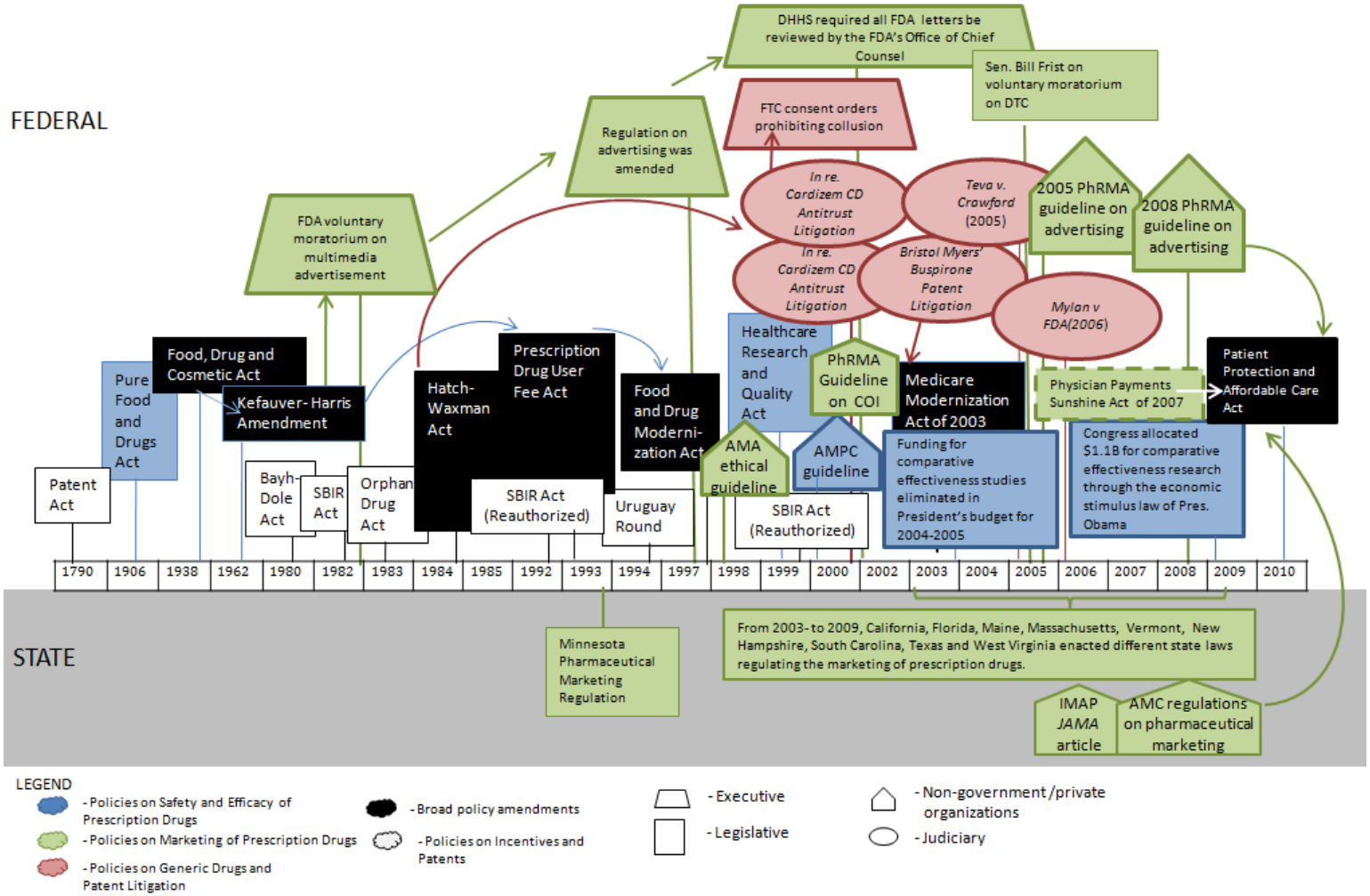
Discussions on the negative impact of conflict of interest brought about by gifts of pharmaceutical companies to health care professionals intensified. Campaigns in favor of stringent pharmaceutical marketing regulation were supported by several health advocacy organizations, academic experts, political leaders and state governments. The hesitation of the federal legislative branch to tighten regulation on advertising was reciprocated by stricter regulations at the state

level. States enacted different laws regulating the marketing of prescription drugs. Academic medical hospitals adopted their own stricter policies on the relationship of pharmaceutical companies and medical professionals.

The snowballing of support from the different state governments and stakeholders on stricter regulation about marketing and interaction between the industry and healthcare professionals made a strong lobby for regulation. The Physician Payments Sunshine Act of 2007, supported by both Democrats and Republicans, was proposed at the US Congress to regulate and make transparent the gifts that pharmaceutical companies are giving to health professionals. However, it was not put into law until 2009 when provisions of the proposed legislation were eventually adopted in the Patient Protection and Affordable Care Act (PPAC).

The following policy map illustrates the discussion on the dynamism of policy formulation on the availability of prescription drugs. It shows the interaction of the different policy players and the movement of policy formulation from one branch of government to another and from one level of government to another.

Figure 1. Policy Dynamics on the Availability of Prescription Drugs



2.5 DEMAND SIDE POLICIES: ACCESSIBILITY OF PRESCRIPTION DRUGS

The policies on availability of prescription drugs are coupled with policies to ensure accessibility of these drugs. Given the increasing prices of prescription drugs, the government adopted a number of policies to achieve greater accessibility of prescription drugs. The inclusion of prescription drug coverage in Medicare is a federal law that affects accessibility of prescription drugs. The states have little participation in the formulation of prescription coverage under Medicare mainly because Medicare is a federally funded program. On the other hand, Medicaid is a program jointly funded by the federal and the state governments. In the past decade, state governments used several policy strategies to maximize its bargaining power against the pharmaceutical industry under the Medicaid program. We have seen the states employ different policy strategies. These include lowering the cost of prescription drugs to be able to provide prescription drug coverage to a greater number of people. This section discusses federal and state initiatives to provide access to prescription drugs.

2.5.1. PRESCRIPTION DRUG COVERAGE

In 2003, Congress amended the Medicare Act by including Part D. Known as the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), Part D of Medicare provided prescription drug coverage to the program's more than 40 million beneficiaries starting January 2006 (Mayes, 2005).

Congress tried to add drug coverage in Medicare through the Medicare Catastrophic Coverage Act of 1988 (MCCA). The law financed the cost of this new coverage through a monthly premium of $4 and fifteen-percent surtax on the federal tax liability of Medicare enrollees with tax

liabilities in excess of $150 (Kaplan, 2005). The objection from senior citizens against this additional charge was so strong that Congress repealed MCAA's financing provisions and the associated drug benefit the following year (Kaplan, 2005). The experience presumably "appears to have soured Congress toward enacting further increases in Medicare benefits for elderly and disabled beneficiaries"(Rice, Desmond, & Gabel, 1990:76).

In 1993, President Clinton took steps towards health care and Medicare reform. He intended to provide a prescription drug benefit to Medicare beneficiaries, but the plan failed to pass when the Democrats lost control of Congress (Channick, 2003). The Republican-held Congress in 1995 made a similar effort at larger scale health care reform. This consisted largely of a plan to move Medicare to a voucher system. Clinton vetoed this measure starting years of partisan disagreement between Congress and the White House that eventually ended in the passage of the Balanced Budget Act of 1997, which included some large cuts in Medicare spending (Rak 2002).

The lack of prescription drug coverage among the elderly gained renewed prominence in the mid-term elections of 2002 (Kaplan, 2005). President George W. Bush wanted to go into the 2004 election with a resolution of this issue so he and the Republican-controlled Congress exerted effort throughout 2003 to provide a drug benefit in Medicare that would update the program's coverage without sparking the same anger that forced the repeal of the MCCA.

Democratic leaders in Congress found themselves in the awkward position of opposing a benefit expansion that they had pursued for more than a decade (Mayes, 2005). The enactment of the MMA was not easy—the bill passed both houses of Congress with slim margins and characterized by "the ugliest and most outrageous breach of standards in the modern history of the

House" (Mayes, 2005:414-415). Congress passed the Act in 2003 and President Bush signed it into law despite a poll showing little support for the bill (Mayes, 2005).

The passage of the bill became possible with the alignment of interests of the American Association of Retired Persons (AARP), the nation's largest senior citizens lobby and Pharmaceutical Research and Manufacturers of America (PhRMA), the biggest pharmaceutical lobbyist. After resisting the proposal to add prescription drug coverage to Medicare for many years, the pharmaceutical lobby shifted positions and poured enormous resources into shaping the legislation. The pharmaceutical companies saw the bill as an opportunity to oppose efforts to allow drug reimportation which they believed would bring price regulation of other countries in the US market.

Since the 2000 election cycle, the industry has contributed $60 million in political donations and spent $37.7 million in lobbying in the first six months of 2003. The drug companies' efforts paid off as they were able to shape Part D to escape legalized importation of lower-cost medicines and government price controls. Drug companies also inserted a provision that prohibits the federal government from negotiating prices on behalf of Medicare recipients (Connolly, 2003). Health care providers, insurers, drug makers and pharmacies are continually trying to influence the implementing rules (Pear, 2005). In 2004, the health care industry spent $325 million—more than any other sector—to influence Congress and federal agencies (Pear, 2005).

In March 2010, President Obama signed the Healthcare Reform Bill into law. The law attempts to close the doughnut hole[7] in Medicare Part D by providing rebates amounting to $250 to older Americans when they hit the cap on their Medicare prescription benefits. Starting in 2011, Medicare recipients will get a 50 percent discount on prescription drugs when they exhausted their prescription drug benefits. The proponents of the bill aim to close the doughnut hole by 2020, but with Medicare recipients still paying 25 percent of their drugs (Khan, 2010).

2.5.2. STATE SUBSTITUTION LAWS

State substitution laws are important in increasing the use of generic drugs. Substitution laws allow pharmacists to substitute generic drugs for multi-source drugs unless prohibited by the physician explicitly. State laws have significant differences. The dispense-as-written laws require physicians to hand write "dispense as written" or "brand medically necessary" on each prescription to prevent generic substitution by pharmacists. Two-line states allow physicians to prohibit substitution of their prescriptions just by signing on the appropriate line or checkbox (Simpson & Neff, 1990). When there is no explicit prohibition that means substitution is allowed and in some states, substitution is mandatory in this situation (Henry G. Grabowski & Vernon, 1979).

Out of all the states, 28% or 14 states have mandatory laws and the rest allows for substitution when the physician does not require "branded only" prescription. Majority of the states allow for dispensing of branded drugs if requested by patient except for Maine, Massachusetts and

[7] This is the coverage gap or the limit of prescription drugs plan of Medicare. When the patient has spent the initial limit on covered drugs, the patient will be responsible for paying the cost of their prescription drugs until the patient reach the catastrophic-coverage threshold.

New York. Of all the states, 33 states has dispense-as-written laws, 12 states are two line states and 5 states allow the physician to "communicate" to the pharmacist that the product should not be substituted (Schachter, 2007).

Prior to substitution laws, states had anti-substitution laws that required pharmacists to dispense what the physicians have prescribed. Most anti-substitution laws were repealed between 1972 and 1978. The last to repeal was Indiana in 1984 (Justice, undated).

2.5.3. OTHER STATE LEVEL INITIATIVES

More recently, because of the substantial impact of increasing cost of prescription drugs to the state budget, the states have resorted to different strategies to address the issue. In 1999, legislators from six New England states, plus New York and Pennsylvania, coalesced and proposed a joint purchasing program to aggregate purchasing power with manufacturers and jointly contract for pharmacy best practice and benefit administration services (National Conference of State Legislatures, 2006b). In 2000, the coalition formally became the National Legislative Association on Prescription Drug Prices (NLARx), a nonpartisan, nonprofit organization of state legislators. It was founded to promote different policy options and model legislations to lower the cost of prescription drugs. The member states in 2006 include Connecticut, Hawaii, Maine, Massachusetts, New Hampshire, New York, Pennsylvania, Rhode Island, Vermont, the District of Columbia and West Virginia. At present, the organization represents all regions of the United States. The primary aim of the organization is to make sure prescription drugs are more affordable and more accessible

especially by reducing prescription drug prices (National Legislative Association on Prescription Drug Prices, undated).

The states adopt different initiatives which include discount programs, bulk purchasing[8], regulation of marketing and advertising of pharmaceutical companies[9], provision of state assistance to augment Medicare Part D and resolutions from different state congresses urging the federal congress to amend Medicare Part D and allow federal negotiation for the price of prescription drugs and reimportation[10]. The libertarians remain skeptical that the policy interventions of the states will setback research and development. California Governor Arnold Schwarzenegger expressed the same sentiment on the efforts to control price of prescription drugs. Quoting Governor Schwarzenegger, "I adamantly oppose efforts to impose price controls on prescription drugs because they will have a chilling effect on the research and development of life saving medicines and harm California's critical biotech industry" ("Governor Schwarzenegger Calls on Federal Government to Allow Consumers to Safely Import Prescription Drugs," 2006).

The most controversial of all the state policy strategies are the drug reimportation and the drug discount program through Medicaid.

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[8] Massachusetts pioneered this program in 1999 by enacting a legislation authorizing a statewide bulk purchasing program. As of mid-2006, there are five operating multi-state bulk buying pools, not counting several additional variations and single state-initiatives.

[9] Some States attempt to regulate the pharmaceutical companies by requiring disclosure and reporting of Rx marketing costs, setting ethical marketing requirement for prescription drugs, requiring drug manufacturers and their marketers to disclose all the gifts that they give to medical practitioners and pharmacies and restricting the monetary value of the gifts to doctors and pharmacies.

[10] Different resolutions were passed by state congresses urging federal congress to amend Medicare part D and allow federal negotiation for the price of prescription drugs and reimportation. Part D actually allows for reimportation of prescription drugs but with the approval of the Secretary of Health and Human Services. According to the Economic and Budget Issue Brief of the Congressional Budget Office (2004) the Secretary has not endorse or approves any program.

(Re)importation of Prescription Drugs

Because of the high cost of prescription drugs in the US, most low income Americans are encouraged to buy their prescription drugs from Mexico or Canada. A simple price comparison of online pharmacies in the Canada and the US would show that patented prescription drugs in Canada are 50-70% cheaper than their counterparts in the US. On average, Americans can save 24% of the price of the drug if purchased in an online Canadian pharmacy compared to a major online US drug chain pharmacy (Quon, Firszt, & Eisenberg, 2005).

The idea behind (re)importation is to allow the US market to import prescription drugs including US-made pharmaceuticals from countries like Mexico and Canada, where the price of prescription drugs are controlled by the government. This is seen as an attempt to free ride on other countries' price control policy which the politicians are unable to do in the US (Reinhardt, 2009). There have been many attempts to legalize (re)importation of prescription drugs in the US. However, none was successful.

The Prescription Drug Marketing Act of 1987 (PDMA) completely banned parallel imports of prescription drugs unless the manufacturer of the drug imported them on its own (Shah, 2006). In the late 1990s, in an attempt to access cheaper prescription drugs in other countries, the International Drug Parity Act of 1999 (IDPA) and the Medicine Equity and Drug Safety Act of 2000 (MEDSA) were filed in Congress. The IDPA intended to expand United States-Canadian pharmaceutical market, but it was not signed into law despite being popular in Congress. It, however, managed to lay the groundwork for MEDSA, which sanctioned the (re)importation of FDA-approved drugs. Congress passed MEDSA in October 2000 but then DHHS Secretary Shalala

de-implemented the statute because she could not certify that implementation of the bill would "pose no additional risk to the public's health and safety." Due to the inability of the Secretary to do so, the bill's importation provision was decertified (Liang, 2006). In 2001, Secretary Thompson of the DHHS also stated that the safety of drugs cannot be guaranteed under MEDSA (U.S. Department of Health and Human Services, 2001).

The House again proposed the Pharmaceutical Market Access Act (PMAA) in July 2003. PMAA was supposed to "allow importation of drugs only if the drugs and the facilities where they were manufactured [were] approved by the Food and Drug Administration," and "to require that imported prescription drugs be packaged and shipped under counterfeit resistant technologies." The Senate never passed the PMAA, and it is unlikely that it will, because of the passage of Part D of Medicare (Shah, 2006).

The federal prohibition on re-importation of prescription drugs invited mixed reaction from the states. Arizona, Oregon and Kansas' State Boards of Pharmacy opposed the storefront distributors of re-imported drugs based on the same reasoning espoused by the FDA and the DHHS. Some states on the other hand, like Minnesota decided to implement its own (re)importation program (Andrisano Jr., 2005). Minnesota's RxConnect was the first state site to go online in 2003 and thereafter, other state and local governments followed. Alabama, Illinois, Vermont, Wisconsin, North Dakota, Rhode Island, New Hampshire, Louisiana, California, Massachusetts, Maine, Maryland and even county and city governments throughout the United States started (re)importation programs for their residents (Goodno & Janisch, 2005).

A Rhode Island statute allows pharmacies licensed in Canada to obtain licensure from the state Department of Health to do business in Rhode Island. The FDA issued a letter to Rhode Island asserting this law conflicts with the Federal Food and Drug Act (National Conference of State Legislatures, 2004).

In November 2003, Vermont submitted a citizen petition to the FDA to allow the Vermont State Employee Medical Benefit Plan to "establish a program for the orderly individual importation of prescription medications." The FDA denied the petition on the grounds that drugs imported into Vermont under the proposed program would violate 21 USC §§ 355 and 381(d). Vermont sued FDA to challenge the denial in 2004. In 2005, A US District Court dismissed the complaint on the basis of legality – the program violated federal law (*Vermont v. Leavitt*, 405 F.Supp.2d 466 (D. Vt. 2005) (Lutter, 2006; William K. Sessions III, 2005).

In 2004, the DHHS has established a task force on drug importation to look at how drug importation might be conducted safely and its potential impact on the health of American patients, medical costs and the development of new medicines.

On March 31, 2005, a couple from Chicago filed a case against the Department of Health and Human Services arguing that restrictions on importation and (re)importation of prescription drugs "violated their Constitutional substantive due process rights." The United States District Court for the District of Columbia found: "The FDA's interest in ensuring the safety of prescription medications is a legitimate governmental interest. The statutory scheme of which plaintiffs complain reasonably furthers this legitimate interest by shielding the public from reimported drugs

that may be adulterated or otherwise unsafe." *Andrews v. HHS*, No. 04-0307, 2005 U.S. Dist. LEXIS 5710, at *8-*9 (D.D.C. Mar. 31, 2005)(Lutter, 2006) .

Twenty-one states have considered (re)importation legislation in 2005 (National Conference of State Legislatures, 2005). Many states considered bills that would have created prescription drug (re)importation programs; however, none has been signed into law as of July 2006 (National Conference of State Legislatures, 2006a).

(Re)importation initiative is supported by many advocacy groups like the American Medical Student Association, Families USA, Medicare Rights Center, and the Senior Citizens League. NLARx, together with AARP, actively lobbied for the Pharmaceutical Market Access Act of 2005 and the Pharmaceutical Market Access and Drug Safety Act, both intended to legalize (re)importation of prescription drugs (Northeast Legislative Association on Prescription Drug Pricing, 2005).

To date, the FDA has not filed a case against any of the states. It however, filed cases against private online enterprises which participate in the (re)importation program. In 2003, the Food and Drug Administration (FDA) filed a case against Rx Depot and Rx Canada for violating the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. Sections 331(d) and (t). Rx Depot is responsible for the creation of approximately eighty-five storefront distributors (Andrisano Jr., 2005). In 2004, A US District Court granted the Department of Justice's motion for preliminary injunction against the storefront distributors in violation of the FCDA because they created "an unacceptable risk that counterfeit, adulterated, misbranded, subpotent, or expired drugs will be sold to American consumers" (Andrisano Jr., 2005:926-927).

In 2009, (re)importation of prescription drugs from Canada was again reintroduced at the federal level by Senator Byron Dorgan. Senate bill no. 1232 or the Pharmaceutical Market Access and Drug Safety Act of 2009 has a bi-partisan support from both the Democrats and the Republicans including former presidential candidate John McCain. The (re)importation bill was also supported by interests group including the National Federation of Independent Businesses and AARP. The Congressional Budget Office estimated the bill to result in $50 billion in direct savings over the next decade.

However, it runs counter with the deal that the Obama administration and Senator Baucus made with the pharmaceutical companies to limit the losses of pharmaceutical companies when they were pushing for the health care reform bill (Grim, 2009; Madrak, 2009; Young, 2009). FDA found itself with PhRMA in lobbying against the bill stating that it could endanger US medical supplies and would be difficult to implement. This was similar to the statements made before by the Department of Health and Human Services during the terms of Presidents Clinton and Bush (Young, 2009). The senate voted in favor of the amendment, 51-48. Unfortunately, it lacked the necessary 60 votes for the passage of the bill (Reinhardt, 2009).

Cost Containment Programs through Medicaid

Among the pioneers in implementing a cost containment programs of prescription drugs through Medicaid are Maine, Florida and Michigan. The Medicaid laws and regulations allow states to demand for rebates from pharmaceutical companies on prescription drugs sold under Medicaid. States can penalize pharmaceutical companies who refuse to provide rebates by requiring them to

apply for authorization before state reimbursement. Maine, Florida and Michigan extended the Medicaid rebates to non-Medicaid purchases of prescription drugs. This is the issue of these three cases filed by PhRMA against the three states.

Pharmaceutical Research and Mfrs. of America v. Walsh

Maine's Rx program seeks to apply federally mandated Medicaid pricing to the new Maine Rx program. The pharmaceutical companies would be required to extend rebates to the Rx program. The Medicaid law allows the federal government to negotiate with pharmaceutical companies regarding the "best prices" they can offer for Medicaid beneficiaries. The "Maine Rx" program extended this negotiated price to individuals who are not covered by the Medicaid program regardless of income level. If a company does not enter into a rebate agreement, its Medicaid sales will be subjected to a "prior authorization" procedure that requires state agency approval to qualify a doctor's prescription for reimbursement ("Pharmaceutical Research and Manufacturers of America v. Walsh," 2003).

In 2000, PhRMA challenged the constitutionality of the Maine Rx Program, claiming that it was pre-empted by the federal Medicaid statute. It argued that the program imposes a significant burden on Medicaid recipients by requiring prior authorization in certain circumstances without serving any valid Medicaid purpose, and that the program effectively regulates out-of-state commerce. The District Court sustained the challenge and enjoined the implementation of the statute. In 2001, the Court of Appeals reversed ("Pharmaceutical Research and Manufacturers of America v. Walsh," 2003).

The United States and the federal government submitted amicus briefs in support of the pharmaceutical companies arguing that the Maine program is invalid as it conflicts with the Medicaid law and it failed to follow administrative procedures by not seeking the approval of DHHS for the implementation of the program ("Pharmaceutical Research and Manufacturers of America v. Walsh," 2003). Those that submitted an amicus brief supporting Maine's program are twenty-eight states and Puerto Rico ("Pharmaceutical Research and Manufacturers of America v. Walsh," 2003).

The U.S. Supreme Court affirmed the decision of the First Circuit and remanded the case to the district court for the determination on the merits. The Court also stressed that "By no means will our answer to [the] question [of whether the district court abused its discretion in entering the injunction] finally determin[e] the validity of Maine's Rx Program" ("Pharmaceutical Research and Manufacturers of America v. Walsh," 2003:660)

After the U.S. Supreme Court's decision, Maine overhauled the Rx program and renamed it Maine Rx Plus. The new statute provides discounts to fewer people than the original plan, and at a lower cost to the state (The National Conference of State Legislatures, 2006). PhRMA sued again to force Maine to submit its program to DHHS for approval and also to enjoin it from implementing Maine Rx Plus pending the Secretary's review ("Pharm. Research & Mfrs. of Am. v. Nicholas," 2005)

The district court denied PhRMA the injunction, reasoning that since Maine changed its statute, PhRMA's claims were not yet ripe for review; especially since the new statute would not impose the prior approval provisions of the original statute against nonparticipating drugs until October of 2005 (Furuya, 2006).

Pharmaceutical Research and Mfrs. of America v. Medows

Florida passed a law that extends Medicaid drug discounts to residents who falls on the income requirements of the program but are not qualified for Medicaid ("Fla. Stat. Ann. § 409.91195(4) West Supp. ," 2005). The District Court denied PhRMA's request for injunction and found that there is no conflict between Florida's statute and the federal policy. The Court of Appeals upheld the denial for injunction and the US Supreme Court denied PhRMA's petition for writ of certiorari ("Pharm. Research & Mfrs. of Am. v. Medows," 2001).

Pharmaceutical Research and Mfrs. of America v. Thompson

In 2002, PhRMA filed a complaint and a motion for a preliminary injunction against Michigan Best Practices Initiative to enjoin the Secretary of the DHHS from approving the statute. They adopted arguments similar to those used in Maine and Florida: that the drug formulary of the program is illegal (Ames, 2005).

The Florida Drop-in Center Association and the International Patient Advocacy Association submitted an amicus curiae brief in support of the Michigan program. Another amicus curiae brief supporting Michigan was submitted by West Virginia, Vermont, North Dakota, Maryland, Maine, Hawaii, Kentucky, the New Mexico Human Services Department, the Missouri Department of Social Services, the Louisiana Department of Health and Hospitals, and the Florida Agency for Health Care Administration.

The District Court ruled that the Secretary did not act arbitrarily or capriciously in approving portions of the initiative, including the prior authorization program, the efforts to secure supplemental rebates, and the requirement that drug manufacturers provide rebates in non-Medicaid programs in order to avoid prior authorization for drugs offered for Medicaid use ("Pharmaceutical Research and Mfrs. of America v. Thompson," 2003). The Court of Appeals affirmed the decision in 2004 ("Pharmaceutical Research and Mfrs. of America v. Thompson," 2004).

Despite these favorable decisions, the Maine and Florida programs have features that may not survive scrutiny the next time PhRMA decides to file a claim (Ames, 2005). The decision of the Courts on these programs is based on the failure of PhRMA to present sufficient evidence to show that the programs harm PhRMA and the Medicaid beneficiaries and not on the merits of the programs.

Ames identified the strengths and weaknesses of the Maine, Florida and Michigan programs (Ames, 2005):

- Prior to the Supreme Court decision, Maine's program did not have an income cap. Although politically popular, the program violates requirements that Medicaid must benefit those financially unable to meet the cost of health care. The Florida program imposes income limits but may still find trouble in justifying the extension of Medicaid benefits to non-qualified residents.

- Neither Maine nor Florida's program sought the approval of the Secretary of the HHS prior to implementation which was deemed necessary according to *Walsh*. The HHS Secretary has not approved the Maine program while Florida received retroactive approval.
- Michigan's program has the most stable framework in terms of cost containment. Michigan sought the approval of HHS prior to implementation. Thus, PhRMA would have to litigate against the state and the federal governments. The Michigan plan emphasized efficacy and safety as the primary basis of the authorization list criteria and the cost of the drug as secondary concern.

These decisions are significant because they encourage other states to adopt similar laws that will continue to test the limit of the courts in interpreting the power of the states to regulate the price of prescription drugs. By 2003, a substantial number of state pharmaceutical laws were enacted in 39 states.[11] Among these is the provision of subsidy to elderly and indigent residents, bulk purchasing or changes in the state's purchasing policies (National Conference of State Legislatures, 2003).

Ballot Initiatives: Letting the People Decide

California Propositions 78 and 79

The battle for access to prescription drugs has reached new levels. Propositions 78 and 79 were two competing initiatives both sought to offer relief to low to moderate-income, uninsured

[11] Alabama, Alaska, Colorado, Connecticut, Delaware, Florida, Hawaii, Illinois, Indiana, Iowa, Kansas, Louisiana, Maine, Maryland, Massachusetts, Montana, Nebraska, Nevada, New Jersey, New Mexico, New York, North Dakota, Ohio, Oklahoma, Oregon, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, Wisconsin and Wyoming

Californians who face prescriptions drug bills they cannot afford. Proposition 78 proposed to establish a voluntary prescription drug insurance plan for state residents whose annual incomes do not exceed 300% of the federal poverty level (Medical News Today, 2005). On the other hand, Proposition 79 will require drug makers to participate in a prescription drug discount program or face exclusion from the Medi-Cal formulary in some cases (Medical News Today, 2005).

Before these propositions were submitted to the ballot, there were efforts at the legislative level of California to lower the cost of prescription drugs. However, Governor Schwarzenegger never supported these measures. In 2004 he vetoed 6 bills with the same intent and in 2005 he vetoed three more bills that were opposed by the drug industry. It is known that the Governor is the second highest recipient of campaign contribution from the pharmaceutical industry, next to President Bush (Wright, 2005).

Pharmaceutical companies also sued to keep Proposition 79 off the ballot. However, the case was so weak it was rejected both by the Superior Court and the Appeals Court (Wright, 2005). When Proposition 79 was filed by health advocates on January 2005, the pharmaceutical industry was forced to file a counter proposal, Proposition 78 and campaign against Proposition 79. California residents rejected both Propositions 78 and 79 (Wright, 2005).

The pharmaceutical industry spent $80 million on the Yes on 78-No on 79 campaign, making the election the most expensive initiative campaign in state history (Wright, 2005). Pharmaceutical companies also tried to scare away the potential funders of Proposition 79 by filing two ballot initiatives, one of which aims to restrict the ability of government employees union to collect political contributions (Wright, 2005). Supporters of both initiatives are committed in

bringing the issue in the state legislature (Medical News Today, 2005). Currently, California has prescription drug discount program extending the Medicaid negotiated price to Medicare recipients.

Ohio's Initiative: Thwarted

In the case of Ohio, senior, consumer and health advocates were just starting to gather signatures to put a measure similar to Proposition 79 and the Maine Rx Program in the ballot when PhRMA sued in over half the counties in Ohio, challenging the signatures on technical grounds. "The advocates were overwhelmed and unable to financially respond to this torrent of litigation, and eventually were forced to agree to a voluntary plan that PhRMA favored" (Wright, 2005). Instead, Ohio implemented a discount drug program similar to Proposition 78 of California called Ohio's Best Rx (Colliver, 2005). Ohio residents can avail of the program if they do not have prescription drug insurance coverage and are age 60 or over or under 60 with no prescription drug insurance and has annual family income below 300% of the Federal Poverty level (Envision Pharmaceutical Services Inc., undated).

Oregon's Measure 44

In November 2006, residents of Oregon voted and approved the proposal to create the Oregon Prescription Drug Program for uninsured residents. The program is expected to reduce the cost of prescription drugs for 780,000 uninsured Oregonians regardless of age or income by enabling Oregon to negotiate for discounts from drug manufacturers and pharmacies. The program was sponsored by AARP of Oregon and state Sen. Bill Morrisette with support from Oregonians for

Health Security and the Service Employees International Union. The policy proposal started as legislation but Morrisette later amended the benefits to be limited to uninsured individuals and filed it as an initiative after the "pharmaceutical lobby thwarted his bill last year" (Colburn, 2006). One of the factors that contributed to the success of the initiative is the fact that PhRMA has not taken a stand on the measure (Colburn, 2006). Morrisette and AARP deliberately made the proposal simple and limited to the uninsured so as not to prompt opposition from PhRMA. They believe that opposing prescription drug insurance for the uninsured will be a "public relations nightmare" for the pharmaceutical industry (Colburn, 2006).

2.6 DISCUSSION

The increasing cost of prescription drugs has forced both the federal government and the state governments to find ways to make prescription drug more accessible to individuals who need them but cannot afford them. There are four main policies in ensuring the accessibility of prescription drugs. These are a) prescription drug coverage under Medicare, b) generic substitution laws and c) prescription drug (re)importation, and d) the different cost containment strategies of state governments.

There has been a strong lobby from organizations like the AARP to add prescription drug coverage to Medicare at the federal level. Given the increasing cost of prescription drugs, both the Republicans and the Democrats agree that prescription drug coverage should be included in Medicare. However, they differ on the approach they should take. Republicans lean towards market driven approach and minimalist government role in providing coverage while the

Democrats wanted the Medicare to be the vehicle to a bigger insurance program of the government. It took 15 years of lobbying for prescription drug coverage to be included in Medicare. This happened with the alignment of the interest of major stakeholders like the AARP and PhRMA. The industry probably realized that the issue has to be confronted and saw the Republican leadership in both the Executive and Congress as a more favorable policy environment. Furthermore, PhRMA saw that supporting this legislation would open an opportunity for them to oppose another policy initiative – the (re)importation of prescription drugs. The law however has major flaws like the "doughnut hole," in which Medicare recipients would have to pay 100% of prescription drug cost when they reach a certain amount of spending and the federal government is not able to negotiate the price of prescription drugs in behalf of the Medicare recipients. Many state governments passed resolution urging the US Congress to amend Medicare Part D, allow for government negotiations on the price of prescription drugs and allow (re)importation under the program. The Patient Protection and Affordable Care Act signed into law by President Obama in 2010 attempts to close the doughnut hole. Because Medicare is a federal government program, the amendments to the law mainly stayed in the US Congress.

To complement the federal policies facilitating the entry of generic drugs in the market, state governments adopted generic substitution laws which allow pharmacists to substitute generic drugs for multi-sourced drugs. These policies reversed previous anti-substitution laws.

The issue of (re)importation is one of the most dynamic with respect to ensuring access to prescription drugs. From the US Congress, policy formulation shifted at the executive, state levels and the courts. (Re)importation allows US residents to buy prescription drugs including US-made

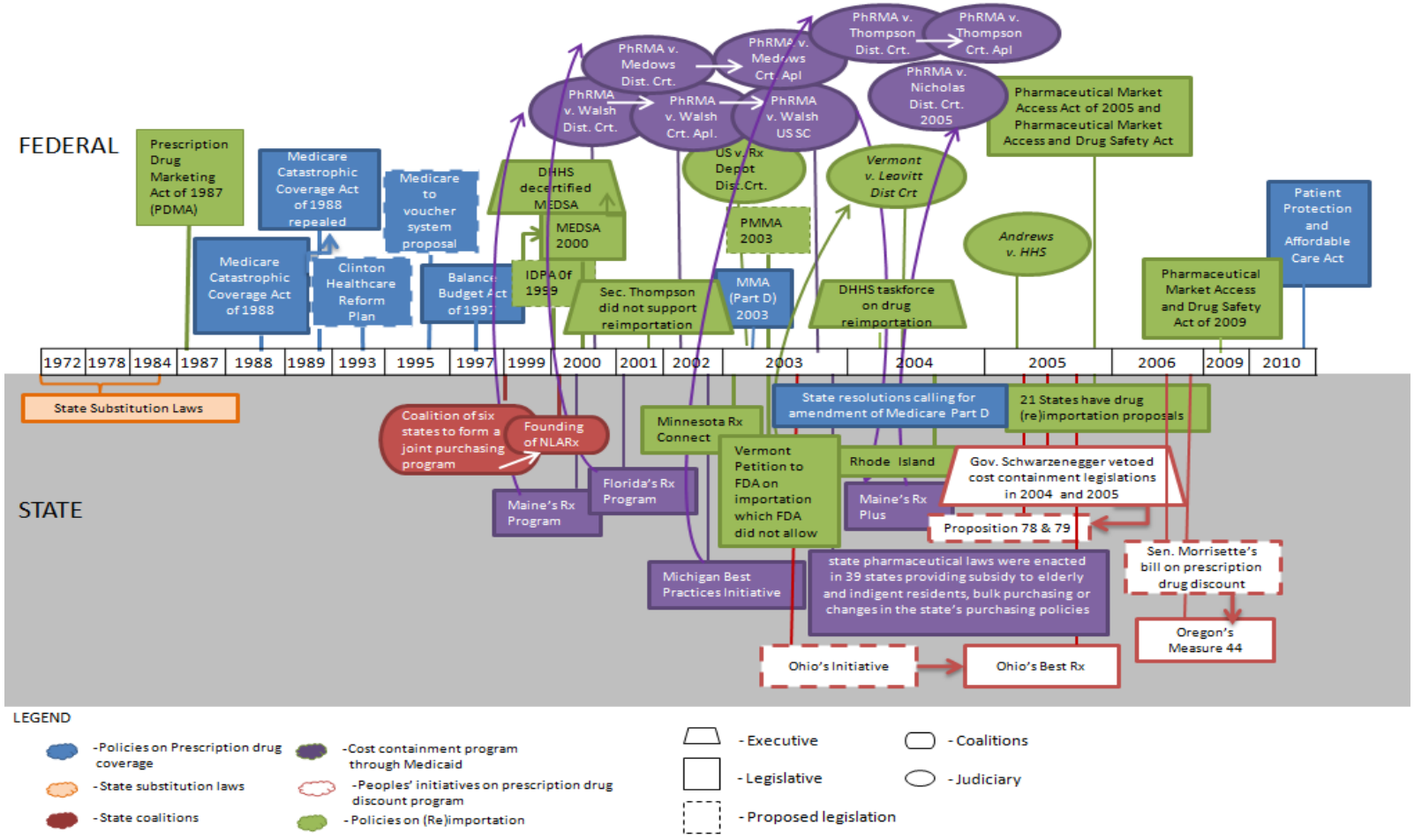
prescription drugs in countries like Mexico and Canada where the price of prescription drugs are regulated. The pharmaceutical industry vehemently opposes such move. In 1987, the Prescription Drug Marketing Act of 1987 banned the (re)importation of prescription drugs. However, in 2000, it was reversed by Medicine Equity and Drug Safety Act of 2000 (MEDSA), which allows for (re)importation of FDA approved drugs. The implementation of the law required the certification of the Secretary of the DHHS that it will not risk public health and safety. The succeeding Secretaries of DHHS during Presidents Clinton and Bush's term did not endorse (re)importation. Thus, the law was not implemented. There have been initiatives to pass laws allowing (re)importation after MEDSA but none was successful. However, as a response, several state governments started implementing (re)importation program starting with Minnesota. Vermont even petitioned the FDA to allow its (re)importation program which the FDA denied. Later on, Vermont sued the FDA but the case was dismissed based on inconsistencies with existing laws. No cases were filed against state governments. However, cases were filed against storefronts allowing purchase of drugs in Canada and Mexico. Private individuals also filed a case against the DHHS on the argument that their constitutional rights are violated with the prohibition of (re)importation. The cases were decided favoring the DHHS and disallowing (re)importation. There are pending (re)importation bills in Congress with bi-partisan support and with support from several advocacy groups. Unfortunately, these bills are not able to muster enough votes to pass Congress. President Obama also made a deal to minimize the losses of the pharmaceutical industry with the passage of the Patient Protection and Affordable Care Act.

The Medicaid program allows state governments to negotiate rebate on prescription drugs that are included in the Medicaid formulary. To take advantage of this opportunity, a number of

state governments implemented prescription drug programs to their residents and extended the rebate that they are getting from the Medicaid program to these new programs. Some of these state programs sought the approval of DHHS prior to implementation. These programs were challenged by PhRMA in courts. So far, the decisions have been favorable to the states encouraging other states to follow. In other states where the legislature or the executive branches were not in favor of cost containment legislations like California and Oregon, peoples' initiatives were conducted. PhRMA battled head on with local advocacy groups in framing the issue of prescription drug discount programs.

The following policy map illustrates the policy strategies and responses of the different policy players at the federal and state level to improve the access to prescription drugs.

Figure 2. Policy Dynamics on the Accessibility of Prescription Drugs



2.7 CONCLUSION

This chapter presented the policies that concern the availability and accessibility of prescription drugs. It showed that policy making emanates not from a single branch of government, but rather, the interaction of the different branches at different levels of government. The interaction of the different government and non-government institutions helped shaped policies. Using a historical approach in presenting the different policies and political strategies, it was illustrated that policy making shifts from one government branch to another. In the case of pharmaceutical policies, policy formulation shifted to the state level when there was an impasse at the federal level. And when there were impasses at the state level, policy formulation shifted to direct people participation through ballot initiatives. The study also showed that the alignment of interests of different policy stakeholders is important in the formation of policies. The differences in the approach in defining problems and finding solution to these problems between the Democrats and the Republicans were also evident in this study.

Over the years, we have seen the shift from market oriented policies to policies that demand greater regulation of the pharmaceutical industry. These regulatory policies gear towards greater access to prescription drugs, clipping the clout of the pharmaceutical industry. The challenge to policymakers remains the same – finding the balance between policies that will nurture the industry and policies that will protect public welfare.

3. PRESCRIPTION DRUG CHOICE: EXAMINING PHYSICIAN PRESCRIBING BEHAVIOR

3.1 INTRODUCTION

The previous chapter showed how the political and market dynamics led to the four types of drugs: breakthrough, generic, me-too and generic me-too drugs.[12] Given these four types, this chapter examines the variables that affect physicians' choice of prescription drugs.

The decision on what drugs to consume is not entirely determined by the consumers' tastes but primarily by the preference of the prescribing physicians and pharmacists who dispensed the drugs. The process of choosing a drug for a patient is a two-stage process—the prescription stage where the physicians choose the medication and method of treatment and the dispensing stage where the pharmacists' influence the consumers' decision on what specific prescription drug to purchase particularly in the case of multisource drugs[13] (Caves, Whinston, Hurwitz, Pakes, & Temin, 1991; S. F. Ellison, Cockburn, Griliches, & Hausman, 1997; Poutiainen, 2007).

This chapter examines the relationship between the physician's choice of medication and the variables that may influence the physician's prescribing behavior like drug characteristics, patient characteristics and physician characteristics. The analysis was done using the 2006 National Ambulatory Medical Care Survey (NAMCS), a cross-sectional consumer-level data. Drugs

[12] The first drug approved by the FDA in the drug class was classified as the "breakthrough drug." The generic version of the breakthrough drug was labeled as the "generic drug." "Me-too drugs" are the new drugs that are not generic drugs, but nevertheless "duplicate the actions of existing drugs" (Rogawski, 2006:23). The generic versions of me-too drugs were classified as "generic me-too drugs" in this study.

[13] Multisource drug or multiple source drug refer to "drug for which there is at least one other drug product which is rated as therapeutically equivalent, is pharmaceutically equivalent and bioequivalent, as determined by the FDA…" (Centers for Medicare & Medicaid Services, 2008).

belonging to the drug classes statins, cardioselective beta blockers, proton pump inhibitors (PPI), selective serotonin reuptake inhibitor (SSRI) were analyzed separately. The specific drugs were classified into four types: breakthrough drugs, generic drugs, me-too drugs and generic me-too drugs.

This section specifically answers the following questions:

1. What factors influence the physician's choice to prescribe breakthrough, me-too or generic or generic me-too drugs?
    - What patient characteristics will increase the likelihood of a physician prescribing a breakthrough, me-too or generic or generic me-too drug?
    - What physician characteristics will increase the likelihood of prescribing a patient with a breakthrough, me-too or generic or generic me-too drug?
    - What drug characteristics will increase the likelihood of prescribing a patient with a breakthrough, me-too or generic or generic me-too drug?
2. What is the relationship between direct-to-consumer advertising and prescribing physician's choice of drugs?

Patient characteristics include the patient's age, gender, ethnicity and number of medication the patient is taking. Physician characteristics include specialization, location of the physician's practice and the physician's primary source of income. These variables were included in the regression model without any predicted effect on the physician's decision to prescribe a specific

type of prescription drug. A patient's generous insurance coverage is predicted to increase the likelihood of being prescribed a more expensive drug like me-too drug than a generic drug.

Drug characteristics include price, and quality indicators like extended or delayed release feature which may differentiate the quality of the drug from the others and the length of time the drug has been in the market. This study tests the hypothesis that an increase in price will decrease the likelihood that a drug is prescribed. This study also hypothesizes that the increase in the length of time the drug has been in the market increases the likelihood that a drug is prescribed. Theory on physician prescribing behavior suggests that physicians tend to prescribe established drugs thus creating a positive relationship between length of time in the market and likelihood of prescribing older drugs. The study also examines the patient's influence to the prescribing physician. Patients' role in choosing their medication has been increasing. Their primary source of information about drugs is direct-to-consumer advertising. In this study, patient's role in choosing their prescription is indirectly reflected by the direct-to-consumer advertising expenditure of the drug. The hypothesis is that direct-to-consumer advertising increases the likelihood of a drug from being prescribed.

The subsequent section presents the review of existing literature on physician prescribing behavior and the factors that may influence the doctor and patient's choice of prescription drug. The quantitative model and the results are presented thereafter.

3.2 REVIEW OF LITERATURE

3.2.1 PHYSICIAN PRESCRIBING BEHAVIOR

Physicians and patients have principal-agent relationship that arises under conditions of imperfect information. As agents, physicians play a huge role in deciding which medication or method of treatment best fits the patients' health condition. Physicians play an important role in the process by which patients would receive branded or generic drugs but these prescribing decisions were not explained by observable patients' characteristics (Hellerstein, 1998).

Physicians prescribing behavior is based largely on customary prescribing rather than on comparative effectiveness of prescription drugs (Caves et al., 1991). Not only is this explained by the limited information available about comparative effectiveness of drugs but because customary prescribing can be a very effective legal defense (Caves et al., 1991). Physicians might hesitate in switching treatment for subsequent prescriptions because of the risk associated with switching treatment especially if the original prescribed drug works for the patient (Gönül, Carter, Petrova, & Srinivasan, 2001:81) . Habit persistence in physicians' prescribing behavior can explain the persistent market shares of branded drugs (Coscelli, 2000:350-351).

3.2.2 ADVERTISING

The effect of direct-to-consumer advertising on the demand for prescription drugs is examined in this study. Direct-to-consumer advertising affects physicians' choice of drugs to prescribe through the patient's input during consultation. Patients are becoming more pro-active in

planning and choosing their medication because of direct-to-consumer advertising. This section provides an overview of economic theories of advertising.

Bagwell (2007) presents a comprehensive review of literature on the economic theory and empirical studies of advertising. The author discussed the three main theories on the economic role of advertising on demand: the persuasive view, the informative view and the complementary view. Persuasive advertising influences consumer choice and creates spurious product differentiation and brand loyalty. It becomes an anti-competitive tool making the demand for the product more inelastic. This results in higher prices of goods but with no real value to consumers. Informative advertising promotes competition in the market by facilitating information. The demand for the good becomes more elastic as the search cost for consumers are reduced. It facilitates entry of new firms through the publication of its existence, prices or products. The third view suggests that advertising is complementary to the advertised good. In Bagwell's example, if a consumer values social prestige, an advertised good may add more prestige thus complimenting the consumption of the good.

Other experts are in agreement that advertising can convey information if it can be easily verified. It brings about market power if producers can hamper consumers ability to gain information from other sources (Hurwitz & Caves, 1988). A survey of empirical analysis of advertising shows the effects of advertising to be industry –specific and vary on a case by case basis (Bagwell, 2007).

The effects of advertising would differ depending on whether the product is a search good or experience good. Search goods have objective features that consumers can easily understand

and verify before making a decision to purchase. Experience goods have complex characteristics that can be verified only upon consumption of the good. Consumers only know the price prior to consumption and this is usually use as an indicator of quality. Experience goods tend to have lower price elasticity than search goods because of consumers' apprehension about unobservable characteristics of cheaper goods (Nelson, 1970).

Advertising may have direct information on the existence, location, price and function of a product. However, it may still have an indirect effect even if it does not have clear informative content (Bagwell, 2007). Advertising for experience goods are mostly indirect information and for search goods are dominantly direct information (Nelson, 1974). Indirect information has three effects for experience goods: 1) signaling-efficiency effect in which firm signals that it is efficient and in turn implies that it offers good deals; 2) match-products-to-buyers effect which allows firms to direct its advertisement to consumers that values it the most and efficiently match products and buyers; and 3) repeat-business effect in which advertising reminds consumers of their previous experience with the product (Bagwell, 2007; Nelson, 1974).

Researches on the economic effects of advertising also looked at the distinction between its effect on "selective"(combative) and "primary" demands (Borden, 1942). Advertising is combative in nature if it is shifting consumer preference to the advertiser without any effect on the overall industry demand. Several studies support this theory (Alemson, 1970; Lambin, 1976; Metwally, 1975, 1976; L. A. Thomas, 1999). There are also studies examining the overall effect of advertising on primary/overall demand but the results of different studies show different outcomes in different industries (Bagwell, 2007).

Bagwell arrives at three major conclusions on the result of empirical studies on advertising and demand: (1) current advertising usually has positive short lived rather than long lived effect on sales; (2) advertising is combative in nature; and (3) advertising's effect on primary/overall demand varies across industries (Bagwell, 2007).

Advertising may also deter or facilitate the entry of new players and innovation of products in the market and the evidence in the literature is mixed (Bagwell, 2007). A relationship between advertising and prices also exists. Bagwell (2007) concludes that there is substantial evidence that retail advertising leads to lower retail prices and may encourage growth of low-price discount outlets.

With respect to advertising-quality relationship, a positive relationship is more likely when advertising conveys direct product-quality information to consumers (Bagwell, 2007). When consumers have insufficient information on the intrinsic quality of the products and markets or when there is no great variance in the nature of the product across brand names, price is used as a measure of quality (Agarwal & Teas, 2002; Gönül et al., 2001; Olson, 1977; Valarie A. Zeithaml, 1988; V.A. Zeithaml, 1991).

Advertising in the Pharmaceutical Industry

In 2008, the U.S. pharmaceutical industry spent around $18 billion dollars on advertising and promotion (IMS Health, 2008). This includes direct-to-consumer advertising, detailing and advertising in professional journals. But if we include spending on continuing medical education

(CME), travel and lucrative honoraria to medical professionals, marketing expenditure directed to medical professionals alone could reach up to $25 billion each year (Donohue et al., 2007).

Pharmaceutical detailing is one of the most aggressive marketing strategies of the pharmaceutical industry. This involves regular visits from medical sales representatives which provide free meals, gifts and drug samples. The industry employed 87,892 detailers in 2001; a ratio of 1 medical sales representative for every 5 physicians (Chin, 2002). Industry spending on lunches for doctors is estimated at roughly $1 billion a year (Saul, 2006). Around 94% of physicians have accepted some form of gifts from the pharmaceutical industry (Campbell, 2007).

Spending on direct-to-consumer (DTC) advertising of prescription drugs has tripled in recent years. It has been the fastest growing marketing expense of the industry (Goozner, 2004:230). Between 1996 and 2005, spending on DTC advertising increased by 330% (Donohue et al., 2007). Pharmaceutical companies spent $4.4 billion on DTC advertising in 2008 (IMS Health, 2008). Overall, this is only a small portion (15.7%) of the industry's marketing expenditure. But if drug samples are excluded in the 2000 marketing expenditure of the industry, DTC advertising would account for 32% of the expenditure (National Institute of Health Care Management, 2001). Pharmaceutical companies promote their products directly to consumers through advertisements in magazines, newspapers, and consumer brochures; on the internet; and on radio and television (United States Government Accountability Office, 2002b). Television advertising accounted for more than half (57%) of prescription drugs' DTC expenditure (National Institute of Health Care Management, 2001).

The Impact of Pharmaceutical Advertising

Physician detailing and journal advertising informs physicians about characteristics and uses of specific drugs (Leffler, 1981:47-48). When physicians and patients have no sufficient knowledge about the intrinsic qualities of competing products, brand names and level of advertising are cues usually use to measure the quality of a product (Agarwal & Teas, 2002; Valarie A. Zeithaml, 1988; V.A. Zeithaml, 1991). Pharmaceutical marketing, however, can be "uninformative and seem simply to harp the products' names in order to persuade doctors to select products out of habit rather than by evaluative choice (Leffler, 1981:47). It imposes social costs when it limits consumers' information on alternative sources (Hurwitz & Caves, 1988:299). Physician detailing is considered persuasive in nature (Hurwitz & Caves, 1988; Leffler, 1981; Vernon, 1971).

There are mix opinions on the effect of direct-to-consumer advertising. Some experts criticize direct-to-consumer advertising to be misleading and increasing the demand for branded, more expensive drugs while others see the benefits of direct-to-consumer advertising as empowering to patients (Almasi, Stafford, Kravitz, & Mansfield, 2006; Auton, 2006). Direct-to-consumer advertising may have positive welfare effects depending on the disease types and patient characteristics (Bhattacharyya, 2005). Direct-to-consumer advertising encourages patients to visit the doctor for a particular illness, increasing the flow of patients treated by doctors for the particular illness. Direct-to-consumer advertising educate the patients about their undiagnosed medical conditions (Aikin, Swasy, & Braman, 2004; D. Bradford & Kleit, 2006; D. W. Bradford et al., 2006; Hosken & Wendling, 2009; Weissman et al., 2004). It has increased patients' role in the

selection of medication by pressuring physicians to respond to independent requests as encouraged by prescription advertisements (Conrad & Leiter, 2004:170). A survey conducted by FDA reported that about half of the patient were prescribed with the medicine they asked about (Aikin et al., 2004). Direct-to-consumer advertising is also associated with increase in adherence to drug therapy (Calfee et al., 2002; Donohue, Berndt, Rosenthal, Epstein, & Frank, 2004; Wosinska, 2005). It averts underuse of medication by encouraging patients to talk to their doctors but at the same time it also promotes overuse of medication and increase use of advertised drugs when alternatives maybe more appropriate (Aikin et al., 2004; Kravitz et al., 2005; United States Government Accountability Office, 2006; Weissman et al., 2004). A majority of the physicians in the FDA survey also felt that patients confuse the relative risks and benefits of the advertised drugs and patients tend to overestimate the efficacy of the medication(Aikin et al., 2004).

The concentration of physician prescribing is correlated with higher levels of advertising, low prices and larger lagged market shares (Stern & Trajtenberg, 1998). Physicians who have more exposure to pharmaceutical advertisements are also more open to DTC advertising of prescription drugs (Gönül, Carter, & Wind, 2000).

Consumers who have an ongoing need for health care -- those with children or with a chronic condition requiring medication, value prescription drug advertising more highly, while older consumers, consumers who have been sick recently or more educated consumers are more likely to trust their physicians instead (Gönül et al., 2000).

Pharmaceutical advertising has a market expansion effect rather than combative effect. It expands the market of the entire therapeutic class (Rosenthal, Berndt, Donohue, Epstein, & Frank,

2003). This is explained by increase awareness on diseases, brand of drugs available and compliance with drug therapy (Calfee et al., 2002; Rizzo, 1999; Rosenthal et al., 2003). Advertising also expands the market of prescription drugs because it encourages off-label uses of drugs and broadens the scope of disease (Gillman, 2006; Healy, 2006; Lacasse & Leo, 2006; Maggini, Vanacore, & Raschetti, 2006; Tiefer, 2006). Direct-to-consumer marketing has a greater effect on the sale of the entire therapeutic class while detailing has greater effect in expanding the market share of a brand (Narayanan, Desiraju, & Chintagunta, 2004).

A study showed that marketing has a positive effect on the sales of anti-ulcer drugs with detailing having the largest impact followed by journal advertising and direct-to-consumer advertising having the smallest (Berndt, Bui, Reiley, & Urban, 1995:104). A vast amount of literature shows the positive relationship between advertising and prescription of the marketed drugs (Adair & Holmgren, 2005; Boltri, Gordon, & Vogel, 2002; Bower & Burkett, 1987; Brewer, 1998; Chew et al., 2000; Chren & Landefeld, 1994; Iserson, Cerfolio, & Sade, 2007; Lurie & et al., 1990; Mizik & Jacobson, 2004; Orlowski & Wateska, 1992; Strong, 2003; Symm, Averitt, Forjuoh, & Preece, 2006; Wazana, 2000).

DTC increases drug consumption and favors heavily advertised drugs (Berndt, 2002:53; Berndt et al., 1995; United States Government Accountability Office, 2002b). A government report states that "drugs that are promoted directly to consumers often are among the best-selling drugs, and sales for DTC-advertised drugs have increased faster than sales for drugs that are not heavily advertised to consumers" (United States Government Accountability Office, 2002b:3). Between 1999 and 2000, the number of prescriptions dispensed for the most heavily advertised drugs rose 25 percent, as

opposed to only 4 percent for drugs that were not heavily advertised (United States Government Accountability Office, 2002b). Calfee, Winston and Stempski (2002), in a study of statin class, concluded however that direct-to-consumer advertising did not significantly affect demand for the new drug in the short run.

Advertising particularly detailing impedes price competition and lowers price elasticity which lead to higher equilibrium prices (Hurwitz & Caves, 1988; Leffler, 1981; Rizzo, 1999; Vernon, 1971). This is consistent with the observation that experience goods have lower price elasticity. The inability of consumers to verify the quality of generic drugs in the market until they consume it makes it less attractive for some patients to shift to generic drugs. However, a recent study showed otherwise. Detailing increases price elasticity while other forms of marketing decreases price elasticity in the case of antihistamine drugs (Narayanan et al., 2004).

Advertising may facilitate the entry of new players in the pharmaceutical market. The pharmaceutical industry has historically favors first market entrants with later market entrants capturing substantially lower market shares, other things being equal (H. G. Grabowski & Vernon, 2000:24). Advertising produces brand-name recall effects that favor established products facing new competition (Leffler, 1981:47-48). Branded drugs are able to preserve their shares from competition from generic drug entrants through goodwill stock and loyalty build up while being marketed exclusively when the drugs were still on patent (Hurwitz & Caves, 1988). In a study by Ellison and Ellison (2007), they observed that incumbents in intermediate size markets have lower level of advertising and are more likely to reduce advertising before patent expiration to deter generic entry. The profitability of the drug of prior to patent expiration is an important

determinant of generic entry (Reiffen & Ward, 2005b; Scott Morton, 2000). While some researches did not find any significant relationship between advertising and new product entry (Henry G. Grabowski & Vernon, 1992; Vernon, 1971), other studies found that advertising is not a barrier to entry for new products including generic drugs (Caves et al., 1991; Leffler, 1981; Scott Morton, 2000; Telser, Best, Egan, & Higinbotham, 1975).

3.2.3 PRICE

The price of the drug is not part of the information provided by medical detailers. Physicians have very limited information on prices of prescription drugs and may not have any incentive to prescribe cheaper medicines (Caves et al., 1991). Other experts suggest that there may be other factors that may make physicians sensitive to prices. Physicians may be affected by the patients' financial situation and the possibility that price-sensitive patients may switch to health care providers who prescribe lower-cost pharmaceuticals (S. F. Ellison et al., 1997; Gönül et al., 2001). However, "patients seem unlikely to select or change physicians simply because they do not prescribe the lowest cost drugs" (Caves et al., 1991:5). Physicians can infer patients' willingness to pay through the type of insurance held or through discussion with the patient (Gönül et al., 2001:80).

Patients are not directly sensitive to the price of prescription drugs because of insurance coverage on prescription drugs. Rather, consumer behavior is more sensitive on cost sharing schemes for prescription drug. Medicaid co-payments reduce prescription drug utilization. Increases in cost-sharing for prescription medicine among privately insured groups have negative significant effects on drug utilization (Coulson & Stuart, 1995:1147).

Doctors may also use price as a signal for quality. When drug efficacy is of prime consideration, physicians might prescribe the more expensive drug on the belief of higher efficacy (Gönül et al., 2001:81). Price are sometimes use as a measure of quality (Olson, 1977). This may happen when consumers have insufficient information about the intrinsic quality of the products or when there is no great variance in the nature of the product across brand names (Valarie A. Zeithaml, 1988; V.A. Zeithaml, 1991).

3.2.4 DRUG QUALITY

There is a lingering perception that generic drugs are inferior in quality and are not perfect substitutes for branded drugs. In 1989, FDA reviewers accepted bribes from generic drug manufacturers to facilitate the approval of their ANDAs. Some generic firms also violated manufacturing procedures and fabricated supporting documents for their application. This "generic scandal" impaired the reputation of generic drug manufacturers (Fernandez-Carol & Kaitin, 1991; Scott Morton, 1999).

Using survey data of pharmacists and physicians, Bearden and Mason concluded that confidence on regulatory control of FDA as a significant determinant of overall support to generic drugs (Bearden & Mason, 1980). A more recent survey showed that consumers perception that generic prescription drugs were riskier than brand name products varied depending on the medical condition being treated. More than half (53.8%) of the respondents thought that generic were riskier than brand name for heart problem. But for medical conditions like high blood pressure, strep throat, pain and cough, 50% or more of the respondents thought that generics were as riskier as brand name drugs. The study also concluded that significantly larger cost savings were required

for consumers to purchase generic prescription drugs with higher perceived risk (Ganther & Kreling, 2000).

In the case of antidepressants, some patients experienced significant difference between the effectiveness of branded and generic drugs in addressing their concerns. A number of them experienced the symptoms of their mental condition when their doctors switched them to the generic version of their medication without their knowledge (Wax, 2007). A particular problem highlighted by those who question the perfect substitutability of generic drugs is the FDA's policy to determine blood serum bioavailability. Bioavailability is "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action"(Center for Drug Evaluation and Research, 2002). The approval for generic drugs require that "the rate and extent of absorption do not show a significant difference from listed drug or the extent of absorption does not show a significant difference and any difference in rate is intentional or not medically significant"(Sherwood, 2006). The FDA uses the plus-or-minus twenty percent test which implies that the amount of active ingredient in the blood over a period of time has to come within plus-or-minus twenty percent of that which is observed when the original branded drug is ingested (Mossinghoff, 1999). This requirement may not be significant for drugs that have a wide index of tolerance but not for drugs that have very narrow therapeutic band like anti-seizure medication (Mossinghoff, 1999:190-191).

Some drugs in the market have been reformulated to have delayed-release and extended-release characteristics. Delayed-release in drugs means "a formulation that has a coating to delay release of the drug until the product has passed through the stomach" while extended-release

indicates “any formulation designed to deliver the dose over a longer interval than what is seen in immediate release products” (National Coordinating Council for Medication Error Reporting and Prevention, 2012).

Delayed or extended-release features of drugs are said to optimize and enhance the performance of the drug by avoiding the side effects “associated with high concentrations and the lack of activity associated with low concentrations” (Fyhr & Downie, 2003; Schaffler, 2007). This feature also increases patient compliance by making it more convenient for patients to take the medication like reducing the number of times the patient has to take the medication in a day (Fyhr & Downie, 2003; Schaffler, 2007). Similarly, delayed or controlled-release formulations are said to optimize treatments and make treatment more convenient to patients (Schaffler, 2007). Studies show superiority of extended release drug over a “regular” drug for patients with major depressive disorder (Silverstone & Ravindran, 1999) and patients with high cholesterol (Fyhr & Downie, 2003). A study also noted the convenience of extended release formulation for patients with hypertension (Fyhr & Downie, 2003). However, studies failed to see the superiority of these features to a drug with flexible dosing regimen for patients with overactive bladder syndrome (Chapplea et al., 2005) or an established medication for depressed patients (Bielski, Ventura, & Chang, 2004).

3.2.5 Health Coverage and Membership in Manage Care Organizations

In general, patients with extensive insurance programs for prescription drugs are less sensitive to price of prescription drugs than patients with less comprehensive or no prescription drug coverage. In the study of the Canadian pharmaceutical consumption, deductible and co-

payment schemes are important variables in the substitution of generic drugs to branded drugs (Anis, 1994). In a randomized controlled trial designed to determine the effect of cost-sharing on the demand for health services and the health status of individuals, individuals with more generous insurance buy more pharmaceuticals but the proportion of brand-name drugs among all drugs purchased in pharmacies was not a function of insurance plan (Leibowitz, Manning, Newhouse, United States Dept. of Health and Human Services, & Rand Corporation, 1985).

Membership to managed care organizations (MCOs) and formulary requirements of different organizations present constraints on the prescribing behavior of physicians and the pharmacists (S. F. Ellison et al., 1997; Gönül et al., 2001). Recent studies show that physicians contacted by managed care drug companies or affiliated with Health Maintenance Organizations (HMO) have a greater awareness of relative prices of prescription drugs (S. F. Ellison et al., 1997:427). Physicians whose patients belong to an HMO or other pre-paid plan are also more likely to prescribe generics to all their patients (Hellerstein, 1994, 1998). Pharmaceutical promotions like detailing and drug samples are less likely to influence physicians who see a higher percentage of HMO or Medicare patients (Gönül et al., 2001). Moral hazard is observed if physicians tend to differentiate the type of drugs they are prescribing to their patients based on their insurance coverage. Howard (1997) in his research found that "self-paying patients are significantly more likely than patients with Medicare or private insurance to be prescribed the generics that are cheapest relative to their brand-name counterparts."

MCOs try to control their expenditure on prescription drugs by controlling price and setting limits on drugs their members can use to treat specific conditions (Levy, 1999). To control the

price, they negotiate discounts from drug manufacturers and pharmacies and use prescription drug capitation programs. To manage the use of drugs, they use drug formularies, generic substitution programs, therapeutic substitution programs, drug utilization review and step-care programs (Cook, 1998; Levy, 1999:31). Anis (1994) found that deductible and co-payment schemes are important variables in the substitution of generic drugs to branded drugs but formularies are not. The rise of generic drug market share is partly attributable to the increase in MCOs (Cook, 1998).

3.3 DISCRETE CHOICE MODEL OF DEMAND

This study uses the discrete choice model of demand in analyzing the relationship between physician prescribing behavior and variables that may influence it like price, direct-to-consumer advertising, quality of drugs, patient characteristics and physician characteristics. The discrete choice model of demand has been commonly used to examine the demand for differentiated products. It describes the decision makers' choices among alternative products, coarse of action or items (Train, 2008). It assumes that a consumer chooses a product that yield the highest utility based on product characteristics and some random components unobservable to outside observers/researchers (Anderson, de Palma, & Thisse, 1992).

The underlying utility function that determines the system of demand for differentiated products in a discrete choice model is the random utility function. Random utility represents a deterministic component which is a function of observable variables and a random component for which a variety of parametric assumptions have been made (Villas-Boas & Winer, 1999). The demand system is estimated in the discrete choice model by analyzing the random utility function as opposed to trying to estimate demand for each alternative product using a system of equation.

The discrete choice model conveniently reduces the data requirements and the number of parameters estimated in a system of demand which makes it feasible to estimate coherent demand system for large and differentiated product markets (Salgado, 2008).

The issue of endogeneity of advertising and price arises in examining the relationship between demand and the said variables. Firms determine price and advertising based on market information and the unobservable variables that affect consumer choice. This brings about the issue of endogeneity as prices and advertising will be correlated with these unobserved demand factors. Failure to account for the endogeneity of these variables could produce misleading results in the estimation process (S. T. Berry, 1994; Villas-Boas & Winer, 1999). The endogeneity of price and advertising are usually addressed using instrumental variables (Villas-Boas & Winer, 1999). Berry Lenvisohn and Pakes (1995) develop a method to estimate the discrete choice model using aggregated data taking into account the endogeneity of prices in the demand system. Aggregated or market level data and individual purchases have both been used to estimate the discrete choice model (Ackerberg, 2001; S. Berry et al., 1995; S. T. Berry, 1994; Chintagunta, Dube, & Goh, 2005; Goolsbee & Petrin, 2004; Nevo, 2000; Petrin, 2002; Train, 2008; Train & Winston, 2007; Villas-Boas & Winer, 1999). Individual level data were used to estimate the discrete choice model for prescription drugs in this study.

3.4 Analytical Framework

Previous studies developed utility models in analyzing physician prescribing behavior. Hellerstein's model (1994) hypothesizes that physician *j* will prescribe the generic form of the drug k to patient *i* if and only if

$$q*_k + c_j + c_k < \Delta P_k(1 - \gamma\theta_{ij}) \quad (1)$$

Where,

$q*_k$ is the quality difference between the brand-name drug and the generic substitute for the *k*th drug;

c_j is the physician-specific component of the prediction error the physician makes when assessing the quality difference (e.g. habit persistence in a physician's prescription decision);

c_k is the drug specific component of the prediction error the physician makes when assessing the quality difference (e.g. drug specific information diffusion);

ΔP_k is the price differential between the brand-name drug and the generic substitute;

γ is the proportion of the cost to the insurer that the physician does not internalize when deciding between brand-name and generic drugs (for example, if this parameter equals 1, the physician internalizes none of the cost to the insurer) which must be between 0 and 1 inclusive; and

θ_{ij} is the proportion of the cost of the drug covered by the patient's insurance, which must be between 0 and 1 inclusive.

Expressing the equation in probabilistic form, the theoretical model becomes equation (2).

$$\mathbf{Prob}[G_{ij} = 1 | \Delta P_k, q*_k, c_j, c_k, \theta_{ij}] = \mathbf{Prob}[(\Delta P_k - q*_k - c_k) - \Delta P_k \gamma \theta_{ij} - c_j + \varepsilon_{ij} > 0] \quad (2)$$

Where G_{ij} indicates whether physician j prescribed patient i the generic or brand-name form of drug k. Using the 1989 NAMCS data, the model was implemented as:

$\Delta P_k - q*_k - c_k$ Represents the price differential of branded and generic version of the drug minus the quality differential between the brand name and the generic forms of drug k and the physician's prediction error that is drug specific. Hellerstein's theoretical model assumes that the physician knows the price differential between branded and generic versions of the drug being prescribed. Price is not included in the model. Instead, a vector C of drug class dummy variable was used to represent the adjusted price. Hellerstein assumes that price and quality differences between branded and generic drugs do not vary within a given class of drugs.

$\Delta P_k \gamma \theta_{ij}$ Represents the price differential that is paid for by the patient's insurance but is not internalized by the prescribing physician. Hellerstein assumes that controlling for drug class, insurance covers the same proportion of drug costs for all patients who have the same type of coverage. Hellerstein represented this in her estimation equation as the interaction between the drug class dummy vector C and a vector X_2 of insurance dummy variables.

c_j Hellerstein estimates the physician-specific prediction error in the physician's assessment of the quality difference using observed

characteristics of the physician and is represented by the following function:

$$S_j\pi_1 + M_j\pi_2 + T_j\pi_3 + R_j\pi_4 + X_j\pi_5 + v_j \quad (3)$$

Where,

S is a dummy variable indicating whether the physician is a specialist (doctor who is not in general practice, family practice or general pediatrics) or a general practitioner

M is a dummy variable indicating whether the physician's practice is in a state with mandatory generic substitution laws

T mmy variable indicating whether the state uses two-line prescription pads

R is a vector of dummies used to identify the region of the country where the physician's practice is located

X is a vector of variables representing the physician's patients' characteristics: average age the percentage who are female, the percentage who are non-white; the percentage who are Hispanic; and for each type of insurance coverage recorded, in the NAMCS, the percentage of patients with that coverage.

Hence, Hellerstein arrives at the following estimation equation and implemented it using a fixed-effects probit specification:

$$P\left[G_{ij} = 1 \middle| C_k, X_{1i}, X_{2i,} S_j, M_j, T_j, R_j, X_j\right]$$

$$= \boldsymbol{P}[\boldsymbol{C_k\gamma} + \boldsymbol{X_{1i}\beta} + \boldsymbol{X_{2i}} \cdot \boldsymbol{C_k\gamma} + \boldsymbol{S_j\pi_1} + \boldsymbol{M_j\pi_2} + \boldsymbol{T_j\pi_3} + \boldsymbol{R_j\pi_4} + \boldsymbol{X_j\pi_5} + \boldsymbol{v_j} + \boldsymbol{\varepsilon_{ij}} > \boldsymbol{0}] \quad (4)$$

Howard (1997) implemented Hellerstein's theoretical model using the 1994 NAMCS data on antimicrobial drugs. He modified Hellerstein's model by adding the variable price and a measure of drug quality. These terms are explained as follows:

ΔP_k This is represented by L, the natural log of the ratio of the generic price to the brand-name price. Ratio of prices was use rather than their difference because the magnitude of the difference is heavily influenced by the dosage in which a drug is prescribed, which is not provided in the NAMCS data. Brand-name/generic price differentials vary considerably based on dosage and product-form, but the ratio of generic price to brand-name price is largely unaffected by these superficial characteristics. The natural log of the ratio is used so that equivalent percentage differences in the ratio will have equivalent impacts.

$q*_k + c_k$ interpreted as the consensus among physicians as to the quality differential between a brand-name drug and its generic substitute. Howard hypothesized that the medical community is risk-averse when faced with a new and untested product. The longer the generic drug has been in the market, the more it is perceived as a substitute for its

branded counterpart.

Generic availability period was used as a proxy for consensus quality differential. This is represented as *A*, the natural log of the ratio of the number of days between the date the generic was approved by the FDA and June 30, 1994 (the mid date of the NAMCS survey) to the total number of days between December 31, 1981 and June 30, 1994. Generics approved prior to 1982 are assigned a ratio of 1. The generic availability ratio is measured in logarithmic terms.

$\Delta P_k \gamma \theta_{ij}$ This is represented by the interaction of a vector ***P*** of price differential dummy variables with the vector $\boldsymbol{X_2}$ of insurance dummy variables that Hellerstein developed. The vector P contains two dummy variables. The first indicates whether the ratio of the price of the generic form of the drug to the price of the brand-name form is above the median price ratio calculated from the drugs in the sample. The second dummy variable is the complement of the first: it indicates whether the drug's generic-to-brand-name price ratio is below the median price ratio for the drugs in the sample. This method presumes that drugs with similar generic-to-brand-name price ratios are equally likely to be prescribed as generics, ceteris paribus, but that drugs with below-median price ratios are more (or less) likely to be prescribed in generic form than drugs with above-median price ratios. On the other side of the interaction, the five dummy variables in X_2 record which of five types of medical insurance the patient used to pay for the physician visit at which the sampled prescription was written. The insurance types are HMO/other prepaid plan, Medicaid, Medicare,

private/commercial insurance and self-pay (no insurance used). Howard hypothesized that drugs with low generic-to-brand-name price ratios and drugs prescribed to uninsured patients are more likely than their respective counterparts to be prescribed in generic form. Thus the below-median price ratio/self pay indicator was omitted for estimation purposes. The resulting coefficients on the other variables in the $\boldsymbol{X_2 \cdot P}$ interaction reflect the impact, ceteris paribus, on the probability of a given drug being prescribed in generic form with respect to low-price-ratio drugs prescribed to self-pay patients. If one or more of these coefficients is significant it may be construed as evidence of moral hazard or the physicians are more likely to prescribe generics to uninsured patients than to patients holding certain types of insurance.

C_i This is represented by the same function developed by Hellerstein, except that M and T terms were dropped due to discontinuation of the variable Hellerstein used to determine the state in which a physician practices and the type of prescription pad the physician used in prescribing the medication.

In addition to the modification in the estimation equation, Howard (1997) also included other independent variables in his estimation equation. A dummy variable $\boldsymbol{O}$ was added to indicate prescriptions written for patients who received at least one other prescription for an antimicrobial drug during the same doctor visit. This was intended to capture variance caused by patients receiving multiple prescriptions. Howard also included a vector D of five individual drug dummy variables to flag prescriptions for five different antibiotics to introduce fixed effects for these five

drugs. With this, Howard's estimation equation was as follows and was implemented using random effects probit model:

$$\mathrm{P}\left[G_{ij} = 1 \middle| L_k, A_k, X_{l1}, X_{2i}, P_k, S_j, R_j, X_j, O_i, D_k\right]$$

$$= \boldsymbol{P}[\boldsymbol{L_k\rho} + \boldsymbol{A_k v} + \boldsymbol{X_{1i}\beta} + \boldsymbol{X_{2i}} \cdot \boldsymbol{P_k\gamma} + \boldsymbol{S_j\pi_1} + \boldsymbol{R_j\pi_2} + \boldsymbol{X_j\pi_3} + \boldsymbol{O_i\omega} + \boldsymbol{D_k\delta} + \boldsymbol{v_j} + \boldsymbol{\varepsilon_{ij}} > \boldsymbol{0}] \quad (5)$$

This study modifies Hellerstein's theoretical model by taking into account patient participation in the selection of prescription medication. Recent studies show how patients are playing a more active role in choosing the appropriate medication for them. Patients' exposure to direct-to-consumer advertisement of prescription drugs provided them with information which they may discuss with their doctors in selecting their medication. With this, Hellerstein's theoretical model was modified to incorporate the contribution the patients make in the decision process of selecting a medication.

$$\boldsymbol{q} *_{\boldsymbol{k}} + \boldsymbol{c_j} + \boldsymbol{c_k} + \boldsymbol{f_k} < \Delta \boldsymbol{P_k}(\boldsymbol{1} - \boldsymbol{\gamma\theta_{ij}}) \quad (6)$$

Where,

- f_k is the quality assessment of the physician on the information provided by the patient about the prescription drug. It is assumed that the information the patient provided to the physician about an alternative prescription drug was most likely from direct-to-consumer advertisement of the prescription drug.

Furthermore, this study expanded the choices of prescription drugs from a choice between branded and generic drug to a choice between breakthrough, generic, me-too and generic me-too drugs.

To implement the model, the physician's choice of prescription drug is a function of the following variables where G_{ij} indicates whether physician *j* prescribed patient *i* the generic, breakthrough, me-too or generic me-too form of drug *k.*

$$\mathbf{Prob}\left[\boldsymbol{G_{ij}} = \mathbf{1}\middle|\Delta \boldsymbol{P_k}, \boldsymbol{q}*_{\boldsymbol{k}}, \boldsymbol{c_j}, \boldsymbol{c_k}, \boldsymbol{f_k}, \boldsymbol{\gamma\theta_{ij}}\right] \qquad (7)$$

$$\boldsymbol{P}\left[\boldsymbol{G_{ij}} = \mathbf{1}|\boldsymbol{C_k}, \boldsymbol{A_k}, \boldsymbol{E_k}, \boldsymbol{Q_{1k}}, \boldsymbol{Q_{1k}}, \boldsymbol{X_{1i}}, \boldsymbol{X_{2i}}, \boldsymbol{S_j}, \boldsymbol{R_j}, \widehat{\boldsymbol{X_j}}, \widehat{\boldsymbol{O}}_{\boldsymbol{i}}, \boldsymbol{V}\right] \qquad (8)$$

Where,

ΔP_k represented by *C*, the average cost of a month supply of the drug.

$q *_k + c_k$ similar to Howard's model, this represents the quality differential between the four types of drugs. In this model, the quality differential between the four types of drugs is represented by the following function:

$$\boldsymbol{A}_k\tau_1 + \boldsymbol{E}_k\tau_2 + \boldsymbol{Q}_{1k}\tau_3 + \boldsymbol{Q}_{2k}\tau_3 + z_k \qquad (9)$$

Where,

A is the length of time the drug was in the market following Howard's model. It is computed as the natural log of the ratio of the number of days between the date the drug was approved by the FDA and June 30, 2006 the date of

the year when the survey was conducted to the total number of days between December 31, 1993 and June 30, 2006. Generics approved prior to 1994 are assigned a ratio of 1.

E Dummy variable indicating whether a drug has delayed-release or extended-release feature

Q_1 Dummy variable (only in the case of statins), indicating superiority of drug in reducing mortality.

Q_2 Dummy variable (only in the case of statins), indicating superiority of drug in reducing the risk of heart attack.

$\Delta P_k \gamma \theta_{ij}$ Operationalized by the vector $\boldsymbol{X_2}$ of insurance dummy variables following Hellerstein's assumption that after controlling for drug class, insurance covers the same proportion of drug costs for all patients who have the same type coverage. Since this study analyzes four different drug classes separately, there is no need for drug class dummy variable.

c_j Physician-specific prediction error in the physician's assessment of the quality difference using observed characteristics of the physician and represented by the following equation:

$$S_j\pi_1 + \boldsymbol{R}_j\pi_2 + \widehat{\boldsymbol{X}}_j\pi_3 + v_j \qquad (10)$$

Where,

S dummy variable indicating whether the physician is a specialist or a general practitioner

R vector of these dummies used to identify the region of the country where the physician's practice is located. The variables that were in Hellerstein's model to represent mandatory generic substitution laws and prescription pads were dropped because these variables were not available in the 2006 NAMCS.

$\hat{X}$ is a vector of variables representing the percentage of physician's patients' with each type of insurance coverage recorded in the NAMCS

f_k The information the patient provided during the doctor visit is represented by V, the natural log of the annual direct-to-consumer advertising expenditure of the prescription drug = *ln* (1+Direct-to-consumer advertising)

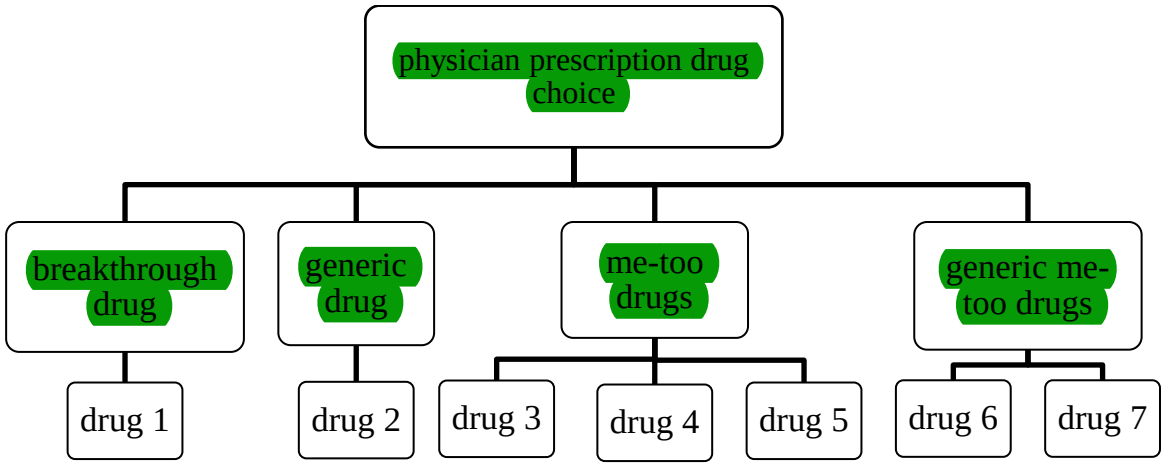
X_1 Vector of patient's characteristics which includes age of the patient and dummy variables for the patient's sex, race (white or non-white), and ethnicity (Hispanic or non-Hispanic).

$\hat{O}$ still intended to capture variance caused by patients receiving multiple prescription (Howard, 1997) but the proxy used was the total number of medication of the patient

3.5 MODEL STRUCTURE

Most studies on physician's choice of prescription drug focus on the option between branded and its generic version. But physicians' options in choosing medication for their patients can further be differentiated by identifying the breakthrough drug, the generic version of the breakthrough drug, the me-too drugs and the generic versions of the me-too drugs in a specific class. A class of drug will have the breakthrough drug—the first drug under a drug class to be approved by the FDA, me-too drugs—branded drugs belonging in the same class that were approved by the FDA after the breakthrough drug, the generic drug which is the generic version of the breakthrough drug and the generic me-too drugs which is the generic version of the me-too drugs. This study expands physicians' choice of prescription drugs between these types of drugs in a class. Figure 3 represents a non-sequential two-tiered structure for prescription choice by physician.

Figure 3. Non-sequential Two-tiered Nested Choice Structure



A non-sequential nested logit model, where the choices of drugs were classified into four nests, was used to estimate equation 8. Nested logit models are used when there are similarities among alternatives. It classifies the alternatives into nests which comprises the choice set, which in this study are the types of prescription drugs. This model relaxes the assumption of independently distributed errors and the independence of irrelevant alternatives inherent in conditional and multinomial logit models by clustering similar alternative into nests (StataCorp, 2007).

Assume J alternatives grouped into L nests. The physician's choice set for prescription drugs can be written as $[c_1,\ldots, c_j] = (c_{1|1},\ldots, c_{j1|1}),\ldots, (c_{1L},\ldots, c_{jL|L})$ (Green, 2000). The probabilistic form of the two-tiered nested logit model takes the forms

$$\boldsymbol{P_{j|l}} = \frac{e^{\beta' x_{j|l}}}{\sum_{j=1}^{J} e^{\beta' x_{j|l}}} \qquad (11)$$

$$\boldsymbol{P_l} = \frac{e^{\gamma' z_l + \tau_l I_l}}{\sum_{l=1}^{L} e^{\gamma' z_l + \tau_l I_l}} \qquad (12)$$

Where,

$P_{j|l}$ Probability physician *n* chooses prescription drug *j* given prescription drug nest *l* (e.g., me-too drugs)

P_l Probability physician *n* chooses prescription drug nest *l*

$\beta' x_{j|l}$ Measurable component of utility for physician *n* choosing prescription drug *j* given prescription drug nest *l*

$\gamma' z_l$ Measurable component of utility for physician *n* choosing prescription drug nest *l*

τ_l Estimated coefficient on inclusive term for prescription drug nest *l*

I_l Inclusive term that measures the correlation among random errors due to unobserved attributes of the choice set (Cervero & Duncan, 2008:11). The inclusive term is defined for the *l*th prescription drug nest as

$$\boldsymbol{I_l} = \ln \sum_{J=1}^{J_l} e^{\beta' x_{j|l}} \qquad (13)$$

The observed portion of utility can be decomposed into two parts (Train, 2008:86):

$$\boldsymbol{U_{ij}} = \boldsymbol{Y_{ij}} + \boldsymbol{W_{il}} + \boldsymbol{\epsilon_{ij}} \qquad (9)$$

for $j \in B_l$, where

Y_{ij} depends on variables that describe alternative *j*. These variables vary over alternatives within nest *l*. The variables in this study include the following:

C the average cost of a month supply of a prescription drug

A the natural log of the ratio of the number of days between the date the drug was approved by the FDA and June 30, 2006 the date of the year when the survey was conducted to the total number of days between December 31, 1993 and June 30, 2006. Drugs approved prior to 1994 are assigned a ratio of 1.

E Dummy variable indicating whether a drug has delayed-release or extended-release feature

Q_1 Dummy variable (only in the case of statins), indicating superiority of drug in reducing mortality.

Q_2 Dummy variable (only in the case of statins), indicating superiority of drug in reducing the risk of heart attack.

V the natural log of the annual direct-to-consumer advertising expenditure of the prescription drug = *ln* (1+Direct-to-consumer advertising)

W_{il} depends only on variables that describe nest *l*. These variables differ over nests but not over alternatives within each nest. The variables in this study include the following:

X_1 vector of patient's characteristics which includes age of the patient and dummy variables for the patient's sex, race (white or non-white), and ethnicity (Hispanic or non-Hispanic).

$\hat{O}$ the total number of medication of the patient

X_2 insurance dummy variables

S dummy variable indicating whether the physician is a specialist or a general practitioner

R vector of dummies used to identify the region of the country where the physician's practice is located

$\hat{X}$ is a vector of dummy variables representing the percentage of physician's patients' with each type of insurance coverage recorded in the NAMCS

Given these variables, the utility function can be re-written as:

$$U = C_j\rho + A_j\tau_1 + \boldsymbol{E}_j\tau_2 + \boldsymbol{Q}_{1j}\tau_3 + \boldsymbol{Q}_{2j}\tau_3 + V_j\varphi + X_{1i}\beta + \hat{O}_i\omega + X_{2i}\gamma + S_i\pi_1 + R_i\pi_2 + \hat{X}_i\pi_3 + \epsilon_{ij} \quad (15)$$

3.6 Endogeneity, Measurement Issues and Instrumental Variables

The endogeneity of advertising and price is a concern in discrete choice estimations. Endogeneity of advertising may arise from the possible association between advertising and other variables like sales, elasticity of demand and profitability (Bagwell, 2007). Because firms determine

price and advertising based on market information and other unobservable characteristics, prices and advertising will be correlated with these unobserved demand factors. The endogeneity of these two variables may produce misleading results in the estimation process.

The other issue on the empirical research of advertising is the identification of the proper measurement for advertising. An example pointed out by Bagwell is the possible effect of current and past advertising on sales and profit. He suggested that a measure of advertising that would take into account these temporal effects is necessary (Bagwell, 2007). However, studies arrived at different conclusions on the temporal effect of advertising on demand. Some studies find carry over effects of advertising on consumer demand (Lambin, 1976). Others see the effect of advertising lasting only about a year (Ashley, Granger, & Schmalensee, 1980; Boyd & Seldon, 1990; Leone, 1995). Nelson (1974) suggested that advertising has initial effects on sales but it is the firm-specific factors that have long term effects on sales. Kwoka's findings were consistent with Nelson's theory. He examined the factors affecting U.S. auto sales and found short term effect for advertising but longer effect for product styling (Kwoka, 1993). Landes and Rosenfield (1994) and Thomas (1989) had similar findings showing that brand loyalty is associated more with product quality than with advertising. In the pharmaceutical industry, researchers found long run effects for pharmaceutical promotion particularly detailing (Hurwitz & Caves, 1988; Rizzo, 1999).

This study did not take into account the possible temporal effect of advertising. Recent studies show current advertising usually has positive short lived rather than long lived effect on sales (Bagwell, 2007). It also fails to identify an instrumental variable for direct-to-consumer

advertising expenditure. Thus, the regression results of the direct-to-consumer advertising variable maybe underestimated and biased.

In the case of price, the parameter of price in the choice model "will be significantly underestimated if endogeneity is not taken into account" (Villas-Boas & Winer, 1999) . To address this, the price of the active pharmaceutical ingredient (API) of the drug was used as instrumental variable of the price of prescription drugs. APIs are the main chemicals used to produce the drug. The price of API was selected as instrumental variable because it makes up a large portion of the cost of producing a drug. It is directly correlated with price of drugs but has no direct or indirect effect on the physician's prescribing behavior as these data are unknown to prescribers. The price of API is a valid instrumental variable because it is related to price, has no direct effect on the dependent variable which is "choice" of prescription drug and is not correlated with the disturbance in the discrete choice model. However, one possible reason for "price of API" to be a weak instrument is that the cost of research is not taken into account in the model. Pharmaceutical companies include research and development as part of the costs of producing breakthrough drugs.

The price of prescription drugs C was regressed on the price of API, P_{API}. The estimated price of prescription drugs, $\hat{C}$, replaced the endogenous variable price, C, in the nested logit model.

$$U = \hat{C}_j\rho + A_j\tau_1 + \boldsymbol{E}_j\tau_2 + \boldsymbol{Q}_{1j}\tau_3 + \boldsymbol{Q}_{2j}\tau_3 + V_j\varphi + X_{1i}\beta + \hat{O}_i\omega + X_{2i}\gamma + S_i\pi_1 + R_i\pi_2 + \hat{X}_i\pi_3 + \epsilon_{ij} \quad (16)$$

3.7 Sample Frame and Summary Statistics

This study uses the 2006 National Ambulatory Medical Care Survey (NAMCS). This is a national probability sample survey of non-federal office-based physicians conducted by the Centers

for Disease Control and Prevention's National Center for Health Statistics, Division of Health Care Statistics. The survey was conducted from December 26, 2005, through December 24, 2006. Each physician is randomly assigned to a 1-week reporting period where data for a systematic random sample of visits are recorded by the physician or office staff on an encounter form provided for that purpose. Data are obtained on patients' symptoms, physicians' diagnoses, and medications ordered or provided. The survey also provides statistics on the demographic characteristics of patients and services provided, including information on diagnostic procedures, patient management, and planned future treatment (Center for Disease Control and Prevention). The NAMCS data were used in previous studies examining physician prescribing behavior (Hellerstein, 1998; Howard, 1997; Stern & Trajtenberg, 1998). For the 2006 sample, 1,455 physicians participated in the survey and 29,392 patient record forms were completed (Cherry, Hing, Woodwell, & Rechtsteiner, 2008). A drug mention data set was created from the 2006 NAMCS data making prescription choice by the physician the unit of analysis. Cases where the patients have other source of payment not identified in the survey, was not charged for the doctor's visit or have missing information on the source of payment were excluded in the study.

The sample in this study will be limited to the drugs belonging to the four of the top ten therapeutic classes based on the number of dispensed prescription (IMS Health).[14] These are: MHG-CoA reductase inhibitors (statins), selective serotonin reuptake inhibitors (SSRI), cardioselective beta blockers and proton pump inhibitors (PPI). Each therapeutic class was analyzed separately.

[14] Available at http://www.imshealth.com/deployedfiles/imshealth/Global/Content/StaticFile/Top_Line_Data/2008_Top_Therapy_Classes_by_U.S._Sales.pdf

Price data are derived from the Consumer Reports Best Buy Drugs publication of Consumers Union (Consumers Union, 2006a, 2006b, 2007a, 2007b). The data were provided to Consumers Union by Wolters Kluwer Health, Pharmaceutical Audit Suite. These data reflect the nationwide retail average. The retail list price also referred to as the average wholesale price (AWP) is currently used by some public and private third-party payers as the basis for reimbursement (The Health Strategies Consultancy LLC, 2005). Different dosages have different corresponding prices. The average of the prices for the different dosages was computed and used in this study.

The 2006 expenditures on direct-to-consumer advertising were incorporated in the model to estimate the role of patients and the effect of pharmaceutical advertising in physician prescribing behavior. The DTC data were provided by TNS Media Intelligence (TNSMI), a leading provider of direct-to-consumer advertising expenditure and occurrence data (TNS Media Intelligence, 2009). The DTC advertising expenditure is composed of expenditure in the major types of media: television, radio, newspaper, magazine, internet and outdoors. Television expenditure includes cable television, network television, Spanish language network television, spot television, branded entertainment, syndication and local clearances of network television (including Spanish) and Syndication. Print includes business to business magazines, consumer magazines, Hispanic magazines, Hispanic newspapers, local magazines, national newspapers and Sunday magazines. Radio includes local radio, national spot radio and network radio. Outdoor advertising includes bulletins, painted walls, transit/bus shelters, in-store displays, convenience stores, shopping malls, airport, taxi displays and truck/mobile advertising. TNSMI tracks the occurrence of the brands or any marketing material associated with the product and collects the rates in doing the

advertisement from networks, publishers, Standard Rate & Data Service (SRDS) Publications among others to compute the actual advertising expenditure (TNS Media Intelligence, 2009).

The 2006 price of the active pharmaceutical ingredient (API) which was used as the instrumental variable for the price of prescription drugs were acquired from IMS, a healthcare informatics organization. The data were collected from manufacturers of the API and were reported as the global average in US dollars of the manufacturers' average price per standard unit (USD/MNF/SHP).

The qualitative indicators on the superiority of some statin drugs in reducing mortality and risk of heart attack were from Consumer Report's Best Buy Drug. The data from this report were based on "an independent scientific review of 347 studies on statin drugs conducted by a team of physicians and researchers at the Oregon Health & Science University Evidence-Based Practice Center" (Cosumers Union of the United States Inc., 2010).

The prescription drugs in the sample were grouped according to the following typology—breakthrough drug, me-too drug, generic drugs and generic me-too drugs. The classification was based on the date the FDA has approved the drug. This information is collected from the FDA Electronic Orange Book (Food and Drug Administration). The first to be approved in the class is labeled the breakthrough drug. The generic drug is the generic counterpart of breakthrough and generic me-too drugs are the generic counterpart of me-too drugs. Branded prescription drugs that were approved by FDA after the breakthrough drugs were the me-too drugs. The breakthrough drug in each therapeutic class has an existing generic counterpart and some of the me-too drugs also have generic counterparts.

3.7.1 Sample: MHG-CoA Reductase Inhibitors (Statin Drugs)

Statins are the newest class of cholesterol/lipid lowering drug. Randomized clinical trials report large reduction in cholesterol and evidence of benefit on stroke and total mortality (Hebert, Gaziano, Chan, & Hennekens, 1997). It has been the top selling class of prescription drugs since 2004 until 2008 when it placed second to antipsychotics via slim margin (IMS Health).

Table 1 summarizes the characteristics of the different statin drugs that were available in 2006. The statin class has eleven drugs in the market in 2006. The breakthrough drug Mevacor entered the market in 1987 and its generic counterpart lovastatin became available in 2001. There are two generic me-too drugs, pravastatin and simvastatin, that became available in the middle of 2006. This study does not include combination drug Vytorin.[15]

These two generic drugs engaged in direct-to-consumer advertising in that year. Four branded drugs (Lipitor, Crestor, Zocor and Pravachol) also engaged in direct-to-consumer advertising. The average costs of a month supply of these drugs were derived from the report of Consumer Reports Best Price Drugs (Consumers Union, 2007b, 2007c). These prices reflect the average (from June to December 2006) nationwide retail cost of a month supply of the prescription drug. It is the average price of all doses combined. Information on whether the prescription drug engaged in advertising from TNS Medial Intelligence is also summarized.

[15] Vytorin is a combination of statin and ezemtimibe.

Table 1: Therapeutic Class: Statins

n=1833

Brand Name	Generic name	n	FDA approval	Type	Direct-to-consumer advertising	Extended release feature	Reduce mortality	Reduce the risk of heart attack	Price
Mevacor	lovastatin	30	8/31/1987	breakthrough drug	no	no	likely	yes	$94.00
Altoprev	lovastatin	0	6/26/2002	~~me-too drug~~	no	yes	likely	yes	$102.00
Pravachol	pravastatin	108	10/31/1991	me-too drug	yes	no	yes	yes	$136.00
Zocor	simvastatin	443	12/23/1991	me-too drug	yes	no	yes	yes	$144.00
Lescol	fluvastatin	29	12/31/1993	me-too drug	no	no	likely	likely	$67.00
Lescol XL	fluvastatin	10	10/6/2000	me-too drug	no	yes	likely	likely	$84.00
Lipitor	atorvastatin	906	12/17/1996	me-too drug	yes	no	yes	yes	$98.00
Crestor	rosuvastatin	141	8/12/2003	me-too drug	yes	no	likely	yes	$90.00
lovastatin		116	12/17/2001	generic drug	no	no	likely	yes	$58.00
pravastatin		7	4/24/2006	generic me-too	yes	no	yes	yes	$90.00
simvastatin		43	6/23/2006	generic me-too	yes	no	yes	yes	$109.00

Information on whether a certain drug has delayed or extended-release feature can be verified in the FDA's Orange book. With respect to reducing heart attacks, evaluation studies of the drugs showed that "atorvastatin , lovastatin, pravastatin and simvastatin have been proven to reduce the risk of heart attack over three to five years of use. Rosuvastatin has been shown to reduce the risk of heart attack over 1.9 years of use. The evidence of heart-attack prevention is less definitive for fluvastatin" (Cosumers Union of the United States Inc., 2010). The Consumer Report noted, however, that studies showing these findings only look at the short term rather than the long term impact of the drugs.

With respect to reduction of deaths, "atorvastatin, lovastatin, pravastatin and simvastatin have been found to reduce deaths from heart attacks among patients with a history of heart disease or risk factors for heart disease, such as diabetes and high blood pressure. Pravastatin and simvastatin were found to reduce the overall risk of dying among people considered to be at low risk of heart disease or heart attack." The report also noted that "lovastatin has not been proven to reduce deaths but the evidence points in that direction." Atorvastatin was tested and found to be effective in reducing deaths among high risk and would also be effective in reducing deaths among low risk people as well (Cosumers Union of the United States Inc., 2010).

Table 1 also includes the frequency of drug mention of the drugs in the 2006 National Ambulatory Care Survey. A total of n= 1,833 drugs in the statin class were included in this analysis. There were cases when the physician prescribed the generic names of Lipitor, Crestor, and Zocor even if the generic versions of these drugs were not available in the market when they were prescribed. In the case of Zocor, the generic simvastatin was approved by the FDA on June 23,

2006. All simvastatin prescriptions before July 2006 (n=28) were recoded as Zocor. Atorvastatin (n=5) were recoded as Lipitor and Rosuvastatin Calcium (n=1) was recoded as Crestor. It was assumed that physicians are aware of the availability of generic versions of drugs.

The succeeding table summarizes the descriptive statistics for the different variables included in this study in relation to the different types of prescription drugs.

Table 2: Summary Statistics for Prescription Drug Class Statins

n=1833

	Breakthrough drug n= 30	Generic drug n=116	Me-too drugs n=1637	Generic me-too drugs n = 50
ALTERNATIVE SPECIFIC CHARACTERISTICS				
average nationwide retail cost of a month supply (in dollars) M(SD)	94.00 (0)	58.00 (0)	111.63 (22.50)	106.34 (6.66)
direct-to-consumer advertising expenditure (in dollars) M(SD)	0	0	95,074,053 (72171562)	280,416 (45776.584)
summary of length of time in the market[a] (in days) M(SD)	6884.63 (99.12)	1,638.90 (105.09)	3875.83 (1224.43)	106.12 (50.78)
CASE SPECIFIC CHARACTERISTICS				
Patient characteristics				
age of patient M(SD)	64.67 (14.83)	65.11 (14.02)	65.22 13.29)	72.26 (11.80)
sex of patient (female) n(%)	20 (66.67)	67 (57.76)	827 (50.52)	19 (38.00)
race of patient (non-white) n(%)	6 (20.00)	20 (17.24)	254 (15.52)	2 (4.00)
ethnicity of patient (Hispanic) n(%)	7 (23.33)	14 (12.07)	139 (8.49)	6 (12.00)
number of medication M(SD)	5.40 (2.31)	5.43 (2.23)	5.98 (2.07)	6.2 (1.82)
patient expected source of	16 (53.33)	62 (53.45)	974 (59.50)	32 (64.00)

payment- private coverage n(%)				
Patient expected source of payment-Medicare n(%)	16 (53.33)	54(46.55)	878 (53.63)	30 (60.00)
Patient expected source of payment-Medicaid n(%)	3 (10.00)	21 (18.10)	199(12.16)	1 (2.00)
Patient expected source of payment- Selfpay n(%)	2 (6.67)	5 (4.31)	67 (4.09)	0 (0.00)
Doctor characteristics				
doctor's specialization (specialized) n(%)	15 (50.00)	81 (69.83)	1217(74.34)	35(70.00)
practicing in the Midwest n(%)	1 (3.33)	25 (21.55)	370 (22.60)	12 (24.00)
practicing in the South n(%)	12 (40.00)	31 (26.72)	513 (31.34)	12 (24.00)
practicing in the West n(%)	9 (30.00)	47 (40.52)	343 (20.95)	10 (20.00)
percent of patient care revenue from Medicare (more than 50%) n(%)	13 (43.33)	47 (40.52)	579 (35.37)	22 (44.00)
percent of patient care revenue from Medicaid (more than 50%) n(%)	2 (6.67)	21 (18.10)	227 (13.87)	5 (10.00)
percent of patient care revenue from private insurance (more than 50%) n(%)	6 (20.00)	42 (36.21)	454 (27.73)	16 (32.00)
percent of patient care revenue from patient payment (more than 50%) n(%)	1 (3.33)	18 (15.52)	178 (10.87)	4 (8.00)

a. date the survey was conducted – date of FDA approval of the drug

The generic drug in the cheapest in the statins class ($58) followed by the breakthrough drug, the generic me-too drugs and the me-too drugs. On average, a month supply of generic me-too drugs cost $106.34 while a month supply of me-too drugs cost $111.63. Only the me-too drugs and the generic me-too drugs engaged in direct-to-consumer advertising.

Me-too drugs entered the market before the patent of the breakthrough drug expired. The breakthrough drug has been in the market for about 18 years in 2006 when NAMCS survey was done. The me-too drugs were about ten years in the market while the generic version of the breakthrough drug was about four years. The generic me-too drugs have been in the market for less than a year.

Patients who were prescribed with generic me-too drugs were older than the ones prescribed with generic, breakthrough or me-too drugs. Most patients were taking other medication aside from the statin drug prescribed by the physician. Majority of the patients pay using private coverage and Medicare.

3.7.2 Sample: Cardioselective Beta Blockers

Cardioselective beta blockers are common medication for high blood pressure as well as irregular heartbeat, angina, and symptoms of anxiety. There are eleven alternative prescription drugs in the therapeutic class of cardioselective beta blockers. Five of these drugs are me-too drugs and four are generic me-too drugs. One of the me-too drugs, Toprol-XL, was reformulated to have the extended-released feature. This is also the only drug in this class that engaged in direct-to-consumer advertising in 2006. Table 6 summarizes the descriptive statistics for cardioselective betablockers.

The prices of cardioselective beta blockers were the monthly cost of the prescription drugs based on the national average of its retail price as reported in the Consumer Reports Best Buy Drugs (Consumers Union, 2006b). The average price of the branded drugs is $90.22 (SD=71.40)

while the average price of generic drugs is $30.20 (SD=18.22). The overall average price for this class is $62.94 (SD=60.54).

Table 3: Therapeutic Class: Cardioselective Beta Blockers

n=1243

Brand name	Generic name	n	FDA approval	Type	Direct-to-consumer advertising	Extended release feature	Price
Lopressor	metoprolol tartrate	96	8/7/1978	breakthrough drug	no	no	$50.50
Kerlone	betaxolol	1	10/27/1989	me-too drug	no	no	$58.50
Toprol-XL	metoprolol succinate	483	1/10/1992	me-too drug	yes	yes	$54.67
Tenormin	atenolol	37	8/19/1981	me-too drug	no	no	$59.67
Sectral	acebutolol	2	12/28/1984	me-too drug	no	no	$234.00
Zebeta	bisoprolol	0	7/31/1992	me-too drug	no	no	$84.00
metoprolol tartrate		222	12/21/1993	generic drug	no	no	$10.50
betaxolol		0	10/22/1999	generic me-too	no	no	$37.00
atenolol		390	7/15/1988	generic me-too	no	no	$12.00
acebutolol		2	4/24/1995	generic me-too	no	no	$52.00
bisoprolol		10	11/16/2000	generic me-too	no	no	$39.50

There were 1,243 mentions of prescription drugs belonging to the cardioselective beta blockers class in the 2006 NAMCS data. Although the 25mg metropolol succinate was approved by the FDA in 2006, the drug did not become available in the market until 2007. There was one prescription of generic metropolol succinate in the dataset which was recoded as Toprol-XL, the branded version of the generic drug.

Table 4 summarizes the descriptive statistics of the key variables for the beta blockers.

Table 4. Summary Statistics for Beta Blockers

n=1,243

	Breakthrough drug	Generic drugs	Me-too drugs	Generic Me-too drugs
	n=96	n=222	n=523	n = 402
ALTERNATIVE SPECIFIC CHARACTERISTICS				
average nationwide retail cost of a month supply (in dollars) M(SD)	50.50 (0)	10.50 (0)	55.72 (11.13)	12.88 (5.11)
direct-to-consumer advertising expenditure (in dollars) M(SD)	0	0	13,838,181 (3986126)	0
summary of length of time in the market[a] (in days) M(SD)	10,150.54 (109.16)	4,557.08 (101.03)	5,532.64 (999.71)	6,404.87 (731.17)
CASE SPECIFIC CHARACTERISTICS				
Patient characteristics				
age of patient M(SD)	69.51 (11.17)	68.22 (13.81)	65.94 15.13)	64.17 (15.98)
sex of patient (female) n(%)	46 (47.92)	101 (45.50)	280 (53.54)	248 (61.69)
race of patient (non-white) n(%)	7 (7.29)	38 (17.12)	64 (12.24)	53 (13.18)
ethnicity of patient (Hispanic) n(%)	10 (10.42)	23 (10.36)	38 (7.27)	32 (7.96)
number of medication M(SD)	6.46 (1.76)	6.27 (1.83)	5.79 (2.10)	5.63 (2.15)

patient expected source of payment- private coverage n(%)	52 (54.17)	121 (54.50)	341 (65.20)	251 (62.44)
patient expected source of payment- Medicare n(%)	67 (69.79)	135 (60.81)	288 (55.07)	205 (51.00)
patient expected source of payment- Medicaid n(%)	13 (13.54)	28 (12.61)	34 (6.50)	45 (11.19)
patient expected source of payment- Selfpay n(%)	2 (2.08)	10 (4.50)	21 (4.02)	25 (6.22)
Doctor characteristics				
doctor's specialization (specialized) n(%)	68 (70.83)	162 (72.97)	401 (76.67)	276 (68.66)
practicing in the Midwest n(%)	29 (30.21)	52(23.42)	122 (23.33)	100 (23.88)
practicing in the South n(%)	25 (26.04)	54 (24.32)	175 (33.46)	102 (25.37)
practicing in the West n(%)	12 (12.50)	51 (22.97)	81 (15.49)	100 (24.88)
practicing in the North n(%)				
percent of patient care revenue from Medicare (more than 50%) n(%)	26 (27.08)	81 (36.49)	188 (35.95)	139 (34.58)
percent of patient care revenue from Medicaid (more than 50%) n(%)	8 (8.33)	28 (12.61)	38 (7.27)	81 (20.15)
percent of patient care revenue from private insurance (more than 50%) n(%)	30 (31.25)	60 (27.03)	128 (24.47)	141 (35.07)
percent of patient care revenue from patient payment (more than 50%) n(%)	7 (7.29)	22 (9.91)	32 (6.12)	62 (15.42)

a. date the survey was conducted – date of FDA approval of the drug

The cheapest drug in this class is the generic drug which only cost $10.50 for a month supply. This is followed by the generic versions of the me-too drugs which cost $12.88 a month. The price of the breakthrough drug and the me-too drugs were $50.50 and $55.72 respectively.

Only me-too drugs engaged in direct-to-consumer advertising. The drugs in the beta blockers class have been in the market in a while. The breakthrough drug Lopressor has been in the market for more than 27 years. The patients' primary sources of payment are private coverage and Medicare.

3.7.3 Sample: Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are a class of drugs used to treat heartburn, gastroesophageal reflux disease (GERD) and ulcers by reducing gastric acid production (Consumers Union, 2007a). Tables 5 and 6 summarize the descriptive statistics of the class proton pump inhibitors. There are seven alternatives in the class of proton pump inhibitors: a breakthrough drug, a generic version of the breakthrough drug and five me-too drugs. All but Zegerid have delayed release features. Aciphex and generic omeprazole did not engage in direct-to-consumer advertising.

Table 5. Therapeutic Class: Proton Pump Inhibitors

n=1,346

Brand Name	Generic Name	N	FDA approval	Type	Direct-to-consumer advertising	Delayed release feature	Price
Prilosec	omeprazole	282	9/14/1989	breakthrough drug	yes	yes	$181.00
Prevacid	lansoprazole	254	5/10/1995	me-too drug	yes	yes	$161.50
Aciphex	rabeprazole	100	8/19/1999	me-too drug	no	yes	$189.00
Protonix	pantoprazole	240	2/2/2000	me-too drug	yes	yes	$152.50
Nexium	esomeprazole	376	2/20/2001	me-too drug	yes	yes	$187.00
Zegerid	omeprazole/sodium bicarbonate	11	6/15/2004	me-too drug	yes	no	$157.50
omeprazole		83	10/18/2002	generic	no	yes	$102.50

The price of the proton pump inhibitors were the average cost of a month supply of the medication based on the average retail prices of all the doses of the drugs. These prices were reported in the Consumer Reports Best Buy Drugs (Consumers Union, 2007a). The price of generic is $102.50 and the average price of the branded drugs is $171.42 (SD=16.09).

There were 1346 mentions of prescription drugs belonging in the proton pump inhibitors class in the 2006 NAMCS. Pysician prescriptions of Rabeprazole sodium (n=1), Esomeprazole magnesium (n=4), and Pantroprazole sodium (n=2), were recoded as Aciphex, Nexium and Protonix as there were no generic versions of these drugs in 2006. There are no generic versions of the me-too drugs when the survey was conducted in 2006.

Table 6 summarizes the descriptive statistics of the key variables for the proton pump inhibitors.

Table 6. Summary statistics for Proton Pump Inhibitors

n= 1,346

	Breakthrough drug n=282	Generic drug n=83	Me-too drugs n=981
ALTERNATIVE SPECIFIC CHARACTERISTICS			
Average nationwide retail cost of a month supply (in dollars) M(SD)	181 (0)	102.50 (0)	171.83 (15.49)
Direct-to-consumer advertising expenditure (in dollars) M(SD)	1,032,800 (0)	0	73,560,914 (84091542)
Summary of length of time in the market[a] (in days) M(SD)	6118.82 (100.19)	1358.57 (103.38)	2621.61 (878.23)

CASE SPECIFIC CHARACTERISTICS			
Patient characteristics			
age of patient M(SD)	61.56 (17.60)	62.84 (15.80)	59.59 (17.05)
sex of patient (female) n(%)	176 (62.41)	48 (57.83)	598 (60.96)
race of patient (non-white) n(%)	38 (13.48)	14 (16.87)	114(11.62)
ethnicity of patient (Hispanic) n(%)	30 (10.64)	5 (6.02)	84 (8.56)
number of medication M(SD)	5.46 (2.48)	5.94 (2.38)	5.44 (2.48)
Patient expected source of payment- private coverage n(%)	157 (55.67)	49 (59.04)	625 (63.71)
Patient expected source of payment- Medicare n(%)	128 (45.39)	42 (50.60)	438 (44.65)
Patient expected source of payment- Medicaid n(%)	54 (19.15)	10 (12.05)	132 (13.46)
Patient expected source of payment- Selfpay n(%)	13 (4.61)	2 (2.41)	35 (3.57)
Doctor characteristics			
doctor's specialization (specialized) n(%)	189 (67.02)	60 (72.29)	716 (72.99)
Practicing in the Midwest n(%)	72 (25.53)	27 (32.53)	245 (24.97)
Practicing in the South n(%)	80 (28.37)	18 (21.69)	366 (37.31)
Practicing in the West n(%)	63 (22.34)	20 (24.10)	152 (15.49)
Practicing in the North n(%)			
Percent of patient care revenue from Medicare (more than 50%) n(%)	22 (26.51)	88 (31.21)	294 (29.97)
Percent of patient care revenue from Medicaid (more than 50%) n(%)	39 (13.83)	9 (10.84)	98 (9.99)
Percent of patient care revenue from private insurance (more than 50%) n(%)	72 (25.53)	30 (36.14)	278 (28.34)
Percent of patient care revenue from patient payment (more than 50%) n(%)	31 (10.99)	8 (9.64)	84 (8.56)

a. date the survey was conducted – date of FDA approval of the drug

The generic drug omeprazole is the cheapest drug in the proton pump inhibitors' class. This is followed by the me-too drugs with an average monthly cost of $171.83. The most expensive drug in this class, Aciphex, is a me-too drug. A month supply of Aciphex costs $189. There are me-too drugs that are cheaper than the breakthrough drug, Prilosec, which caused the average price of me-too drugs to be lower than the price of the breakthrough drug.

Both the breakthrough drug and the me-too drugs spent for direct-to-consumer advertising in 2006. The breakthrough drug spent $1,032,800 on direct-to-consumer advertising while the me-too drugs spent an average of $73,560,914. The breakthrough drug has been in the market for more than six years when the survey was conducted in 2006. Me-too drugs entered the market before the generic version of the breakthrough drug Prilosec became available.

Patients who received me-too drugs were slightly younger compared to those prescribed with the breakthrough drug or generic drug. The patients who were in proton pump inhibitors have, on average, five other medications. The expected sources of payment for majority of the patients were private coverage and Medicare.

3.7.4 Sample: Selective Serotonin Reuptake Inhibitors (SSRI)

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants. They have simpler dosing and less toxic effects compared to other anti-

depressants. A study showed that paroxetine, fluoxetine and sertraline were similar in effectiveness for depressive symptoms (Kroenke et al., 2001).

Prozac has been marketed by Eli Lilly as the breakthrough drug in the SSRI class of antidepressant drugs. There were eight me-too drugs in this class and four of them have generic counterparts. Two were reformulated to be delayed released and extended released. Sarafem, coded as a me-too drug, is a rebranded Prozac. One generic drug (sertraline) and two me-too drugs (Zoloft and Lexapro) spent for direct-to-consumer advertising in 2006. Table 7 summarizes the information on the SSRIs.

Table 7.Therapeutic Class: Selective Seratonin Reuptake Inhibitors

n=1308

Brand name	Generic name	N	FDA approval	Type	Direct-to-consumer advertising	Delayed release/ controlled-release feature	Price
Sarafem	fluoxetine	6	7/6/2000	me-too drug	no	no	$191.00
Prozac	fluoxetine	188	12/29/1987	breakthrough drug	no	no	$225.33
Celexa	citalopram	123	7/17/1998	me-too drug	no	no	$107.00
Lexapro	escitalopram	333	8/14/2002	me-too drug	yes	no	$97.67
Paxil	paroxetine	168	12/29/1992	me-too drug	no	no	$118.25
Paxil CR	paroxetine	14	2/16/1999	me-too drug	no	yes	$114.67
Prozac Weekly	fluoxetine	0	2/26/2001	me-too drug	no	yes	$139.00
Zoloft	sertraline	319	12/30/1991	me-too drug	yes	no	$104.33
Pexeva	paroxetine	4	7/3/2003	me-too drug	no	no	$112.00
fluoxetine		77	8/2/2001	generic drug	no	no	$49.50
citalopram		34	10/28/2004	generic me-too	no	no	$45.00
paroxetine		37	7/30/2003	generic me-too	no	no	$63.75
sertraline		5	6/30/2006	generic me-too	yes	no	$85.67
fluvoxamine		0	11/29/2000	generic me-too	no	no	$94.00

Prices of the SSRIs were based on the average cost of a month supply of SSRI based on the average retail price in September, 2006. These information were published by Consumers Union through the Consumer Reports Best Buy Drugs (Consumers Union, 2006a). The average price for branded drug under this class is $134.36 (SD=44.23) while the average price for generic drugs is $67.58 (SD=21.66). The overall average price is $110.51 (SD=49.50).

There were a total of n=1308 drug mention in the 2006 National Ambulatory Care Survey that belonged to the SSRI class that were included in this analysis. There were 13 mentions of the prescription drug Luvox. Although this drug was approved by the FDA in 1997, it was not available in the market in 2006. These cases were excluded in the analysis. There were also mentions of sertraline prior to its approval and release in the market on June 30, 2006. These four cases were recoded as Zoloft which is the brand name version of sertraline.

Table 8. Summary statistics for prescription drug class SSRI

n=1,308

	Breakthrough drug n=188	Generic drugs n=77	Me-too drugs n=967	Generic Me-too drugs n =76
ALTERNATIVE SPECIFIC CHARACTERISTICS				
average nationwide retail cost of a month supply (in dollars) M(SD)	213.50 (0)	47.60 (0)	105.52 (9.85)	56.80 (11.94)
direct-to-consumer advertising expenditure (in dollars) M(SD)	0	0	4,980,014.40 (5389297.40)	28,085.53 (106537.6)
summary of length of time in the market[a] (in days) M(SD)	6,737.53 (99.04)	1,789.07 (94.46)	3,524.56 (1746.73)	771.62 (300.10)

CASE SPECIFIC CHARACTERISTICS				
Patient characteristics				
age of patient M(SD)	45.59 (17.78)	52.30 (15.57)	49.56 (19.14)	59.05 (17.06)
sex of patient (female) n(%)	131 (69.68)	49 (63.64)	666 (68.87)	44 (57.89)
race of patient (non-white) n(%)	16 (8.51)	6 (7.79)	108 (11.17)	4 (5.26)
ethnicity of patient (Hispanic) n(%)	11 (5.85)	16 (20.78)	89 (9.20)	10 (13.16)
number of medication M(SD)	4.14 (2.49)	4.31 (2.51)	4.40 (2.55)	5 (2.40)
patient expected source of payment- private coverage n(%)	106 (56.38)	41 (53.25)	609 (62.98)	45 (59.21)
patient expected source of payment- Medicare n(%)	38 (20.21)	22 (28.57)	279 (28.85)	32 (42.11)
patient expected source of payment- Medicaid n(%)	17 (22.08)	38 (20.21)	148 (15.31)	7 (9.21)
patient expected source of payment- Selfpay n(%)	26 (13.83)	9 (11.69)	110 (11.38)	12 (15.79)
Doctor characteristics				
doctor's specialization (specialized) n(%)	125 (66.49)	58 (75.32)	731 (75.59)	56 (73.68)
practicing in the Midwest n(%)	54 (28.72)	28 (36.36)	227 (23.47)	12 (15.79)
practicing in the South n(%)	51 (27.13)	7 (9.09)	291 (30.09)	21 (27.63)
practicing in the West n(%)	35 (18.62)	29 (37.66)	197 (20.37)	23 (30.26)
practicing in the North n(%)				
percent of patient care revenue from Medicare (more than 50%) n(%)	38 (20.21)	18 (23.38)	227 (23.47)	20 (26.32)
percent of patient care revenue from Medicaid (more than	28 (14.89)	20 (25.97)	143 (14.79)	17 (22.37)

50%) n(%)				
percent of patient care revenue from private insurance (more than 50%) n(%)	78 (41.49)	35 (45.45)	350 (36.19)	24 (31.58)
percent of patient care revenue from patient payment (more than 50%) n(%)	29 (15.43)	13 (16.88)	151 (15.62)	11 (14.47)

a. date the survey was conducted – date of FDA approval of the drug

3.8 Empirical Results and Discussion

Prior to implementing the nested logit models of the four classes of drugs, the estimated value of the price of prescription drugs was derived using the price of active pharmaceutical ingredient (API) of the prescription drug as an instrumental variable (IV) for price, [C = fn (P_{API})].

A single first stage regression was used to estimate the value of price for all four second stage regressions. The sample is composed of all the drugs in the four classes examined in this study (n=41). The n is too small for inclusion of other independent variables in the first stage regression. The sample size of the drugs in each class is also too small to allow for separate first stage regression for the instrumental variable of each drug class. The result of the regression estimation is as follows:

Table 9. First –stage regression of the variable price on the instrumental variable API price

n = 41

		Coef.	t	*p*>|t|	
P_{API}		31.859	2.02	0.051	*
Cons		82.927	5.98	0.000	
Summary Statistics					
Number of obs	=	41			
F(1,39)	=	4.07			
Prob>F	=	0.05			
R^2	=	0.09			
Adjusted R^2	=	0.07			

*Significant at .05 level

The regression results show that the API has a statistically significant effect on price ($F_{1,39}$= 4.07, p =.05). This may suggest that API is a weak instrument for price. However, the low F and the weak statistical significance can be attributed to the small sample size. The estimated value of price, $\hat{C}$ =E(P|P_{API}), was included in the nested logit model. Note that the estimation was done manually by running two separate regressions. The standard errors were not manually adjusted. This will make the standard errors of the nested logit models incorrect. The coefficients of the model are still correctly estimated but this may overestimate the statistical significance of the variables.

The results of the nested logit models for statins, beta blockers, proton pump inhibitors (PPIs) and selected serotonin reuptake inhibitors (SSRIs) are summarized in the following sections. The estimates were derived using full information maximum-likelihood estimation. Nested logit model clusters alternatives into nests thus relaxing the assumption of independently distributed errors and the independence of irrelevant alternatives inherent in standard multinomial and conditional logit models. The results of this study are limited to the analysis of factors that may

affect the prescription of the specific type of drug and not the specific drug in the class. The results presented are limited to first level probabilities and coefficients.

3.8.1 STATINS

The non-sequential two-tiered tree structure for the statins is presented below. The first level presents the four nests which correspond to the types of prescription drugs (generic, breakthrough, me-too and generic me-too drugs). The second level presents the different alternatives in each nest.

Figure 4: Tree Structure Specified for the Nested Logit Model of Statins

Type	N	Alternatives	N	k
Generic drug	1,833	lovastatin	1,833	116
Breakthrough drug	1,833	Mevacor	1,833	30
Me-too drugs	12,831	Lescol XL	1,833	10
		Crestor	1,833	141
		Altoprev	1,833	0
		Pravachol	1,833	108
		Zocor	1,833	443
		Lescol	1,833	29
		Lipitor	1,833	906
Generic me-too drugs	2,077	simvastatin	885	43
		pravastatin	1,192	7
Total			18,574	1,833

k = number of times alternative is chosen
n = number of observations at each level

Nested Logit Model Results for Drug Class Statins

The following table summarizes the result of the nested logit model for drug class statin.

Table 10. Nested Logit Model with IV Results on Prescribing Choice of Physicians for Statins

Parameters		Coef.	z	P>|z|	
Predicted price, $\hat{C}$		-0.013	-2.62	0.009	**
Length of time ratio, A		1.024	4.27	0.000	***
Direct-to-consumer advertising expenditure, V		0.176	6.82	0.000	***
Reduces mortality		0.114	0.34	0.734	
Prevents heart attack		-0.589	-1.60	0.109	
Delayed/extended release feature		-0.171	-0.58	0.563	
Generic drug (base)					
Patient characteristics					
Age x	breakthrough drugs	-0.024	-1.78	0.075	
	me-too drugs	-0.021	-2.36	0.018	*
	generic me-too drugs	-0.004	-0.28	0.779	
Sex x	breakthrough drugs	0.396	0.89	0.376	
(male)[a]	me-too drugs	-0.310	-1.52	0.128	
	generic me-too drugs	-0.863	-2.39	0.017	*
Race x	breakthrough drugs	0.563	1.02	0.307	
(white)	me-too drugs	0.163	0.59	0.557	
	generic me-too drugs	-0.945	-1.20	0.229	
Ethnicity x	breakthrough drugs	0.784	1.41	0.160	
(non-hispanic)	me-too drugs	-0.131	-0.41	0.680	
	generic me-too drugs	1.038	1.79	0.073	
Number of medication x	breakthrough drugs	0.026	0.28	0.778	
	me-too drugs	0.116	2.50	0.012	*
	generic me-too drugs	0.121	1.41	0.159	

Patient expected source of payment (self pay)					
Private Insurance x	breakthrough drugs	0.306	0.57	0.572	
	me-too drugs	0.372	1.40	0.162	
	generic me-too drugs	0.384	0.82	0.415	
Medicare x	breakthrough drugs	0.562	0.95	0.344	
	me-too drugs	0.643	2.36	0.018	*
	generic me-too drugs	0.723	1.41	0.157	
Medicaid x	breakthrough drugs	-1.049	-1.41	0.159	
	me-too drugs	-0.445	-1.38	0.168	
	generic me-too drugs	-2.189	-2.01	0.045	*
Doctor characteristics					
Doctor specialization x	breakthrough drugs	-1.129	-2.44	0.015	*
(general practice)	me-too drugs	0.231	0.99	0.322	
	generic me-too drugs	-0.430	-1.06	0.289	
Region of practice (Northeast)					
Midwest x	breakthrough drugs	-2.855	-2.55	0.011	*
	me-too drugs	-0.941	-2.60	0.009	**
	generic me-too drugs	-1.025	-1.90	0.058	
South x	breakthrough drugs	-0.828	-1.47	0.141	
	me-too drugs	-0.843	-2.44	0.015	*
	generic me-too drugs	-1.387	-2.72	0.007	*
West x	breakthrough drugs	-1.284	-2.16	0.031	*
	me-too drugs	-1.594	-4.74	0.000	***
	generic me-too drugs	-1.897	-3.57	0.000	***
Percentage of patient care revenue from Medicare greater than 50% x	breakthrough drugs	0.614	1.23	0.221	
	me-too drugs	-0.369	-1.49	0.136	
	generic me-too drugs	0.208	0.48	0.633	
Percentage of patient care revenue from Medicaid greater	breakthrough drugs	-0.588	-0.55	0.579	
	me-too drugs	0.363	0.77	0.440	

than 50% x	generic me-too drugs	0.301	0.33	0.742
Percentage of patient care revenue from private insurance greater than 50% x	breakthrough drugs	-0.333	-0.56	0.574
	me-too drugs	-0.489	-1.88	0.060
	generic me-too drugs	-0.067	-0.14	0.888
Percentage of patient care revenue from self-payment greater than 50% x	breakthrough drugs	-1.018	-0.69	0.488
	me-too drugs	-0.026	-0.05	0.962
	generic me-too drugs	-1.072	-0.97	0.333
Dissimilarity parameters				
τ generic drug	— [b]			
τ breakthrough drugs	— [b]			
τ me-too drugs	0.676			
τ generic me-too drugs	2.591			
Summary Statistics				
No. of cases	1,833			
Log likelihood	-2672.376			
Wald chi^2	1021.05 (0.000)			
LR test for IIA = χ^2 (prob.)	13.32 (0.001)			

a. Reference category in parentheses

b. Degenerate nest. Parameter not defined.

*Significant at .05 level

**Significant at .01 level

***Significant at .001 level

The results show that increase in price decreases the likelihood that a drug will be prescribed relative to other drugs in the same class. This is significant at $p \leq .01$. On the other hand, increase in the length of time in the market and direct-to-consumer advertising expenditure increase the likelihood that a drug will be prescribed relative to other drugs in the same class. These findings are significant at $p \leq .001$ level. Indicators of drug quality like possible effects on

mortality and heart attack and extended feature are not significant predictors of prescribing behavior of physicians in the class of statins.

In terms of patient characteristics, an increase in age decreases the probability of being prescribed me-too drugs relative to the probability of being prescribed generic drug ($p \leq .05$). Females are also more likely to be prescribed generic drugs than generic me-too drugs compared to males ($p \leq .05$). An increase in the number of medication increases the probability of being prescribed me-too drugs relative to the probability of being prescribed generic drugs ($p \leq .05$). Medicare as an expected source of payment also increases the probability that a patient will be prescribed me-too drugs relative to the probability of being prescribed a generic drug ($p \leq .05$). On the other hand, Medicaid as an expected source of payment increases the probability of a patient being prescribed generic drug relative to being prescribed generic me-too drugs ($p \leq .05$).

In terms of physician characteristics, physicians with specialized practice are less likely to prescribe breakthrough drugs than generic drug compared to those with general practice ($p \leq .05$). Physicians who are practicing in the Midwest are less likely to prescribe breakthrough and me-too drugs than the generic drug compared to physicians in the Northeast ($p \leq .01$). Physicians in the South are less likely to prescribe me-too drugs and generic me-too drugs than generic drugs compared to physicians in the Northeast ($p \leq .05$; $p \leq .01$). Physicians in the West are less likely to prescribe breakthrough, me-too and generic me-too drugs than generic drug compared to physicians in the Northeast ($p \leq .05$; $p \leq .001$; $p \leq .001$).

The dissimilarity parameter (τ) is a measure of the degree of correlation of random shocks within each nest (StataCorp, 2007:443). The value of the dissimilarity parameters (τ) ≤ 1 indicates

whether the model is consistent with the random utility model. In this case, the dissimilarity parameters for generic drugs and breakthrough drugs are undefined because these are degenerate nests; each branch has only one alternative. The dissimilarity parameter of me-too drugs is 0.676 but the dissimilarity parameter for generic me-too drugs is slightly higher than 1.0. This value makes this model inconsistent with the random utility model. While this is so, the model is still mathematically correct and gives well behaved probabilities between 0 and 1 and that sum to 1 (Cameron & Trivedi, 2010:515). The likelihood ratio test for independence of irrelevant alternatives (IIA) is significant at $p. \leq 001$ indicating that we can reject the null hypothesis that the IIA requirement holds. This implies that nested logit model maybe more appropriate than conditional logit or standard multinomial logit model.

The results of the alternative-specific variables for the nested logit model without the instrumental variable on price are presented for comparison with the nested logit model with IV.

Table 11. Nested Logit Model Results for Alternative-Specific Variables on Prescribing Choice of Physicians for Statins

Parameters	Coef.	z	P>|z|	
Price, *C*	0.006	3.17	0.002	**
Length of time ratio, *A*	0.979	4.20	0.000	***
Direct-to-consumer advertising expenditure, *V*	0.157	7.51	0.000	***
Reduces mortality	-0.111	-0.41	0.684	
Prevents heart attack	-0.589	-1.60	0.040	
Delayed/extended release feature	-0.171	-0.58	0.789	

The results show that the use of instrumental variable on price has resulted to the reversal of the sign of the price coefficient from positive to negative. The price coefficient on the model with the IV is more consistent with the hypothesis of this study that an increase in price will reduce the likelihood of a drug from being prescribed. This suggests that the price was indeed endogenous and using the instrumental variable was helpful in addressing endogeneity. Accordingly, the inclusion of the IV in the model has also reversed the sign of the coefficients for length of time in the market, direct-to-consumer advertising and the qualitative measure for the reduction of mortality. The inclusion of the IV also made the effects of these variables more consistent with the hypotheses of the model that increase in length of time in the market and increase in advertising expenditure will also increase the likelihood of a drug from being prescribed.

3.8.2 CARDIOSELECTIVE BETA BLOCKERS

The following figure presents the non-sequential two-tiered tree structure for cardioselective beta blockers. The first level are the four nests which represent the types of prescription drugs while the second level presents the alternatives in each nest.

Figure 5. Tree Structure Specified for the Nested Logit Model of Cardioselective Beta Blockers

Type	N	Alternatives	n	k
Generic drug	1,242	metoprolol	1,242	222
Breakthrough drug	1,242	Lopressor	1,242	96
Me-too drugs	4,968	Zebeta	1,242	0
		Tenormin	1,242	37
		Spectral	1,242	2
		Toprol XL	1,242	483
Generic me-too drugs	3,726	bisoprolol	1,242	10
		atenolol	1,242	390
		acebutolol	1,242	2
		betaxolol	1,242	0
Total			11,178	1,242

k = number of times alternative is chosen
n = number of observations at each level

Nested Logit Model Results for Drug Class Cardioselective Beta Blockers

The following table summarizes the result of the nested logit regression model for the drug class cardioselective beta blockers.

Table 12. Nested Logit Model Results for Prescribing Choice of Physicians for Cardioselective Beta Blockers

Parameters		Coef.	z	P>|z|	
Predicted price, $\hat{C}$		-0.334	-4.75	0.000	***
Length of time ratio, A		-0.473	-3.12	0.002	**
Direct-to-consumer advertising expenditure, V		0.136	5.00	0.000	***
Generic drug (base)					
Patient characteristics					
Age x	breakthrough drugs	-0.011	-1.35	0.178	
	me-too drugs	-0.015	-2.18	0.029	*

	generic me-too drugs	-0.013	-2.08	0.038	*
Sex x	breakthrough drugs	0.051	0.20	0.838	
(male)[a]	me-too drugs	0.397	2.38	0.017	*
	generic me-too drugs	0.764	4.36	0.000	***
Race x	breakthrough drugs	-1.013	-2.24	0.025	*
(white)	me-too drugs	-0.340	-1.39	0.163	
	generic me-too drugs	-0.466	-1.85	0.064	
Ethnicity x	breakthrough drugs	0.063	0.15	0.879	
(non-hispanic)	me-too drugs	-0.498	-1.71	0.088	
	generic me-too drugs	-0.481	-1.59	0.111	
Number of medication x	breakthrough drugs	0.012	0.19	0.846	
	me-too drugs	-0.142	-3.30	0.001	**
	generic me-too drugs	-0.142	-3.23	0.001	**
Patient expected source of payment (self pay)					
Private Insurance x	breakthrough drugs	0.058	0.20	0.844	
	me-too drugs	0.257	1.27	0.205	
	generic me-too drugs	0.323	1.51	0.130	
Medicare x	breakthrough drugs	0.634	1.83	0.067	
	me-too drugs	0.079	0.34	0.730	
	generic me-too drugs	0.029	0.12	0.901	
Medicaid x	breakthrough drugs	0.488	1.18	0.238	
	me-too drugs	-0.547	-1.75	0.080	
	generic me-too drugs	-0.103	-0.34	0.737	
Doctor characteristics					
Doctor specialization x	breakthrough drugs	-0.042	-0.15	0.881	
(general practice)	me-too drugs	0.140	0.71	0.476	
	generic me-too drugs	-0.106	-0.53	0.594	
Region of practice (Northeast)					
Midwest x	breakthrough drugs	0.119	0.36	0.716	

	me-too drugs	0.104	0.45	0.654	
	generic me-too drugs	0.107	0.44	0.661	
South x	breakthrough drugs	-0.034	-0.10	0.918	
	me-too drugs	0.443	2.00	0.046	*
	generic me-too drugs	0.296	1.25	0.212	
West x	breakthrough drugs	-0.650	-1.64	0.101	
	me-too drugs	-0.246	-1.02	0.310	
	generic me-too drugs	0.262	1.07	0.286	
Percentage of patient care revenue from Medicare greater than 50% x	breakthrough drugs	-0.423	-1.34	0.179	
	me-too drugs	0.150	0.76	0.447	
	generic me-too drugs	-0.120	-0.56	0.576	
Percentage of patient care revenue from Medicaid greater than 50% x	breakthrough drugs	-0.489	-0.74	0.460	
	me-too drugs	-0.349	-0.82	0.409	
	generic me-too drugs	0.609	1.54	0.125	
Percentage of patient care revenue from private insurance greater than 50% x	breakthrough drugs	0.261	0.83	0.407	
	me-too drugs	-0.099	-0.44	0.657	
	generic me-too drugs	0.085	0.37	0.713	
Percentage of patient care revenue from self-payment greater than 50% x	breakthrough drugs	0.226	0.29	0.768	
	me-too drugs	-0.159	-0.32	0.753	
	generic me-too drugs	0.007	0.01	0.988	
Dissimilarity parameters					
τ generic drug	— [b]				
τ breakthrough drugs	— [b]				
τ me-too drugs	0.284				
τ generic me-too drugs	0.216				
Summary Statistics					
No. of cases	1,242				
Log likelihood	-1664.7571				
Wald chi^2 (51)	382.08				

Prob>chi^2	0.000
LR test for IIA = χ^2 (prob.)	115.33 (0.000)

a. Reference category in parentheses

b. Degenerate nest. Parameter not defined.

*Significant at .05 level

**Significant at .01 level

***Significant at .001 level

The results of the nested logit model show that an increase in the price of the prescription drug will result in the decrease the likelihood of a drug from being prescribed. This is statistically significant at $p \leq .001$. The length of time the drug has been in the market is a significant determinant of physician prescribing behavior for cardioselective beta blockers at $p \leq .01$. An increase in the length of time in the market decreases the likelihood of a drug from being prescribed. An increase in the spending on direct-to-consumer advertising will increase the likelihood of a type of drug from being prescribed and this is significant at $p \leq .001$.

In terms of patient characteristics, older patients are more likely to be prescribed generic drugs than me-too and generic me-too drugs ($p<.05$). Females are more likely to be prescribed me-too and generic me-too drugs than generic drugs compared to males. These findings are statistically significant at $p<.05$ and $p<.001$ respectively. Non-whites are less likely to be prescribed the breakthrough drug than the generic drug compared to whites ($p<.05$). As the patient's number of medication increases, the likelihood that patient will be prescribed a me-too or generic me-too drugs than a generic drug decreases ($p<.01$). In the cardioselective beta blockers class, the patient's expected source of payment is not a significant determinant of the physician's prescribing decision.

Physicians practicing in the South are more likely to prescribe me-too drugs than generic drugs compared to physicians practicing in the Northeast (p<.05).

The dissimilarity parameters τ for generic and breakthrough drugs were undefined because they are degenerate nests. The dissimilarity parameter for me-too drugs and generic me-too drugs are 0.284 and 0.216. These values are less than 1 which implies that this model is consistent with the random utility model. The likelihood ratio test for independence of irrelevant alternatives (IIA) is significant at p <.001. The hypothesis that the IIA assumption holds can be rejected which implies that the nested logit model is more appropriate than conditional or multinomial logit model.

The results of the nested logit model without the IV for alternative-specific variables are presented for comparison to the model with IV.

Table 13. Nested Logit Model Results for Alternative-Specific Variables on Prescribing Choice of Physicians for Beta Blockers

Parameters	Coef.	z	P>|z|	
Price, *C*	-0.044	-2.27	0.023	*
Length of time ratio, *A*	-0.111	-0.52	0.606	
Direct-to-consumer advertising expenditure, *V*	0.164	3.29	0.001	**

Unlike the effect of the IV in the statin class, the inclusion of IV in the model did not change the directionality of the coefficient for beta blockers. Price has remained negative. The results on price for both models are consistent with the hypothesis that increase in price will reduce the likelihood of a drug from being prescribed. Direct-to-consumer advertising has also remained

positive and consistent with the hypothesis of this research. As explained in the previous section, the sign of the coefficient for length of time is not consistent with the hypothesis that length of time in the market increases the likelihood of a drug from being prescribed.

3.8.3 PROTON PUMP INHIBITORS

There were no generic me-too drugs at the time the NAMCS survey was conducted in 2006. Hence, there are only three nests in the first level of the nested logit model. The following table presents the non-sequential two-tiered tree structure for the nested logit model.

Figure 6. Tree Structure Specified for the Nested Logit Model for Proton Pump Inhibitors

Type	N	Alternatives	n	k
Generic drug	1,346	omeprazole	1,346	83
Breakthrough drug	1,346	Prilosec	1,346	282
Me-too drugs	6,730	Protonix	1,346	240
		Zegerid	1,346	11
		Aciphex	1,346	100
		Nexium	1,346	376
		Prevacid	1,346	254
Total			9,422	1,346

k = number of times alternative is chosen
n = number of observations at each level

Nested Logit Model Results for Prescription Drug Class Proton Pump Inhibitors

The following table summarizes the results of the nested logit regression model for the drug class proton pump inhibitors.

Table 14. Nested Logit Model with IV Results on Prescribing Choice of Physicians for Proton Pump Inhibitors

Parameters		Coef.	z	P>|z|	
Predicted price, $\hat{C}$		0.012	3.26	0.001	**
Length of time, A		0.105	0.83	0.408	
Direct-to-consumer advertising expenditure, V		0.051	3.88	0.000	***
Drug has extended/delayed release feature		2.572	4.00	0.000	***
Generic drug (base)					
Patient characteristics					
Age x	breakthrough drug	0.013	1.57	0.117	
	me-too drugs	-0.005	-0.53	0.593	
Sex x	breakthrough drug	0.237	0.94	0.349	
(male)[a]	me-too drugs	0.143	0.61	0.541	
Race x	breakthrough drug	-0.485	-1.35	0.176	
(white)	me-too drugs	-0.547	-1.68	0.093	
Ethnicity x	breakthrough drug	0.496	0.97	0.331	
(non-hispanic)	me-too drugs	0.379	0.78	0.435	
Number of medication x	breakthrough drug	-0.088	-1.58	0.114	
	me-too drugs	-0.069	-1.35	0.176	
Patient expected source of payment (self pay)					
Private Insurance x	breakthrough drug	0.183	0.57	0.567	
	me-too drugs	0.371	1.24	0.214	
Medicare x	breakthrough drug	-0.294	-0.81	0.416	
	me-too drugs	0.031	0.09	0.925	
Medicaid x	breakthrough drug	0.691	1.61	0.107	
	me-too drugs	0.430	1.04	0.298	
Doctor characteristics					
Doctor specialization x	breakthrough drug	-0.196	-0.68	0.500	
(general practice)	me-too drugs	0.069	0.26	0.797	
Region of practice (Northeast)					

Midwest x	breakthrough drug	-0.186	-0.55	0.580	
	me-too drugs	-0.180	0.57	0.566	
South x	breakthrough drug	0.463	1.30	0.195	
	me-too drugs	0.700	2.07	0.038	*
West x	breakthrough drug	0.019	0.05	0.959	
	me-too drugs	-0.349	-1.03	0.304	
Percentage of patient care revenue from Medicare greater than 50% x	breakthrough drug	0.292	0.84	0.402	
	me-too drugs	0.390	1.21	0.228	
Percentage of patient care revenue from Medicaid greater than 50% x	breakthrough drug	0.519	0.72	0.470	
	me-too drugs	0.218	0.32	0.752	
Percentage of patient care revenue from private insurance greater than 50% x	breakthrough drug	-0.610	-1.95	0.052	
	me-too drugs	-0.378	-1.36	0.175	
Percentage of patient care revenue from self-payment greater than 50% x	breakthrough drugs	0.042	0.05	0.958	
	me-too drugs	-0.133	-0.17	0.863	
Dissimilarity parameters					
τ breakthrough drug	— [b]				
τ generic drug	— [b]				
τ me-too drugs	1.032				
Summary Statistics					
No. of cases	1,346				
Log likelihood	-2275.2117				
LR test for IIA = χ^2 (prob.)	0.03 (0.986)				

a. Reference category in parentheses

b. Degenerate nest. Parameter not defined.

*Significant at .05 level

**Significant at .01 level

***Significant at .001 level

The results of the nested logit model show that price, direct-to-consumer advertising expenditure and the extended/delayed release feature of the prescription drug are all significant determinants of physician prescribing behavior. Price, direct-to-consumer advertising expenditure and extended/delayed release feature increases the likelihood of a drug to be prescribed by a physician. These variables are significant at $p<.01$, $p<.000$ and $p<.000$, respectively. The prescription drug's length of time in the market is not a significant determinant of physician prescribing behavior in the PPI class.

None of the patient characteristics are statistically significant to influence physician prescribing behavior in the proton pump inhibitors class. With respect to physician characteristics, practicing in the South increases the likelihood of a physician to prescribe me-too drugs than the generic drug in the class compared to practicing in the Northeast ($p<.05$).

The dissimilarity parameters for τ breakthrough drug and generic drug were undefined as these are degenerate nests. The dissimilarity parameter for me-too drugs is 1.032. This value is slightly higher than 1.0 which may challenge the consistency of the nested logit model with the random utility model. But like the previous results, the model is still mathematically correct and gives well behaved probabilities between 0 and 1 and that sum to 1 (Cameron & Trivedi, 2010:515). The likelihood ratio test for independence of irrelevant alternatives (IIA) is not statistically significant indicating that the null hypothesis that the IIA assumption holds. It may indicate that conditional logit or standard multinomial logit model may work in the class of PPI.

The results of the nested logit model without the IV for alternative-specific variables for the proton pump inhibitors are presented for comparison with the nested logit model with IV:

Table 15. Nested Logit Model Results for Alternative-Specific Variables on Prescribing Choice of Physicians for Proton Pump Inhibitors

Parameters	Coef.	z	P>|z|	
Price, *C*	0.009	3.30	0.001	**
Length of time, *A*	0.141	1.01	0.310	
Direct-to-consumer advertising expenditure, *V*	0.079	5.37	0.000	***
Drug has extended/delayed release feature	3.010	4.27	0.000	***

In the case of proton pump inhibitors, the effect of the inclusion of IV in the nested logit model did not result in the change of the sign of the alternative-specific coefficients. The sign of the price coefficient remained positive and is inconsistent with the hypothesis of this study. This suggests that the IV was a weak instrument for this class of prescription drugs. The signs of other variables in both models are consistent with the hypothesis that they will increase the likelihood of being prescribed.

3.8.4 SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRI)

The following figure presents the non-sequential two-tiered tree structure for SSRIs. The first level are the four nests which represent the types of prescription drugs while the second level presents the alternatives in each nest.

Figure 7. Tree Structure Specified for the Nested Logit Model of SSRI

Type	N	Alternatives	n	k
Generic drug	1,308	Fluoxetine	1,308	77
Breakthrough drug	1,308	Prozac	1,308	188
Me-too drugs	10,464	Sarafem	1,308	6
		Lexapro	1,308	333
		Paxil CR	1,308	14
		Pexeva	1,308	4
		Zoloft	1,308	319
		Paxil	1,308	168
		Celexa	1,308	123
		Prozac weekly	1,308	0
Generic me-too drugs	4,543	Sertraline	619	5
		Paroxetine	1,308	37
		Fluvoxamine	1,308	0
		Citalopram	1,308	34
Total			17,623	1,308

k = number of times alternative is chosen
n = number of observations at each level

Nested Logit Model Results for Prescription Drug Class Selective Serotonin Reuptake Inhibitors (SSRI)

Table 16. Nested Logit Model Results for Prescribing Choice of Physicians for SSRIs

Parameters		Coef.	z	P>|z|	
Predicted price, $\hat{L}$		0.044	5.05	0.000	***
Length of time ratio, A		0.393	4.79	0.000	***
Direct-to-consumer advertising expenditure, V		-0.013	-1.78	0.075	
Drug has delayed/extended release feature		-1.362	-4.46	0.000	***
Generic drug (base)					
Patient characteristics					
Age x	breakthrough drugs	-0.008	-0.99	0.321	
	me-too drugs	-0.011	-1.41	0.159	

	generic me-too drugs	-0.005	-0.49	0.622	
Sex x	breakthrough drugs	0.664	2.30	0.022	*
(male)[a]	me-too drugs	0.478	1.93	0.053	
	generic me-too drugs	-0.261	-0.80	0.421	
Race x	breakthrough drugs	0.041	0.08	0.937	
(white)	me-too drugs	0.478	1.05	0.295	
	generic me-too drugs	-0.278	-0.41	0.685	
Ethnicity x	breakthrough drugs	-1.253	-2.89	0.004	**
(non-hispanic)	me-too drugs	-0.724	-2.27	0.023	*
	generic me-too drugs	-0.475	-1.04	0.299	
Number of medication x	breakthrough drugs	0.067	1.05	0.294	
	me-too drugs	0.065	1.16	0.244	
	generic me-too drugs	0.044	0.61	0.543	
Patient expected source of payment (self pay)					
Private Insurance x	breakthrough drugs	0.423	1.19	0.235	
	me-too drugs	0.765	2.44	0.015	*
	generic me-too drugs	0.111	0.28	0.778	
Medicare x	breakthrough drugs	-0.140	-0.33	0.743	
	me-too drugs	0.382	1.04	0.300	
	generic me-too drugs	0.392	0.80	0.421	
Medicaid x	breakthrough drugs	0.541	1.27	0.203	
	me-too drugs	0.196	0.51	0.608	
	generic me-too drugs	-1.205	-2.11	0.035	*
Doctor characteristics					
Doctor specialization x	breakthrough drugs	-0.002	-0.01	0.995	
(general practice)	me-too drugs	0.278	1.04	0.298	
	generic me-too drugs	-0.319	-0.93	0.355	
Region of practice (Northeast)					
Midwest x	breakthrough drugs	-0.160	-0.44	0.661	

	me-too drugs	-0.561	-1.73	0.084	
	generic me-too drugs	-1.539	-3.31	0.001	**
South x	breakthrough drugs	1.209	2.49	0.013	*
	me-too drugs	0.994	2.18	0.029	*
	generic me-too drugs	0.497	0.94	0.345	
West x	breakthrough drugs	-0.603	-1.60	0.109	
	me-too drugs	-0.824	-2.57	0.010	*
	generic me-too drugs	-0.755	-1.83	0.067	
Percentage of patient care revenue from Medicare greater than 50% x	breakthrough drugs	-0.006	-0.01	0.989	
	me-too drugs	-0.045	-0.12	0.904	
	generic me-too drugs	-0.142	-0.30	0.764	
Percentage of patient care revenue from Medicaid greater than 50% x	breakthrough drugs	-0.760	-1.67	0.094	
	me-too drugs	-0.502	-1.33	0.182	
	generic me-too drugs	0.561	1.13	0.260	
Percentage of patient care revenue from private insurance greater than 50% x	breakthrough drugs	0.028	0.09	0.926	
	me-too drugs	-0.435	-1.63	0.104	
	generic me-too drugs	-0.766	-2.06	0.039	*
Percentage of patient care revenue from self-payment greater than 50% x	breakthrough drugs	0.546	1.05	0.295	
	me-too drugs	0.542	1.17	0.240	
	generic me-too drugs	-0.145	-0.24	0.813	
Dissimilarity parameters					
τ generic drug	— [b]				
τ breakthrough drugs	— [b]				
τ me-too drugs	0.602				
τ generic me-too drugs	0.929				
Summary Statistics					
No. of cases	1,308				
Log likelihood	-2644.0724				
Wald chi^2 (52)	698.18				

Prob>chi^2	0.000
LR test for IIA = χ^2 (prob.)	14.91 (0.001)

a. Reference category in parentheses

b. Degenerate nest. Parameter not defined.

*Significant at .05 level

**Significant at .01 level

***Significant at .001 level

Price, length of time in the market, and the delayed/extended release feature are all significant variables. An increase in the price of prescription drugs will increase the likelihood of the physician prescribing the drug (p<.001). An increase of the length of time in the market will also increase the likelihood of the drug being prescribed by the physician (p<.001). Having the delayed/extended release feature will reduce the likelihood of the physician to prescribe the drug (p<.001).

With respect to patient characteristics, physicians in the study are more likely to prescribe breakthrough drugs than generic drugs to female than male patients (p<.05). Hispanics are more likely to be prescribed generic than breakthrough or me-too drugs (p<.01, p<.05). Breakthrough and me-too drugs are both branded drugs. Physicians in this sample were more likely to prescribe me-too drugs than generic drugs to patients who are expected to pay through private insurance compared to self-pay patients (p<.05). Patients who are expected to pay through Medicaid were more likely to receive generic drugs than generic me-too drugs compared to patients who were expected to self-pay (p<.05).

Physicians practicing in the Midwest were more likely to prescribe the generic drug in the class than generic me-too drugs compared with physicians in the Northeast (p<.01). Physicians in the South were more likely to prescribe the breakthrough and me-too drugs than the generic drug compared with physicians in the Northeast (p<.05). Physicians practicing in the West are less likely to prescribe me-too drugs than the generic drug compared to physicians in the Northeast (p<.05). Physicians whose percentage of patient care revenue from private insurance is greater than 50% were more likely to prescribe the generic drug than the generic me-too drugs in the SSRI class (p<.05).

The dissimilarity parameters for τ breakthrough drug and generic drug were undefined as these are degenerate nests. The dissimilarity parameters for me-too drugs and generic me-too drugs are 0.602 and 0.929. These values are less than 1.0 which suggests that this nested logit model is consistent with the random utility model. The likelihood ratio test for independence of irrelevant alternatives (IIA) is statistically significant at (p<.01) indicating that the null hypothesis that the IIA assumption holds can be rejected. It suggests that the use of the nested logit model is appropriate.

The results of the nested logit model with the actual price variable are presented for comparison to the model with instrumental variable on price:

Table 17. Nested Logit Model Results for Alternative-Specific Variables on Prescribing Choice of Physicians for SSRIs

Parameters	Coef.	z	P>|z|	
Price, *C*	-0.001	-7.85	0.000	***
Length of time ratio, *A*	0.008	7.56	0.000	***
Direct-to-consumer advertising expenditure, *V*	0.001	-6.60	0.000	***
Drug has delayed/extended release feature	-0.034	-7.67	0.000	***

The results show that the instrumental variable reversed the sign of the price coefficient to the direction that is not consistent with the hypothesis of the study. While the nested logit model without the instrumental variable resulted in a negative coefficient indicating the negative relationship between price and choice of prescription drugs, the inclusion of the instrumental variable resulted in the positive relationship between price and choice of prescription drugs. The sign of the coefficient for direct-to-consumer advertising expenditure was also reversed to the direction that is also not consistent with the hypothesis of the study. In the nested logit model without the IV, direct-to-consumer advertising is statistically significant and increases the likelihood for a drug from being prescribed. In the model with IV, direct-to-consumer advertising expenditure negatively affects the likelihood of choosing a particular type of prescription drug. The delayed/extended release feature has remained negative in both models.

3.9 Summary of Findings

Based on the results of the nested logit models with IV for the four classes of drugs, price influences physician prescribing behavior. However, the relationship between price and physician

prescribing behavior is not consistent across the four classes of drugs. In the classes of statins and cardioselective beta blockers, an increase in price decreases the likelihood that a drug will be prescribed. Both were statistically significant at $p<.01$. In the case of SSRIs and PPIs, an increase in price will increase the likelihood that the drug will be prescribed. Both were also statistically significant at $p<.001$.

Older studies suggest that physicians are not price sensitive. Price is not part of the information provided by medical detailers. Physicians have very limited information on prices of prescription drugs and may not have any incentive to prescribe cheaper medicines (Caves et al., 1991). This study suggests otherwise. The findings suggest that physicians' may have some level of awareness on the price of prescription drugs. Some literature explains that there may be other factors that may make physicians sensitive to prices. Physicians may be sensitive to patients' financial situation (S. F. Ellison et al., 1997; Gönül et al., 2001). A recent study shows that physicians contacted by managed care drug companies or who are affiliated with Health Maintenance Organizations (HMO) have a greater awareness of relative prices of prescription drugs (S. F. Ellison et al., 1997:427). A positive relationship between price and demand for prescription drugs may be explained by the use of price as an indicator of quality (Gönül, Carter, Petrova, & Srinivasan, 2001; Olson, 1977; Valarie A. Zeithaml, 1988; V.A. Zeithaml, 1991). This study supports previous findings that price significantly influences physician prescribing behavior. The directionality of the relationship depends on the class of prescription drugs.

The regression results for the four classes of drugs show different relationships between the length of time in the market and the physician prescribing behavior. The results of statin and

SRRIs validate our hypothesis that an increase in the length of time in the market will increase the likelihood that a drug will be prescribed. In the case of beta blockers, an increase in the length of time in the market reduces the likelihood of a drug from being prescribed. For PPIs, the variable is not statistically significant. The difference in the results of the length of time variable maybe explained by the sensitivity of patients to the quality of drugs, which varies depending on the class of drugs. It should be recalled that the older drugs in the class are the breakthrough drugs and some me-too drugs. Generic drugs usually enter the market 15 to 20 years after the branded drugs were introduced in the market. The lingering perception that generic drugs are inferior than branded drugs may influence the preference for established branded drugs in the class of statin and SSRIs. The concerns with respect to the difference in the "bioavailability" of active ingredient between branded and generic drugs particularly for drugs with very narrow therapeutic band like SSRIs can also explain the preference for established drugs in the market.

The positive relationship between the drug's length of time in the market and physician prescribing behavior in the statins, and SSRIs is also consistent with the theory that physicians prescribing behavior was a result of customary prescribing or habit persistence (Caves et al., 1991). Not only is this explained by the limited information available about comparative effectiveness of drugs but because customary prescribing can be a very effective legal defense (Caves et al., 1991). Physicians might hesitate in switching treatment for subsequent prescriptions because of the risk associated with switching treatment especially if the original prescribed drug works for the patient (Gönül et al., 2001:81). Habit persistence in physicians' prescribing behavior can explain the persistent market shares of branded drugs (Coscelli, 2000:350-351).

In the case of cardioselective beta blockers, the negative correlation between length of time and physician preference supports the view that generic drugs are as riskier as brand name drugs. Furthermore, since most of these cardioselective betablockers are maintenance medication. Patients are expected to regularly take them in the long term. This has implication on costs. The generic drugs have been in the market for a fairly shorter period of time than the branded drugs. Preference to prescribe generic drugs is consistent with the previous finding that physicians favor cheaper drugs among cardioselective beta blockers.

In the case of PPIs, length of time in the market is not s significant determinant of physician prescribing behavior. Similar to price, the effect of the drug's length of time in the market on physician prescribing behavior depends on the class of drugs.

Other quality indicators of prescription drugs were included in the model. In the class of statins, indicators on the drug's ability to reduce the likelihood of heart attack, mortality or if it has the extended-release feature were included in the model but none of these variables were statistically significant. For the three other classes of drugs, the indicator on whether the drug has the extended-release or delayed-release feature was included. In the case of cardioselective beta blockers, the indicator was dropped because it was correlated with advertising. The only drug that spent on the direct-to-consumer advertising is also the only drug that has the extended-release feature. For proton-pump inhibitors, the delayed-release feature increases the likelihood that the drug will be prescribed. The positive relationship may support concerns of doctors about patient compliance to medication regimen or patient sensitivity to side effects associated with fluctuations in the concentration of drugs in the body system.

For SSRIs, the delayed-release/controlled-release feature reduces the likelihood that the drug will be prescribed (p<.01). Studies were mix on the superiority of extended release over regular drugs in the SSRI class. Drugs with extended-release feature maybe superior for patients with major depressive disorder but not for depressed patients with established medication. Like the other variables, the effect of this indicator on the prescribing behavior of physicians seems to be class specific.

The statistically significant positive relationship between direct-to-consumer advertising and physician prescribing behavior is consistent in the three classes of drugs – statin, cardioselective beta blockers and PPIs. This variable is not statistically significant in the class of SSRIs. An increase in direct-to-consumer advertising expenditure increases the likelihood that the prescription drug will be prescribed by a physician. The significance of direct-to-consumer advertising expenditure in the physician's choice of prescription drug may suggest that patients play a role in the selection of their prescription drugs. Information gathered by patients from direct-to-consumer advertising empowered patients to play a role in the selection of their medication. The significant effect of direct-to-consumer advertising in the prescribing behavior of physicians may also be explained by the correlation between higher levels of advertising and concentration of physician prescribing (Stern & Trajtenberg, 1998).

This research found some patient characteristics to be statistically significant in influencing physician prescribing behavior. In the case of statins, an increase in age increases the likelihood that a physician will prescribe a generic drug than a me-too drug (p<.05). Older persons tend to be prescribed generic drug than me-too drug. The same observation applies to cardioselective beta

blockers. An increase in age increases the likelihood that a person will be prescribed a generic drug than a me-too drug or generic me-too drugs. Both are significant at $p<.05$. This suggests that physicians are more likely to prescribe the generic drug to older patients. Age is not a statistically significant variable for SSRIs and PPIs.

Sex is also a statistically significant determinant of physician prescribing behavior in statins, cardioselective beta blockers and SSRIs. In the case of statins, females are less likely to be prescribed generic me-too drugs than the generic drug compared to males. The opposite is true with cardioselective beta blockers. Females are more likely to be prescribed me-too and generic me-too drugs than the generic drug compared to males. For SSRIs, females are more likely to be prescribed the breakthrough drug than the generic drug compared to males. The findings suggest that the sex of the patient is likely to influence physician prescribing behavior, depending on the class of drugs.

Race was also a significant determinant in the case of cardioselective beta blockers. Being non-white decreases the physician's likelihood of prescribing breakthrough drug than the generic drug compared to being white ($p\leq.05$). Race is not significant in the other classes of drugs. Ethnicity is statistically significant in the SSRIs. Hispanics are more likely to be prescribed a generic drug than breakthrough or me-too drugs compared to non-hispanics. Both the breakthrough and me-too drugs are branded drugs.

The patient's number of medication is a statistically significant determinant of physician prescribing behavior in statins and cardioselective beta blockers. In the statins class, an increase in the number of medication increases the probability of a physician prescribing me-too drugs relative

to the probability of prescribing generic drug. In the case of cardioselective beta blockers, an increase in the number of medication decreases the probability of the physician prescribing me-too and generic me-too drugs relative to the probability of prescribing generic drug. Again, the nature of the relationship depends on the class of drugs.

For SSRIs and statins, the patient's source of payment is also a statistically significant predictor of physician prescribing behavior. In the class of statins, Medicare as an expected source of payment increases the probability of a physician prescribing me-too drugs than generic drug compared to self-paying patients (p<.05). In the class of SSRIs, patients with private insurance are more likely than self-paying patients to be prescribed me-too drugs than generic drug (p<.05). In both statins and SSRIs, patients with Medicaid are more likely than self-paying patients to receive a generic drug prescription than generic me-too drugs prescription ($p \leq .05$).

This finding that some types of patients' source of payment are statistically significant in influencing physician prescribing behavior suggests moral hazard. The observation that patients with Medicare or private insurance are more likely than self-paying patients to receive a prescription of me-too drugs than generic drug and patients with Medicaid are more likely than self-paying patients to receive a prescription for generic drug than me-too drug is consistent with the theory of moral hazard and previous findings that patients with more generous insurance coverage tent to receive more expensive drugs. Howard's findings on moral hazard when he examined the antibacterial drug class using the 1994 NAMCS data showed that self-paying patients are significantly more likely than patients with Medicare or private insurance to be prescribed the generics (Howard, 1997).

There are some physician characteristics that are statistically significant in this study. These findings suggest that some physicians have the propensity to prescribe generic drugs while others tend to prescribe the breakthrough drug or me-too drugs, consistent with Hellerstein's findings (Hellerstein, 1994). In the case of statins, physicians with specialized practice are less likely than physicians with general practice to prescribe breakthrough drugs than generic drug (p<.05). This variable is not statistically significant in the other classes of drugs examined in this research.

In addition, there are regional differences in physician prescribing behavior. In the statins class, physicians who are practicing in the Midwest are less likely than physicians in the Northeast to prescribe breakthrough and me-too drugs than the generic drug (p<.05). Physicians in the West are more likely than physicians in the Northeast to prescribe generic drug than breakthrough, me-too and generic me-too drugs (p<.05). Physicians in the South are more likely than physicians in the Northeast to prescribe generic drug than me-too drugs and generic me-too drugs (p<.05). On the contrary, in the case of cardioselective beta blockers and PPIs, physicians who practice in the South are more likely than physicians in the Northeast to prescribe me-too than generic drugs (p<.05). In the case of SSRIs, physicians from the Midwest are more likely than the physicians from the Northeast to prescribe generic than generic me-too drugs (p<.01). Physicians from the South are more likely than patients in the northeast to prescribe branded drugs (breakthrough and me-too drugs) than generic drug (p<.05). Physicians from the West are more likely than physicians from the Northeast to prescribe generic drug than me-too drugs (p<.05). These may be explained by different state policies influencing physician prescribing behavior. However, because of limited

data, this study was not able to test that. Further studies can be done on regional/state level differences in prescribing patterns of physicians.

In proton pump inhibitors, physicians with greater than 50% patient care revenue from private insurance are more likely to prescribe the generic drug than the breakthrough drug compared to physicians with less than 50% patient care revenue from private insurance ($p<.05$). Similarly, in the SSRI class, physicians with greater than 50% patient care revenue from private insurance are more likely to prescribe the generic drug than generic me-too drugs compared to physicians with less than 50% patient care revenue from private insurance ($p<.05$). Further studies can be done in establishing the relationship between physician characteristics and the propensity to prescribe certain types of drugs.

3.10 CONCLUSION

This research concludes that price, direct-to–consumer adverting and certain characteristics of drugs that may indicate quality affects the likelihood of a drug to be prescribed. The effects of price, the drug's length of time in the market and the delayed/extended release feature of the drug are class specific. Sometimes, an increase in price increases the likelihood of being prescribed. In other times, it decreases. It suggests that physicians have certain level of awareness on price of drugs. An increase in drug's length of time in the market is likely to increase the prescription of the drug but in the class of proton pump inhibitors, physicians are more likely to prescribe newer drugs. In all the classes of drugs, an increase in direct-to-consumer advertising increases the likelihood that the drug will be prescribed. This supports previous findings on the

increasing role of patients in selecting their medication and the effect of advertising on the demand for prescription drugs.

Certain patient characteristics like age, sex, race, ethnicity and number of current medication influences physician prescribing behavior. The trend differs in each class. There is an indication of moral hazard when the patient's expected source of payment increases the likelihood of the patient from receiving one type of the drug over the other. More generous insurance coverage is associated with more expensive drugs.

There is also evidence that some physicians tends to prescribe one type of drug over the other. Significant physician characteristics include the region of practice, specialization and primary source of revenue. Further studies can be done to verify regional or stated differences in physician prescribing behavior taking into account the differences in state policies.

4. THE EFFECT OF THE ENTRY OF ME-TOO DRUGS ON THE DEMAND FOR GENERIC DRUGS

4.1 INTRODUCTION

The previous section presented the discrete choice analysis of physician prescribing behavior. It showed the relationship between physicians' choice of drugs and the price of drugs, direct-to-consumer advertising, drug quality, patient and physician characteristics. Most of the relationships between physician prescribing behavior and the variables examine were class specific. The results vary between classes. However, there is one relationship that is consistent in all the four classes of drugs examined in this study. Direct-to-consumer advertising increases the likelihood of a drug to be prescribed by a physician. It suggests that patients have increasing role in determining their medication. It also suggests that direct-to-consumer advertising may increase the demand for such drug. Data shows that drugs that spent heavily on direct-to-consumer marketing are me-too drugs.

In section 2, we mentioned the proliferation of me-too drugs in the pharmaceutical market. Me-too drugs are reformulated drugs which have only marginal new benefits for conditions for which treatments are already available (Shtilerman, 2006a). They are drugs that did not present significant clinical improvement and modified versions of older highly profitable drugs. Me-too drugs are further discussed in this section.

The entry of me-too drugs in the market has implications on research and development of new drugs as they tend to reduce the monopoly profit of breakthrough drugs. Me-too drugs

compete with breakthrough drugs when introduced during patent exclusivity (J. A. DiMasi, 2000; Lee, 2004; Lu & Comanor, 1998). The period of marketing exclusivity for breakthrough drugs have fallen overtime from a median of 10.2 in the 1970s to 1.2 years in the late 1990s (Joseph A. DiMasi & Paquette, 2004).

Me-too drugs also have implications on drug spending. Some me-too drugs are produced by the same company that manufactured the breakthrough drug. In some instances, they are introduced in the market when the patent of the breakthrough drug is about to end and generic versions of the breakthrough drug will soon be available in the market. It may be seen as a strategy of the pharmaceutical company to prevent patients from shifting to generic drugs, enabling the company to keep its market share and profit. However, this may result in overall increase in prescription drug spending but with little associated quality gain. The entry of new drugs in the market in the 1990s is a major driver of drug-spending growth (Danzon & Pauly, 2002). According to the Center for Medicare and Medicaid Services, spending for prescription drugs grew at an average annual rate of 14.5 percent from 1997 to 2002. About $162 billion was spent for prescription drugs in 2002. The growth of drug spending is faster than other spending on medical goods and services.

Using the regression results in the previous section, the effect of me-too drugs on the demand for the different types of prescription drugs is examined. This is done by looking at average marginal effects of price, direct-to-consumer advertising and drug's length of time in the market. The average marginal effect "measures the instantaneous rate of change" in the demand for

prescription drug with a unit change in the independent variable (price, DTC advertising and length of time in the market).

4.2 OVERVIEW: ME-TOO DRUGS

"Once the first breakthrough discovery is made of a new pharmacological activity for a new molecule, subsequent years saw the emergence of a host of new molecules or 'me-too' drugs from the same chemical class and possessing the same pharmacological profile" (Nair, 2003). Me-too drugs have similar chemical structure or mechanism of action with a drug that is already in the market which usually referred to as the breakthrough drug (Joseph A. DiMasi & Paquette, 2004). The breakthrough drug and me-too drugs are assumed to belong to the same class and may have the same therapeutic activity or class effect. Because patent is based on specific chemical structure and not on mechanism, many drugs in the market are "functionally similar"(Cook, 1998). This allowed the marketing of me-too drugs as substitute of proven drugs in the same class (Furberg & Pitt, 2001:1456-1457).

The production of me-too drugs has been part of the evolution of the pharmaceutical industry. Goozner (2010) narrated the history of me-too drugs. Immediately after Gerhard Domagk published his discovery of the anti-bacterial properties of one of his red dyes at Bayer laboratories, every drug company began creating and peddling their own version of sulfanilamide. These are the first me-too drugs (Goozner, 2004:210). The entry of other drug companies in the production of sulfanilamide resulted in intense competition driving the price of the drug to fall. Similar patterns happened in the development of the first two generation of antibiotics. The government developed the procedure to mass produce penicillin and licensed five companies to sell

the drug. These companies engaged in fierce competition. Selman Waksman discovered and patented streptomycin in the late 1940s. But since the drug was developed in a research conducted at a public university, the drug was eventually licensed broadly and sold generically even though he initially licensed the drug to Merck Research Laboratories (Goozner, 2004:211-212).

Other drug companies began scouring for new antibiotics. They patented new medicines comparable to streptomycin. The price of the new drugs soared as the pharmaceutical companies marketed them to be improved versions of the generic antibiotic predecessors, despite the fact that the new drugs were very similar in outcomes to the generic antibiotics penicillin and streptomycin (Goozner, 2004:212). The Federal Trade Commission discovered that the drug companies refused to engage in price competition and argued that competition took place in the quality of the drug – in terms of frequency of dosage and method of getting the drug into the body. This is the beginning of the me-too drugs as we know it today (Goozner, 2004:213).

In the early 1960s, a series of Congressional hearings headed by Senator Kefauver investigated the industry's penchant in spending much of its time and resources in producing me-too drugs that rarely resulted in price competition. This resulted in the 1962 amendments to the Food and Drug Act requiring drug companies to prove that their drugs were not only safe but effective. It did little though to reduce me-too drugs. From then on, the introduction of comparable or similar drugs in the market resulted in vicious marketing competition between drug companies (Goozner, 2004:214).

The Hatch-Waxman Act extended the patent of branded drugs to three years for improvements of existing products that requires additional research. This provision resulted in the

reformulations of existing products like the delayed-release and extended-release versions of already marketed drugs (Levy, 1999). The development of these drugs usually cost about one-fourth of the cost to develop new molecular entities especially if clinical trials are no longer required (Congressional Budget Office, 2006). These reformulated drugs will have longer patent life (greater than the three year extension provided by the Hatch-Waxman Act) if new patent is obtained (Reiffen & Ward, 2005a).

The early 1990s is characterized by soaring drug prices and health care cost. The industry claimed me-too drugs have fewer side effects and provide choice to some patients who responded differently to drugs (Goozner, 2004). David Kessler, then Commissioner of the FDA stated that many of the drugs approved by the FDA between 1989 and 1993 are me-too drugs. "Only a minority offered a clear clinical advantage over existing therapies" (Kessler et al., 1994). A report by the National Institute of Health Care Management also agrees to this observation. Although there was an increase in the number of drugs that entered the market in the 1990s, most of these drugs only provide modest innovation. They are also responsible for driving the increase in drug spending between 1995 and 2000 (National Institute of Health Care Management, 2002).

An update of the data from the U.S. Food and Drug Administration shows that from 1990 to 2006, 77% of the 1,135 drugs approved by the FDA are classified for standard review (CDER, 2004, 2007). Standard review is granted to drugs that "appears to have therapeutic qualities similar to those of one or more already marketed drugs" in contrast to priority review which is granted to drugs which present "significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease" (CDER, 2004). Most of the growth in new drugs seeking FDA

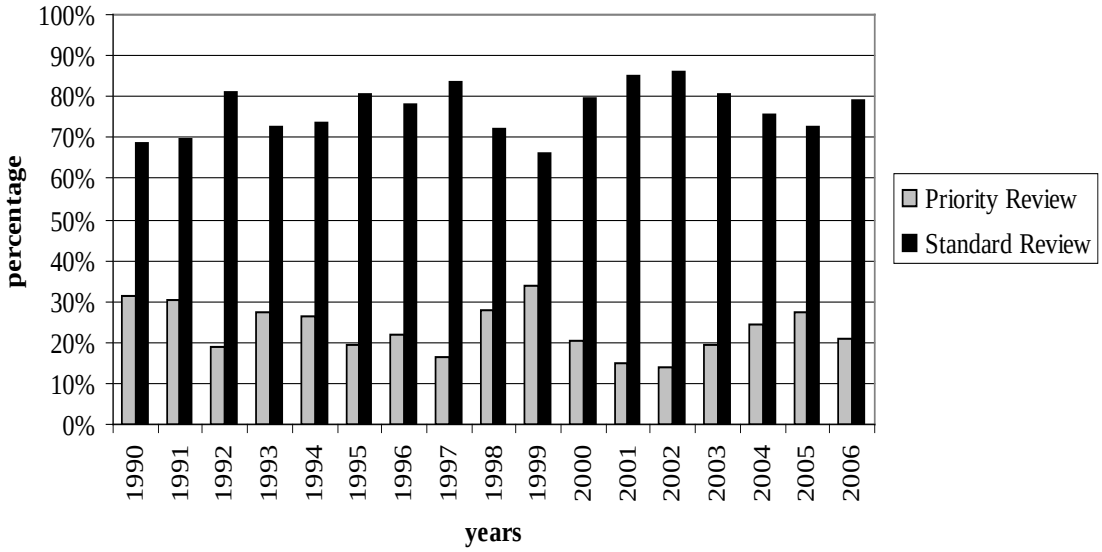
approval between 1989 to 2000 are me-too drugs (National Institute of Health Care Management, 2002).

Table 18. FDA approved new drugs 1990-2006

Calendar Year	Priority Number Approved	Standard Number Approved
1990	20	44
1991	19	44
1992	17	74
1993	19	51
1994	16	45
1995	16	67
1996	29	102
1997	20	101
1998	25	65
1999	28	55
2000	20	78
2001	10	56
2002	11	67
2003	14	58
2004	29	90
2005	22	58
2006	21	80
TOTAL	336	1135
Percentage (%)	22.84%	77.16%

Source: US Food and Drug Administration

Figure 8. New Drug Application Approved 1990-2006



The pharmaceutical industry spent billions of dollars in researching for alternatives that will bring renewed patent life to their top selling drugs whose patents are about to expire. Forty-two of the fifty-two drugs with more than $1 billion in sales in 2000 lose their patent protection in 2007. Most of these alternatives were me-too or just copy of the original drugs intended to be marketed as "new and improved medicines" (Goozner, 2004:222). Between 1996 and 2001, the pharmaceutical companies' spending on research and development increased by 40 percent, but the number of new drugs reaching the market decreased by 50 percent (Lansbury, 2003). Almost 75% (23 out of 31) of the blockbuster drugs (those with annual sales of $1 billion or more) launched between 1992 and 2001 were me-too drugs for common conditions such as allergies and inflammation (Lansbury, 2003). There is a mismatch in the amount of investments allocated in drugs that have only marginal new benefits for conditions for which treatments are already

available and chronic and emerging diseases that present substantial social burden (Croghan & Pittman, 2004; Shtilerman, 2006b). The increase in me-too drugs is expected to continue given the financial, legal, technological and regulatory environments (National Institute of Health Care Management, 2002).

This aggressive search for me-too drugs is coupled by the rapid rise of drug companies marketing expenses. The pharmaceutical companies conduct seeding trials to entice doctors to prescribe the new product, make false and misleading claims about superiority of their products and switch campaigns (Kessler et al., 1994). Between 1996 and 2000, marketing expenses rose by 71.4 percent to $15.7 billion with direct-to-consumer advertising representing the fastest growing expense (Goozner, 2004:230). Advertisements are being used to change physicians' behavior and differentiate among products that are "virtually indistinguishable" (Kessler et al., 1994). Many of these advertisements have incomplete or misleading information about their respective products in areas which the FDA has set explicit standards of quality (Wilkes, Doblin, & Shapiro, 1992).

Me-too drugs enable pharmaceutical companies to keep their business afloat until another profitable blockbuster drug is discovered (Opderbeck, 2005:519). However, competition in the same therapeutic class means competing for the same market. Pharmaceutical companies engage in intensive marketing and advertising to expand their profit. Examining the data submitted to the Securities and Exchange Commission (SEC) by nine U.S pharmaceutical companies that market the top selling 50 drugs for seniors, Families USA concluded that:

> Eight of those companies—Merck, Pfizer, Bristol-Myers Squibb, Pharmacia, Abbott Laboratories, American Home Products, Schering-Plough, and Allergan—

> spent more than twice as much on marketing, advertising, and administration as they did on R&D. The remaining company, Eli Lilly, spent more than one and one-half times as much on marketing, advertising, and administration as it did on R&D (Families USA, 2001:3)

4.3 Effects of Me-too Drugs on Price, Quality, Innovation and Choice

Experts have analyzed the impact of me-too drugs in three areas: price and quality of drugs in the same class, innovation in the pharmaceutical industry and consumer choice. Researches about price competition between me-too drugs and breakthrough drugs have mix results. In some cases, the average list price of branded drugs continues to increase faster than inflation after the introduction of me-too competitors (Cook, 1998; Lu & Comanor, 1998). Lu and Comanor (1998) observed that the rate of price increase is slower for drugs with brand name competitors and the introductory price of drugs tended to be lower when several me-too drugs are already in the market. Similar studies found that me-too drugs compete with breakthrough drugs and lower the price of drugs in the same class (Dao, 1984; J. A. DiMasi, 2000; Lee, 2004). On the other hand, an examination of a dozen of latest entrants introduced between 1995 and 1999 showed no price break for eight drugs and a price differential within 10 percent of the median price of existing drugs in the class for the remaining drugs (Goozner, 2004:232).

Doctors tend to prescribe customarily which may give breakthrough drugs some advantage over me-too drugs. Doctors have experience with it first and are usually hesitant to switch to new drugs unless they were proven more effective (Cook, 1998). However with aggressive advertising

(switch campaigns, seeding trials, etc.), physicians' incomplete information about the comparative price of prescription drugs and the notion that new drugs are better, enable pharmaceutical companies to sell and charge higher prices for me-too drugs (Kessler et al., 1994). Me-too drugs with small advantages over existing medication may have lower introductory price but once they become widely accepted, their prices rise rapidly (Cook, 1998; Lu & Comanor, 1998).

Me-too drugs tend to have a negative effect on innovation as pharmaceutical companies expend more energy in the advertising of me-too drugs and less on research and development of new drugs (Families USA, 2001; Hollis, 2005). Breakthrough drugs are estimated to have only one to six years of pure market exclusivity before a me-too drug enters the market (Cook, 1998). This reduces the incentive to engage in research as the potential return on investment is threatened by competition from me-too drugs.

Me-too drugs give patients and doctors options in finding a drug that works well for the individual patient (Blochl-Daum, 2006; Joseph A. DiMasi & Paquette, 2004; Furberg et al., 1999; M. Thomas & Mann, 1998). The availability of different drugs of similar therapeutic effects may have varied side effects and efficacy profiles to different individuals. Some me-too drugs may have lesser side effects and better treatment effect to some patients (Cook, 1998). Reformulated drugs or incrementally modified drugs can result in better health of patients due to increase adherence to treatment (Congressional Budget Office, 2006). However, there is insufficient evidence that they differ in effect (Angell, 2004; Goozner, 2004; Hollis, 2005:1991; Kessler et al., 1994).

The impact of me-too drugs on the market may not be limited to the demand for breakthrough drugs. The perceived improvement of me-too drugs from breakthrough drugs,

although untested, may further reduce the potential market share of generic drugs. The literature shows that the generic price discount has no significant effect in their market share (Hurwitz & Caves, 1988). Furthermore, there is a lingering perception that generic drugs are riskier than branded drugs (Fernandez-Carol & Kaitin, 1991; Ganther & Kreling, 2000; Scott Morton, 1999). When consumers have insufficient information on the intrinsic quality of the products and markets or when there is no great variance in the nature of the product across brand names, price is used as a measure of quality (Gönül et al., 2001; Olson, 1977; Valarie A. Zeithaml, 1988; V.A. Zeithaml, 1991). Physicians lack information on the effectiveness of and risks entailed by substitutable drugs that their choice is based strongly on customary prescribing which not only minimizes effort but also provides a legal defense (Caves et al., 1991:5 citing Temin 1980.) Physicians may also hesitate to switch treatment for subsequent prescriptions because of the risk associated with it especially if the original prescribed drug works for the patient (Gönül et al., 2001:81). Habit persistence in physicians' prescribing behavior can explain the persistent market shares of branded drugs (Coscelli, 2000:350-351). All these factors may play a role in favoring branded or me-too over generic drugs.

4.4 POST ESTIMATION ANALYSIS

The post estimation analysis using the regression results in the previous chapter are presented. The results show the effect of the changes in the significant alternative-specific predictors in the models on the demand of the other drugs in the market. The subsequent tables show the average marginal effect of changes in price,[16] length of time in the market and direct-to-

[16] "Price" refers to the average cost of a month supply of the drug.

consumer advertising[17]. The average marginal effects show the change in the estimated probabilities of the different types of drugs as predictors change.

4.7.1 POST ESTIMATION ANALYSIS FOR DRUG CLASS STATIN

Predicted Probabilities

The predicted probabilities of each type of drug were computed based on the estimated nested logit model for drug class Statin. The predicted probabilities were interpreted as the market shares of generic, breakthrough, me-too and generic me-too drugs.

Table 19: Summary of Predicted Probabilities for Statin

Classification of prescription drug	Mean	Std. Dev.
Generic drug	0.062	0.044
Breakthrough drug	0.016	0.022
Me-too drug	0.892	0.069
Generic me-too drug	0.050	0.056

The results suggest that me-too drugs have the biggest predicted share of the market at 89%. The generic drug has 6.2% predicted share, the generic me-too drug has 5% predicted share and the breakthrough drug has 1.6% predicted share of the market.

[17] "Direct-to-consumer advertising" refers to annual spending on direct-to-consumer advertising.

Marginal Effects

The average marginal effects of each of the statistically significant alternative-specific predictors (price, length of time in the market and direct-to-consumer advertising expenditure) were computed. The average marginal effects show the change in the estimated probabilities of the different types of drugs with the change in the predictors.

Table 20 shows the average marginal effects of a unit change in the price of prescription drug. A dollar increase in the price of the drug has a negative effect on the probability of the drug being prescribed and positive effect on the probabilities of the other alternatives.

Table 20. Summary of Average Marginal Effect of Change in Price for Statin

Classification of prescription drug	AME	Std. Dev.
Δ generic drug		
Generic drug	-0.001	0.000
Breakthrough drug	0.000	0.000
Me-too drug	0.001	0.000
Generic me-too drug	0.000	0.000
Δ breakthrough drug		
Generic drug	0.000	0.000
Breakthrough drug	-0.000	0.000
Me-too drug	0.000	0.000
Generic me-too drug	0.000	0.000
Δ me-too drug		
Generic drug	0.001	0.000
Breakthrough drug	0.000	0.000
Me-too drug	-0.001	0.001

Generic me-too drug	0.001	0.001
Δ generic me-too drug		
Generic drug	0.000	0.000
Breakthrough drug	0.000	0.000
Me-too drug	0.000	0.001
Generic me-too drug	-0.001	0.001

A dollar change in the price of generic drug will decrease its market share by 0.1%. This will have a minimal negative effect on the market shares of breakthrough and generic me-too drug but will increase the market share of me-too drugs by 0.1%. The effect of a dollar change in the price of me-too drug will decrease its market share by almost 0.2% and will increase of both the market shares of generic and me-too generic drugs by 0.1%.

The change in the length of time for statin has similar effect. A unit change of the length of time of the drug has been in the market will have a positive effect on the probability of the drug to be prescribed and negative effect on the probability of the other drugs to be prescribed.

Table 21.-Summary of Average Marginal Effects of Change in Length of Time for Statin

Classification of prescription drug	Mean	Std. Dev
Δ generic drug		
Generic drug	0.058	0.037
Breakthrough drug	-0.001	0.002
Me-too drug	-0.055	0.035
Generic me-too drug	-0.003	0.004
Δ breakthrough drug		
Generic drug	-0.001	0.002

Breakthrough drug	0.016	0.020
Me-too drug	-0.014	0.017
Generic me-too drug	-0.001	0.002
Δ me-too drug		
Generic drug	-0.055	0.035
Breakthrough drug	-0.014	0.017
Me-too drug	0.093	0.049
Generic me-too drug	-0.042	0.042
Δ generic me-too drug		
Generic drug	-0.002	0.003
Breakthrough drug	-0.000	0.001
Me-too drug	-0.024	0.039
Generic me-too drug	0.046	0.046

* Note that the predictor variable "length of time" is in natural log form

A 10% increase in the length of time of a generic drug will increase its market share by 0.6% and will reduce the market share of me-too drug by about 0.5%. Both breakthrough drug and generic me-too drugs predicted market share will be reduced by very small percentage. A 10% increase in the length of time in the market of the breakthrough drug will result in the increase in market share of the breakthrough drug by 0.15% and a decrease in the market share of the generic drug by 0.01%, me-too drug by .13% and generic me-too drug by 0.01%. A 10% increase in the length of time the me-too drugs are in the market will increase the market share of me-too drugs by about 0.89% and will reduce the market share of generic drugs by 0.52%, breakthrough drug by 0.13% and generic me-too drugs by 0.40%. A 10% increase of the length of time the generic me-too drug is in the market will result in an increase in its market share by 0.44% and a decrease of about 0.02% in market share of generic drugs, 0% of breakthrough drugs and 0.23% of me-too drugs.

The next table summarizes the average marginal effects of a unit change in direct-to-consumer advertising expenditure to the probabilities of the different classification of drugs for the drug class Statin. A unit increase in direct-to-consumer advertising expenditure has positive effect on the probability of that drug from being prescribed and negative effect on the probabilities of the other alternatives.

Table 22. Summary of Average Marginal Effects of Change in Direct-to-Consumer Advertising Expenditure for Statin

Classification of prescription drug	Mean	Std. Dev
Δ generic drug		
Generic drug	0.010	0.006
Breakthrough drug	-0.000	0.000
Me-too drug	-0.009	0.006
Generic me-too drug	-0.000	0.001
Δ breakthrough drug		
Generic drug	-0.000	0.000
Breakthrough drug	0.003	0.003
Me-too drug	-0.002	0.003
Generic me-too drug	-0.000	0.000
Δ me-too drugs		
Generic drug	-0.009	0.006
Breakthrough drug	-0.002	0.003
Me-too drug	0.016	0.008
Generic me-too drug	-0.007	0.007
Δ generic me-too drugs		
Generic drug	-0.000	0.000
Breakthrough drug	-0.000	0.000
Me-too drug	-0.004	0.007

Generic me-too drug	0.008	0.008

* Note that the predictor variable "direct-to-consumer advertising" is in natural log form

A 10% increase in direct-to-consumer advertising expenditure increases the predicted market share of generic drug by 0.10% and decreases the market share of me-too drugs by 0.10%. A 10% increase in the direct-to-consumer advertising of breakthrough drug increases market share of breakthrough drug by 0.03% and decreases the market share of me-too drugs by 0.02%. A 10% increase in me-too drug's direct-to-consumer advertising results in an increase in me-too drug's market share by 0.15% and a decrease in the market shares of generic drug by 0.09%, breakthrough drug by 0.02% and the generic me-too drug by 0.07%. A 10% increase in the direct-to-consumer marketing expenditure of generic me-too drug increases the predicted market share of generic me-too drug by 0.08% and decreases the market share of me-too drug by 0.04%.

4.7.2 POST ESTIMATION ANALYSIS FOR DRUG CLASS BETA BLOCKERS

Predicted Probabilities

The estimated nested logit model for the drug class beta blockers was used to estimate the probabilities of generic, breakthrough, me-too and generic me-too drugs. The probabilities are interpreted as the predicted market shares of the drugs.

Table 23. Summary of Predicted Probabilities for Beta Blockers

Classification of prescription drug	Mean	Std. Dev.
Generic drug	0.179	0.071

Breakthrough drug	0.078	0.048
Me-too drug	0.423	0.108
Generic me-too drug	0.321	0.112

The results show that me-too drugs have a predicted market share of 42.3%. The generic drug has a predicted market share of 17.9%. The breakthrough drug has a predicted market share of 7.8% and the generic me-too drugs have a predicted market share of 32.1%.

Marginal Effects

The average marginal effects of changes in price and direct-to-consumer advertising expenditure were computed. The length of time the drug has been in the market is not a significant predictor variable in the model. Table 20 shows the average marginal effect of a unit change in the price on the market share of the drugs. An increase in price decreases the predicted market share of the drug and increases the predicted market shares of the alternative drugs in the drug class Beta Blockers.

Table 24. Summary of Average Marginal Effects (AME)of Change in Price for Beta Blockers

Classification of prescription drug	Mean	Std. Dev.
Δ generic drug		
Generic drug	-0.047	0.014
Breakthrough drug	0.005	0.004
Me-too drug	0.024	0.009
Generic me-too drug	0.018	0.008
Δ breakthrough drug		
Generic drug	0.005	0.004

Breakthrough drug	-0.023	0.012
Me-too drug	0.011	0.006
Generic me-too drug	0.008	0.004
Δ me-too drugs		
Generic drug	0.024	0.009
Breakthrough drug	0.011	0.006
Me-too drug	-0.078	0.009
Generic me-too drug	0.043	0.012
Δ generic me-too drugs		
Generic drug	0.018	0.008
Breakthrough drug	0.008	0.004
Me-too drug	0.043	0.012
Generic me-too drug	-0.069	0.011

A dollar increase in the price of the generic drug decreases the predicted market share of the generic drug by 4.7%. The biggest gainer in an increase in price of the generic drug is the me-too drug with an increase in predicted market share of 2.4%. This also increases the predicted market shares of breakthrough drug by 0.5%and generic me-too drugs by 1.8%. A dollar increase in the price of breakthrough drug decreases the predicted market share of the breakthrough drug by 2.3%. This increases the predicted market share of me-too drug by 1.1%, the generic drug by 0.5% and generic me-too drugs by 0.8%. A similar increase in the price of me-too drugs results in the decrease of me-too drug's predicted market share by 7.8%. This increases the generic drug market share by 2.4%, breakthrough drug by 1.1% and generic me-too drug by 4.3%. A dollar increase in the price of generic me-too drugs will decrease its market share by 6.9%. This will

increase the market share of the generic drug by 1.8%, the breakthrough drug by 0.8% and the me-too drug by 4.3%.

The succeeding table shows the average marginal effect of a unit change in the length of time the drug has been in the market on the predicted market shares of the respective drugs. A unit increase in the length of time a particular drug has been in the market will have a negative effect on the predicted market share of that drug and positive effects on the predicted market shares of the other drugs in the beta blockers class of drugs.

Table 25. Summary of Average Marginal Effects of Change in Length of Time for Beta Blockers

Classification of prescription drug	Mean	Std. Dev.
Δ generic drug		
Generic drug	-0.067	0.020
Breakthrough drug	0.007	0.006
Me-too drug	0.034	0.012
Generic me-too drug	0.026	0.011
Δ breakthrough drug		
Generic drug	0.007	0.006
Breakthrough drug	-0.033	0.018
Me-too drug	0.015	0.008
Generic me-too drug	0.011	0.006
Δ me-too drug		
Generic drug	0.034	0.012
Breakthrough drug	0.015	0.008
Me-too drug	-0.110	0.012
Generic me-too drug	0.061	0.016
Δ generic me-too drug		
Generic drug	0.026	0.011

Breakthrough drug	0.011	0.006
Me-too drug	0.061	0.016
Generic me-too drug	-0.097	0.015

* Note that the predictor variable "length of time in the market" is in natural log form

A 10% increase in the length of time the generic drug has been in the market will decrease its predicted market share by 0.64%. It will increase the predicted market shares of breakthrough drugs by 0.07%, me-too drugs by 0.32% and the me-too drug market share by 0.25%. A 10% increase in the length of time the breakthrough drug has been in the market will reduce its predicted market share by 0.31% and will increase the predicted market share of generic drug by 0.07%, the predicted me-too drug market share by 0.14% and the predicted generic me-too drug market share by 0.10%. A 10% increase in the length of time the me-too drug has been in the market will reduce its predicted market share by 1.05% and will increase the predicted market shares of generic drug by 0.32%, breakthrough drug by 0.14% and the generic me-too drug by 0.58%. A 10% increase in the length of time the generic me-too drug has been in the market will reduce the generic me-too drug market share by 0.92% and will increase the predicted market share of generic drug by 0.25%, the breakthrough drug by 0.10% and the me-too drug market share by 0.58%.

The next table summarizes the average marginal effects of the change in direct-to-consumer advertising expenditure of prescription drugs in the class of beta blockers. A unit change in direct-to-consumer advertising expenditure of a respective drug will have a positive effect on its predicted market share and a negative effect on the predicted market shares of other drugs. Table 22 summarizes the results.

Table 26. Summary of the Average Marginal Effects of Change in Direct-to-Consumer Advertising Expenditure for Beta Blockers

Classification of prescription drug	Mean	Std. Dev.
Δ generic drug		
Generic drug	0.019	0.006
Breakthrough drug	-0.002	0.002
Me-too drug	-0.010	0.004
Generic me-too drug	-0.007	0.003
Δ breakthrough drug		
Generic drug	-0.002	0.002
Breakthrough drug	0.010	0.005
Me-too drug	-0.004	0.002
Generic me-too drug	-0.003	0.002
Δ me-too drugs		
Generic drug	-0.010	0.004
Breakthrough drug	-0.004	0.002
Me-too drug	0.032	0.004
Generic me-too drug	-0.018	0.005
Δ generic me-too drugs		
Generic drug	-0.007	0.003
Breakthrough drug	-0.003	0.002
Me-too drug	-0.018	0.005
Generic me-too drug	0.028	0.004

* Note that the predictor variable "direct-to-consumer advertising" is in natural log form

A 10% increase in direct-to-consumer advertising expenditure of the generic drug will result in a 0.18% increase in its predicted market share. This will also result in a slight decrease in market shares of breakthrough drug by 0.02% and the me-too drug by 0.1% and the generic me-too drug by 0.07%. A 10% increase in direct-to-consumer advertising expenditure of breakthrough

drug will increase the predicted market share of the breakthrough drug by 0.10% and will decrease the predicted market shares of generic drug by 0.20%, me-too drug by 0.04% and generic me-too drug by 0.03%. A 10% increase in direct-to-consumer advertising expenditure of me-too drugs increases the market share of me-too drugs by 0.30% and decreases the market shares of generic drug by 0.1%, breakthrough drug by 0.04% and generic me-too drugs by 0.17%. Finally, a 10% increase in direct-to-consumer advertising expenditure of generic me-too drugs increases the predicted market share of generic me-too drugs by 0.27% and decreases the predicted market share of generic drug by 0.07%, breakthrough drug by 0.03% and me-too drug by 0.17%.

4.7.3 Post Estimation Analysis for Drug Class Proton Pump Inhibitors

Predicted Probabilities

The estimated nested logit model for the drug class proton pump inhibitors was used to estimate the probabilities for generic, breakthrough and me-too drugs. There are no generic me-too drugs in this class when the NAMCS survey was conducted in 2006. The estimated probabilities are interpreted as the predicted market shares of the drugs.

Table 27. Summary of Predicted Probabilities for Proton Pump Inhibitors

Classification of prescription drug	Mean	Std. Dev
Generic drug	0.063	0.032
Breakthrough drug	0.208	0.063
Me-too drug	0.729	0.073

The predicted probabilities show that me-too drugs have the largest predicted market share for proton pump inhibitors at 72.9%. This is followed by the breakthrough drug with a predicted market share of 20.8% and the generic drug with the predicted market share of 6.3%.

Marginal Effects

The average marginal effects of price and direct-to-consumer advertising expenditure are presented in the succeeding tables. The results show the change in the predicted probabilities of the different types of drugs with a unit change in the predictor.

The following table shows the average marginal effect of a dollar change in the price of prescription drugs. A dollar increase in the price of prescription drug increases the predicted market share of the drug and decreases the predicted market shares of the alternative drugs.

Table 28. Summary of the Average Marginal Effects of Change in Price for Proton Pump Inhibitors

Classification of prescription drug	Mean	Std. Dev
Δ generic drug		
Generic drug	0.001	0.000
Breakthrough drug	-0.000	0.000
Me-too drug	-0.001	0.000
Δ breakthrough drug		
Generic drug	-0.000	0.000
Breakthrough drug	0.002	0.000
Me-too drug	-0.002	0.000
Δ me-too drugs		
Generic drug	-0.001	0.000

Breakthrough drug	-0.002	0.000
Me-too drug	0.002	0.000

A dollar increase in price of generic drug increases the predicted market share for the generic drug by 0.1% and slightly decreases the predicted market share for the breakthrough drug and me-too drug by 0.1%. A dollar increase in the price of breakthrough drug results in an increase in the predicted market share of breakthrough drug by 0.2%. The predicted market share of me-too drug will decrease by 0.2%. A dollar increase in the price of me-too drugs will increase the predicted market share of me-too drugs by 0.2% and decrease the predicted market share of the breakthrough drug by 0.2%.

Table 25 shows the average marginal effect of a unit change in direct-to-consumer advertising expenditure. A unit increase in direct-to-consumer advertising expenditure will have a positive effect on the predicted market share of that drug and a negative effect on the predicted shares of the alternative drugs in the PPI market.

Table 29. Summary of Average Marginal Effects of Change in Direct-to-Consumer Advertising Expenditure for Proton Pump Inhibitors

Classification of prescription drug	Mean	Std. Dev
Δ generic drug		
Generic drug	0.003	0.001
Breakthrough drug	-0.001	0.000
Me-too drug	-0.002	0.001
Δ breakthrough drug		
Generic drug	-0.001	0.000

Breakthrough drug	0.008	0.002
Me-too drug	-0.007	0.002
Δ me-too drugs		
Generic drug	-0.002	0.001
Breakthrough drug	-0.008	0.002
Me-too drug	0.010	0.002

* Note that the predictor variable "length of time in the market" is in natural log form

A 10% increase in the direct-to-consumer advertising expenditure of the generic drug increases the predicted market share of that drug by 0.03%. This decreases the predicted market shares of breakthrough drug by 0.01% and the me-too drugs by 0.02%. A 10% increase in the direct-to-consumer advertising expenditure of the breakthrough drug increases its predicted market share by 0.08% and decreases the predicted market shares of generic drug by 0.01% and the me-too drug by 0.07%. Increasing the direct-to-consumer advertising expenditure of me-too drugs by 10% increases the predicted market share of me-too drugs by 0.10% and decreases the predicted market shares of generic drug by 0.02% and breakthrough drug by 0.08%.

4.7.4 POST ESTIMATION ANALYSIS FOR DRUG CLASS SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Predicted Probabilities

The estimated nested logit model for the drug class SSRI was used to estimate the probabilities for generic, breakthrough, me-too and generic me-too drugs. The estimated probabilities are interpreted as the predicted market shares of the drugs.

Table 30. Summary of Predicted Probabilities for SSRIs

Classification of prescription drug	Mean	Std. Dev
Generic drug	0.062	0.049
Breakthrough drug	0.137	0.051
Me-too drug	0.736	0.079
Generic me-too drug	0.066	0.054

The predicted probabilities show that me-too drugs have the largest predicted market share for SSRI at 73.6%. The breakthrough drug has a predicted market share of 13.7%. The generic drug's predicted market share is 6.2% while the predicted market share of generic me-too drugs is 6.6%.

Marginal Effects

The average marginal effects of price and length of time in the market are presented in tables 31 & 32. Direct-to-consumer advertising expenditure is not a significant predictor of physician prescribing behavior in the PPI class. The results show the change in the predicted probabilities of the different types of drugs with a unit change in the predictor. The following table shows the marginal effect at mean of a unit change in the price of prescription drugs. A dollar increase in the price of prescription drug increases the predicted market share of the drug and decreases the predicted market shares of the alternative drugs.

Table 31. Summary of the Average Marginal Effects of Change in Price for SSRIs

Classification of prescription drug	Mean	Std. Dev

Δ generic drug		
Generic drug	0.002	0.002
Breakthrough drug	-0.000	0.000
Me-too drug	-0.002	0.001
Generic me-too drug	-0.000	0.000
Δ breakthrough drug		
Generic drug	-0.000	0.000
Breakthrough drug	0.005	0.002
Me-too drug	-0.004	0.002
Generic me-too drug	-0.000	0.000
Δ me-too drugs		
Generic drug	-0.002	0.001
Breakthrough drug	-0.004	0.002
Me-too drug	0.008	0.002
Generic me-too drug	-0.002	0.001
Δ generic me-too drugs		
Generic drug	-0.000	0.000
Breakthrough drug	-0.000	0.000
Me-too drug	-0.002	0.001
Generic me-too drug	0.003	0.002

A dollar increase in the price of generic drug will increase its predicted market share by 0.2%. This will result in the corresponding decrease in the market share of me-too drugs by 0.2%. A unit increase in the price of breakthrough drug will result in the increase in its predicted market share by 0.5% and a decrease in the predicted market share of me-too drugs by 0.4%. A dollar increase in the price of me-too drugs will result in the increase of its predicted market share by 0.8% and a decrease in the predicted market shares of generic drug by 0.2%, breakthrough drug by

0.4% and generic me-too drugs by 0.2%. A dollar increase in the price of generic me-too drugs will result in the increase of its predicted market share by 0.3% and a decrease in the predicted market share of me-too drugs by 0.2%.

Table 32 shows the average marginal effect of a unit change in the length of time the drug was in the market. A unit change on a drug's length of time in the market has a positive effect on the predicted market share of that drug and negative effect on the predicted market shares of the alternative drugs in the market.

Table 32. Summary of the Average Marginal Effects of Change in Length of Time in the Market for SSRIs

Classification of prescription drug	Mean	Std. Dev.
Δ generic drug		
Generic drug	0.022	0.015
Breakthrough drug	-0.003	0.003
Me-too drug	-0.017	0.011
Generic me-too drug	-0.002	0.003
Δ breakthrough drug		
Generic drug	-0.003	0.003
Breakthrough drug	0.045	0.014
Me-too drug	-0.039	0.013
Generic me-too drug	-0.003	0.002
Δ me-too drugs		
Generic drug	-0.017	0.011
Breakthrough drug	-0.039	0.013
Me-too drug	0.074	0.013
Generic me-too drug	-0.018	0.013
Δ generic me-too drugs		

Generic drug	-0.002	0.003
Breakthrough drug	-0.003	0.002
Me-too drug	-0.018	0.013
Generic me-too drug	0.023	0.016

* Note that the predictor variable "length of time in the market" is in natural log form

A 10% increase in the length of time in the market of the generic drug will increase its predicted market share by 0.21% and will decrease the predicted market shares of breakthrough drug by 0.03%, me-too drugs by 0.16% and generic me-too drug by 0.02%. A 10% increase in the length of time in the market of the breakthrough drug will increase its predicted market share by 0.43% and will decrease the predicted market shares of generic drug by 0.03%, me-too drug by 0.37% and generic me-too drug by 0.03%. A 10% increase in the length of time in the market of the me-too drug will increase its predicted market share by 0.71% and will decrease the predicted market shares of generic drug by 0.16%, breakthrough drug by 0.37% and generic me-too drug by 0.17%. A 10% increase in the length of time in the market of generic me-too drug will increase its market share by 0.22% and will reduce the predicted market share of me-too drug by 0.17%, breakthrough drug by 0.03% and generic drug by 0.02%.

4.5 ANALYSIS

Me-too drugs have the largest predicted market shares in the four classes of drugs. The market share of me-too drugs is biggest in the statin class, with 89% of the market. This is followed by the predicted market share of me-too drugs in the SSRIs with 74% share. Me-too drugs are predicted to have a market share of 73% in the class of proton pump inhibitors. For the beta blockers, the market share of me-too drugs is 42%.

The breakthrough drug has the lowest market share in statin (2%) and beta blockers (8%). In the case of proton pump inhibitors, the breakthrough drug has a higher market share than the generic drug, 21% compared to 6%. Branded drugs (me-too and breakthrough drug) has around 90% of the predicted market share of proton pump inhibitors. The generic drug has a slightly higher market share than the generic me-too drugs in the statin class, 6% compared to 5%. But they have a much lower market share than the generic me-too drugs in the beta blockers class, 18% compared to 32%. Non-branded drugs (generic and generic me-too drugs) have the largest combined predicted market share in the beta blockers (50%). The predicted market shares of generic drug and generic me-too drug in SSRIs is 6% and 7% respectively. Breakthrough drug has predicted market share of 14%.

The effect of price is the same for statin and beta blockers. An increase in price decreases the market share of the drug and increases the market shares of the alternative drugs in these two classes of drugs. For statins, a dollar increase in the price of generic drug will decrease its predicted market share by 0.1% and will increase the predicted market share of me-too drugs by the same amount and vice versa. In the beta blockers, a dollar increase in the price of generic drug will reduce its market share by 4.7% and will increase the predicted market share of me-too drugs by 2.4%, the breakthrough drug by 0.5% and the generic me-too drugs by 1.8%. A dollar increase in the price of me-too drug will decrease its market share by 7.8%. The biggest gainer in the increase in price of beta blockers are the generic me-too drugs with an increase of predicted market share by 4.3% followed by the generic drugs by 2.4% and breakthrough drug by 1.1%.s

For SSRIs and PPIs, the increase in the price of drug will have a positive effect on the predicted market share of that drug. For SSRIs, a dollar increase in the price of generic drug will result in the increase in its predicted market share by 0.2%. This will result in the decrease in the market shares of me-too drug by 0.2%. A similar increase in the price of breakthrough drugs will cause the predicted market share of breakthrough drug to increase by 0.5% and for the predicted market share of me-too drugs by 0.4%. An increase in the price of me-too drugs will cause its predicted market share to increase by 0.8% and for the breakthrough drug to decrease by 0.4%, the generic and generic me-too drugs by 0.2% each. In the case of PPIs, a dollar increase in the price of generic drug will increase the predicted share of generic drug and decrease the share of me-too drugs by 0.1%. An increase in the price of breakthrough drug will affect the market share of me-too drugs more than the generic drug and vice versa.

The length of time the drug has been in the market is not a significant determinant of demand for PPIs. The length of time the drug has been in the market has positive effects on the market share of drugs in statin and SSRI classes. The longer the drug has been in the market, the larger its predicted market share is. However, the opposite is the effect of length of time in beta blockers. The longer the drug is in the market, the less its market share is. In the statins, a 10% increase in the length of time in the market for generic drugs will result in the increase in its predicted market share by about 0.6%. This will reduce the market share of me-too drugs by 0.5%. Similarly, an increase in the length of time in the market of breakthrough and generic me-too drugs will negatively affect the market share of me-too drugs more than the generic drugs. An increase in the me-too drugs length of time in the market will negatively affect the market share of generic drug and generic me-too drugs more than the breakthrough drug predicted market share. Similar

observations can be made in the case of SSRIs except that the increase in the length of time in the market of me-too will negatively affect the predicted market share of breakthrough drugs more than the generic and generic me-too drugs.

In the case of beta blockers, an increase in the length of time in the market for generic drugs will reduce its market share and will increase the market share of the other types of drugs. Me-too drugs get the biggest increase in market share with the increase in length of time of generic, breakthrough and generic me-too drugs. An increase in me-too drugs length of time in the market reduces its market share and increases the market share of generic me-too drugs more than the increase in the market share of generic and breakthrough drugs.

Direct-to-consumer advertising is a significant determinant of predicted market share in drug classes statin, beta blockers and PPIs. It has positive effect on the predicted market share of the advertised drug and negative effect on the probabilities of the other alternatives. Increasing the direct-to-consumer advertising of generic drug will increase its market share and reduce the market shares of the other drugs. In the case of statin, a 10% increase in direct-to-consumer advertising of generic drug, breakthrough drug or the generic me-too drugs will increase its share and will reduce the market share of me-too drug by almost same amount as the increase in share of the respective drug. If me-too drug increases its direct-to-consumer advertising by 10%, its market share will increase by 0.15%. The increase in the market share of me-too drugs will have greater negative effects on the market shares of generic and generic me-too drugs than the market share of breakthrough drug.

In the case of beta blockers, a 10% increase in the direct-to-consumer advertising expenditure of generic drug will increase its predicted market share and will reduce the predicted market share of me-too drugs more than breakthrough drugs and generic me-too drugs. Same observation can be seen when breakthrough and generic me-too drugs' direct-to-consumer advertising expenditure increases. Me-too drugs' market share is most negatively affected by the increase in advertising expenditure of the other types of drugs. If me-too drugs' direct-to-consumer advertising expenditure increases, generic me-too drugs loose more than generic and breakthrough drugs in terms of predicted market share.

Similar observations can be made with the PPI class where an increase in direct-to-consumer advertising expenditure of generic or breakthrough drug will have the most negative impact on the market share of me-too drugs. An increase in the direct-to consumer marketing of me-too drugs will increase its market share and will reduce the predicted market share of breakthrough drugs more than the decrease in market share of generic drug.

4.6 CONCLUSION

This study showed how changes in in price, length of time in the market and direct-to-consumer advertising expenditure will affect the predicted market share of the different types of drugs in the market. The effects of price and length of time in the market on predicted market shares are mixed. They depend on the drug class. However, the effect of an increase in direct-to-consumer advertising expenditure is consistent across classes. It increases the market share of the advertised drug and decreases the market shares of the other drugs. This suggests that direct-to-consumer advertising can have combative effect in the pharmaceutical industry, shifting consumer

preference to the advertised products. This should be tested further, controlling for the overall industry demand.

Among these types of drugs, me-too drugs frequently engage and invest huge amount of money on direct-to-consumer advertising. In the drug classes' statins and beta blockers, an increase in direct-to-consumer advertising expenditure of me-too drugs negatively affects the predicted market shares of generic drugs (both the generic and generic me-too drugs combined) more than the breakthrough drug. In PPIs, increase in direct-to-consumer advertising of me-too drugs negatively affects the predicted market share of the breakthrough drug more than the generic drug. This section showed that the spending of me-too drugs on direct-to-consumer advertising greatly contributes in the increase in its market share. In most cases, the increase in market share of me-too drugs because of direct-to-consumer advertising negatively affects the market share of generic drugs. The effects of the changes in direct-to-consumer advertising of me-too drugs on the market share of breakthrough drugs and generic drugs support previous findings that the entry of me-too drugs in the market reduces the incentives to conduct research of new drugs as it reduces the market exclusivity of breakthrough drugs. Me-too drugs also increase drug spending. An increase in the direct-to-consumer advertising expenditure of me-too drugs reduces the market share of generic drugs, which usually are the cheaper drugs in the market.

5. LIMITATIONS OF THE STUDY

The results of this research are based on the regression results of two-tiered non-sequential nested logit models of four different classes of prescription drugs. These four classes of prescription drugs are among the most prescribed drugs in the United States. This, however, does not address the limitation that the results of this research is not generalizable and may not apply to the wide spectrum of classes of prescription drugs. The effect of other variables are class specific except for direct-to-consumer advertising which has consistent effect on physician prescribing behavior across the four classes of drugs.

Although the results of the models show very significant effect of direct-to-consumer advertising on prescribing behavior of physicians, this may not be attributed to the effect of this variable alone. Because of limitations to access data on pharmaceutical marketing, the study was not able to control for other advertising variables like physician detailing and journal advertising, forms of marketing that is more directed to physicians. Incorporating physician-directed marketing may reduce the effect of direct-to-consumer advertising. On the other hand, the literature shows growing positive perception of physicians to direct-to-consumer advertising (Huh & Langteau, 2007). It is the fastest growing marketing expenditure of the pharmaceutical industry and comprises more than 30% of the total pharmaceutical marketing expenditure (National Institute of Health Care Management, 2001). This emphasizes the growing importance of direct-to-consumer advertising in affecting the demand for pharmaceutical drugs.

This study estimated the demand for prescription drugs using physician's choice of medication for their patient. The final determination of what the patient will get as a medication, however, happens in the pharmacy where pharmacists are required by law in some states to substitute generic drugs to branded prescription drugs. The result of this study may not reflect the actual demand for prescription drugs. It is, however, important to look at physician's choice of drugs because ultimately the physicians' opinions are still the most important in determining the best medication for the patients and the ones held accountable for their patient's health.

Because of privacy laws, the publicly available NAMCS data does not include physician patient identifiers like the state where the physician was practicing. It will be to the advantage of this study to examine the effect of substitution policies and other state policies that may affect physician prescribing behavior but unfortunately the data are not available.

While the study was able to address the endogeneity of price by using an instrumental variable, the study did not use an instrumental variable for direct-to-consumer advertising which may result in underestimation and bias.

Nevertheless, despite these limitations, the study has very significant findings with regard to the significant positive effect of direct-to-consumer advertising to physician prescribing behavior. This may suggest the growing role of patients in selecting their medication. It also validates previous findings that direct-to-consumer advertising increases the demand for the advertised product. The direction of the effects of the other variables were class specific but we can conclude that patient characteristics influence physician prescribing behavior, moral hazard exists in the selection of prescription drugs, physician prescribing behavior vary according to the location

where they practice and their specialization. The market share of generic drugs is not as sensitive to changes in prices and direct-to-consumer advertising expenditure compared with the market share of me-too drugs. In most cases, increase in direct-to-consumer advertising of me-too drugs negatively affects the market share of generic drugs. These findings warrant further studies.

6. CONCLUSION

This research set out to determine the factors that influence physician's choice of prescription drugs. Is it the individual characteristics of patients that increase the likelihood that he or she will be prescribed a me-too, generic, generic me-too or breakthrough drug? Is it the physician's individual characteristics that play more significant roles in the physician's choice of medication to his or her patients? Do drug characteristics like price, quality and direct-to-consumer advertising expenditure influence physician prescribing behavior?

This research found certain patient characteristics like age, sex, race, ethnicity and number of current medication influence physician prescribing behavior. The effects and significance of the different variables differ in each drug class. These findings suggest that physicians consider some patient characteristics in prescribing medication.

There is also evidence that some physicians tend to prescribe one type of drug over the other. Significant physician characteristics include the region of practice, specialization and their primary source of revenue. Again, the results depend on the class of drugs. Further studies should be done to examine the relationship between state policies and physician prescribing behavior.

The study also found an indication of moral hazard. The patient's expected source of payment increases the likelihood of the patient from receiving one type of the drug over the other. In case of statin, patients with Medicare are more likely to be prescribed me-too drugs than generic drugs and patients with Medicaid are more likely to be prescribed the generic drug than the generic me-too drugs compared with self-paying patients. In SSRIs, patients with private insurance are

more likely than self-paying patients to be prescribed me-too drugs than generic drugs. Patients with Medicaid are more likely than self-paying patients to be prescribed the generic drug than the generic me-too drugs compared to self-paying patients. This is consistent with previous findings that patients with generous insurance tend to receive more expensive medication.

With respect to drug characteristics, price, direct-to–consumer adverting and certain characteristics of drugs that may indicate quality affects the likelihood of a drug to be prescribed. The effects of price, the drug's length of time in the market and the delayed/extended release feature of the drug are class specific. Sometimes, an increase in price increases the likelihood of a drug from being prescribed. In other times, it decreases. It suggests that physicians have certain level of awareness on price of drugs. An increase in drug's length of time in the market is likely to increase the prescription of the drug but in the class of proton pump inhibitors, physicians are more likely to prescribe newer drugs.

This study also set out to find out the relationship between physician prescribing behavior and direct-to-consumer advertising. The study found that direct-to-consumer advertising significantly affect physician prescribing behavior. The nature of the effect of direct-to consumer advertising on the prescribing behavior of physicians is consistent across the four classes of drugs. Direct-to-consumer advertising increases the likelihood that the drug will be prescribed. This result supports previous findings on the increasing role of patients in selecting their medication as reflected by the positive effect of direct-to-consumer advertising on physician prescribing behavior and the positive effect of advertising on the demand for prescription drugs.

Another question that this research tried to answer is the effect of direct-to-consumer advertising of me-too drugs on the market share of generic drugs and breakthrough drugs. This study explored how changes in in price, length of time in the market and direct-to-consumer advertising expenditure affect the predicted market share of the different types of drugs in the market. The effects of price and length of time in the market on predicted market shares are mixed. They depend on the drug class. However, the effect of an increase in direct-to-consumer advertising expenditure on predicted market shares of prescription drugs is consistent across classes. It increases the market share of the advertised drug and decreases the market shares of the other drugs.

Me-too drugs are the most advertised drugs in the market. In the drug classes' statins and beta blockers, an increase in direct-to-consumer advertising expenditure of me-too drugs negatively affects the predicted market shares of generic drugs (both the generic and generic me-too drugs combined) more than the breakthrough drug. In PPIs, increase in direct-to-consumer advertising of me-too drugs negatively affects the predicted market share of the breakthrough drug more than the generic drug. Spending of me-too drugs on direct-to-consumer advertising greatly increases its market share. This increase in market share of me-too drugs because of direct-to-consumer advertising negatively affects the market share of generic drugs.

The findings on the effect of direct-to-consumer advertising expenditure of me-too drugs on the market share of generic drugs and breakthrough drugs give empirical support to the proposed policy of approving new drugs on the basis of their efficacy against existing drugs in the market. They validate previous findings that entry of me-too drugs in the market will have negative effect

on research and will increase drug spending because of its negative effect on market share of breakthrough and generic drugs. Me-too drugs compete with breakthrough drugs when introduced during patent exclusivity (J. A. DiMasi, 2000; Lee, 2004; Lu & Comanor, 1998). With direct-to-consumer advertising, the findings of this study suggest that the me-too drugs may reduce the market share of breakthrough drugs. This has negative implications on research and development of new drugs as the monopoly profit which serves as incentives for research and development is reduced.

This study also suggests that direct-to-consumer advertising of me-too drugs will increase its market share and reduce the market share of generic drugs. This implies an increase on prescription drug spending with little associated quality gain. With this, the current government policy regarding the approval of prescription drugs on the basis of its efficacy against a placebo should be amended. It is important that the efficacy of new drugs be tested against the existing drugs in the market to make sure that patients are getting the worth of every additional dollar spent on medications. Pharmaceutical advertising is the primary instrument in informing patients about drugs. Comparing the efficacy of new drugs versus old drugs and branded drug versus generic drugs and their relative cost-effectiveness are important information that should be highlighted in advertising. This information will make direct-to-consumer advertising an important and useful instrument in helping physicians and patients make the right choice of medication.

Before setting out to answer the key research questions, a policy context on the regulation of prescription drugs in the United States was presented. The section focused on the concern on availability and accessibility of prescription drugs. It showed the interplay of the different branches

at different levels of government and of different actors in shaping policies. This policy interplay is critical in understanding the paradigms of the different stakeholders in influencing the rules and laws governing the industry.

The alignment of interests of different policy stakeholders is important in the formation of policy. The shift from market-oriented policies to policies that demand greater regulation of the pharmaceutical industry opens space for policy reforms recommended by this paper.

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ANNEX A

Table 33: State Regulations Related to Pharmaceutical Marketing[18]

California	In 2004, the state legislature of California enacted a law requiring pharmaceutical companies to adopt policies on detailing and limits on gifts to health care professionals. The state legislature also adopted a resolution that would memorialize the President and Congress of the United States to recognize the problems caused by direct-to-consumer advertising and to take specific actions in the regulation of DTC.
Florida	In 2006, the state sets some limit on advertising, allows for the development and regulation of electronic prescribing practices and establishes disclosure and confidentiality requirements for medical and prescription records.
Maine	Maine has three separate laws on pharmaceutical marketing enacted in 2003, 2005 and 2007. The different laws require full disclosure of prescription drug marketing costs, public access to clinical trial requirements, prohibition on DTC unless material meets federal guidelines and prohibition on the sale of pharmaceutical information that identifies directly or indirectly the practitioner who ordered the prescription drug.
Massachusetts	Enacted in 2008, Massachusetts requires the development and promotion of evidence-based outreach and education program about the therapeutic and cost-effective utilization of prescription drugs for physicians, pharmacists and other health care professionals authorized to prescribe and dispense prescription drugs, adoption of a standard marketing code of conduct for all pharmaceutical or medical device manufacturing companies that engaged in detailing and disclosure of the value, nature, purpose and particular recipient of any fee, payment, subsidy or other economic benefit with a value of at least $50 any health practitioner.
Minnesota	In 1993, Minnesota enacted a law prohibiting any gifts to health

[18] This table is a portion of NCSL's table summarizing state bills and laws related to pharmaceutical marketing available at http://www.ncsl.org/default.aspx?tabid=14461.

practitioner of more than $50 in value.

Vermont	In 2007, a law was enacted increasing "transparency of prescription drug pricing and information" by limiting "fraudulent" advertising of prescription drugs to consumers and health care professionals, requiring notice to clients by pharmacy benefit managers that certain types of contracts are available, establishing an evidence-based education program, providing additional pricing information including "AMP" and "Best Price," to the Medicaid program from drug manufacturers and requiring disclosure of education programs funded by drug manufacturers. Also establishing regulation of PBMs including requiring that all financial and utilization information requested by a health insurer be provided, disclose the costs and financial arrangements with any formulary management, drug substitution including rebate and discount agreements. Such disclosures may be defined as confidential and not subject to court inquiry. In 2009, Vermont enacted a law regulating the kinds of gifts that health-care professionals may receive from manufacturers. The law prohibits nearly all financial and other gifts like food, travel, entertainment, subscriptions or "anything else of value" from pharmaceutical and medical equipment companies to doctors, nurses, hospital staff and others.
New Hampshire	In 2006, a law was enacted that prohibits individual prescription information from being transferred or sold for any commercial purpose except for the limited purpose of reimbursing the pharmacy. Commercial purposes include advertising, marketing, promotion, or any activity that could be used to influence sales or market share of a pharmaceutical product, influence or evaluate the prescribing behavior of an individual health care professional, or evaluate the effectiveness of a professional pharmaceutical detailing sales force. It does not prevent the collection of such data, nor does it prevent its use for reimbursement, research, utilization review, compliance, education, or as provided by law. Commercial use of prescriber identity is also allowed by zip code or medical specialty.
South Carolina	Enacted the Prescription Drug Discount Card Registration Act in 2006; providing for registration with the Department of Consumer Affairs of persons and representatives engaged in the sale, marketing, promotion, advertisement, or distribution of prescription drug discount cards or other purchasing devices

Texas	In 2007, the state legislature passed a law that requires the TX Attorney General to develop a public awareness campaign to educate consumers about solicitations by email or Internet, including information on distinguishing reputable pharmacies from unlicensed or fraudulent sales. The campaign may use brochures, advertisements and similar outreach and may accept grants and donations to fund the effort. Enacted in 2009, the law requires a study regarding the confidentiality of prescription information records and the use and sale of prescription information records containing patient-identifiable and practitioner-identifiable information by pharmacy benefit managers, insurers, electronic transmission intermediaries, pharmacies and other similar entities for the purpose of advertising, marketing, or promoting pharmaceutical products. Also provides a civil penalty up to $5,000 for companies that fail to provide required information.
West Virginia	West Virginia Pharmaceutical Availability and Affordability Act (2004) 1) establishes a state-sponsored clearinghouse for consumer Rx information; 2) establishes a state-sponsored prescription drug discount card program for residents with annual incomes up to 200 percent of federal poverty guideline. The program may use voluntary manufacturer rebates but may not use formularies or preferred drug lists; 3) establishes a state Council that "shall establish a pricing schedule using or referencing the FSS (Federal Supply Schedule) prices", which requires a future, additional legislative vote of approval or rejection. Also provides that the state shall "explore the feasibility of using or referencing, the federal supply schedule or Canadian pricing. 4) requires the state to "investigate the feasibility of purchasing prescription drugs from Canada," including feasibility of serving as a wholesale distributor of prescription drugs in the state." 5) requires reporting of Rx advertising costs.

ANNEX B

Table 34. Summary of Policies on Availability of Prescription Drugs

	Research Incentives and Patent Laws
1790	Patent Act
1980	Bayh-Dole Act – provided funding for research and encourage transfer of knowledge
	Stevenson-Wydler Technology Innovation Act of 1980
1982	The Small Business Innovation Development Act
1983	Orphan Drug Act
1984	Hatch-Waxman Act - extended the marketing exclusivity of pioneering companies for drugs that are already in the pipeline
1992	The Small Business Innovation Development Act – reauthorized
1992	Prescription Drug User Fee Act of 1992 (patent extension)
1994	Uruguay Round Agreements Act (patent extension)
1997	Food and Drug Modernization Act (patent extension)
2000	The Small Business Innovation Development Act – reauthorized
2011	Congress has not reauthorized the SBIR but the programs funded by the law are extended until September 30, 2011
	Safety and Efficacy
1906	Pure Food and Drugs Act
1938	Food, Drug and Cosmetic Act was enacted providing the Food and Drug Administration
1962	Kefauver-Harris Drug Amendment requires pharmaceutical companies to show that their drugs are sufficiently effective and safe.
1992	The Prescription Drug User Fee Act, which authorizes FDA to collect fees from companies that produces human drug and biological products, is responsible for expediting the approval process of new drugs renewed in 1997, 2002, 2007
1997	Food and Drug Modernization Act of 1997 mandated the Agency for Healthcare Research and Quality (AHRQ) to conduct research on comparative effectiveness and safety of drugs, biological products, and devices

1999	The Healthcare Research and Quality Act of 1999 expanded the mandate of AHRQ to 1) conduct state-of-the-art research, 2) provide objective clinical information to clinicians, patients, pharmacists, and others, and 3) improve the quality of health care
2000	the Academy of Managed Care Pharmacy (AMCP) first issued its formulary guidelines advising health plans to formally request drug companies to submit a standardized dossier containing detailed information including the cost effectiveness of the prescription drug compared to alternative therapies
2003	Medicare Prescription Drug Improvement, and Modernization Act law authorized $50 million for the Agency for Healthcare Research and Quality (AHRQ) to conduct comparative clinical effectiveness studies
2003	the funding for the proposed comparative effectiveness studies were eliminated in the President's budget for 2004-2005
2009	Congress allocated $1.1 billion for comparative effectiveness research trough the economic stimulus law of President Obama
2010	President Obama signed the Patient Protection and Affordable Care Act. It created the Patient-Centered Outcomes Research Institute, a quasi-government enterprise mandated to fund comparative effectiveness research

Approval of Generic Drugs

1984	Hatch-Waxman Act of 1984.
2002	Cardizem and Hytrin
2002	Federal Trade Commission issued consent orders prohibiting the drug companies from entering into agreements in which a generic drug company
2002	Bristol Myers with its drug Buspar and Biovail's Tiazac- addressed by MPDIMA 2003
2003	Medicare Prescription Drug Improvement, and Modernization Act of 2003 - requires branded and generic drug firms to notify the FTC and Department of Justice within 10 days of any agreements involving the 180-day exclusivity period
2005	*Teva Pharmaceutical Industries v. Crawford*
2006	*Mylan Pharmaceuticals v. FDA*

Marketing of Prescription Drugs

1938	The Wheeler Lea Act of 1938 1938 gave the jurisdiction to regulate advertising of prescription drugs to the Federal Trade Commission
1962	Kafauver-Harris amendments to the Federal Food, Drug and Cosmetic Act (FFDCA) transferred the authority to FDA TO REGULATE advertising
1982	Voluntary moratorium on DTC advertisement
1997	Regulation on advertising was amended to require presentation of accurate info
2002	DHHS required that all FDA regulatory letters be reviewed by FDA's Office of Chief Counsel before they are sent out
July 2005	Bill Frist asked industry for a voluntary moratorium on DTC from the day it was introduced in the market
2005	PhRMA guidelines on DTC – revised in 2008

ANNEX C

Table 35. Summary of Policies on Accessibility of Prescription Drugs

Medicare Part D	
1988	Medicare Catastrophic Coverage Act of 1988 (MCCA 1988)
1989	Medicare Catastrophic Coverage Repeal Act of 1989
1993	Clinton Healthcare reform plan (unsuccessful)
1995	Plan to move Medicare to a voucher system
1997	Balanced Budget Act reducing Medicare spending
2003	Medicare Prescription Drug, Improvement, and Modernization Act of 2003
2010	Obama Health Reform Law

Reimportation	
1987	Prescription Drug Marketing Act of 1987 (PDMA) completely banned parallel imports of prescription drugs unless the manufacturer of the drug imported them on its own
1999	the International Drug Parity Act of 1999 (IDPA) was filed in Congress. intended to expand United States-Canadian pharmaceutical market, but it was not signed into law despite being popular in Congress
2000	Medicine Equity and Drug Safety Act of 2000 (MEDSA) was filed in Congress. sanctioned the reimportation of FDA-approved drugs. Congress passed MEDSA in October 2000
2000	DHHS Secretary Shalala de-implemented the statute because she could not certify that implementation of the bill would "pose no additional risk to the public's health and safety." Due to the inability of the Secretary to do so, the bill's importation provision was decertified
2001	Secretary Thompson of DHHS made statement on safety of reimportation
2003	Pharmaceutical Market Access Act (PMAA) to "allow importation of drugs only if the drugs and the facilities where they were manufactured [were] approved by the Food and Drug Administration," and "to require that imported prescription drugs be packaged and shipped under counterfeit resistant technologies.
2003	Minnesota's Rx Connect was the first. other state and local governments followed. Alabama, Illinois, Vermont, Wisconsin, North Dakota, Rhode Island, New Hampshire,

	Louisiana, California, Massachusetts, Maine, Maryland and even county and city governments throughout the United States started reimportation programs for their residents
2004	Rhode Island statute allows pharmacies licensed in Canada to obtain licensure from the state Department of Health to do business in Rhode Island. The FDA issued a letter to Rhode Island asserting this law conflicts with the Federal Food and Drug Act
2003	Vermont submitted a petition to FDA to allow the Vermont State Employee Medical Benefit Plan to "establish a program for the orderly individual importation of prescription medications." FDA denied the petition
2004	Vermont sued FDA *Vermont v. Leavitt*
2005	US District Court dismissed the Vermont complaint because the program violates the law *Vermont v. Leavitt*
2005	*Andrews v. HHS*
2003	the Food and Drug Administration (FDA) filed a case against Rx Depot and Rx Canada for violating the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. Sections 331(d) and (t). Rx Depot is responsible for the creation of approximately eighty-five storefront distributors
2004	A US District Court granted the Department of Justice's motion for preliminary injunction against the storefront distributors in violation of the FCDA because they created "an unacceptable risk that counterfeit, adulterated, misbranded, subpotent, or expired drugs will be sold to American consumers"
2004	DHHS has established a task force on drug importation to look at how drug importation might be conducted safely and its potential impact on the health of American patients, medical costs and the development of new medicines.
2005	A US District Court dismissed the Vermont complaint on the basis of legality – the program violated federal law (2005)
2005	Twenty-one states have considered reimportation legislation in 2005
2005	Pharmaceutical Market Access Act of 2005 and Pharmaceutical Market Access and Drug Safety Act, proposed legislations both intended to legalize reimportation of prescription drugs
2009	Senate bill no. 1232 by Senator Byron Dorgan- reintroducing reimportation of prescription drugs from Canada.
	Cost Containment Programs through Medicaid
1999	Six New England plus New York and Pennsylvania coalesced and proposed a joint purchasing program to aggregate purchasing power with manufacturers and jointly contract for pharmacy best practice and benefit administration services

2000	Founding of the national Legislative Association on Prescription Drug Prices (NLARx). . It was founded to promote different policy options and model legislations to lower the cost of prescription drugs.

Maine

2000	Maine's Rx program
2000	PhRMA challenged the constitutionality of the Maine Rx Program – Pharmaceutical Research and Manufacturers of America v. Walsh
2000	The District Court sustained the challenge and enjoined the implementation of the statute
2001	Court of Appeals reversed
2003	The U.S. Supreme Court affirmed the decision of the First Circuit and remanded the case to the district court for the determination on the merits. The Court also stressed that "By no means will our answer to [the] question [of whether the district court abused its discretion in entering the injunction] finally determin[e] the validity of Maine's Rx Program"
2004	After the U.S. Supreme Court's decision, Maine overhauled the Rx program and renamed it Maine Rx Plus.
2005	PhRMA sued again to force Maine to submit its program to DHHS for approval and also to enjoin it from implementing Maine Rx Plus pending the Secretary's review – Pharm. Research & Mfrs. Of Am v. Nicholas
2005	The district court denied PhRMA the injunction, reasoning that since Maine changed its statute, PhRMA's claims were not yet ripe for review; especially since the new statute would not impose the prior approval provisions of the original statute against nonparticipating drugs until October of 2005

Florida

2001	Florida passed a law that extends Medicaid drug discounts to residents who falls on the income requirements of the program but are not qualified for Medicaid (Florida Rx Program)
2001	The District Court denied PhRMA's request for injunction and found that there is no conflict between Florida's statute and the federal policy. ("Pharm. Research & Mfrs. of Am. v. Medows," 2001).
2001	The Court of Appeals upheld the denial for injunction and the US Supreme Court denied PhRMA's petition for writ of certiorari ("Pharm. Research & Mfrs. of Am. v. Medows," 2001).

2002	PhRMA filed a complaint and a motion for a preliminary injunction against Michigan Best Practices Initiative to enjoin the Secretary of the DHHS from approving the statute(PhRMA v.Thompson)
	Dist.Crt.
2003	The District Court ruled that the Secretary did not act arbitrarily or capriciously in approving portions of the Initiative, including the prior authorization program, the efforts to secure supplemental rebates, and the requirement that drug manufacturers provide rebates in non-Medicaid programs in order to avoid prior authorization for drugs offered for Medicaid use(PhRMA v.Thompson)
2004	The Court of Appeals affirmed the decision in 2004(PhRMA v.Thompson)
2003	2003, a substantial number of state pharmaceutical laws were enacted in 39 states[19] providing subsidy to elderly and indigent residents, bulk purchasing or changes in the state's purchasing policies
2004	Governor Schwarzenegger never supported measures for cost containment of prescription drugs. In 2004 he vetoed 6 bills with the same intent and in 2005 he vetoed three more bills that were opposed by the drug industry.
2005	Proposition 78 & 79 - Propositions 78 and 79 were two competing initiatives both sought to offer relief to low to moderate-income, uninsured Californians who face prescriptions drug bills they cannot afford. Proposition 78 proposed to establish a voluntary prescription drug insurance plan for state residents whose annual incomes do not exceed 300% of the federal poverty level (Medical News Today, 2005). On the other hand, Proposition 79 will require drug makers to participate in a prescription drug discount program or face exclusion from the Medi-Cal formulary in some cases
2003	Ohio's initiative
2005	Ohio's Best Rx implemented similar to Prop. 78 of California
2006	Sen. Morrisette's bill on prescription drug discount
2006	Oregon's Measure 44

[19] Alabama, Alaska, Colorado, Connecticut, Delaware, Florida, Hawaii, Illinois, Indiana, Iowa, Kansas, Louisiana, Maine, Maryland, Massachusetts, Montana, Nebraska, Nevada, New Jersey, New Mexico, New York, North Dakota, Ohio, Oklahoma, Oregon, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, Wisconsin and Wyoming