The London School of Economics and Political Science

Pharmaceutical Competition within Molecule Markets Post-Patent Expiry: Evidence from the USA, the UK, Germany and France 2000 - 2005

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DECLARATION

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ABSTRACT

In the interest of understanding the nature and degree of competition within off-patent molecule markets and improving purchasing efficiency, this thesis uses IMS Health data to analyse dimensions of competition within the off-patent omeprazole and paroxetine molecule markets in the USA, UK, France and Germany during the 2000q-2005q1 period.

The main theoretical findings include:

- Regulation in homogeneous markets may inhibit generic price competition. Generic manufacturers may also product differentiate, resulting in a Bertrand-like model of "softened" price competition.
- Other forms of product differentiation in off-patent molecule markets may include strength segments and the OTC market.

The main empirical findings include:

- Generic price competition appears stronger in the USA and the UK than in Germany and France, although it is imperfect in all four countries. The USA and the UK achieve some of the lowest generic prices, while the UK is the most effective at actually purchasing its lowest prices.
- Generic penetration appears weak in less common strength segments, allowing original brand manufacturers' the opportunity to retain relatively large market shares. This results in higher purchased prices and, hence, significant purchasing inefficiencies.
- There appears to be competition between over-the-counter and prescription omeprazole in the USA, but not in the UK. OTC prices are relatively low in the US, offering the opportunity for cost savings. In the UK, patients may face a financial disincentive to purchase OTC omeprazole, possibly masking the opportunity for improved self-care.

Certain countries may want to re-evaluate their generic reimbursement schemes in the interest of more price competitive markets and increased purchasing efficiency. Countries could also benefit from encouraging generic entry in less common strength markets. Finally, in approving an OTC switch, regulators should ensure that demand-side financial incentives are consistent with the goals of achieving cost containment and/or facilitating increased patient self-care.

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This PhD is dedicated to my precious daughters--Abigail, my 14-month old, and the baby girl in my bump.

PREFACE

In 2008, the Department of Social Policy approved new regulations which permit students who are doing their PhD in economics-related areas to submit a series of publishable papers as a thesis. The regulations stipulate that the publishable papers should be thematically linked, and be tied together with an introduction chapter, a conclusion chapter and any other appropriate chapters. This thesis follows this new format.

It begins with an introductory chapter that introduces the motivation behind these studies as well as the main research questions and contributions to the literature. The second chapter includes a broad overview of the literature on the main theme of this thesis—competition in the pharmaceutical market (in developed countries)—and discusses these studies' contributions to the literature. The next chapter is the methodology chapter, which provides background information on the sample used in this thesis, including the dataset, the molecules and the countries. It also explains the type of research approach I have chosen and outlines the theory and methods used in each chapter. Because this thesis follows the publishable papers format, the next three main analytical chapters are also inclusive of the relevant literature and the specific methods used. Finally, the concluding policy chapter ties together the findings of the four analytical chapters and acknowledges the areas of weakness in this research as well as areas of potential further research. These three main analytical chapters have therefore been created so that they could stand alone as publishable papers – but in addition my intention is that when integrated together into this thesis they will tell a broader story of pharmaceutical competition in a way that is both interesting and useful to health policymakers.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

AESGP: Association of the European Self-Medication Industry
AFSSAPS: French Agency for the Medical Safety of Health Products
AWP: Average Wholesale Price
CBO: Congressional Budget Office
CDER: The FDA's Center for Drug Evaluation and Research
CEPS: Comite' Economique des Produits de Sante
DDD: Daily Defined Dosage
DH: UK Department of Health
DHHS: US department of Health and Human Services
EBD: Arkansas State Employee Benefits Division
EMEA: European Agency for the Evaluation of Medicinal Products
FDA: U.S. Food and Drug Administration
FMOH: French Ministry of Health
FSS: Federal Supply Schedule
GERD: Gastroesophageal Reflux Disease
GSL: General Sales List
IMS: Intercontinental Medical Statistics
INN: International Nonpropriety Name
IQWiG: German Institute for Quality and Efficiency in Health Care
Mg: Milligrams
MHRA: Medicines and Healthcare Regulatory Agency
MPA: The Swedish Medical Product's Agency
NDA: New Drug Application
NHS: The UK's National Health Service
NICE: National Institute of Clinical Efficacy
OBIG: Österreichisches Bundesinstitut Fur Gesundheitswesen
OECD: Organisation for Economic Co-operation and Development
OFT: The UK's Office of Fair Trade
OTC: Over-The-Counter
OXERA: Oxford Economic Research Associates
P: Pharmacy Medicine
PBMs: Prescription Benefit Managers
PILs: Patient Information Leaflets
POM: Prescription Only Medicine
PPI: Proton Pump Inhibitor
PPRS: Pharmaceutical Price Regulation Scheme
PRODIGY: Prescribing Rationally with Decision Support in General Practice
SA: Suspended Action
SE: Standard Error
SSRI: Selective Serotonin Reuptake Inhibitors
UK: The United Kingdom
USA: The United States of America
USD: United States Dollars
WHO: World Health Organization

CHAPTER 1: BACKGROUND AND MOTIVATION

1.1 Background

Pharmaceutical innovations in the 20th and 21st centuries have undoubtedly made a substantial contribution to the health of individuals around the world. From vaccinations that prevent against diseases such as polio and diphtheria, to the discovery of antibiotics which can cure many bacterial infections, through to modern-day advances such as medicines to treat low birth-weight infants and medicines for chronic illnesses such as depression and cardiovascular disease, pharmaceuticals offer health benefits that may increase quality of life and can sometimes significantly extend a patient's length of life (Cutler, 2004). Pharmaceutical treatments are therefore a vital part of the health care system.

However, many pharmaceutical treatments are notorious for being costly. They consume billions of dollars of health care expenditures in OECD countries every year. For example, pharmaceutical sales in the UK exceeded £12 billion in 2004 (Bharat Book Bureau, 2005). In addition, pharmaceutical expenditures have been growing rapidly. Specifically, table 1-1 shows that pharmaceutical expenditure per capita increased significantly across all select countries during the 1995 to 2005 period, and for example more than doubled in Canada, Spain and the USA. This growth outpaced overall health care cost increases such that pharmaceutical expenditure increased its share of total health spending in most OECD countries.

Table 1-1 Comparison of Health and Pharmaceutical Expenditures across Select OECD Countries, 1995-2005

	Total expenditure on health % of gross domestic product			Total expenditure on pharma and other nondurables per capita, USA exchange rate			Total expenditure on pharma and other nondurables as a % of total expenditure on health		
	1995	*2000*	*2005*	*1995*	*2000*	*2004*	*1995*	*2000*	*2005*
Canada	9.2	8.9	9.9	252	330	537	13.8	15.9	18.2
France	9.4	9.2	10.5	451	418	676	17.6	20.3	18.9
Germany	10.1	10.3	10.6	401	322	494	12.8	13.6	14.1
Italy	7.1	8.1	8.7	299	339	546	21.1	21.9	20.3
Spain	7.4	7.2	8.1	217	220	447	19.2	21.3	22.8
United Kingdom	7.0	7.3	8.4	209			15.3		
United States	13.3	13.3	15.3	325	535	752	8.9	11.7	12.3

Note: Underlined data was not yet available for 2005, so reflects 2004.

Source: The Author, using OECD Health data, 2006

At the same time that pharmaceutical spending has been consuming an increasing share of total health spending, governments around the world struggle with the acute challenge of allocating society's scarce resources on health care services. One illustration of this challenge is the case of the UK's National Health Service (NHS). From April 1999 to March 2008, spending on the NHS in England grew by an average of 6.4% a year in real terms (Emmerson, 2008), and although it improved services and reduced waiting times for elective procedures, it resulted in a deficit of over £600 million in 2006 (BBC, 2006). This led to claims of hospital mismanagement, among others. Consequently, to the dismay of hospital employees, more than 6,000 hospital jobs were cut in 2006, waiting times for operations increased in many hospitals, and some mental health service wards were closed (BBC, 2006).

This NHS example demonstrates that scarcity of health care resources can have real consequences. Therefore, it is vital that health policymakers purchase health services efficiently so that society can reap the maximum benefits from the available health resources. In the process of striving for overall health system purchasing efficiency, it is also critical to consider the extent to which health policymakers succeed in efficiently purchasing prescription pharmaceuticals,

particularly as pharmaceutical spending has increased substantially both in absolute terms and as a proportion of health spending in many OECD countries.

To the extent that research is able to guide policymakers on how to improve pharmaceutical purchasing efficiency, resources can be allocated accordingly. In the case of the NHS, an improvement in pharmaceutical purchasing efficiency may have been able to offset the £600 million deficit, thereby preventing job losses and service cuts. The scarcity of resources in times of recession also calls for rationality and difficult decisions in the resource allocation process and the use of available funds. A recent report projects an NHS real-terms budget reduction of £8-10bn during the 2011-2014 period, which would likely result in significant staff cuts and could impact the pharmaceutical budget (BBC, 2009).

The challenge of spending scarce health resources—in particular, pharmaceutical resources in the case of this dissertation— is not a UK phenomenon and is paralleled in most other OECD countries. Another example is the USA, where pharmaceutical spending has increased substantially in recent years as a result of the implementation of the Medicare prescription drug benefit (Kaiser Family Foundation, 2008). Around the time that the Medicare prescription drug benefit was approved, a study acknowledged that the stability of the Medicare prescription drug benefit—and hence access to drugs for millions of seniors—largely relies on payors' abilities to contain drug spending (Hass, 2005), which further underscores the importance of purchasing pharmaceuticals as efficiently as possible. This is not just a challenge in times of economic distress, but is likely to be at the forefront of health policy for generations to come.

In order for governments to strive for pharmaceutical purchasing efficiency, it is first necessary to understand the nature of pharmaceutical spending. There are three dimensions to pharmaceutical spending: the first is utilization, which mainly relates to the volume of drugs consumed; the second is drug prices; and the third is the drug mix, i.e. the share of different drugs that are consumed. If health policymakers are interested in improving pharmaceutical purchasing efficiency, they may need to target spending from all three angles—by improving utilization management, by optimizing prices and by altering the mix of drugs consumed.

Improving utilization management may involve trying to reduce the unnecessary consumption of drugs. However, this is a particularly challenging task in that some of the measures that attempt this feat, such as prescription cost-sharing,

may also reduce the necessary consumption of drugs, as seen in the RAND Health Experiment (Brook, Ware. et al, 1984). Optimizing prices may involve reducing the price of patented drugs and/or off-patented drugs. In the case of reducing prices of patented drugs, policymakers also need to be very cautious about the implications of price reductions for innovation itself.[1]

Finally, policymakers may also strive to improve pharmaceutical purchasing efficiency by altering the mix of drugs. This may include shifting consumption between molecules or shifting consumption amongst drugs made from the same molecule. Shifting consumption between molecules to improve purchasing efficiency is challenging as policymakers may need to compare the cost-effectiveness of different molecules as well as overall cost-benefit implications. Altering the mix of drugs made from the same molecule may include shifting from original brand name to generic equivalents, from one generic equivalent to another or from prescription (original brand or generic) to OTC (original brand or generic).

In summary, policies that target the prices of off-patent drugs and attempt to alter the mix of drugs made from the same molecule (from higher priced drugs to lower priced drugs) have the distinct advantage of being relatively straightforward for policymakers because they have the potential to reduce pharmaceutical spending without altering the benefits to patients. More specifically, they do not attempt to reduce utilization (risking the reduction of necessary drugs), nor do they attempt to shift consumption to drugs that may offer inferior therapeutic benefits (assuming good manufacturing practice for generic equivalents). As a result, attempts to improve pharmaceutical purchasing efficiency through pricing and mix changes within the same molecule may be particularly attractive to policymakers. In addition to these methods being relatively easy to implement, they also have the potential to

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[1] It is important to note that many governments in OECD countries in this thesis seek to create and preserve incentives for the pharmaceutical industry to invest in research and development. This occurs largely through the patent system, but also through other direct and indirect incentives. They value the pharmaceutical industry for the contribution it makes to improving people's health, as well as the contribution it makes as an employer in terms of stimulating economic activity. There is much literature that focuses on the government's need to preserve research and development. Many of these articles warn of the negative effect that regulation, particularly price controls, may have on pharmaceutical firms' incentives to invest in research and development (Vogel 2004; Calfee 2001; Emilien 2004). For example, one study estimates that price controls could decrease R & D by 23.4 to 32.7%, while another study conducts a cross-country comparison that shows the negative impact price regulation may have on launches of new drugs (Vernon 2005; Danzon 2005). Although preservation of R&D is outside of the scope of this thesis, pharmaceutical policymakers must understand its importance when seeking to contain pharmaceutical costs.

achieve significant cost savings in absolute terms. For example, a study on generic utilization in the USA estimates that for non-institutionalized adults, substituting generics for brand name drugs in 2000 could have saved 11% ($8.8 billion) of drug expenditures (Hass, 2005). Therefore, it is not surprising that policymakers in many countries have chosen to focus on increasing generic penetration rates, as is discussed in the following chapters.

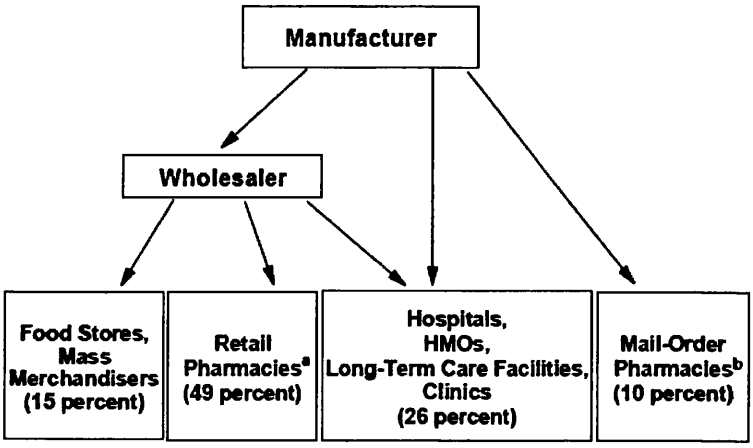
Current policymaking primarily focuses on improving purchasing efficiency within molecule markets by increasing generic penetration. However, this thesis argues that molecule-level generic penetration is a crude measure that just skims that surface of purchasing efficiency within a molecule market and misses significant complexity at the micro-level. Therefore, this thesis focuses on several unstudied dimensions of molecule markets at a micro-level that may offer policymakers additional opportunities to improve purchasing efficiency. Given the challenges of scarce financial resources and increasing pharmaceutical costs, this thesis therefore aspires to push the thinking in an area of utmost importance to societal welfare.

1.2 Interventions in the Pharmaceutical Market

Pharmaceutical purchasing efficiency can be attained by altering the mix and targeting the prices of drugs at the molecule level, as outlined above. Payors can help to alter the mix of drugs by substituting original brand drugs with lower-priced generic equivalents, a policy that targets costs while, *ceteris paribus*, holding volume constant. In the process of influencing the mix and price of off-patent pharmaceuticals, payors may mandate substitution and impose direct generic price controls, or may seek to influence the price and mix of off-patent molecules by introducing off-patent pharmaceutical policies that encourage market competition. An example of a policy that may influence, but not directly control, generic prices is allowing pharmacists to negotiate discounts rather than stipulating distribution margins. In addition, an example of a policy that may influence, but not directly control, the mix of drugs at the molecule level is allowing pharmacists to substitute generics for original brand drugs and possibly even offering a higher dispensing fee for generics. In order to achieve improved purchasing efficiency, the implications of directly controlling prices and the mix of drugs within a molecule market need to be understood versus taking a more market-oriented approach by encouraging price competition in off-patent pharmaceutical markets.

It is important to understand the structure of the pharmaceutical market. Figure 1-1 shows that the majority of drugs flow from manufacturers to wholesalers, and then on to retail outlets (pharmacies) and hospitals, where they reach patients; in some cases, manufacturers bypass wholesalers by selling directly to hospitals (CBO, 1998); this occurs generally in the hospital market for both branded originator and off-patent drugs and, very often, in the off-patent retail market. Some drugs are sold "over-the-counter" (OTC), and therefore do not require prescriptions from physicians. Depending on regulations, these drugs may only be available behind the counter of pharmacists at retail pharmacies, or may be available without the guidance of pharmacists at retail pharmacies, food stores and through mail order. Patented and off-patent drugs that require a prescription may only flow through the hospital, retail pharmacy or mail order channels. Some off-patent (whether original brand or generic) drugs may also be available as OTC depending on whether they have OTC status.

Figure 1-1 Channels of Distribution for Prescription Drugs[2]



SOURCE: Congressional Budget Office based on Micky Smith, *Pharmaceutical Marketing Strategy and Cases* (New York: Pharmaceutical Products Press, 1991), Chapter 3; Boston Consulting Group, *The Changing Environment for U.S. Pharmaceuticals* (Boston: Boston Consulting Group, April 1993); and Pharmaceutical Research and Manufacturers of America, *1997 Industry Profile* (Washington, D.C.: PhRMA, March 1997), p. 31.

NOTES: Figures in parentheses represent shares of the prescription drug market in 1996, calculated as a percentage of total U.S. sales at manufacturer prices.

HMOs = health maintenance organizations.

a. Some chain-store pharmacies buy directly from the manufacturer.

b. Some mail-order pharmacies go through a wholesaler.

Within the context of the operation of the pharmaceutical market, various interventions are often implemented whether on the supply- or the demand-side, or both, aiming to contain costs and improve efficiency. Figure 1-2 illustrates these interventions. In this case, the supply side is assumed to be characterized as the manufacturers and the wholesalers. Physicians and pharmacists make up the "proxy demand side," while third party payors and patients make up the most visible parts of the demand side itself.

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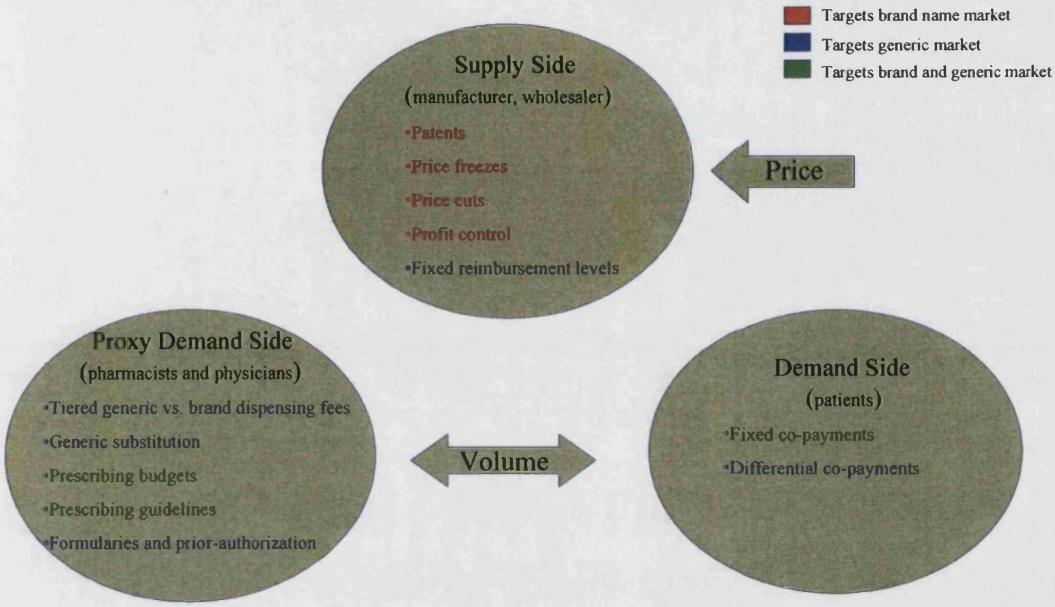
[2] The percentages in this figure reflect pharmaceutical distribution in the US in 1996.

Figure 1-2 Supply- and Demand-Side Pharmaceutical Interventions



Source: The Author.

For each of these regulations, there is a multitude of evaluative literature. For example, within the UK context and in the case of assessing the impact of financial incentives on GPs, one study found that compared to non-budget holders (non-fundholders), the rate of generic prescribing increased for budget holders (fundholders), while the rate of growth in pharmaceutical costs slowed (Wilson, Buchan and Walley, 1995). In other studies of prescribing patterns, findings show that physicians in the USA respond to their patients' insurance coverage and co-payment arrangements, and that prescribing budgets in Germany led to increased generic prescribing and hence lower prescribing costs (Hellerstein, 1998; Busse and Howorth, 1999).

These evaluative studies are relevant domestically, but in many cases are not generalizable across countries because policies are implemented differently across countries, but also because such studies do not take into account differences in other factors, such as individual pharmaceutical market characteristics. In order to influence pharmaceutical costs, one must understand the various economic factors that drive firms' competitive and strategic decisions.

1.3 The Focus of this Thesis

This thesis focuses on the supply-side of pharmaceutical cost containment by identifying the market characteristics that are likely to have the largest impact on pharmaceutical competition particularly in off-patent markets, and directly incorporates them into a quantitative model of competition. It also incorporates relevant payors' supply-side regulations into the analysis of pharmaceutical competition. While it is outside the scope of this research to quantify the effects of pharmacist and physician policies on pharmaceutical price and market share competition, the concluding discussion chapter does consider this proxy demand side, as well as the role of patients in further containing pharmaceutical costs.

The goal of this thesis is therefore to address the following overarching research questions:

- First, what is the role of product differentiation in softening Bertrand-like price competition in off-patent molecule markets and in what forms, if at all, does product differentiation exist?
- Second, what hybrid of market and regulatory factors stimulate competition in off-patent molecule markets, resulting in improved pharmaceutical purchasing efficiency?

In doing so, the thesis addresses the above questions with the following case-specific research questions:

Case 1: What are the determinants of generic prices in the omeprazole and paroxetine retail markets in the USA, UK, Germany and France? To what extent do purchasers maximize savings from genericisation and what can the potential be for further savings?

Case 2: To what extent does the degree of competition between the original brand and generics within strength segment markets[3] differ across these strength segment markets of the retail omeprazole and paroxetine markets in Germany, France, the UK and the USA?

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[3] The term "strength segment markets" refers to the segments of a molecule market in which drugs of that molecule consist of a particular strength. For example, depending on the country, omeprazole may have multiple strength segment markets, possibly including 10 mg, 20 mg, 30 mg and 40 mg. Within a molecule market, all drugs of the same strength are classified into the same strength segment market, regardless of formulation (e.g. tablet versus capsule) and the size (e.g. 100 tablets versus 500 tablets) of the package sold to the pharmacy.

Case 3: What is the nature and degree of competition between the OTC omeprazole and retail prescription omeprazole markets in the USA and the UK from market entry onwards?

In pursuit of answers to these research questions, the studies in this report use proprietary data covering the period from 2000 Q1 – 2005 Q1 and make the following key contributions to the literature (see also "Gaps in Literature and Key Contributions" in Chapter 2 for a detailed discussion):

First, the Application of Industrial Organization Theory to Off-Patent Molecule Markets: This thesis makes a theoretical contribution by building on, applying and enhancing the current industrial organization framework/theory for markets with homogeneous products to off-patent pharmaceutical molecule markets. In doing so, this thesis shines light on aspects of competition that may have not yet been incorporated into the current industrial organization models, thereby generating new hypotheses that offer more complete versions of these industrial organization models.

Second, by addressing new Dimensions of Generic Competition: By modelling unstudied dimensions of competition in off-patent pharmaceutical molecule markets, this thesis offers a newfound understanding of ways in which payors could improve pharmaceutical purchasing efficiency. Specifically, these new dimensions include:

- Case One: modelling generic versus generic price competition between products of the same molecule at the presentation level in order to understand the detailed ways in which generic manufacturers may product differentiate, thereby carving out niches within what would other-wise be homogeneous markets.
- Case Two: modelling original brand versus generic market share competition between products of the same molecule within strength segments in order to determine the extent to which original brand manufacturers may be able to retain more dominant market positions than a simple generic penetration analysis would suggest.
- Case Three: modelling OTC versus prescription drug substitutability and degree of price competition in order to determine the extent to which the OTC market may directly compete with its prescription market

counterpart in cases where medicines of the same molecule are approved for both the prescription and OTC distribution channels.

Third, analysis using a Comparative Perspective: This thesis conducts panel data analysis to study the above dimensions of pharmaceutical competition in off-patent molecule markets across four countries that exhibit differing health care systems and regulatory environments. This allows for the opportunity to compare findings across settings in order to gain a greater understanding of how pharmaceutical industrial organization may differ across countries. In addition, it will help payors to understand how opportunities to improve pharmaceutical purchasing efficiency may also vary across country settings.

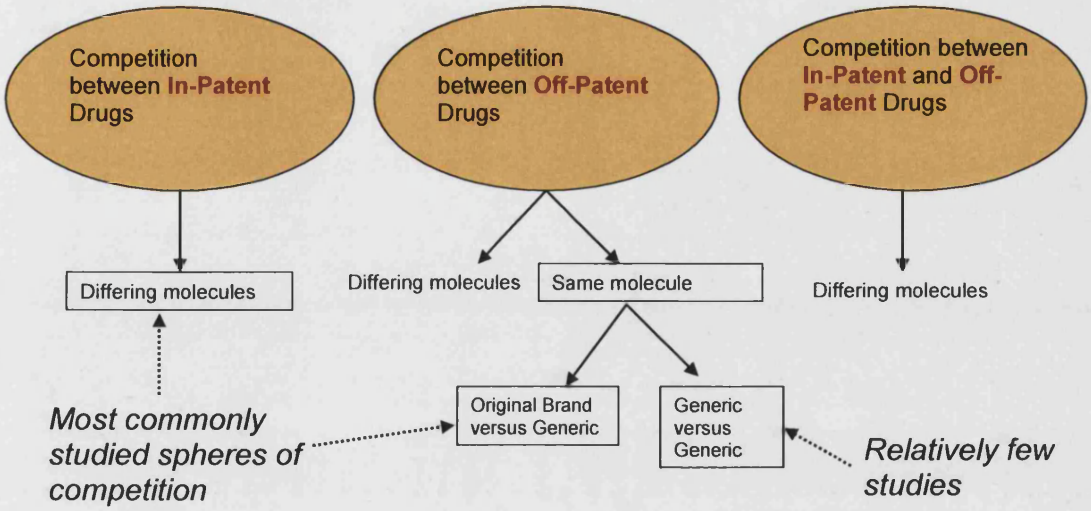
CHAPTER 2: LITERATURE REVIEW AND THE CONTRIBUTION OF THE THESIS TO THE LITERATURE

2.1 Background

There are three potential spheres of pharmaceutical competition—competition between in-patent drugs, competition between off-patent drugs and competition between in-patent and off-patent drugs. Figure 2-1 depicts these spheres and subdivides them by whether or not competition may occur between drugs of differing molecules or the same molecule. Most of the literature on competition in the pharmaceutical markets focuses on competition between in-patent drugs of differing molecules (that are usually within the same therapeutic class) and competition between off-patent original brand and generic drugs of the same molecule. In addition to the vast amount of literature on competition between off-patent original brand and generic drugs of the same molecule, a body of literature on competition between off patent generic drugs of the same molecule has begun to emerge in order to determine whether generic markets really offer the opportunity for purchasing efficiency that policymakers assume to be the case.

Following a review of the current literature, this chapter discusses the key contributions that this thesis makes to the gaps in the literature (as of August 2008). Studies that take a broad approach of analyzing competition across spheres may be referenced in several sections of this literature review.

Figure 2-1 Potential Spheres of Pharmaceutical Competition



Source: The Author

2.2 Competition in pharmaceutical markets

2.2.1 Sphere One: Competition between In-Patent Drugs

Although it is commonly assumed that in-patent drugs do not face competition (by nature of having a monopoly on that molecule market), there is a significant body of evidence that challenges this assumption. In a recent study, researchers analyzed the determinants of competition between patented statins in the UK, Germany, France, and the Netherlands, using IMS Health Data from 1992-2002 (Kanavos, Costa Font and McGuire, 2007). They accounted for the effect of relevant supply side regulations and market characteristics on patented statins' prices and market shares by including the following explanatory variables in the model: cost effectiveness used in price setting, price regulation, price cuts in operation, potential market size, and potential market competition. Findings showed that although there was no observable price decline as competitors entered the therapeutic market, competition did exist in the form of product differentiation. Specifically, patented statins seemed to compete on "quality" attributes and branding. Varying levels of prices for the same drug in different countries was also evidence of product differentiation. Although the statins did not compete directly on price, product

differentiation shifted demand from the first entrant, pravastatin, to the second entrant, simvastatin. Thus, this study showed that in the statins class, the first mover advantage of dominant market share diminished with the entry of competing drugs.[4] It also notes that this shift in market share suggests price sensitivity in the statins class, even though prices of both statins continued to increase in the growing market.

Consistent with the above findings, another study found that first entrant drugs continued to increase real prices even after competitors entered the therapeutic class (CBO, 1998). Specifically, the study tracked prices of breakthrough drugs and me-too drugs from 1991-1994 for 5 therapeutic classes.[5] In four of the five classes, breakthrough drugs' prices continued to increase in real terms after me-too drugs entered the market, while in just one of the five classes, the real price of the breakthrough drug decreased after entry by competitors.

In addition to the above, another study looks at the price trends of breakthrough and me-too drugs within therapeutic classes (Lu and Comanor, 1998). Using IMS Health Data, it analyzed over a hundred products that were marketed during the late 1970s and 1980s in the USA. Findings showed that the vast majority—90%—of the drugs in the study had close substitutes, and that the larger the therapeutic advantage of the competitor, the larger the degree of substitutability. Similarly to previous studies, the CBO findings showed that the real price of patented drugs continued to rise after the entry of competing drugs, albeit at a slower rate. Taking it a step further, this study also observed a distinct price trend amongst these competing me-too drugs. Competing me-too drugs tended to enter the market with relatively low prices. However, within time, increased brand and quality recognition of these me-too drugs gave their manufacturers market power, allowing

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[4] A study noted that breakthrough drugs have a first mover advantage over me-too drugs in that physicians are hesitant to switch their patients from a breakthrough drug to a me-too drug until they feel confident that the me-too drug is more effective or has fewer side effects (Scherer and Ross 1990, quoted in CBO 1998).

[5] In this study, breakthrough drugs are defined as the first drug to treat a specific therapeutic mechanism (hence first entrant into a therapeutic class). Successive entry of drugs which have different chemical/molecule formulations, but target a similar therapeutic mechanism are called me-too drugs. Often me-too drugs aim to product differentiation through product formulation (such as time release capsules), superior therapeutic efficacy, and/or fewer side effects. In some cases, me-too drugs enable pharmaceutical firms to capitalize on profitable patented markets by developing and patenting similar, but not equivalent drugs. Findings from the CBO study show that while on-patent, breakthrough drugs may actually have only 1 to 6 years of pure market exclusivity before a me-too drug enters the market. Specifically, the CBO study found that 6 out of 13 breakthrough drugs in its data sample experienced competition from a me-too drug within one year of entering the market. In six other cases, the breakthrough drugs experienced competition from a me-too drug within two to six years.

them to increase prices. For thirteen drugs that received an A rating from the FDA as most innovative (breakthrough drugs), the average real price was just 7% higher than the launch price eight years earlier. Comparatively, after 8 years of marketing, the average prices of forty-eight B rated drugs and sixty-nine C rated (least innovative) drugs increased by 32% and 62% respectively. These price increases for B and C rated drugs (me-too drugs) occurred despite the fact that their launch prices were not significantly below the prices of competing drugs that were already on the market. Thus, these studies above all suggest that patented drugs within therapeutic classes do seem to compete through product differentiation. Over time, promotional spending gains new drugs favourable branded recognition, which increases their market power and respective price.

Some studies found significant elasticities between therapeutic substitutes (Ellison, 1997). However, other studies were less conclusive, finding that the relationship between the price of patented drugs and the number of competitors within a class was unclear due to contradictory findings that resulted from differing methods (Wiggins and Maness, 1998). Specifically, the inverse specification of sellers produced a marginally significant effect, whereas the nested specification produced a statistically insignificant effect.

Two reasons why competition within a therapeutic class may be difficult to model are the complexities of discounts and promotional expenditures. Using IMS Health data, researchers studied therapeutic competition in the USA, Canada, France, Italy, Germany, and the UK in 1992 (Danzon and Chao, 2000). In looking at competition within a therapeutic class, the number of substitute molecules did not correlate with prices in most cases. These insignificant findings were attributed to the omission of discount and promotional spending variables (due to a lack of data). In France, Italy, Germany, and the UK, there was some evidence of therapeutic class entry having a small negative effect on the first entrant's price. This was potentially due to the increased number of me-too drugs in these countries, which manufacturers introduce for the purpose of obtaining price increases. According to the researchers of this study, countries with strict regulatory schemes encourage production of me-too drugs, rather than truly innovative drugs. Thus, competition at the therapeutic class level did not appear to be strong in any country, although the degree of competition varied based on the countries' regulatory environments and the significance of the omitted promotional and discount variables.

In summary, literature on competition within therapeutic classes has found the following:

- Despite entry of competing drugs (i.e. me-too drugs), first entrant (i.e. breakthrough drugs) prices continued to increase in real terms.
- Me-too drugs tend to enter at prices that are lower than the first entrant into the therapeutic class; however, once they gain brand recognition, they increase their prices substantially, usually at rates that far surpass the price increases of breakthrough drugs.
- Competition at the therapeutic class level is characterized by product differentiation in the form of quality and branding. Thus, both price and therapeutic efficacy (i.e. quality) must be taken into account in this model of competition.
- In order to differentiate their products in the therapeutic market, firms invest in promotional spending. Consequently, promotional spending is a significant factor that should be taken into account when analyzing competition in this sphere.

2.2.2 Sphere Two: Competition between Off-patent Original Brand and Generic Drugs of the Same Molecule

While there has been some evidence to the contrary[6], most researchers agree that generics are of the same quality as their original brand equivalents, as they are identical molecules, have equal bioavailability[7], and are therefore determined by the FDA to be bioequivalent. The FDA itself concludes that "there is no substantial evidence of significant differences, either in bioavailability or general quality (in terms of purity, potency, or other methods of quality control) between brand-name and unbranded products, or between products made by large and small manufacturers" (From Drug Product Selection, quoted in Hurwitz and Caves, 1988).

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[6] One study argues that because generic producers have less goodwill to lose, they may not invest as heavily in the fixed costs of quality control. It also points out that recalls and failed inspections occur proportionally more in the generic industry, despite the fact that final generic products have never shown evidence of inferior clinical performance. (Schwartzman 1976, quoted in Hurwitz and Caves 1988)

[7] Bioavailability measures the quantity and rate at which the drug's active ingredient reaches the bloodstream and the site of therapeutic action.

Thus, this thesis assumes that there is no quality difference between brand drugs and their generic equivalents in these developed country markets.

Since there are no differences in quality between original brand drugs and their generic equivalents, the Bertrand model of competition between identical products might predict that post-patent competition erodes high brand name prices that were set while under patent, thereby driving down expenditure on that drug. However, a review of the literature below shows that this is not the case. In summary, the literature on competition between original brand drugs and their generic equivalents concludes that:

- Generic entry depends largely on the expected profitability in the market.
- Where generic entry does occur quickly, original brand name prices do not fall to comparable generic levels; in most cases, original brand prices stay at the same level, and in some cases actually increase after they go off patent.
- There are some discrepancies between studies as to how quickly these relatively high priced original brand name drugs lose market share; in most cases, the share they retain is significant.

In order to understand these findings, it is necessary to look more closely at the literature. The analysis on competition between off-patent original brands and their generic equivalents has been sub-divided into two thematic areas— first, the study of what factors determine the degree of generic entry, and, second, the study of original brands' prices and market shares after generic entry has occurred. The reason for reviewing both thematic areas is that while generic entry is a pre-requisite for competition, it is not a sufficient measure of the intensity of competition. The reason for considering them separately is that each follows a distinct model of competition that looks at a different set of explanatory variables. Studies that discuss both of these categories will therefore be referenced in both sections.

2.2.2.1 Generic Entry

Before the effects of competition on prices and market shares of original brand drugs can be analysed, generic entry must first take place. In the USA, however, this was not the case in the early 1980s. Research studying a sample of drugs from 1983 and 1984 revealed that 65% of the off-patent drugs did not face competition (Grabowski and Vernon, 1986). Suspecting that this was due to the

onerous FDA requirement that generic companies conduct their own clinical trials, the study compared these findings to pre-1962 drugs and antibiotics, whose generic manufacturers were not required to conduct their own clinical trials. Only 10% of drugs in these categories had no competitors. Thus, the study concluded that the USA' Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Act) would spur competition by allowing all generic manufacturers to simply prove bioequivalence with the brand name drug, rather than undergo their own clinical trials.[8] The study also noted that competition would increase as a result of extraneous environmental changes, such as the emergence of managed care and state substitution laws.[9] The study concluded by predicting that an increase in number of generic competitors would result in substantial price reductions.

The above prediction that the number of generic competitors would increase after the Hatch-Waxman Act proved correct. Another study researched 21 original brand drugs in the USA that went off patent between 1991 and 1993 and found that all but 2 of the 21 drugs experienced generic entry within one year of patent expiration; for many drugs, entry occurred within 3 months (CBO, 1998). These two studies show that the percentage of off-patent original brand drugs facing no generic competition decreased from 65% in the early 1980s to roughly 10% in the early 1990s.

The various market characteristics that may influence generic manufacturers' entry decisions have also been studied in the literature (Scott-Morton, 2000). By analyzing USA IMS Health data from 1986 to 1991 (the time period following the introduction of the Hatch-Waxman Act), the study sought to explore whether original brand manufacturers used advertising as a barrier to generic entry. In addition to detailing and journal advertising 2-3 years before patent expiration, some of the other explanatory factors the study regressed on generic entry[10] included: chronic

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[8] The Hatch-Waxman Act also extended the effective life of patents, and permitted generic manufacturers to go through the approval process before patent expiration. In addition, the Hatch-Waxman Act gave the first generic entrant a six-month exclusivity period, thereby de facto creating a short-term duopoly. The regulatory changes decreased the average generic entry delay (following patent expiration) from an average of three years to three months.

[9] By the early 1980s all states had repealed old anti-substitution laws that had forbidden pharmacists from substituting generic drugs for original brand drugs without the explicit permission of the physician.

[10] Generic entry was measured as the number of generic approvals within 1 to 2 years of patent expiration and the number of generic applications within 6 months—before and after—of patent expiration

condition dummy, the proportion of drug revenues from hospital sales, pre-patent expiration revenues and number of months the drug had been sold under patent (a proxy for goodwill). The results were not what the study had predicted. It had hypothesized that leading up to patent expiration, original brand manufacturers would use advertising as a strategic barrier to entry. Instead, the results surrounding the advertising variable were ambiguous, leading to the conclusion that advertising was not a significant barrier to entry. The largest predictor of generic entry was the revenue size of the drug market (a proxy for expected profit since marginal generic costs are so low). In addition, findings showed that generic entry was positively correlated with the percent of drug revenue from hospitals, and with drugs that treat chronic conditions. This indicates that the hospital market is more price sensitive than the retail market, and the chronic drug market is more price sensitive than the acute/sporadic drug market. The reason for the hospital market being more price sensitive is that hospital and retail pharmacy procurement practices differ, suggesting that the hospital and retail markets should be studied separately.

Using Swedish data from the Medical Products Agency (MPA) on 22 different molecules, another study researches the factors determining generic entry over the 1972 to 1996 period in Sweden (Rudholm, 2001). The study analyzed the effect that expected profit opportunities (measured by the original brand manufacturer's profit in the year preceding patent expiration), the age of the original brand drug, and regulatory changes had on the number of generic manufacturers that entered the market. By employing a fixed effects model for panel data analysis, it was able to estimate the effects for each specific substance at each point in time. In addition, the study attempted to quantify two regulatory changes—implementation of reference pricing and drug approval changes (which were similar to the Hatch-Waxman Act). However, the dummy coefficient for regulatory changes was not significant, perhaps because the two regulatory changes, which occurred in the same year, had offsetting effects. Similar to the above study, the most significant finding was that large profits was the biggest factor in attracting competing generic manufacturers. It also found that in general, entry was less frequent in markets where the original brand had a relatively long effective patent life[11].

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[11] During much of a drug's patent period, its manufacturer is still undergoing clinical trials and drug approval. Thus, effective patent life measures the time a drug was actually marketed while under patent. Although patents typically last around 14 years, the effective patent life (period of time the

Another study used USA IMS Health Data from 1978 and 1983, and, consistent with the above studies, found that the number of entrants increased with the total size of the market (measured in volume), and decreased with the original brand's length of effective patent life (goodwill stock) (Hurwitz and Caves, 1988). This study did find that to a degree, the original brand manufacturer's advertising deterred generic entry. However, findings showed that the original brand manufacturer decreased promotional spending as more generics entered. This study used data from before the enactment of the Hatch-Waxman Act. Thus, it is likely that original brand manufacturers were willing to invest in promotional activities in the year preceding patent expiration because generic manufacturers were far slower to enter the market under the burdensome approval requirements; benefits of promotional activities such as increased market size were therefore more likely to accrue directly to the original brand manufacturer.

The role of advertising as a deterrent to entry can be further understood through another study, in which findings were in agreement with Scott-Morton 2000—that promotional expenditures are not used as a deterrent to generic entry (Caves, 1991). Using IMS Health data on 30 drugs that went off patent between 1976 and 1987, the study found that on average, the original brand's promotional expenditures fell 10% two years before patent expiration, an additional 20% after the first generic entry, and an additional 40% and 20% when five and ten generics (respectively) entered the market. This supports the theory that original brand promotional expenditures are used to expand the drug market—not as a deterrent to entry—and that the free rider effect of generic entrants on expanded markets acts as a disincentive for original brand promotional spending. The study also found that original brand promotional spending declined more quickly in larger markets than in smaller markets. Since more generics enter larger markets (because of larger expected profitability), it is likely that promotional spending decreases faster in larger markets because of the increased free rider effect. Thus, the study concludes that while there may be some demand side barriers to generic entry (i.e. original brands' accumulated goodwill assets), original brand manufacturers do not attempt to thwart generic competition on the supply side with promotional or pricing

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drug can be marketed) is often around 8 years. In the US, regulatory changes under the 1994 Hatch-Waxman Act and the 1997 Food and Drug Administration Modernization Act have attempted to streamline and expedite the drug approval process in order to lengthen drugs' effective patent lives.

strategies.[12] Rather, original brand manufacturers take generic entry as a given, and optimize their return accordingly. It is important to note, however, that although the study uses data from before and after the Hatch-Waxman Act, it does not directly control for the regulatory change. Thus, the results could be biased, depending on the period of time in which most of the drugs went off patent.

Another study researches the determinants of generic entry in an attempt to identify strategies that original brand manufacturers may use to deter entry (Grabowski and Vernon, 1992). By using IMS Health data from 1984 and 1988, it studied generic entry for eighteen products during the period following the Hatch-Waxman Act. Also consistent with previous studies, it found that expected profitability (calculated as percent mark-up of original brand price over marginal cost at point of initial entry) was positively correlated with generic entry. The study did find that in four out of the eighteen cases, the original brand manufacturer attempted to stave off competition by differentiating its product. Such methods may include altering the delivery system (e.g. time-release capsules), taste, packing (to fill hospital dispensing units), or the appearance of a pill (e.g. the "purple pill"). In one case, the introduction of a "slow-release" dosage form succeeded in capturing 81% of the sales in the molecule market post patent expiry of the originator. However, the study found that in most cases, original brand manufacturers did not attempt to thwart entry through these product differentiation strategies mentioned above, or through price or promotional strategies.

Finally, a recent study models the effect that regulation (e.g. reference pricing arrangements) and product differentiation have on generic entry (Kanavos, Costa-Font and Seeley, 2008). Unlike the above studies that primarily focused on one country, this study analyzes the factors that influenced the generic entry of 12 molecule markets during the 2000 to 2005 time period in the UK, Germany, France, Spain, Italy, Canada and the USA. Thus, it is able to offer a comparative analysis on the determinants of generic entry in regulated (Germany, Spain, France, Italy) and less regulated (the USA, UK and certain provinces of Canada) countries and by

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[12] In some industries, the original brand manufacturer could use its monopolist position to drop prices as a means of deterring entrants. However, research clearly shows that original brand manufacturers do not take this approach, indicating that sunk costs for generic manufacturers may not be very high, especially in light of the improved regulatory approval process. One study acknowledges that while there may be some technical difficulty in developing a generic drug, there are no substantial scale-economy barriers in production or distribution (Caves, 1991).

studying originator and generic competition at molecule level and at company level.[13] Findings were consistent in both the molecule level and company level models; reference price systems were positively associated with generic entry. Given the downward rigidity of generic prices in reference price systems, it is not surprising that reference price systems encourage generic entry, as downward price rigidity implies relatively high expected profits for generic manufacturers, which is consistent with the above studies' findings that expected profitability is positively correlated with generic entry. Moreover, product differentiation (measured as the number of formulations and the number of presentations) was also found to be positively associated with generic entry, which suggests that product differentiation enables increased marketing opportunity for generics.

In summary, research on generic entry shows that:

- The strongest determinant of entry is market size/market profitability.
- Accumulated goodwill assets deter entry to a degree, although not enough to offset the positive correlation associated with a profitable market.
- Original brand promotional/advertising expenditures do not significantly deter entry.
- Assuming the regulatory/approval costs are low, generic entrants face few supply side deterrents. Thus, original brand manufacturers do not attempt to optimize their return by thwarting competitors. Instead, they pursue a 'market harvesting strategy,' which this thesis discusses in the section below.
- Reference price regulations and opportunities to product differentiate further encourage generic entry.

2.2.2.2 Original brands' Prices and Market Shares after Generic Entry

In addition to assessing barriers to entry, one of the above studies focuses on determinants of pharmaceutical competition by analyzing original brand manufacturers' post patent price responses (Grabowski and Vernon, 1992). Findings

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[13] Germany has been categorized as a regulated country because of its reference price system, which has historically applied only to off-patent drugs. In the case of in-patent drugs, pharmaceutical pricing in Germany is predominantly unregulated. In the case of Canada, certain provinces have implemented reference pricing, while others have not. The degree of regulation in Canada therefore depends on the province in question.

show that despite generic entry, the prices of original brand drugs increased faster than inflation, and faster than their therapeutic category's producer price index. Anti-infective drugs were the only cases in which the original brand prices decreased relative to their therapeutic category. Despite the relatively high prices that the original brand manufacturers maintained, in most cases, generic manufacturers had only gained roughly half of the market two years after entry. Thus, the study concludes that the market for a given molecule is segmented into two groups—a price sensitive group that the generics capture, and a price insensitive, brand loyal group that the original brand retains. The existence of a brand loyal, price insensitive group suggests that the original brand enjoys a 'first mover advantage.' Being the first to enter the market gives the original brand manufacturer the advantage of being able to keep prices relatively high, while continuing to hold on to a significant share of the market. Notably, the study finds that generic manufacturers achieved a larger market share for inpatient drugs than for retail drugs. Hence, the first mover advantage is greater for retail drugs.

Another study models the original brand price responses of 32 drugs from a variety of therapeutic areas that experienced generic entry between 1984 and 1987 (Frank and Salkever, 1997). A fixed-effects model is estimated that assumed generic entry to be exogenous as well as a random-effects model with instrumented generic entry variables (time since patent expiration and market size before patent expiration). Both models were consistent in showing that generic entry was associated with original brand price rises. Specifically, the parameter in the fixed-effects model showed that each generic entrant is associated with a .7% rise in the original brand price.

In one of the other studies above, researchers analyzed original brands' price responses in the USA by studying a sample of 34 original brand retail drugs that first faced generic competition after 1991 (CBO, 1998). Findings showed that after generics entered the market, original brand prices continued to rise faster than inflation. Specifically, the average original brand price increase between 1991 and 1994 was 22%, compared to a price increase of 24.5% for brand drugs that did not face generic competition over the same period. Meanwhile, original brand drug prices that faced generic competition before 1991 increased by a similar 22.4%. Thus, this study concludes that generic competition does not precipitate a decrease in original brand prices (unless this competition leads to original brand discounts that

are not reflected in the data). However, it finds that in seven cases, generics were able to achieve a market share of 65% or more by 1994, compared to a generic market share of 50% in the above study (Frank and Salkever, 1997). This difference could be due to the two studies' different time periods. The above study (Frank and Salkever, 1997) took place immediately following the Hatch-Waxman Act implementation, whereas these researchers (CBO, 1998) conducted their study nearly a decade after the act. Thus, it could be that as a lagged response to the changed regulations, generics entered the market more quickly and in larger numbers during this study's time period, leading to lower generic prices, and hence a larger generic market share.

In the late 1990s, another study researched price and market share competition between original brand and generic drugs, this time separating the data into two time periods—8 drugs that experienced patent expiration between 1986 and 1987, and 11 drugs that experienced patent expiration between 1989 and 1992 (Grabowski and Vernon, 1996). On average, the generic drugs in the earlier time period gained a 38% market share within a year of entry, compared to a 50% generic market share for drugs in the later time period. These findings support the above theory that generic market share was larger in studies from the early 1990s than in studies from the mid 1980s because of the increased generic competition that resulted in the years following the Hatch-Waxman Act. Notably, this study and the CBO study above report differing generic market shares for drugs in the early 1990s—50% in this study and 65% in the CBO study. One possible explanation for this difference could be that they used different samples of drugs, as well as different data sources. The researchers of the CBO study also point out that their findings may differ from these findings because they included all formulations of a drug in their market share calculations, even if certain formulations were still on patent. Their reason for doing this was to take into account the three year extended patent exclusivity period original brand manufacturers have to introduce a new dosage form, such as time-release tablets. For these reasons, comparing the generic market shares across studies is not an apples to apples comparison. Nonetheless, these studies' findings consistently show that during the 1980s and the 1990s, competition between original brand drugs and their generic equivalents in the USA seems to have increased in the form of faster generic entry and increased generic market share. At the same time, the above studies show that original brand drugs continued to enjoy a

first mover advantage by continuing to increase their prices after generic entry and maintaining a significant market share (albeit a decreasing market share over time as generics penetrate the market).

The above studies show that original brand prices continued to increase after generic entry. However, some studies report relative original brand price decreases after generic entry. In its examination of 30 drugs whose patents expired between 1976 and 1987, a study reported that although the prices of many original brand drugs increased after generic entry, they increased at slower rates than they would have in the absence of competition (Caves, 1991). The study concludes that with five generic competitors, brand name prices were on average 8.5% lower than they would have been; with ten generic competitors, prices were 15% lower. Despite these slowed price increases, an average generic/branded price ratio of .456 (with five generic competitors) only led to a generic market share of 25.2%. Thus, findings in this study are consistent with the conclusion that original brand drugs and generic drugs segment the market into price insensitive/brand loyal and price sensitive groups. According to the author of this study, "the relatively muted brand price response, the small market share generics achieve despite their relatively low prices, and the different effects that generic entrants have on generic prices than on brand prices" are evidence of this product differentiation (Caves, 1991). Consistent with other research findings, this study also finds the hospital market to be more price sensitive than the retail market; original brands' price responses to generic entry were roughly 70% larger in the hospital market.

Most research finds little price competition between generic manufacturers and original brand manufacturers. However, multiple studies show or acknowledge that this is not the case with the anti-infective class of drugs. One of the above studies found that anti-infectives were the only drugs whose original brand prices decreased (relative to their class) following generic entry (Grabowski and Vernon, 1992). Both this study and the CBO study note that compared to other therapeutic classes, antibiotics experience rapid generic entry, large generic market share and strong price competition (CBO, 1998). Using USA IMS Health data from 1985 to 1991, one study analyzes the elasticities of cephalosporins, an anti-infective class of drugs, at both the therapeutic level and the molecule level (Ellison, 1997). The high elasticities between original brand drugs and their generic substitutes supported the

assertion that the anti-infective class is characterized by unusually high price competition.

Wiggins and Maness use USA IMS Health data to analyze price competition in the anti-infective class from 1984 to 1990 (Wiggins and Maness, 2004). Based on the assumption that the firms in their study are identical, they theorize that the main determinant of price for a given molecule is the number of generic and brand competitors. In contrast to the above studies, findings show that original brand prices significantly declined with generic entry. Thus, this study concluded that original brand drugs and generic drugs do in fact compete on price, and that the first mover advantage theory (that predicts market segmentation between the price sensitive group and the price insensitive/ brand loyal group) does not hold true. It does not, however, acknowledge that its findings may contradict the above studies because the anti-infective class is unique. One possible explanation for why competition in the anti-infective class differs in the USA is that historically, many anti-infective drugs had not been subject to the burdensome FDA approval regulations that the Hatch-Waxman Act repealed.

With the exception of anti-infectives, research consistently shows large price differences between original brand drugs and their generic equivalents. However, the extent to which large price differences result in decreased original brand market share differs across studies, and across therapeutic class. Recall that the studies above show generic market shares that range from 25.2% to 65%. These market shares depend on the study's time period (which reflects different regulatory environments), the number of competing generic competitors, and the original brand vs. generic price difference.[14] In addition, the extent to which large price differences influence generic market share could also depend on the therapeutic class. Using Swedish data from the MPA from 1972 to 1996, another study analyzed the effect of time (a proxy for innovation), relative brand vs. generic prices, and the reference pricing system on the original brand market share for fourteen therapeutic classes (Aronsson, Bergman and Rudholm, 1998). Findings show that in five of the fourteen classes, large price differences resulted in a significant original brand market share decrease. For three of the classes, the reference pricing system had a significant negative effect on original brand market shares. Consistent with above studies, these

[14] All three of these variables could be endogenous.

findings show varying degrees of price sensitivity across therapeutic classes, depending on whether the class is more concentrated in the hospital or retail market, and whether it treats chronic or acute conditions. In the hospital market, it could be that demand is more price sensitive because hospitals have more incentive to keep costs down (through hospital-wide formularies that physicians must follow) than individual physicians who prescribe in the retail market. Regarding the chronic vs. acute market, it could be that patients with chronic conditions are more price sensitive because they have more time to look for the lowest price. Or, it could be that costs add up more quickly with chronic conditions, creating a greater financial incentive for patients to shop around.

In summary, literature on the effect of generic competition on original brands' prices and market shares, has found that:

- In most cases, original brand prices do not moderate after generic entry; in some cases, they may even increase at a faster rate.
- Unlike other therapeutic classes, the entry of generic competitors in the anti-infective class seems to result in decreased original brand prices.
- Competition may result in varying levels of generic market share. In general, research shows that generic market share correlates positively with the number of generic competitors, the original brand vs. generic price difference, the time period (in the case of the USA), the hospital (vs. retail) market, and chronic (vs. acute) conditions.
- Original brand manufacturers seem to follow the market harvesting strategy, which is "the maintenance of premium price positions while market shares erode over time" (Grabowski and Vernon, 1992).

2.2.3 Sphere Two: Competition between Off-patent Generic Drugs of the Same Molecule

As shown in Figure 1-3 in Chapter 1, a large body of literature has focused on competition between off-patent drugs. More specifically, competition between off-patent original brands and their generic equivalents is most commonly studied because of payors' expectations that once a drug loses its patent protection, competition should ensue and prices should decline. In addition, differences in quality attributes do not exist, in principle, in this sphere, making the model of

competition potentially simpler to study. Comparatively, studies on competition between patented drugs in a therapeutic class must account for more complicated factors such as quality differences, promotional expenditures, and significant market growth. Nonetheless, research has still sought to define this model of competition. However, in the case of competition between off-patent generic drugs made from the same molecule, many studies that acknowledge this dimension of the broader second sphere (competition between off-patent drugs) have only done so as a side note, while focusing on competition between original brands and their generic equivalents. Only a few studies have actually attempted to model some of the determinants of competition amongst generics of the same molecule (Kanavos, Costa Font and Seeley, 2008; Hollis, 2002; Frank and Salkever, 1997).

Studies sometimes assume that off-patent generic medicines belong to a commodity market where no product differentiation exists and where competitors compete purely on price. For this reason, some studies that have examined competition between generics have focused on the correlation between the number of competitors and generic prices (Caves, 1991; CBO, 1998). One study found that the average prescription price of a generic drug with 1 to 5 generic manufacturers was $23.40, compared to the average price of $19.90 with 16 to 20 manufacturers (CBO, 1998).

In addition to modelling the original brand price response (i.e. the price insensitive portion of the market) to generic entry, one of the above studies also modelled the effect of generic entry on the average generic prices for each given molecule (i.e. the price sensitive portion of the market). In this case, the number of generic entrants was treated as an endogenous variable. The model found that each generic entrant was associated with an average generic price decline of between 5.6% and 7.2% (Frank and Salkever, 1997).

Another one of the studies above also includes the "generic versus generic" competition dimension in its analysis by modelling the determinants of company level generic prices and the determinants of the minimum generic prices across 12 molecules in the UK, USA, France, Germany, Spain, Italy and Canada (Kanavos, Costa-Font and Seeley, 2008). At company level, generic prices appear to decline over time. Reference pricing has a small, but sluggish downward effect on generic prices at the company level (-1.4% to -2.7%), in comparison to non-reference price systems. This is intuitive in that because health insurance systems adjust reference

prices over time, any decrease in generic prices would result in a downward ratchet effect for all generic reimbursement. Moreover, product differentiation (measured as the number of formulations and number of presentations) is found to be associated with price increases, which is consistent with the fact that product differentiation is also associated with increased generic entry. This suggests that manufacturers are able to avoid unbridled price competition by altering the formulation, package size and/or strength of their horizontal products (i.e. products of the same molecule). Interestingly, the lowest generic prices seem to increase marginally over time, although findings reveal that the reference price system reduces the minimum generic price by up to 47% in countries where reference pricing systems exist. However, while this study models the determinants of the lowest generic price, it does not provide information on how the market shares of these lowest price generics differ across countries.

Two studies do analyze the nature of competition amongst generics by focusing on the market shares of the products (of the same molecule). One was an exploratory study that observed the prices of generic drugs and their corresponding market shares (Grabowski and Vernon, 1992). The findings were somewhat uncharacteristic of a commodity market in that generic prices varied significantly, and in half of the 18 molecule markets studied, the lowest price generic did not achieve the largest market share. In some cases, the first generic entrant captured the largest market share, despite its relatively high prices. These findings indicate the possible existence of a first mover advantage amongst generics in the US, which may partially reflect the six month exclusivity period that first generic entrants receive as a result of the Hatch-Waxman Act.

The second study focused on the possible existence of first mover advantages amongst generic entrants. Findings suggest that a first mover advantage exists amongst generics in Canada, potentially due to pharmacist preferences and patient switching costs[15] (Hollis, 2002). Specifically, the first generic entrant is able to maintain 25-30% more market share (compared to what it would have achieved had it not been first) for at least the first 4 years. Moreover, the benefits of the first

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[15] The patient switching costs that are incurred when pharmacists switch from one generic manufacturer to another generic manufacturer reflect the time that pharmacists may need to spend in order to reassure patients that despite possible differences in packaging, their new generic medicine should have the same quality attributes as their old generic medicine.

generic mover are often reaped by pseudo-generics (generics that are marketed by the original brand manufacturer), thereby discouraging future entry and hence generic competition. The study also concludes that the reference pricing system, which reimburses the lowest cost generic in Canada, actually inhibits price competition by forcing all generic competitors to follow suit when one company cuts prices (less resort to the inevitable loss of market share that ensues when patients are forced to pay the difference between the reference price and the actual price). The result is that generic manufacturers have no financial incentive to cut prices, as they would not achieve a larger market share in exchange for doing so (since most other manufacturers would also cut prices). This finding is consistent with the previous study (Kanavos, Costa-Font and Seeley, 2008), which also finds reference pricing to result in generic prices moving sluggishly downwards.

In summary, literature on competition between generic equivalents has found the following:

- In general, average generic prices decline as the number of generic competitors increase.
- In many cases the lowest price generic does not achieve the largest market share; there is also some evidence of a first mover advantage amongst generics.
- Reference pricing seems to result in generic prices moving sluggishly downwards, while product differentiation results in relatively higher generic prices and therefore less generic price competition.

2.3 Gaps in the Literature and the Contribution of this Thesis

Having reviewed the literature on competition in pharmaceutical markets, we now turn attention to the gaps in the literature and the contribution this thesis makes to the literature on pharmaceutical competition. In particular, the thesis makes empirical as well as theoretical contributions and also adds a comparative dimension in the analysis of competition in pharmaceutical markets.

2.3.1 Empirical Contribution: Three New Dimensions of Generic Competition, a Closer Look at Cost Control Potential

Given that pharmaceutical competition is so complex and multidimensional, it is not surprising that there are many gaps in the literature. Literature on

pharmaceutical competition seems to have targeted the well-known dimensions, which are easily researchable and in which pharmaceutical policymakers have traditionally sought to contain the cost of prescription drugs, namely competition between in-patent drugs of the same therapeutic class (in order to understand the effect that the introduction of follow-on drugs may have on prices and, therefore, on pharmaceutical spending) and competition between off-patent original brand and generic drugs of the same molecule. However, research has not sought to study pharmaceutical competition between off-patent drugs of differing molecules or between in-patent drugs and off-patent drugs of differing molecules within a therapeutic class (see Figure 2-2 below). Moreover, within the sphere of competition between off-patent drugs of the same molecule (original brand versus generic and amongst generics), research has primarily been conducted at aggregate levels. For example, individual product prices are often aggregated to the molecule level by using average or weighted prices. In a relatively disaggregated example, product prices were only aggregated to the manufacturer level (Kanavos, Costa-Font and Seeley, 2008). Thus, to date, no study has modelled prices at the most disaggregated level, the presentation level. This "presentation level" reflects the fact that there are a large number of ways in which pharmaceutical products of the same molecule may be packaged. The strength and formulation may vary as well as the package size, and with a number of manufacturers competing in the same molecule market, this may result in a large permutation of competing "presentations."

In order to understand the true nature of price competition amongst generics and the degree of purchasing efficiency that payors have achieved, this thesis contributes to the literature by studying price competition amongst generics of the same molecule at the product presentation level. Theory may predict that homogeneous products such as generics compete in a commodity-like market. However, a recent study suggests that this may not be the case (Kanavos, Costa-Font and Seeley, 2008). Rather, factors such as regulations and product differentiation may result in a more complex picture where countries may have differing degrees of price competition amongst generics, resulting in more or less efficient generic purchasing. This thesis argues that it is by understanding price competition at the disaggregated, presentation level, that the effect of factors such as product differentiation and regulations on price competition amongst generics can really be understood. In addition, evidence suggests that although the average generic price

declines with increased generic entry, the lowest priced drug does not necessarily achieve the largest market share, a finding that highlights the need for more in-depth research on competition amongst generics (Grabowski and Vernon, 1992; CBO, 1998). Thus, this case on competition amongst generics further contributes to the literature by analysing the full distribution of these presentations' prices, which must be understood in order to determine the extent to which actual purchasing practices are taking advantage of the lowest prices.

Secondly, this thesis contributes to the literature by studying the degree of competition between off-patent original brand and generic drugs and amongst generics of the same molecule at the strength level (within a molecule market). For example, this thesis studies competition between the original brand and generic products in the 10mg omeprazole market separately from original brand and generic products in the 20mg omeprazole market. This is different from existing literature, where all studies of original brand versus generic competition within molecule markets aggregate the various strengths of a molecule by standardizing presentations' strengths and package sizes. In doing so, they are able to calculate overall generic penetration levels within the broader molecule market. While this may provide a seemingly clear picture of the degree to which policymakers have succeeded in encouraging generic penetration, the reality is that it may mask differing degrees of generic penetration across strength segments within a molecule market, to the extent that strength segments of a molecule behave as separate submarkets. This thesis will therefore contribute to this gap in the literature by analysing competition between off-patent original brand and generics and amongst generics of the same molecule at the strength segment level in order to assess the extent to which the nature and degree of competition is the same across strength markets of the same molecule. To the extent that the degree of competition between the original brand and generic products and amongst generics differs across strength segments of the same molecule, policymakers who are seeking to improve purchasing efficiency may want to introduce policies that encourage competition in the less competitive strength markets.

Thirdly, this thesis will explore OTC versus prescription drug competition of the same molecule. Policymakers and researchers alike assume that altering the mix of original brand versus generic prescription products (either retail or hospital) achieves the greatest savings within a molecule. However, in the process of focusing

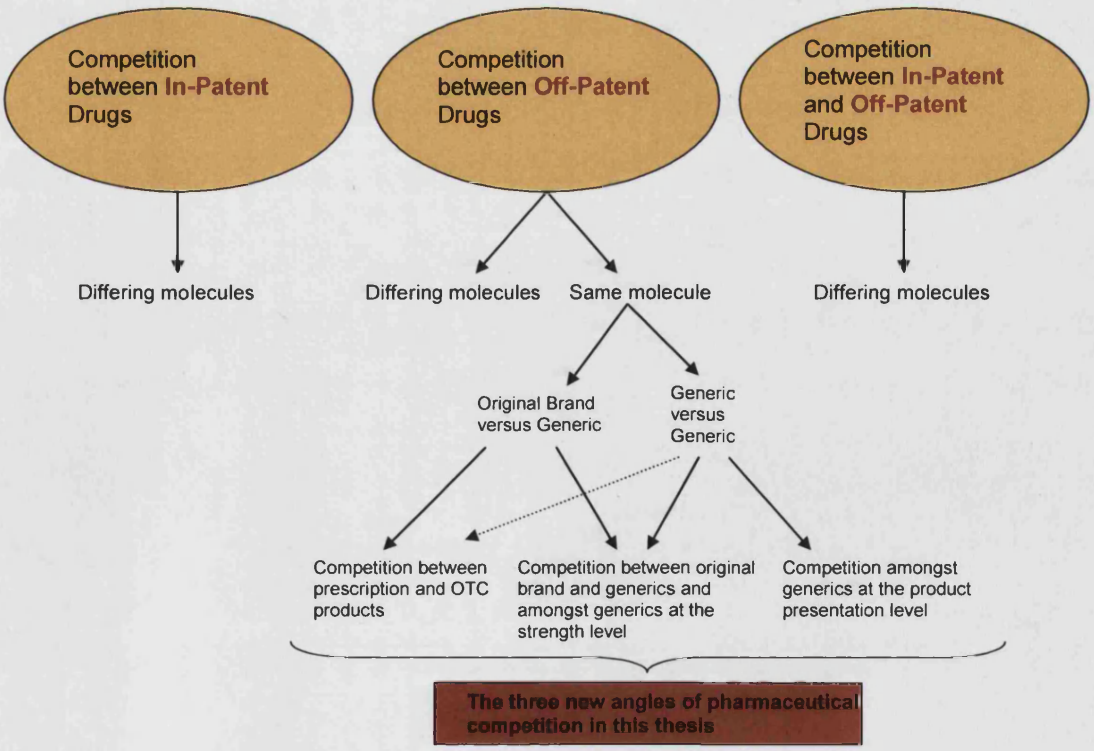
on only the prescription market, they ignore other ways in which purchasing efficiency within a molecule could be improved. For example, where a molecule is available through both the prescription and over-the-counter distribution channels, market share competition between the over-the-counter and prescription products could shift demand toward lower cost over-the-counter drugs. The literature on OTC switch estimates the total cost savings that individual purchasers have achieved in switching members to an OTC drug (West, 2006). However, no study has yet analyzed the interface between OTC and prescription markets and the type of competition that may ensue for a molecule that has been switched to OTC status. Thus, this thesis addresses this gap in the literature by studying whether OTC and prescription drug products of the same molecule actually compete in the same market (i.e. compete for some of the same patients) and if so, whether they engage in price competition. By doing so, this study may then help to inform policymakers on the extent to which the OTC market acts as a compliment or a substitute to the prescription market (of the same molecule), and therefore whether approving an OTC switch is cost saving or cost increasing.

In summary, Figure 2-2 depicts the three new dimensions of competition between off-patent drugs of the same molecule that this thesis studies—generic vs. generic competition of the same molecule at the presentation level, competition between off-patent original brand and generics and amongst generics of the same molecule within strength segment markets and prescription versus over-the-counter competition of the same molecule. By studying the extent of competition within these unstudied dimensions of the molecule market, the thesis provides a more detailed, sophisticated understanding of pharmaceutical competition between drugs of the same molecule and offers a newfound understanding of ways in which payors could more efficiently contain pharmaceutical expenditures. The findings are also particularly relevant to the pharmaceutical policy arena since countries have implemented so many policies that aim to increase genericisation, without necessarily taking into account the market dynamics in off-patent markets.

A further strength of focusing on unstudied dimensions of pharmaceutical competition within molecule markets (as opposed to *across* molecule markets) is that these studies can empirically estimate the implications that the findings have on purchasing efficiency without having to contend with issues such as quality differences between differing molecule. Although some recent pharmaceutical

policies have begun to encourage substitution within therapeutic classes (see the description of countries' pharmaceutical policies in Appendix A), this practice is controversial and carries with it a host of complicated issues such as measures of cost-effectiveness and quality issues for patients, which make it difficult for policymakers to determine what purchasing practices are efficient at this level. Thus, the studies in this thesis have the potential to make significant contributions to enhancing the effectiveness of pharmaceutical purchasing efficiency since their recommendations are more politically acceptable than recommendations to improve purchasing efficiency on the therapeutic level. Although a comprehensive study of the therapeutic markets are outside of the scope of the thesis, it should be acknowledged that these molecule markets likely do experience some degree of competition from other molecules in their therapeutic class, and that further research in this area would also fill a significant gap in the literature and may contribute to policymakers' understanding of pharmaceutical competition as well as the implications of certain, more recent policies, such as Germany's therapeutic level reference pricing.

Figure 2-2 Three New Dimensions of Pharmaceutical Competition



Source: The Author

2.3.2 Theoretical Contribution

By analyzing the nature of competition within three unstudied dimensions of the molecule market, this thesis makes an empirical contribution by offering a newfound understanding of ways in which payors could more efficiently contain pharmaceutical expenditures. In addition to this empirical contribution, these studies also make a theoretical contribution to the current understanding of the industrial organization of competition within pharmaceutical molecule markets. Industrial organisation theory predicts that manufacturers of homogeneous goods may compete on price as long as their capacities are not restricted by increasing marginal costs of production and assuming that manufacturers are not able to product differentiate (Tirole, 1988). This would be consistent with a Bertrand model of competition, where manufacturers engage in unbridled price competition, resulting in prices converging to marginal cost and market shares distributing evenly.

However, the literature review reveals that in the case of competition between original brand and generic manufacturers, original brand manufacturers follow a Market Harvesting Strategy, where they keep their prices flat or even increase their prices, in exchange for accepting the inevitable loss of the price sensitive portion of the market. On a theoretical level, this would be a case of original brand manufacturers leveraging their products as Experience Goods (Tirole, 1988), i.e. goods that some consumers are hesitant to substitute due to their positive historic experience. Thus, in the case of competition between the original brand versus generic equivalents, the null hypothesis is that the original brand manufacturers follow the market harvesting strategy. However, because policy makers have been increasingly aggressive about mandating or encouraging generic substitution, the null hypothesis must also acknowledge that original brand manufacturers may be limited in their ability to retain a significant share of the market, even in cases where a significant share of patients may have otherwise been brand loyal. By analyzing original brand versus generic competition at the strength level, this study expects to accept the part of the null hypothesis that original brand manufacturers continue to pursue the Market Harvesting Strategy, but to reject the part of the null hypothesis that assumes that original brand manufacturers no longer have any recourse for maintaining significant market share in the current policy environment that favours generic substitution. Instead, this study expects that analyzing competition at the

strength level will reveal ways in which original brand manufacturers remain relatively shielded from generic competition, such that the market harvesting strategy is more long-lasting in certain strength segments of the molecule market than theory would predict.

On generic versus generic competition, the null hypothesis is that generics within a molecule market are homogeneous goods that are not constrained by increasing marginal costs of production and therefore follow the Bertrand model of perfect price competition. As discussed in the literature above, there is some evidence suggesting that generic manufacturers may be able to product differentiate, thereby avoiding unbridled price competition (Kanavos, Costa Font and Seeley, 2008). As a result, this study expects to reject the null hypothesis of Bertrand price competition. Instead, it expects that while the nature of competition is likely to resemble the Bertrand model in some ways (by being based more on prices than market share as a result of fairly flat marginal costs), generic manufacturers' abilities to differentiate their products results in generics no longer being perfectly homogeneous, resulting in an equilibrium of ranging prices and unevenly distributed market shares.

Finally, the study of OTC versus prescription drug competition contributes to theory by exploring the nature and degree of competition in a molecule market that is fragmented by differing demand-side characteristics and regulations. While industrial organization theory does not seem to directly address such a circumstance, this study's null hypothesis is that prescription and OTC markets do not engage in direct competition as a result of being approved for different uses. This study expects to reject the null hypothesis, in favour of the fact that despite differing regulatory guidelines and fragmented demand sides, OTC and prescription manufacturers may engage in direct competition, where the regulations and patient incentives are aligned correctly. In this case, OTC products may become a form of product differentiation within the broader molecule market, rather than existing as an independent market from the prescription market, which likely results in a model whereby certain manufacturers are able to sustain profitable prices and relatively large molecule market shares by marketing in the OTC category, despite still facing some degree of competition from the prescription market.

In conclusion, the thesis makes a theoretical contribution to the current understanding of the industrial organization of competition within pharmaceutical molecule markets by exploring the three dimensions of competition.

2.3.3 Comparative Perspective

The problem of pharmaceutical cost containment is similar in many developed countries, making comparative studies across countries particularly valuable. One cannot assume that a hybrid of solutions in one country is directly generalizable, as each country is unique politically, culturally, and economically. However, facing similar problems and applying similar policies does mean that there is potential for countries in this thesis (and several other developed countries) to learn from each other, and to apply similar generic drug policy approaches or principles. Moreover, there is evidence that in some cases, even where local circumstances differ, general health system ideas and micro-instruments, such as diagnostic related groups, may be transferrable between countries (Klein, 2003).

Many of the studies that model the determinants of competition (rather than just observing price differences) focus on a single country, typically the USA[16], making it difficult to assess the extent to which findings are attributable to confounding or unobservable factors. Modelling competition in the context of this thesis (generics versus generics at the product presentation level, prescription versus OTC, competition within strength markets of a molecule) across countries helps to shed light on the extent to which findings are unique to the country's own pharmaceutical regulatory environment and market characteristics versus similar across countries and therefore more reflective of pharmaceutical markets in general.

There have been a number of studies that compare pharmaceutical prices in Western Europe and North America. These then broadly attribute their findings to countries' regulatory and health system differences (Johnson, 1994; Rovira, 2001). However, these do not attempt to fully model the determinants of competition, and thus, do not have a genuine understanding of the individual factors that influence price differences. Thus, this thesis identifies similar trends and commonalities across countries, and highlights differences, in order to gain a greater understanding of how

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[16] There are also some articles on Sweden and Canada (Rudholm 2001; Wiggins and Maness 2004;Lexchin 2004).

pharmaceutical policies relate to off-patent drug markets and of how the pharmaceutical prices and corresponding market shares differ across settings.

CHAPTER 3: METHODOLOGY

3.1 Introduction

This thesis adopts a case study approach to assessing the nature and degree of competition in the omeprazole and paroxetine off-patent retail molecule markets in Germany, France, the UK and the USA, using IMS Health data during the 2000q1 – 2005q1 time period. [17] Three dimensions of competition are analysed: 1) generic versus generic competition at presentation level in Germany, France, the UK and the USA, 2) competition at strength level in Germany, France, the UK and the USA and 3) OTC omeprazole versus prescription omeprazole competition in the UK and the USA. Germany and France could not be included in the assessment of OTC versus prescription competition in this case because omeprazole has not been approved for OTC use in these countries.[18]

By restricting the study to two molecules, instead of a large sample of molecules, the analysis can shine light on various levels of competition over time and across countries in a way that a large sample could not allow. For example, in the analysis of strength markets of a given molecule, a case study approach enables this study to trace manufacturer-level market data over time in order to determine which strength markets (and how many) each manufacturer decided to enter into.

3.2 Sample

3.2.1 Molecules

The molecules in this thesis, omeprazole and paroxetine, have been chosen deliberately with the following factors in mind. First, omeprazole and paroxetine were both blockbuster drugs, drugs that are defined by the European Commission to have achieved annual global revenues of over USA $1 billion (European Commission, 2008). As a result, the estimates of ways to improve purchasing efficiency in these molecule markets may have significant cost saving implications

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[17] The research approach in this thesis is a quantitative adaptation to Kathleen Eisenhardt's qualitative case study, theory-building approach (i.e. the building of new theories through the use of hard evidence), through which this thesis can offer newfound insights on areas of competition that are in their early stages of research, which can act as a springboard for further theory-proving research (Eisenhardt 1989).

[18] Paroxetine is not available for OTC use in these countries, so could not be included in this study on OTC versus prescription competition.

for these countries. Furthermore, because these molecules treat chronic diseases, the long-term costs implications to payors further contributes to the opportunities for improved purchasing efficiency. Second, because their respective market sizes are large, they are likely to attract a relatively large number of manufacturers as market size seems to be a determinant of generic entry. This large number of competitors may result in individual manufacturers having to devise ways in which to remain profitable, which makes these markets ripe cases for studying manufacturers' attempts to product differentiate from other manufacturers in the market. Table 3-1 shows the 2004 market size (in USA dollars), number of manufacturers and number of product presentations in the omeprazole and paroxetine markets in Germany, France, the USA and the UK.

Table 3-1 Size of Omeprazole and Paroxetine Markets in 2004, measured by the Sales (USD), Number of Manufacturers and Number of Presentations

	2004 Sales (USD)		Number of Manufacturers in 2004q4		Number of Presentations in 2004q4	
	Omeprazole	Paroxetine	Omeprazole	Paroxetine	Omeprazole	Paroxetine
Germany	$611,993,000	$53,722,000	35	36	284	204
France	$317,382,000	$214,470,000	15	9	38	10
UK	$180,053,000	$85,723,000	7	5	38	14
USA	$903,099,000	$1,493,462,000	9	8	37	58

Source: The Author, using IMS Health data.

Third, both molecules belong to therapeutic classes that are the most therapeutically superior classes of treatment for their respective disease areas, which likely reduces the extent to which patients would switch out of these classes to another therapeutic class (Kaiser Family Foundation, 2005). Omeprazole was the first molecule to enter into the Proton Pump Inhibitor (PPI) therapeutic class of drugs, which treats gastroesophageal reflux disease, also known as acid reflux. Paroxetine was the second molecule to enter into the Selective Serotonin Reuptake Inhibitors class (SSRIs) of drugs, which treat depression, anxiety, and compulsive disorders. Fourth, by selecting molecules in the retail market that treat chronic conditions and where the most widely consumed form of medication is taken orally, these studies are able to eliminate a number of demand-side confounding factors that may arise in pharmaceutical pricing studies, namely the fact that price elasticities are higher for chronic diseases than for acute illnesses and the fact that demand conditions may vary between different formulations such as oral medication (tablets, capsules, etc.) and topical treatments. Consequently, it is likely that findings from

this thesis would be the most generalizable to the population of other drugs that are primarily concentrated in the retail market, treat chronic conditions and are taken orally. It should be noted, however, that omeprazole treats a physical illness, while paroxetine treats a mental illness. This could result in slightly different demand conditions, despite their other similar properties. However, all molecules that treat different illnesses are likely to experience somewhat different market conditions since each illness has a different set of characteristics that are unique to it (such as the patient population, the nature of symptoms, the seriousness of the disease etc.).

Fifth, omeprazole has been chosen because it has the unique characteristic of having been approved for dual prescription and OTC status around the same time period in two of these study countries, which enables this study to be the first of its kind to compare the nature of and extent of prescription versus OTC competition across regulatory settings.

3.2.2 Countries

The study countries are the USA, UK, Germany and France because their pharmaceutical policies represent four different national approaches to pharmaceutical regulation. On one end of the spectrum, the USA has one of the most unregulated pharmaceutical pricing environments, whereas on the other end of the spectrum, France has historically had a much more tightly regulated pharmaceutical pricing environment. In a case-study theory-building research approach, researchers note that "given the limited number of cases which can usually be studied, it makes sense to choose cases such as extreme situations and polar types in which the process of interest is 'transparently observable'" (Eisenhardt, 1989). The salient features of each country's supply-side off-patent pharmaceutical policies are briefly discussed in the paragraphs below. In addition, Table 3-2 summarises policies in each of the study countries. It is important to note that in order to put the studies into context, these off-patent pharmaceutical policy descriptions match the selected study time period. A more comprehensive overview of the four countries' pharmaceutical regulations is provided in Appendix A.

In the area of off-patent pharmaceutical price regulation, the USA and the UK approaches may be characterised as free market-oriented, both for pricing and reimbursement, whereby manufacturers set prices, which are subsequently reimbursed by payors. Germany's approach consists of free pricing combined with a

reference pricing reimbursement system and France has historically implemented a system of price control for both original brand and generic drugs that has recently been combined with a reference pricing reimbursement system.

In the USA, the plurality of the health insurance system has led to a plurality of off-patent pharmaceutical pricing policies. For example, on behalf of the private insurance market and Medicare Part D enrolees, pharmaceutical benefit manufacturers may negotiate a percentage discount (in the form of a rebate) off retail prices directly with the manufacturers. Distribution chain discount practices are also permitted. Meanwhile, Medicaid stipulates a percentage discount for off-patent drugs, while the uninsured face full retail prices in most cases.

In the UK, the NHS reimburses one price for generics of the same molecule, called the Drug Tariff, that is based on freely set manufacturer and wholesaler prices. Similarly to the USA, distribution chain discount practices are also permitted in the UK. However, in contrast to the USA, the UK's single payor system lends itself to a centralized purchasing policy for off-patent pharmaceuticals (in comparison with the USA's pluralist system of multiple purchasers and consequently, varying rebates), whereby the NHS is able to retain a share of these discounts in the form of a clawback from retail pharmacies.

Germany also allows manufacturers of off-patent pharmaceuticals to freely set prices. However, distribution chain mark-ups are regulated. In addition, Germany was one of the first countries to pioneer the practice of reference pricing, whereby sickness funds set one reimbursement price for each reference group (based on the price in the lowest third of the group). During the study period, this reference pricing was applied at the molecule level, which grouped together original brand drugs and their generic equivalents, although in recent years, Germany has also introduced reference pricing at the therapeutic level for certain classes.

Finally, France has historically stipulated that generic prices not exceed a certain percentage (30-40%) of original brand prices. In addition, distribution chain mark-ups have been regulated. Discount practices are also permitted, although these discounts occur within the distribution chain, so are not captured by payors. Around the turn of the century, France introduced a number of generic pharmaceutical policies with the aim of increasing generic penetration rates. As part of this initiative, molecule level reference pricing was introduced in 2003 for off-patent pharmaceuticals, although the molecules in this study were not included in this

reference price system during this study period. As a result, the generic molecules in this study were subject to the stipulated price cap percentages, which may have resulted in uniform pricing, to the extent that price caps act as price floors in practice.

3.3 Data Sources

The data used in the thesis come from Intercontinental Medical Statistics (IMS). IMS Health is a for-profit organization that contracts with pharmaceutical companies to provide pharmaceutical marketing research through a method of retail and hospital pharmacy sampling. For example, in the USA, IMS Health gathers its data by surveying 34,000 retail pharmacies, which includes independent pharmacies, chains, pharmacies within foodstores, mass merchandisers and mail order. In the USA, this accounts for over 60% of retail pharmacies and over 70% of the prescriptions filled (USA Department of Health and Human Services, 2000). This thesis has used IMS Health retail pharmacy (as well as food stores and mail order in the USA) price and sales data for omeprazole and paroxetine from 2000q1-2005q1 on a quarterly basis. Price and sales revenue data can be used to arrive at corresponding volume data. Data is presented by drug molecule name, country, manufacturer, strength, package size, formulation, and generic/brand status. OTC status is also discernable via the manufacturer's name. At this level, each observation is referred to as a presentation. Having access to data at this level of specificity is therefore highly valuable, as it enables subdivision of the omeprazole and paroxetine molecule markets into the relevant smaller markets such as generic markets, OTC markets, prescription markets and strength markets.

IMS Health is the gold standard data source for pharmaceutical market research, which is reflected in the fact that most of the above literature uses this data as well as the industry itself (USA Department of Health and Human Services, 2000). In addition, because it is the only consistent source of pharmaceutical market data that exists on an international level, it also allows comparisons across countries.

Because of the surveying method, the pharmacy retail prices are reflective of the actual purchased prices at the retail pharmacy level. This is therefore inclusive of pharmacy retail discounts in the USA as well as any discounts that are negotiated within the distribution chain in the USA and the UK. This makes IMS Health price data more reflective of the actual prices paid than the commonly quoted average wholesaler prices in the USA (see Appendix A for a description of average

wholesaler prices). However, these retail prices do not reflect manufacturer rebates in the USA since this information is proprietary. To date, the specific USA manufacturer rebates that are tied to each drug do not exist in any data source that is accessible to the public. Moreover, the manufacturer rebates in Germany are also not reflected in this data. Thus, Germany's and the USA's prices may be biased upwards. However, since the manufacturer rebates in Germany apply evenly to all manufacturers, they should not distort price competition since manufacturers' prices would still be the same, relative to one another. These data discrepancies are also discussed in the conclusion/policy implications chapter.

Finally, in the UK, the generic manufacturer's association has reached an agreement with IMS Health that some of the generic manufacturers' individual names be kept private. As a result, the UK is likely to have a few more generic manufacturers in the omeprazole and paroxetine markets than this data suggests, biasing the number of manufacturers downwards. These manufacturers' presentations are all included in the dataset, however, under an anonymous manufacturer named "unbranded." This dataset is therefore still inclusive of the total sales in the UK for these given molecules. None of the other variables are affected by this discrepancy.

3.4 Study Period

It is necessary to consider the study period, 2000q1-2005q1, in the context of the regulatory changes (see Appendix A for a full discussion). In the USA, there were not any large, centralized changes that should bias the analysis of pharmaceutical competition. Likewise in the UK, the 2000q1-2005q1 time period does not include any significant regulatory changes. In France, the introduction of the reference price system did occur during the 2000q1-2005q1 time period. However, omeprazole and paroxetine were not included in the French reference pricing system during this time period. Thus, the analysis on pharmaceutical market competition in France is more relevant for the molecules that have remained outside of the reference pricing system. The authorisation of pharmacist generic dispensing in France did occur during this time period as well. However, since both omeprazole and paroxetine did not go off-patent until after substitution became legal in 2002, any changes in generic demand in France should not be distorted by this policy change. Finally, in Germany, the significant price freezes did not occur during the 2000q1-

2005q1 period for off-patent drugs.[19] This is pertinent because the manufacturer price freezes in Germany would result in price freezes along the whole distribution chain since the margins are regulated. Thus, static retail prices could incorrectly be interpreted to reflect an uncompetitive market rather than the price freezes if the prices freezes had occurred during this period. Finally, the introduction of therapeutic reference pricing in Germany did apply to omeprazole in 2004, which is during this study period. However, since omeprazole was the first drug in its PPI class to go off-patent, it would likely have been the lowest priced as well. Thus, the recalculation of the reference price would likely have reflected the omeprazole prices regardless, assuming they were in the lowest third of the PPI prices, as the oldest and most genericised PPI products on the market.

In conclusion, it is important to reiterate that the analyses in this thesis reflect the regulatory environments in these countries during the 2000q1-2005q1 time period. Table 3-2 provides a summary of the key pharmaceutical policy components in these study countries during this study period.

[19] Recall that in Germany, from January 1, 2003 to December 31, 2004, patented drugs' manufacturer prices were frozen at the October 1, 2002 price level. In addition, the Act on Economic Provision with Pharmaceuticals introduced a manufacturer price freeze for all medicines (at the November 1, 2005 level) from May 1, 2006 to March 31, 2008 (OBIG 2006).

Table 3-2 Overview of Main Pharmaceutical Policies in the USA, UK, Germany and France during the 2000-2005 Study Period

	Patented Drugs		Off Patent: Generic and Original Brand	
	Supply-side	**Demand-side**	**Supply-side**	**Demand-side**
USA (free market approach with reimbursement rules set by private payors)	• Free Medicare and private payor pricing; possibility of discounts via formularies • Medicaid Best Pricing Rule; the better of 15.1% off AMP, or best price in private market	• Tiered co-payments • Prior authorisation for some physician prescribing • Some physician profiling	• Free Medicare and private payor pricing; possibility of discounts for private payors and MAC • Medicaid Best Pricing Rule; 11% discount off of AMP • No distribution chain mark-up limits • Discounting allowed in the distribution chain	• Co-payments • Generic substitution permitted • Some health plans offer higher dispensing fees to pharmacists for generics
UK (regulatory approach with free market incentives)	• Pharmaceutical industry profit control through Pharmaceutical Price Regulation Scheme (PPRS); 4% price cut • Cost-effectiveness guidance from National Institute of Clinical Evidence	• Co-payments for a select population (not tiered, so do not depend on brand/generic status or price) • Physician profiling	• Maximum reimbursement price • claw back from pharmacies • No distribution chain mark-up limits • Discounting allowed in the distribution chain	• Co-payments for a select population • Generic substitution not permitted • Physicians prescribe by INN •
Germany (free market & reference pricing)	• Free pricing • May use price freeze measures (not applicable during this study period)	• Molecule-level reference pricing still dominant (early phases of the therapeutic reference phase-in)	• Free pricing • Molecule-level reference pricing • Combination of flat and regressive distribution chain mark-up regulations	• Capped co-payments • Generic substitution permitted • Regional pharmaceutical spending caps (not necessarily enforced)
France (price setting approach)	• Free pricing for products without reimbursement status and price allowances for highly innovative products • Price setting through negotiations between government and industry; considers cost-effectiveness, prices of competing drugs, drug market size, industry's national presence.	• Some degree of cost-sharing, although most costs are covered by supplemental plans	• Stipulated 30% - 40% off branded prices • Early phase of molecule-level reference pricing phase-in (not applicable to products in this study) • Regressive Distribution Chain mark-up regulations • Discounting allowed in the distribution chain	• Permits generic substitution • Some degree of cost-sharing, although most costs are covered by supplemental plans • Physicians encouraged to prescribe generic through target schemes

Sources: The author, from OBIG 2006 and Kanavos and Gemmill 2005.

3.5 Conceptual Framework

The nature of competition within a market differs depending on whether the products are heterogeneous (vertical competition) or homogeneous (horizontal competition) and on the way in which manufacturers may be able to product differentiate. Tirole's book on industrial economics categorizes types of product differentiation into separate models of competition (Tirole, 1989). The commonality in all of these models, and in all areas of competition in this thesis, is that manufacturers try to avoid the Bertrand paradox of unbridled price competition by leveraging their distinctive product qualities. For example, drugs of differing molecules within the same therapeutic class are an example of vertical competition, whereby heterogeneous products can leverage their superior therapeutic efficacies.

Pharmaceutical competition within a molecule market, as is the case in the areas of competition that this thesis studies, is more nuanced since manufacturers of the same molecule must find ways in which to product differentiate other than quality. In the absence of product differentiation, manufacturers of homogeneous products may become vulnerable to the Bertrand model of unbridled price competition, which predicts that prices converge to marginal cost, while market shares distribute evenly. Under this scenario, pharmaceutical manufacturers of the same molecule would struggle to sustain a significant share of the market at profitable prices, thereby driving manufacturers out of the market. Since the product markets studied in these cases may be characterized as homogeneous (by nature of being the same molecule), the null hypothesis, in accordance with the Tirole's Bertrand model, is that these manufacturers engage in a fierce battle of price competition, which results in prices converging to marginal cost and an even distribution of market shares. In practice, however, it is more likely that pharmaceutical manufacturers of the same product have discovered ways in which to product differentiate and fragment the market such that their products may no longer be considered to be perfectly homogeneous. Evidence from the literature review indicates such practices in the form of original brand manufacturers product differentiating by leveraging their accumulated goodwill (brand loyalty) and generic drugs sometimes enjoying a first mover advantage and/or finding nuanced ways in which to product differentiate. Thus, based on the preliminary evidence to date, it is expected that the null hypothesis of perfect price competition in these markets of

supposedly homogeneous goods will be rejected in favour of a more complex picture, in which pharmaceutical products of the same molecule find ways to avoid a situation of Bertrand competition, whereby the degree of price competition is diluted by strategic product differentiation and fragmented markets. This then, is expected to result in an equilibrium of imperfect price competition whereby some manufacturers are able to hold on to significant shares of the market at relatively high prices.

This thesis assesses the nature and degree of competition within a molecule market amongst generics, within strength segments of a molecule and between the OTC and prescription market of a molecule. In the section below, a discussion on the relevance of Tirole's models of Bertrand, Cournot and Experience Goods competition (in the case of competition between original brand and generic manufacturers within strength segments) precedes the research question in order to put the research question into context. In addition, a more detailed discussion on the application of current industrial organization models to these cases is provided in the cases themselves. In these cases, Tirole's theoretical industrial economic models of competition are unlikely to apply perfectly. Instead, this thesis predicts that pharmaceutical manufacturers are able to alter the conditions of what would otherwise be homogeneous markets by product differentiating and fragmenting the market. In addition, certain market-specific characteristics such as reimbursement schemes and different demand-side structures (as is the case in the OTC versus prescription market case) make the pharmaceutical market unique, resulting in models of competition that do not conform perfectly to Tirole's models of Bertrand and Cournot competition (between homogenous products). Thus, in the process of assessing pharmaceutical competition in three, unstudied dimensions of the pharmaceutical market, this thesis makes a theoretical contribution to the literature by building new hypotheses on the nature of pharmaceutical competition in molecule markets. Further research on other molecule markets could then be conducted in order to support these findings.

3.6 Research Questions and Methods

3.6.1 Case 1: Competition amongst generics in the retail omeprazole and paroxetine markets in Germany, France, the UK and the USA, 2000q1-2005q1

3.6.1.1 Economic Theory Applied to Case 1

Because generics of the same molecule are therapeutically equivalent and by definition, do not have the competitive advantage of brand loyalty, it would seem that generics compete almost solely on price. This type of price competition would be an example of the classic Bertrand model, where both the products and the firms are assumed to be homogeneous, resulting in prices that converge to marginal cost, and evenly distributed market shares. Under this model of perfect competition, firms do not profit, even in the case where there are only two firms competing. In reality, the Bertrand model is an imperfect application for the generic market (and most other markets), as competing firms do possess certain proprietary advantages. Evidence shows that the lowest priced generics do not achieve the highest market share, which is contradictory to Bertrand competition (Grabowski and Vernon, 1992). Thus, it seems that some generics are able to retain market share while keeping their prices high, relative to the lowest price in the market. Two possible explanations for this that are offered in the literature are a first generic mover advantage and product differentiation, although current studies have yet to explore these concepts for individual molecule markets at the presentation level. It may be that since the unpredictable timing of the drug approval process often results in entry lags, the first entrant has an advantage. Alternatively, certain generic manufacturers may have the advantage of being more experienced in some therapeutic areas or being larger, and therefore having stronger client relationships in general. Thus, the current evidence indicates a market of imperfect Bertrand-like competition.

In determining whether competition amongst generics of the same molecule resembles the Bertrand model of perfect price competition, the Cournot model of competition between homogeneous goods must also be considered, whereby firms choose their quantities ex-ante due to sharply rising marginal costs. In this case, the outcome of sustainable market shares despite varying pricings seems to more closely resemble the Cournot model. However, because it seems unlikely that manufacturers of generic drugs face sharply rising marginal costs, considering that a well-known

study assumes the marginal cost of generics to be virtually zero (Caves, Whinston and Hurwitz, 1991), this case assumes the Bertrand model to be the most applicable model of competition for the generic industry. Nonetheless, the Bertrand model's prediction of unbridled price competition seems an imperfect fit as well.[20] Thus, this study expects to reject the Bertrand model's null hypothesis of unbridled price competition in favour of a more complicated picture of product differentiation and fragmented markets.

What, then, are the drivers of price competition amongst generics? Some of the literature in Chapter 1 assesses competition in the off-patent market by analyzing determinants of entry, thereby treating generic entry as a proxy for generic price competition based on the evidence that average generic prices in the USA decline as generic entry increases. However, Tirole (1989) shows that while generic entry is a pre-requisite for competition, it is only one explanatory variable, and is not a measure of competition itself.[21,22] Thus, this case models the determinants of generic prices themselves, in order to determine the variables that spur or inhibit price competition.

3.6.1.2 Case 1 Main Research Question

What were the determinants of generic prices in the omeprazole and paroxetine retail markets over the 2000q1-2005q1 period in the USA, UK, Germany and France? To what extent did purchasers maximize generic savings and what is the potential for further savings?

3.6.1.3 Case 1 Methodology

This case assesses the factors that explain generic prices per defined daily dosage (DDD) at the presentation level across the study countries. The fixed-effects panel data method has been used, due to the Hausman Test's rejection of the appropriateness of the random-effects method. In this case, the fixed-effects method

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[20] It should be noted that Tirole offers certain soft solutions to the Bertrand paradox, such as diseconomies of scale.

[21] For example, generic entry may be high, but average generic prices may also remain relatively high, as was the case in Germany (Monique 2001).

[22] Generic entry is also an appropriate explanatory variable because evidence in the literature shows that there are few supply side barriers (such as low original brand pricing , high promotional expenditures, or burdensome approval requirements) for generic entry, making it an exogenous variable.

likely controls for unobserved differences in the omeprazole and paroxetine markets since the explanatory variables are at the market level. Explanatory variables include the dominant generic manufacturer's market share, the number of generic competitors, the number of presentations in the market (to indicate product differentiation) and the price of the originator brand. This case also analyses the distribution of generic omeprazole and paroxetine prices across study countries and calculates the savings that countries could have realized if they had purchased more efficiently.

3.6.2 Case 2: Original brand versus generic competition within strengths market in the omeprazole and paroxetine retail molecule markets in Germany, France, the UK and the USA

3.6.2.1 Economic Theory Applied to Case 2

Competition between original brands and their generic equivalents is an example of Tirole's 'experience goods' model of product differentiation, where competition between differentiated products occurs even though the products are physically identical. Therefore, it is possible that in an attempt to avoid the Bertrand paradox of unbridled price competition, original brand manufacturers use their accumulated goodwill[23] to establish market niches across different strengths of the same molecule through which they retain some market power. The space they occupy within each strength market, therefore, is where customers tend to be brand loyal, and hence face 'customer inertia' when it comes to switching to lower cost generics. In this product differentiation model, the original brands enjoy the first mover advantage of keeping prices high in exchange for some loss in market share. A recent study acknowledges the possibility that this market harvesting strategy may operate within the context of a Stackelberg Model of competition (Kanavos, Costa Font and Seeley, 2008). In this model of competition, the original brand and generic manufacturers directly compete on quantity in a game-theory setting, where the original brand manufacturer chooses its quantity a priori (as the incumbent in the market) and sets its price accordingly, while the generic manufacturers (as the followers) respond by picking up the additional demand requirements and setting

[23] On the role of goodwill, "Consumers do not treat products they have experienced and products they have not experienced as identical even if the products are in fact the same. Consumers who have experienced a good match with a product or observed its high quality will not try a rival product unless it is considerably cheaper (Tirole 1989)."

their prices accordingly. Without a comprehensive survey of pharmaceutical manufacturers, it is difficult to assess the extent to which original brand generic manufacturers truly engage in this sort of strategic competition. Thus, this study does not attempt to prove or disprove whether the market harvesting strategy definitely fits within the context of the Stackelberg Model. However, it does briefly consider the likelihood that this type of competition is occurring, based on the findings of this study of competition at the ultra micro strength segment level.

In the market harvesting model of product differentiation, generics are left with the price sensitive portion of the market, and under this model, should theoretically be able to sustain prices above marginal cost as long as they too find ways to product differentiate, as discussed in the first case. Thus, similarly to the above case on competition amongst generics at the presentation level, competition amongst generics within strength segment markets is expected to resemble the Bertrand model more than the Cournot model due to expectation that marginal costs of production are fairly flat. However, also similarly to the model above, generic manufacturers are expected to product differentiate in order to avoid unbridled price competition.

In assessing the nature of competition between original brand and generic manufacturers and amongst generic manufacturers, the literature review shows that there should not be significant supply-side barriers to entry for generics since evidence shows that, first, original brand manufacturers scale back on their advertising shortly before patent expiration and do not attempt to deter generic entry by significantly cutting their prices and, second, regulatory requirements in the USA and Europe only require generics to prove bioequivalence to the original brand rather than requiring them to conduct their own clinical trials. Consequently, as long as drug approval requirements and sunk costs are low, generics may freely enter markets and should in theory face a marginal cost of production that is similar to that of original brands. In the case of competition within strength markets, generic manufacturers must conduct separate lab tests and in some cases, submit separate applications in order to gain approval for each strength product, although these fixed costs for generic manufacturers of gaining approval to market in different strengths should not be too high (reflecting the fact that in these study countries, they need only prove bioequivalence to the original band product of the same strength). Thus,

in theory, generics should be free to enter into differing strength markets in order to compete for market share with the original brand products.

3.6.2.2 Case 2 Main Research Question

To what extent does the degree of competition between the original brand and generics within strength market segments differ across strength market segments of the retail omeprazole and paroxetine markets in Germany, France, the UK and the USA during the 2000q1 – 2005q1 period?

3.6.2.3 Method for Case 2

This study compares the number of strengths and the strength market shares (as a percentage of the total molecule market) within these molecule markets across the study countries. This case assesses the factors that explain original brand prices, original brand market shares and generic prices within strength segments of the omeprazole and paroxetine markets in Germany, France, the UK and the USA during this study period. Of particular interest is the extent to which generic entry is associated with enhanced competition in each strength market. Similarly to the case on generics, this case uses a fixed-effects panel data method due to the Hausman Test's rejection of the appropriateness of random effects. The unobserved factors that are likely controlled for include differences in the omeprazole and paroxetine market as well as any differences that are unique to each strength market. This study then estimates the increased purchasing efficiency that could have resulted if the degree of competition within each strength market had equalled the most competitive strength market. Finally, this study compares prices across strength segment markets and calculates the potential savings that these countries could have realized if they were to take advantage of nonlinear pricing by splitting pills or if the paroxetine controlled release line extension had not been introduced in the USA market.

3.6.3 Case 3: Competition between OTC omeprazole and prescription (retail) Omeprazole in the USA and the UK

3.6.3.1 Economic Theory Applied to Case 3

In order to determine the nature and degree of competition between drugs of the same molecule in the prescription and OTC markets, it is necessary to recall the theoretical implications of the Bertrand and Cournot models of competition. Under

the Cournot model of competition, manufacturers would have predetermined capacities due to sharply rising marginal costs of production. Thus, under the assumption that both OTC manufacturers and prescription manufacturers of omeprazole would face fairly flat marginal costs of production, the Cournot model is not applicable to this case. Under a Bertrand Model, manufacturers would compete on price until the price of the prescription products equals the price of the OTC products. However, since the OTC products are theoretically differentiated from the prescription products by indication or strength (as required under regulatory approval), and since the payment side is structured differently in the OTC market (e.g. the payment is primarily through consumer out-of-pocket spending rather than third party payment), it is very unlikely that a perfect model of Bertrand competition would exist between the prescription and OTC markets. Nonetheless, in order to understand the nature of competition between the prescription and OTC markets, it is important to study the extent to which some degree of market share and price competition does exist, despite the demand-side fragmentation. Evidence of some degree of price competition between the two markets could suggest that manufacturers may use the OTC market as a form of product differentiation within the context of the broader molecule market.

It is important to note that in assessing competition between the prescription and OTC markets of the same molecule, there are barriers to entry for generic manufacturers in that although they may apply for OTC approval, the ultimate decision lies with the original brand manufacturers in these countries. In addition, where the original brand manufacturer initiates the switch in the USA, a 3 year exclusivity period (in the OTC market) may be awarded by the FDA, creating additional barriers to entry for the generic manufacturer. For these reasons, the original brand manufacturer may view the OTC market as a valuable opportunity to product differentiate, as long as it expects the profits it earns in this market to exceed any associated costs (including regulatory costs as well as any market share that its prescription products lose to the OTC products).

3.6.3.2 Case 3 Main Research Question

What was the nature and degree of competition between the OTC omeprazole and retail prescription omeprazole markets in the USA and the UK from market entry to 2005q1?

3.6.3.3 Method for Case 3

This case first analyzes the growth of prescription original brand versus prescription generic versus OTC omeprazole from OTC omeprazole entry in the USA and the UK to 2005q1 in order to determine whether the products are complements or substitutes. Evidence that they are substitutes suggests the existence of competition. Where there is evidence that the prescription and OTC omeprazole markets act as substitutes, this case uses a random-effects panel data model to assess the determinants of OTC prices. In this case, the Hausman test confirms the appropriateness of the random-effects model, indicating that there are not any unobserved factors that are unique to each observation. This is likely due to the fact that the explanatory variables are all at the market level, and since this case studies one market (the omeprazole market), there are no differences in markets to control for. In addition, this case compares OTC and prescription omeprazole prices in the USA and the UK, and calculates the potential savings that payors could have realized had they covered the OTC omeprazole version and shifted additional patients from prescription to OTC omeprazole.

CHAPTER 4: COMPETITION IN GENERICS PHARMACEUTICAL MARKETS: THE PRICE THAT HEALTH SYSTEMS PAY FOR REGULATION

4.1 Background

Between 1998 and 2003, annual rates of growth in drug spending were nearly double the rate of health spending in the USA, France and Germany (OECD Health Data, 2005). Because of the scarcity of health care resources, these high levels of pharmaceutical spending and growth rates have significant opportunity costs. For example, rising pharmaceutical expenditures may result in policymakers shifting costs to patients through increased copayments, which could threaten access to treatment. Moreover, fewer resources may be left for the rest of the health care system, limiting the ability to cover other services. As a result, policy makers in many OECD countries have continued to grapple with the effects of pharmaceutical spending growth increases.

One of the policy options that should aid pharmaceutical expenditure cost containment is to switch to generic use once an originator drug's patent has expired. While there has been some evidence to the contrary (Schwartzman, 1976)[24], it is agreed upon that generics are of the same quality as their original brand equivalents, as they are identical molecules, have similar bioavailability[25], and are therefore determined by regulatory authorities to be bioequivalent to the originator molecule.

In theory, price competition between an originator brand drug and its generic equivalents should follow patent expiration, thereby driving down the price of that molecule without any compromise in access or quality. However, evidence suggests that this may not occur. During the 1980s and 1990s, originator brand prices did not decline after generic entry in the USA, and in some cases, even increased at a faster rate (Caves, Whinston and Hurwitz, 1991; Grabowski and Vernon, 1996; Frank and Salkever, 1997). This was described as the market harvesting strategy, maintaining premium prices while market shares erode over time (Grabowski and Vernon, 1992).

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[24] Because generic producers have less goodwill to lose, they may not invest as heavily in quality control. Recalls and failed inspections occur proportionally more in the generic industry, although final generic products have never shown evidence of inferior clinical performance.

[25] Bioavailability measures the quantity and rate at which the drug's active ingredient reaches the bloodstream and the site of therapeutic action.

Because of the originator brand's continued price premium following patent expiration, much of the discussion on how to increase pharmaceutical purchasing efficiency within molecule markets has focused on the relationship between the original brand and generic. Supply-side policy responses have been implemented in North America and Western Europe to improve generic entry and hence generic penetration. An example of such a policy is the Hatch-Waxman Act in the USA, which permits generic manufacturers to prove bioequivalence to original brand equivalents in order to receive marketing approval, rather than having to conduct their own clinical trials. In addition, many countries across West Europe and North America have introduced a variety of demand-side policies that have been largely successful at promoting generic prescribing and use. Substitution laws and mark-up regulations have targeted pharmacists, while budgets and generic (INN) prescribing have targeted physicians. In the USA, many insurers have introduced tiered co-payments based on generic/brand status in an attempt to make the consumer more cost conscious. The result was that by 2001, the share of generic volume had reached 52, 47, 36 and 8.4 percent of the total prescription drug market in the UK, USA, Germany and France respectively (Mossialos, Mrazek and Walley, 2004). The variation in the share of generics across countries reflects differences in generic entry, different uptake of generic medicines, the variability in the supply- and demand-side policy-mix and differences in the implementation of policies favouring generic medicines. Thus, countries have had varying degrees of success in improving generic penetration. In addition, national regulations also vary in the way in which they attempt to achieve low generic prices. Some countries attempt to stimulate price competition amongst generics through a free market environment that allows free pricing of generics, while others attempt to control generic prices through reimbursement schemes such as generic price caps and reference pricing.

Studies observed that in the USA, the average generic price for a molecule tends to decrease as the number of generic competitors increases (Grabowski and Vernon, 1986; Caves et al., 1991; CBO, 1998; Kanavos, Costa-Font and Seeley, 2008); in 1994, the average prescription price of generic drugs that had 1 to 5 generic manufacturers (in their molecule markets) was $23.40, compared to the average price of $19.90 with 16 to 20 manufacturers (CBO, 1998). The relationship between generic price and market share is less clear. A USA study showed that generic prices varied significantly and in half of the 18 product markets the lowest price generic did

not achieve the largest market share, while in some cases the first generic entrant captured the largest market share despite relatively high prices (Grabowski and Vernon, 1992). It is argued that there may sometimes be a first mover advantage due to pharmacist- and patient-switching costs, in which the first generic entrant sustains for at least four years a 25-30% higher market share than if it had not been first (Hollis, 2002). The benefits of the first generic entrant are sometimes reaped by pseudo-generics, which are marketed by the originator brand manufacturer, thereby discouraging future entry and hence generic competition (Hollis, 2002). This study also concludes that the Ontario Province's reference price system, which reimburses the lowest priced generic, results in a disincentive for generic manufacturers to cut prices, as they would not achieve a larger market share in exchange for doing so (since most other manufacturers would also cut prices). This finding is consistent with another study (Kanavos, Costa-Font and Seeley, 2008), which also finds reference pricing to have a negative effect on generic price competition and that the lowest generic prices are up to 47% higher in reference priced systems, compared to nonreference priced systems (Kanavos, Costa-Font and Seeley, 2008). Moreover, there is some preliminary evidence that product differentiation may lead to higher generic prices, although this phenomenon is not discussed specifically in light of countries' differing regulatory systems (Kanavos, Costa-Font and Seeley, 2008).

Despite the sizeable amount of literature on originator brand versus generic competition, little is known about how the nature of price competition amongst generic products differs across settings. Studies have found that reference pricing is associated with relatively higher generic prices, but have not yet determined how individual market characteristics influence generic prices at the most disaggregated level within these different regulatory environments. The impact that supply-side pricing and reimbursement regulation might have on the amplitude and extent of competition among generic alternatives across different settings is also not yet well-understood. This is important because the distribution of generic prices partly determines the extent of savings to health insurance post generic entry, to the extent that the lowest priced generics do not necessarily achieve the largest market shares. Consequently, it is difficult to assess the effectiveness of generic policies in delivering significant savings to health insurers.

This chapter studies the nature of competition and its determinants amongst generic medicines and the extent to which this is affected by regulatory practices in

different regulatory settings, exemplified by the inclusion of the USA, the UK, Germany and France in the study. It also compares the distribution of generic prices across these four countries, and analyzes the extent to which health insurance succeeds in purchasing at low available generic prices. In so doing, it assesses whether further savings can be achieved and whether health insurers are currently optimizing their benefits from generic medicines. Section 2 discusses the conceptual framework; section 3 outlines the methodology used in the analysis; sections 4 and 5 present the results and discuss them respectively and; finally, section 6 draws the main conclusions and policy implications.

4.2 Conceptual framework

Assuming that generics made from the same molecule are homogeneous, non-differentiated goods, and that generic manufacturers do not face significant capacity constraints, generic manufacturers would likely compete on price in the absence of price controls, where demand responds to price, in accordance with the Bertrand Model of price competition (Tirole, 1988). Economic theory predicts that two non-differentiated goods are perfect substitutes and because demand responds to price, firms at the same price achieve equal market shares. Since firms do not face capacity constraints, they always meet the demand they face at their given price. Market size is assumed to be constant as consumers demand the same quantity of the product, regardless of price. Under a Bertrand price competition model, the lowest priced generic should achieve the largest market share. Therefore, manufacturers have an incentive to compete on price until price equals marginal cost. Assuming two competitors with prices $p_1 > p_2 > c$, where p_1 = the price of one generic manufacturer's product, p_2 = the price of the other generic manufacturer's product and c = marginal cost, then under Bertrand competition, the manufacturer charging p_2 will capture the entire market, leaving the manufacturer that charges p_1 with zero market. Demand is therefore denoted by:

$$D(p_1, p_2) = \begin{cases} D(p_1) & \text{if } p_1 < p_2 \\ \tfrac{1}{2} D(p_1) & \text{if } p_1 = p_2 \\ 0 & \text{if } p_1 > p_2 \end{cases} \qquad (1)$$

This will result in the higher priced manufacturer undercutting the lower-priced manufacturer and the pattern will continue until,

$$p_2 = p_1 = c \qquad (2)$$

Where homogeneous goods face fairly flat marginal costs, manufacturers are more likely to compete on price than on market share, thereby making prices the better strategic variable to analyze over market share (Giralt, 2007; Tirole, 1988). However, the Bertrand model assumes that there are no switching costs—that physicians, pharmacist and patients are not resistant to switching between generic equivalents.[26] The Bertrand Paradox also assumes that manufacturers are not able to tactically undercut their competitors, which is unrealistic, given the numerous ways in which pharmaceutical manufacturers may differentiate their products (e.g. branding, developing proprietary relationships with distributors and altering formulation, package sizes and strength).

A more realistic approach to the Bertrand model is one that recognizes manufacturers' abilities to strategically prevent this unbridled price competition. Thus, most analyses of price rivalry will concern the determination of the factors that induce tough or soft competition (Tirole, 1988). One such factor that may prevent perfect price competition is product differentiation. The most well known way for manufacturers to differentiate their products is via branding. It is through brand loyalty that demand for homogeneous goods may become less price sensitive, thereby allowing manufacturers of branded products to maintain price premiums. This can be seen in the case of originator brand versus generic competition. Another way in which manufacturers can differentiate their products is by packaging them differently. By concentrating on certain strengths, package sizes and forms, generic manufacturers may be able to carve out niche parts of the molecule markets, and therefore prevent rampant price competition. Hence, assessing the relationship between product differentiation within each generic market and generic prices may provide an indication of the extent to which product differentiation does soften generic competition. Finally, generic manufacturers may be able to undercut their competitors by developing proprietary relationships with distributors (i.e.

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[26] In reality, switching may incur significant costs. For example, pharmacists may be resistant to switching which generic product they dispense as a result of having to inform patients of these switches (Hollis 2002).

wholesalers and retail pharmacies). To the extent that one manufacturer is able to gain a dominant market position, either as a result of being the first to enter the market, or as a result of having established contractual advantages over other firms (e.g. through historic relationships, etc.), it is also important to consider the effects that such presence may have on price competition.

A factor that may induce intense competition is the number of generic competitors. It is important to note that much of the research that assesses generic versus generic competition has identified the number of companies as the outcome of interest, under the assumption that the number of companies acts as a proxy for lower prices (Hollis, 2002). The first generic mover may deter further generic entry further, thereby assuming generic prices are likely to be higher where there are fewer competitors. In addition, the observational studies in the USA also focus on the number of generic competitors as the outcome that determines price (Caves et al, 1991; CBO, 1998). However, evidence suggests that across countries, this negative correlation between number of companies and price does not necessarily hold (Kanavos, Costa-Font and Seeley, 2008). Consequently, in order to assess the determinants of prices and the extent of price competition amongst generics, it is important to study the effect that the number of competitors has on generic prices, rather than assuming that this number acts as generic price proxy.

Finally, in generic pharmaceutical markets, regulation on the supply-side may altogether deter the extent of price competition amongst generic firms. Reference pricing may be an example in this context. By setting a maximum reimbursement ceiling, price competition may be inhibited because generic manufacturers have no financial incentive to cut prices below that ceiling, as they would not achieve a larger market share in exchange for doing so (Hollis, 2002).

Consequently, generic prices should, in principle, be determined by the degree of product differentiation within the context of otherwise homogeneous products, the presence of a dominant generic manufacturer, the number of generic competitors and countries' different regulatory systems.

In light of the above, the model that may explain price competition in genericised markets deviates from the standard Bertrand model as shown in equation (3). The proposed structure results in an enhanced Bertrand model which allows for the effects of some price competition in the presence of regulation and attempts to product differentiate:

$$P_i = f(MS_i^{\max gen}, NGEN_i, P^{orig}, REG_i, \Delta PDIFF_i) \quad (3)$$

$$i = 1, 2, \ldots, n$$

where P_i is the generic price per daily defined dosage (DDD)[27] at the presentation level, $MS_i^{\max gen}$ is the market share of the dominant generic manufacturer; $NGEN_i$ is the number of generic competitors; P^{orig} is the price of the originator brand to determine the extent of price rigidity; REG_i encompasses regulatory aspects and; $\Delta PDIFF_i$ relates to product differentiation. Equation (3) is therefore expected to allow for a new equilibrium:

$$p_1 > p_2 > \ldots > p_n > c \quad (4)$$

4.3 Methods

We test the amplitude and extent of competition in off-patent markets by analyzing competition patterns in two products across four OECD countries. The products studied are omeprazole and paroxetine, and the markets are the USA, UK, Germany and France. Both omeprazole and paroxetine treat chronic illnesses with high prevalence and incidence in developed countries; omeprazole treats gastro-esophageal reflux disease and paroxetine treats depression, anxiety, and compulsive disorders. Both drugs are primarily sold on an outpatient basis through retail pharmacies.[28] In addition, both drugs are dispensed on prescription, although omeprazole is also available over the counter (OTC) in the USA and the UK.[29] Finally, both products have gone off-patent recently enough to enable generic price competition analysis in the context of relatively recent regulatory developments and

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[27] The term 'daily defined dosage' refers to a unit of measurement that was first developed by the World Health Organization's Collaborating Centre for Drug Statistics Methodology in an effort to standardize pharmaceutical utilization measures across countries. In accordance with the World Health Organization's definition, "The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults" (WHO, 2009).

[28] Recall from Chapters 1-3 that the hospital market is excluded in this study as a result of hospitals' and retail pharmacies' differing demand-side characteristics.

[29] Specifically, 20mg omeprazole became available over the counter in the US in 2003Q3, while 10mg omeprazole became available over the counter in the UK in 2004Q1. In the US, omeprazole OTC was approved under the original brand name, Prilosec. In the UK, it was approved under a different brand name, Zanprol. As a result, OTC omeprazole in the US is considered an original brand drug, while OTC omeprazole in the UK is considered a generic drug. Thus, in the US, OTC omeprazole could have influenced prescription generic prices through the original brand prices variable, while in the UK, OTC omeprazole was part of the dependent variable, generic price. The effects of omeprazole OTC switch in the US and the UK and its implications for the prescription market are analysed separately in chapter 7.

long ago enough such that the generic market has had time to mature in the study countries, which offers insights into generic price competition over time.

The two products are suitable for this analysis because of their large market size and the chronic nature of the conditions they treat, as patients may need to continue their treatment for several years. Additionally, omeprazole and paroxetine represent novel treatments and belong to two advanced therapeutic classes, proton pump inhibitors (PPIs) and serotonin selective re-uptake inhibitors (SSRIs) respectively. The molecules' superior efficacies compared with previous treatments, combined with the chronic nature of the conditions they treat have resulted in high expenditure in all study countries. Between 2000 and 2005, the retail pharmacy generic paroxetine and omeprazole markets accounted for $5.5 billion in the USA, $5.4 billion in Germany, $1.0 billion in the UK and $0.7 billion in France. High expenditure, combined with these countries' focus on generics, have, in principle, resulted in large generic markets, offering the opportunity for significant savings to health insurance through enhanced generic price competition and improved purchasing.

4.3.1 Data

The study uses Intercontinental Medical Statistics (IMS) Health data. IMS collects pharmaceutical pricing and sales data across numerous countries and provides a robust source of comparative data, with data being subject to internal validation (IMS, 2002). Retail sales and price data was available for omeprazole and paroxetine on a quarterly basis from 2000Q1 to 2005Q1. The data was available at the most disaggregated level, namely the product presentation level, which includes various permutations of strength, formulation, and package size. The manufacturer's name (both originator and generic) can also be distinguished at presentation level. This data allows for the calculation of market (molecule) level information, such as the number of presentations and manufacturers.

Using price and sales data, the quantity of packages sold was determined. Subsequently, the total volume of each presentation sold was arrived at by adjusting for package size (i.e. number of pills, tablets or capsules) and strength based on defined daily dosage (DDD). All prices were inflation-adjusted by each country's consumer price index, and then converted to USA dollars based on the quarterly exchange rates.

4.3.2 Choice of study countries

The choice of study countries reflects differences in supply- and demand-side regulatory and incentive structures affecting the uptake and use of generic medicines. The USA represents a relatively free generic market in that there is no generic price control or regulation for the majority of generic drugs at the federal level, although requirements exist for discounts by different insurers and there exists a variety of measures incentivising the use of generics. Medicaid, the health insurance program for low-income people, does stipulate that generic prices be discounted 11% off of AMP (USA DHHS, 2007), whereas private insurers in the USA often categorize drugs into tiered formularies based on generic/brand status, price and therapeutic efficacy. They then use this leverage to negotiate rebates with the manufacturers. Private insurers then base patient co-payments on these tiers in order to promote generics and other cost-effective drugs.[30] Finally, the USA Veteran's Administration achieves the largest pharmaceutical discounts in the USA through the Federal Supply Schedule (see Appendix A), while the uninsured face full retail prices in the USA. Thus, with the exception of some discounting practices, manufacturers, wholesalers and retailers are able to price freely in the USA.

The majority of the generics market can also be characterized as free pricing in the UK, with the exception of the Maximum Price Scheme (see Appendix A), which was in effect from 1999 to 2005 and applied to several products which witnessed supply shortages (DH, 2000). The intention of this scheme was to protect the NHS against unpredictable price increases for certain products (such as antibiotics) (Kay, 2000). However, in most cases, the price caps under the Maximum Price Scheme were still determined by the generic manufacturers and wholesalers (OXERA, 2001). Today, the Drug Tariff (see Appendix A) in the UK establishes a generic reimbursement price for each molecule of a given strength that is based on reported manufacturer and wholesaler supply prices (The Drug Tariff, 2005). In the process of procurement, retail pharmacies are permitted to negotiate discounts off of this retail list price for their profit. They must then give a percentage of this discount back to the NHS in the form of a clawback. The clawback ranges between 5.93% and 12.52%, depending on the number of prescriptions dispensed on a monthly basis.

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[30] The role of these private insurers has become especially significant recently in that the Medicare prescription drug benefit is also administered by these insurers. However, the Medicare prescription drug benefit had not yet been implemented during this study period.

In the case of Germany and France, generic prices and reimbursement are more heavily regulated. Both countries have a reference pricing system. From 1989 through 2004, Germany had a system of molecule-level reference prices, whereby upon patent expiry, all products of the same molecule were subject to the same reference price (Kanavos and Reinhardt, 2003).[31] According to recent legislation, a generic is only cost-effective if it is in the lowest third of the price range for the molecule (Häusler, 2002). Similarly to other medicines, the prices of generic products can be freely set by their manufacturers. The manufacturer or importer of the original brand is free to choose whether to maintain its price or change it when generic competition appears. The implementation of reference pricing implies that a ceiling exists on reimbursement and that patients will need to pay the difference between the reference price and the drug of choice if the latter's price is higher. Unlike the USA and the UK, Germany also regulates distribution chain mark-ups. Beginning in 2004, pharmacists receive a payment of €8.10, plus a fixed margin of 3%, which represents a change over previous years, whence pharmacies were remunerated on a regressive margin basis (Kanavos and Gemmill, 2005).

The reference pricing system in France is relatively new. Until 2003, France operated a system of direct generic price controls, whereby generic prices were not allowed to exceed 60-70% of the original brand price. However, in September 2003, France introduced molecule-level reference pricing for twenty nine molecules, translating into sixty one groups of generic drugs and corresponding to seventy two reference groups. These molecules were selected based on their generic penetration rates. Specifically, this reference group list included molecules with 2003 generic penetration rates of between 10 and 45 percent (FMOH, 2003). A further wave of molecules was added to the reference price system in 2005. Under this reference price system, once a drug loses its patent, the reimbursement price for all drugs of that molecule is set at the average generic price, not to exceed the original price cap

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[31] In 2005, the reference pricing system in Germany changed from being at the molecule level to the therapeutic level. Under the new regulations, IQWiG determines whether the product will become part of the reference pricing system, depending on how innovative it is. In-patent products that are not the first in their therapeutic classes are therefore more likely to be included in the reference price system while still on-patent than the first entrants into the class. From 2005, in-patent products that are included in the reference pricing system are subject to the same reimbursement as other molecules that may be generic. However, this study does not capture the effect of this switch.

of 60-70% of the original brand price. In the case of this chapter, generic entry did not occur for omeprazole in France until 2004, and the generic penetration rate for paroxetine in France was still under the required 10 percent during the first half of 2003. Thus, both study molecules were not included in the first wave of reference price groups. France also regulates distribution chain mark-ups and varies the stipulated mark-ups by price tiers, with a regulated margin of 10.74% for products up to a price of €22.90, and 6% for products with prices above this amount.

4.3.3 Variables

The dependent variable in this study is generic price per DDD, at the presentation level (P^{gen}). The explanatory variables are market share of the dominant manufacturer ($MS_i^{\max gen}$), number of generic companies in the market ($NGEN_i$), change in the number of presentations[32] with a positive market share ($\Delta NPRES_i$) and the originator brand price (P^{orig}). The IMS Health dataset provides full market data for the UK at the presentation level, but does not distinguish between some of the unbranded generic manufacturers (in the UK). As a result, it is not possible to determine the dominant generic manufacturer market share in the UK. All prices have been converted to USA dollars and adjusted by inflation, strength and package size. The definition of market is limited to the retail generic market only. The originator brand price is included in the analysis in order to identify whether it determines generic prices. All variables employed in the analysis are shown in Table 4-1.

[32] A presentation is defined as a product of a specific dosage, form and package size that is sold by a specific manufacturer. For example, a molecule in tablet form of 10mg that is sold in a package size of 100 tablets by manufacturer A is considered to be one presentation.

Table 4-1 Variables and their Definitions for Generic Competition Econometric Analysis, 2000 Q1 – 2005 Q1

		USA		UK		Germany		France	
		Omeprazole	Paroxetine	Omeprazole	Paroxetine	Omeprazole	Paroxetine	Omeprazole	Paroxetine
Variable	Definition	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
P^{gen}	Adjusted Generic Prices per DDD	1.077 (.556)	.512 (.630)	.323 (.312)	-.068 (.157)	.466 (.181)	.367 (.134)	.489 (.024)	-.122 (.173)
$MS_i^{max\ gen}$	Market Share of Dominant Firm	.696 (.229)	.643 (.038)	--	--	.317 (.030)	.550 (.286)	.251 (.020)	.451 (.224)
$NGEN_i$	Number of Generic Competitors	3.600 (1.965)	5.429 (1.764)	--	--	16.238 (3.422)	10.810 (7.838)	13.000 (1.004)	5.375 (2.191)
P^{orig}	Price of original brand product	4.821 (.515)	2.862 (.137)	1.844 (.143)	1.054 (.074)	3.776 (.428)	2.015 (.197)	2.455 (.275)	1.142 (.135)
$\Delta NPRES_i$	Number of Presentations	1.333 (1.158)	5.667 (4.157)	.091 (1.382)	.385 (.928)	5.700 (6.150)	3.650 (5.590)	1.333 (1.90)	.857 (.840)
Time	Number of quarters since generic entry	5.500 (2.879)	4.000 (2.003)	6.500 (3.459)	7.500 (4.052)	13.00 (6.056)	15.00 (6.057)	2.500 (1.123)	4.500 (2.307)

Source: The Author, using IMS Health data.

4.4 Econometric specification

In order to assess the determinants of generic prices, a linear model is estimated from equation (3):

$$P_i^{gen} = \beta_o + \beta_1 MS_i^{\max gen} + \beta_2 \text{NGEN}_i + \beta_3 P^{orig} + \beta_4 \text{NPRES}_i + \varepsilon \quad (5)$$

From equation (5) we first seek to determine the relationship between generic prices and the dominant generic manufacturer's market share ($MS_i^{\max gen}$). While there is no evidence in the USA, Germany and France of a first mover advantage in the form of sustained higher market share by the first generic entrant, there is evidence of a dominant generic manufacturer in each market that is able to maintain a higher market share than its competitors over time. If it is true that the presence of a dominant generic manufacturer deters price competition (Hollis, 2002), then the association between its market share and generic prices would be positive. On the other hand, industrial organization theory suggests that while evidence of concentration may be useful in assessing some degree of competition amongst firms, it does not show a systematic relationship with prices (Tirole, 1988). The number of companies (NGEN_i) is included in the model as a supply side variable. In accordance with the Bertrand model of price competition, the number of companies should be independent of the number of generic manufacturers (Tirole, 1988). Finally, the change in the number of presentations (ΔNPRES_i) is also included in the model as a potential measure of the degree to which generic manufacturers are successfully able to avoid the Bertrand paradox through product differentiation. The change in the number of presentations may be a proxy for product differentiation, including separating the market into different strengths, changing the appearance of the product through different formulations (pills vs. tablets vs. capsules), colours and package sizes. Product differentiation of this nature may also have the knock on effect of decreasing price transparency, since it may be difficult for payors to adjust prices by these factors, thus, having an impact on price.

In order to avoid multicollinearity between the product differentiation variable and the number of generic companies, product differentiation is defined as the *change* in the number of presentations that are sold in the generic market in that given quarter. This also avoids the possibility of endogeneity that could exist between the total number of presentations sold in the market and generic prices.

Some studies assume that the number of generic competitors is exogenous (Grabowski and Vernon, 1992; Wiggins and Manes, 1994), while a different study assumes it to be endogenous (Frank and Salkever, 1997). In order to take both scenarios into account, the results are presented from both the non-instrumented model and a model where the number of generic competitors is instrumented by $Time_i$, defined as the number of quarters since generic entry. (In the UK, the variable Time has been added to the non-instrumented model as a proxy for the number of generic competitors since the number of generic competitors cannot be distinguished in the data.) The significance and direction of the relationships between the explanatory variables and the dependent variable are the same in both the non-instrumented and instrumented model.

Across all study countries, the Hausman test rejects the appropriateness of the random effects model. Fixed effects are used to control for the molecule- and presentation-specific effects. For robustness, both omeprazole and paroxetine have been included in the same model. However, all variables still reflect the separate omeprazole and paroxetine generic markets. In order to account for the heterogeneity across countries' generic markets, e.g. their differing regulatory environments, the models have been run separately for each country. This allows for each independent variable's slope to vary across countries. One limitation of the fixed effects method is that time-invariant characteristics that have not changed during the study period, such as Germany's reference price regulation, cannot be dummied out since they are already implicitly controlled for.

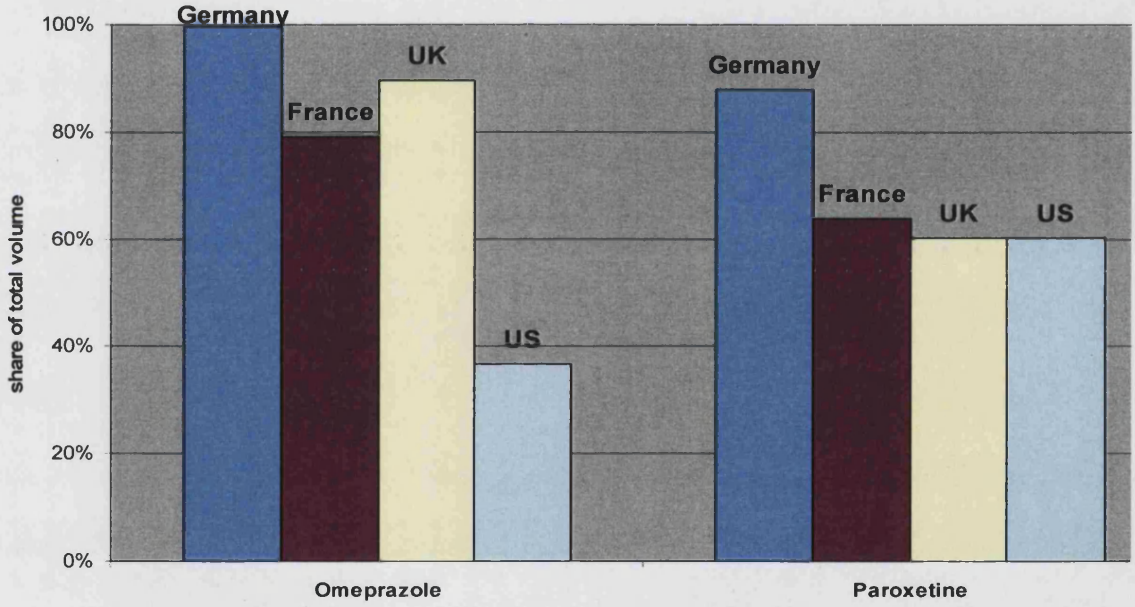
4.5 Results

4.5.1 Descriptive analysis

A close examination of the data leads to three observations. First, in terms of generic penetration, omeprazole is highly genericised in the UK, Germany and France, but seemingly less so in the USA, whereas in the case of paroxetine, generics account for the vast majority of the market in all study countries (Figure 4-1). The low level of omeprazole generic penetration in the USA can be explained by the brand name's (Prilosec) availability as an OTC, accounting for a large share of the brand category. In the case of paroxetine, France has managed to achieve a higher paroxetine generic penetration than the USA and UK, despite paroxetine's patent

expiration occurring later in France. In the case of the US, this may be due in part to the presence of paroxetine suspended release, which was still on patent during this study period. (See Chapter 5 for a detailed analysis on the implications of the introduction of paroxetine suspended release to the US paroxetine molecule market.) In Germany, the relatively high rates of genericisation can be explained by its earlier patent expirations than in the USA, UK and France, and by its reference pricing system. While there is still some room for improving genericisation, particularly in paroxetine in France, UK and the USA, it seems that the shift from originator brand to generic has been almost fully realized for omeprazole in Germany and the UK.

Figure 4-1 Generic Penetration in the Omeprazole and Paroxetine Markets, 2005Q1



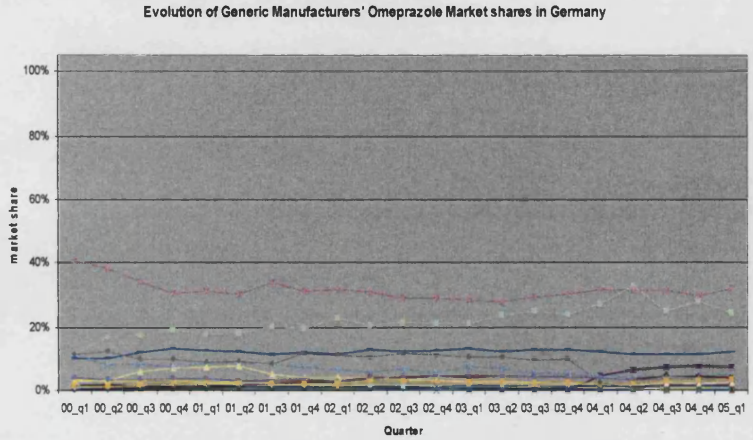
Source: The author from IMS.

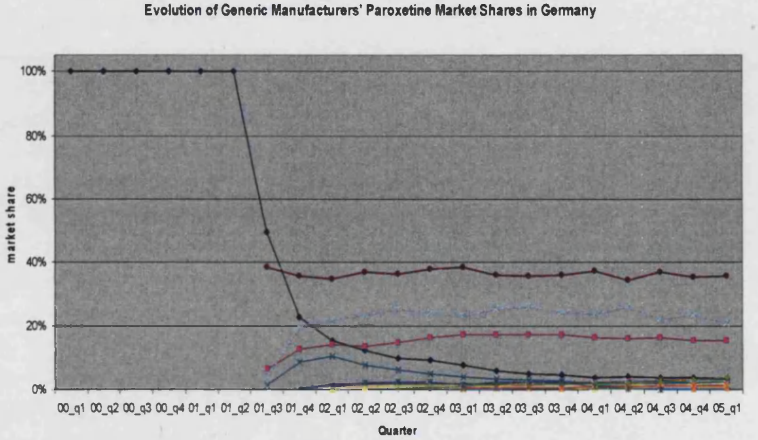
Second, Figure 4-2 shows entry and market shares of different generic competitors following entry and suggests that there may be a dominant generic manufacturer, which is not the first entrant in any of the cases, that is able to sustain a higher generic market share than its competitors over time. In half of the cases (omeprazole in Germany and France and paroxetine in the USA), there was not even a discernable first generic entrant. In markets where there were first generic entrants, such as for paroxetine in Germany and France and omeprazole in the USA, the market shares of these first movers collapsed within a year of other generics entering the market. This is particularly interesting in the USA, where one might have expected to see a first generic mover advantage result from the six month exclusivity

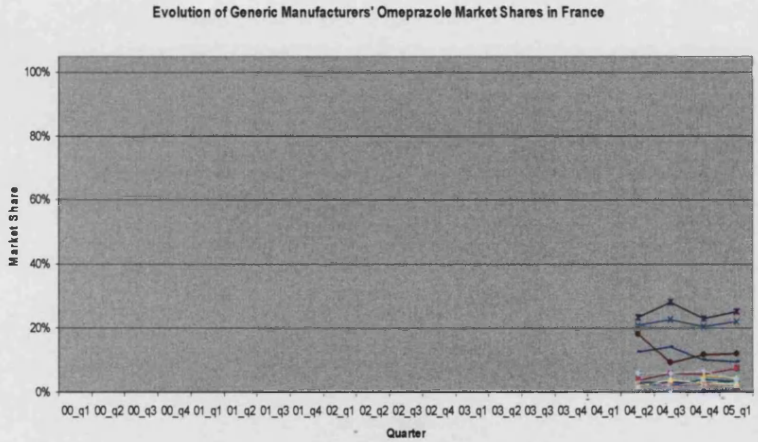
period that is granted to the first generic entrant. Notably, this finding challenges the literature that attributes the dominant generic manufacturer's market power to being the first entrant (Hollis, 2005).[33]

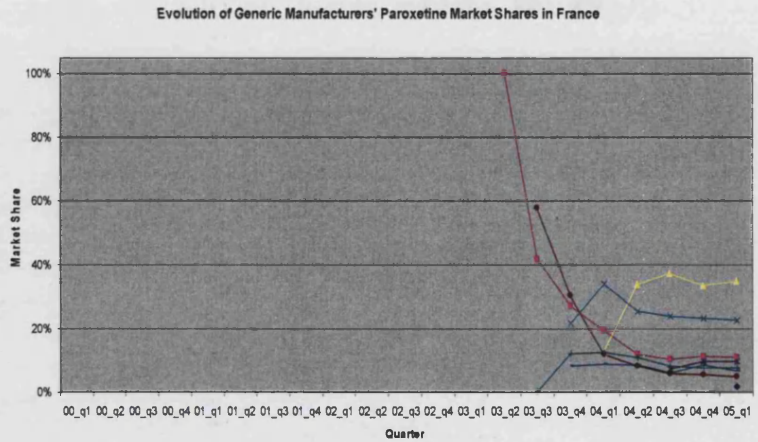
[33] This finding also has significant implications for the industrial organization of generic competition. Where there is evidence of a first mover advantage, competition between the first generic entrant and other generics may resemble the Stackelberg cournot model (Hollis 2005), where the first mover may determine how much it wants to sell, leaving the subsequent entrants to compete for the remaining market share. Under this model, the assumption of increasing marginal production costs would need to be relaxed since it is unlikely that marginal product costs increase significantly in the generic industry.

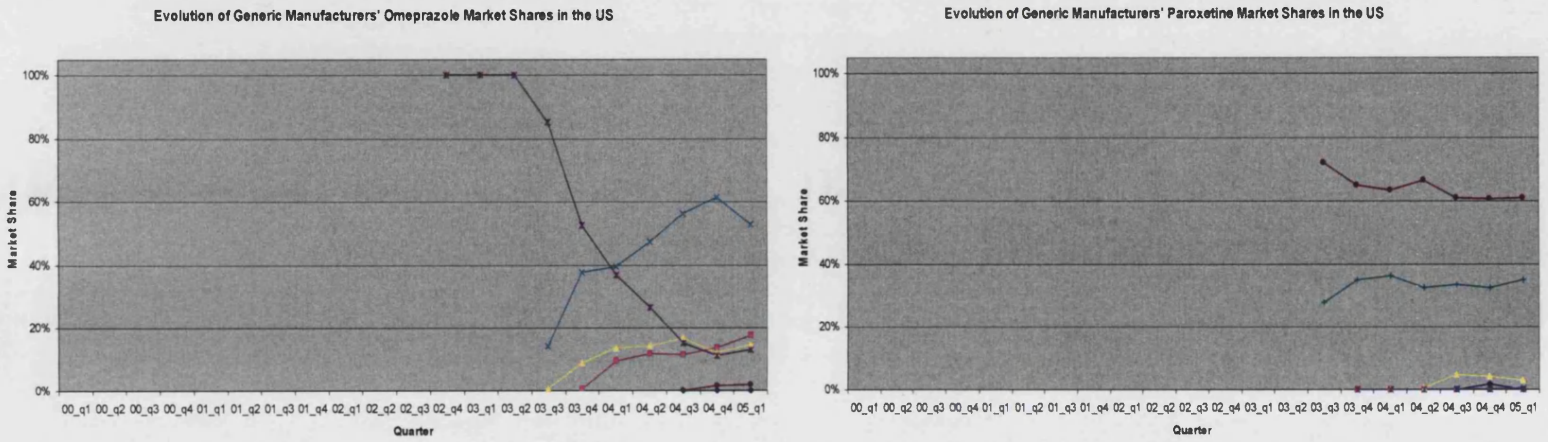
Figure 4-2 Evolution of Generic Market Shares in the USA, Germany and France, 2000q1-2005q1











Source: The author from IMS.

Third, in terms of intra-country variability, Table 4-2 shows that the dominant manufacturers' prices were not necessarily lower than their generic competitors' prices, as would be expected in a competitive market. In Germany, the dominant generic manufacturers' prices were seven to eight percent lower than the generic median price. This likely reflects the fact that Germany's reference price is based on the lowest third of the market, thus, resulting in the dominant manufacturer's price being at or just below the reference price so as to not lose the inevitable market share that would ensue should patients have to pay the difference out of pocket. In France, however, the dominant generic manufacturers' prices were equal to the median price, and in the USA, the dominant generic manufacturers' prices were significantly higher than the median generic price, especially in the case of omeprazole, where the dominant generic manufacturer was able to maintain a price premium of approximately 25 percent above the generic median price. Interestingly, in the case of omeprazole in the USA, the dominant manufacturer's price premium was similar to first generic mover's price premium (1.26 percent above to the median price compared to 1.21 percent respectively), despite the dominant manufacturer's ability to maintain a market share of 53% in 2005Q1 compared to the first generic mover's collapsed market share of 13 percent in the same time period. Therefore, it seems that the dominant generic manufacturers are able to maintain their leading market shares over time for reasons other than relatively low prices and entry timing (i.e. resistance to switching), since in these cases, they are not first movers. The reason for the dominant manufacturers' high market shares, despite their average or relatively high prices, could relate to vertical competition issues, such as the stickiness of contractual arrangements along the distribution chain (e.g. between the manufacturer and the wholesaler).

Table 4-2 Relative Price per DDD of Dominant Generic Manufacturer (Average Price per DDD of Dominant Generic Manufacturer / Median Generic Price per DDD) in 2005Q1

	Germany	France	USA
Omeprazole	.92	1.0	1.26
Paroxetine	.93	1.0	1.03

Source: The Author, using IMS Health data.

4.5.2 Econometric analysis

Table 4-3 shows the results of the multivariate models on the determinants of generic prices. In the USA, dominant manufacturer market share, originator brand price, the change in the number of presentations and the number of generic manufacturers were all significant predictors of generic price per daily defined dosage at the presentation level. In particular, the market share of the dominant manufacturer and the number of generic manufactures both correlate negatively with prices, while the change in the number of presentations and the originator brand price correlates positively. One possible explanation for the negative correlation between the dominant manufacturer's market share and price is that as the dominant manufacturer's market share increases, a larger portion of the market that is resistant to switching becomes tied up with this manufacturer, thereby leaving the other manufacturers with the most price sensitive customers, and hence spurring price competition in this portion of the market. These findings suggest that, as is found in the literature, an increase in the number of generic manufacturers in the USA omeprazole and paroxetine markets spurs price competition, while an increase in the number of presentations is associated with price increases, as one might expect from product differentiation. Meanwhile, originator brand prices correlate positively and significantly with generic prices. This could suggest a lack of price competition, since in theory, generic prices should be independent of originator brand prices in a price competitive market. However, since the original brand drug was also available in relatively low prices over the counter in the USA from 2003q3, it could be that lower original brand prices were associated with lower generic prices, which would suggest a price competitive market.

In the UK, all of the determinants correlate significantly with price. Time since generic entry correlates negatively with prices, perhaps reflecting the entry of more manufacturers and, hence, a negative correlation between the number of manufacturers and generic prices or changes in market concentration over time. However, since the time variable may also be picking up a number of other factors that may be changing in the market, the direction and significance of this variable are only indicative. Unlike the USA, the originator brand price correlates negatively with generic prices, perhaps reflecting the market harvesting strategy; when patents expire, originator brand prices sometimes increase in order to maximize profit on the

most price insensitive portion of the market, while generics compete on price in the remainder, price sensitive segment of the market. Indeed, evidence confirms this phenomenon in the UK, where the average originator brand price of omeprazole increased from $1.90 in 2002Q1, the quarter before generic entry, to $2.36 in 2005Q1. Similarly, in the case of paroxetine, the average originator brand price increased from $0.95 in 2001Q3, the year before generic entry, to $1.12 in 2005Q1. Similarly to the USA, the change in the number of presentations in the UK correlates positively with generic prices. This indicates product differentiation, through which companies can segment the market into a variety of strengths and pack sizes, thereby inhibiting price competition.

In Germany, all determinants are significant, and are positively correlated with generic prices, except the change in the number of presentations. As the dominant generic manufacturer's market share increases, so does the price. This is consistent with the concern that a more concentrated market could inhibit price competition (Hollis, 2002). In addition, the findings show that as the number of companies increase, so does price. This correlation is inconsistent with the Bertrand model of price competition, under which the number of companies is expected to be independent of generic prices. One possible explanation could be that generic manufacturers have to spend more on marketing (since the generics market in Germany is a branded generics market) when the number of companies increase, thereby increasing their costs and hence prices. The change in the number of presentations correlates negatively with generic prices in Germany, although the size of the effect is very small. This could indicate that the change in the number of presentations reflects both some degree of product differentiation as well as increased supply and available choice, with combine to produce a net effect of slightly enhanced price competition. Thus, the effects of the dominant generic manufacturer and the number of companies are both indicative of a lack of competition in that since the dominant manufacturer's market shares have levelled off over time, and the number of companies increased over time, there is little evidence of factors that spur price competition in this setting. This is not surprising, given the incentives under the reference pricing system, whereby the reference price is determined by the price in the lowest third of the price range. Under this reimbursement scheme, if generic manufacturers were to lower their prices, they would all need to follow suit in order to not lose market share, thereby reducing all of

their profits. Instead they have the incentive to compete along different lines, such as branding and patient or physician loyalty. Meanwhile, the originator brand price correlates positively with generic prices, most probably because the reference pricing system forces originator brands to reduce their prices when generics reduce their prices, else loose market share when patients switch to products for which they do not have to pay the difference between the reference price and the reimbursed price. Even in cases where patients are willing to pay some difference, it is unlikely that patients would be willing to pay more and more, as would be the case if the originator brand price did not decrease with generic prices.

In France, the number of companies and the originator brand price correlate significantly with generic prices. The effect of regulations capping the generic prices as a percentage of original brand prices is that as the original brand price increases/decreases, so does the generic price. The result is that the price cap acts more as a floor than a ceiling. This is evidenced in the fact that in the vast majority of cases, the generic prices were between fifty five and sixty percent of the original brand price. Thus, over time, as the originator brand price increased, so did the generic prices, despite the increase in the number of generic manufacturers, resulting in the positive correlation between the number of generic manufacturers and generic prices. Nevertheless, the number of presentations correlates negatively with generic prices in France, although the effect is small. This is likely reflective of an increase in the supply choice of omeprazole and paroxetine, which is not surprising, given the fact that the omeprazole and paroxetine markets in France are less differentiated (e.g. have fewer numbers of strengths) than in the other study countries. Finally, it is important to note that the dominant generic manufacturer's market share was not a significant fact in predicting generic prices. This finding is consistent with the price cap regulations, which resulted in generic manufacturers responding more to the original brand price than to each other's prices. Thus, despite a small amount of evidence that an increase in supply may be associated with a small decrease in prices, the majority of the evidence in this model suggests that the generic omeprazole and paroxetine markets in France were not price competitive.

Table 4-3 The Determinants of Generic Prices: a Fixed Effects Approach

	USA (fixed effects)		UK (fixed effects)	Germany (fixed effects)		France (random effects)	
	NI	I	NI	NI	I	NI	I
$MS_t^{max\ gen}$	-1.599*** (.434)	-1.541*** (.436)		.816*** (.040)	.900*** (.040)	.068 (.073)	.068 (.074)
$NGEN_t$	-.213*** (0.035)			.014*** (0.000)		.018*** (.004)	
Time#		-.245*** (.040)	-.042*** (.006)		.018*** (.001)		.018*** (.014)
P^{orig}	2.427*** (0.359)	2.225*** (.379)	-1.315*** (.177)	.142*** (.004)	.132*** (.004)	.094** (.036)	.094** (.037)
$\Delta NPRES_t$	.060*** (0.007)	.058*** (.007)	.019** (.008)	-.001*** (0.000)	-.001*** (.000)	-.002 (.002)	-.002 (.002)
No. of obs.	324	324	229	3202	3202	129	129
No. of groups	67	67	28	286	286	37	37
R^2 within	.587	.586	.737	.48	.47	.56	.56
Hausman test	13.7***		48.78***	22.76***		167.56***	

*p < 0.10: **p < 0.05: ***p < 0.01

In the USA, Germany and France, the Time variable serves as an instrument for the number of generic companies. In the UK, the Time variable serves as a direct proxy for the number of generic companies (in a non-instrumented model).
Note: NI stands for non-instrumented model and I stands for Instrumented model.
Source: The Author, using IMS Health data.

4.6 Discussion

The analysis in the preceding section has shown that in the USA, there is evidence of price competition in the segment of the market that the dominant manufacturer does not control. There is also evidence of price competition in the fact that as the number of generic manufacturers increase, generic prices decrease. However, the change in the number of presentations is associated with upward price movements, which is indicative of product differentiation. In addition, the positive relationship between the originator brand price and generic prices suggests some

price stickiness in the USA. In the UK, the negative relationships between generic prices and the dominant manufacturer's market share, the originator brand price and time since entry suggests price competition, while the positive coefficient of product differentiation suggests limitations to competition. In France, the positive relationships between generic price and the number of companies and generic price and the originator brand price suggest lack of competition. However, the negative relationship between generic price and number of presentations, suggests that there is some competition at the presentation level, though the size of the coefficient is much smaller to balance the previous two effects. In Germany, the findings suggest that generic manufacturers do not compete on price. This is not surprising in a reference price system, where if one manufacturer reduces prices, the reference price may be adjusted accordingly, forcing all manufacturers to suffer. The can, in turn, accommodate greater number of firms without generic prices declining significantly and without significant impact on the dominant generic manufacturer's market share. One important finding across all study countries is that regardless of regulation and generic market characteristics, there is no evidence of a first generic mover advantage in the form of first entrants' sustained market share dominance, although dominant manufacturers do emerge across all markets.

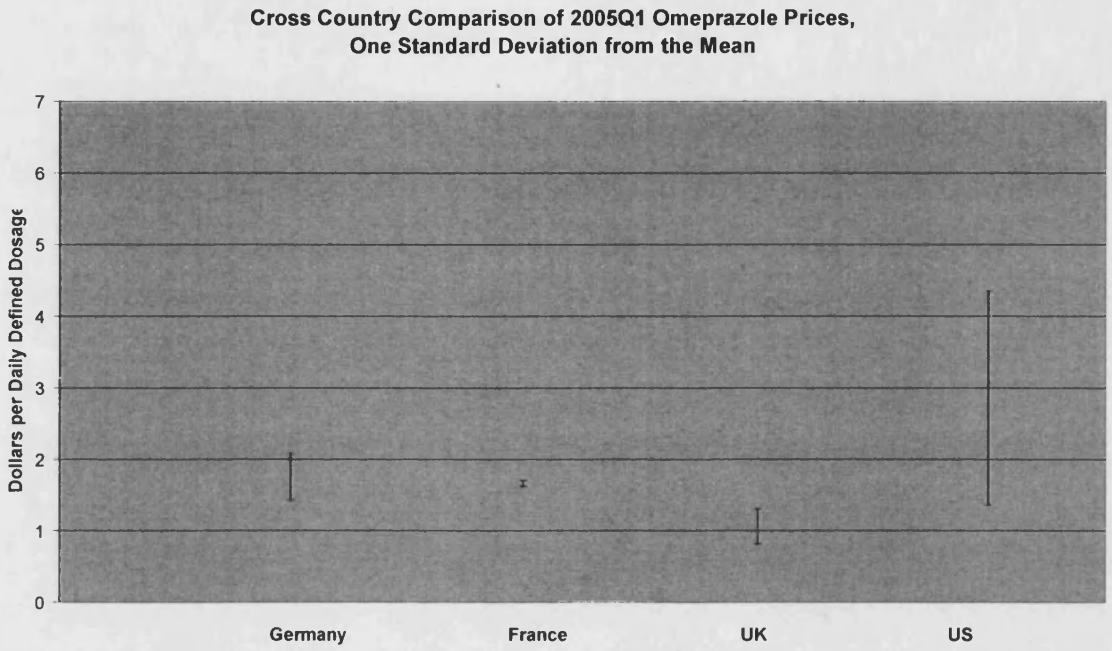
Across all four countries, these findings reject the null hypothesis of unbridled price competition, as the Bertrand model would predict. Instead, a new hypothesis is generated, whereby price competition amongst generics becomes diluted, as a result of product differentiation and/or countries' regulatory schemes, which may result in a new equilibrium of ranging prices and market shares. Specifically, in the case of the USA and the UK, it appears as though there is still some degree of price competition, despite manufacturers' successful attempts to fragment the market with product differentiation strategies. However, in Germany and France, it seems that there is relatively little price competition, as a result of the effects of the regulatory schemes affecting generic markets.

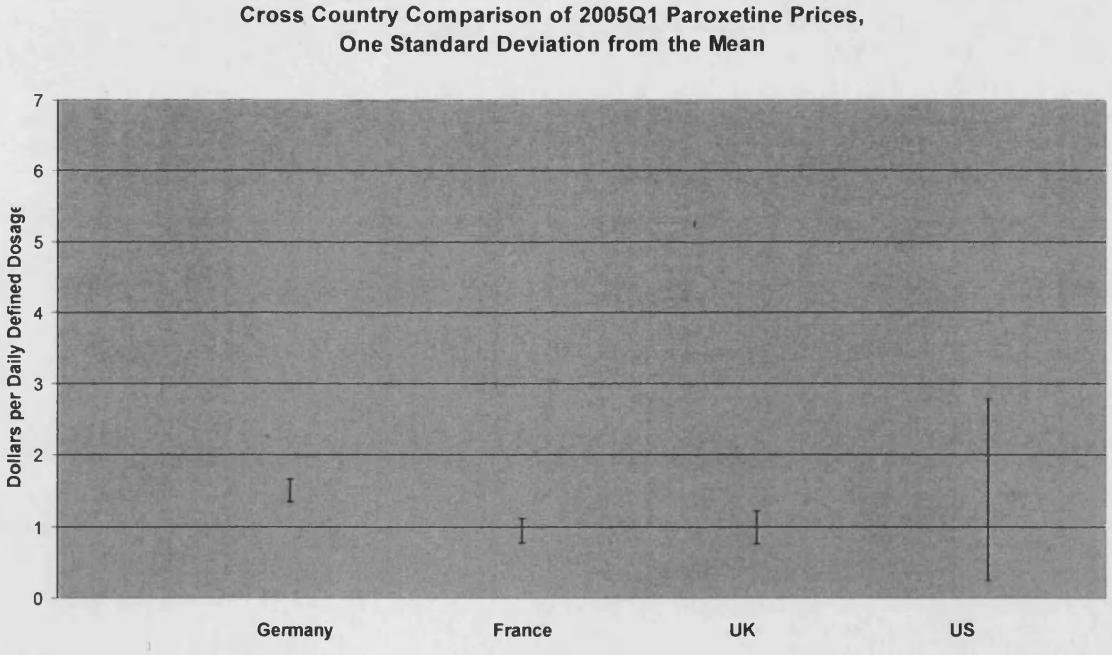
While the discussion so far offers insights into the factors that affect generic prices across countries, it does not address the issue of how prices range across countries and whether the lowest generic prices are the prices of choice for health insurance. As Figure 4-3 indicates, there is significant variability in prices for both products and across all study countries. In both the omeprazole and paroxetine markets, generic prices that are one standard deviation from the mean range

significantly more in the USA than in the UK, Germany or France. An interesting finding that emerges from looking at the graphs in Figure 4-3 is that the USA has a larger range of prices, despite Germany having a larger number of generic competitors in these markets than the USA. This is likely reflective of the reference pricing system in Germany, which results in manufacturers clustering their prices. In addition, Figure 4-4 shows that the lowest prices in the USA omeprazole and paroxetine markets are significantly lower than in Germany, despite the fact that Germany has significantly more manufacturers competing in these markets. These findings support the econometric results, which show that the degree of price competition in generics markets is dependent on a number of factors besides just the number of generic manufacturers. In absolute terms, Figures 4-3 and 4-4 show that the UK exhibits some of the lowest omeprazole prices while the USA exhibits some of the lowest paroxetine prices among the study countries.

There are several ways in which countries could contain generic costs. One is to focus policies exclusively on the supply side determinants (described in the econometric models above) so that the entire distribution of prices is shifted downwards, keeping the generic mix (i.e. market shares) constant, but altering the prices themselves. Another way would be to focus policies on the demand side so that the lowest prices are actually purchased, keeping the prices constant, but altering the mix (i.e. market shares) of generic products. In order to determine whether health insurers have been successful at purchasing the lowest available generic prices, a weighted price was constructed for each product and country, taking into account product presentations and market shares for each.

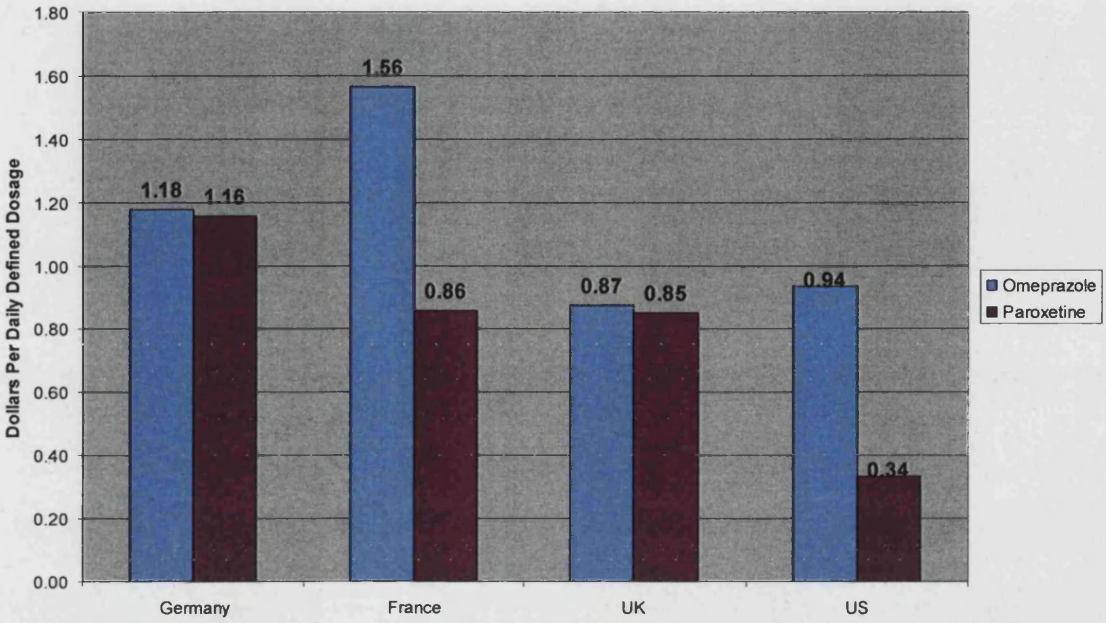
Figure 4-3 Cross Country Comparison of Omeprazole and Paroxetine Prices





Source: The Author, using IMS Health data.

Figure 4-4 Cross Country Comparison of Lowest Generic Prices, 2005Q1



Source: The author from IMS.

A comparison of the weighted price[34] for each product with the lowest generic price reveals interesting patterns (Table 4-4). Germany faces both the highest purchased prices and the highest lowest prices out of the four study countries. Its purchased price to lowest price ratios are 1.41 and 1.28 for omeprazole and paroxetine respectively. This is roughly consistent with the reference price system, where the generic reimbursement price is set equal to the lowest third price in the market.[35] France seems to have achieved some of the better purchased price to lowest price ratios although this is not surprising, given the small standard deviation of prices. As a result, France paid the same per DDD for omeprazole in 2005Q1 as Germany, despite its lowest price being much higher than Germany. This is an example of where the mix (i.e. market shares) of products is just as important in influencing total spending as the availability of low prices. The ratios on Table 4-4 illustrate that the USA was the worst at actually purchasing the lowest prices in the market, although comparatively speaking, the (weighted) price at which they purchased was lower than France and Germany (for omeprazole) and all other study countries (for paroxetine). The relatively high purchased price to lowest price ratio

[34] The weighted generic price is an aggregated price index whereby each generic presentation's price is weighted by its respective generic market share.

[35] The prices are not expected to exactly equal the lowest third of the prices in the generic molecule market since the reference prices during this time period varied by strength, rather than being calculated on a per DDD basis, as has been done here.

in the USA is not surprising, given the large range of prices in the USA and the nature of agreements between manufacturers and insurers, pointing at discount practices. Consequently, despite facing a lowest omeprazole price that was twenty percent lower than Germany's lowest omeprazole price, the actual purchased price in the USA was only seven percent lower than Germany's actual purchased omeprazole price. In the case of paroxetine, it is noteworthy that the USA was still able to achieve a lower purchased price than the UK, despite having a ratio of purchased price to lowest price that was more than twice that of the UK. This example shows the relative importance of the supply side, in that even though the purchasers did not successfully take advantage of the lowest paroxetine prices in the USA, many of the available prices were still so much lower than in Germany France and the UK, that the USA achieved the lowest purchased price. The UK was the most consistent country in achieving both some of the lowest prices, and some of the best purchased price to lowest price ratios. The standard deviation of paroxetine prices was larger in the UK than in Germany, but the UK still managed to achieve a better purchased price to lowest price ratio.

Table 4-4 Cross-Country Comparison of Purchased Price and Lowest Prices in 2005Q1

	Omeprazole			Paroxetine		
	Purchased Price	Lowest Price	Ratio of Purchased Price to Lowest Price	Purchased Price	Lowest Price	Ratio of Purchased Price to Lowest Price
Germany	$1.66	$1.18	**1.41**	$1.48	$1.16	**1.28**
France	$1.66	$1.56	**1.06**	$0.90	$0.86	**1.05**
USA	$1.55	$0.94	**1.66**	$0.80	$0.34	**2.39**
UK	$0.91	$0.87	**1.04**	$0.96	$0.85	**1.13**

Source: The Author, using IMS Health data.

Overall, Germany and the USA face some of the highest supplied prices, although the USA also faces some of the lowest supplied prices. In both the USA and Germany, the high purchased-to-lowest-price ratios suggest there is still significant room for savings to health insurance for both omeprazole and paroxetine. The UK appears successful at both achieving low generic prices as well as purchasing at these prices, while generic prices in France fall in the middle across the study countries, and range very little. These observations suggest a larger degree of

price competition in the USA and the UK than in Germany and France and are consistent with the econometric results.

Finally, it is worth considering the total savings that could have been realised had the lowest generic prices been purchased during the time following patent expiry, holding the generic penetration rate constant. Table 4-5 shows that during the time period following patent expiry, efficient omeprazole and paroxetine purchasing (defined as purchasing at the lowest available price in the generic molecule market) could have saved approximately $812 million in the USA, $61 million in the UK, $682 million in Germany and $9 million in France. This represents a 30.2 percent savings in the US, a 12.0 percent savings in the UK, a 25.0 percent savings in Germany and a 2.5 percent savings in France. Thus, the USA and Germany had the most to gain from efficient purchasing (as would be expected from their high purchased-to-lowest price ratios), although the savings were significant across all countries. Moreover, the total savings that could be realised from the efficient purchasing of all generic drugs would clearly be monumental in helping policymakers contain pharmaceutical costs.

Table 4-5 Cross Country Comparison of the Potential Savings from Purchasing at the Lowest Available Generic Prices following Patent Expiry

		Date of Patent Expiry	Savings in USD if Purchased at Lowest Generic Price, patent expiry - 2005q1	Percentage Savings, patent expiry - 2005q1
Germany	Omeprazole	2000q1	650,362,096	25.4%
	Paroxetine	2000q1	31,783,452	19.0%
	Total Savings		682,145,547	25.0%
France	Omeprazole	2004q2	3,084,441	1.2%
	Paroxetine	2003q2	6,166,919	5.5%
	Total Savings		9,251,360	2.5%
UK	Omeprazole	2002q2	55,403,568	14.1%
	Paroxetine	2001q4	5,212,668	4.6%
	Total Savings		60,616,236	12.0%
US	Omeprazole	2002q4	438,589,139	24.2%
	Paroxetine	2003q3	373,733,487	42.8%
	Total Savings		812,322,626	30.2%

Source: The Author, using IMS Health data.

The analysis pursued in the previous sections is not without limitations. First, there are a small number of products in this study, although this is not necessarily a disadvantage because it enables a more thorough analysis, which leads to a better understanding of the complexities of generic competition as well as the range of

generic prices available at the product presentation level. Findings from this case study analysis may be generalisable to other classes of drugs that are primarily concentrated in the retail market and treat chronic conditions. Second, the pricing data used are not able to capture fully the extent of discounts off list prices. While this is a limitation that affects the study countries, evidence suggests that where these discounts exist, they primarily affect the distribution chain and may operate horizontally across products and product presentations (Kanavos and Taylor, 2007; Kanavos, 2006).

4.7 Conclusion

In an environment of strong generic policies pursued by policy-makers in the USA, UK, Germany and France, the findings of this study may shed some light on how effective these countries' policies are at improving the intensity of generic competition and optimising savings for health insurance through efficient purchasing. We find that all four countries have achieved significant levels of generic penetration, although, clearly, this could be enhanced further. What is disconcerting, however, are the numerous signs that price competition is weak, resulting in payors not reaping the benefits of the low generic prices that a competitive market would produce. It is surprising that generic markets, generally characterized by homogeneous products, can be associated with product differentiation and that this impacts positively on generic prices in some markets. Yet, this was a finding for the USA and the UK. It was also worrying that despite there being no evidence of a first generic mover advantage in these markets, the dominant manufacturers' market shares are associated with increases in generic prices in Germany. Moreover, the number of generic competitors was associated with generic price increases in Germany and France rather than price decreases. The analysis also reveals that there is significant variability in generic prices and moreover, that generic prices may be linked to originator brand prices. Although this appears to be surprising for commodity products and may be indicative that payors may not be maximizing the pecuniary benefits from genericisation, it is partly due to regulatory action from the payors' side.

In conclusion, evidence of product differentiation (in the form of altered strength, formulation and package size) inhibiting price competition in the US and the UK, regulations inhibiting price competition in Germany and France and the

presence of a dominant generic manufacturer in all four study countries suggests that generic manufacturers are successful at carving out profitable niches within the generics markets of all four study countries. As a result, the null hypothesis of unbridled price competition, as the Bertrand model would predict, is rejected in favour of an enhanced model of Bertrand-like price competition, whereby price competition amongst generics becomes diluted, resulting in a new equilibrium of ranging prices and market shares. Relatively speaking, the degree of this Bertrand-like price competition appears stronger in the USA and the UK than in Germany and France, indicating that while generic manufacturers may differentiate their products, price competition still remains more intense than it would in more regulated markets.

Finally, the generic price variation within countries has shown that the USA and the UK achieve the lowest purchased prices, although all four study countries are purchasing above the lowest available generic price. This may be due to regulatory imperfections, such as reference pricing in Germany, or other bottlenecks in the system (e.g. invisible discounting practices at distribution level). The removal of such barriers could have resulted in significant savings to payors in all four countries.

Overall, it appears that where policymakers attempt to control generic prices, they have stopped short of implementing policies that stimulate price competition amongst generics with a view to achieving even lower generic prices and realizing further savings.

CHAPTER 5: UNDERSTANDING PHARMACEUTICAL COMPETITION WITHIN STRENGTH SEGMENT MARKETS AND THE EFFECT OF THESE SEGMENTED MOLECULE MARKETS ON PURCHASING EFFICIENCY

5.1 Introduction

In an attempt to explain competition in the off-patent pharmaceutical market, numerous studies have analyzed the competitive pricing and market share dynamics between the original brand drug and their generic equivalents (Frank and Salkever, 1997; Caves et al, 1991; Grabowski and Vernon, 1992). The findings consistently show that oppositely from what one might expect, original brand manufacturers do not necessarily drop their prices when generics enter. Rather they keep their prices level and in some cases, even increase their prices, thereby retaining the brand loyal, price insensitive segment of the population and forgoing the price sensitive segment of the population to the generic market. This phenomenon has been called the market harvesting strategy and the generics paradox. While its name may sound esoteric, its implication is anything but. On a practical level, this research has helped policymakers come to understand that because original brand prices remain relatively high after generic entry, it is crucial that purchasers shift consumption to generics in order to contain pharmaceutical costs. As a result, literature often uses the barometer of generic penetration as a measure of countries' successes in pharmaceutical policy cost containment (CBO, 1998; Haas, 2005; Express Scripts, 2005; Kanavos Costa-Font and Seeley, 2008). In these cases, generic penetration is defined as the percentage of a molecule market (measured in volume units such as daily defined dosages or prescriptions) that is dispensed generically. For example, a generic penetration rate of 90% for a molecule market would be high, compared to 50%.

This chapter argues, however, that solely using generic penetration rates at the molecule level is not a sufficient means by which purchasing efficiency can be achieved. The hypothesis behind this assertion is that there are likely submarkets of competition within a molecule market that must be studied and more closely understood before implementing genericisation policies. Consider the example where evidence shows a generic penetration rate of 70% in a given molecule market. With this level of information, policymakers could incorrectly conclude that they need to more aggressively target physicians, pharmacists or patients in order to

increase the generic penetration rate. However, physicians prescribe appropriate dosages for their patients that are based on need, thereby segmenting a molecule market into submarkets. Thus, it could be that when stratifying the data, evidence further shows that the molecule is sold in two strengths, one of which has a generic penetration rate of 90 percent, while the other strength has a generic penetration rate of 50%. In this case, supply side regulations that target the strength market with a low penetration rate may be necessary instead of demand side regulations, to the extent that the generic penetration rates differ because of supply side factors such as original brand versus generic prices or generic entry in that strength segment. Thus, the nature of competition within these strength segment markets of a molecule needs to be understood in order to determine what factors should be influenced in the pursuit of purchasing efficiency.

This chapter contributes to the current understanding of pharmaceutical competition by stratifying strength market segments of a molecule and analyzing the degree to which competition between the original brand and generics differs within different strength market segments of the same molecule. This, then, will provide a more detailed level of understanding of pharmaceutical competition in the off-patent market. As part of the analysis, this study will also explore original brand and generic manufacturers' motivations for entering into different strength market segments through a descriptive analysis and will discuss the nature of product differentiation and price discrimination within a molecule market as it applies to differing strengths and formulations. Through this analysis, a more complicated picture arises than the over-simplified one in which studies assume that manufacturers of the same molecule all engage in direct price or market share competition, regardless of the strength and formulation of their products.

Second 2 provides an overview of the literature that discusses product differentiation within molecule markets. Section 3 outlines the theoretical framework for assessing competition within strength segments of molecule markets. Section 4 outlines this study's sample selection and research questions. Sections 5 and 6 present the empirical as well as theoretical findings on competition within strength segments. Section 7 analyses the efficiency implications of these findings as well as the opportunity for costs savings that could result from increased competition within strength segments. Section 8 focuses on product differentiation and price discrimination across strength segments and section 9 models possible scenarios for

cost savings in these product differentiated markets. Finally, section 10 draws the findings together from this study and discusses its broader policy implications.

5.2 Background and Literature Review

In order to analyze the nature of pharmaceutical competition in molecule markets, studies may convert the volume of drugs of the same molecule but different forms and strengths into standardized units, such as daily defined dosage[36] (Chapters 4 and 5; Kanavos, Costa-Font and Seeley, 2008). In doing so, it is assumed that competition occurs at the molecule level. Within that molecule market, they do acknowledge that there are certain segments of competition, such as competition amongst generics (Kanavos, Costa-Font and Seeley, 2008; Hollis, 2002; Frank and Salkever, 1997).

Another way in which studies have divided the molecule market into submarkets is by differentiating the degree of price competition in the hospital versus retail pharmacy market, noting that the hospital market is relatively more price sensitive than the retail market, and therefore is more biased toward generics or original brand manufacturers that are willing to offer significant discounts (Hurwitz and Caves, 1988; Caves et al, 1991; Grabowski and Vernon, 1992; Scott-Morton, 2000).

One study argues that it is not appropriate to combine doses marketed in different forms and strengths when studying competition between original brand and generics because the FDA's information on equivalency pertains only to pills of identical dosage form and strength (Hurwitz and Caves, 1988). However, rather than studying the various strength submarkets separately, the study only includes the most popular dosage form in its analysis. It is only recently that a few studies have turned attention toward the effect that the segmentation of a molecule market into various strengths and forms can have on pharmaceutical price competition and spending (Danzon, 2008; Kanavos, Costa-Font and Seeley, 2008).

One of these studies seeks to explain the USA's relatively high prices (for a given molecule) by highlighting the fact that the average strength consumed for a

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[36] Recall from Chapter 4 that the term 'daily defined dosage' refers to a unit of measurement that was first developed by the World Health Organization's Collaborating Centre for Drug Statistics Methodology in an effort to standardize pharmaceutical utilization measures across countries. In accordance with the World Health Organization's definition, "The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults" (WHO, 2009).

given molecule is higher in the USA than in most of the other study countries,[37] except Spain, France and Canada (Danzon, 2008). The inference from this claim is that higher strength doses are consistently priced higher than lower strength doses across countries, although this study does not provide price data to support its assumption. It also justifies the USA's high prices by the fact that relatively high priced long-acting formulations comprise a larger percent of the market volume in the USA—roughly 8 percent, compared to 1-7 percent in other countries. This study (Danzon, 2008) argues that these long-acting formulations substitute quality for quantity by improving compliance and leading to fewer total doses, hence justifying their higher prices.

The above studies find that the existence of submarkets within molecule markets changes the nature of competition, which affects prices and expenditures. In these cases, the segmentation of the molecule market is assumed to be the result of payor fragmentation (in the case of hospital versus retail markets) or clinical need, which the above study (Danzon, 2008) assumes is the driver of strength and formulation segmentation. However, some studies take the analysis of segmented molecule markets and their effect on competition a step further by finding that the segments are often the result of manufacturers' attempts to distinguish their products from one another rather than just the result of payor fragmentation or clinical need—i.e. product differentiation. Thus, in these studies, the outcome of interest—segmented molecule markets—is the same, but the driver of these segments is industry-led rather than payor or patient-led. These studies find that manufacturers seek to differentiate their products from each other by varying the form (i.e. method of administration, such as capsule, tablet, liquid, suppository), strength (e.g. 10 mg vs. 20 mg vs. 40 mg, etc.) and package size (100 tablets versus 500 tablets, etc) (Frank and Salkever, 1997; Kanavos, Costa-Font and Seeley, 2008). In this way, products compete by attempting to carve out niches within the molecule market so as to avoid the unbridled price competition that would occur in a market of homogenous products. Consequently, some evidence shows that this product differentiation within molecule markets adversely impacts price competition by contributing to downwards price rigidity (Kanavos, Costa-Font and Seeley, 2008).

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[37] Study countries include the US, Canada, France, Germany, Italy, Spain, the UK, Japan, Australia, Brazil, Chile and Mexico.

5.3 Conceptual Framework

While the literature has acknowledged that segmented molecule markets—either because of manufacturers' attempts to product differentiate or clinical need—may result in relatively higher overall purchased prices at the molecule level, none have gone so far as to actually study whether the degree of competition between original brand and generics differs within strength market segments of the same molecule. For example, they have not looked in depth at whether the degree of generic entry is different in some strength segment markets than other strength segment markets (of the same molecule) and whether the degree of competition between the original brand and the generics differs in some strength market segments than in other strength market segments. Moreover, research on competition amongst generics also has not stratified molecule markets by strength segments. To this end, researchers and policymakers that have primarily used genericisation at the molecule level as a barometer to measure whether policies are successful in containing costs do not yet understand where there may be a need to increase competition between original brand and generic equivalents within molecule submarkets, and consequently, whether policies that seek to increase purchasing efficiency are well-targeted.

Finally, one of the above studies (Danzon, 2008) makes the assumption that higher strength products are priced higher than lower strength products and that long-acting formulations are also priced higher than their immediate release competitors, which explains higher overall prices where demand for high strength and/or long-acting formulations is relatively high (in comparison with countries where it is relatively low). However, despite these assumptions, there is not yet any macro level research on the pattern of pricing across strengths and long-acting formulations within molecule markets. Therefore, this study also compares prices across strengths and a long-acting formulation within a molecule market in order to determine whether or not manufacturers are able to use these segmented markets to price discriminate. Where evidence suggests the possibility of price discrimination, substituting some strengths/formulations for others may offer additional opportunity to increase purchasing efficiency in molecule markets (in addition to increasing competitive dynamics within strength markets). However, this practice would have

to very carefully consider clinical need and safety, which is discussed in the sections below.

5.3.1 Overarching Theoretical and Empirical Questions

On the competitive dynamics within strength markets, this study seeks to answer two broad theoretical and empirical questions. On a theoretical level: What form does competition take in this dimension and how do traditional industrial organization paradigms help explain competition between originator brand and generics within strength market segments? On an empirical level: To what extent does the degree of competition between the original brand and generics within strength market segments of the same molecule differ across strength market segments and what are the findings' implications for purchasing efficiency?

On the role of product differentiation and price discrimination, this study seeks to answer two additional policy questions: 1) How do prices compare across strength/form segment markets (of the same molecule) and what implication does this have for the degree of price competition across strength segmented markets and 2) What are the ways in which payors could take advantage of pricing disparities by substituting certain strengths (within a molecule) and what degree of savings could these strategies achieve?

5.3.2 Theoretical Framework

This study first seeks to understand the theoretical implications of strength segmented molecule markets on the industrial organization and degree of competition between original brand and generic equivalents. It then discusses the empirical implications these findings may have; where overall prices may appear higher than if the molecule market were not segmented into submarkets of strength, there may be room for increased purchasing efficiency.

In order to assess the degree of competition within strength segment markets, this study first assesses whether original brand manufacturers employ the market harvesting strategy in each strength segment market, and how the resulting original brand to generic price ratio compares across strength segment markets. This study then conducts a descriptive analysis of original brand versus generic market shares within strength submarkets of a molecule across countries with a view to comparing how the number of generic competitors differs across strength submarkets of a

molecule. Finally, this study uses fixed-effects panel data analysis to model the factors that determine the original brand prices within strength segment markets, the original brand market share within strength market segments and generic prices within strength segment markets.

5.3.2.1 Entry into Strength Segmented Markets

Before analyzing the degree of competition within strength segment markets, it is important to understand what factors may determine the number of strengths within a molecule market and how these factors (and hence the number of strengths) differ across countries.

First and foremost, for a strength market segment to exist, a manufacturer must have the financial incentive to enter into that strength. Entry would therefore depend on whether a manufacturer expects to profit from such a decision. In other words, in accordance with the profit function, the expected profit will be:

$$\Pi = R - C \quad (1)$$

Where Π = profit, R = total revenue and C = total cost

Thus, $\Pi > 0$ if $R > C$.

$$\text{Then } R = V \times R \quad (2)$$

Where V = volume and P = price

$$C = fc + vc \quad (3)$$

Where fc = fixed costs and vc = variable costs

It follows that profit, and therefore a manufacturer's decision to enter a strength submarket is a function of:

$$\Pi_i = f(V_i, P_i, fc_i, vc_i) \quad (4)$$

Where $_i$ represents a strength submarket

The volume (V_i) of a product of a given strength that a manufacturer may sell depends on the size of the country's patient population for the molecule, the size of the patient population for that specific strength, the culture of prescribing (i.e. whether physicians have the tendency to prescribe the DDD first, or start with the lowest strength first and then increase if need be), the payment system and the expected degree of competition in the market. Likewise, the price (P_i) at which the manufacturer may sell the product of a given strength may differ across countries,

depending on the country's regulations, the payment system, the type of market regulation and the degree of competition in the market. The fixed (fc_i) and variable costs (vc_i) associated with manufacturing the product of a given strength may be similar across countries[38], although the distribution costs associated with the wholesaler and retail mark-ups are known to differ significantly across countries. Finally, the fixed, sunk costs of obtaining marketing authorization and coverage approval may be a significant factor that differs across countries.

Although it is outside the scope of this study to analyze the effect of all of the above factors on expected profit (and hence original brand or generic entry into a strength segment of a molecule), this study discusses the dimension of how the costs of applying for marketing authorization for different strengths of the same molecule may differ across regulatory settings. In addition, it discusses the possible influence that countries' coverage and payment systems may have on whether a manufacturer chooses to introduce multiple strengths into a market. This discussion of regulations is then combined with descriptive evidence in an attempt to explore possible explanations for the differing numbers of strengths in the study's sample molecule markets across countries. Following the analysis on how the number of strength segment markets and their respective market shares (as a percent of the total molecule market) differ across countries, this chapter studies the degree of competition between the original brand manufacturer and generics of the same molecule within strength segmented markets, as outlined below.

5.3.2.2 Original Brand Prices and Market Shares within Strength Segment Markets

The current literature on competition between original brand and generic manufacturers of the same molecule clearly demonstrates that original brand manufacturers pursue the market harvesting model. This strategy has been characterised by the original brand manufacturer's decision to keep their prices flat, or increase their prices, following patent expiry. In the process of doing so, they accept that they will lose the price sensitive portion of the market to generic manufacturers, but will retain the brand loyal segment. Thus, this decision to leverage the fact that because they held a patent for a number of years, they were

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[38] This pertains to developed countries where the cost of labour is similar and pharmaceuticals may be manufactured in the same location and distributed afterwards.

able to develop a branded product a priori to other firms' entry into the market, may be considered product differentiation in the form of experience goods, whereby a certain share of the demand side may face an inertia to switching to generics based on their positive experience with the branded product (Tirole, 1988).

The market harvesting strategy predicts that original brand manufacturers do not engage in price competition with generics, but instead often increase prices and accept the inevitable loss in market share that accompanies generic entry. In order to determine whether the original brand manufacturers employ the market harvesting strategy within strength segment markets, this study assesses the extent to which original brand prices are a function of generic entry. In accordance with the market harvesting strategy as the null hypothesis, it is expected that P_i^{OB} is not significantly associated with N_i^{gen}. Oppositely, evidence that P_i^{OB} is significantly associated with N_i^{gen} would suggest that original brand manufacturers engage in some form of direct price or market share competition with generic manufactures instead of independently pursuing their market harvesting strategy.

In addition to assessing the relationship between P_i^{OB} and N_i^{gen} as a means of determining whether original brand manufacturers pursue the market harvesting strategy within strength segments, the extent to which the original brand market share is associated with original brand prices is also assessed. Notably, an association in this case may not indicate a causal relationship, but rather, changes on the demand side. For example, assuming that a portion of the demand side that has historically been resistant to switching represents physicians who prefer to prescribe brands they are familiar with, it may be that as demand-side regulations increasingly favour generics (and in the process, provide additional information to these physicians that had previously had imperfect knowledge of such generic products or in other cases, mandate substitution), the original brand manufacturers loses additional market share, while they keep their prices flat. In accordance with the market harvesting strategy, it is therefore expected that either the relationship between P_i^{OB} and MS_i^{OB} be insignificant or negative. Evidence of a positive relationship, whereby original brand manufacturers actually experience an increase in market share, despite keeping their prices flat and/or increasing prices, would

suggest a more complicated model of competition between original brand and generic manufacturers that is not indicative of the market harvesting strategy.

In addition, it is necessary to assess the extent to which the variable strength market share is associated with original brand prices in order to capture any heterogeneity between more common strength market segments, such as the daily defined dosage, which has the largest strength market share, and the less common strength market segments (i.e. markets with the smallest strength market share). Finally, whether the brand name product is available over-the-counter may influence the competitive dynamics within strength markets. Thus, in order to assess whether original brand manufacturers employ the market harvesting strategy consistently within strength segments, this study assesses the extent to which the price of the original brand within strength segment markets is a function of:

$$P_i^{OB} = \mathrm{f}(N_i^{gen}, MS_i^{OB}, SMS_i, DOTC)$$

$$i = 1, 2, \ldots, n$$

Where P_i^{OB} represents the average price of the original brand in that strength segment market, N_i^{gen} represents the number of generic entrants in that strength segment market, MS_i^{OB} represents the original brand market share within that strength segment market, SMS_i represents the strength segment market share, $DOTC$ represents whether the drug is available over-the-counter in that strength and i represents the strength segment market.

In addition, in order to understand the nature of competition between original brand and generic manufacturers within strength markets, it is important to examine the drivers of the original brand market shares within strength segments. Thus, this study examines the extent to which the original brand to generic price ratio within strength segments is associated with the original brand market share at the strength segment level as well as the number of generic companies in that strength, the strength segment market share and whether the molecule is available over-the-counter in that strength segment, such that:

$$MS_i^{OB} = \mathrm{f}(PRAT_i, N_i^{gen}, SMS_i, DOTC)$$

$$i = 1, 2, \ldots, n$$

Where MS_i^{OB} represents the original brand market share within the strength market, $PRAT_i$ represents the original brand to generic price ratio within the strength market, N_i^{gen} represents the number of generic companies within the strength market, SMS_i represents the strength market share of the strength market, $DOTC$ represents whether the drug is available over-the-counter in that strength and i represents the *strength* segment market.

A recent study assumes that the market harvesting strategy operates within the context of a Stackelberg Cournot model of competition, whereby the first mover advantage of high original brand market share is expected to erode as generics enter the market since companies compete on market share (Kanavos, Costa-Font and Seeley, 2008). In this case, it would be expected that MS_i^{OB} is negatively associated with N_i^{gen}. However, this study argues that a positive association between the original brand market share and the number of generic manufacturers does not necessarily indicate market share competition. Instead, it may reflect the fact that changes in the demand side (such as regulations that increase genericisation) act as a confounding factor between the two. Thus, this study briefly considers the extent to which the market harvesting strategy may operate within the context of the Stackelberg Cournot model of competition, which assumes that the first mover directly competes with followers by strategically setting its price, while at the same time maximizing its quantity, whilst the followers directly respond to the incumbent's prices in the determination of their prices.

5.3.2.3 Generic Prices within Strength Segments

Consistent with the findings in chapter 4, generics of the same molecule in these product/country markets are assumed to be relatively homogeneous goods that product differentiate by carving out niches in the molecule market, either by entering into different strength segments, by gaining preferential status in the contractual process (as is assumed to be the case for the dominant manufacturers in case one) or by altering the packaging. Recall that a model of perfect Bertrand competition would predict that where generics of the same molecule are homogeneous, non-differentiated goods, and where generic manufacturers do not face significant capacity constraints, generic manufacturers of the same molecule would likely

compete on price until prices equal marginal cost, in accordance with the following model:

Assuming two competitors with prices $p_1 > p_2 > c$, where p_1 = the price of one generic manufacturer's product, p_2 = the price of the other generic manufacturer's product and c = marginal cost, then under Bertrand competition, the manufacturer charging p_2 will capture the entire market, leaving the manufacturer that charges p_1 with zero market. Demand is therefore denoted by,

$$D(p_1, p_2) = \begin{cases} D(p_1) & \text{if } p_1 < p_2 \\ \tfrac{1}{2} D(p_1) & \text{if } p_1 = p_2 \\ 0 & \text{if } p_1 > p_2 \end{cases} \qquad (1)$$

This will result in the higher priced manufacturer undercutting the lower-priced manufacturer and the pattern will continue until,

$$p_2 = p_1 = c \qquad (2)$$

Instead, product differentiation amongst generics allows for a new equilibrium, whereby,

$$p_1 > p_2 > \ldots > p_n > c \qquad (3)$$

To the extent that the strength segment market is significantly associated with generic prices, it may be that generic manufacturers strategically locate themselves in more or less common strengths as a means of trying to product differentiate, while at the same time, continuing to locate themselves where the demand is concentrated in accordance with spatial competition.

Similarly to Chapter 4, this model of price competition amongst generics at the strength segment level also includes the number of generic competitors as a variable in order to assess the extent to which the number of generic competitors induces tough competition as well as the original brand market share, in order to determine the extent to which generic manufacturers respond to original brand prices in addition to engaging in price competition with each other. Other variables that generic prices are likely to be a function of at the strength segment level include countries regulations (such as reference pricing) and whether or not the drug is

available over-the-counter in that strength. Thus, generic prices are assessed at the strength segment level, such that:

$$P_i^{gen} = f(N_i^{gen}, P_i^{OB}, SMS_i, \text{REG}_i, DOTC)$$

$$i = 1, 2, \ldots, n$$

Where P_i^{gen} is the average generic price within that strength market, N_i^{gen} represents the number of generic companies within the strength market, P_i^{OB} represents the average original brand price within that strength market, SMS_i represents the strength market share of the strength market, REG_i encompasses regulatory aspects and $DOTC$ represents whether the drug is available over-the-counter in that strength and i represents the *strength* segment market.

5.3.3 Empirical Implications: Comparison of Prices across Strength Markets within a Molecule

This study then compares purchased prices across strength segments within molecule markets in order to determine the extent to which demand conditions differ across strength markets and whether there is evidence of manufacturers using segmented strength markets as an opportunity to reap larger profits through price discrimination.

5.4 Methods

In order to gain a more comprehensive understanding of how competition differs within strength segments of off-patent molecule markets, this study analyzes competition between the original brand and generics within off-patent retail pharmacy strength market segments of omeprazole and paroxetine in the USA, UK, France and Germany during the 2000q1-2005q1 time period. A case study approach is appropriate in this case in order to probe at a sufficient level of detail, which includes tracing manufacturers' entry and exist decisions in each strength market segment over time and across countries.

Omeprazole is part of a broader therapeutic class of drugs called Proton Pump Inhibitors, which treat Gastroesophageal Reflux Disease (GERD), also known as heartburn. Paroxetine is part of a broader therapeutic class of drugs called Selective Serotonin Reuptake Inhibitors (SSRIs), which treat anxiety and depression.

These two molecules are particularly suitable for this study because their molecule markets are so large (in volume) that their strength submarkets are still conducive to a robust sample size. Moreover, because their strength submarkets are such large markets in and of themselves, the price and efficiency implications remain large in absolute terms even at this sublevel. This underscores the significance of studying competition at this disaggregated level. Finally, since retail omeprazole and paroxetine were only available in oral (whether pill, tablet or capsule) form, these two molecules provide a unique opportunity to isolate the effect that the existence of multiple strength market segments of a molecule may have (on the degree of competition within that molecule market and the likely implication for efficiency savings across countries), without being complicated by the influence of a different mix of formulations in different strengths.[39] The one exception is in the case of the controlled-release version of paroxetine in the USA, which this chapter takes advantage of as an opportunity to do a case study on the cost implication of a product-line extension. Finally, these two molecules recently went off patent in all study countries, which enables an analysis across different countries' regulatory environments that is reflective of modern pharmaceutical policies.

5.4.1 Data

The study uses Intercontinental Medical Statistics (IMS) Health data. IMS collects pharmaceutical pricing and sales data across numerous countries and provides a robust source of comparative data, with data being subject to internal validation (IMS, 2002). Retail sales and price data was available for omeprazole and paroxetine on a quarterly basis from 2000Q1 to 2005Q1. The data was available at the most disaggregated level, namely the product presentation level, which includes various permutations of strength, formulation, and package size. The manufacturer's name (both originator and generic) can also be distinguished at the presentation level. This data allows for the calculation of market (molecule) level information, such as the number of manufacturers and original brand market share. The detailed nature of the dataset results in a total sample size of N=11,210. Using price and sales data, the quantity of packages sold was determined. Subsequently, the total volume of each presentation sold was arrived at by adjusting for package size (i.e. number of pills,

[39] Paroxetine and omeprazole were also available in liquid form in the hospital market, which is not included in this study.

tablets or capsules). Because the analysis is at the strength sub-market level, the units do not need to be standardized into daily defined dosages (DDDs), but rather are on a per pill basis. All prices were inflation-adjusted by each country's consumer price index, and then converted to USA dollars based on the quarterly exchange rates.

5.4.2 Choice of Study Countries

This study focuses on original brand versus generic competition within strength sub-markets of omeprazole and paroxetine in the USA, UK, Germany and France. The choice of countries reflects differences in supply- and demand-side regulatory and incentive structures affecting the uptake and use of generic medicines. Specifically, the USA represents a relatively free market in that there is no centralized price control or regulation for the majority of drugs at the federal level. The majority of the pharmaceutical market can also be characterized as free pricing in the UK, with a system of profit control for patented drugs. In the case of Germany and France, however, pharmaceutical pricing and reimbursement are more heavily regulated. Historically, Germany has allowed free pricing for patented drugs, but has been a pioneer of molecular-level reference pricing for off-patent drugs.[40] Notably, there are separate reference groups for different strengths of a molecule in Germany. Reference pricing is a system in which a common reimbursement price is set for a group of drugs. Where the price of the drug is higher than the reference price, the patient must pay the difference. France, on the other hand, is the one country in this study that maintains direct control over the reimbursement prices of patented drugs, as well as generics, which it caps at a percentage (around 60%) of the original brand price (Kanavos and Gemmill, 2005). As of 2003, France also has moved a number of its molecules into an off-patent reference price system, although they did not include omeprazole and paroxetine during this study period. (See chapter 3 on methods and Appendix A for a more detailed description of the pharmaceutical regulations in the USA, the UK, Germany and France.) These regulatory differences

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[40] In 2004, Germany expanded its molecule-level reference price system to the entire therapeutic class for certain drugs. In these cases, some patented drugs were included in the reference price system. PPIs, and therefore omeprazole, were included in the therapeutic class reference price system. However, since omeprazole was the first drug in its class, omeprazole prices within strength submarkets are unlikely to have been affected by the inclusion of other PPIs into the reference group since omeprazole prices would likely have been the lowest as a result of being the first molecule in the PPI class to go off patent.

enable a comparison of how competition within strength market segments of omeprazole and paroxetine differs across regulatory environments. Moreover, the regulatory differences across countries enables a descriptive comparative analysis on what factors may influence the number of strengths within molecule markets besides clinical need.

5.4.3 Research Questions

Recall from the conceptual method section above that there are four main empirical questions. On the competitive dynamics within strength markets: 1) To what extent does the degree of competition between the original brand and generics within strength market segments differ across strength market segments (of the same molecule) and 2) What are the findings' implications for purchasing efficiency? On the role of product differentiation and price discrimination: 3) How do prices compare across strength/form segment markets (of the same molecule) and 4) What are the ways in which payors could take advantage of pricing disparities by substituting certain strengths (within a molecule) and what degree of savings could these strategies achieve?

Recall also that before launching into an analysis of competition within strength segment markets, it is first necessary to explore the ways in which in the number of strength submarkets of a molecule may differ across countries, as well as their corresponding strength market shares. Furthermore, this study conducts a descriptive analysis on how the number of strengths and their corresponding strength market shares differs across countries and what factors may influence the number of strengths within a molecule market.

The first two research questions are therefore:

1. How did the number of strengths and their corresponding strength market shares compare in the omeprazole and paroxetine markets in the USA, UK, France and Germany during the patent expiry to 2005q1 period?
2. What regulatory factors may influence the number of strengths in a molecule market in the USA, UK, France and Germany?

This study then conducts a descriptive analysis of original brand versus generic market shares within strength submarkets of a molecule across countries, and compares how the number of generic competitors differs across strength submarkets of a molecule. Finally, this study uses a fixed-effects panel data technique to model

the factors that determine the original brand prices within strength segment markets, the original brand market share within strength market segments and generic prices within strength segment markets. Finally, recall that this study also analyses purchased prices in order to determine the extent to which manufacturers are able to price nonlinearly across strengths in order to maximize profits.

In order to answer the empirical questions using this sample selection, the remaining research questions are therefore:

3. What were the determinants of original brand prices within omeprazole and paroxetine strength segment markets in the USA, UK, France and Germany during the 2000q1-2005q1 period and what does this evidence say about whether original brand manufacturer employed the market harvesting strategy within strength segment markets?
4. How do the original brand strength segment market shares relate to generic strength segment prices within and across omeprazole and paroxetine strength segments in the USA, UK, France and Germany during the patent expiry to 2005q1 period?
5. How did original brand strength segment market shares compare across paroxetine and omeprazole strength segments in the USA, UK, France and Germany during the patent expiry to 2005q1 period and what were the determinants of the original brand strength segment market shares?
6. To what extent was generic entry associated with generic price declines across strengths in the omeprazole and paroxetine markets in the USA, UK, France and Germany during the patent expiry to 2005q1 period and what were the determinants of generic prices?
7. How much could countries have saved if original brand versus generic competition was equivalent within all strength segment markets (of a molecule) to the strength segment with the most competitive dynamics?
8. How did purchased prices compare within and across omeprazole and paroxetine strength submarkets in the USA, UK, France and Germany during the 2000q1 to 2005q1 period and what does this suggest about the degree of price competition within molecule markets?
9. What are the implications of payors taking advantage of nonlinear pricing patterns?

10. What are the implications for payors of an original brand manufacturer introducing a line- extension, as seen in the case of paroxetine suspended release in the US?

5.5 The Implications of Strength-Segmented Molecule Markets on Original Brand versus Generic Competition

5.5.1 Empirical Analysis/Observations

5.5.1.1 A Comparison of Strengths across Molecule Markets and Countries

In order to address the first two research questions, this study begins by conducting a descriptive analysis on how the number of strengths and their corresponding strength market shares differs across countries and what factors may influence the number of strengths within a molecule market. The strength market share is calculated as the percentage of a molecule market (based on numbers of pills) that a strength accounts for. For example, a 10mg strength market share of 10 percent would imply that for that given molecule, ten percent of the dispensed pills were 10mg.

Figure 5-1 shows how the number of strengths and their corresponding market shares in the omeprazole and paroxetine markets compared across the USA, UK, France and Germany in 2005q1.

Figure 5-1 A Comparison of Omeprazole Strength Market Shares in each of the Study Countries in 2005q1

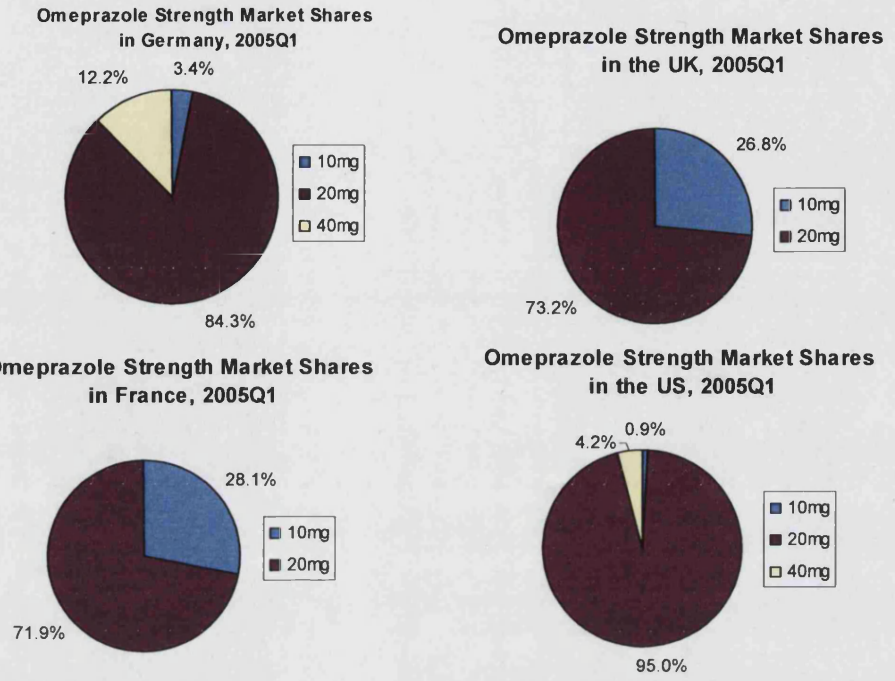
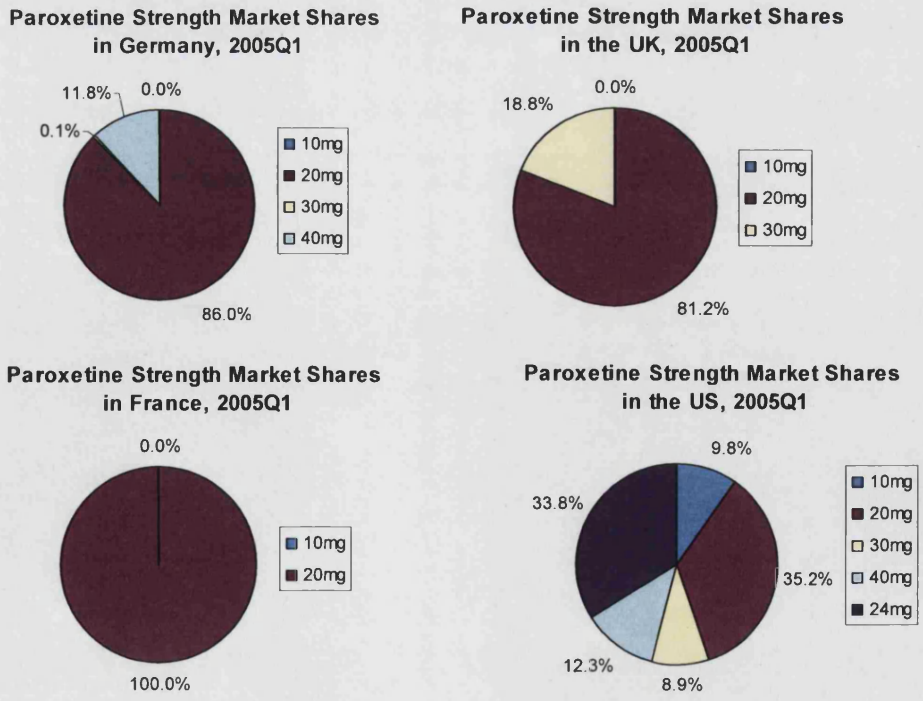


Figure 5-2 A Comparison of Paroxetine Strength Market Shares in each of the Study Countries in 2005q1



Source: The author from IMS.

In France and the UK, omeprazole was available in two strengths—20 mg and 10 mg. The 20 mg market comprised nearly three quarters of the total molecule market in both the UK and France, while the 10 mg market accounted for the other quarter of the market. In Germany and the USA, however, omeprazole was sold in three strengths—10 mg, 20 mg and 40 mg. The 20 mg dosage comprised the vast majority of the molecule markets—84% and 95% in Germany and the USA respectively—while the 40 mg markets had the next largest market shares, followed by the 10 mg markets.

With regards to paroxetine, Figure 5-2 shows that Germany and the USA had the largest number of strengths, while the UK and France had the smallest. In France, paroxetine was only available in one strength—20mg—in 2005q1. In the UK, it was available in 20 mg and 30 mg, with the 20 mg strength comprising the vast majority of the market. Paroxetine was available in 20 mg, 30 mg and 40 mg in Germany, with the 20 mg market comprising the vast majority of the molecule market and the 40 mg market comprising most of the rest. Interestingly, the 30 mg market comprised only 0.1% of the molecule market in Germany. It was introduced in 2004q1 by two generic manufacturers, which had 3% and 20% of the total molecule market share. Finally, in the USA, paroxetine was available in four strengths—10mg, 20mg, 30mg, 40mg—and a fifth form/strength, 24 hour controlled release. Paroxetine controlled release was introduced into the market by the original brand manufacturer of paroxetine[41], in 2002q1, roughly a year before the first generic entered the paroxetine market. The original brand manufacturer claimed that in comparison with immediate release paroxetine, its controlled release version was associated with a lower rate of nausea during the first week of treatment, thus, offering higher quality treatment (at a higher price). The 24-hour controlled release version had a unique rate of bioabsorption into the body, so could not be considered to be bio-equivalent to any of the other paroxetine strengths. As a result, it could not be grouped into any of the paroxetine strength submarkets. However, since its chemical ingredient is identical to other paroxetines, it is appropriate to group this line extension into its own sub-market within the broader paroxetine molecule market.

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[41] GlaxoSmithKline

Interestingly, none of the five paroxetine submarkets (10mg, 20mg, 30mg, 40mg and 24SA[42]) captured the majority of the molecule market in the USA in 2005q1. The 20mg and 24SA presentations each comprised roughly a third of the molecule market. The remaining third of the market was relatively evenly split amongst the 10mg, 30mg and 40mg strengths.

Interestingly, the lower strengths have relatively high strength market shares in the omeprazole and paroxetine markets in France and the UK. Specifically, the case of omeprazole shows that the lowest strength (10mg) occupied a relatively higher market share in the UK and France than in the USA and Germany. Likewise, in the case of paroxetine, the highest strength (40mg) captured a significant share of the market in the USA and Germany, but did not even exist in the UK and France.[43]

5.5.1.2 Factors Influencing an Original Brand Manufacturer's Decision to Enter/Create a New Strength Market within a Molecule

The two most obvious factors that influence the number of strengths in a molecule market and the corresponding strength market shares are clinical need[44] and prescribing habits[45]. However, recall from the conceptual method section that a

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[42] 24 hours suspended action

[43] One hypothetical (albeit unsubstantiated) explanation for this could be that physicians in the UK and France follow step-therapy guidelines more closely than the US and Germany.

[44] Intuitively, the most obvious factor that determines the number of strengths is the size of the patient population for that given molecule, or in other words, the clinical need. At first glance, the relatively static nature of the number of strengths and their respective market shares in each country as seen in Figures 5-1 and 5-2 might seem to suggest that the number of strengths is based largely on exogenous factors such as clinical need rather than on factors such as generic entry. However, a cross country comparison suggests that there may be other factors, in addition to clinical need, that determine the number of strengths. Since all countries in this study share the Western Culture in common and have a similar level of development, it seems unlikely that the disease profiles of heartburn and depression/anxiety differ enough to justify such significant differences in the number of strengths and their market shares across the USA, UK, France and Germany. Thus, the extent to which clinical need (both in terms of the incidence and acuity of the diseases across countries) drives the number of strengths and their corresponding market shares is an area that could benefit from further research.

[45] Since physicians choose which strength to prescribe a patient, and since pharmacists are not allowed to change the strength that the physician prescribed, physicians' prescribing habits are likely to be a strong determinant of the number of strengths in each market as well as the strength market share. The driving factors behind physicians' prescribing habits, however, likely differ across settings. Numerous factors may influence prescribing habits, including: pharmaceutical marketing/advertising and the role of clinical guidelines and whether they give specific orders to use step-therapy (the practice of trying the lower strengths first and then increasing the dosage if the low strength is not effective). For example, in the UK, NICE issues guidelines on specific diseases/illnesses, which reflect the cost-effectiveness of various lines of treatment. In 2000, NICE (The National Institute for Clinical Excellence) issued specific guidelines on the use of PPIs. They state that: "In circumstances where it is appropriate to use a PPI and where healing is required, the optimal dose to achieve this should be prescribed initially. Once healing is achieved, the lowest dose of the PPI that provides effective symptom relief should be used.... The least expensive appropriate PPI should be used" (NHS NICE, 2000).

manufacturer's decision to enter into a strength market, which is a prerequisite for the existence of a strength market, is a function of a number of factors besides clinical need and prescribing patterns. It is also a function of the price which the manufacturer expects to receive as well as the expected costs of marketing the product. Certain costs associated with marketing a product may be similar across these study countries, such as manufacturing costs. However, other costs may differ with each country's regulatory system, such as the costs of obtaining marketing authorization and coverage approval for a new strength.

In France, manufacturers of a new, branded product must prove the drug's additional therapeutic value in comparison with other drugs on the market and must negotiate a price that is based on expected sales volume in order to be approved for marketing and included on the reimbursed list of drugs. Thus, the approval process and the pricing processes are intertwined. (See Appendix A.) In the UK, the marketing authorization process for additional strengths is relatively straightforward in comparison with France. In cases where original brand manufacturers wish to receive approval for a new strength or form, they need only prove the drug's quality, safety and efficacy through an abridged application, which only requires the necessary pre-clinical and clinical data instead of forcing pharmaceutical companies to repeat the tests and trials on animals and humans (MHRA). They can then price freely and are only constrained insofar as NICE guidelines influence physicians towards or away from prescribing their product. Thus, the UK approval and marketing process is more liberal than France.

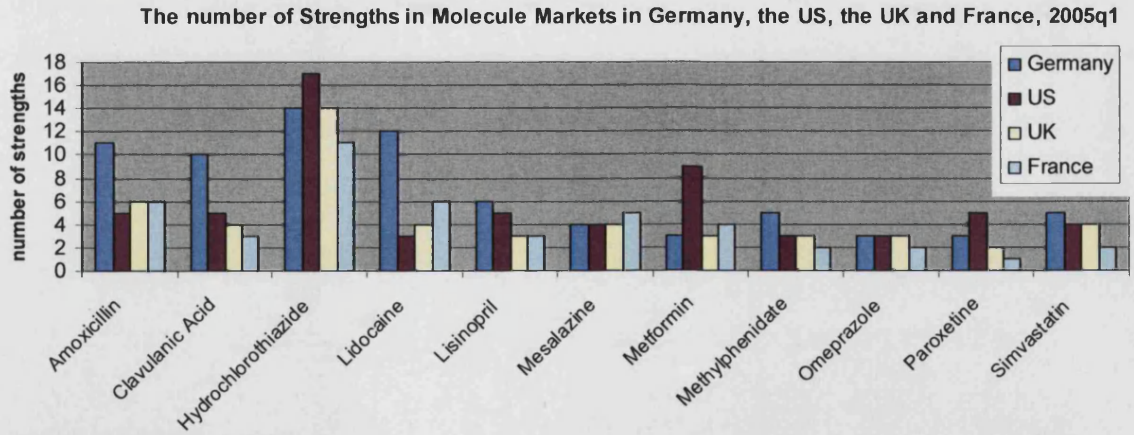
However, the approval and marketing process in the USA and Germany appear to be the most liberal. In the USA, original brand manufacturers do not even need to submit separate applications in order to receive approval for multiple strengths, as long as they are "intended for the same route of administration and the same general indication(s)" (FDA, 2004). (They do, however, have to submit a separate application for the approval of different dosage forms, such as oral vs. injectible vs. suppository, which requires its own clinical data.) This reduces the number of application fees they face as well as the cost of time that is associated with submitting a formal application. Moreover, once a drug has been approved in the USA, there is no centralized process by which the drug's cost-effectiveness is

assessed. Instead, most drugs are automatically covered by the pluralist system of private and public insurance groups.[46]

Similar to the USA, the criteria for licensing and marketing new drugs in Germany are quite liberal. Manufacturers need only demonstrate safety and efficacy, which requires only a marginal beneficial effect that is demonstrated with a small patient sample. Cost-effectiveness plays no role in the approval or coverage decision-making process (Busse and Riesberg, 2004).

Thus, the regulatory leniency in both Germany and the USA, both on the marketing approval and coverage sides, could be one contributing factor to the greater number of strengths in each molecule market that is shown below. Figure 5-3 shows that in nine out of a sample of eleven molecules, either the USA or Germany had the most number of strengths. Meanwhile, France had the fewest number of strengths in six of the eleven molecule markets, whereas the UK lied in the middle of the spectrum. The extent to which the regulations governing marketing approval and coverage influence the number of strengths in a molecule market must be interpreted with caution, however, since this is a simple piece of descriptive evidence that does not imply cause and effect.

Figure 5-3 The Number of Strengths in Molecule Markets in Germany, the USA, the UK and France, 2005q1



Source: IMS Health Data.

[46] Private insurers in the US, however, do often group drugs into tiers based on price and therapeutic superiority. Thus, manufacturers are at least somewhat limited on the reimbursement side. However, the private insurance companies are unlikely to tier drugs based on strength.

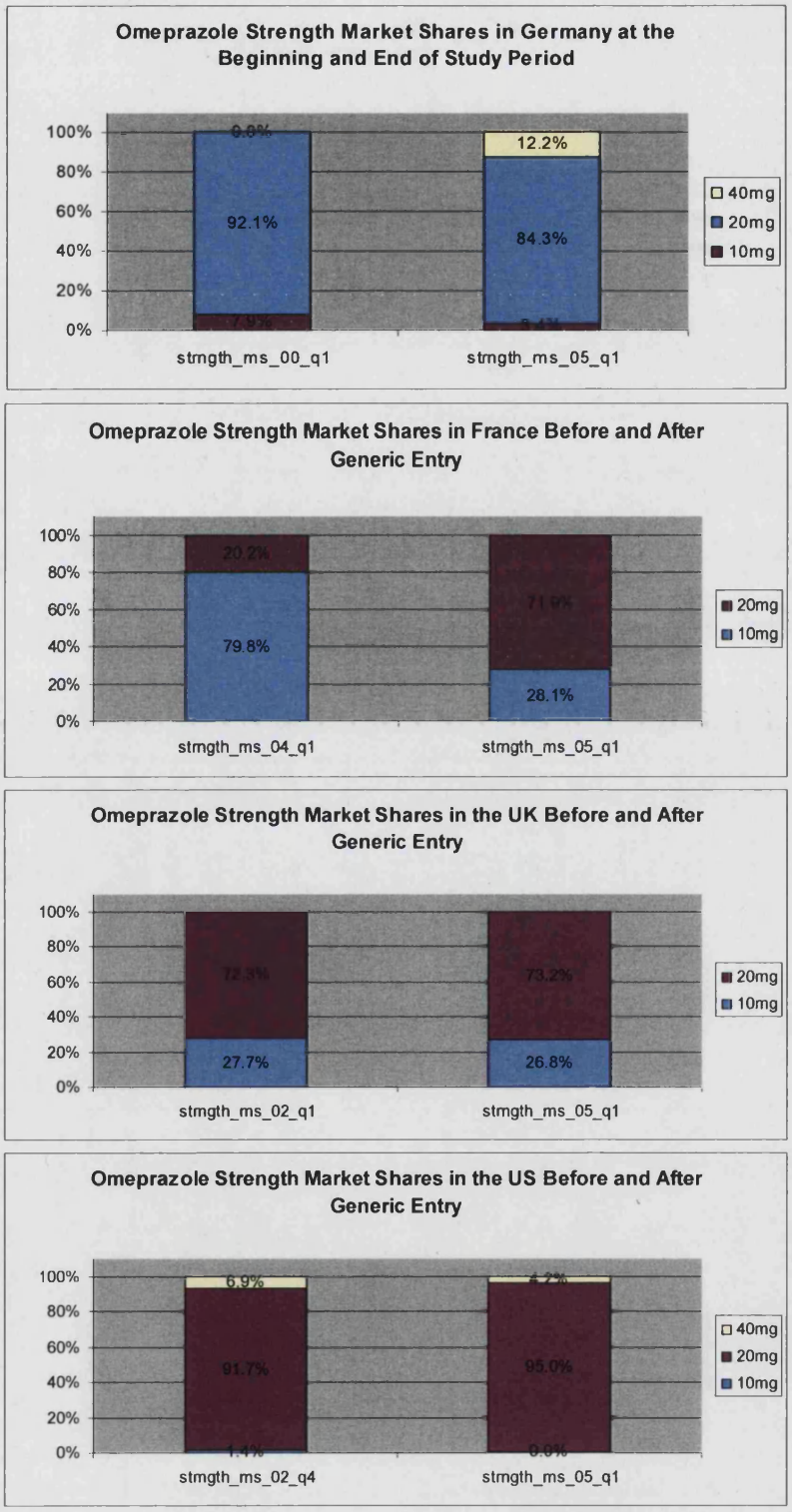
5.5.1.3 Generic Entry into Strength Markets

The approval process for generic drugs is similar in the USA, the UK, France and Germany, where generic manufacturers are exempt from having to perform their own costly animal and clinical trials. Instead, generic manufacturers are simply required to meet good manufacturing standards and prove bio-equivalence. In the USA, the FDA states that generic drugs must fulfil the following obligations (FDA, 2009):

- Contain the same active ingredients as the innovator drug (inactive ingredients may vary)
- Be identical in strength, dosage form, and route of administration
- Have the same use indications
- Be bioequivalent to the originator
- Meet the same batch requirements for identity, strength, purity and quality
- Be manufactured under the same strict standards of FDA's good manufacturing practice regulations required for innovator products

Assuming the original brand molecule exists in that strength, there is a cost to the generic manufacturers for entry into additional strength market segments, although the marginal cost is not high (Scott-Morton, 2000). For approval in each strength market, generic manufacturers are only required to show the necessary laboratory work that meets the relevant batch requirements. It would, however, be more costly for generic manufacturers to receive approval for a strength that is not yet on the market. In this case, they would need to submit a full application with data on the safety of that strength. As a result, generic manufacturers are unlikely to segment the market into additional strengths that do not include the original brand manufacturer. Evidence of this is seen in Figures 5-4 and 5-5.

Figure 5-4 Omeprazole Strength Market Shares in the Study Countries before Generic Entry and in 2005q1 (end of study period) [47]



Source: The Author, using IMS Health data.

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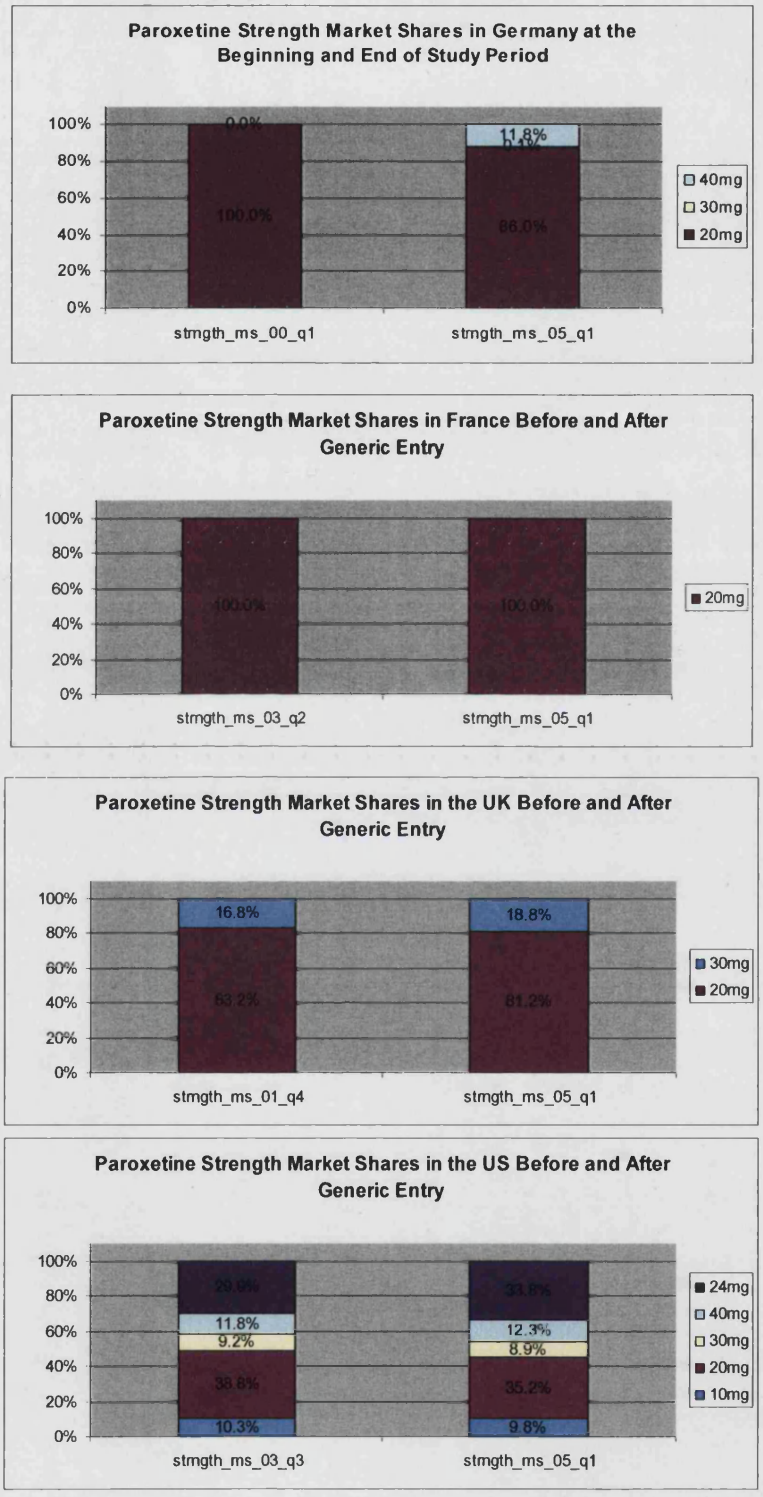
[47] In Germany, generic entry for omeprazole and paroxetine occurred just before the study period. Thus, 2000q1 data has been used instead of data just preceding generic entry.

Figure 5-5 Paroxetine Strength Market Shares in the Study Countries before Generic Entry and in 2005q1 (end of study period)

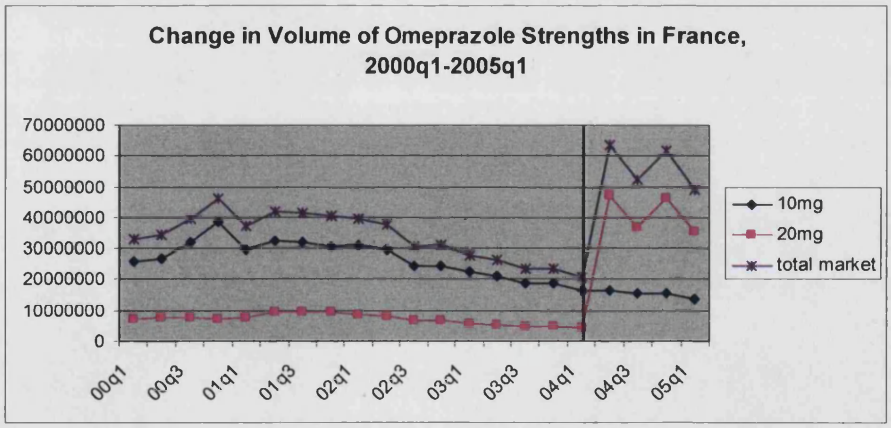


Source: The Author, using IMS Health data.

In Germany, generic manufacturers did introduce new strengths into the omeprazole and paroxetine markets. Specifically, the 40mg omeprazole market, as shown in Figure 5-4 and the 40mg and 30mg paroxetine markets, as shown in Figure

5-5 were introduced by generic manufacturers. However, in the USA, UK and France, generic entry did not result in more strengths in the market. Moreover, in nearly every case, the overall strength market shares did not change substantially before and after generic entry. The one exception is France, where generic entry into the omeprazole market was associated with a significant shift in strength market shares; the 20mg strength held only twenty percent of the omeprazole market share before generic entry, while the 10mg strength held the remainder 80 percent. After generic entry, the market shares nearly reversed, with the 10mg strength only accounting for 28 percent while the 20mg strength accounted for 72 percent. Figure 5-6 shows the change in volume (measured as number of pills) across omeprazole strength market segments in France. The volume of 10mg omeprazole decreased slowly from 2001 to 2005q1. A possible explanation for this shift is that during this time period, France introduced a number of policies that encourage the use of generics (see methodology chapter and Appendix A). It may be that patients who were taking other PPIs which were still on patent switched to the 20mg omeprazole once it experienced generic entry in 2004q2 instead of the 10mg omeprazole, which had not yet experienced generic entry as of 2005q1.

Figure 5-6 Change in Volume of Omeprazole and Strengths in France, 2000q1-2005q1



Note: The solid line denotes the point of generic entry.

Source: The Author, using IMS Health data.

In conclusion, generics did not create new strength segments in the omeprazole and paroxetine markets in the study countries, except in the case of Germany. Nor did generic entry seem to significantly change the strength market

shares in most cases (with the exception of omeprazole in France), as evidenced by the relatively static market shares before and after generic entry. Rather, most generic manufacturers limited themselves to the strength market segments that already existed and strategically decided which strength market segments to enter into and when.

Thus, in the case of omeprazole and paroxetine, the patent expiration and subsequent entry of generic competitors does not seem to be a determinant for the number of strengths. (In Germany, the introduction of additional strengths occurred years after[48] the first generic entered the molecule markets, making it unlikely that patent expiration/generic entry was the cause either.) This suggests that in the omeprazole and paroxetine markets, competition between the original brand and generics may not be one of the principal determinants of the number of strengths. In Germany, however, there seems to be some preliminary evidence that in the omeprazole and paroxetine markets, competition amongst generics may be result in more strength segments. It should be noted, however, that these findings can only contribute to hypothesis building theories since they are descriptive in nature. Since the number of strengths did not change in the omeprazole and paroxetine markets in the USA, UK and France during the study period, this dataset is not conducive to running statistical models that test the relationship between the number of strengths and generic entry/competition.

5.5.1.4 A Comparison of the Competitive Dynamics across Strength market segments

5.5.1.4.1 Generic Entry and Average Generic Prices

One of the driving factors of prices and expenditures within strength markets is the competitive dynamics in that strength segment market. Thus, it is important to first understand the nature of generic entry into strength segment markets, which is a prerequisite for competition (CBO, 1998; Kanavos, Costa-Font and Seeley, 2008).

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[48] Specifically, a generic manufacturer created the 40mg omeprazole segment in 2000q3, which was likely years after generic entry in the omeprazole molecule market, given the fact that there were already 13 generic entrants in 2000q1, the beginning of this study period. In addition, two generic manufacturers created the 40mg paroxetine segment in 2002q1 and one generic manufacturer (different from the two that created the 40mg market) created the 30mg paroxetine market in 2004q1, while generic entry occurred in the paroxetine molecule market before 2000q1.

Figure 5-7 below describes how many strength market segments each generic manufacturer decided to enter into in each country's molecule market and the sequence of entry.

Figure 5-7 Generic Entry into Strength Omeprazole and Paroxetine Strength market segments in Germany, France the UK and the USA

	Germany	France	UK	USA
Omeprazole	• 14 manufacturers entered into 1 strength market (20mg) • 1 manufacturer entered into 2 strength market segments • 7 manufacturers entered into 3 strength market segments (a few entered them at the same time, most entered into one, then two, then three) • 1 manufacturer entered into 3 strength market segments and then left the market*	• 14 manufacturers entered into 1 strength market (20mg)	• 2 manufacturers entered into 1 strength market • 2 manufacturers entered into 2 strength market segments (all entered into both at the same time) • 1 manufacturer entered into 2 strength market segments and then dropped down to 1**	• 1 manufacturer entered into 1 strength market • 5 manufacturers entered into 2 strength market segments (3 entered at the same time and 2 entered into one then two)
Paroxetine	• 16 manufacturers entered into 1 strength market (20mg) • 5 manufacturers entered into 2 strength market segments (all entered into one then two) • 1 manufacturer entered into 2 strength market segments and then left the market*	• 8 manufacturers entered into 1 strength market (though there was only 1 strength in the market)	• 2 manufacturers entered into 1 market (20mg) • 1 manufacturer entered into 2 markets (one, then two) • 1 manufacturer entered into 2 markets and then dropped down to 1**	• 7 manufacturers entered into 4 strength market segments (5 entered into four at the same time, 1 entered into 3 and then 4, and 1 entered into 1 and then 2 and then 4)

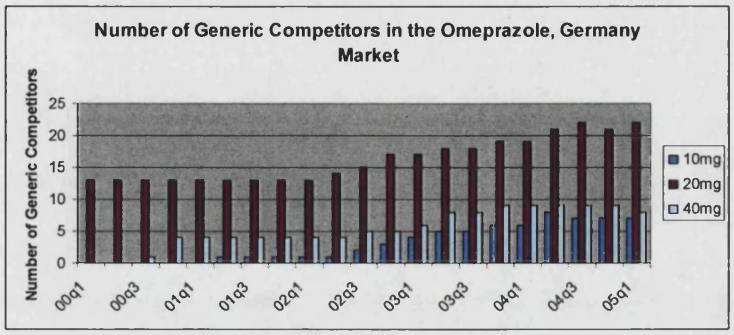
* The same generic manufacturer exited the omeprazole and paroxetine markets in Germany.
**These were not the same company.
Source: The Author, using IMS Health data.

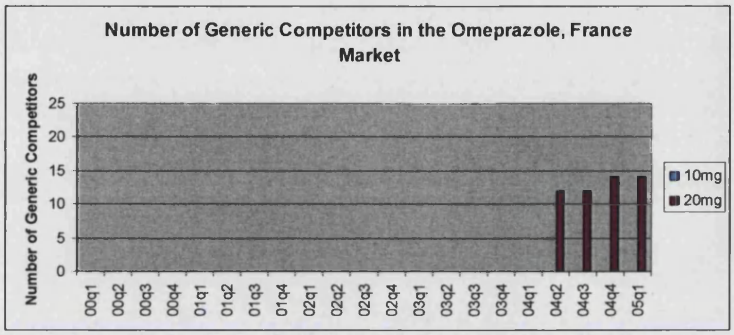
In nearly every case, manufacturers first entered into the 20mg strength segment market upon entry into the omeprazole and paroxetine molecule markets, and remained in that 20mg strength segment market. Thus, in cases where manufacturers were only in one market, they were in the 20mg market. (The only exceptions were two manufacturers in the UK which only entered into the 10mg omeprazole market, one of which was the 10mg OTC omeprazole market.) In cases where manufacturers entered into multiple markets in step-wise fashion, they always entered into the 20mg first (sometimes just a quarter or two before entering into

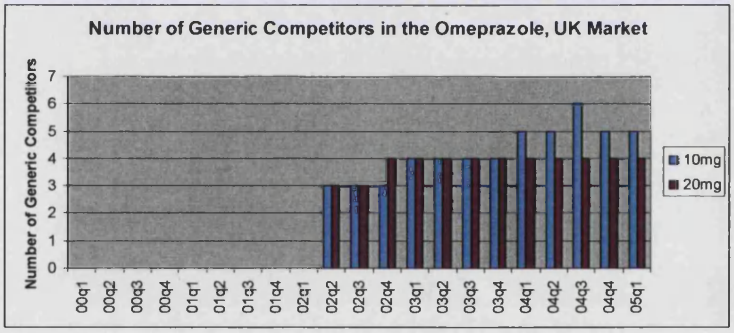
another strength market, while at other times a year or two before entering into another strength market).

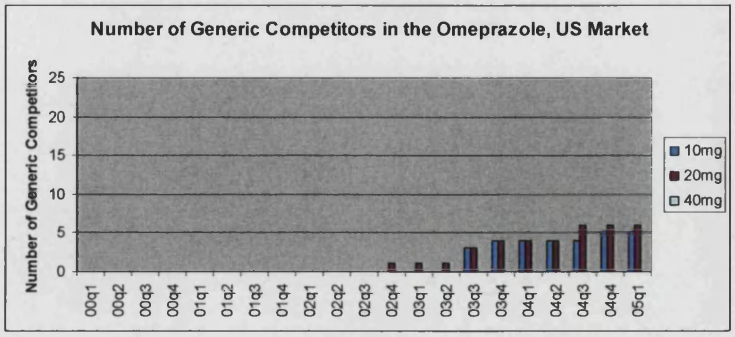
Figures 5-8 and 5-9 show the evolution of the number of generic competitors over time in each strength segment market. It is clear that the number of generic competitors is consistently higher in the 20mg strength segment markets than in other strength segment markets. The two exceptions are in the case of the USA, where the number of generic competitors remains approximately equal across 10mg, 20mg, 30mg and 40mg strength segment markets and in the case of the UK, where there were more generic competitors in the omeprazole 10mg strength segment market than the omeprazole 20mg strength segment market as of 2004q1. The legions in these graphs show the strength segment markets that exist (i.e. that have experienced either original brand or generic sales) in the molecule market. A lack of corresponding generic competitors in the graph indicates that generic entry had not occurred in that strength segment market as of 2005q1. This was the case in the 10mg omeprazole strength segment market in France and the 24SA paroxetine strength/formulation segment market in the USA.

Figure 5-8 A Comparison of the Number of Generic Competitors in each Omeprazole Strength Segment Market across Study Countries, 2000-2005q1



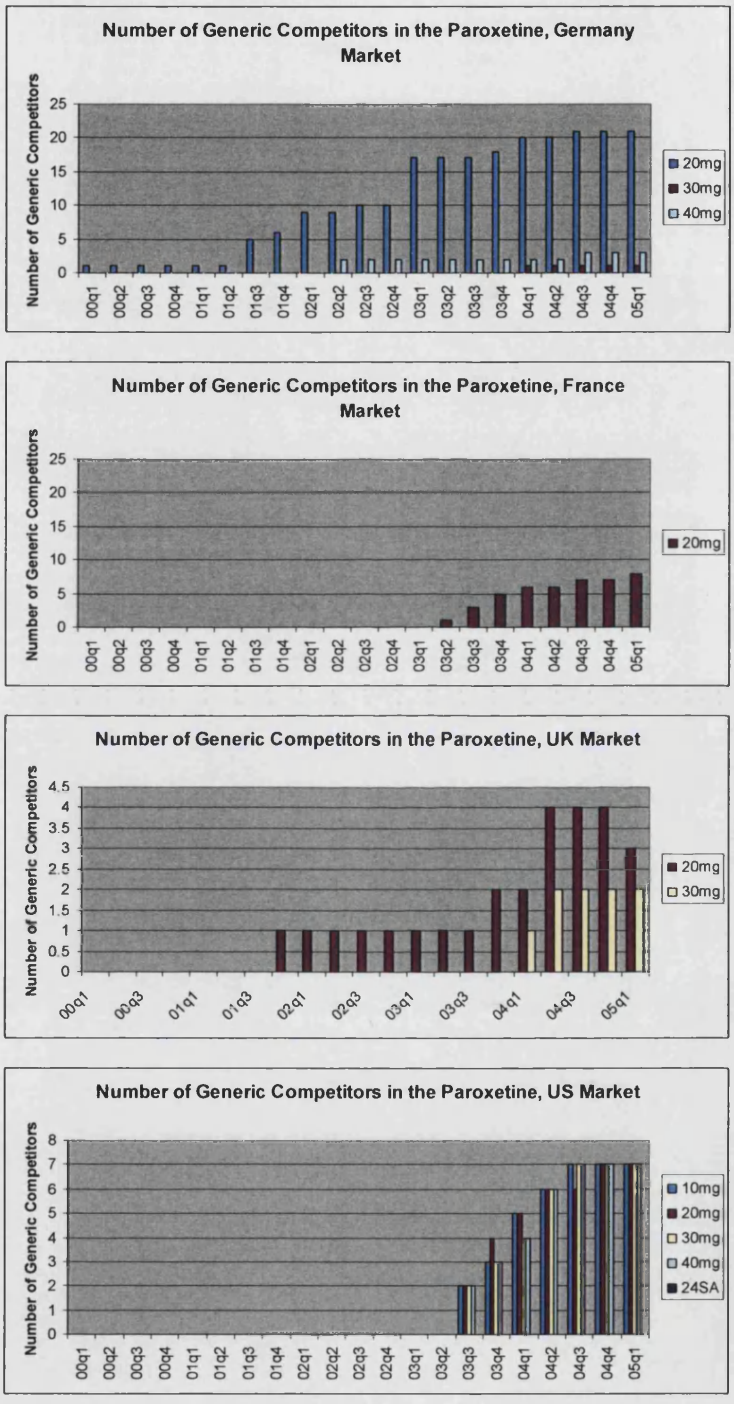






Source: The Author, using IMS Health data.

Figure 5-9 A Comparison of the Number of Generic Competitors in each Paroxetine Strength Segment Market across Study Countries, 2000-2005q1



Source: The Author, using IMS Health data.

Since the 20mg markets for both omeprazole and paroxetine were the daily defined dosages, and likewise, had the highest strength market shares (as seen in Figure 5-1), it appears that the decision of which strength market to enter into is

largely based on expected volume for generic manufacturers. Table 5-1 below provides evidence that there is a positive correlation between the number of generic competitors in each strength market and the strength market share in most omeprazole and paroxetine markets.

Table 5-1 The Correlation between the Number of Generic Competitors in each Omeprazole and Paroxetine Strength Market and the respective Strength Market Share (within the total molecule market), 2000q1-2005q1[49]

	Germany	France*	UK	USA
Omeprazole	.866	.262	-.003	.251
Paroxetine	.541	--	.351	-.203

*In France, the correlation statistic cannot be run for the paroxetine since there is only one strength in the market.
Source: The Author, using IMS Health data.

It is not surprising that the correlation is the strongest in Germany, where a relatively large majority of the omeprazole and paroxetine markets are concentrated in one strength (as seen in Figures 5-1 and 5-2). In the UK, the very weak negative association between the number of generic competitors in each strength market and the strength market shares in the case of omeprazole is likely reflective of the two manufacturers that only entered into the 10mg market, and not the 20mg market, as mentioned in the discussion above. In the USA, the negative association in the case of paroxetine may reflect the fact that the 24SA formulation captured a large market share, but was still on patent and therefore not open to generic entry. Thus, the fact that every generic manufacturer entered into the 20mg market first and foremost and that the number of generic competitors across strengths correlates positively (in most cases) with the strength market share suggests that generic manufacturers base their entry decision primarily on the expected volume.

How, then, do average generic prices across strength market segments correlate with generic entry across strength market segments, and how does this compare across countries? Table 5-2 below shows the correlation between the number of generic manufacturers in each strength market and the average generic price. Nearly all of the generic manufacturers in these strength market segments

[49] For example, this statistic measures the correlation between the number of generic manufacturers in the 20mg omeprazole strength segment and the 20mg omeprazole strength market share (within the total molecule market) for each given country, the number of generic manufacturers in the 10mg omeprazole strength segment and the 10mg omeprazole strength market share (within the total market) for each given country, and so on.

remained in the market (until 2005q1) after entering, with the exception of the one manufacturer in Germany that exited the market, as mentioned in Figure 5-7 above. Thus, this correlation statistic provides evidence on whether an increase in the number of generic competitors in each strength market was associated with a decrease (or an increase) in the average generic prices in each strength market.

Table 5-2 The Correlation between the Number of Generic Manufacturers across Strength market segments and the Average Generic Price across Strength market segments in Germany, France, the USA and the UK, 2000q1-2005q1

	Germany	France	UK	USA
Omeprazole	.009	.775	-.808	-.927
Paroxetine	-.697	-.654	-.057	-.593

Source: The Author, using IMS Health data.

In Germany and France, the correlation between generic entry and average generic prices across strength market segments differs by molecule. Specifically, an increase in generic competitors is associated with a decrease in average generic prices in the paroxetine markets in Germany and France, but not the omeprazole markets. Rather, there does not seem to be a strong correlation in either direction in the omeprazole market in Germany, which may reflect the influence of the reference pricing system, which often prevents generic prices from decreasing over time (Danzon and Chao, 2000; Kanavos, Costa-Font and Seeley, 2008). In addition, the generic entry into omeprazole strength market segments in France is associated with an increase in the average generic price. However, the increase in average generic price is likely due to the increase in the original brand price, not the increase in the number of generic competitors itself. This is a result of France's policy that the price of generics should not exceed a fixed percentage of the original brand price (50-60%), which effectively acts as a price ceiling.[50]

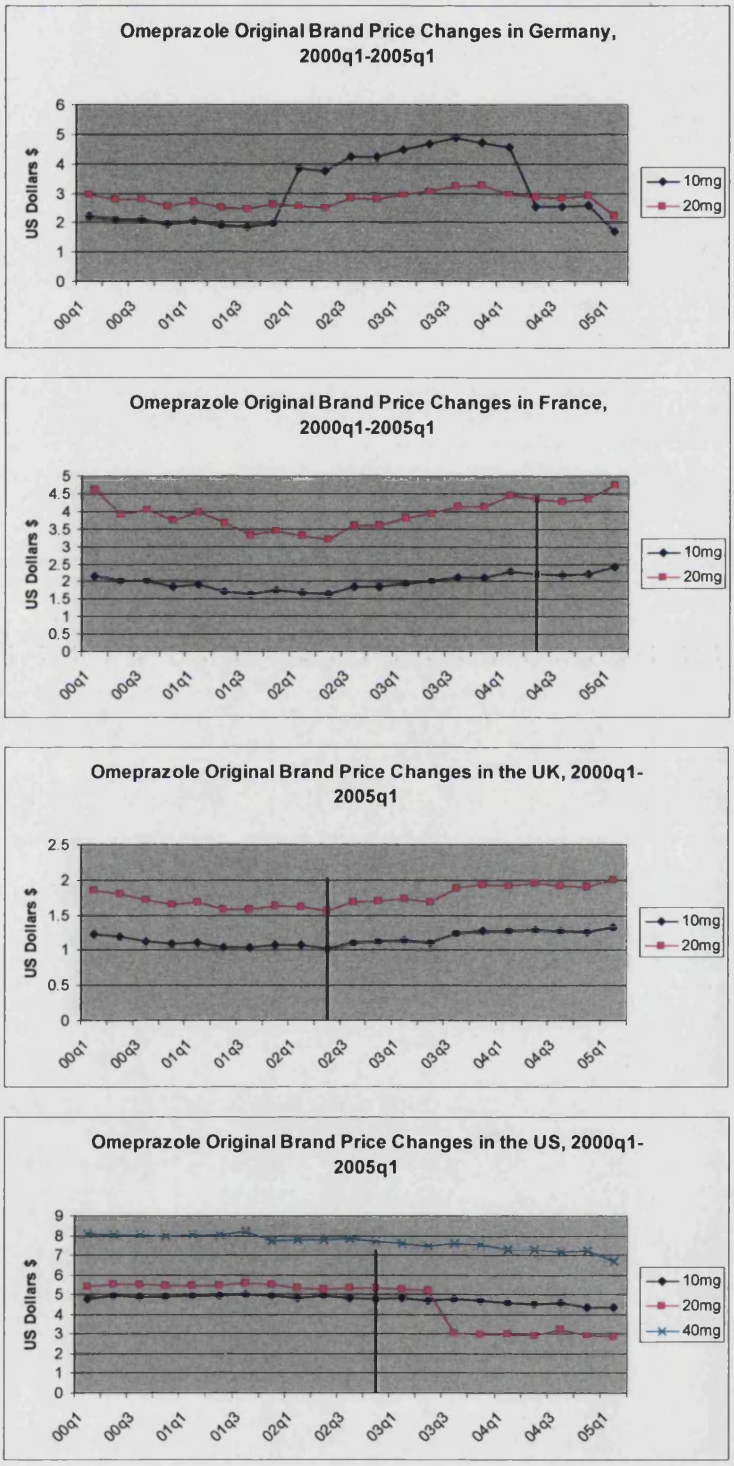
The USA and the UK, however, show consistent signs of generic prices decreasing when generic entry increases. This indicates that some degree of price competition amongst generics does exist within strength market segments, as would be expected.

[50] This price ceiling phenomena is also discussed in case one of this thesis.

5.5.1.4.2 Original Brand Prices and Market Shares in Strength market segments following Generic Entry

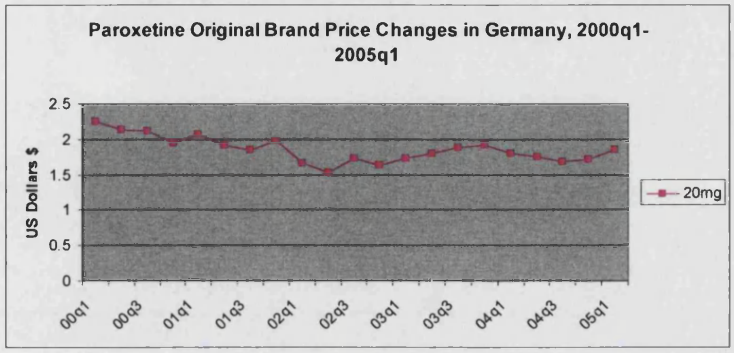
Numerous studies of original brand versus generic competition at the molecule level show that original brand manufacturers pursue a market harvesting strategy post generic entry by either increasing or keeping constant their prices, thereby retaining brand loyal customers and accepting that the price sensitive portion of the market will switch to generics (Frank and Salkever, 1997; Caves et al, 1991; Grabowski and Vernon, 1992). Figures 5-10 and 5-11 show that in nearly all cases, the original brand prices either stayed the same or increased at the same rate across strength segment markets. Moreover, following patent expiration, original brand manufacturers of omeprazole and paroxetine employed this market harvesting strategy consistently across strengths, regardless of the number of generic entrants in each strength market or the average generic price.

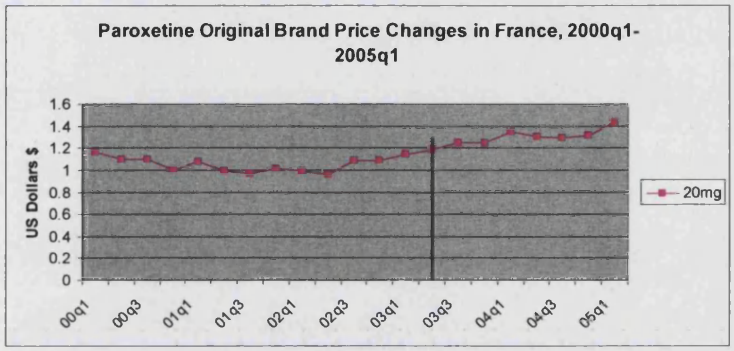
Figure 5-10 Original Brand Manufacturers' Prices across strengths before and after Generic Entry in the Omeprazole Markets in Germany, France, the UK and the USA, 2000q1-2005q1

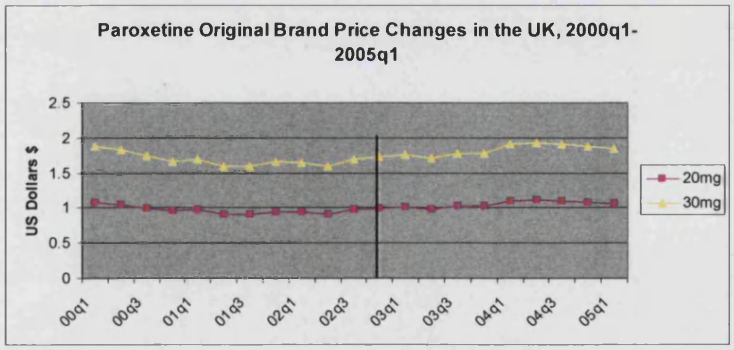


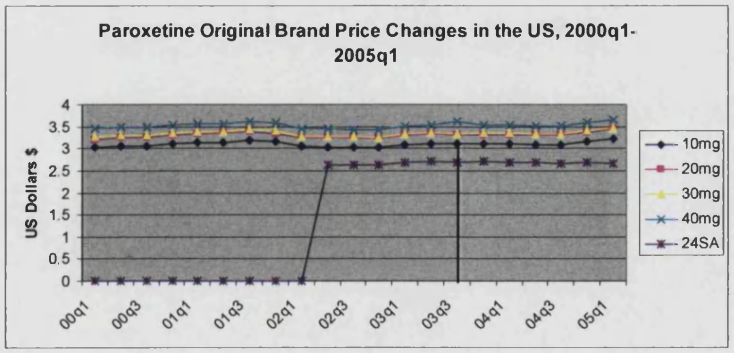
Note: Solid lines denote time of generic entry. In Germany, generic entry occurred before study period
Source: The Author, using IMS Health data.

Figure 5-11 Original Brand Manufacturers' Prices across strengths before and after Generic Entry in the Paroxetine Markets in Germany, France, the UK and the USA, 2000q1-2005q1









Note: Solid lines denote time of generic entry. In Germany, generic entry occurred before study period
Source: The Author, using IMS Health data.

The one exception was for 20mg omeprazole in the USA, where the original brand manufacturer decreased its price at the time of OTC switch. The original

brand manufacturers even increased their prices in strength market segments where there was not yet generic entry. Examples of this include the 10mg omeprazole market in France, which had not experienced generic entry by 2005q1, despite generic entry occurring in the 20mg market in 2004q2, and the 30mg paroxetine market in the UK, which did not experience generic entry until 2004q1, despite generic entry occurring in the 20mg market in 2001q4. Thus, on the one hand, the original brand manufacturers of omeprazole and paroxetine treated different strength products as though they were in the same market by increasing prices consistently across strength segments. However, on the other hand, some original brand manufacturers treated different strength products as though they were in different markets (and hence benefit from this segmentation) when they introduced the products to the markets with nonlinear (and sometimes discriminatory) prices (as discussed below) at the first instance.

Another way in which strength market segments benefited the original brand manufacturers was in their ability to retain a larger share of the strength market in strengths were there were fewer generic entrants. Table 5-3 below shows the original brand market shares across strengths alongside the number of competitors in that market and the original brand to generic price ratio (calculated as the average original brand price to average generic price ratio). The strength market share is also included in order to put the original brand market share in each strength market into the context of the larger molecule market.

Figures 5-7, 5-8, and Table 5-3 all show that in most omeprazole and paroxetine markets in Germany, France, the UK and the USA, the 20mg DDD has the largest number of generic competitors. This is not surprising given that strength market share correlates positively with generic entry (Table 5-1), and the 20mg strength market segments have the highest strength market share. Additionally, the original brand to generic price ratio differs across strength markets of the same molecule, which is also not surprising given that number of generic entrants correlates strongly (in most cases) with average generic prices across strength market segments (see Table 5-2). The most interesting finding in Table 5-2 is that original brand market shares are significantly different across strengths of the same molecule market. For example, for omeprazole in France, the original brand market share ranges from 5% for 20mg to 100% for 10mg. Meanwhile, in Germany, there are multiple strength market segments where the original brand is not even in the market.

Table 5-3 A Comparison of Original Brand and Generic Market Shares and Prices across Omeprazole and Paroxetine Strength market segments in Germany, France, the USA and the UK in 2005Q1

	Omeprazole															
	Germany				France				UK				US			
	Strength Market Share	Original Brand Market Share	Number of Generic Competitors	Original Brand to Generic Price Ratio	Strength Market Share	Original Brand Market Share	Number of Generic Competitors	Original Brand to Generic Price Ratio	Strength Market Share	Original Brand Market Share	Number of Generic Competitors	Original Brand to Generic Price Ratio	Strength Market Share	Original Brand Market Share	Number of Generic Competitors	Original Brand to Generic Price Ratio
10mg	3%	19.6%	7	1.43	28%	100.0%	0		27%	8.0%	5	2.19	1%	18.3%	5	1.99
20mg	84%	0.1%	22	1.27	72%	5.3%	14	2.85	73%	10.9%	4	2.26	95%	60.2%	6	1.34
40mg	12%	0.0%	8		0%								4%	100.0%	0	
total market		1%	22	1.06		32%	14	2.40		10%	6	2.21		62%	6	2.13

	Paroxetine															
	Germany				France				UK				US			
	Strength Market Share	Original Brand Market Share	Number of Generic Competitors	Original Brand to Generic Price Ratio	Strength Market Share	Original Brand Market Share	Number of Generic Competitors	Original Brand to Generic Price Ratio	Strength Market Share	Original Brand Market Share	Number of Generic Competitors	Original Brand to Generic Price Ratio	Strength Market Share	Original Brand Market Share	Number of Generic Competitors	Original Brand to Generic Price Ratio
10mg				0									10%	7.9%	7	2.30
20mg	86%	16.1%	21	1.18	100%	36.2%	8	1.51	81%	38.2%	3	1.24	35%	8.8%	7	2.24
30mg	0%	0.0%	1						19%	44.5%	2	0.93	9%	8.5%	7	2.48
40mg	12%	0.0%	3										12%	7.4%	7	2.82
SA tabs													34%	100.0%	0	
total market		14%	21	1.09		36%	8	1.51		39%	4	1.12		39%	7	2.36

Source: The Author, using IMS Health data.

The only cases where the original brand strength market shares are within a few percentage points of each other are paroxetine in the USA and omeprazole in the UK. At first glance, it seems that it could be due to the number of generic competitors being relatively equal across strength market segments. However, the case of omeprazole in the USA shows that the original brand market shares can still be significantly different across strength market segments even when the number of generic competitors is relatively similar across markets. What, then, are the determinants of original brand market share?

5.5.2 Econometric Analysis

Since the average original brand prices are significantly higher than the average generic prices, as seen in the original brand to generic price ratios, high original brand market shares at the strength level are likely to lead to inefficient spending for purchasers. Thus, it is of utmost policy significance to understand what determines the original brand prices and original brand market shares within strength segment markets as well as the generic prices within strength market segments. The following models test the likely determinants of original brand prices, original brand market shares and generic prices within omeprazole and paroxetine strength segment markets in Germany, France, the UK and the USA from 2000q1-2005q1[51]:

$$P_i^{OB} = \beta_o + \beta_1 N_i^{gen} + \beta_2 MS_i^{OB} + \beta_3 SMS_i + DOTC + \varepsilon$$

$$MS_i^{OB} = \beta_o + \beta_1 N_i^{gen} + \beta_2 PRAT_i + \beta_3 SMS_i + DOTC + \varepsilon$$

$$P_i^{gen} = \beta_o + \beta_1 N_i^{gen} + \beta_2 P_i^{OB} + \beta_3 SMS_i + DOTC + \varepsilon$$

Where P_i^{gen} represents the average generic prices within strength segments, P_i^{OB} represents the average original brand price within the strength segment market, N_i^{gen} represents the quarterly number of generic competitors in each strength, MS_i^{OB} represents the original brand market share within that strength segment, SMS_i represents the quarterly strength market share (in the context of the broader molecule market), $DOTC$ represents a dummy variable for whether the original

[51] Notably, the strength market segments for both paroxetine and omeprazole have been combined into the same model across all countries for rigor, as some of the markets, such as those in France, only had one or two strengths and therefore could not be run separately. Thus, while regulatory aspects were implicitly controlled for through fixed-effects, they cannot be displayed separately as they were in the first case.

brand drug was available over the counter in that strength for that given quarter[52] and $PRAT_i$ represents the quarterly average original brand to average generic price ratios in each strength, as described in Figure 5-12 below.

Figure 5-12 Variables and their definitions for econometric analysis, 2000Q1-2005q1

Variable	Definition	Mean (SE)
P_i^{OB}	The average price of the original brand in that strength segment market	3.015 (1.627)
P_i^{gen}	The average generic price in that strength segment market	1.731 (.693)
MS_i^{OB}	The original brand market share within the strength segment market	.653 (.410)
N_i^{gen}	Number of generic competitors in that strength segment market	2.640 (4.685)
T_i	Number of quarters since generic entry in that strength segment market	6.223 (5.050)
$PRAT_i$	The ratio of the average original brand price to average generic price in that strength segment market	1.738 (.678)
$LAGPRAT_i$	The lagged ratio (by one quarter) of the average original brand price to average generic price in that strength segment market	1.717 (.686)
SMS_i	The strength market share (percentage of total pills of that molecule that are dispensed of that strength)	.414 (.368)
$DOTC_i$	Dummy for Availability of the original brand drug OTC in that strength segment market	

Source: The Author, using IMS Health data.

With a total of 22 strength market segments over a 21 quarter time frame, this study uses a fixed effects panel data regression method. A fixed effects model is appropriate in these three models in order to control for the strength-specific disturbances, where the explanatory variables' disturbance terms correlate with the strength level residuals. The Hausman test for the appropriateness of the random effects model versus the fixed effects model confirms this, as shown in Figure 5-12, Table 5-4 and Table 5-5.

This study presents the results for two versions of the models that test the determinants of the strength segment original brand market shares and the average generic prices within strength segment market shares. The N_i^{gen} variable in the model that tests the determinants of the original brand prices within strength segment markets is treated as exogenous in accordance with the market harvesting strategy, which predicts that original brand prices are independent of the degree of generic entry following patent expiration.

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[52] This dummy variable for original brand OTC is different from the OTC dummy variable in case one, which includes both original brand OTC products (as was the case with OTC omeprazole in the US) and generic OTC products (as was the case with OTC omeprazole in the UK).

The first version for the *original brand market shares model* is a single-equation panel data fixed effects regression where variables N_i^{gen}, $PRAT_i$, SMS_i and $DOTC$ are all treated as exogenous.[53] The second version of this model is a two-staged least-squares panel data fixed effects regression which treats N_i^{gen} and $PRAT_i$ as endogenous by using T_i as an instrument for N_i^{gen} and $LAGPRAT_i$ in place of $PRAT_i$.[54]

Similarly, the first version of the generic price model is a single-equation panel data fixed effects regression where variables N_i^{gen}, P_i^{OB}, SMS_i and $DOTC$ are all treated as exogenous. The second version of this model is also a two-staged least-squares panel data fixed effects regression which treats N_i^{gen} as endogenous by using T_i as an instrument for N_i^{gen}. Notably, Table 5-5 and 5-6 show that the significance and direction of the associations between the explanatory and dependent variables are the same in both the instrumented and non-instrumented versions, rendering the results consistent regardless of whether exogeneity or endogeneity is assumed.

Table 5-4 Model testing for the Determinants of the Average Original Brand Prices across Strengths in the Omeprazole and Paroxetine Markets in Germany, France, the UK and the USA, 2000q1-2005q1

Dependent variable: P_i^{OB}	Fixed Effects Model
N_i^{gen}	-.007 (.009)
MS_i^{OB}	-.316*** (.097)
SMS_i	.123 (.221)
$DOTC$	-2.509*** (.160)
No. of observations	369
No. of groups	18
R^2 (within for fe model)	.421
Hausman test	9.55**

*p < 0.10: **p < 0.05: ***p < 0.01

[53] For other literature that treats the number of generic companies as an exogenous variable, see Grabowski and Vernon 1992 and Wiggins and Manes 1994.

[54] For other literature that treats the number of companies as an endogenous variable, see Frank and Salkever 1997. In addition, for other literature that lags relative prices in order to deal with potential endogeneity see Aronsson & Bergman 1998.

Table 5-5 Model testing for the Determinants of Original Brand Market Shares across Strengths in the Omeprazole and Paroxetine Markets in Germany, France, the UK and the USA, 2000q1-2005q1

Dependent variable: MS_i^{OB}	Fixed Effects Model Without Instruments	Fixed Effects Instrumented Model
N_i^{gen}	-.056*** (.007)	
T_i (instrument for N_i^{gen})		-.074*** (0.009)
$PRAT_i$	-.102*** (.029)	
$LAGPRAT_i$		-.095*** (0.028)
SMS_i	-3.337*** (.945)	-6.021*** (1.162)
$DOTC$	.300*** (.110)	.600*** (0.110)
No. of observations	158	143
No. of groups	15	15
R^2 (within for fe model)	.5213	.5513
Hausman test	42.50***	

*p < 0.10: **p < 0.05: ***p < 0.01

Source: The Author, using IMS Health data.

Table 5-6 Model testing for the Determinants of Original Brand Market Shares across Strengths in the Omeprazole and Paroxetine Markets in Germany, France, the UK and the USA, 2000q1-2005q1

Dependent variable: P_i^{gen}	Fixed Effects Model Without Instrument	Fixed Effects Instrumented Model
N_i^{gen}	-.074*** (.011)	
T_i (instrument for N_i^{gen})		-.100*** (0.017)
P_i^{OB}	-.065 (.051)	.058 (.052)
SMS_i	-7.617*** (1.612)	-10.833*** (2.310)
$DOTC$	-1.092*** (.219)	-.945*** (0.236)
No. of observations	158	157
No. of groups	15	15
R^2 (within for fe model)	.5067	.4871
Hausman test	228.18***	

*p < 0.10: **p < 0.05: ***p < 0.01

Source: The Author, using IMS Health data.

The results from the first model (Table 5-4) show that there is a significant, negative relationship between the original brand market shares within strength segments and the average original brand prices within strength segments. These results are consistent with Figures 5-10 and 5-11, which suggest that the original brand manufactures are pursuing the traditional market harvesting strategy, whereby they often respond to the inevitable decrease in market share (of their original brand) by increasing their prices so as to profit more (on the margin) from the brand loyal, price insensitive segment of the market. However, there is not a significant relationship between the number of generic competitors and the average original brand prices within strength segment markets. In this respect, the degree of generic entry does not affect the average original brand prices within strength segment markets. Additionally, the relationship between the strength segment market shares and the average original brand prices within strength segment markets is also not significant. This is consistent with the findings in Figures 5-10 and 5-11, where the

original brand manufacturers seem to employ their market harvesting strategy consistently across strength segment markets, regardless of the strength market shares. Finally, there is a negative, significant relationship between the dummy variable OTC availability (within that strength segment market for that given quarter) and the original brand price. This is consistent with the results in the OTC case, which show Prilosec OTC priced significantly lower than prescription Prilosec.

The results from the second model (Table 5-5) show that there is a significant, negative relationship between the number of generic competitors and the original brand market share at the strength level, reflecting the fact that as additional generic competitors enter the market, the original brand manufacturer loses more market share, possibly because of the increased availability of drug manufacturers, and the increased supply of generic products to choose from. This effect is separate from the effect of the average generic price being lower than the average original brand price, which is captured through the PRAT variable. In this case, the association is also significant and negative, reflecting the likelihood that as the price gaps between the original brand and generic manufacturers increase, a larger share of the price sensitive payors switch to generics. Finally, there is a significant, negative relationship between the strength market share and the original brand market share. This reveals that in high strength market segments, the original brand is not as able to hold onto its market share. One possible explanation for this is that pharmacists and payors are more conscientious of substituting generics for original brand drugs for the more popular strengths because that is where the most significant savings lie. It could also be that generic substitution in the more popular strength market segments is more common because generics are more likely to exist in these markets (separate from the number of generics that exist).

In the third model (Table 5-6), there is a significant, negative relationship between the number of generic manufacturers and the average generic prices within strength segment markets. This is consistent with the findings in Table 5-2, which show a negative correlation between the number of generic manufacturers and the average generic prices with most omeprazole and paroxetine strength segment markets in the study countries. These findings within strength segment markets are also consistent with the literature, which finds that generic price competition increases with generic entry within molecule markets (Chapter 4; CBO, 1998; Frank and Salkever, 1997; Kanavos, Costa-Font and Seeley, 2008). Meanwhile, there was

not a statistically significant relationship between the average original brand price and the average generic price, indicating that the generic manufacturers and original brand manufacturers operate independently in the price sensitive and price insensitive portions of the strength segment markets respectively. There was a significant relationship between the strength market shares and the average generic prices within strength markets, which is consistent with the findings in the second model above, whereby it could be that generic competition in the more popular strengths is more intense because pharmacists and payors tend to focus more on achieving cost savings in these strength segment markets. Finally, there was a significant, negative relationship between the dummy variable OTC availability (within that strength segment market for that given quarter) and the average generic prices. This is consistent with case one, which found that in the USA 20mg omeprazole market, Prilosec OTC competed with both the prescription original brand and prescription generic omeprazole products.

5.5.3 The Theoretical Implications of the degree of Competition within Strength Segmented Molecule Markets

The above findings show that in the omeprazole and paroxetine markets in the study countries, original brand manufacturers seem to employ the market harvesting strategy consistently across strength segments by responding to patent expiration with similar price changes across strength segment markets, despite the simultaneous decrease in market share and regardless of the degree of generic entry within strength segment markets. However, the extent to which they are able to hold on to their original brand market share differs significantly across strength market segments. In general, they are more able to hold on to a larger share of the market where fewer generics have entered, their prices are not as high (relative to generics) and the strength is not as common. Thus, where the regulatory process is not too burdensome, and where there is a prospect of significant sales, original brand manufacturers should theoretically have the incentive to introduce various strengths into the molecule market while their drug is still on patent. Where original brand manufacturers are able to employ this strategy of product differentiation in the form of segmenting molecule markets into strengths prior to patent expiration—provided this can be justified on clinical grounds—they may be able to capitalise on a larger share of the total molecule market after patent expiration than if their drug were only

available in the standard daily defined dosage. While the market harvesting strategy remains the primary industrial organization model that original brand manufacturers use in response to patent expiration, evidence that the degree of competition between original brand and generic manufacturers differs across strength segments of a molecule markets suggests that original brand manufacturers may sometimes be able to surreptitiously use their first mover advantage to strategically locate themselves in various strength segments where they have a greater chance of retaining their dominant market positions following patent expiry. In order to determine the extent to which this phenomenon of perpetuated original brand manufacturer dominance in the less common strength segments is a result of the original brand manufacturers' strategic decisions earlier in the product life versus the passive result of generics not entering into this product space, further research would need to be conducted that better explains original brand manufacturers' decisions surrounding entry into (and creation of) strength segments.

Meanwhile, the degree of price competition amongst generics appears to be greater in more common strength markets and also appears to increase as generic entry increases within strength markets. There is no evidence of generic prices being dependent on original brand prices in the omeprazole and paroxetine strength submarkets.

This evidence of generic prices operating independently of original brand prices is contradictory to the findings in the first case, where there seemed to be some price stickiness between original brand and generic prices. Thus, this analysis demonstrates the importance of conducting studies of pharmaceutical competition at the micro level. By running the models at the strength segment levels, generic and original brand prices have not been distorted by the DDD standardizations most studies use when analyzing competition at the molecule level. As a result, confounding factors that may exist at the molecule level (when calculating average original brand prices) such as nonlinear pricing and differing original brand versus generic strength segment market shares are eliminated in this model, which reveals a clearer picture of competition amongst generics.[55] Thus, the evidence that original brand manufacturers employ the market harvesting strategy consistently across

[55] It is likely that this price stickiness did exist in these markets in France, as a result of the price caps (which stipulated that generic prices not exceed a given percentage of original brand prices).

strength segments, regardless of the degree of generic entry, along with the evidence that price competition amongst generics appears to be independent of original brand prices, suggests that original brand and generic manufacturers operate side by side in the same molecule market, but do not engage in direct price or market share competition with one another. Rather, the market share shift from original brand products to generics may be driven more by the demand side (e.g. increasing regulatory attempts to genericise, improved information for physicians and consumers about the quality equivalence of generics, improved availability of generics in the supply chain for pharmacies to contract with, etc.) than by strategy quantity competition on behalf of the manufacturers. The implication of these findings are that the original brand market harvesting strategy is separate from the Stackelberg Model that is briefly referenced in a few studies, which would require that original brand and generic manufacturers strategically respond to each others' decisions in an attempt to compete directly for market share (Tirole, 1988).

In the case of competition amongst generics, the less common strength segment markets that tend to have relatively high original brand market shares, despite the relatively high original brand prices, should theoretically be as conducive to generic competition and, therefore, lower prices as the more common strength segment markets. The relatively lesser degree of generic entry into these less common strength segment markets may be a result of generic manufacturers weighing the trade-offs between locating themselves where demand is concentrated (i.e. the DDD strength segment) versus product differentiating by strategically locating themselves in a less saturated area of the product space, similarly to the linear city model (Tirole, 1988). However, the notion that entry into multiple strength markets may be a trade off implies that entering into multiple strength markets at the same time would incur additional fixed costs for generic manufacturers, which may depend on characteristics of the market, such as drug approval regulations.

In conclusion, this analysis of competition amongst generics at the strength segment level supports the conclusion in case one that competition amongst generics appears Bertrand-like in that generics compete on price, but that generic manufacturers are able to soften competition by product differentiating (in this case, by strategically deciding which strength markets to enter into, and when) so that their

products are no longer perfectly homogenous. This results in a range of generic prices and market shares within and across strength segment markets.

5.5.4 The Efficiency Implications of Relatively High Original Brand Market Shares in Some Strength Markets

This larger original brand market share in various strength market segments may explain the downward price rigidity (at the molecule level) that one study attributes to product differentiation (Kanavos, Costa-Font and Seeley, 2008). In general, generic prices do continue to decline as generics enter into individual submarkets, especially in the USA and the UK. However, since original brand prices remain higher, larger original brand market shares in some strength submarkets contribute to higher weighted purchased prices for those strengths (and thus, higher weighted purchasing prices at the molecule level), resulting in inefficient spending for payors. A weighted purchased price for a strength submarket is calculated as the sum of the drugs' strength segment markets shares times their prices. In other words,

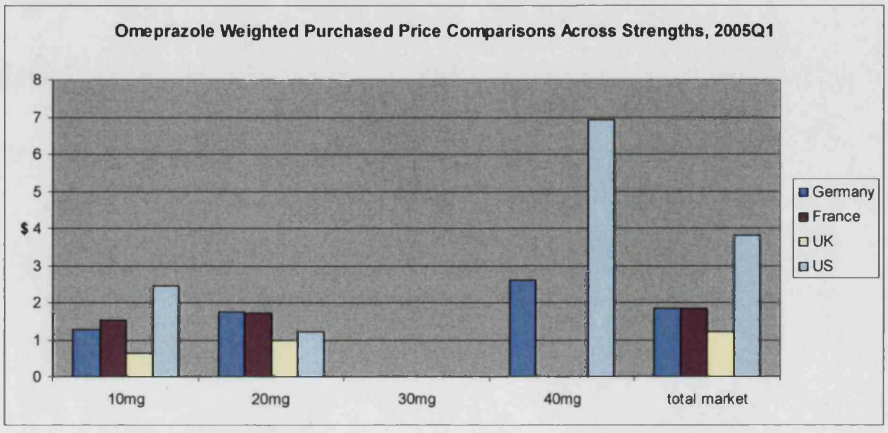
$$WPP^{sm} = P_i^{brand} \text{ x } MS_i^{sm} + P_i^{gen} \text{ x } MS_i^{sm}$$

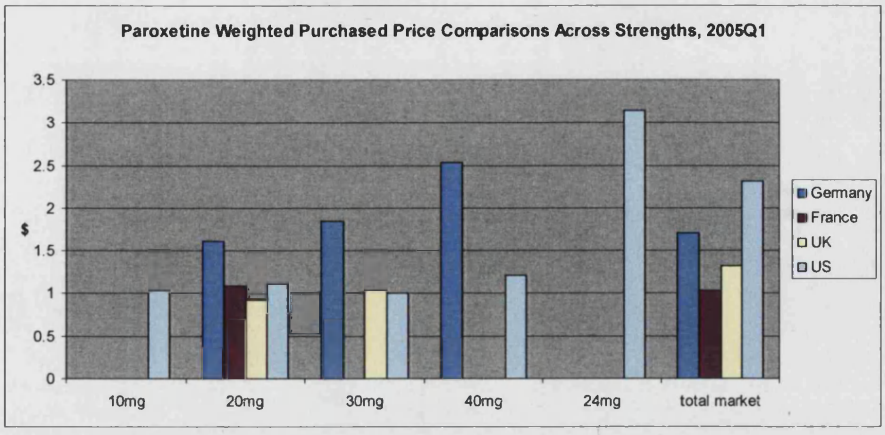
$$i = 1, 2, \ldots, n$$

Where WPP^{sm} is the weighted purchased price for a strength market, P_i^{brand} is the price of an original brand presentation, MS_i^{sm} is the market share of that presentation within the strength segment, P_i^{gen} is the price of the generic presentation and MS_i^{sm} is the market share of that presentation within the strength market. This equation shows that with relatively high original brand prices, in comparison with generic prices, a high corresponding original brand market share (and consequently relatively low generic market share) within less common strength segments results in a higher overall weighted purchased price for payors. Thus, the weighted purchase price reflects demand through the market share variable and supply through the price variable. Since this case pertains to equivalent drugs within strength submarkets of a molecule, a higher original brand market share in some strength submarkets results in purchasers paying unnecessarily high prices for the same total volume (and quality), in comparison with the alternative scenario of a higher generic market share in that strength submarket. This is what makes a higher weighted purchased price for certain strength submarkets inefficient.

Figure 5-13 compares the weighted purchased prices across omeprazole and paroxetine strength market segments in Germany, France, the UK and the USA. Consistent with the findings in chapter 4, the UK purchases at relatively low prices while Germany purchases at relatively high prices. The high purchased prices in Germany likely reflect the reference price system, which provides a disincentive for price competition, as discussed in chapter 4. However, the evidence in this chapter shows that in both the omeprazole and paroxetine markets, the USA faces the highest total weighted purchased price. This is contradictory to the USA's relatively low generic prices (Chapter 4; Kanavos, Costa-Font and Seeley, 2008). A likely explanation for the USA's relatively high weighted purchased prices is the high original brand prices seen in certain strength market segments where there was no generic competition. Specifically, there were no generic competitors in the USA' 40mg omeprazole market and the 24SA paroxetine market (see Table 5-3), which was still on patent. The high purchased price in the 24SA paroxetine market—nearly three times the purchased 20mg price—along with its high strength market share of 34% (see Table 5-3) drives the total weighted paroxetine purchased price significantly higher in the USA than Germany, France or the UK.

Figure 5-13 A Comparison of Weighted Purchase Prices per Pill across Strength market segments in the Omeprazole and Paroxetine Markets in Germany, France, the UK and the USA in 2005q1





Source: The author from IMS.

In conclusion, there is evidence of competitive, low weighted purchased prices in the 20mg DDD omeprazole and paroxetine markets in the USA, while product differentiation in the form of segmented strengths and forms in the USA appears to result in higher weighted purchased prices at the omeprazole and paroxetine molecule level, and hence, inefficient spending. It could be that the relatively competitive omeprazole and paroxetine generics markets (see Chapter 4) in the USA is one of the driving factors behind original brand manufacturers' decisions to segment the omeprazole and paroxetine markets into various strengths and forms. Additionally, relatively liberal regulations and the fragmented payment system in the USA further enable this market outcome. In Germany, product differentiation in the omeprazole and paroxetine market appears common as well, although it is difficult to determine the extent to which some of Germany's high purchased prices are due to product differentiation versus their reference price system, which contributes to downwards price rigidity (see Figure 5-11; Kanavos, Costa-Font and Seeley, 2008).

The UK and France seem to avoid the degree of product differentiation (in the form of multiple strength market segments) in the omeprazole and paroxetine molecule markets that exists in the USA and Germany. This could be due to a stronger emphasis on clinical- and/or cost-effectiveness in their health care systems. However, the overall prices seem lower in the UK omeprazole and paroxetine markets, where there is evidence of more price competition (see chapter 4), and somewhat mixed in France, where the market did not determine the prices of omeprazole and paroxetine during this study period. Rather, original brand prices were initially agreed upon by the France Economic Committee (CEPS) and subsequent generic entrants were prohibited from exceeding 60% of this price.

5.5.5 The Opportunity for Cost Savings if Genericisation within Strength Submarkets was Improved

The previous section explains that the original brand market shares remain relatively high in some of the strength market segments within a molecule, resulting in higher total purchased prices in these strength submarkets (since the original brand prices remain significantly higher than the generic prices within strength submarkets), and consequently, inefficient spending. How much, then, could payors have saved if the original brand market shares within strength segments had been equivalent to the original brand market share in the strength segment market with the lowest original brand market share for that given molecule, for each respective quarter? In other words, how much could payors have saved if the genericisation rates within every strength submarket were equal to the strength submarket (of that molecule) with the highest genericisation rate for each respective quarter, in accordance with the following equations?

$$SAV^{mol} = \text{SUM}\,(ActSpnd_i^{mol} - HypSpnd_i^{mol})$$

$$i = \text{quarter1, 2, ..., n}$$

$$ActSpnd_i^{mol} = TotQ_i^{mol} \text{ X } WPP_i^{mol}$$

$$HypSpnd_i^{mol} = \text{SUM}(HypSpnd_i^{sm})$$

$$sm = \text{strength segment markets 1, 2, ...}$$

$$HypSpnd_i^{sm} = (TotQ_i^{sm} \text{ X } MINMS_i^{brandsm} \text{ X } WPP_i^{brandsm}) + (TotQ_i^{sm} \text{ X } (1 - MINMS_i^{brandsm}) \text{ X } WPP_i^{gensm})$$

Where SAV^{mol} is the total savings for the molecule during this study period, $ActSpnd_i^{mol}$ is the actual spending on a molecule in that given quarter, *i*, $HypSpnd_i^{mol}$ is the hypothetical spending for that molecule in that given quarter, $TotQ_i^{mol}$ is the total quantity (number of pills) purchased for that molecule in that given quarter, WPP_i^{mol} is the molecule level weighted purchased price for that given quarter, $HypSpnd_i^{sm}$ is the hypothetical spending for that strength segment in that given quarter, $TotQ_i^{sm}$ is the total quantity (number of pills) purchased for that strength segment in that given quarter, $MINMS_i^{brandsm}$ is the minimum (lowest) original brand market share within strength segments of that molecule, $WPP_i^{brandsm}$ is

the weighted purchased price for the original brand for the given strength segment in the given quarter and WPP_i^{gensm} is the weighted purchased price for the generic for that given strength segment in the given quarter.

Table 5-7 shows the possible genericisation savings across the omeprazole and paroxetine strength markets in Germany, France, the UK and the USA in accordance with these calculations (such that all of the strength market segments within the omeprazole and paroxetine molecules experienced the same degree of generic penetration as the strength market in that molecule for that country with the lowest original brand market share). The greatest total savings (in absolute value) would have been in the omeprazole market in Germany, which amounted to over $37 million and in the paroxetine market in the USA, which amounted to over $17 million during the 2000q1-2005q1 time period. In Germany, the savings from maximizing genericisation in the 10mg omeprazole market were over 18% of what was actually spent, largely because genericisation was assumed to be 100%, as was the case in the 40mg omeprazole market. In most country's strength submarkets, the percentage savings were relatively low, representing a few percent or less. However, Table 5-7 shows that because absolute spending was so large in these molecule submarkets, even a fraction of a percent savings would have represented hundreds of thousands, and often millions of dollars. Thus, to the extent that other molecules also experience uneven genericisation rates across strength segment markets, there could be room for significant savings that together add up to hundreds of millions and even billions of dollars over a large sample of drugs. Moreover, this study uses conservative parameters to estimate improved genericisation in that markets without generic entry (such 10mg omeprazole in France and 40mg omeprazole in the USA) were held constant at zero genericisation.[56] In addition, the lowest original brand market share was used in each quarter to represent the maximum point of genericisation. These improved genericisation rates across strength markets should therefore be achievable since they actually existed in one of the strength markets of that molecule.

Notably, the omeprazole and paroxetine markets in France would not have achieved savings under this scenario since both markets had only one strength

[56] This takes into account the possibility that patents in those strength markets may not have expired, or that there was a specific economic reason that generics chose not to enter that strength market which is not clear in this study.

segment market that experienced generic entry. It is also interesting to note that in two strength markets—20mg omeprazole in the USA and 30mg paroxetine in the UK—the improved genericisation rates would actually have cost payors more rather than resulted in savings. Figure 5-14 shows that in both cases, the generic purchased prices were actually higher than the original brand purchased prices. This is because in the 20mg omeprazole market in the USA, the original brand had already started marketing its product over the counter as Prilosec OTC, which was lower priced than prescription generic omeprazole. In the 30mg paroxetine market in the UK, the anomaly of the generic purchased price being higher than the original brand purchased price was likely a result of the fact that there were only two generic competitors in the 30mg market, which may have given them the market power to price similarly to the original brand manufacturer. Thus, in addition to improving genericisation rates across strength submarkets, it would be prudent to first ensure that the generic purchased prices are in fact lower than the original brand purchased prices.

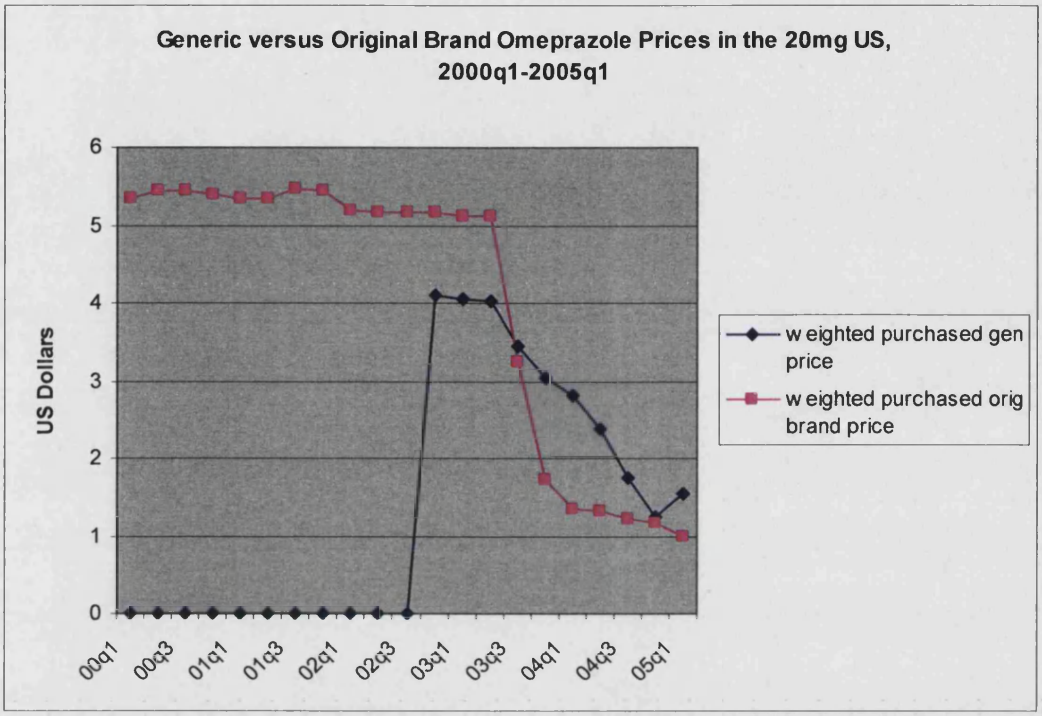
Table 5-7 Possible savings if genericisation were maximized across all strength markets of omeprazole and paroxetine in Germany, France, the UK and the USA, 2000q1-2005q1

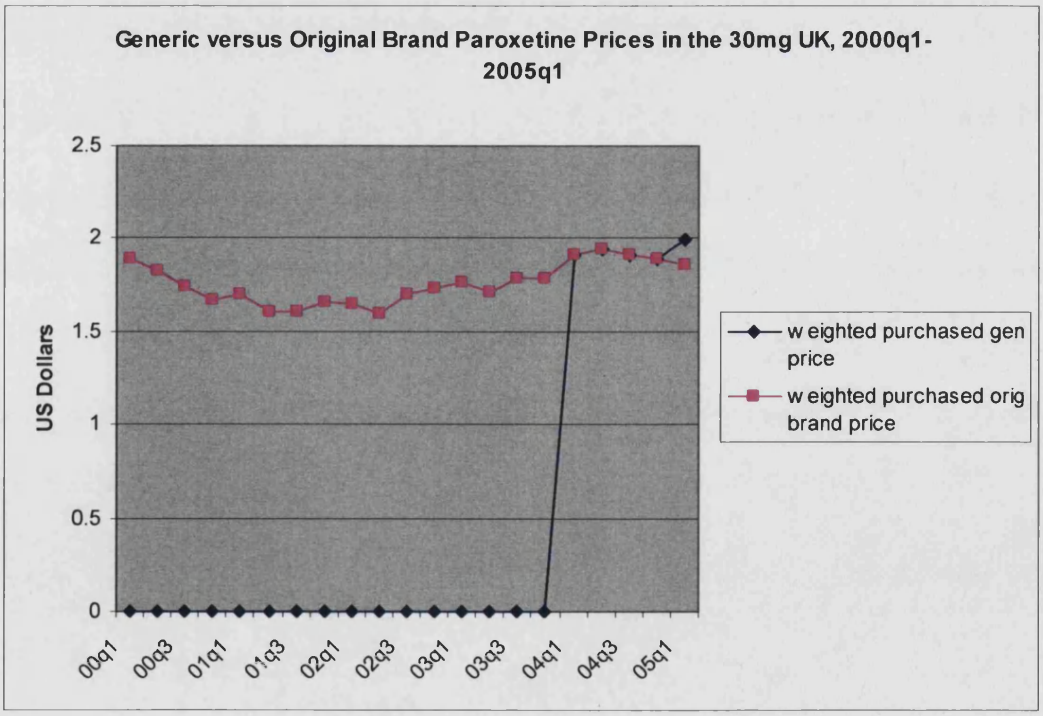
	Omeprazole								Paroxetine							
	Germany*		France**		UK***		US****		Germany#		France##		UK		US	
	Savings	% Sav	Savings	% Sav	Savings	% Sav	Savings	% Sav	Savings	% Sav	Savings	% Sav	Savings	% Sav	Savings	% Sav
10mg	$21,363,512	18.51%			$274,902	0.09%	$1,634,384	0.45%							$3,093,187	0.25%
20mg	$15,717,683	0.66%	$0	0.00%	$2,581,911	0.22%	-$130,303,742	-0.96%	$7,884,770	2.77%	$0	0.00%	$0	0.00%	$12,338,011	0.24%
30mg									$0	0.00%			-$25,057	-0.01%	$1,615,062	0.16%
40mg	$0	0.00%			$84	8.34%			$0	0.00%					$670,893	0.05%
24SA																
Total	$37,081,196		$0		$2,856,897		-$128,669,358		$7,884,770		$0		-$25,057		$17,717,154	

* In Germany, a generic manufacturer created the 40mg omeprazole market segment in 2000q3, so the lowest original brand market share was 0% in all quarters following 2000q3.
** In France, there were no generics in the 10mg omeprazole market, rendering the 20mg omeprazole market the only market with generic entry.
*** In the UK, the 40mg omeprazole market only existed in 2004q3, at which point one generic entered and then exited the market in the subsequent quarter.
**** In the US, there were no generics in the 40mg omeprazole market, rendering that market unsuitable for this model.
# In Germany, a generic manufacturer created the 40mg paroxetine market segment in 2002q2, so the lowest original brand market share was 0% in all quarters following 2002q2.
In France, 20mg was the only strength sold in the paroxetine market, rendering this molecule market unsuitable for this model.

Source: The Author, using IMS Health data.

Figure 5-14 A comparison of the Original Brand and Generic Purchasing Prices in 20mg omeprazole market in the USA and the 30mg paroxetine market in the UK





Source: The Author, using IMS Health data.

5.6 Product Differentiation by Strength, and Price Discrimination

The previous section analyzes original brand and generics price and market share dynamics within strength segment markets of omeprazole and paroxetine in order to assess the nature of competition *within* strength segment markets and to determine where there is room for increased purchasing efficiency within segmented molecule markets. This section furthers the discussion of strength segmented markets by assessing the extent to which the existence of strength segment markets may affect the overall degree of price competition within molecule markets (i.e. *across* strength segmented markets) and the ensuing implication for purchasing efficiency. In some cases, manufacturers may be able to capitalise on the existence of strength segment markets by price discriminating. In these cases, strength segmented markets may symbolize another way in which product differentiation may lead to less competitive molecule markets. (Recall from the previous section that strength segmented markets may also lead to lower degrees of original brand versus generic competition within molecule markets.) This, then, may lead to higher prices and hence higher expenditures.

Consequently, this section studies the extent to which price discrimination across strength segment markets may exist as another example of how product differentiation may negatively impact competition within a molecule market, and then estimates the potential savings that could accrue to payors that encourage pill splitting practices or limit coverage of line-extensions. This study does not have data to prove or disprove the existence of price discrimination, as strength-level cost data would be needed. However, it is able to use pricing evidence to determine whether some degree of price discrimination looks likely. In addition, it must also be noted that the pill-splitting and line-extension purchasing efficiency scenarios in this section may have significant clinical, ethical, safety and quality implications. To this end, this study does not advocate such practices, but rather, considers the clinical/safety issues alongside the purchasing efficiency estimates in order to assess the effectiveness of these payors' cost containment strategies.

In Figures 5-15 and 5-16, unit prices have been converted into prices per DDD (20mg in both the omeprazole and paroxetine markets) in order to enable a direct price comparison across strengths. The graphs show that the average original brand price per DDD for 10mg omeprazole is higher than the average original brand

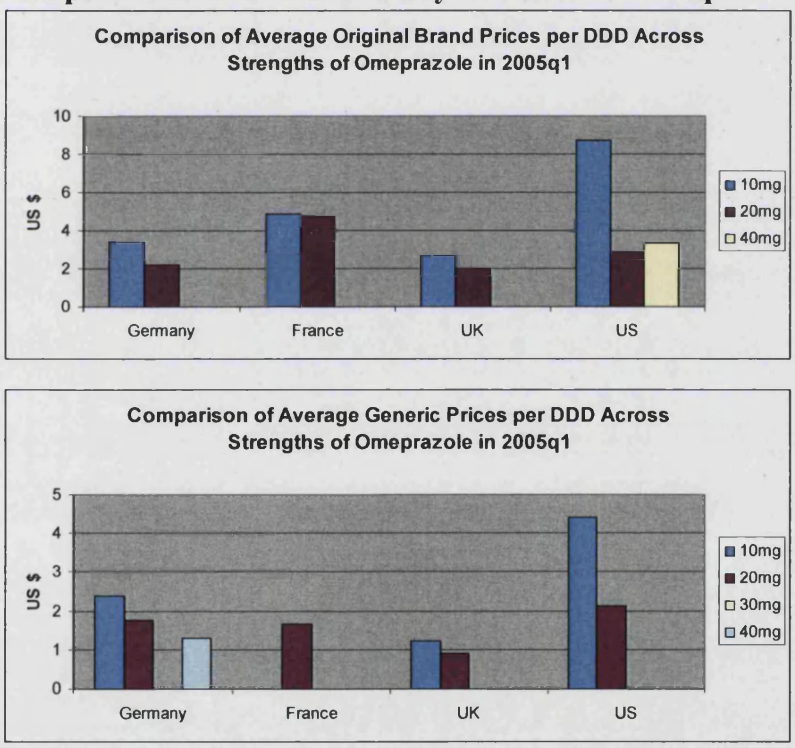
price per DDD for 20mg omeprazole in all four study countries. The same is true for the average original brand price (per DDD) of 10mg paroxetine in the USA, which is higher than 20mg. Similarly, the average original brand price (per DDD) of 20mg paroxetine is higher than the average original brand price (per DDD) of 40mg paroxetine in the USA, and the average generic price (per DDD) is higher for 20mg than for 40mg in the omeprazole market in Germany and the paroxetine markets in Germany and the USA. These are examples of nonlinear pricing across strengths, where the higher strengths are not priced proportionally more than the lower strengths in order to reflect their relative strengths. Instead, they cost more, but disproportionally so. That is, they are more expensive on a per pill basis, but are actually cheaper on a per daily defined dosage basis. There are two possible explanations for this. One is that the strength segment markets are sufficiently competitive such that the price differences mostly reflect cost differences. If this were the case, then the nonlinear pricing would result from a nonlinear cost manufacturing structure where the fixed costs of manufacturing are the same for pills of different dosages, but the ingredient costs are higher for higher dosages, resulting in disproportionally higher costs for higher strengths.

The other possible explanation for nonlinear pricing is price discrimination. Where products are homogeneous, any difference in price that cannot be explained by cost differences reflects price discrimination (Clerides, 2004). Without data on how the manufacturing costs differ across strengths segments in the omeprazole and paroxetine markets, claims of price discrimination cannot be made in the above cases where prices increase disproportionately with strength (since this could be reflective of cost differences). However, there seems to be evidence of price discrimination in the USA, where the original brand and generic prices *per pill* of 10mg omeprazole are actually higher than their respective original brand and generic prices per pill of 20mg. Similarly, the generic prices *per pill* for 10mg and 20mg paroxetine in the USA are both higher than the generic prices *per pill* for 30mg and 40mg paroxetine. In these cases, it seems unlikely that the manufacturing costs of lower strength pills would exceed the manufacturing costs of higher strength pills.[57] Rather, the lower

[57] Another possible explanation for the lower strength pills being marketed at higher retail prices than the higher strength pills is that the distribution chain has higher mark-ups for lower strength medicines. This analysis assumes that this is not the case—that the distribution chain does not systematically apply different market-ups by strength segments.

strength omeprazole and paroxetine markets in the USA are either less price competitive than the higher strength markets, or the lower strength omeprazole and paroxetine markets are more price insensitive than the higher strength in the USA.[58] In either of these cases, the manufacturers would be able to price discriminate across omeprazole and paroxetine strength segments, which would result in higher profits (in the lower strength markets) and on the other side of the coin, inefficient purchasing for payors. Based on this logic, it is likely that manufacturers may be able to use strength segmented markets as an opportunity to reap larger profits through price discrimination practices without there necessarily being a clinical reason for this non-linear pricing structure.

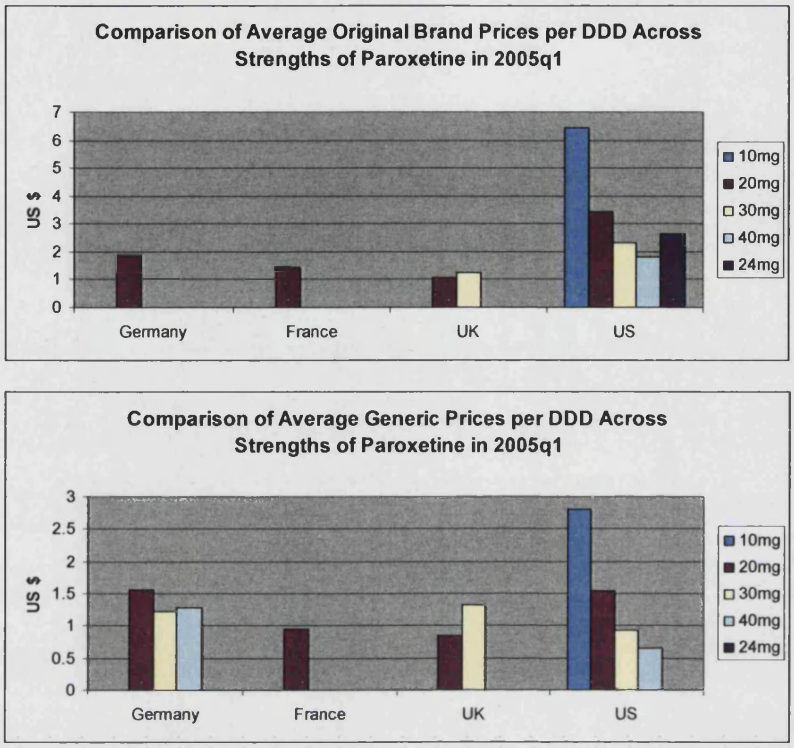
Figure 5-15 A comparison of Average Original Brand Prices per DDD in the Omeprazole market across Study Countries in 2005q1



Source: The Author, using IMS Health data.

[58] One possible explanation for the lower strength products being priced disproportionately less than higher strength products is that payors are relatively price insensitive at the bottom end of the price range for the daily cost of treatment, but quickly become price sensitive to higher prices for higher strengths, whose marginal benefit may be difficult to estimate (unless physicians adhere to strict step-therapy, whereby they ensure that patients are taking the minimal doses necessary for clinical efficacy).

Figure 5-16 A comparison of Average Original Brand Prices per DDD in the Paroxetine market across Study Countries in 2005q1



Source: The Author, using IMS Health data.

5.6.1 Product Differentiation and the Opportunity for Cost Savings

Because product differentiation in the form of strength segmented markets may lead to price discrimination, which in turn implies a lesser degree of price competition within molecule markets, there may be opportunities for payors to improve purchasing efficiency within molecule markets. This section models certain substitution scenarios in order to quantify the extent of these savings. Due to clinical, ethical, safety and quality considerations, it does not advocate such practices, but rather attempts to provide policymakers and payors that are currently implementing these strategies with information on the degree to which they may be effective.

5.6.1.1 Pill Splitting and Price Discrimination

The practice of splitting pills in order to save on costs has sprung up in the recent decades in the USA and elsewhere. Its intention is to help purchasers and patients save on costs by taking advantage of the fact that manufacturers often pursue flat or discriminatory pricing strategies across strength segments, rather than making prices linear with increasing strengths. It may often be the case that it would be less

expensive to the third party payor for a patient to split a higher strength pill into two doses than to take two doses of a lower strength pill. Moreover, the incentive to split pills is compounded by the nature of flat co-pays, which would halve in cost to patients.

In order for payors and/or patients to benefit, however, physicians must be willing to prescribe the medication at twice the strength of the desired dose. Research shows that physicians believe it is important to take patients' costs into account when prescribing drugs (Khan and Sylvester, 2008). However, physicians' willingness to prescribe a different dose than the one required so that patients can pill split requires that they feel confident in their patients' abilities to split the pill, and adhere to the desired dose regime. The American Pharmaceutical Association, the American Medical Association and the American Pharmacists Association are against pill splitting because of their concern about patients' pill splitting abilities and poor adherence implication (Consumer Reports, 2006). Such concern was validated by a study where the authors attempted to split 45 tablets with a kitchen knife and 45 with a pill splitter, only to find that they were not able to split the pills evenly in either case (Kaiser Daily Health Policy Report, 2004). Moreover, the size of the split pills ranged from 50% to 150% of the intended size. Their conclusion was that patients would not be able to guarantee that they consumed the proper dose of medicine if they split their pills.

Despite these findings, there have not yet been any studies which provide evidence that pill splitting has a negative impact on health outcomes (Consumer Reports, 2006). Instead, a number of studies show that under the right circumstances, pill splitting can be safe, and can save payors and patients money (Cohen and Cohen, 2002; Stafford and Radley, 2002; Choe and Stevenson, 2007). These circumstances require that patients to be capable of splitting their pills, which young to middle-aged adults are more (likely) able to do, compared to seniors who may suffer from chronic debilitating conditions, such as Parkinson's disease, arthritis, poor eyesight, dementia and other conditions which make pill splitting difficult. In addition, the type of drug is pertinent in whether it is a good candidate for being split. Drugs that enter and are metabolized by the body quickly are unlikely to be suitable since variations in the pill doses (after being split) would result in uneven levels of the drug in a person's body. Some drugs that treat chronic conditions, however, remain active in the body for days, so small fluctuations in the

doses would not significantly change the level of the medication in the person's body at any one point in time, and would therefore not alter the clinical efficacy. Conversely, some drugs have a narrow therapeutic index, which means that in order to be effective, very specific doses need to be administered, e.g. HIV drugs. These types of drugs make pill splitting impractical and potentially dangerous. Other drugs that would need to be excluded from splitting practices include extended-release pills, pills that combine two drugs or more and capsules. Thus, the practice of pill splitting is only safe in certain instances. However, studies do show that in these instances, pill splitting can be a very safe and effective mechanism for saving money (Cohen and Cohen, 2002; Stafford and Radley, 2002; Choe and Stevenson, 2007).

Antidepressants have been identified as ideal for pill splitting because their efficacy depends on long-term alterations in neurotransmitters, rendering small fluctuations in doses insignificant (Cohen and Cohen, 2002; Stafford and Radley, 2002). One of these studies focuses on the cost savings that could accrue to the USA health care system from splitting eligible antidepressants (e.g. excluding time-release forms, etc.). This represented 42% of antidepressant medications in 2000. The findings concluded that in 2000, purchasers could have saved over $1.7 billion, with the bulk of savings coming from sertraline, paroxetine and citalopram (Cohen and Cohen, 2002).

Another study used data from a private health plan with 19,000 members to estimate the possible savings that could result from pill splitting (Stafford and Radley, 2002). First, eligible drugs were selected based on the above criteria (e.g. no polypharmacy drugs, no extended-release drugs, no capsules, etc.). The eleven medications that were determined to offer significant cost savings and be clinically appropriate for pill splitting included: clonazepam, doxazosin, atorvastatin, pravastatin, citalopram, sertraline, paroxetine, lisinopril, nefazadone, olanzapine and sildenafil. The study found that for these medicines, pill splitting could save the plan as much as $259,500 annually, in comparison with the current practice of pill splitting, which was only saving the plan $6,200 annually, representing only 2% of potential savings.

In another study, a group of researchers conducted a prospective randomized controlled trial, in which a group of relatively well educated patients from a university-based health plan were asked to participate in a statin spill-splitting program (Choe and Stevenson, 2007). After 6 months, 89% of the trial participants

said that they would continue splitting their statin pills for a 50% copayment reduction. Regarding safety, there were few reported problems, and the low density lipoprotein cholesterol levels in participating patients were found to be roughly equivalent to the control group of patients who did not split their pills. Thus, the authors concluded that if patients were given financial incentives, pill splitting could be a safe and effective practice under the right circumstances (e.g. with relatively educated patients who are taking eligible medicines).

Due to the findings in these studies, and health plans' incentives to cost save, a number of pill splitting programs currently exist in the USA. The University of Michigan used the findings from the above statin study to justify the introduction of a pill splitting program into their health plan in 2006. The result was a savings of $195,000 in the first full year, and a savings of $25,000 in co-payment costs for patients (University of Michigan Health System, 2007). In addition, Kaiser Permanente has introduced a voluntary pill-splitting plan, as well as United Healthcare and the Veteran's Administration, which was able to save $46.5 million in 2003 by requiring patients to split Zocor (Kaiser Daily Health Policy Report, 2005).

Thus, most studies on pill splitting have estimated the savings that accrue to specific plans. Few have looked at the opportunity for savings on a national level, and none have compared the opportunity for savings across countries. This study models the total nationwide savings that could have accrued to purchasers during the 2000q1-2005q1 time period for omeprazole and paroxetine, assuming for the moment, that omeprazole and paroxetine are both safe to split, and that all 20mg and 40mg pills are eligible for splitting (i.e. that they are not in capsule form, etc.). With these assumptions, Table 5-8 shows that splitting 20mg pills into 10mg halves would result in cost savings for omeprazole in Germany, France, the UK and the USA and for paroxetine in the USA. (There were no savings opportunities for splitting 20mg paroxetine in Germany, France and the UK because there was no 10mg strength market.) For the USA, the percentage cost savings for splitting paroxetine 20mg into 10mg was 6%, representing over a half a billion dollars during this time period for just paroxetine. Potential cost savings for omeprazole in Germany, France, the UK and the USA were also significant, with the largest possible percentage savings existing in the UK.

Table 5-9 shows the model that also assumes that all 20mg pills are substituted with split 40mg pills results in cost increases for Germany and the USA. (The results are the same for the UK and France for both models because they do not have 40mg strength market segments.) This suggests that on average, the quarterly weighted purchased price for 40mg pills is actually cheaper per daily defined dosage than the quarterly weighted purchased price for 20mg in Germany and the USA. Thus, if the purchasing practices remained unchanged, pill splitting could actually cost more in certain cases, as indicated by the negative savings estimates in Table 5-9. It is therefore crucial that purchasers carefully study the price differences across strengths before advocating pill splitting.

Table 5-8 Savings from Pill Splitting if Everyone Taking 10mg Splits 20mg pills.*

	Omeprazole			Paroxetine		
	Spending	Savings	% Savings	Spending	Savings	% Savings
Germany	$2,761,293,134	$61,661,477	2%	$305,482,035	$0	0%
France	$1,174,547,439	$49,407,159	4%	$1,134,638,717	$0	0%
UK	$1,445,669,368	$75,397,968	5%	$504,941,272	$0	0%
US	$15,317,927,205	$169,604,460	1%	$9,704,183,226	$594,988,758	6%

*This model assumes that the 30mg pills and the 24SA pills are not eligible for splitting.
Source: The Author, using IMS Health data.

Table 5-9 Savings from Pill Splitting if Everyone Taking 10mg Splits 20mg pills and Everyone Taking 20mg Splits 40mg pills.*

	Omeprazole			Paroxetine		
	Spending	Savings	% Savings	Spending	Savings	% Savings
Germany	$2,761,293,134	-$18,135,498	-1%	$305,482,035	-$6,048,273	-2%
France	$1,174,547,439	$49,407,159	4%	$1,134,638,717	$0	0%
UK	$1,445,669,368	$75,398,260	5%	$504,941,272	$0	0%
US	$15,317,927,205	-$79,999,226	-1%	$9,704,183,226	-$432,175,728	-4%

*This model assumes that the 30mg pills and the 24SA pills are not eligible for splitting.
Source: The Author, using IMS Health data.

Moreover, this model assumes that all 20mg and 40mg omeprazole and paroxetine pills are eligible for splitting. In reality, however, some of these pills are capsules, which are not eligible for splitting. In addition, while studies list paroxetine as one of the safe pills for splitting (Consumer Reports, 2006; Stafford and Radley, 2002), omeprazole is actually listed as unsafe for splitting (Consumer Reports, 2006). Thus, it is worth modelling omeprazole pill splitting in order to compare hypothetical cost saving opportunities across countries. However, in practice, policies need to first carefully determine which drugs may be safely split. Once purchasers have selected drugs that can be safely split and have determined

which higher strength market segments offer potential for cost savings, they then need to think about how to encourage the practice of pill splitting.

The financial incentives of pill splitting may vary, depending on the health system. For example, patients who are uninsured, as is the case for roughly 15% of people in the USA (Kaiser State Health Facts, 2007), would find pill splitting to be cost savings as long as the price per dose is lower for the higher strength pill than the lower strength pill. Where patients have private or public health insurance and there are co-payments for prescription drugs, there is potential for both the patient and the third party payor to benefit financially from pill splitting. The payor would benefit as long as the price per DDD is lower for the higher strength pill, while the patients benefit in the form of halved co-payments (since a month supply of pills at double the strength that they need can last for two months, once cut). This is especially the case in the USA, where co-payments are often significant. In the USA, the average 2004 monthly co-pay for private health plans was $10 for generics and $21 for preferred drugs (Kaiser Family Foundation, 2004). Thus, on average, patients with private health plans in the USA could have saved $60 per year in 2004 if the drug was generic and $126 per year if the drug was a preferred brand (assuming they consume one pill per day). Even low income populations on Medicaid usually face small co-pays of $1 or $2 per monthly supply. In the UK, the roughly 15% of the population that faces prescription co-pays (Robinson, 2002) would benefit, along with the populations that face co-pays in Germany and France. Finally, where patients are insured and do not face co-payments, such as in the case of the 85% of the population in the UK that is exempt from co-payments (Robinson, 2002), payors would save as long as the price per DDD was lower for higher strength drugs, while pill splitting would be cost neutral for patients. In this instance, payors would need to provide patients or pharmacists with a financial incentive to split pills. Otherwise, patients and/or pharmacists would likely err toward the less time consuming option of taking the lower dose pill that doesn't require splitting. In addition, it is important that patients consult with their physicians on how to safely pill split. For example, patients are advised to split pills the day they intend to consume them rather than splitting many days supply at once since some pills can deteriorate once exposed to air (Consumer Reports, 2006).

Finally, other ways in which purchasers could encourage pill splitting, besides providing patients with financial incentives, include providing pharmacists

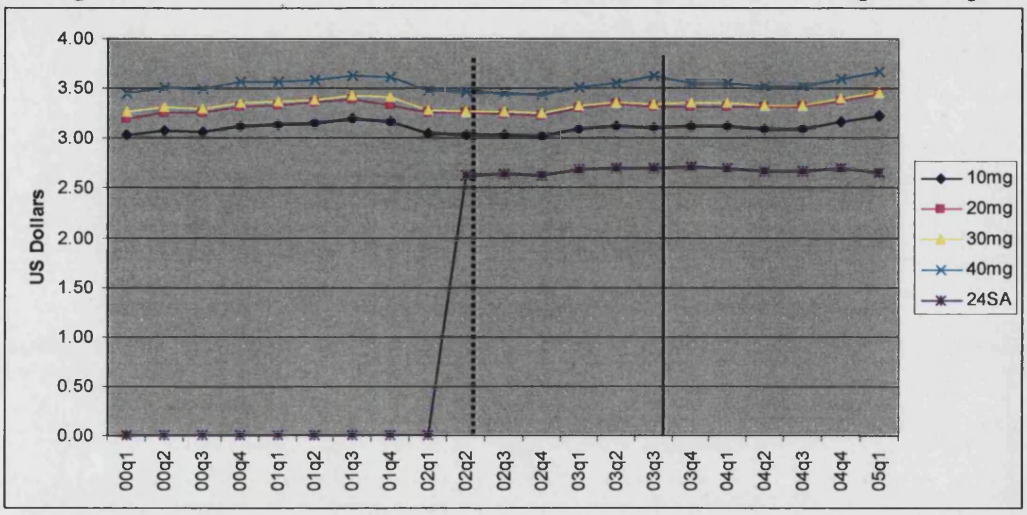
with financial incentives to split pills for patients, requiring pharmacists to fill physicians' prescriptions for split doses and mandating that manufacturers score all pills that are eligible for splitting (Cohen and Cohen, 2002). Purchasers would need to be careful when introducing such large-scale policies, however, as it is possible that pharmaceutical companies could respond by increasing the price of higher strength products, at least to the extent that the higher strength market is not price competitive.

5.6.1.2 The Example of Suspended Release Paroxetine in the USA

GlaxoSmithKline introduced Paxil Controlled Release®, the original brand name for 24SA paroxetine, into the market during the second quarter of 2002. It is associated with a lower rate of nausea than the original immediate release version. However, one study shows that the treatment discontinuation as a result of nausea was not significantly different for the controlled release version than the immediate release version, which calls into question its therapeutic advantage (Golden and Nemeroff, 2002).

Figure 5-17 shows that the original brand paroxetine prices remained constant across all strength/formulations in the USA during this study period. Interestingly, the original brand manufacturer introduced Paxil CR® at a price that was lower than all of its immediate release versions, despite claiming its (Paxil CR®) therapeutic advantage. This pricing behaviour suggests that the original brand manufacturer attempted to shift volume from its immediate release version to its new, controlled release version.

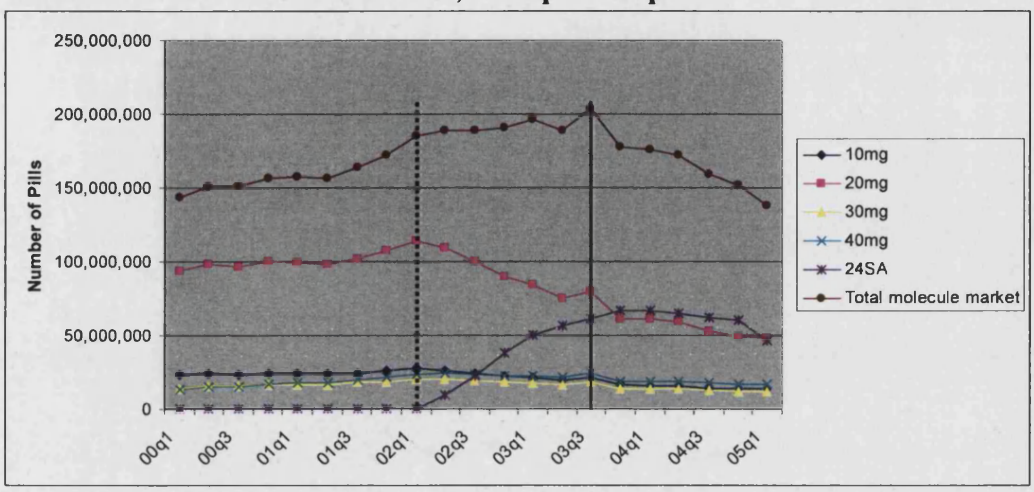
Figure 5-17 A Comparison of Average Original Brand Prices across Strengths/Forms in the USA Paroxetine Molecule Market, 2000q1-2005q1



Note: The dashed line denotes the point of 24SA entry and the solid line denotes the point of generic entry in the immediate release versions.
Source: The Author, using IMS Health data.

Consistent with this hypothesis, Figure 5-18 shows that following the introduction of Paxil Controlled Release® in 2003q1, the volume (measured as the number of pills) of the conventional 20mg immediate release version declined at a rate similar to the rate at which the 24SA version increased. Meanwhile, the volume of conventional 10mg, 30mg and 40mg immediate release versions remained roughly constant during this period. Moreover, Table 5-10 shows that from 2002q2 to 2005q1, there was a near perfect negative correlation between the 20mg segment market share and the 24SA segment market share. This descriptive evidence strongly suggests that the 24SA controlled release version acted as a substitute for the 20mg immediate release version. Notably, the total volume of the molecule market seemed to increase at a relatively steady rate from 2000q1 until the patent expiry of the immediate release version in 2003q3, after which point the total paroxetine market volume decreased. One possible explanation for this is the introduction of another SSRI into the market at this time, although this is beyond the scope of this study.

Figure 5-18 A Comparison of Volume Changes across Strengths/Forms in the USA Paroxetine Molecule Market, 2000q1-2005q1



Note: The dashed line denotes the point of 24SA entry and the solid line denotes the point of generic entry in the immediate release versions.
Source: The Author, using IMS Health data.

Table 5-10 The Relationship between the market share of 20mg and 24SA paroxetine in the USA

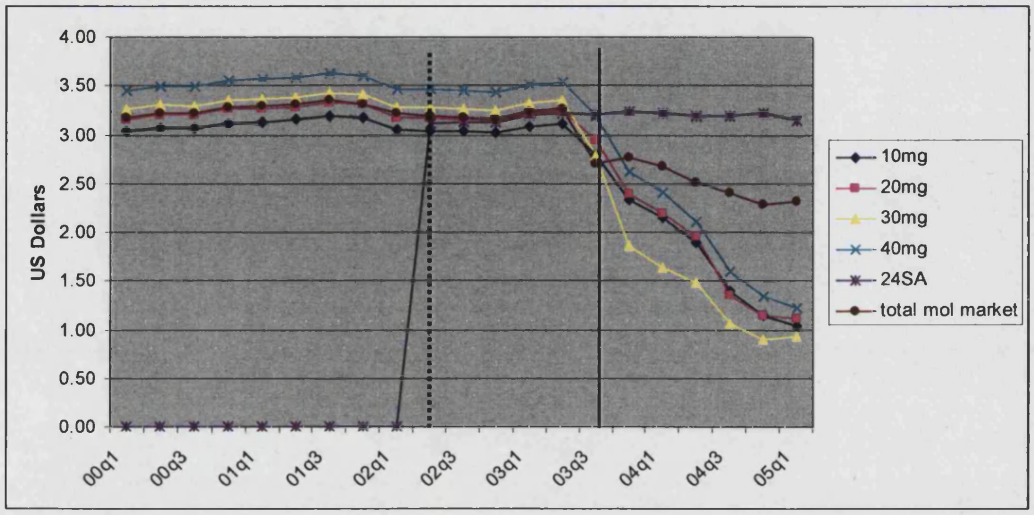
	02q2	02q3	02q4	03q1	03q2	03q3	03q4	04q1	04q2	04q3	04q4	05q1
20mg market share	58%	53%	47%	43%	40%	39%	34%	35%	34%	33%	32%	35%
24SA market share	5%	12%	20%	26%	30%	30%	38%	38%	38%	39%	39%	34%
correlation between 20mg market share and 24SA market share						-0.99717						

Source: The Author, using IMS Health data.

Meanwhile, Figure 5-19 shows that after experiencing generic entry in 2003q3, the weighted purchased prices (which are weighted price indices that aggregate both generic and original brand products[59]) declined in all of the immediate release paroxetine strength submarkets. The purchased price of Paxil CR® remained constant since this version was still on patent as of 2005q1 and therefore did not experience generic entry during this study period. Because the total weighted purchased price of paroxetine at the molecule level takes into account the market shares of the various products and because Paxil CR® achieved a large share of the market, the total weighted purchased price of paroxetine at the molecule level was rigidly downward following patent expiry of the immediate release versions.

[59] See "The Efficiency Implications of Relatively High Original Brand Market Shares in Some Strength Markets" section above for how weighted purchased prices are calculated.

Figure 5-19 A Comparison of Purchased Prices across Strengths/Forms in the USA Paroxetine Molecule Market, 2000q1-2005q1



Note: The dashed line denotes the point of 24SA entry and the solid line denotes the point of generic entry in the immediate release versions.
Source: The Author, using IMS Health data.

The 24SA paroxetine example in the USA shows the advantage that original brand manufacturers can reap if they introduce line extensions with incremental therapeutic benefits, such as a new form of a molecule already on the market, as was the case with Paxil CR. As seen in Figure 5-15, the original brand manufacturer was able to capture over one third of the molecule market with its Paxil CR®, despite generic entry, and therefore the availability of significantly lower prices, in the 20mg DDD segment. This ability to retain a relatively high market share with a product that was priced significantly above generic products in the molecule market allowed the original brand manufacturer to secure a stronger position in the paroxetine molecule market following patent expiry (of the immediate release versions) than if they had only pursued the market harvesting strategy.

Thus, the case of Paxil CR is evidence of the additional profits original brand manufacturers can reap if they introduce new forms of their molecule, and on the other side of the coin, the forgone savings that payors may face as a result of these original brand manufacturers' decisions. The result was that in the aggregate, payors spent significantly more on paroxetine than they would have had Paxil CR® not been introduced. Moreover, the debatable therapeutic superiority of Paxil CR®, in comparison with the immediate release version, suggests that the introduction of

Paxil CR® may have lead to purchasing inefficiencies for payors (since the higher spending on Paxil CR® may not have been cost-effective).[60]

This study estimates the savings that payors would have realized in the USA, had Paxil CR® not been introduced into the market, as was the case in the other study countries. Assuming all of the 24SA pills were substituted for 20mg pills at the quarterly 20mg segment purchased prices, the payors in the USA would have saved approximately 40% of the money the total money they spent on paroxetine during the 2004q4 and 2005q1 quarters, as seen in Table 5-11. In total, the accumulated savings would have been over a half a billion dollars on paroxetine alone from the point of generic entry in the immediate release versions in 2003q3 to 2005q1. Notably, since the original brand manufacturer introduced Paxil CR® at a lower price than its other original brand immediate release versions, substituting the 20mg immediate release version for the 24SA version would not have been cost saving until generic entry occurred in the 20mg segment in 2003q1.

Table 5-11 The Possible Savings from substituting 20mg Paroxetine for Paxil CR during the 2002q2-2005q1 time period

	Prior to Generic Entry in the Immediate Release Versions					Post Generic Entry in the Immediate Release Versions						
	02q2	02q3	02q4	03q1	03q2	03q3	03q4	04q1	04q2	04q3	04q4	05q1
Spnd with 24mg	$603,758,602	$601,724,663	$604,662,104	$637,599,294	$618,372,438	$616,829,198	$476,624,071	$448,749,904	$413,209,261	$330,399,794	$298,235,260	$246,482,000
Spnd if 20mg was subst for 24SA	$604,302,687	$602,388,028	$605,696,807	$638,798,109	$620,081,405	$601,030,439	$420,738,990	$380,634,772	$332,065,984	$216,481,051	$173,913,719	$151,687,703
Total savings from subst	-$544,085	-$663,366	-$1,034,703	-$1,198,815	-$1,708,968	$15,798,758	$55,885,080	$68,115,132	$81,143,277	$113,918,743	$124,321,541	$94,794,297
Percentage savings from subst	-0.09%	-0.11%	-0.17%	-0.19%	-0.28%	2.56%	11.73%	15.18%	19.64%	34.48%	41.69%	38.46%
						Total savings during the 2003q3-2005q1 period				$553,976,828		

Source: The Author, using IMS Health data.

5.7 Conclusion

In summary, the number of strengths and their relative strength market shares in molecule markets differs across countries, depending on a number of factors, including the countries' marketing approval process for various strengths and the health care systems' willingness to pay for various strengths, once approved. Evidence reveals that the omeprazole and paroxetine molecule markets in Germany and the USA are fragmented into more strengths than in the UK and France, and that in general, the lower strengths have relatively larger strength market shares in the UK and France.

In most cases, the strength market shares in the omeprazole and paroxetine markets in Germany, France the UK and the USA did not change significantly after patent expiration and subsequent generic entry. In addition, once the patents expired

[60] Notably, the fact that Paxil CR was not available in Germany, France or the UK as of 2005q1 supports the hypothesis that the introduction of Paxil CR in the US may have been a result of marketing strategy rather than just an innovative response to clinical need.

in the study countries' omeprazole and paroxetine molecule markets, evidence shows that original brand manufacturers implemented the market harvesting strategy consistently across strengths. That is, they either keep constant or increase their prices at the same rate across all strengths, regardless of the differing degrees of generic entry across strengths. However, the degree to which the original brand manufacturer experienced (market share) competition from generic entry did seem to significantly differ within strength market segments. Specifically, generic manufacturers tend to enter into the daily defined dosage market first and foremost; some entered into other strength market segments simultaneously, while others entered into other strength market segments (in addition to the DDD strength segment) in a step-wise fashion over time, and others remain only in the DDD. The result was that in general, generic penetration, and hence, generic versus original brand market share competition, was lower in the less common strength market segments, resulting in higher original brand market shares. Specifically, the number of generic competitors, the strength market share and the original brand to generic average price ratio were all negatively associated with the original brand market share. Where generic penetration did occur, the nature of competition amongst generics within strength markets appears to be similar to that described by studies that focus on generic competition at the molecule level (Chapter 4; Kanavos, Costa-Font and Seeley, 2008). That is, additional entry of generic manufacturers seems to have intensified price competition amongst generics in that segment, especially in the most common strength submarkets, such as the DDD segment market.

Thus, to the extent that it is in the power of original brand manufacturers to do so, segmenting a molecule market into various strengths may be a profitable strategy that allows them to hold on to a larger share of the market at their relatively high prices than if the entire molecule market only consisted of one strength. Moreover, where the competition from generics appeared to be competitive across all strength markets, it seems that the strategy of introducing a line-extension, such as Paxil CR® may be another way in which the original brand manufacturer may hold on to a relatively large share of the molecule market at a high price. The implication of these segmented molecule markets is purchasing inefficiency for payors. If genericisation was maximized within all of the omeprazole and paroxetine strength markets, these study countries could have saved millions of dollars during this study period. Thus, to the extent that other molecule strength segment markets resemble

omeprazole and paroxetine, savings to countries' health care systems from increased genericisation within strength segment markets could easily approach hundreds of millions, and even billions of dollars. Certain policies could help to achieve such savings, such as mandating generic substitution across all strengths and encouraging generic entry across all strengths by making the approval process as quick, easy and inexpensive as possible.

Finally, evidence reveals a nonlinear pricing structure across strength segments of omeprazole and paroxetine, which could reflect some degree of price discrimination across strength market segments within molecules, especially in the USA. The prices of different strengths segments within a molecule do not seem to directly reflect the relative strength itself. In some markets, pills of different strengths are close in price, despite their different strengths, while in other markets, lower strength pills are actually priced above higher strength pills. Moreover, since generic entry is inconsistent across strength market segments, prices are often not the result of competitive market forces, but are rather kept at inflated levels that result in inefficient spending for purchasers.

Analysis on the opportunity for cost savings across strength market segments shows that where a line extension has been introduced, and not yet exposed to generic entry, such as the case of Paxil CR® in the USA, total molecule spending can be approximately 40% higher than it would otherwise be. In a market as large as the USA, this represents millions of dollars per year of expenditures that may not be cost effective, to the extent that the incremental therapeutic benefits of the new line extension do not justify these costs. Thus, purchasers may want to carefully consider which forms of a molecule they are willing to cover and at what prices.

Finally, one way in which patients, pharmacists and physicians may collaborate to save on the cost of certain drugs, such as paroxetine, is by introducing pill splitting programs. This takes advantage of the industry's lack of uniform pricing (per daily defined dosage) across strengths, and produces savings that often could benefit both the third party purchaser and the consumer. However, it is crucial that these programs only apply to drugs that can be split safely and that purchasers first determine which strength market segments would result in savings in the case of pill splitting as opposed to increased costs.

The analysis pursued in the previous sections is not without limitations. First, there is a small number of products in this study, which enables the data to be

explored on a detailed level by, in some cases, manually tracing patterns over time, such as the order that generic manufacturers enter into the different strength markets of a molecule. The trade off for being able to analyze the data at such a disaggregated level, however is that the small number of products necessitate that the four study countries be combined into one model in order to achieve a rigorous sample size. As such, the effect of country-specific regulations such as reference pricing is implicitly controlled for through the fixed effects method, but cannot be separated out in the results. Nonetheless, the finding that original brand versus generic competition varies across strength categories of these molecules seems to hold across these study countries, regardless of their regulatory differences. Findings from this case study analysis may be generalisable to other classes of drugs that are primarily concentrated in the retail market and treat chronic conditions. Second, the pricing data used are not able to capture fully the extent of discounts off list prices. While this is a limitation that affects both the USA and the three European countries, evidence suggests that where these discounts exist, they primarily affect the distribution chain and may operate horizontally across products and product presentations (Kanavos and Taylor, 2007; Kanavos, 2007).

In conclusion, this study on segmented strength markets offers an enhanced understanding of how competitive dynamics and pricing patterns differ within and across submarkets of molecules. Once purchasers have a more detailed understanding of pharmaceutical competition and pricing *within* molecule markets, they can respond by introducing policies that increase price competition within strength segments and that substitute lower priced products, when appropriate, resulting in lower prices and more efficient spending.

CHAPTER 6: THE VALUE OF AN OTC SWITCH: IMPLICATIONS FOR COMPETITION

6.1 Introduction

As seen in the introduction chapter, literature on competition within the pharmaceutical market usually defines the market to be at the level of the therapeutic class or the molecule. Within the molecule market, research often divides competition into two submarkets, the original brand market and the generics market. A closer look at the molecule market reveals there to be strength segment submarkets, which exhibit differing degrees of original brand versus generic competition (as shown in Chapter 5). Analysis at this level has the opportunity to offer insights on the determinants of pharmaceutical competition and how payors can purchase more efficiently. However, there is an additional submarket within the broader molecule market that may exist, which the majority of research on pharmaceutical competition has not yet addressed—the over-the-counter market. Increasingly, regulatory bodies in developed countries are becoming more receptive to approving chronic disease medicines for over-the-counter status, while still allowing those medications to be available on prescription as well. While safety concerns remain at the forefront of every OTC approval decision, the motivations that initiate such a switch include manufacturers' desires to create new profit opportunities, payors' desires to contain costs and an increasing trend toward patient self-management.

Studies of pharmaceutical competition within a molecule market often deliberately exclude OTC products, presumably to avoid the complexities that arise when studying competition within the framework of different regulations, payors and insurance coverage. Moreover, OTC versions of a molecule may be intended for a subset of patients, such as lower-risk patients who do not need the medicine long-term. (It should be noted, however, that there are usually populations of differing acuity within the prescription market as well, which reflects the differing strengths.) A consequence of omitting this OTC submarket when studying a molecule is that little is known about the extent to which an over-the-counter product acts as a substitute with its prescription counterparts, or in other words, the extent to which the over-the-counter market competes for some of the same patients as the prescription

market. To this end, there has been no research on the extent to which the over-the-counter and prescription markets engage in competition within a molecule market when a molecule becomes available over-the-counter, while simultaneously retaining its prescription status, and there is little research on the macroeconomic implications of this type of OTC switch.

This chapter takes a case study approach to analyzing and comparing the macroeconomic implications of a chronic disease medicine becoming available in both the OTC and prescription markets in the context of two different health systems and regulatory frameworks. The intention is to determine whether, on a theoretical level, an OTC switch may be a form of product differentiation on behalf of original brand manufacturer and/or generic manufactures in their attempt to soften competition versus a result of payors' desires to improve purchasing efficiency and regulatory bodies' desires to increase patients' self-care. This study may also provide policymakers with information on the effect of regulations and health system incentives on patients accessing these OTC products as well as whether the goal of cost containment is achieved.

Section 2 provides an overview of general regulatory aspects involved with the approval of an OTC switch. Section 3 reviews the existing literature on the financial implications of an OTC switch. Section 4 discusses the aims and conceptual framework of this study and gives a detailed explanation of how the OTC regulations work in these study countries. Section 5 presents the findings and results from this study. Section 6 simulates possible savings scenarios that could result from this OTC switch and section 7 concludes with a discussion on whether some of the goals of the OTC switch may have been achieved in these study cases.

6.2 Overview of the Regulations and Motivations behind OTC Switches for Chronic Disease Medication

6.2.1 Regulatory Overview

In most countries, the legal/regulatory system allows medicines to be distributed via two different channels; one category requires a physician prescription, while the other category, called over-the-counter medications, does not require a physician prescription. The term over-the-counter is used broadly to describe drugs that are either sold behind the counter of a pharmacist and/or, are available on the general shelves of stores. Where a drug has first been available as a prescription-

only medicine and later receives approval to be marketed in the over-the-counter category, this is called an "OTC switch." It is important to note that some OTC switches result in the product no longer being available through the prescription channel, while in other OTC switch cases, products may retain their prescription availability while also gaining the dual status of over-the-counter availability. In this case, if prescribed by a physician, it is up to the payor to decide whether to reimburse the product.

Table 6-1 shows how OTC product availability can vary across countries as a result of countries' differing legal, regulatory and health system frameworks. There is no centralized OTC switch approval process in Europe. However, the EC Directive on medicinal products for human use (2001/83/EC) did include guidance principles for the OTC market, with which member states must comply. The UK's Medicines and Healthcare products Regulatory Agency (MHRA) summarizes the criteria for which prescription control is required as follows:

- a direct or indirect danger exists to human health, even when used correctly, if used without medical supervision; or
- there is frequent incorrect use which could lead to direct or indirect danger to human health; or
- further investigation of activity and/or side effects is required; or
- they are normally prescribed by a doctor to be administered parenterally—that is, by injection (MHRA, Changing the Legal Classification in the United Kingdom).

The decision of whether a drug meets these criteria will therefore depend on the evidence a country uses during the approval process, as well as subjective opinion, resulting in differing ranges of OTC availability across countries.

Table **6-1** Availability of Over-The-Counter Products, 2005

	Percentage of total molecules, with		
	OTC only availability	Rx and OTC availability	Rx only availability*
U.S.	17.1%	10.0%	72.9%
Canada	3.7%	5.4%	90.0%
France	17.1%	10.9%	72.0%
Germany	30.6%	7.4%	62.0%
Italy	11.4%	8.9%	79.7%
Spain	10.3%	7.0%	82.7%
U.K.	20.8%	8.9%	70.3%
Japan	2.2%	6.1%	91.7%
Australia	25.6%	10.7%	63.7%
Brazil	3.4%	10.4%	86.2%
Chile	29.2%	9.8%	61.0%
Mexico	7.1%	9.3%	83.6%

* It is important to note that in the case of some countries, particularly developing countries, medicines that are only meant to be available with a prescription may be sold informally by pharmacists, who may profit from such cases. This study, however, is only concerned with regulatory frameworks in which the legal status of medicines is enforced.
** This study does not disclose the number of molecules that are included in the calculations.
Source: IMS Health data 2005, adapted from Danzon 2008

Historically, regulatory agencies in developed countries have concentrated primarily on OTC switches for drugs that treat non-chronic conditions, such as ibuprofen. It is important to note that similar to the prescription market, OTC products can be both branded and generic, as seen in the case of Advil and Neurofen, the branded versions of ibuprofen in the USA and the UK respectively.

The primary criterion for OTC switches is safety, notably that patients can easily self-diagnose and can follow the treatment course without being at high risk of significant side effects. The requirements ensuring that these safety criteria are met differ across countries; some countries heavily involve the pharmacist in ensuring safety, while others require actual OTC use studies before a drug is approved for the OTC market. While safety remains the key concern during the approval process, regulatory agencies have recently begun to approve OTC switches for drugs that treat chronic, and, sometimes, serious illnesses. This shift is primarily motivated by three main factors—industry strategy, payors' desire for cost containment and a broader self-care movement (Cohen, 2005). The sections below discuss in greater detail these three motivations.

6.2.2 Industry Strategy

In developed countries, a drug is often not eligible for OTC approval until it has gone off patent. Once the patent has expired, however, both original brand and generic manufacturers may petition to have the drug approved over-the-counter. A manufacturer's application for an OTC switch demonstrates the desire to carve out a niche market position through OTC status, through which they have potential to reap substantial profits above what they would have had in the prescription market. Of course, the size of profits that a manufacturer may make from an OTC product depends on a number of factors, including the degree of substitution from the prescription market, and the degree of competition within the OTC market. It also depends on timing. A switch that is initiated by the original brand manufacturer in the USA may enjoy a three year market exclusivity period, as discussed more extensively in Appendix B. This would enhance the original brand manufacturer's degree of product differentiation in the molecule market. Even without market exclusivity, a first OTC mover advantage may exist, in which the first manufacturer to enter the OTC market is able to set prices.

Besides competition and timing, two other significant factors that influence a manufacturer's decision to apply for an OTC switch may include the costs of applying for OTC status and the probability of approval (Hollenbeak, 1999). The direct costs of applying for OTC status may differ across regulatory agencies. In most developed countries, there are user fees associated with applying to have a drug approved in the OTC market. In addition, in the USA, manufacturers must conduct studies that demonstrate the safety of the drug in the OTC market, which could be very costly. For example, in an attempt to receive OTC approval for the statin Mevacor, Merck commissioned a pivotal study under FDA guidelines to demonstrate that patients are capable of choosing when to use and when to discontinue use (i.e. selection and deselection) of OTC simvastatin. As part of this study, Merck provided a consumer telephone question and answer service to 11,000 people, as well as opening up storefronts with trained personnel that could mimic pharmacies (Sipkoff, 2004). They then recorded the incidence of people who were able to accurately self-diagnose and self-treat with simvastatin. Ultimately, Merck's application was denied on the grounds that not enough users were able to properly select and deselect the drug (see Appendix B). This is an example of a case in which a manufacturer faced

large costs that it was not able to recover through higher profits in the OTC market. Because of the large costs that manufacturers in the USA may face in receiving OTC approval for a prescription drug, it may be that smaller manufacturers, or generic manufacturers with a less profitable portfolio, are less able to take these risks, creating a barrier to entry for these companies.

This then leads to the next point that manufacturers must consider, the probability of an application being approved. Since the shift from OTC medicines treating acute conditions to OTC medicines treating chronic conditions has occurred in the past decade, it may be difficult to predict the probability that a new drug in a new therapeutic class will be approved for OTC use, as regulatory bodies do not have standardized criteria for an acceptable risk-benefit ratio, forcing them to evaluate the risks and benefits on a case by case basis. Moreover, it may be difficult to measure certain long term benefits, such as in the case of Mevacor. Finally, regulators need to decide whether the OTC population should be for the same indication as the prescription population.

Lastly, another factor manufacturers must consider is the extent to which they expose themselves to potential litigation should OTC availability reveal undiscovered harmful adverse effects. This was the case with phenylpropanolamine, a decongestant that was withdrawn from the USA OTC market due to evidence that it increased the risk of stroke in young women (FDA, 2009).

All of these factors must be taken into account by manufacturers when making the decision of whether to apply for OTC switch. Ultimately, the expected profit in the OTC market and the probability of approval must be sufficiently high to justify the costs associated with making the switch.

6.2.3 Payors' Desire for Cost Containment

In addition to industry strategy, cost containment is a factor that catalyzes OTC approval. The desire for cost containment could be achieved either by delisting drugs once they become available OTC (i.e. shifting the costs to the patients), or by shifting demand to the OTC market and continuing to cover these OTC drugs, assuming OTC drugs are on average cheaper than prescription drugs. An OTC switch could also help payors save on physician costs, as long as patients are in fact able to accurately self-diagnose and self-treat such that they do not end up needing more acute care down the road. Cost savings could be substantial for payors under

these circumstances, particularly in the case of OTC medicines treating chronic conditions.

An example of where a payor initiated an OTC switch can be seen in the case of loratadine (Claritin ®) in the USA. WellPoint, a health insurer, petitioned the FDA to switch loratadine, certirizine and fexofenadine while they were still on patent, due to their high costs. Despite the FDA's overall positive recommendation in 1998, the original brand manufacturers were still granted the right to make the final decision. Only loratadine was switched in November 2002, in an attempt by its manufacturer (Schering-Plough) to avoid the impending generic competition. At the time of approval, five different formulations of Claritin® were approved for OTC use.

6.2.4 An increasing Trend toward Self-Care and Increased Access

The third main motivation behind the OTC switch for drugs that treat chronic conditions is a cultural shift toward more self-care, which is propagated by availability of information. Increasingly, patients are assuming more responsibility for their own health, including the prevention and maintenance of chronic conditions. In the case of OTC drugs, this assumes that patients are capable of self-diagnosing, medication selection, adherence, and discontinuation, in the event of an adverse reaction or should the medication not be effective.

Finally, another motivation behind OTC switch is to improve health outcomes, to the extent that the OTC switch increases access. If a lower dosage becomes available through OTC switch, then it may introduce a market for preventative treatment, as was intended in the case of OTC simvastatin in the UK. It is important to note, however, that it is difficult to measure the extent to which OTC medications may safely prevent adverse health outcomes in the long run, making it a contentious issue. Reflecting the sentiments of cost containment and increased access in a press release following the Prilosec switch, the FDA commissioner at the time (McClellan) said "As has been the case for many other over-the-counter switches, the availability of Prilosec® OTC will help reduce costs and expand the availability of treatment options for millions of Americans" (FDA News, 2003).

6.3 Literature Review

The above section describes how two of the motivations behind a recent increase in OTC switches are a trend toward increased access to medicines so that patients can play a larger role in managing their own health care and cost containment for payors. Despite there being evidence that regulators in many developed countries have become more receptive to OTC switches on these grounds, relatively few studies have been conducted to measure the extent to which these goals are accomplished. This section reviews the literature that does exist on the economic implications of an OTC switch.

There have been two recent studies in the USA on the financial impact that OTC switches may have on health plans. One of these evaluates the cost savings that result from a payor's coverage of OTC Prilosec (omeprazole) (West, 2006). Specifically, on March 1, 2004, the Arkansas State Employee Benefits Division (EBD) decided to add OTC omeprazole to its benefits, with a $5 copayment. This was in response to the persistently high omeprazole prices it faced ($123.40 per month for branded omeprazole and $91.71 per month for generic omeprazole), even after patent expiry. With PPIs accounting for 12% of the EBD's pharmaceutical costs in 2003, switching patients to lower OTC omeprazole price of $18.90 per month offered significant opportunity for cost savings. Initially, the EBD eliminated coverage of 20mg brand and generic omeprazole (in the prescription market) altogether. However, there was a shortage of OTC omeprazole in retail outlets, which necessitated the reintroduction of generic omeprazole coverage. Since both prescription generic and OTC omeprazole were covered benefits, the EBD attempted to steer patients toward OTC omeprazole by requiring a co-pay of $5, compared to $10 for the generic prescription. The EBD also incentivized pharmacists to make the switch by increasing the omeprazole dispensing fee from $2.50 to $13. This financial incentive was intended to cover the increased time costs that pharmacists faced when they obtained permission from the physician and when they explained the switch to the patient. The result of these integrated policies was that within 15 months of the coverage change, OTC omeprazole accounted for 41 percent of all PPI claims (down from the 55 percent of claims that was achieved before the OTC omeprazole shortage occurred). After netting out the increased dispensing fees and the loss in patients' cost sharing revenue, this policy change produced an annualized

savings in 2004-2005 of $43.4 million, representing a 38% cost savings on PPI expenditures. These savings were achieved without a decrease in overall PPI utilization. It is important to note, however, that the EBD's policy focused on switching patients to omeprazole OTC who were already taking a PPI. It did not seek to open up a new market by providing omeprazole coverage to patients without prescriptions.

The second study on the financial impact of an OTC switch on health plans found that providing some coverage of OTC antihistamines, while still keeping prescription antihistamines as a second-tier prescription benefit, would be cost-effective for payors (Sullivan and Nichol, 2004). Specifically, managed care organizations and employers would face increased costs per member per month of approximately $0.30 and $0.13 respectively, compared to the alternative of shifting all antihistamine coverage to the third-tier prescription benefit. Medicaid, on the other hand, was projected to actually save $.02 per member per month. This increase in expenditures for private payors reflects the net effect of losing the high third-tier co-payments. Despite costing private payors' marginally more, the move to OTC coverage, with second-tier prescription benefits, was found to be more cost-effective than the third-tier benefit alternative because of higher utilization and lower OTC prices. Moreover, managed care organizations and employers could benefit from hard-to-measure benefits, such as increased labour productivity.

In a more comprehensive study on the economic implications of OTC switches at the national level, the Association of the European Self-Medication Industry (AESGP) estimated the total potential savings that could accrue to society as a result of shifting eligible drugs to OTC status. In this case, prescription drugs were only deemed eligible for OTC status if they treated minor illnesses (defined as illnesses lasting less than three days), which was estimated to be the case for at least 5 percent of all prescribed medicines. At this assumed 5 percent substitution rate, the study concludes that the total annual savings across seven European countries would exceed 16 billion Euros. In particular, in the UK, the savings of €1.4 million was thought to be an underestimate since the British Market Research Bureau reports that 14 percent of all prescriptions in 1996 were related to minor ailments, making the 5 percent assumed substitution rate very conservative. These savings figures took into account the costs of physician treatment, treatment with medicines, patient co-payments, freed up doctor' time, work absenteeism due to treatment, work

absenteeism due to illness and patient travel time. It is important to note, however, that this study assumes there to be a direct 1 to 1 substitution effect between prescription and OTC drugs, based on evidence that there is a strongly negative relationship between the volume of prescriptions for minor illnesses and the volume of OTC medicines for these illnesses (AESGP, 2004). To the extent that countries' health systems vary in regulatory frameworks and pharmaceutical prices, this effect may be stronger or weaker on a national, product level.

Finally, there have been a few studies on the economic effect of OTC switches for acute conditions versus chronic conditions. In a cost-benefit analysis, the deregulation (i.e. switching from prescription to OTC status) of loperamide and hydrocortisone were estimated to save the UK NHS £4.2 million and £2 million respectively in 1987 (Bond, 2004). However, some studies reveal that the potential cost savings from switching a drug to OTC status may not be quite as clear cut. For example, for acute conditions, such as the case of topical acyclovir, which treats cold sores, data shows the after a drug has been switched to OTC status, prescribing for that drug falls, and the government saves money (Bond, 2004). Nevertheless, this study does not, however, take into account whether prescribing for other similar drugs changes. In the case of H2 blockers, which treat chronic ulcer conditions, prescribing for this condition actually increased over the long-run (Bond, 2004). This could be because patients who purchased through the OTC market were first time H2 blockers users who had previously purchased simple antacids. Once the patients learned of the improved effectiveness of H2 blockers, however, they had the financial incentive to go their physician to obtain a prescription for longer term use (Bond, 2004). Thus, in this case, the OTC switch of H2 blockers did not result in a substitution effect from the prescription to the OTC market, but rather increased the size of the H2 blockers market. Similar results were found for antihistamines (Bond, 2004). Thus, the switch of drugs that treat chronic conditions from prescription to OTC status may have different financial implications for payors than the switch of drugs that treat acute conditions.

A Johnson and Johnson Merck-commissioned study on the potential effect of a low-dose statin switch on managed care plans and pharmacy benefit management companies in the USA shows that where the drug also remains available in the prescription market, an OTC switch could increase costs (Sipkoff, 2004). In its findings, the majority of payors expected the switch to significantly increase overall

plan costs as a result of the increased awareness of the dangers of high cholesterol that the low-dose OTC availability would precipitate. It was projected that a certain population of new users would try the low-dose OTC statin, but would eventually move up the spectrum of care by visiting their physician and obtaining a higher-dose statin in order to achieve better control. However, the study also acknowledged that access to OTC low-dose statins could produce cost savings in the long run by preventing cardiac events. Thus, the short and long term budgetary effects may be different for OTC drugs that treat chronic conditions than for OTC drugs that treat acute conditions.

In conclusion, while there have been a few studies on the budgetary effects that OTC switches have had or may have on payors, there is a lack of literature that compares the economic implications of an OTC switch for a chronic disease medicine across differing regulatory and health systems. Moreover, no studies have compared prices in the prescription versus OTC market for these chronic disease medicines as well as the extent to which these two markets of a molecule may act as substitutes or compliments. That is, despite potential differences in indications, policymakers do not yet understand whether this interface of OTC versus prescription chronic disease medications of the same molecule offers an opportunity for enhanced competition within a molecule market (as would exist in the case of substitution) or whether they remain two separate markets with little overlap. It is only through this enhanced understanding of the OTC versus prescription market dynamics that policymakers can know the full macroeconomic effect of these types of switches (of chronic disease medicines becoming available in both the prescription and OTC markets) and whether they have successfully contained costs and/or increased access for patients.

6.4 Methods

The above studies show that the budgetary implication of an OTC switch in which a chronic disease medicine becomes available through both the prescription and OTC markets largely depends on whether the patients are substituting the OTC drug for the prescription drug, or whether the patients who are purchasing the OTC drug are new users. If there is no evidence of substitution between the prescription and OTC markets, then this suggests that users in each market are separate (i.e. that the OTC and prescription products do not compete for patients), and there are no

societal savings. Thus, in order to answer the policy questions of how much money payors (government and private health insurance) and consumers save when a chronic disease medicine is approved for OTC status and how the switch affects patients' access to the medicine, the nature and degree of competition between the prescription and OTC markets (of the same molecule) must first be studied determined. Where there is a substitution effect between the prescription and OTC markets, this is evidence that the two markets may compete for some of the same patients, which may in turn produce a cost savings to payors. The extent of the cost savings to payors and access for consumers will then depend on the price difference between the prescription drug and the OTC drug, and who pays (i.e. the government and private payors versus the consumer).

6.4.1 Sample Selection

This analysis takes a case study approach that analyzes the effect of the omeprazole OTC switch in the USA and the UK. The USA and the UK are particularly suitable for this study because their regulatory approaches to ensuring safety in the OTC omeprazole market resulted in differing incentives for manufacturers and differing degrees of access for patients. Moreover, the set of financial incentives for patients to purchase OTC products also differs in the USA and the UK, which further enables this study to compare the effect of an OTC switch in the context of two different health systems and regulatory frameworks. A description of how the USA and the UK's OTC market regulations compare and contrast is provided in the sections below and, more extensively, in Appendix B.

Omeprazole is a drug in the proton pump inhibitor therapeutic class that treats heartburn and GERD. Approximately 33-44% of the population experiences heartburn at least once a month, while 4-7% of the population suffers from heartburn on a daily basis (MHRA, 2003). It is estimated that roughly 25% of people who experience heartburn consult with their GP in the UK, while the majority self-medicate with over-the-counter drugs from various therapeutic classes, including antacids and H2-Receptor Antagonists (MHRA, 2003).[61] Thus, in theory, there is a significant population who may be interested in purchasing a therapeutically superior

[61] OTC omeprazole had not yet been marketed when this MHRA report was released.

(in comparison with antacids and H2-Receptor Antagonists) drug such as omeprazole in the over-the-counter market.

Nationwide in the USA and the UK, omeprazole spending totalled $4.09 billion and $241.92 million respectively in the 12 months prior to omeprazole OTC marketing.[62] Therefore, to the extent that there is some degree of competition (i.e. substitutability) between the prescription and OTC markets, payors have the potential to realize significant cost savings from an omeprazole OTC switch.

6.4.1.1 OTC Market and Regulations Overview in the USA and the UK

In the USA, there are currently about 80 therapeutic categories of OTC drugs on the market, amounting to a market size of $10 billion a year (as of 2004, at the manufacturer level) (Sipkoff, 2004). OTC drugs as a percent of total unit volume range from 1 percent in Japan to 43 percent in Mexico (Danzon, 2008). The USA and the UK fall roughly in the middle, at 28% and 25.5% respectively.

The USA and the UK also seem to exhibit similar OTC availability rates with OTC-only molecules accounting for 17.10% and 20.80% of total molecules in the USA and UK respectively and dual status (OTC and prescription approved) molecules accounting for 10.0% and 8.9% of total molecules in the USA and UK respectively (Danzon, 2008). Finally, the OTC markets in the USA and the UK are similar in that prescription requirements for medicines are enforced so that products are not available in the OTC market unless they have been officially approved for such use by each country's regulatory body.

Given the similar percentage volumes of OTC medicines in the two countries, it is interesting that OTC prices in the USA and the UK are comparatively so different. A recent study calculated that OTC prices in the UK are roughly twice that of OTC prices in the USA (Danzon, 2008). (When comparing the USA with other countries, a similar trend emerges, with prices being at least 80% higher in all other countries studied (Danzon, 2008).) This is in contrast with price differences in the prescription market, where UK prices are reportedly 23% lower (Danzon, 2008). According to the study, part of the reason for the relatively low OTC prices in the USA in comparison with other countries may be due to the USA's large chain

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[62] Moreover, for the average US health plan in 2004, PPIs accounted for about 9% of total drug benefit spending, with prescription omeprazole accounting for roughly 1.8% of total drug benefit spending (Curtiss 2004).

pharmacies, which can produce their own OTC products and benefit from large economies of scale.[63] However, OTC prices are only one factor that may determine the size of the OTC market. Regulations and the degree of competition between the prescription and OTC markets are also likely to play a large role. Before discussing the conceptual framework for this study, it is first important to provide a brief explanation of the OTC regulations in the USA and the UK and additional background information on the OTC omeprazole switch in the USA and the UK. (For a comprehensive overview of OTC regulations in the USA and the UK, see Appendix B.)

OTC regulations in the USA and the UK are similar in three key ways. First, the primary concern of both countries' regulatory agencies in approving a switch is safety. Second, a product may be available via both the prescription and OTC channels as long as it is marketed at a lower dosage and/or is approved for a different use. Third, in both countries, applicants need support from a manufacturer in order to receive approval. In the case of the USA, the FDA defers to the original brand manufacturer before granting OTC marketing authorisation to an applicant.

The main way in which the countries differ is how they ensure OTC safety. The USA requires that applicants conduct patient label comprehension studies as well as, in some cases, actual use studies. Upon approval, the OTC product is then available on the shelves of foodstores, pharmacies and through mail order. In compensation for performing the actual use studies, manufacturers in the US may receive 3 years of OTC marketing exclusivity rights, as was the case with Prilosec® OTC. In the UK, actual use studies are not required. However, the MHRA retains the option of either approving the drug for general sales list status (GSL) or pharmacy status (P), whereby OTC drugs are only available behind-the-counter of pharmacists, who act as professional intermediaries in ensuring safety. In addition, in most cases, the MHRA requires that OTC products be marketed under different brand names than their prescription equivalents as a result of receiving their own marketing licenses.

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[63] However, there are also large chain pharmacies in the UK, which produce their own OTC products. OTC prices may therefore also depend on nations' demand-side factors, such as patients' incentives to purchase OTC products.

Finally, it is worth noting that for reasons discussed in the above sections, both the USA FDA and the UK MHRA have become more receptive to over the counter switches with medicines that treat chronic diseases (see Appendix B).

6.4.1.2 Background on the Omeprazole OTC Switch

One study has shown that omeprazole is particularly suitable for the OTC market because patients are capable of adhering to the guidelines on when to purchase OTC omeprazole and when to consult with a physician (Fendrick et al, 2004). A recent study in the UK reveals that pharmacists feel that there are fewer risks associated with selling OTC (behind the counter) omeprazole to patients than OTC (behind the counter) simvastatin due to concerns that patients in the OTC simvastatin market would not be as capable of adherence and cardiovascular risk assessment (Stewart et al,. 2007).

It is not surprising, then, that Prilosec®, the original brand version of omeprazole, was approved for OTC status in the USA in June 2003.[64] In this case, 20mg omeprazole was approved OTC in 14, 28 and 42 pill package sizes, based on the OTC guidelines that a patient is not to exceed 3 courses per year of a 14 day (one pill per day) treatment unless he or she consults a physician (US DOHHS, 2003). Notably, 20mg omeprazole was also able to retain its prescription status because the prescription indication was for the treatment of Gastroesophageal Reflux Disease (GERD) in more serious cases that require a physician's supervision.

The FDA announced that two clinical studies performed by AstraZeneca showed that Prilosec was "effective in increasing the proportion of patients with no heartburn over 24 hours and that the effectiveness of Prilosec OTC increases from Day 1 to Day 14" (FDA News, 2003). Thus, in compensation for having performed these studies, the FDA awarded three years of over-the-counter omeprazole exclusivity to Astrazeneca/Proctor & Gamble.

Meanwhile, omeprazole 10mg was approved for the pharmacy (P) category by the UK MHRA in early 2004.[65] Similarly to the USA, the MHRA approved the

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[64] This was in response to Proctor and Gable Co.'s application, in partnership with AstraZeneca. AstraZeneca partnered with Proctor and Gamble in order to leverage their large consumer marketing division.

[65] This was in response to an application by GlaxoSmithKline Consumer Healthcare, in partnership with Galpharm Healthcare Ltc. Galpharm is a generics manufacturer that has significant experience with POM to P switches, and the heartburn OTC market itself, as the marketer of Zantac.

omeprazole switch with a limited package size of 14 pills for relief of "reflux-like symptoms (e.g. heartburn) in sufferers aged 18 and over" (MHRA, 2003). However, in this case, the lower strength of 10mg (compared to 20mg in the USA) was approved in order to ensure that OTC availability would not mask more serious cases.

In addition, it is important to note that because UK regulations require that lower strength OTC medicines be marketed under a different brand name from their prescription counterparts, and since the original brand manufacturer (AstraZeneca) was not involved with the switch, OTC omeprazole in the UK could not use the Losec® brand name as was done with Prilosec® in the USA. Instead, OTC omeprazole in the UK is marketed under the trade name Zanprol.

6.5 Data

This study uses Intercontinental Medical Statistics (IMS) Health data. IMS collects pharmaceutical pricing and sales data across numerous countries and provides a robust source of comparative data, with data being subject to internal validation (IMS, 2002). Specifically, national-level OTC data was available for 7 quarters in the USA (from 2003q3 to 2005q1) and 5 quarters in the UK (from 2004q1 to 2005q1). In the USA, 9 different presentations of OTC omeprazole were sold over the 7 quarters, the presentations varying by package sizes of 14, 28 and 42 pills, and three different distribution channels—retail pharmacies, food stores and mail order. Meanwhile, in the UK, the restriction of the pharmacy category results in only one distribution channel, retail pharmacies. In addition, only one package size of 14 pills is sold in the UK. In both countries, there was only one manufacturer in the market since Proctor & Gamble retained a license for market exclusivity during this time period in the USA, while in the UK, Galpharm Healthcare Ltc was the only manufacturer that had received a marketing license during this time period.

This data allows for the calculation of market (molecule) level information, such as the OTC market share (as a percentage of the total molecule market). Using price and sales data, the quantity of packages sold was determined. Subsequently, the total volume of each presentation sold was arrived at by adjusting for package size (i.e. number of pills, tablets or capsules), which enabled all omeprazole products to be standardized into daily defined dosages (DDDs) in order to compare across strength categories in the prescription market. All prices were inflation-adjusted by

each country's consumer price index, and then converted to USA dollars based on the quarterly exchange rates.

6.6 Research Questions

The main questions this study seeks to address are: To what extent did the OTC omeprazole switch achieve the goals of cost containment and improved patient access? In addition, how could the USA and the UK better utilize their omeprazole OTC markets in order to achieve improved omeprazole purchasing efficiency? In order to answer these questions, this chapter will first focus on three sub questions:

1 What is the nature (e.g. market share versus price competition) and degree of competition between the OTC omeprazole and prescription omeprazole markets in the USA and the UK?
2 How do prices in the OTC omeprazole market compare with prices in the prescription omeprazole market in the USA and the UK?
3 What savings can payors and consumers achieve when a prescription drug is approved for OTC status?

6.7 Conceptual Framework

In order to understand the nature of competition between OTC omeprazole and the prescription markets, it is first important to understand the incentives manufacturers would face in deciding whether to apply for OTC marketing status. In recent literature, one study models the incentives a manufacturer must face in order to apply for a switch, and concludes that generics will apply for a switch only if being a leader in the OTC market is more profitable than being a follower in the prescription market. It also concludes that original brand manufacturers will apply for a switch only if there is an advantage to being first in the OTC market—i.e. if the OTC market is a Cournot model with a Stackelberg leader (Hollenbeak, 1999). However, this study does not consider the possibility that a manufacturer may chose to sell the molecule in both the prescription and OTC markets (assuming the regulations allow this) and that competition may therefore exist at the molecule level between original brand prescription medicines, generic medicines and OTC medicines.

To the extent that competition does exist at the molecule level between prescription and OTC medicines, manufacturers' incentives would be very different

than if competition does not exist, in that they would need to carefully consider whether marketing an OTC product would threaten the sales of their prescription product.[66] Moreover, the implications of an OTC switch for payors would also be different if competition exists between the prescription and OTC markets than if it does not. On a theoretical level, if there is no competition between the prescription and OTC markets, and if the manufacturer is allowed to market in both categories (because of the different OTC approved use and/or strength) then a manufacturer would have the incentive to apply for OTC approval in addition to retaining its prescription version as long as the expected profit in the OTC market exceeds the costs of applying. This is because the manufacturer's prescription version would not experience additional market share or price competition as a result of the OTC switch. At the same time, payors that only cover prescription medicines would see no change in their expenditures, while a new population of users purchase the OTC medicines. If payors do cover OTC medicines, then their expenditures would theoretically increase.[67] Oppositely, where some degree of competition (i.e. substitutability) does exist between the prescription and OTC markets, manufacturers' profits would depend on their competitive position in the broader molecule market, whereas payors should theoretically experience cost savings, assuming purchased prices are, on average, lower (due to a shift to lower priced OTC products).

On a theoretical level, this chapter therefore first discusses the possibility of competition between the prescription and OTC market. This is assessed as part of a two-part framework which, first, seeks to understand whether the prescription and OTC markets are complements or substitutes, and second, seeks to understand the nature of competition, given the degree of substitutability. Where competition is likely, this chapter assesses the empirical implications that this competition between prescription and OTC market may have on payors.

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[66] This analogy is similar to the scenario where original brand manufacturers market generics of the same molecule, and must therefore carefully weigh the profitability of its generic product versus any potential loss with its original brand product.

[67] Under this scenario, payors would therefore only have the incentive to cover an OTC medicine if there was a significant health benefit for the OTC population.

6.7.1 Are Prescription and OTC Omeprazole Substitutes in the USA and the UK?

In other to assess the implications of an OTC switch (where the drug also remains available on prescription) on the degree competition within a molecule market, this study must first assess the extent to which OTC omeprazole is a substitute for prescription omeprazole. If OTC omeprazole is a substitute for prescription omeprazole, then:

$$\Delta Q_{i-j}^{OTC} = f(\Delta Q_{i-j}^{OB}, \Delta Q_{i-j}^{gen}) \qquad (1)$$

$$i = 1, 2, \ldots, n$$

$$j = i\text{-}1 \ldots n$$

Where ΔQ_i^{OTC} is the change in total volume of OTC medicine in a given quarter, i, ΔQ_i^{OB} is the change in total volume of original brand medicine in that respective quarter and ΔQ_i^{gen} is the change in total volume of generic medicine in that respective quarter.[68] Evidence of a negative relationship between ΔQ_i^{OTC} and ΔQ_i^{OB} and between ΔQ_i^{OTC} and ΔQ_i^{gen}, where the prescription volumes decrease as the OTC volume increases may suggest that there is substitution away from the prescription market into the OTC market. Evidence of the prescription market volume increasing after generic entry may suggest that new users switch from the OTC market into the prescription market. Because of the above study's assumption that the prescription and OTC markets are mutually exclusive (Hollenbeak, 1999) and because the FDA and MHRA have approved OTC omeprazole with the intention of short-term use (versus the intended long-term use in the prescription market), the null hypothesis in this study is that OTC and prescription omeprazole are not substitutes, and therefore do not compete with one another. If this is the case, then there will not be a discernible relationship between ΔQ_i^{OTC} and ΔQ_i^{OB} and ΔQ_i^{gen}, such that:

$$\Delta Q_i^{OTC} \neq f(\Delta Q_i^{OB}, \Delta Q_i^{gen}) \qquad (2)$$

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[68] In order to capture substitutability instead of total volume effects that may result from extraneous factors such as the introduction of other molecules into the therapeutic class, the relationships between volumes' deltas should be assessed rather than volumes themselves.

Alternatively, there may be evidence that OTC and prescription omeprazole are not substitutes (and therefore do not compete) if the relationship between ΔQ_i^{OTC} and ΔQ_i^{OB} and/or between ΔQ_i^{OTC} andΔQ_i^{gen} is positive, which may suggest that the products are complements. Because OTC omeprazole in the USA is assumed to be easily accessible (as a result of there being no behind-the-counter category in the USA, and of the massive distribution network of foodstores and pharmacies that may stock the OTC product), this study expects to reject the null hypothesis that OTC and prescription omeprazole are not substitutes. This implies that the products are in fact substitutes and do engage in a certain degree of competition with one another. In the UK, however, this study does not expect to reject the null hypothesis that OTC and prescription omeprazole are not substitutes due to the more restrictive behind-the-counter category, which likely enforces (at least to some extent) the shorter-term use indication.

6.7.2 Price Competition between the OTC and Prescription Omeprazole markets in the USA and the UK

If OTC and prescription omeprazole are not substitutes (i.e. if they are complements or there is no discernible relationship), then the next question is whether competition exists between them. Theoretically, a perfect model of Cournot competition would assume that manufacturers have predetermined capacities. In the case of medicine production, however, it is unlikely that the marginal cost would increase significantly with scale, restricting capacity. Thus, market share competition between the prescription and OTC markets would likely face fewer constraints than the Cournot model implies. As a result, it is more realistic that where manufacturers of homogeneous products do not face constrained capacities, they engage in price competition (Giralt, 2007). Recall that in a perfect model of Bertrand price competition, the following conditions hold:

$$D(p_1, p_2) = \begin{cases} D(p_1) & \text{if } p_1 < p_2 \\ \tfrac{1}{2} D(p_1) & \text{if } p_1 = p_2 \\ 0 & \text{if } p_1 > p_2 \end{cases} \qquad (3)$$

Resulting in a market equilibrium where:

$$p_2 = p_1 = c \qquad (4)$$

Thus, in a model of Bertrand price competition:

$$p_2 = f(p_1, c) \qquad (5)$$

and likewise,

$$p_1 = f(p_2, c) \qquad (6)$$

However, since the OTC products are differentiated by indication (as required under regulatory approval), and since the payment side is structured differently in the OTC market (e.g. the payment is primarily via consumers rather than third party payors), it is unlikely that a perfect model of direct price competition would exist between the prescription and OTC markets. Thus, where there is evidence of competition between the OTC and prescription omeprazole markets (i.e. where this study is able to reject the null hypothesis that these products do not act as substitutes), this study expects to reject the null hypothesis of a Bertrand model of perfect price competition in favour of an equilibrium that would reflect a market of homogeneous goods with product differentiation, such that:

$$p_2 > p_1 > c \qquad (7)$$

In accordance with the Bertrand model, whereby prices are a function of one another, this study seeks to understand whether OTC omeprazole prices are a function of prescription generic and original brand prices in order to determine whether there is in fact some degree of price competition between OTC and prescription omeprazole, such that:

$$P_i^{OTC} = f(P_i^{OB}, P_i^{gen}, MS_i^{OTC}, \mathrm{MO}, \mathrm{FS}) \qquad (8)$$

$$i = 1, 2, \ldots, n$$

Where P_i^{OTC} equals the price of the OTC product at the presentation level, P_i^{OB} equals the average original brand price and P_i^{gen} equals the average generic price. Evidence of a positive association between the prescription original brand and/or generic omeprazole prices and OTC prices may suggest some degree of price competition between the two sectors. This study has also included MS_i^{OTC}, OTC market share (as a percentage of the total molecule market), as an explanatory variable in order to capture any influence that a change in the market position of the

OTC manufacturer may have in the OTC omeprazole prices. Finally mail order and food store dummy variables have been added to assess the effect that the different distribution channels may have had on OTC omeprazole prices in the USA.

6.8 OTC Omeprazole vs. Prescription Omeprazole in the USA and the UK

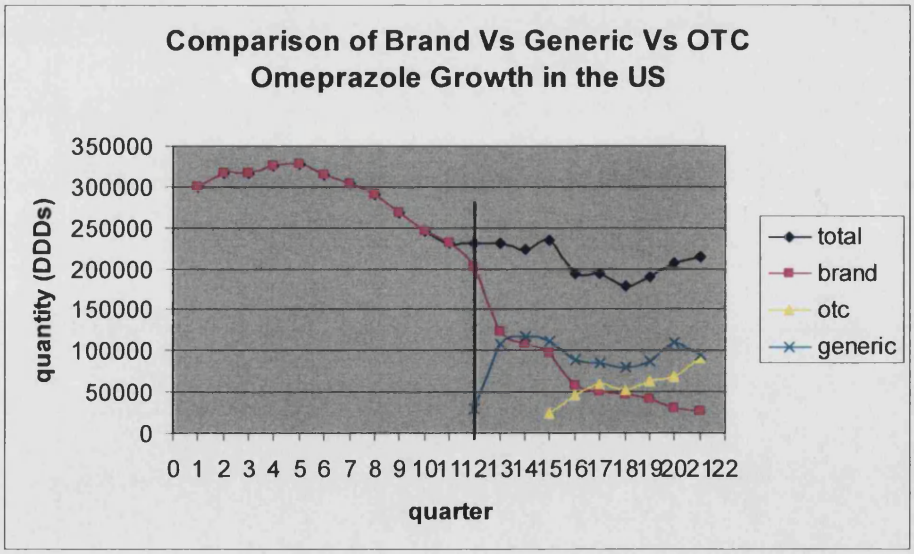
6.8.1 Empirical Observations

Because the total volume of OTC medicine is a market-level variable, there is not enough data to regress the volumes on each other in the USA or the UK. This is because the presentation-level data would be lost in the USA, reducing the number of observations to 7 quarters in the USA and 5 quarters in the UK, which is not conducive to a rigorous time series econometric analysis. Moreover, simple correlation statistics between the OTC volume and the generic and original brand volumes would not separate out how the three-way relationship—that is, the extent to which the prescription original brand and generic markets were substitutes (separate from the effect of the OTC market), the extent to which the prescription original brand and OTC market were substitutes (separate from the effect of the generic market) and the extent to which the prescription generic and OTC market were substitutes (separate from the effect of the original brand market). However, it is possible to develop hypotheses about whether the original brand and generic prescription versions are substitutes with the OTC versions through graphical analysis.

Figure 6-1 shows that in the USA, the original brand volume decreases steadily over time, with the steepest drop occurring after generic entry. Generic volume increases rapidly in the first few quarters, and then plateaus upon OTC entry, at which point OTC volume increases steadily over time. By 2005, generic volume seems to be holding steady, while original brand volume continues to decrease and OTC volume continues to increase. Generic omeprazole seems to lose volume to OTC omeprazole, whereas original brand omeprazole seems to lose volume both to generic omeprazole and OTC omeprazole. The decline in original brand omeprazole volume can be partly attributed to generics because it started before OTC entry, when generic volume was increasing; it can also be attributed to OTC entry because it continues to decline when generic volume declines and OTC volume continues to increase. This is not surprising, given the fact that the original brand omeprazole

product and the OTC omeprazole product in the USA are marketed under the same brand name, Prilosec, which likely makes the products close substitutes.[69] At first glance, it may seem surprising that a manufacturer (e.g. AstraZeneca) would initiate an OTC switch for a product that could compete so intensely with its original brand product. However, the high rates of generic penetration in the USA prescription omeprazole market suggest that the original brand would likely lose market share to generic competition if there were no OTC product available. Thus, it may be an optimal strategy for the original brand manufacturer to introduce a competitive advantage into the molecule market via the OTC switch, and accept a decline in its original brand market share as inevitable. The total size of the omeprazole market in the USA remains relatively level around the point of patent expiration, and it subsequently declines for a period of time. This indicates that OTC omeprazole may not increase the total size of the market, but instead competes with the prescription market.[70] The result is that in the USA, OTC omeprazole market share increases substantially from 11% during the quarter of OTC entry to 43% in 2005q1, as shown in Figure 6-2.

Figure 6-1 Comparison of Brand versus Generic versus OTC Omeprazole Growth in the USA



Note: The vertical line denotes the point of patent expiration.

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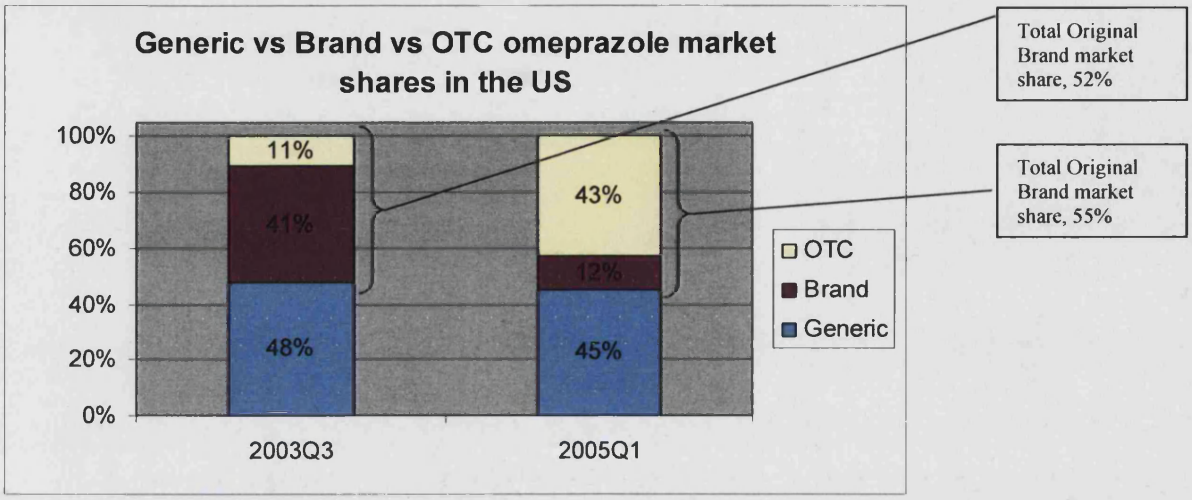
[69] If it weren't for the differing payment arrangements between the prescription and OTC markets, they may be near perfect substitutes.

[70] It may also be that some of the users from the prescription market switched to other PPIs during this period, while new users entered into the OTC market, thereby keeping total volume steady. An analysis of the entire therapeutic class would be required to validate this possibility. In practice, it is likely that this occurred as well as some users switching from the prescription omeprazole market to the OTC omeprazole market.

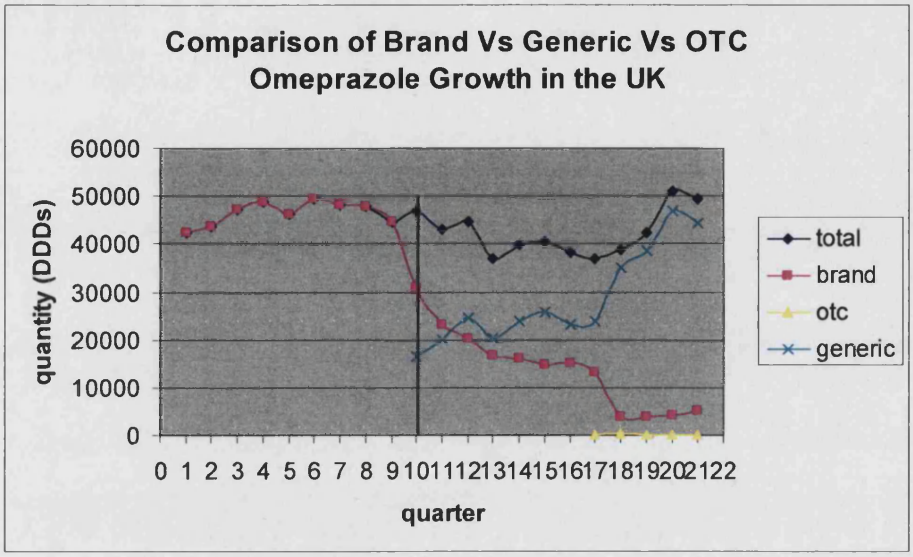
Figure 6-2 Generic versus Brand versus OTC Omeprazole Market Shares in the USA



Source: The Author, using IMS Health data.

Similarly to the case of omeprazole in the USA, Figures 6-3 and 6-4 show that in the UK, original brand omeprazole volume decreases steadily over time with the steepest drop occurring after generic entry. Meanwhile, generic volume increases steadily over time. In contrast to the case of omeprazole in the USA, however, OTC volume in the UK does not increase significantly upon OTC entry. In addition, both trends of decreasing original brand volume and increasing generic volume in the UK continue unabated after OTC entry, indicating a lack of competition between OTC omeprazole and prescription omeprazole in the UK. Interestingly, the total size of the omeprazole market in the UK decreased after patent expiration, but then increased significantly around the time of OTC entry, despite the OTC market's relatively insignificant size. One possible explanation is that new users of the OTC version were able to quickly switch to the generic prescription market, resulting in a constant revolving door in the OTC market and an increase in the total omeprazole market size. Figure 6-4 provides further evidence of the relatively insignificant OTC omeprazole market share in the UK, in comparison with generic and original brand market shares; by 2005Q1, OTC omeprazole market share in the UK had not even reached 1%.

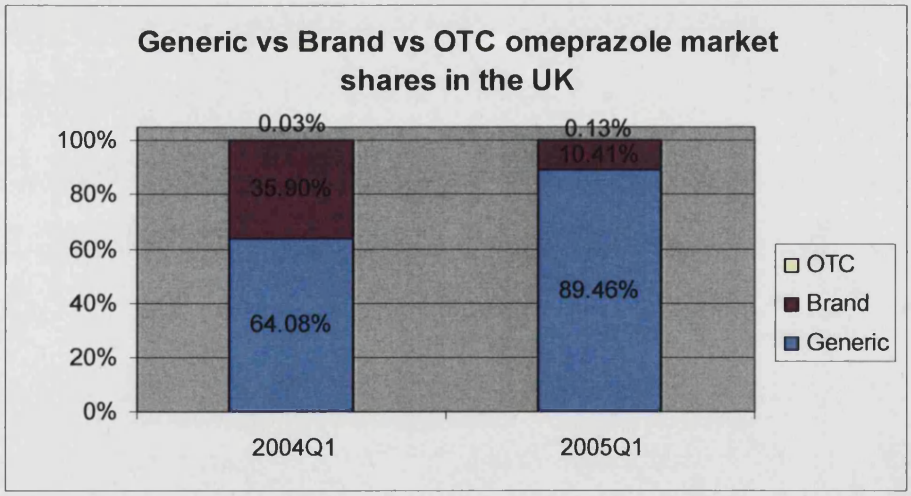
Figure 6-3 Comparison of Brand versus Generic versus OTC Omeprazole Growth in the UK



Note: The vertical line denotes the point of patent expiration.

Source: The Author, using IMS Health data.

Figure 6-4 Generic versus Brand versus OTC Omeprazole Market Shares in the UK



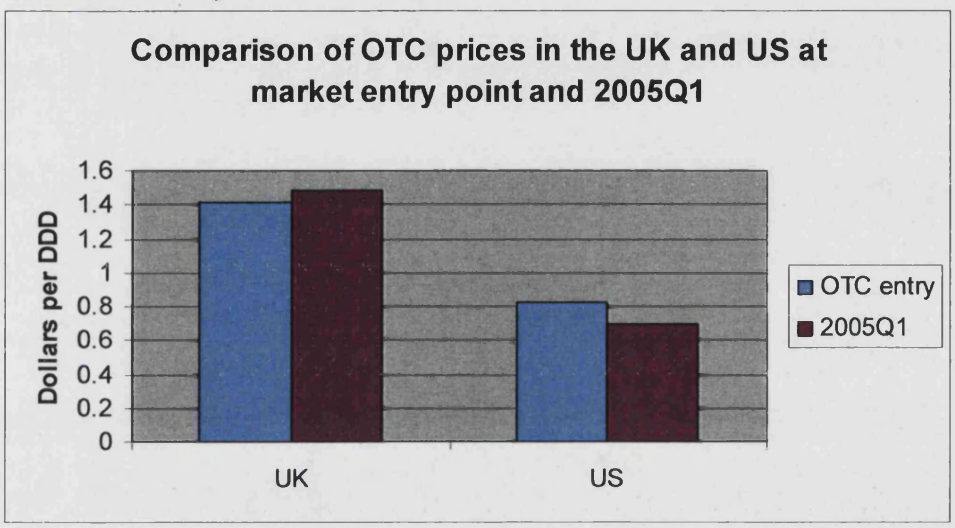
Source: The Author, using IMS Health data.

Where prescription and OTC drugs are substitutes, as shown in the US case, competition between the two markets may exist. In contrast, where the products do not appear to be substitutes, as is the case in the UK, there seems to be a lack of competition between OTC and prescription omeprazole.

Figure 6-5 suggests that the OTC omeprazole market may have engaged in price competitive behaviour with the prescription omeprazole market in the USA, but

not the UK. From OTC entry (2004Q1 in the UK, 2003Q3 in the USA) to 2005Q1, real OTC omeprazole prices decreased in the USA, while they increased slightly in the UK.

Figure 6-5 Comparison of OTC Prices in the UK and the USA at Market Entry Point and 2005Q1



Source: The Author, using IMS Health data.

6.8.2 Econometric Analysis

To determine the type of competition (i.e. Bertrand-like or Cournot-like) that exists between OTC and prescription omeprazole in the USA, it is important to assess the extent to which competition is based on price.[71] Evidence that the price of one product drives the price of another product may suggest the presence of Bertrand-like competition in the USA. Thus, the degree of price competition between OTC and prescription omeprazole in the USA is tested using the below model, which follows from equation (8):

$$P_i^{OTC} = \beta_o + \beta_1 P_i^{avrggen} + \beta_2 P_i^{avrgorig} + \beta_3 MS_i^{OTC} + \beta_4 \mathrm{MO} + \beta_5 \mathrm{FS} + \varepsilon \quad (9)$$

where P_i^{OTC} represents the quarterly price of the OTC medicine at the presentation level, $P_i^{avrggen}$ represents the quarterly average generic price (calculated across all generic competitors), $P_i^{avrgorig}$ represents the quarterly average original brand price,

[71] Testing the nature of competition between the prescription and OTC markets in the US is worthwhile due to the preliminary investigation that suggests a strong degree of competition. Such a test is not necessary in the UK, given the strong evidence which suggests that the OTC market is not competitive with the prescription market. Moreover, the single distribution channel does not provide enough data in a five quarter time period to run a rigorous model of price competition in the UK.

MS_i^{OTC} represents the quarterly OTC market share, MO is a dummy variable for the mail order distribution channel and FS is a dummy variable for the food stores distribution channel. (See Figure 6-6 for exact variable definitions.) With 9 presentations over a 7 quarter time frame, this study uses a random effects panel data regression method. A random effects model is appropriate in this case because the explanatory variables are all market level variables. As a result, the explanatory variables' disturbance terms do not correlate with the presentation level residual. The Hausman test for the appropriateness of the random effects model versus the fixed effects model confirms this, as shown in Table 6-2 below. Notably, because a random effects model is appropriate, the mail order and food stores variables can be dummied out of the equation in order to assess their effects.

Figure 6-6 Variables and their Definitions for OTC versus Prescription Omeprazole Econometric Analysis, 2000Q1-2005q1

Variable	Definition	Mean (SE)
P_i^{OTC}	The OTC price per DDD at the presentation level	.778 (.205)
$P_i^{avrggen}$	The average generic price per DDD	1.677 (.904)
$P_i^{avrgorig}$	The average prescription original brand price per DDD	4.095 (1.072)
MS_i^{OTC}	The share of the total omeprazole market (percentage of DDD) that was purchased OTC.	.271 (.118)
MO	Dummy variable for medicines that were purchased through the mail order service distribution channel	
FS	Dummy variable for medicines that were purchased from food stores	

Source: The Author, using IMS Health data.

The results from the model testing for Bertrand-like price competition between OTC and prescription omeprazole in the USA are presented in Table 6-2 below. There is a significant, positive relationship between the average generic price and the presentation-level OTC prices, reflecting the fact that a decrease in the average generic price is associated with a decrease in the presentation-level OTC prices. Meanwhile, there does not appear to be a significant relationship between the average original brand price and the presentation-level OTC prices. This suggests that price competition may exist between the generic and OTC omeprazole markets, but not between the original brand and OTC omeprazole markets.

The relationship between the OTC market share (within the context of the entire molecule market) and the presentation-level OTC prices is significant and negative. Thus, an increase in the OTC market share is associated with a decrease in

the presentation-level OTC prices, possibly reflecting economies of scale in the production of OTC omeprazole. Finally, the mail order dummy variable is significant and negative, while the food store dummy variable is not significant. This reflects the fact that mail order OTC omeprazole is lower priced than retail pharmacies' OTC omeprazole, while the price of OTC omeprazole in food stores is not significantly different from that of retail pharmacies. This is not surprising, as the mail order distribution channel is able to avoid the bricks and mortar costs of production, while food stores and retail pharmacies would likely face a similar structure of production costs.

To the extent that the case of omeprazole is reflective of other molecules, this study therefore suggests that there may be competition between the OTC and prescription markets in the USA. However, it is important to note that the small sample bias may question the validity of these results. These findings are therefore more useful in generating the hypothesis that competition between OTC and prescription markets may exist in the US, than they are generalizable.

Table 6-2 Model testing for Bertrand-like price competition between OTC and prescription omeprazole in the USA: Dependent variable P_i^{OTC}

	USA (random effects)
$P_i^{avrggen}$	.046**
	(.020)
$P_i^{avrgorig}$	.003
	(.008)
MS_i^{OTC}	-.363***
	(.076)
MO	-.128**
	(.060)
FS	-.006
	(.060)
No. of observations	63
No. of groups	9
R^2 (within for re model)	.59
Hausman test	1.00

*p < 0.10: **p < 0.05: ***p < 0.01

6.8.3 A Comparison of OTC and prescription Omeprazole Prices in the USA and the UK

The previous section discusses OTC versus prescription omeprazole volume effects in the USA and the UK and explores the relationship between the prices of OTC and prescription omeprazole in the USA. It is also important to understand how prices in the OTC market compare with prices in the prescription market in order to determine whether OTC switch can be used as a vehicle for cost savings. Figure 6-7 shows that in 2005Q1, the weighted purchased OTC omeprazole price per DDD in the USA was significantly lower than the weighted purchased omeprazole prices per DDD in the original brand and generic prescription markets. Meanwhile, in the UK, the weighted purchased OTC omeprazole price per DDD was lower than the weighted purchased original brand price per DDD, but higher than the weighted purchased generic price per DDD. Thus, in the USA, purchasers are receiving better value for their money in the OTC omeprazole market than in the generics omeprazole market, whereas in the UK, purchasers are receiving better value for their money in the generics omeprazole market than in the OTC omeprazole market.

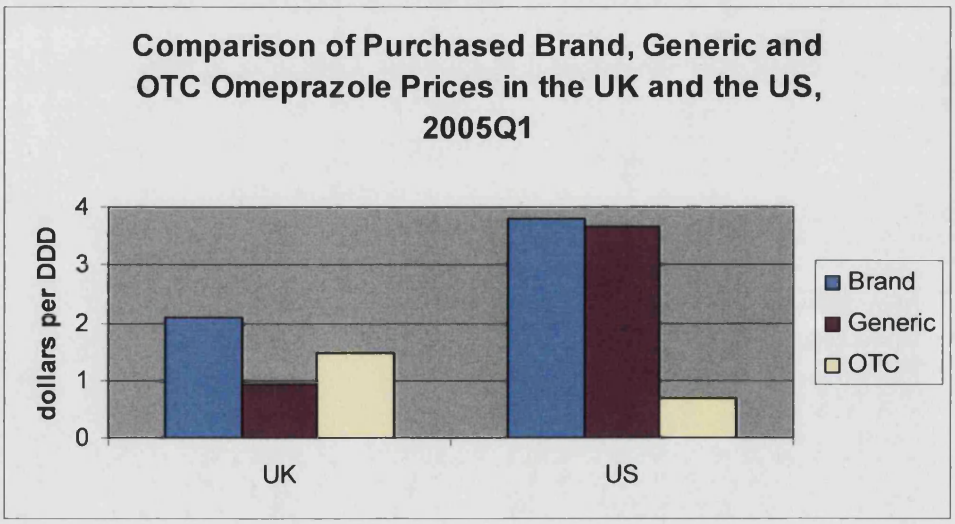
Figure 6-8 shows that the weighted purchased OTC omeprazole price is nearly the same in the UK as the lowest available OTC omeprazole price because of the single distribution channel and package size. In the case of the USA, Figure 6-8 shows that OTC omeprazole was available at a lower price ($0.57 per DDD) than the weighted purchased price of $0.69 per DDD. Specifically, in 2005Q1, OTC omeprazole in the USA was available by mail order, at retail pharmacies and at food stores, and came in package sizes of 14, 28 and 42 pills at each distribution channel. In 2005Q1 prices therefore ranged from a high of $0.78 per DDD for a 14 pill package at retail pharmacies to a low of $0.57 per DDD for a 42 pill package by mail order. However, despite these low mail order prices, the total percentage of omeprazole (as a percent of DDD) that was purchased through the mail order channel in 2004 was only 22.6%, while 64.9% was purchased through retail pharmacy stores and 12.5% was purchased through food stores. Thus, purchasers of OTC omeprazole in the USA could achieve greater savings by shifting a larger share of their purchasing to mail order OTC omeprazole.

When comparing the lowest available omeprazole prices per DDD in the OTC, generic and original brand markets, the picture remains the same in the UK as when comparing the weighted purchased omeprazole prices per DDD—generic

omeprazole is the lowest priced, with OTC omeprazole available at a significantly higher price per DDD (than generic omeprazole) and original brand omeprazole available at the relatively highest price per DDD. However, in the USA, the lowest generic omeprazole price is lower than the lowest OTC omeprazole price, which suggests that if payors in the USA want to save money, they could either switch coverage to the OTC product, or could attempt to improve their generic purchasing efficiency by purchasing generic omeprazole at a lower price.

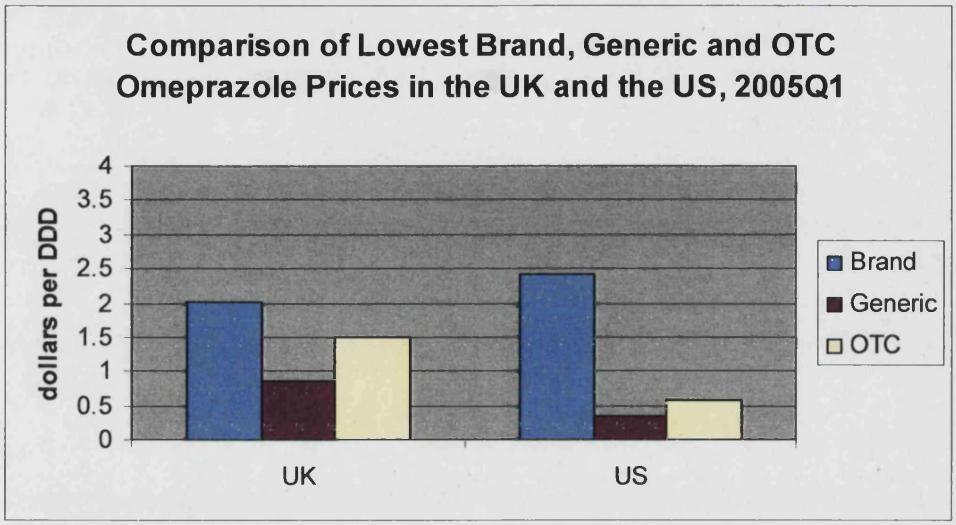
Figures 6-7 and 6-8 also show that the omeprazole price per DDD was significantly lower in the USA than in the UK in 2005Q1. Specifically, the 2005Q1 OTC omeprazole weighted purchased price per DDD was $0.69 in the USA, compared to $1.48 in the UK. This number needs to be interpreted with some caution, though, since prices are expressed per daily defined dosage. If compared on a per pill basis, weighted and lowest OTC omeprazole prices in the USA are $.69 and $.28, compared to $.74 and $.74 in the UK respectively. (For a more in-depth analysis on the role of strength in product markets across countries, refer to the previous chapter.) Thus, on a per pill basis, the weighted purchased omeprazole prices in the USA and the UK are more closely aligned, although the USA OTC omeprazole market still offers greater value than the UK OTC omeprazole market.

Figure 6-7 Comparison of Purchased Brand, Generic and OTC Omeprazole Prices in the UK and the USA, 2005Q1



Source: The Author, using IMS Health data.

Figure 6-8 Comparison of Lowest Brand, Generic and OTC Omeprazole Prices in the UK and the USA, 2005Q1



Source: The Author, using IMS Health data.

6.8.4 Competition between OTC and Prescription Omeprazole in the USA and the UK: Theoretical Implications

Based on the rejection of the null hypothesis that OTC and prescription omeprazole are not substitutes, the findings in this study suggest that there may be some degree of competition between the prescription and OTC omeprazole markets in the USA. In the case of the UK, this study fails to reject the null hypothesis and concludes that there is no evidence of direct competition between the OTC and prescription omeprazole markets in the UK. Instead, there seems to be preliminary evidence that the OTC and prescription omeprazole markets may actually act as complements—that the OTC omeprazole market may be funnelling some patients into the prescription omeprazole market.

In regards to the degree of competition in the USA, findings from this study reject the null hypothesis of Bertrand price competition, as expected. Instead, evidence indicates the presence of Bertrand-like price competition between the generic and OTC omeprazole markets in the USA, where the OTC market may act as a form of product differentiation (on behalf of the original brand manufacturer, in this case) that allows for an equilibrium of ranging prices and market shares, as seen in Figures 6-7 and 6-8 above. Notably, the lack of evidence of price competition between the prescription original brand and OTC omeprazole is not surprising, given the fact that they are manufactured by the same company. It seems that the original brand manufacturer pursues the relatively passive market harvesting strategy for its

prescription original brand product, while at the same time, using the OTC market as a strategic means by which to further product differentiate (beyond just leveraging itself as an experience good) and in the process, compete with the prescription generic product.

6.8.5 Models of Potential Cost Savings from an Omeprazole OTC Switch in the USA and UK

The total omeprazole expenditure decreased from $4,094,610,000 in the 12 months preceding the OTC switch to $2,212,964,000 in the 12 months following the OTC switch in the USA. This reflects both the decrease in the average purchasing price and the decreased total omeprazole utilization, as seen in Figure 6-1. Meanwhile, in the UK, the total omeprazole expenditure decreased from $241,980,000 in the 12 months preceding the OTC switch to $180,053,000 in the 12 months following the OTC switch. This largely reflects the increased generic penetration, as seen in Figures 6-3 and 6-4. Thus, the changes in total utilization and original brand versus generic mix make it difficult to separate out the effect that a shift to OTC omeprazole had on total expenditures.[72]

However, it is possible to simulate what the financial implications of a policy could have been, had it shifted a larger percentage of people from the prescription omeprazole market to the OTC omeprazole market, holding total omeprazole utilization constant. Tables 6-3 and 6-4 show the possible additional cost savings (beyond what was actually saved) to society in the USA and the UK in 2004 following the approval of omeprazole OTC. At a 50% OTC market share in 2004, purchasers in the USA would have saved an additional 22% if OTC omeprazole was purchased at the 2004 weighted OTC purchased price and 26% if the OTC omeprazole was purchased at the 2004 lowest OTC price. This represents a nationwide savings of approximately $394 million and $461 million respectively. Notably, a 50% OTC omeprazole market share in 2004 would have cost UK purchasers 18% more at the OTC weighted purchased price due to the higher OTC weighted purchased price relative to the generics weighted purchased price and 17%

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[72] This could be modelled in an econometric regression. However, because the dependent variable in this case, total omeprazole utilization, is market level (instead of presentation level), there would only be one presentation of data, rendering the results insignificant since there are only seven and five quarters of data in the US and UK. For a rigorous time series regress, there would need to be years of additional data.

more at the lowest 2004 OTC omeprazole price. (The small discrepancy between the 18% and 17% increased costs is due to the fact that the weighted purchased price represents an annual weighted average, whereas the lowest purchased price reflects the lowest quarterly price available in 2004.) Table 6-4 below shows that if the OTC market share were to increase to 75%, even further possible savings in the USA could have amounted to as much as 43%, while the cost increase in the UK could have been as much as 29%.

Table 6-3 Potential Cost Savings from the OTC Omeprazole Approval in the USA and the UK in 2004, assuming a 50% OTC Market Share

			A Substitution of 50% OTC Market Share at the Weighted Purchased OTC Price*			A Substitution of 50% OTC Market Share at the Lowest OTC Price*		
	Total Actual Molecule Spending in 2004	Average Actual OTC Market Share in 2004	Total Spending	Total Savings	Percent total Savings	Total Spending	Total Savings	Percent total Savings
USA	1,766,782,000	31.72%	1,373,102,370	**393,679,630**	**22%**	1,306,017,871	**460,764,129**	**26%**
UK	184,847,199	0.29%	218,083,207	**-33,236,008**	**-18%**	216,420,159	**-31,572,960**	**-17%**

*Assumes all substitution comes from generics
Note: Market share, and therefore substitution, is based on daily defined dosage units.
Source: The Author, using IMS Health data.

Table 6-4 Potential Cost Savings from the OTC Omeprazole Approval in the USA and the UK in 2004, assuming a 75% OTC Market Share

			A Substitution of 75% OTC Market Share at the Weighted Purchased OTC Price*			A Substitution of 75% OTC Market Share at the Lowest OTC Price*		
	Total Actual Molecule Spending in 2004	Average Actual OTC Market Share in 2004	Total Spending	Total Savings	Percent total Savings	Total Spending	Total Savings	Percent total Savings
USA	1,766,782,000	31.72%	1,098,959,488	**667,822,512**	**38%**	998,332,739	**768,449,261**	**43%**
UK	184,847,199	0.29%	239,363,578	**-54,516,379**	**-29%**	236,869,006	**-52,021,807**	**-28%**

*Assumes all substitution comes from generics
Note: Market share, and therefore substitution, is based on daily defined dosage units.

Tables 6-3 and 6-4 assume that the total omeprazole volume remains constant, and that an increased OTC market size is the result of substitution from the generic prescription market to the OTC market. In reality, it is likely that the FDA and MHRA's decisions to approve different strengths of omeprazole OTC have significant implications for the degree of substitutability between the prescription and OTC markets in the USA and the UK, and Thus, for the potential cost savings for payors and consumers. In the USA, the approval of the most common dosage, 20mg, implies a larger degree of substitutability, especially since pharmacists are not required to restrict the OTC patient population in the USA (since there is not a behind the counter category). Specifically, roughly 50% of the total omeprazole pills dispensed in 2005 in the US were 20mg prescription products, which indicates that there was still ample room for substitution from the prescription market to the OTC market, assuming patients remained under the guidance of their physician, when necessary. (The prescription 10mg and 40mg strengths only accounted for just over 5% of the total number of omeprazole pills dispensed in the USA in 2005q1.) One study noted that "the availability of omeprazole OTC in the same strength as omeprazole Rx presents a potential opportunity for health plans to cover an OTC product" (West, 2006).

Meanwhile, the approval of a lower dose version in the UK represents a more intentional aim to open up a new preventative market for lower risk people, rather than to encourage substitution from the prescription market to the OTC market. In addition to the prescription and OTC markets having different brand names, the requirement that the pharmacists must ensure that the OTC version is sold in accordance with the OTC license (in cases of P status) further prevents the OTC omeprazole market from acting as a substitute to the prescription omeprazole market in the UK. Theoretically, there was still significant room for substitution from the prescription to OTC omeprazole market in the UK since 27% of the total omeprazole pills dispensed in 2005 were 10mg prescription products. However, in practice, consumers in the UK are more apt to enter into the OTC market and then funnel into the prescription market if they discover that they are unresponsive to the 14-day course or want to take the drug long-term. This study shows evidence that this may have happened, given that the generic market increases significantly after OTC entry.

Consequently, the 50% and 75% OTC omeprazole market shares in Tables 6-3 and 6-4 above are more realistic in the USA than in the UK. In the UK, the

introduction of the OTC omeprazole market does not seem to offer possible cost containment through substitution (from the prescription to the OTC market), but rather may actually have increased costs for the UK by increasing the size of the generic market.

Another factor that Tables 6-3 and 6-4 do not take into account is the costs of physician visits. According to Richard Stevens, GP and chairman of the Primary Care Society for Gastroenterology, roughly 5% of all consultations are for GERD/heartburn (The Pharmaceutical Journal, 2004). Thus, to the extent that there is a shift from the prescription market to the OTC market, as was the case in the USA, there would also likely have been large cost savings to the health care system from decreased physician visits. This assumes that patients are capable of determining when physician visits are necessary, and therefore do not jeopardise their health in the long run by going to the physician less in the short run. Such was the concern in the case of OTC simvastatin. Evidence shows, however, that in the case of GERD/heartburn, patients are capable of adhering to OTC guidelines on when to visit a physician (Fendrick et al, 2004).

In the UK, it is possible that the introduction of the OTC omeprazole market actually increased the number of physician visits, if new patients were in fact funnelled into the health care system. Notably, a study on the effect of an H2-receptor antagonist OTC switch found that the mean number of prescriptions dispensed for H2-receptor antagonists was reduced by 1.5 prescriptions and that the OTC switch did not result in an increase in physician visits overall or for GERD-related conditions (Andrade, Gurwitz and Fish, 1999). This finding is in contrast with the findings in this study, which imply an increase in generic omeprazole prescriptions after the OTC switch. One possible explanation for this is that the H2-receptor antagonist OTC was available for general sales and at the same strength instead of behind-the-counter and at a lower strength, thereby rendering the OTC H2-receptor antagonist a better substitute for the prescription product.

6.8.6 OTC Switch Financial Implications for Private and/or Government Purchasers

The above section discusses the possible total cost savings of an OTC switch on a societal level. However, whether public/private purchasers benefit most, or whether the patients themselves benefit depends on the purchasers' coverage

decisions. In an attempt to understand the financial implications that an OTC switch could have on the purchasers and patients, table 6-5 below models the four coverage scenarios:

- the payor continues to cover the prescription version of the drug and does not cover the OTC version of the drug
- the payor continues to cover the prescription version of the drug and does cover the OTC version of the drug
- the payor discontinues coverage of the prescription version of the drug and does not cover the OTC version of the drug
- the payor discontinues coverage of the prescription version of the drug and does cover the OTC version of the drug

The possible revenue and possible forgone revenue from co-payments also needs to be considered. Table 6-5 below simulates what the financial implications would have been for payors and patients in 2004 under each coverage scenario.

Table 6-5 The Costs of Prescription and/or OTC Omeprazole Coverage in 2004

	Coverage of prescription, no coverage of OTC	*Coverage of prescription and OTC*	*No coverage of prescription, coverage of OTC*	*No coverage of prescription, no coverage of OTC*
USA				
Prescription Costs	$1,341,219,000	$1,341,219,000	$0	$0
Revenue from prescription co-payments	$83,689,043	$83,689,043	$0	
OTC costs	$0	$180,151,000	$180,151,000	$0
Revenue from OTC co-pays	$0	$42,896,304	$42,896,304	$0
Total Public/Private Payor Costs	$1,257,529,957	$1,394,784,653	$137,254,696	$0
Total Cost Bore by Patients	$263,840,043	$126,585,347	$1,384,115,304	$1,521,370,000
	Coverage of prescription, no coverage of OTC	***Coverage of prescription and OTC***	***No coverage of prescription, coverage of OTC***	***No coverage of prescription, no coverage of OTC***
UK				
Prescription Costs	$180,053,000	$180,053,000	$0	$0
Revenue from prescription co-payments	$5,400,555	$5,400,555	$0	
OTC costs	$0	$682,000	$682,000	$0
Revenue from OTC co-pays	$0	$177,576	$177,576	$0
Total Public/Private Payor Costs	$174,652,445	$175,156,869	$504,424	$0
Total Cost Bore by Patients	$6,082,555	$5,578,131	$180,230,576	$180,735,000

* Assumes a 32% OTC Market Share, 22% Original Brand Market Share and 47% Generic Market Share, which is based on the average 2004 omeprazole market share distribution in the USA.
**Based on the average weighted purchased prices and volumes for OTC, original brand and generic omeprazole in the USA.
*** Based on the average 2004 generic drug co-pay of $10 and preferred drug co-pay of $21 and the assumption that there were only co-pays from private health plans, which represents 53% of the population and therefore prescriptions (Kaiser Family Foundation, 2004).
****Assuming the OTC co-pay equals the generics co-pay.
§ Assumes a .29% OTC Market Share, 15.75% Original Brand Market Share and 83.96% Generic Market Share, which is based on the average 2004 omeprazole market share distribution in the UK.
§§ Based on the average weighted purchased prices and volumes for OTC, original brand and generic omeprazole in the USA.
§§§ Based on a co-pay of 6pounds in the UK in 2004 and the assumption that only 15% of the patients actually paid this co-pay (Robinson, 2002).
§§§§ Assuming the OTC co-pay equals the generics co-pay.

Based on these figures, if USA purchasers had decided to cover prescription and OTC omeprazole in 2004 rather than just prescription omeprazole, they could have offset the $137,254,696 cost increase by shifting 9.47% of the total omeprazole market from generic omeprazole to OTC omeprazole.[73] These figures are derived from the following equations:

- Cost increase to USA purchasers = total public/private payor costs for coverage of prescription and OTC – total public/private payor costs for coverage of prescription but not OTC
- Cost increase to USA purchasers = $1,394,784,653 - $1,257,529,957 = $137,254,696
- Percentage Generic to OTC Shift that is Necessary in Order to Save $137,254,696 = (Cost increase to USA purchasers/ (weighted generic purchased price per DDD – weighted OTC purchased price per DDD)) / total number of DDDs in the USA omeprazole market
- Percentage Generic to OTC Shift that is Necessary in Order to Save $137,254,696 = ($137,252,696 / ($3.67 - $.69)) / 487,557,211 = 9.47%

This cost neutral policy would then save patients $137,254,696, while maintaining the same utilization level. The UK, on the other hand, could not offset an OTC coverage cost increase by shifting patients from generics to OTCs since generic omeprazole is less expensive than OTC omeprazole in the UK.

In order to illustrate the financial implications of coverage decisions, Table 6-5 above assumes a constant omeprazole market size and constant OTC, brand and generic market shares. Of course, in practice, patients' financial incentives would differ significantly under each coverage decision, which would in turn influence the OTC and prescription market shares. The following factors in Table 6-6 may influence patients' purchasing decisions:

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[73] This assumes that there is not a large increase in total omeprazole utilization as a result of the coverage decision. To offset the cost increases of any new patients entering into the market, a larger shift from prescription to OTC medicines would need to occur.

Table 6-6 A comparison of the Costs Associated with Obtaining Medicine in the USA and the UK

	Costs Associated with Obtaining the Prescription Drug		Costs Associated with Obtaining the OTC Drug	
	Direct Costs	Indirect Costs	Direct Costs	Indirect Costs
USA	• The cost of the prescription drug itself if uninsured or a copayment of at least $10* for 30 day supply if private insurance	• Physician visit full payment or copayment of $15** • Travel time to and from doctor's office and waiting time (usually during work hours) • Travel time to pick up drug at pharmacy • Time and financial costs of obtaining prescription renewal	• Cost of the OTC drug itself: roughly $21 for 30 day supply in the USA	• Travel time to pick up drug at pharmacy or food store; or no travel time if mail order
UK	• A copayment of roughly $11 for 90 day supply for about 15% of the population; no charge for the other 85% of the population	• No charge for physician visit. • Travel time to and from doctor's office and waiting time (usually during work hours) • Travel time to pick up drug at pharmacy • Time costs of obtaining prescription renewal	• Cost of the OTC drug itself: roughly $67 for 90 day supply in the USA***	• Travel time to pick up drug at pharmacy; possible conversation with the pharmacist

* In 2004, 84% of covered workers faced prescription drug co-pays for generics, preferred and non-preferred tiers. The average co-pay for generic drugs in the USA was $10; for preferred drugs was $21, and for non-preferred drugs was $33 (Kaiser Family Foundation, 2004).
** In 2004, 80% of people in all plans in the USA faced an office visit of at least $15 per visit (Kaiser Family Foundation, 2004).
***The $67 cost for a 90 day supply is based on the cost of 90 10mg pills, rather than the daily defined dosage comparison.
Source: The Author, using IMS Health data.

Additional factors may include:

- Whether they are aware of the drug's availability OTC
- Whether they want to consult with a physician
- Whether a physician would be willing to write them a prescription for the drug
- Whether the patient was already taking prescription omeprazole at the time of the switch, and therefore faces an inertia cost

In the case of the USA, the 15% of patients without health insurance (Kaiser State Health Facts, 2007) would have a much stronger incentive to purchase the drug over-the-counter since the direct costs of the physician's visit and the prescription

omeprazole drug itself would be significantly higher than the direct cost of the OTC omeprazole drug. For patients with insurance, one study found that eight out of twelve leading managed care organisations in the USA dropped omeprazole from their formularies[74] (Cohen, Paquette and Cairns, 2005). This finding is especially interesting, given that the FDA intended for OTC omeprazole to be only be used on a short-term basis, and therefore did not necessarily intend for health plans to treat it as a perfect substitute for prescription omeprazole. (Health plans may be less apt to remove a drug from their formulary if the OTC version is only available in a lower strength, as was the case in the UK.) Thus, in these cases, the patients would face similar costs to uninsured patients, except that they would only have to pay a co-payment for the doctor's visit, rather than the full cost. Thus, since the cost of prescription omeprazole in the USA was significantly higher than OTC omeprazole, and since there would be a physician visit co-payment and higher indirect costs associated with purchasing the prescription omeprazole, these patients would likely purchase the OTC omeprazole. Furthermore, where managed care organizations in the USA continued to cover the prescription omeprazole and do not cover the OTC version, the patient would still have a strong incentive to switch given the fact that the price of 30 days of OTC omeprazole in 2004 was $21, which was only $11 more than the average generic prescription co-pay, before taking into account all of the indirect costs. Thus, in the USA, many patients would have the incentive to switch, including a significant percentage of those with prescription coverage.

The story is very different in the UK, where the NHS continued to cover prescription omeprazole. Roughly 15% of patients would have faced a prescription co-pay of approximately 6 pounds for 90 days worth, but this is only a small fraction of the $67 cost (for 90 days worth) they would have faced if purchasing the OTC omeprazole directly (Robinson, 2002).[75] Moreover, in accordance with licensure regulations, the pharmacist would be unlikely to give the patient more than two packages at a time. Thus, instead of having the incentive to purchase the OTC omeprazole, new users in the UK who try the OTC omeprazole and who could have

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[74] None eliminated the entire PPI class from their formularies, although seven raised PPI copayments. This is somewhat different from the case of OTC loratadine, where all twelve organisations removed loratadine from their formularies and one third took all second generation antihistamines off their formulary.

[75] The $67 cost figure is for 90 days of 10mg pills. A patient taking the daily defined dosage of 20mg would face double the OTC cost.

safely self-medicated, would have a strong financial incentive to obtain the drug through the prescription market. This type of moral hazard leads to inefficient use of health system resources in that prescribing becomes driven by social consideration rather than out of medical necessity (Bond, 2004).

6.9 Discussion

In summary, in the USA, empirical evidence seems to suggest that OTC omeprazole is a substitute for prescription original brand and generic omeprazole, with the strongest substitution effect between the original brand and OTC products. The result was that in the USA, OTC omeprazole had achieved a 43% omeprazole market share by the end of this study period—2005q1. In the USA, there is also evidence of price competition between the OTC omeprazole market and the generic omeprazole market. Given the evidence that a large percentage of health plans dropped prescription omeprazole from their list of covered benefits, it could be that generic manufacturers responded to OTC entry with price decreases in hopes of remaining on health plans' formularies.

Conversely, in the UK, evidence of the generic omeprazole market share increasing after OTC entry while OTC omeprazole achieved less than a one percent market share suggests that OTC omeprazole does not act as a substitute for prescription omeprazole. Rather, evidence of the total omeprazole market size increasing—particularly the generic omeprazole market size—after OTC entry suggests that OTC omeprazole may be drawing new patients into the omeprazole market who eventually switch into the prescription omeprazole market. Thus, the OTC omeprazole market in the UK does not show signs of competing with the prescription omeprazole market.

In the USA, the weighted purchased OTC omeprazole price is significantly lower than the weighted purchased generic and original brand prices. However, the lowest generic price is lower than the lowest OTC omeprazole and original brand omeprazole price. Within the USA OTC omeprazole market, the larger package sizes offer better value than smaller package sizes, as does the mail order distribution channel, in comparison with the food stores and pharmacies.

In contrast, in the UK, both the weighted purchase OTC omeprazole price and the lowest available OTC omeprazole price are more than 50% higher than the weighted purchased and lowest available generic omeprazole prices.

Table 6-4 shows that if the OTC omeprazole market shares were to increase to 75%, purchasers in the USA could realise a 43% savings (assuming constant omeprazole prices and total omeprazole volume), while the UK would face a 29% increase in costs. Thus, at the current prices, purchasers in the USA may want to encourage more patients to switch to OTC omeprazole, assuming they continue to receive guidance from physicians. One study shows that many purchasers are forcing a shift from prescription to OTC omeprazole by dropping prescription omeprazole coverage. However, the result from this could either be that patients switch to a different (and often more expensive) prescription PPI (The Economic and Public Health Value of Self-Medication; AESGP) in order to avoid the OTC omeprazole costs, or that patients are forced to take on larger direct financial costs in the OTC market, which could reduce necessary utilization (and therefore threaten long term health). Thus, in order to ensure that necessary utilization does not decline, purchasers may want to consider covering OTC omeprazole, similarly to the Arkansas State Employee Benefits Division's experiment as a model. By introducing a copayment for OTC omeprazole and shifting ten percent of the total omeprazole market from generic to OTC omeprazole, purchasers could offset cost increases associated with the OTC coverage and still provide patients with cost savings as well (since the indirect costs associated with the OTC market are so much lower than the prescription market).[76]

One possible unintended effect that could result from payors covering OTC omeprazole in the USA is that new patients could enter into the omeprazole market, thereby increasing utilization. However, this would still be a pareto optimal move in that the health plans would likely save on physician visit costs, as discussed above, as well as the long term costs that could result from patients' GERD going untreated (such as Barret's esophageal, a pre-cancerous condition that can develop if GERD goes untreated). In addition, potential may exist for health plans to further offset increased utilization by switching an even larger percentage of patients from the prescription market to the OTC market.

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[76] There is some concern in the health care industry that managed care plans would find it too administratively difficult to cover OTC drugs due to possible reporting problems and ensuring that the consumer is the one actually using the drug (Sipkoff 2004). However, one study shows that about a third of health plans in the US already cover at least one OTC medicine (Sipkoff 2004). In addition, pilots such as the Arkansas State Employee Benefits Division demonstrate that it is possible (West 2006).

In addition to encouraging more patients to switch from prescription omeprazole to OTC omeprazole, regulators in the USA may want to consider measures that will stimulate more price competition amongst OTC products such as omeprazole. While the three-year exclusivity reward provides a good incentive for manufacturers to incur the necessary application costs (including the safety studies, etc.), it also deters competition, which results in high OTC prices. In theory, health plans should have the incentive to petition for the switch, in which case the OTC manufacturer would not receive the three-year exclusivity, and price competition in the OTC market could ensue.

However, the incentive for a health plan to apply for this switch may be stymied by the fact that the original brand manufacturer must agree with the petition. Assuming that the product has gone off-patent, it is unclear why the ultimate decision should lie with the original brand manufacturer (as long as safety studies are conducted by whichever party applies). Thus, the FDA may want to re-evaluate this bias toward the original brand manufacturer in favour of a more competitive OTC market by allowing purchasers and third party organisations to petition for switches of off-patent products without needing ultimate approval from the original brand manufacturer.

In the UK, coverage of OTC omeprazole could provide a huge financial incentive for patients to switch from the prescription market (and may also encourage price competition between prescription generic omeprazole and OTC omeprazole). However, this financial incentive would be inconsistent with the MHRA's intention for OTC omeprazole to be used by a different population of patients than prescription omeprazole. To ensure this, the behind-the-counter barrier prevents the prescription to OTC switch, as does the availability of OTC omeprazole in the 10mg strength rather than the daily defined dosage. Finally, the requirement that OTC omeprazole have a different brand name than prescription omeprazole likely prevents widespread recognition of the product by prescription omeprazole users.[77] Thus, it seems that the MHRA's dual goals of allowing low-risk patients to self-medicate while luring high-risk patients into the prescription omeprazole market

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[77] In this case, OTC omeprazole is not marketed by AstraZeneca, so would not likely be called Losec even if this regulation did not exist. However, if NHS policies encouraged more patients to use OTC omeprazole, then AstraZeneca may have petitioned for the switch in the UK, as they did in the US, in which case, marketing under the brand name may have helped to expand the omeprazole OTC market.

through OTC omeprazole is convoluted in that there are likely many low-risk patients who would switch into the prescription market due to financial incentives despite being capable of managing their risks themselves. Thus, if the MHRA's intention is to make omeprazole more widely available to patients, and to promote increased self-management of GERD to low risk patients, then it may want to consider approving omeprazole in the general sales category, as well as making the product more financial affordable to patients, either by providing NHS coverage, or by encouraging additional manufacturers to enter the market, which may drive down the OTC price.

The analysis pursued in the previous sections is not without limitations. First, there is only one product in this study, for which data was only available for a relatively small number of quarters following OTC entry. As a result, the results from the econometric model must be interpreted with some caution. Moreover, the single distribution channel and package size in the UK does not offer the opportunity to conduct panel data regressions, as this study was able to do in the USA. Nonetheless, this study was still able to utilize the data in such a way that reveals profound differences between the UK and USA OTC markets for the same drug. Moreover, the need to conduct a macroeconomic study on the implications of a chronic disease medicine OTC switch far outweighs the data limitations. The strength of this case, then, it that is has generated hypotheses in this relatively unstudied area of OTC switches, which further studies may build on with additional examples and data. Findings from this case study analysis may be generalisable to other chronic disease medicine OTC switches that are subject to similar regulations and health insurance coverage structures. Second, the pricing data in the USA is not able to capture fully the extent of discounts off list prices. These discounts off of list prices would only affect the original brand and generic products; the OTC product prices would not be subject to the same discount structure, but rather reflect the actual price that patients face.

6.10 Conclusion

In conclusion, OTC approvals are an increasing phenomena in both the USA and the UK, which are likely to increase in the years to come due to the manufacturers' financial incentives to profit in the OTC market, the purchasers' incentives to cost save through the OTC market and an increasing tendency for

patients to become more active in their health care management. The Association of the European Self-Medication Industry describes some of the challenges facing regulatory agencies and society in a recent statement: "While the value of self-care in general terms is widely recognized, a systematic debate on the skills needed to practice self-medication responsibly has not really taken place. This is in sharp contrast with the growing willingness of people to take more responsibility in moving from a passive patient to an active "self-care manager" (AESGP, 2004).

The OTC omeprazole example in the USA shows that in cases where government regulators are able to give autonomy to patients, and to the extent that patients have the financial incentive to purchase and manage their medication, competition may exist between the OTC and prescription markets, which may create significant room for cost savings to society, both for purchasers and patients. However, where there are multiple barriers, including both direct financial costs and indirect regulatory obstacles, such as in the case of the UK, the role of the OTC market is unclear and provides little opportunity for the targeted population of patients to become better self-care managers.

CHAPTER 7: POLICY CONSIDERATIONS AND CONCLUSION

7.1 Introduction

The previous chapters in this dissertation outlined and analyzed unstudied dimensions of competition within the omeprazole and paroxetine molecule markets in the USA, UK, France and Germany during the 2000q1-2005q1 period. Specifically, the main analytical chapters focused on: 1) competition amongst generics manufacturers in these molecule markets, 2) competition between the original brand and generics manufacturers and amongst generics within strength segments of these molecule markets and 3) competition between the prescription original brand manufacturer, prescription generics manufacturers and OTC manufacturers (whether original brand or generic). In light of the findings on the nature and degree of competition between these suppliers, these studies also estimated the implications for increased purchasing efficiency in these markets. This chapter begins by discussing the key empirical findings of these studies as well as their main contributions to the literature. In addition to the case-specific findings, there were two main cross-cutting themes that emerged from all three analyses—the role of segmented molecule markets as they relate to pharmaceutical competition and the role that product differentiation (in molecule markets) plays in preventing a Bertrand model of unbridled price competition. This chapter then provides an overview of the theoretical implications that these findings may have on industrial organization within pharmaceutical molecule markets, followed by a discussion on the empirical findings from each study.

A stakeholder analysis is then provided in order to shed light on the ways in which these findings may affect the pharmaceutical industry, payors, physicians, pharmacists and patients. Finally, this chapter concludes by discussing the limitations to the analyses followed by areas for further research.

7.2 Overview of Key Findings and Contributions to the Literature

The three studies on dimensions of competition within the off-patent omeprazole and paroxetine markets in the USA, the UK, Germany and France during the 2000q1-2005q1 period offer new perspectives that further the current

understanding of competition and purchasing efficiency within molecule markets. Below is an overview of these studies' key contributions to the literature.

7.2.1 An Overview of Empirical Findings

7.2.1.1 Price Competition amongst Generics

This study contributes to the literature on competition amongst generics with the following new findings:

- There are dominant generic manufacturers in the omeprazole and paroxetine markets that are not the first generic entrants, nor do they sell at the lowest price.[78]
- Price competition amongst generics seems imperfect in all four study countries, although there are more signs of competitive behaviour in the USA and the UK than in France and Germany. Although this finding has recently been identified in another study on competition amongst generics (Kanavos, Costa-Font and Seeley, 2008), this thesis has further contributed to the weak body of evidence by investigating the determinants of prices at presentation level separately for each of the four countries in order to arrive at a more detailed understanding of how the determinants of price competition differ across countries. This allows varying intercepts for each country, which reveals which determinants spur versus inhibit competition in each country. For example, the findings that product differentiation is associated with higher generic prices at the presentation level in the USA and the UK, but not Germany and France, and that the number of generic manufacturers does not drive lower generic prices in Germany and France, but does in the USA and the UK, is new to this literature.
- Finally, this is the first study of its kind to compare the distribution of generic prices within a molecule market across countries and to analyze the extent to which these countries take advantage of the lowest prices by purchasing efficiently. Previously, the only studies that have compared prices across countries have done so using weighted purchased prices and

[78] This phenomenon points to the possibility of preferential contracting between purchasers and manufacturer that is based on unknown criteria, such as the size or reputation of the manufacturers. For further discussion on this finding, see the section on areas for further research.

lowest prices. However, they have not looked at the standard deviation of prices in order to understand the full range of prices supplied within markets. Thus, this study has been able to show that generic prices may range significantly in the USA and Germany, despite the generics markets appearing more price competitive in the USA than Germany. Additionally, there are some countries, such as the UK, where the market appears relatively price competitive and prices range little. Thus, as shown by this study, in order to understand purchasing efficiency, policymakers must understand how to lower the full range of prices and how to purchase at the best available prices on the market.

7.2.1.2 Original Brand versus Generic Competition within Strength Segment Markets

The study on competition within strength segment markets is the only of its kind. To date, no other study has disaggregated competition within a molecule market by identifying each strength segment as a submarket that may exhibit a differing degree of original brand versus generic competition than other strength segments of the same molecule. Thus, all of the findings in this case contribute to the understanding of competition within molecule markets and purchasing efficiency. Some of the most significant findings include:

- The number of strength segments in the omeprazole and paroxetine markets, as well as their respective strength segment market shares differs across countries. Thus, the extent to which clinical need versus prescribing patterns versus industrial strategy determines the existence and relative market shares of strength segments is unclear.
- In all four study countries, original brand manufacturers of omeprazole and paroxetine applied the market harvesting strategy consistently across strength segments, regardless of the degree of generic entry or competition within that strength segment.
- The degree of generic entry and the ensuing degree of market share competition amongst original brand and generic manufacturers differed within strength segments of omeprazole and paroxetine in all four study countries. This finding of uneven generic penetration rates reveals

significant purchasing inefficiencies within the omeprazole and paroxetine molecule markets.

- Where generic entry did occur, the nature of competition amongst generics seems similar to that described in the case on competition amongst generics in this dissertation.
- The example of Paxil CR® in the USA is the first case study on the macroeconomic financial implications of a line-extension. Thus, the findings on the relatively large market share of Paxil CR® within the context of the broader molecule market, along with the relatively high prices (compared to the generic, immediate release versions) suggests that line-extensions may result in significant purchasing inefficiencies to the extent that their higher costs do not justify their therapeutic benefits.

7.2.1.3 Market Share Competition between the Prescription and OTC Omeprazole Markets

The study on market share competition between the prescription and OTC omeprazole markets in the USA and the UK is the first of its kind. To date, there have not been any macroeconomic studies analysing the competitive dynamics and purchasing efficiency within a molecule market following the OTC approval of a chronic disease medicine that continues to be available through the prescription channel. Moreover, this is a comparative study across countries, which offers insights to researchers and policymakers on the effects of contextual factors (such as OTC regulations and broader health system characteristics) on the degree of market share competition between OTC omeprazole and prescription omeprazole and the implications for purchasing efficiency. Some of the key findings from this case are as follows:

- The approval of OTC omeprazole resulted in OTC omeprazole comprising a large share of the market in the USA, compared to a tiny share of the market in the UK. Corresponding with these findings, it seems that OTC omeprazole directly competed for market share with prescription omeprazole in the USA, but not the UK.
- Since the price of OTC omeprazole was relatively low in the USA, the substitution from prescription omeprazole to OTC omeprazole resulted in

cost savings to society, although care needs to be taken to ensure that these costs do not fall disproportionately on patients.

- In the UK, OTC omeprazole was priced higher than prescription generic omeprazole, indicating that it would not increase purchasing efficiency to shift some of the omeprazole market from the prescription market to the OTC market.
- In conclusion, the differences in the USA and UK's OTC regulations as well as their differing health systems lead to the approval of OTC omeprazole having totally different purchasing efficiency implications in the two countries. Interestingly, in the case on competition amongst generics, one of the countries that seem to succeed in balancing regulations with free market incentives (in the interest of achieving price competition) is the UK. However, this study shows that in the case of OTC omeprazole, the structure of the UK's OTC behind-the-counter market offers little opportunity for an OTC switch to result in cost savings, oppositely from the USA. Thus, while the case on generic competition hails the UK as superior to the USA when it comes to achieving purchasing efficiencies, the case of OTC omeprazole shows that there are areas where the USA is superior to the UK in achieving this.

7.2.1.4 Pharmaceutical Competition and Segmented Molecule Markets within differing Regulatory Frameworks

The literature review shows that most studies that analyze competition within molecule markets standardize the different permutations of strengths, forms and package sizes into daily defined dosages in order to analyze market dynamics at the molecule level. However, in the process of assuming that products within molecule markets all engage in direct price competition, any existence of segmented, submarkets within these broader molecule markets is ignored. The one main exception to this is in the case of original brand versus generic products, which most studies have separated from each other in order to understand competitive dynamics. This dissertation is the first to explore the competitive dynamics within strength segment markets of a molecule and between OTC and prescription segments of a molecule within the context of countries' differing regulatory systems.

The findings show that the degree of competition between original brand and generic manufacturers differs significantly within strength segments of the study molecules in all study countries. In the omeprazole OTC switch case, findings show that the nature and degree of competition between the OTC omeprazole and prescription omeprazole markets differs due to countries' varying regulations and health system incentives. Thus, while standardising products' volumes into DDDs can facilitate direct volume comparisons within molecule markets, thereby enabling analysis on competition within broader molecule markets, it also may mask the layers of competition that exist within molecule markets. This dissertation therefore shows that it is difficult to define the market in which pharmaceutical competition occurs, and that in order to understand the various dimensions of pharmaceutical competition, molecule markets may be standardized and studied as one market, but must also be disaggregated and studied at this more detailed level.

This is seen in the case of omeprazole in the USA. The case on competition amongst generics shows that the original brand price in the USA was positively associated with generic prices in the USA during this time period. At the outset, this may lead to the conclusion that this is a sign of anticompetitive behaviour, as it is in Germany and France, where generic prices seem to float upwards over time, along with original brand prices. However, the case on OTC omeprazole in the USA shows that since OTC omeprazole was marketed by the original brand manufacturer, and since OTC omeprazole was priced relatively low, the evidence of the positive relationship between the original brand price and the generic prices in the USA may have been evidence of some degree of price competition between the OTC and generics market, rather than anticompetitive behaviour.

7.2.1.5 The Role of Product Differentiation within Molecule Markets

To the extent that segmented molecule markets represent manufacturers' attempts to prevent price or market share competition by carving their own, separate niches within the molecule market, this may be thought of as product differentiation. On a broader level, the cumulative effect of all types of product differentiation may be proxied by the number of presentations, including permutations of products with different forms, strength and package size that are manufactured by original brand and generic companies. Or, product differentiation may be studied in greater detail,

for instance by studying products that are differentiated by strength and line-extensions, and OTC versus prescription status respectively.

At the outset, one might expect that product differentiation would lead to higher expenditures in a market, reflecting the manufacturer's greater ability to profit as a result of having carved out these niches. This was the case in some instances. For example, the case on competition amongst generics reveals that the cumulative effect of all types of product differentiation within the generic market seems to be associated with higher generic prices in the USA and the UK. Moreover, when studying the strength segmented markets, it seems that across all four countries, original brand manufacturers experienced less generic entry in less common strength markets, and therefore lesser degrees of market share competition in these strength markets, which drove up expenditures since original brand prices remained higher than generic prices. However, the case of OTC omeprazole in the USA shows that some types of product differentiation actually have the potential to reduce overall costs. In this case, the original brand manufacturer was able to secure significantly higher omeprazole market share than it otherwise would have. However, from the payor perspective, the lower prices in the OTC market actually offered an opportunity to save on costs (assuming the total volume is held constant). Thus, these studies reveal that while manufacturers' attempts to product differentiate may sometimes have the effect of driving up expenditures for payors, there are instances where it may actually benefit payors.

7.2.2 Theoretical Implications for the Industrial Organization of Pharmaceutical Molecule Markets

7.2.2.1 The Perpetuation of Original Brand Manufacturers' Market Harvesting Strategy at Micro-levels

Recall that the literature has shown that original brand manufacturers usually pursue the market harvesting strategy, whereby they are able to retain brand loyal customers at high prices, while accepting the inevitable loss of the price sensitive portion of the market. This is an example of original brand manufacturers leveraging their products as Experience Goods, whereby a certain share of customers face inertia to switching to generics as a result of their positive experience with the original brand product. The study of competition between the original brand and generic products within strength segments of the omeprazole and paroxetine markets

in these countries shows that original brand manufacturers seem to employ the market harvesting strategy consistently across strength segments, despite the fact that strength segments seem to experience differing degrees of genericisation rates. The result is that in the relatively less common strength segment markets, original brand manufacturers are able to retain a relatively large share of the strength segment market, despite refusing to reduce their prices. Thus, by studying original brand versus generic competition at the ultra-micro strength level for the first time, a new way is revealed in which original brand manufacturers may be able to perpetuate the effectiveness of this market harvesting strategy, despite payors' increasing number of policies that seek to encourage generic substitution. That is, by entering into multiple strength segments, where the regulations allow and where demand is expected to be significant, original brand manufacturers may be able to continue marketing a number of their products post patent expiration where there has been little (and in some cases, no) generic entry. Thus, even where policymakers stipulate that generics must be substituted, original brand manufacturers are sometimes shielded from this occurrence due to the lack of generic substitutes available. In conclusion, this case offers a new dimension to the relatively simple market harvesting model, whereby original brand name products may be able to leverage both their brand names (as experience goods) across all markets as well as the fragmentation of the market itself in order to retain their space (and hence higher prices) within the broader molecule market.

7.2.2.2 Generic Price Competition in the Presence of Product Differentiation

Discussions throughout this thesis have used industrial organisation models of competition between homogeneous goods as a theoretical reference point. The Bertrand model of unbridled price competition appears to be the most applicable to competition amongst generics because unlike the Cournot model, it assumes fairly flat marginal costs, which is likely the case in the production of off-patent molecules such as omeprazole and paroxetine. However, the Bertrand model assumes a market in which there is perfect price competition, such that prices converge to marginal cost and market shares distribute evenly. In reality, evidence shows that this is not the case in generic molecule markets. Rather, as the study on competition amongst generics reveals, prices in most countries tend to range, along with market shares, which do not necessarily reflect relative price positions in the market. That is, the

lowest priced products do no necessarily achieve the highest market shares, and conversely, the manufacturers with the highest market shares are often not the lowest priced products in these countries' molecule markets. This therefore suggests that while some of the assumptions of the Bertrand model may apply to competition amongst generics, there are additional, more complicated factors that may soften competition. These more complicated factors may be classified as product differentiation, whereby generic manufacturers may have the ability to leverage unique product characteristics that allow them to carve out space within the market. Industrial organization models of competition within homogenous markets offer some examples of product differentiation, such as spatial models, whereby firms strategically choose their geographic locations, etc. However, none of the industrial organization product differentiation models seem to apply perfectly to these cases, as a result of the pharmaceutical industry's unique regulatory and market characteristics. Examples of product differentiation that are specific to these cases include: 1) characteristics that are unique to the dominant generic manufacturer, possibly reflecting the size of the manufacturer or the manufacturer's experience in certain disease categories, 2) strategically choosing which strength segments to enter into, and when, as well as engaging in nonlinear pricing (as well as possible, price discrimination) practices across strength segments, 3) packaging pills differently in the form of package sizes and/or forms (e.g. in this case, pills versus capsules versus tablets) and 4) fragmenting the demand side by marketing the product over-the-counter (after having achieved authorisation).

The case on OTC versus prescription competition in the omeprazole markets in the USA and the UK has shown that both original brand and generic manufactures may attempt to distinguish their products from those in the prescription market by applying for over-the-counter status. This may be another example of an original brand manufacturer's attempt to leverage its power as an Experience Good. Or, it may be another example of a way in which the generic manufacturer attempts to differentiate its product in order to compete with the other generic manufacturers.

In conclusion, industrial organization amongst generics of the same molecule seems Bertrand-like in that generics of the same molecule are relatively homogeneous products that face fairly flat marginal costs. However, evidence from these cases suggests that the nature of price competition amongst generic pharmaceuticals of the same molecule may differ from the Bertrand model due to

pharmaceutical manufacturers' unique abilities to product differentiate. As a result, these studies provide evidence that supports a new theory about competition amongst generics, which is that in the process of product differentiation, generic manufacturers may be able to distinguish their products in such a way where they are no longer perfectly homogeneous, resulting in a Bertrand-like model of competition between "homogeneous" goods, where product differentiation results in an equilibrium of ranging prices and market shares.

7.3 Stakeholder Analysis

The findings on the nature of competition within these molecule markets and how it differs across these countries' regulatory environments may have significant implications for pharmaceutical manufacturers' abilities to profit. The stakeholder analysis therefore begins with a discussion on the implications of these findings for the industry during this time period, separating out the original brand and generic manufacturers. It then considers the implications that each study's findings may have on purchasing efficiency for payors. As part of the stakeholder analysis for payors, this section also reviews potential policy options in light of each study's findings. Finally, the stakeholder analysis acknowledges the implications that these findings and policy options may have on physicians, pharmacists and patients.

7.3.1 Implications for Original Brand Manufacturers: Competition and the Potential to Profit

7.3.1.1 The implication of Competition within Strength Segment Markets on Original Brand Manufacturers

The evidence in the study on competition within strength segments shows that in most cases, the number of strengths and the respective strength market shares did not change significantly before and after patent expiration. Moreover, the original brand manufacturers pursued the market harvesting strategy consistently across strength segment markets by either keeping constant, or increasing, their prices. Thus, original brand manufacturers seemed to treat different strength products as though they were part of the same broader market of competition. However, a closer look at the data revealed that the generic penetration, and therefore the original brand market shares, varied significantly within strength segments of the same molecule.

Specifically, this study found that in nearly all cases, generic manufacturers entered into the strength markets with the largest market share (which was the daily defined dosage for both molecules across all four study countries). In some cases, generic manufacturers simultaneously entered into other strength segment markets, while in other cases, generic manufacturers entered into other strength segment markets in a more step-wise fashion. The results from the econometric models showed that the strength market share, the number of generic competitors and the ratio of original brand to generic prices were all negative predictors of the original brand market shares. This implies that original brand manufacturers were able to retain larger shares of the strength segment markets in less common markets, where generic entry and overall competition from generics was less, thereby profiting more in these markets (since their prices remained high). Notably, in some cases, there were as few as one or even zero generics in the strength markets, allowing the original brand manufacturers to retain the majority of the strength segment market after patent expiration.

Furthermore, in the case of Paxil CR® in the USA, the original brand manufacturer was able to retain as much as a third of the total molecule market by introducing this line extension shortly before the immediate release version lost patent. This strategy seemed particularly successful in this case since all of the immediate release paroxetine strength segment markets in the USA experienced intense competition from generics shortly after patent expiration (unlike the less common strength segment markets in most of the study countries' omeprazole and paroxetine strength segment markets during this study period), which drastically reduced the original brand market shares in these immediate release strength segment markets.

Thus, to the extent that it is in the power of original brand manufacturers to do so, segmenting a molecule market into various strengths and forms seems to be a profitable strategy that enables the original brand manufacturer to retain a larger share of the overall molecule market at relatively high prices post patent expiry.

7.3.1.2 The Implication of an OTC switch on Original Brand Manufacturers

Besides entering into less common strength markets, these studies reveal that another way in which original brand manufacturers of chronic disease medicines may retain a larger share of the market after patent expiration is by applying for an OTC

switch, where a medicine retains its status as both a prescription and OTC medicine. However, the extent to which an OTC product is able to achieve a large share of the broader molecule market is dependent on the country's OTC regulations as well as the incentives patients face under the public or private health insurance system.

Original brand manufacturers' incentives to apply for an OTC switch depend on a number of factors, including the costs of applying for approval and the expected profit in the OTC market, which is largely dependent on the expected OTC price and the potential OTC market size once approval for marketing is achieved. In the USA, any manufacturer or private payor may initiate a switch. However, the FDA defers to the original brand manufacturer before making the final decision, regardless of which organization made the actual application. In addition, OTC regulations in the USA require that the applicant conduct OTC use safety studies, which may be costly. The reward, however, may be a three year exclusivity period in the OTC market, allowing the applicant of the OTC-switched medicine to deter direct price or market share competition in the OTC market.

The OTC omeprazole switch case in the USA is an example of where, within the context of the right regulatory and health system environment, an original brand manufacturer may use the OTC switch route as a strategy to retain a significantly higher market share than it otherwise would have. Evidence seems to suggest that although 20mg (the DDD) OTC omeprazole was initially approved for patients to use only on a short term basis, in practice, the OTC version may have acted as a substitute with prescription original brand and prescription generic omeprazole, largely due to patients' financial incentives to purchase through the OTC market. The result was that the original brand manufacturer's OTC omeprazole, which retained the same brand name as its well-known prescription product, Prilosec®, was able to achieve a 43% market share by 2005q1. Although it may seem counterintuitive that the original brand manufacturer would introduce an OTC product that would compete for market share with its own prescription product, it is likely that the original brand manufacturer's prescription product would have lost the majority of its market share to competition from prescription generics had it not introduced the OTC product. Thus, in the USA, applying for an OTC switch has the potential to be a very profitable strategy for original brand manufacturers.

In contrast, evidence from the UK shows that the omeprazole OTC switch probably would not have been a profitable strategy for the original brand

manufacturer. In this case, a generic manufacture applied for the switch. However, instead of having the 20mg DDD version approved, as it was in the USA, the MHRA approved a lower dose, 10mg version, which was also intended (similarly to the USA) for patients to try on a short-term basis. In addition, OTC omeprazole was only approved for behind-the-counter status in the UK, which requires that pharmacists act as a intermediary for patients who want to purchase the drug. Notably, many OTC products in the UK are required to be marketed under different names than their branded equivalents, so that patients do not confuse them as direct substitutes. Finally, because the majority of patients do not face co-pays under the NHS (and those who do face lower prescription co-pay costs than the direct OTC costs), patients do not have the financial incentive to purchase OTC products on a long-term basis like they may in the USA. The result of all of these factors was that the original brand manufacturer did not apply for an OTC omeprazole switch in the UK. Rather, a generic manufacturer applied, and achieved less than a one percent market share (compared to the 43% in the USA). This suggests that the OTC omeprazole product in the UK did not compete for market share with the prescription omeprazole products. Instead, the prescription generic omeprazole market continued to increase after OTC entry, both in absolute size and as a percentage of the total molecule market. OTC omeprazole in the UK may therefore have been drawing new patients into the omeprazole market who eventually switched from the OTC version to the prescription generic version. Regardless of whether the new prescription generic users were coming from the OTC market or not, the evidence strongly suggests that an original brand manufacturer would be unlikely to profit significantly from receiving approval to market its chronic disease medicine in the behind-the-counter OTC market.

In conclusion, findings from these studies reveal that there are some ways in which original brand manufacturers may be able to retain a larger share of the total molecule market that is relatively consistent across countries, such as by entering into strength segment markets that have a relatively low strength market share and have therefore not experienced comparable levels of competition from generic equivalents, in comparison with the DDD strength segment. However, other original brand manufacturers' strategies may vary across countries, depending on the regulatory environment and health system characteristics. For example, the original brand manufacturer was able to receive approval for a paroxetine line extension and

subsequently, retain a large share of the market. However, there was not evidence of this line extension in the other study countries during this time period. In addition, the original brand manufacturer of omeprazole was able to retain a large share of the molecule market in the USA by receiving approval to market its OTC version. Evidence of a generic manufacturer receiving omeprazole OTC approval as a behind-the-counter product shows, however, that this strategy probably would not have been as successful for the original brand manufacturer in the context of the UK regulatory environment and health care system. Thus, original brand manufacturers may have the opportunity to retain a larger share of the molecule market after patent expiration than the simple market harvesting strategy may imply, although the extent to which certain opportunities exist differs across countries.

7.3.2 Implications for Generic Manufacturers: Competition and the Potential to Profit

For generic manufacturers, it seems that competition is more complicated than theory might predict in a market of homogenous goods. Firstly, the evidence of a preferential generic manufacturer that is not necessarily based on them having the lowest price or being the first entrant reveals that some generic manufacturers may have significantly more market power than others. It is very interesting that in these two molecule markets across these study countries, this pattern emerged, regardless of the differing regulatory frameworks. Moreover, in Germany the dominant generic manufacturer was associated with negative generic prices.

Other findings also emerged that suggest limitations to competition amongst generics, especially in Germany and France, where there was a positive relationship between the number of generic manufacturers and generic prices. In general, the omeprazole and paroxetine generics markets in the USA and UK appeared to experience larger degrees of price competition. However, even in these markets, there was evidence of product differentiation that impacted positively on generic prices. In addition, evidence that generic prices may have been linked to originator brand prices in the USA, France and Germany causes increasing reason for concern.

Although generic manufacturers were consistent in entering into the strength segment with the largest market share (the DDD market, in these cases) first and foremost, their decisions to enter into the other strength segment markets varied, which further implies that generic manufacturers market strategically rather than just

engaging in unbridled price competition across all sub-markets. Where generic penetration did occur within strength segment markets, competition amongst generics seemed to intensify with generic entry in most markets. In the case of the line extension, Paxil CR®, generics were shut out of a third of the molecule market because the patent for Paxil CR® had not yet expired. In this case, generic manufacturers did not have the opportunity to compete in a large share of the market, so were not able to optimize any diversification strategies.

Finally, in addition to Paxil CR®, certain other exogenous factors, such as whether the original brand manufacturer applies for the OTC switch in the USA, seem capable of significantly undercutting the generics market. In the USA, there was evidence that OTC omeprazole acted as both a substitute for prescription original brand and prescription generic omeprazole, reaching a 43% market share. There was also evidence that after the OTC switch, OTC price decreases were associated with generic price decreases, which may have represented an attempt by prescription generic manufacturers to prevent health plans from dropping coverage of their products.

Thus, it seems that the FDA's approval of original brand OTC omeprazole significantly affected the profitability of many prescription generic omeprazole manufacturers. In theory, generic manufacturers could prevent such a loss by pre-empting the original brand manufacturer's OTC switch application with their own OTC switch application. However, there may be barriers to entry in the USA OTC market, such as costly safety studies on OTC use, that discourage generic manufacturers from applying. Even if the studies do not discourage generic manufacturers from applying, the incentive for a generic manufacturer to apply for an OTC switch for a chronic disease medicine may be stymied by the fact that the FDA ultimately defers to the original brand manufacturer before approving such a switch.

In contrast with the USA, evidence indicates that the OTC omeprazole switch may have positively impacted generic omeprazole manufacturers. Firstly, the manufacturer that received authorisation to market the OTC omeprazole behind-the-counter product was a generic manufacturer. Although this generic manufacturer achieved less than a one percent market share, the high price of the OTC omeprazole product suggests that it may still have been a profitable endeavour for this generic manufacturer. For prescription generic manufacturers, the prescription generic

market size (in absolute terms) and the prescription generic market share (as a percentage of the total molecule market) both increased significantly after the OTC switch approval. This indicates that either the OTC switch approval actually increased the prescription generic market size by funnelling patients into the prescription market, or that the prescription generic market size increased for reasons that were unrelated to the OTC switch. Either way, the omeprazole OTC switch in the UK did not appear to threaten the profitability of generic manufacturers in the omeprazole market the way it did in the USA market.

In conclusion, it seems that generic manufacturers have their own strategies that help moderate or altogether eliminate the extent of unbridled price competition. A clear pattern of a dominant generic manufacturer emerged in all of these product markets, across all countries. For the remaining generic manufacturers, such profit-maximizing strategies differ across regulatory environments, and may include product differentiation, piggy-backing off original brand prices and strategic entry into different strength segments. Moreover, a generic manufacturer in the UK attempted to carve out its own niche in the omeprazole market by marketing OTC omeprazole. Despite these strategies, there was evidence that in some cases, original brand manufacturers' successful attempts to product differentiate may have significantly threatened generic manufacturers, as was the case with Paxil CR® and Prilosec OTC in the USA. Thus, countries' differing regulatory environments surrounding generic pricing and reimbursement, and marketing authorization of specialised products, may result in the generic industry profiting significantly more in some markets than in others.

7.3.3 Implications for Payors: Purchasing Efficiency and Policy Recommendations

7.3.3.1 Implications for Generic Purchasing Efficiency on the Supply Side

By focusing on the supply-side determinants of generic prices, policymakers could shift the entire range of generic prices downwards, thereby achieving increased purchasing efficiency. The econometric model on the determinants of generic prices offers insight on some of these levers that policymakers could pull. Specifically, evidence that the number of generic companies was not associated with lower generic prices in Germany and France casts doubt on whether the generic pricing and reimbursement policies during this time period were conducive to competition

amongst generics. Moreover, the positive relationship between the original brand price and generic prices, during a time when the original brand prices actually increased (as opposed to the positive relationship indicating simultaneous original brand and generic price decreases), also calls into question the competitiveness of the generics market.

Meanwhile, although the generics markets in the USA and the UK appear more price competitive than in France and Germany, evidence of product differentiation driving generic price increases in the USA and the UK suggests a need for policies that may further improve generics price competition in these markets as well. Finally, the presence of a dominant generic manufacturer that does not sell at one of the lowest prices raises a red flag for policymakers in all four study countries, especially Germany, where there is a positive association between the dominant generic manufacturer's market share and the rest of the generic prices in the molecule market.

7.3.3.1.1 Supply-Side Generic Policy Considerations to Increase Purchasing Efficiency

To increase the degree of price competition in generic markets, policymakers during this time period had the option to revise their supply-side generic policies in the following manner:

- In Germany, the reference price system may have been largely responsible for an increase in the number of generic manufacturers not resulting in lower generics prices. This would be due to the disincentive that manufacturers had in lowering prices, and the outcome of generic prices floating upwards with original brand pries. The German government could have abolished the reference price system in favour of freer market incentives, such as allowing distribution chain discounts, while implementing a percentage clawback system, as in the UK (see Appendix A). Alternatively, the Germany government could have devised broader pharmaceutical policies in a way that incentivised lower generic prices, such as by retaining the reference price system, but deregulating the distribution chain mark-ups to incentivise lower cost drug dispensing.

- In France, abolishing the price capping system in favour of freer market incentives could potentially have addressed the anticompetitive signs in the generics market. It is not surprising that generic prices increased with original brand prices when the price cap was effectively treated by generic manufacturers as a percentage price peg. Moreover, since they had pegged their prices to the original brand prices, it was also not surprising that an increase in the number of generic manufacturers did not reduce generic prices.
- Finally, in all four study countries, policymakers may want to address the presence of a dominant generic manufacturer that is not price competitive. In order to do so, additional information would be needed about what factors make the market conducive to the presence of this market power.[79]

7.3.3.2 Implications for Generics Purchasing Efficiency on the Demand Side

In addition to considering supply-side policy options that influence generic prices, policymakers may want to consider demand-side options that improve the degree to which the lowest available prices are actually purchased. Findings from the study on generic competition show that the USA exhibited the largest range of prices in the omeprazole and paroxetine markets, thereby having some of the highest and lowest available prices. Meanwhile, the UK exhibited relative low prices, while Germany exhibited some of the highest prices and France's price lied in the middle.

In terms of the actual prices paid by health insurance, Germany had the highest prices. The purchased prices in the USA were low in comparison with the other countries, although the USA's high purchased price to lowest price ratios reflect relatively weak purchasing efficiency. France had a good purchased price to lowest price ratio, although this was more a reflection of the small standard deviation of prices than strong purchasing policies. The UK was the one country that exhibited strong purchased price to lowest price ratios, as well as low prices in absolute terms.

Regardless of the countries' differing degrees of demand-side purchasing efficiency, there was significant room for increased purchasing efficiency in all four study countries, resulting in significant gains to payors. It is important to note that the high degree of savings in the USA and Germany reflects both their weaker

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[79] For further discussion on this, see the Further Research section.

purchased price to lowest price ratios as well as their larger market size and relatively early patent expirations, in comparison with France, which did not experience generic entry until later in the study period.

7.3.3.2.1 Demand-Side Generic Policy Considerations to Increase Purchasing Efficiency

To increase the degree of purchasing efficiency in generic markets, a number of policy options are available, as follows:

- In Germany, the purchased price to lowest price ratios of 1.41 and 1.28 for omeprazole and paroxetine respectively were likely reflective of fact that the reference pricing system set the generic price reimbursement equal to the lowest third price in the market. Thus, the calculation of the reimbursement price under the reference price system could have been revised to reflect the lower prices, for example, by reimbursing the lowest price within each strength segment. However, care would need to be taken in order to ensure that this didn't further disincentive generic manufacturers from reducing prices, the way research shows it may have in Canada (Hollis, 2005), where the reference price was adjusted to the lowest price.
- In France, the fact that the price cap acted as a price floor resulted in little distribution in prices. In this case, there was less opportunity for improved demand-side purchasing policies to achieve cost savings. Thus, it would have been necessary to first improve the supply-side policies in order to see how effective the demand-side really is within the context of Frances' regulatory schemes.
- The UK seemed relatively successful at achieving demand-side purchasing efficiency. One way in which the UK could have improved its purchasing efficiency was by changing the equation it used to calculate the reimbursed generic price, so that greater weight was given to lower available prices. However, care would have needed to be taken so that this did not result in a disincentive for all of the generic manufacturers to lower prices, as may occur in reference price systems. The UK also could have achieved greater purchasing efficiency by increasing the percentage of the discount that it claws back from the pharmacies. However, care

would also need to be taken here in order to ensure that the percentage clawback balances the incentive for pharmacists to negotiate lower generic prices with the need for improved purchasing efficiency. One way to improve this clawback system may be to increase the clawback percentage for chain pharmacies since there is speculation that chain pharmacies are retaining a larger percentage of their discounts under the current system than individual pharmacies (Kanavos, 2007).

- Finally, in the USA, the relatively weak purchased price to lowest price ratios may be reflective of pricing transparency problems, or pricing accessibility problems, whereby there are preferential arrangements between purchasers and manufacturers, pointing at discount practices. One policy option toward addressing these pricing ambiguities is that greater price transparency be legislated. Again though, care would need to be taken in order to ensure that great pricing transparency does not result in manufacturers being less willing to offer rebates.

7.3.3.3 Implications for Purchasing Efficiency within Strength Markets

The findings from this study on competition within strength markets show that original brand manufacturers apply their marketing harvesting strategy by keeping flat or increasing their prices consistently across strength segments. Where generic entry occurs in strength segments, evidence shows that increases in the number of generic manufacturers and an increase in the original brand to generic price ratio are associated with a decrease in the original brand market shares. Strength segment markets that are less common are also likely to retain larger original brand market shares. In most of this study's molecule markets, an increase in the number of generic entrants is associated with a decrease in generic prices themselves. Notably, consistent with the findings in the study on competition amongst generics, this relationship does not seem to apply to both the omeprazole and paroxetine molecule markets in Germany and France, which may be a reflection of the anticompetitive effects of Germany's reference price scheme and France's generic price caps. Regardless of whether additional generic competitors drive down generic prices, two constant findings across countries were that there were fewer generic entrants in less common strength segments and original brand market shares remained higher in these strength segments.

Savings that would have accrued to the study countries if generic penetration within each strength segment market was equal to the strength segment market with the highest generic penetration were found to be significant in Chapter 5. These estimated savings were conservative estimates since strength segment markets without any generic entry were excluded from the analysis on the grounds that the patents may not have expired yet in these strength segment markets. Interestingly, in the omeprazole market in the USA and the paroxetine market in the UK, increasing the generic penetration rate would have actually cost payors more money since the original brand prices were lower in these strength segment markets, which, in the USA, was reflective of the original brand omeprazole OTC switch. Thus, policymakers need to carefully examine the original brand and generic price differences before encouraging further generic substitution. Assuming that generic prices are in fact lower than original brand prices, policymakers may have implemented the following policies.

7.3.3.3.1 Policy Considerations to Increase Generic Penetration within Strength Segment Markets

- In order to improve generic penetration rates within strength segments, policymakers would first need to ensure that the approval process facilitates generic entry into additional strength segments. One way to do this may be to allow generic manufacturers to apply for the license to market in multiple strengths within only one application fee. Additionally, where generic manufacturers want to enter into strength segments in a step-wise fashion, which would require separate applications, regulators could reduce the fees for subsequent applications and may want to fast-track this approval process.
- On the demand side, payors may want to mandate or provide financial incentives for pharmacists to substitute generics in every strength segment where generics exist. By increasing generic penetration, the hope would be that an increase in the generic market size would also encourage further generic entry.

7.3.3.4 Nonlinear Pricing and its Implication for Purchasing Efficiency

Evidence from the omeprazole and paroxetine markets in the study countries reveals a pattern of nonlinear pricing across strength categories. That is, in some cases, products of differing strengths are priced similarly on a per pill basis. In other cases, such as in the USA, lower strength products are priced above higher strength products, which indicate the possibility of price discrimination. Moreover, the fact that the degree of competition differs within strength segment markets suggests that these nonlinear prices may in some cases be inflated, rather than the result of competitive market forces.

As a result, some health plans in the USA have promoted pill splitting in order to save on costs. In addition, individuals may initiate the practice of pill splitting in order to save directly on costs if they are uninsured, or to save on the costs of co-pays if they are insured. This study modelled the potential cost savings to society from splitting pills and found that in certain cases, such as splitting 20mg paroxetine in the USA, savings of as much as 6% (representing nearly $6 billion dollars) of total paroxetine expenditures were possible. However, in other cases, such as splitting 40mg pills instead of purchasing 20mg pills, estimates show that in many cases, countries would have actually spent more than the status quo of patients purchasing the actual desired dosage. This reveals that despite evidence of nonlinear pricing, pill splitting cannot be assumed to be cost saving to society in all cases (although it may still be cost saving to patients who face standard monthly co-pays).

7.3.3.4.1 Policy Considerations for Using Pill Splitting Programs to Increase Purchasing Efficiency

- Formalised pill splitting programs would require the collaboration of physicians, pharmacists and patients in order to ensure safety. First and foremost, both physicians and pharmacists would need to have access to reliable information on which types of medicines are conducive to safe and effective pill splitting programs. Physicians would then need to be willing to prescribe in accordance with the scheme (i.e. prescribing half the number of pills at twice the desired dosage), where clinically appropriate. The next step would be for pharmacists to confirm the safety of splitting that pill and to help determine the best way for that patient to actually split the pill. Either pharmacists could split the pills themselves

or they could help educate patients on how they could split pills. This would likely require increased pharmacists payments in order to compensate them for their time spent pill splitting and/or educating patients. Finally, in addition to physicians and pharmacists understanding which medications can be safely split, they would also need to understand which populations of people are capable of participating in pill splitting programs. For example, middle-aged educated people would be more likely to successfully split pills themselves than seniors who may not have steady hands, clear vision or be in a clear mental state.

- Once these safety measures of engaging physicians and pharmacists are put into place, policymakers must carefully study pricing data in order to determine which strength market segments would result in savings from pill splitting as opposed to increased costs. In addition, policymakers would need to ensure that where individuals attempt to engage in the practice of pill splitting independently, their individual financial incentives are not in contrast with that of the payors'. In other words, it is possible that individuals and physicians may collaborate to split pills across strengths segments in such a way that patients save on co-pay costs, but the health plan pays more. To prevent this purchasing inefficiency, health plans could inform physicians and patients that were they are engaging in pill splitting schemes, they should notify health plans in the event that the health plan may be able to alter the patients' co-pays so that patients may save the same amount without pill splitting.[80]
- Finally, another unintended consequence of splitting pills on a large-scale basis is that it may incentivize manufacturers to alter their pricing patterns so that it's not beneficial for payors to engage in pill splitting practices. Manufacturers' abilities to respond in this way would depend on how competitive the strength segments are, and the extent to which they are price setters in the market. Thus, payors would need to be aware of manufacturers' possible responses and would need to carefully monitor

[80] Under this scenario, health plans would need to ensure that they are able to detect the occurrence of pill splitting without encouraging new practices of pill splitting in clinically inappropriate cases.

the data in order to ensure that overall costs do not increase as a result of pill splitting.

7.3.3.5 Line Extensions and their implication for Purchasing Efficiency

The evidence on Paxil CR® shows that where an original brand manufacturer has introduced a line-extension of a product shortly before patent expiry, and where this line-extension acts as a substitute with the original product, payors may face millions of dollars in increased costs on an annual basis. In the case of Paxil CR®, the total spending on paroxetine in the USA was as much as 40% higher than it would have been, had Paxil CR® not been introduced. In order to justify this degree of cost increase, the additional therapeutic benefits of the line-extension product over the original product would need to be substantial. While the degree of cost-effectiveness my be debatable in some cases, evidence on Paxil CR® suggests that this controlled-release version of paroxetine may not be worthy of its price premium, which was roughly 3 times its 20mg immediate release substitute.

7.3.3.5.1 Policy Considerations for Preventing the Possible Purchasing Inefficiencies of Line-Extensions

Before automatically covering line-extensions at their available price, purchasers in the USA may want to be more discernable about these purchases by basing their coverage decisions on cost-effective criteria. This could mean not covering Paxil CR® if a comprehensive review of its comparative therapeutic benefits shows that it is not therapeutically superior to the immediate release version. Alternatively, if there is evidence of this line extension's therapeutic superiority, then payors may want to determine how much more they are willing to pay for this marginal benefit and set the price accordingly. During this study period, Paxil CR® had only been introduced in the USA. However, were it to receive marketing authorisation in these other study countries, the purchasing efficiency implications would likely differ than in the case of the USA. In Germany, their reference pricing scheme would have only reimbursed this controlled-release line-extension at the lowest price of the immediate release version, assuming that policymakers would have placed this line-extension product into the same reference price group as its immediate release version. However, in this case, policymakers in Germany would need to take care that they are not eliminating access to a product if it offers

therapeutic benefits above its comparators. Under France's pharmaceutical pricing and reimbursement system, the price negotiation agreement between the original brand manufacturers and CEPS may be more likely to achieve the balance of preserving access while not overpaying, although even in France, the lack of explicit cost-effectiveness criteria may hinder this balance from being achieved. The UK is the only country in this study where their system of formalised NICE evaluations may have resulted in efficient purchasing strategies and unlikely coverage of this line extension.

7.3.3.6 The Financial Implications of the OTC Omeprazole Switch in the USA and the UK

The findings from this study reveal that the original brand version of OTC omeprazole in the USA, called Prilosec OTC, competed for market share with the prescription original brand and prescription generic omeprazole products. As described in the above section *on the implication of an OTC switch for original brand manufacturers*, the result was that Prilosec OTC had achieved 43% of the omeprazole molecule market by the end of this study period. There was also evidence of some degree of price competition between the prescription generic omeprazole manufacturers and the OTC omeprazole manufacturer, which may have reflected generic manufacturers' attempts to stay on health plans' lists of covered drugs.

In contrast, in the UK, the generic version of OTC omeprazole, called Zanprol, achieved less than a one percent market share by the end of this study period. In this case, evidence showed that instead of competing with the prescription market for omeprazole market share, it is possible that the availability of OTC omeprazole as a behind-the-counter product in the UK may have resulted in patients funnelling into the prescription market, resulting in an increased overall size of the prescription—in particular, the generic—omeprazole market.

On prices, evidence shows that the weighted purchased price for OTC omeprazole was significantly lower in the USA than the weighted purchased price for prescription original brand or generic omeprazole, although the lowest prescription omeprazole generic price was lower than the weighted purchased OTC omeprazole price. This indicates that in practice, OTC omeprazole was better value than prescription omeprazole for society, although there was potential for the

prescription generic omeprazole market to be better value than the OTC omeprazole market. Moreover, larger package sizes and the mail order distribution channel (in comparison with food stores and retail pharmacies) were associated with lower OTC omeprazole prices in the USA. In the UK, the weighted purchased OTC omeprazole price was more than 50% higher than the weighted purchased prescription generic omeprazole price, pointing toward better value for payors in the prescription market in this case.

Because the OTC original brand omeprazole market offered better value than the prescription generic omeprazole market in the USA, estimates show that an increase in the OTC omeprazole market share to 75% would have resulted in a 43% cost savings in the USA; in the UK, this scenario would have resulted in a cost increase of 29%.

The substantial difference in OTC omeprazole market shares in the USA and the UK and the OTC omeprazole price versus prescription omeprazole prices in the USA and the UK were likely a result of both regulatory factors and the countries' respective health systems, which resulted in differing financial incentives for patients. Below is a list of these regulatory and health care system differences, as they related to OTC omeprazole in the USA and the UK:

- OTC omeprazole was approved in the 20mg DDD strength in the USA, while it was approved in the 10mg strength in the UK. This approval of a lower strength in the UK was part of the MHRA's intention that the OTC omeprazole product only be marketed to patients with relatively less severe symptoms that required a short-term omeprazole regime. The remainder of patients who needed the prescription on a long-term basis were intended to purchase the product under the guidance of a physician in the prescription market.
- In order to ensure that patients safely adhere to the OTC omeprazole guidelines, OTC omeprazole was approved for behind-the-counter status in the UK, which resulted in it only being available for purchase under the supervision of pharmacists, in comparison with the general sales OTC category, through which OTC medicines may be available in the UK on the shelves of pharmacies and food stores (without the supervision of pharmacists). In contrast, an OTC product in the USA only has one

category, which is the equivalent of the general sales category in the UK. As a result, there were no checks and balances on the purchase of OTC omeprazole in the USA like there were in the UK, although the USA version was also only intended for patients who needed to purchase the medicine on a short-term basis. Meanwhile, the USA has its own safety measure, whereby actual OTC use studies must be conducted by the applicant prior to the OTC approval; the UK does not require such studies.

- The FDA allows OTC products to retain the original brand name where the original brand manufacturer has marketed or licensed the marketing for the product. In the UK, the MHRA stipulates that the product be marketed under a different name than the prescription version, regardless of whether the manufacturer is the original brand or a generic manufacturer. As a result, patients in the UK may be less likely to know that the product is available OTC.
- In lieu of conducting the OTC omeprazole actual use studies in the USA, the original brand manufacturer of OTC omeprazole was granted a three-year exclusivity period in the USA, during which manufacturers were not permitted to enter the market. The generic manufacturer of OTC omeprazole in the UK was not granted an exclusivity period, although regulations stipulated that any information used from its application not be used in the event of applications from other manufacturers, which may have discouraged entry to some degree.
- Patients in the USA had larger financial incentives to purchase omeprazole OTC than patients in the UK. This was due to the fact that a larger percentage of the population in the USA faced prescription co-payments as well as the roughly 15 percent uninsured population in the USA, the delisting of omeprazole by some health plans in the USA and high indirect costs to obtaining prescription medications in the USA, such as physician office co-payments.

7.3.3.6.1 Policy Considerations for Using the OTC Omeprazole Switches to Increase Purchasing Efficiency in the USA and the UK

In line with the findings from this study and the above regulatory differences, policymakers may want to consider the following measures:

- Given the lower weighted purchased prices in the OTC omeprazole market than the prescription market in the USA during this time period, payors could have increased purchasing efficiency by adding OTC omeprazole to its list of covered benefits, similarly to the way Arkansas State Employee Benefits Division did. Notably, this study found that by shifting ten percent of the total omeprazole market from prescription generic omeprazole to OTC omeprazole, and by introducing a copayment for OTC omeprazole, both third party purchasers and patients could have realized cost savings (since, for patients in the USA, the indirect costs of obtaining an OTC medicine are significantly lower than those of obtaining a prescription medicine), which, in turn, would increase access for patients who faced delisting of prescription omeprazole, but could not afford OTC omeprazole. An increase in OTC omeprazole coverage could therefore result in increased utilization. While this increase in benefits (e.g. improved health for GERD patients) from increased access would likely justify the increased costs (i.e. would be an example of purchasing efficiency), health plans in the USA would still have the option of offsetting these higher costs by shifting an even larger share of the prescription market to the OTC market.
- In addition to discussing the financial implication of purchasers in the USA shifting prescription patients to the OTC omeprazole product, it is critical that the safety of such a switch be considered. While the FDA may have intended for OTC omeprazole to only be used by patients on a short-term basis, evidence shows that in practice, patients who take omeprazole on a long-term basis may have switched from the prescription market to the OTC market. At the outset, this may appear to threaten the safety of these patients. However, an actual OTC omeprazole use study in the USA clearly showed that patients were capable of determining when to consult with a physician. Thus, it may be that patients who

switched from prescription omeprazole to OTC omeprazole were still receiving guidance from their physicians on the use of omeprazole, despite no longer receiving prescriptions. If this were not the case, then health plans may want to devise a mechanism to ensure that patients who purchase OTC omeprazole visit their physicians (such as receiving proof that the patient has visited his/her physician every year) before continuing to cover the OTC version.

- On another safety note, evidence that a significant percentage of health plans in the USA dropped omeprazole from their list of covered benefits suggests that some health plans may have been ignoring the FDA's safety guidelines that OTC omeprazole be used on a short-term basis. On this note, the FDA may want to clarify whether they view long-term use of OTC omeprazole as safe, under the assumption that patients are still capable of eliciting guidance from their physicians when clinical necessary. If the FDA does not take this position, then the financial incentives that encouraged (if not forced) patients to switch from the prescription to the OTC omeprazole may threaten their health, in which case the USA legislature may want to consider passing a law that makes it illegal to drop coverage of a chronic disease medicine that has been approved for both prescription and OTC use for different populations of patients.
- Although the OTC omeprazole weighted purchased price was lower than the prescription omeprazole weighted purchased prices in the USA, purchasers in the USA would likely have faced even lower OTC omeprazole prices if generic manufacturers had been permitted to enter the market shortly after the original brand OTC entry. On the other side of the coin, the OTC marketing exclusivity period may serve as fair compensation for the actual use studies that the applicants are required to perform. Thus, the FDA may want to reconsider whether the length of the marketing exclusivity period could be shortened in order to encourage quicker price competition within the OTC market, while still offering some degree of compensation for costs incurred by the first applicant.

- In addition, to encourage health plans and generic manufacturers in the USA to incur the necessary costs involved with applying for an OTC switch, the FDA may want to reconsider whether the ultimate decision should continue to lie with the original brand manufacturer. It is difficult to imagine that actual use studies that are performed by health plans or generic manufacturers would be of lesser quality than actual use studies performed by the original brand, which, in theory, should provide all of the necessary safety information to the FDA for consideration of such a switch. Thus, it seems unlikely that the original brand manufacturer needs to consent in order to ensure safety.
- In contrast to the OTC omeprazole switch in the USA, such a shift in coverage from the generic prescription omeprazole market to the OTC omeprazole market in the UK would have resulted in cost increases to both purchasers and patients, so would not have improved purchasing efficiency.
- In a recent survey, pharmacists in the UK cited the "excessive cost" of OTC omeprazole as a problem (Stewart, 2007). This is consistent with the findings and analyses in this study, which clearly shows that the OTC omeprazole prices are very high, in comparison with the costs patients face in the prescription market. In order to ensure that OTC (behind-the-counter) omeprazole is accessible to the population of patients in the UK that the MHRA intended, policymakers need to make the price more affordable to patients. Supply-side policies could include making the behind-the-counter market more attractive to manufacturers by allowing them to promote their products. In 2003, the MHRA did take steps toward allowing OTC products treating a greater range of disease areas, including serious gastrointestinal diseases, to be advertised to the public (MHRA, 2003). In addition, the MHRA may want to consider allowing original brand manufacturers to market the product on their brand name so that patients are more aware of the OTC product availability, thereby creating a bigger market and incentivizing more manufacturers to enter into the market.

- In addition, the NHS may want to consider actually covering the cost of these chronic disease OTC medicines on a long-term basis, as long as the pharmacists have documented that the patients are receiving guidance from them and their physicians. Such a measure would require that the MHRA clarify whether they perceive the long-term purchase of OTC medicines to be safe for relatively lower risk patients, as long as pharmacists act as a source for consultation and patients continue to receive guidance from their physicians. Continuing to allow only the 10mg product to be available OTC may serve as a good filtering mechanism where the lower risk patients retain the ability to self-medicate Such a decision would allow relatively low risk patients to manage their own symptoms while funnelling higher risk patients (who require higher dosages) into the prescription market.
- Finally, given the studies on OTC omeprazole actual use safety in the USA, the UK may want to reconsider whether switching OTC omeprazole to the general sales category would be safe. It so, then this measure would likely make the product more accessible for patients.

7.3.4 Physicians and Pharmacists: Their role in Improving Purchasing Efficiency within Molecule Markets

The studies in this dissertation have focused on the supply side determinants of competition within molecule markets. However, policy considerations must take into account the role of physicians and pharmacists, who act as the proxy demand side by prescribing, guiding and dispensing medications for patients. The above discussion alludes to the importance of physicians' and pharmacists' involvement with improving purchasing efficiency. A comprehensive analysis on the influences and roles of physicians and pharmacists could easily lend itself to its own dissertation. However, without their participation, the above schemes could not be successfully implemented. Thus, it is worth briefly considering the ways in which these policy considerations require buy-in from physicians and pharmacists.

7.3.4.1 Physicians

- On improving generic penetration within strength segments, physicians must be willing to prescribe by the generic name in countries such as the

UK, where pharmacists are not allowed to substitute generics for brand name prescriptions. In countries where generic substitution is permitted, such as the USA (as of the 1980s) and France and Germany (in more recent years), physicians must be willing to allow generic substitution to occur by not overriding such practices (by writing dispense as written, etc.).

- On prescribing line-extensions, such as Paxil CR® over the immediate release version, it is crucial that physicians have updated knowledge on the extent to which these follow-on products really offer improved health outcomes. Guidelines, such as those issued by NICE, may help assist physicians in determining the cost-effectiveness of prescribing such follow-on products to different populations of patients.
- On pill splitting programs, physicians must have knowledge of which medications may be split and which patients are capable of splitting the medications themselves versus needing assistance. Where pill splitting is deemed to be safe and effective, physicians must be willing to prescribe patients twice the desired dosage at half volume (i.e. one month supply of 20mg paroxetine instead of two months supply of 10mg paroxetine).
- On the prescription to OTC switch, physicians must be knowledgeable on which medications are available over-the-counter and which populations of patients are suitable for this OTC market. They must then keep updated records of which patients have switched from prescription to OTC medications and should initiate periodic appointments with these patients in order to ensure that they continue to receive appropriate guidance. They should also communicate with patients during well-visits or any sick visits, regarding whether the patient has initiated taking an OTC medication, and if so, whether a prescription version may be more effective.

7.3.4.2 Pharmacists

- On purchasing some of the lowest priced generic medications (within a molecule), the role of pharmacists is instrumental. Pricing and reimbursement policies must be consistent with the incentives that pharmacists face in dispensing medications. First and foremost,

pharmacists must have the incentive to contract with the lowest price generic manufacturers. Germany and France have moved toward these policy goals in recent years by progressively tiering mark-ups allowances. However, these may still result in pharmacists receiving higher margins for higher priced medications in some cases. Thus, it may make more sense for Germany and France to deregulate the distribution chain mark-ups. Alternatively, it may prove effective to allow pharmacists set mark-up amounts for different ranges of prices, rather than percentage mark-ups, although these set-amounts would need to be carefully determined so that pharmacists overall fees are not reduced.

- Regarding the dispensing of their lowest priced generics, pharmacists must either be neutral in which generic they dispense, thereby allowing the payor to determine which generic is dispensed, or they must be given the financial incentive to dispense the lowest priced generic that they stock. Thus, payors may want to act more deliberately and directly by either requiring pharmacists to dispense one of the lowest priced medications or by providing pharmacists with higher dispensing fees for dispensing lower priced generics, similarly to the way payors in the USA sometimes offer pharmacists higher dispensing fees for dispensing a generic over a brand name.
- On improving genericisation within strength segments, policymakers may want to ensure that pharmacists dispense generics over original brand consistently across strength segments. In order to accomplish this, it is first important to ensure that pharmacists stock at least one generic for each available strength in the market. Higher dispensing fees for generics, as discussed above, may help to provide this incentive.
- On pill splitting, the role of pharmacists in ensuring safety for patients is crucial. Because pill splitters are likely to be purchased at pharmacists, they have the ability to counsel patients when they are making such purchases in order to ensure that the practice is safe. In addition, where medications may be safely split, but where certain populations are not capable of splitting them, it may be beneficial for pharmacists to split the medications. All of these practices would require additional time on

behalf of pharmacists, both in terms of speaking with patients, communicating back to physicians and at times, splitting the pills themselves. Thus, payors would need to offer increased compensation to pharmacists, which could come from a portion of the savings that they reap from such practices.

- The role of pharmacists in patients purchasing medications over-the-counter is also instrumental. In the case of the behind-the-counter category in the UK, they are at the forefront of ensuring that patients' purchases are appropriate and safe. In this way, they act as gatekeepers to behind-the-counter OTC medications in the UK, making them capable of determining the extent to which patients are correctly following the guidelines (by asking patients questions at the point of purchase) and by assessing the extent to which patients turn away from purchasing the product once they learn of the price. Surveys, such as the one recently conducted in the UK, demonstrate that pharmacists have their fingers on the pulse of issues around access, safety and prices of OTC chronic disease medications in the UK. Thus, it is crucial that policymakers defer to pharmacists on the issues and challenges associated with patients appropriately accessing this behind-the-counter category of medications.
- On the issue of general sales OTC medication in the USA, the role of pharmacists remains important, despite their involvement not being as direct as in the case of behind-the-counter medications in the UK. Given that a large percentage of patients in the USA likely purchase their OTC medications from retail pharmacies (65% in the case of OTC omeprazole in the USA in 2004), they may still defer to pharmacists with questions. Thus, pharmacists may still play a role in ensuring that OTC chronic disease medications are safely purchased in the USA as well as the UK.

7.3.5 Patients

7.3.5.1 Access

In the pursuit of purchasing efficiency, access for patients should remain the number one public health priority. This study focuses on purchasing efficiency within molecule markets by assessing the determinants of competition amongst

manufacturers, which drives prices, and by measuring the extent to which payors actually purchase at the lowest prices. It then considers the possible cost savings that could result from substituting the less expensive products for the more expensive products, such as by 1) substituting original brand products with generic products within strength categories, 2) substituting higher priced generics with lower priced generics, 3) substituting lower strength pills with higher strength pills that are cheaper per daily defined dosage and may be safely split, 4) substituting Paxil CR® with 20mg paroxetine immediate release and 5) substituting prescription omeprazole with OTC omeprazole in the USA. In nearly all of these cases, the exact same molecule is being substituted, which results in the patients receiving the same therapeutic benefit. The only case in which there is a slight altercation of the molecule being substituted is the case of Paxil CR®. The policy considerations above therefore acknowledge that to the extent that Paxil CR® is therapeutically superior to the immediate release version, patients' access to this product should be preserved, when clinically necessary. In this case, instead of substituting the 20mg immediate release version, purchasing efficiency should be achieved through reimbursement mechanisms that link the price to the relative therapeutic benefit.

Thus, under this set of policy considerations, patients should retain the same degree of access to the medications they were already purchasing during this study period. Moreover, certain policy considerations, such as payors adding OTC omeprazole to their list of benefits could improve patients' access, thereby increasing utilization and total public health benefits. Patients using pill splitting as a mechanism to reduce their copayments also has the potential to increase access to the degree that these medications become more affordable, thereby increasing prescription fill rates, etc.

7.3.5.2 Safety

In assessing the effect that the above policy options have on patients, there is another dimension, in addition to access, that must be considered, that of safety. While the volume and type of medicine that patients are consuming is not changing, the way in which they consume these medications does change in certain instances. In the case of substituting prescription original brand drugs with generics or in substituting higher priced generics with lower priced generics, there are no safety issues (assuming good manufacturing practice for generics). However, in the case of

pill splitting and purchasing OTC products, safety is called into question. The studies and policy considerations above discuss these safety issues in depth. To summarize, on the issue of pill splitting, certain medications may be safely and effectively split, while other medications may not. It is therefore crucial that payors, physicians, pharmacists and patients all be aware of which medications may be safely split and that there is open communication between these stakeholders during the process of pill splitting in order to ensure checks and balances. In addition, certain populations, such as middle-aged, educated individuals are more capable of successfully splitting pills, while other populations, such as the elderly, are not. It is therefore also crucial that pill splitting programs only require the participation of individuals who are capable (of participating), and that where individuals are not, the pills be split for them (e.g. by pharmacists).

In addition to pill splitting, safety issues also lie at the forefront of patients purchasing OTC medications, especially in the case of patients purchasing chronic disease medications on a long term basis, as seems to be the case with OTC omeprazole in the USA. The instructions label on Prilosec OTC read:

> Do not use for more than 14 days unless directed by your doctor. Repeated 14-Day Courses (if needed): You may repeat a 14-day course every 4 months. Do not take for more than 14 days or more often than every 4 months unless directed by a doctor. (CVS Omeprazole OTC)

Thus, under the assumption that the FDA had to approve this label, it seems that patients' long-term use of OTC omeprazole is in fact consistent with the FDA's safety guidelines, as long as patients are still under the supervision of their doctors. And, since OTC omeprazole actual use studies show that patients are capable of determining when they need to see a doctor, this study further assumes that switching a percentage of patients from prescription to OTC omeprazole is also consistent with the safety guidelines.

The safety of OTC omeprazole is less in question in the UK, where evidence of OTC omeprazole not even achieving a one percent market share suggests that there was likely little use of OTC omeprazole on a long-term basis. Moreover, the relatively high price of OTC omeprazole means that a shift from the prescription omeprazole market to the OTC omeprazole market would not have increased purchasing efficiency (but rather would have been inefficient). However, to the extent that the price of OTC omeprazole was to decrease in the future, it seems that

pharmacists could guide a larger number of low-risk patients on the safe consumption of OTC omeprazole (Stewart et al, 2007). Finally, another point to consider is that while access to omeprazole in the UK is not hindered by high OTC omeprazole prices (because the NHS continues to cover all available strengths of prescription omeprazole), the extent to which a certain population of low-risk, capable patients may safely become responsible for their own self-care is hampered. To this end, as long as the consumption of OTC omeprazole is safe and access for patients is not threatened, the UK may want to alter the economic incentives so that the low-risk population that OTC omeprazole was intended to reach is able to become more responsible for their own medication.

7.3.6 In conclusion

The above discussion offers insight into policies that may be considered, in the interest of purchasing efficiency, while keeping in mind the role of physicians and pharmacists as well as issues of access and safety for patients. What this discussion does not give strong consideration to, however, is the effect that these policies may have on the pharmaceutical industry. The beginning of this stakeholder analysis discusses these studies' findings in light of the incentives original brand and generic manufacturers may face in their pursuit of profit. On one side of the coin, policies that seek to increase purchasing efficiency may reduce costs for payors. However, on the other side of the coin, these same policies may threaten the profit of original brand and generic manufacturers. And, while some degree of profit trimming may be equitable to the health system at large, replacing manufacturers' abilities to profit with markets of unbridled price competition may not be in the best interest of society to the extent that they do not allow for a viable pharmaceutical industry. Thus, policymakers may want to strive for a balance, whereby manufacturers can safely cover their costs and profit enough to invest in other pipelines, while payors may purchase more efficiently than they do today. This balance is likely to be more of an art than a science, which must take into consideration aspects such as the political environment of the pharmaceutical industry within countries, these countries' abilities to sustain a profitable pharmaceutical industry, while at the same time ensuring fair prices.

7.4 Limitations

IMS Health data is commonly considered to be the golden standard for pharmaceutical market research due to its large sample size and internal validations, as well as the fact that it is the only comprehensive pharmaceutical market data available across countries. While some countries have national sources of data, certain countries, such as the USA, do not have any other source of national level data. Indeed, most of the data limitations that are involved in research that is conducted with IMS Health data pertains more so to the extent to which researchers have access to IMS Health's full dataset, rather than to the nature of the data itself. This is because IMS Data can be very costly and therefore difficult to obtain. Nevertheless, IMS Health data is not without its imperfections.

The first limitation to IMS Health data is that it does not capture the effect of discounts off of retail prices. In Germany, France and the UK, discounts primarily occur within the distribution chain, so have a limited affect on the retail purchased prices. However, in the USA, discounts are often negotiated between the manufacturer and the purchaser in the form of rebates. Information on these rebates is proprietary in nature, so is not available to the public or researchers. The only body with full information on these rebate levels is the federal government, which requires that information on rebates be submitted by manufacturers in order to ensure that Medicaid is in fact receiving the best price. However, because research shows that discounts operate horizontally across products and presentations, rebates are unlikely to bias these studies' findings on the factors influencing pharmaceutical competition (Kanavos and Taylor, 2007; Kanavos, 2007). Rather, the likely effect of rebates in the USA is that the actual prices may be lower than data reveals. Consequently, a comparison of prices across countries may render somewhat inflated USA prices. However, in the study on competition amongst generics, the USA appears to purchase at some of the lowest prices, even before rebates have been taken into account. As a result, this study's analyses on how generic prices compare across countries is unlikely to be affected by the lack of rebate data.

The one case that may be affected by the lack of information on rebates in the USA is the OTC omeprazole case. Rebates occur in the prescription market as a result of payors' abilities to leverage their purchasing power. However, they do not occur in the over-the-counter retail market due to the fact that people are responsible

for purchasing these medicines on an individual basis. Thus, the comparison between the prescription original brand, prescription generic and OTC omeprazole prices may slightly overstate the price differences between the OTC and prescription markets in the USA. Nevertheless, the fact that the prescription omeprazole was higher priced than OTC omeprazole in the USA was still likely to be the case since prescription purchased prices were roughly four times the OTC purchased prices, which was much larger than the estimated two to thirty five percent range of rebates (Report to the President, 2000).

The second limitation to this data is that some of the generic manufacturers in the UK cannot be distinguished due to an agreement that was made between the generic manufacturers' association and IMS Health. As a result, the number of generics manufacturers variable and the dominant generic manufacturer's market share variable were not able to be calculated in the case of the UK. Consequently, this study used the time variable in order to capture any time-related changes in the market, including the change in the number of generic manufacturers. Notably, the dataset for the UK still included all of the presentations that were purchased, so did not exclude any market data in the process of omitting the names of some generic manufacturers. As a result, none of the other calculated variables in the UK should have been affected.

In addition to data limitations, another limitation is that the country-specific-regulations such as their generic reimbursement systems and their distribution chain mark-up regulations on pharmaceutical competition cannot be quantified due to their time-invariant nature. In the case on competition amongst generics, the cumulative effect of countries' regulations and other unobservable factors can be seen in their differing explanatory variables' intercepts. However, in the case of competition within strength categories, the regulatory effects have been implicitly controlled for with the fixed-effects method. As a result, the analyses on the effect of these countries' regulatory differences are conjecturing in nature (based on these findings and other existing literature) and cannot be considered to be reflective of actual causes and effects.

A final limitation is the small number of products in these studies. In the case of the OTC omeprazole analysis, this study only had access to data for one product, which was only available over a small number of years. This limited the degree to which rigorous econometric models could be run, especially in the UK where there

was only one distribution channel, in comparison to the USA's multiple distribution channels. However, in an era where regulatory bodies are increasingly approving chronic disease medicines for dual status (prescription and OTC) availability, it is crucial that a body of literature be built around the implications of such a switch. This study therefore derives its value from its pioneering nature and its keen policy significance, despite being limited in data. Moreover, the selection of a small number of products in the other studies have enabled a more in-depth analysis, which leads to a more sophisticated understanding of issues such as the range of generic prices within countries and the order of generic entry into strength markets. With the small number of products in these studies, these analyses are more case-based in nature, and are therefore able to generate new hypotheses on dimensions of competition that have never before been studied. It may also be that findings are generalisable to other classes of drugs that are sold primarily in the retail market and treat chronic conditions.

7.5 Areas for Further Research

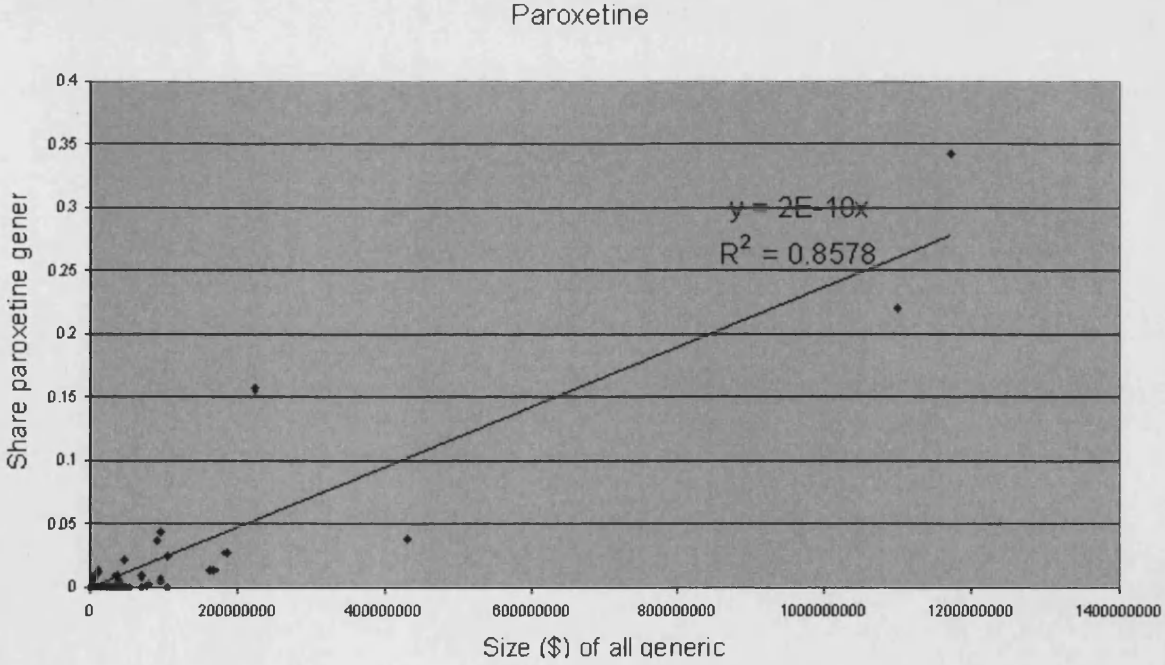
Exploration begets unto itself the need for more exploration. During the process of this thesis, many questions arose which lend themselves to areas of further research. Below is a discussion of these areas.

7.5.1 Dominance amongst Generic Manufacturers

The case on competition amongst generics reveals the existence of a dominant generic manufacturer in both molecules and across all four study countries. In all cases, dominant generic manufacturers did not offer the lowest priced generics, nor were they the first generic entrant. Thus, it would be interesting to conduct further research into the factors that determine which manufacturers are able to achieve this dominant role. In the USA and the UK, where there are large chain pharmacies, it may be whichever generic manufacturer achieves these nationwide contracts. It may also reflect large chain pharmacies vertically integrating with wholesalers and producing their own generic products. However, France and Germany do not have the same degree of concentration in their retail pharmacy network, suggesting that it may be some other factor besides achieving contracts with large chain pharmacies.

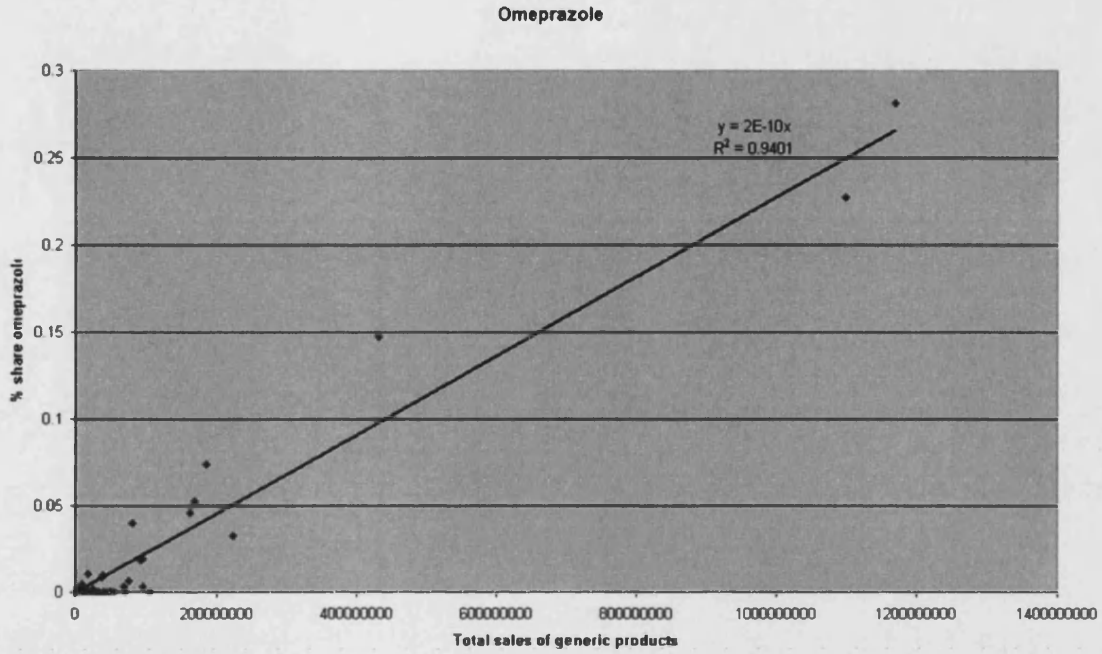
Another potential explanation for this preferential contracting may be that larger generic manufacturers have stronger contractual relationships with pharmacies, thereby biasing pharmacies toward them even if their generic prices are not the lowest. The study on competition amongst generics did not have data on the size of each generic company in each country during each respective quarter during this study period, so could not measure this effect. However, after requesting this information from IMS Health, I received the following graphs via email (from IMS Health). They indicate the strong likelihood that the size of the generic manufacturer may be one of the determinants of the generic market share a generic manufacturer is able to achieve after it has entered into the market. In Figures 7-1 and 7-2, IMS Health plotted the relationship between generic manufacturers' total generic sales in Germany in 2005 (a proxy for the size of the manufacturer) on the x-axis against the manufacturers generic market share for the given molecule on the y-axis. (IMS Health did not disclose how market shares were calculated in these graphs.)

Figure 7-1 Generic Manufacturers' Total Generic Sales in Germany versus Generic Manufacturers' Individual Market Shares in the Paroxetine Generics Market, 2005



Source: IMS Health.

Figure 7-2 Generic Manufacturers' Total Generic Sales in Germany versus Generic Manufacturers' Individual Market Shares in the Omeprazole Generics Market, 2005



Source: IMS Health.

The evidence of such a strong relationship supports the assertion that the size of the generic manufacturer may be a strong determinant of its market share. Thus, it would be interesting to obtain full information on the size of the generic manufacturers in these study countries over time in order to quantify the extent to which these determines the dominant generic manufacturer's market share. Evidence of such a determinant may suggest stickiness in the distribution chain contractual process that inhibits competition. Furthermore, evidence on the role of wholesalers would need to be incorporated into this analysis on the determinants of the dominant manufacturer's market share.

7.5.2 The Determinants of the Number of Strength and the Respective Market Shares

In order to better understand the nature of segmented strength markets and their effect on competition within the broader molecule market, it would be worthwhile to gain a greater understanding on the degree to which strength segments are formed as a result of clinical need and prescribing practices versus

manufacturers' attempts to product differentiate. This information, however, would be difficult to obtain quantitatively. Instead, it would likely require original qualitative research in the study countries, including surveying original brand manufactures on their decisions to enter into different strength segment markets across countries, as well as surveying physicians on the practice of prescribing differing strengths. As part of this, it would be particularly interesting to determine whether it is more or less difficult for original brand manufacturers to receive approval and health insurance coverage (as well as to be able to freely set prices across different strength categories) for various strengths in some countries over others, especially in the case of France, where the pricing process following approvals appears somewhat less transparent than in the other study countries. Informally, I spoke about this issue on what determines the number of strengths in a molecule market with a few contacts from Merck who work in France. They, however, were not knowledgeable on the subject and referred to possible marketing differences across countries (with physicians) as being the explanation for countries' differing strengths and strength market share.

7.5.3 An OTC Switch Case in the USA and the UK where the Product is Available in the General Sales Category in the UK

In addition to researching the OTC omeprazole switch in the USA and the UK, it would be interesting to research the economic implications of a switch in the USA and the UK where the MHRA has approved the product for general sales status instead of behind-the-counter status. Notably, patients' financial incentives would still differ in the USA and the UK due to the countries' differing health care systems. However, such a case would provide a more apples to apples comparison with OTC availability in the USA on a regulatory level in terms of patients not having to go through a pharmacist to obtain access. This study did not have access to data for a product that fulfils these criteria. However, an example of one such product is loratadine, which is available over-the counter in the USA and both behind-the-counter (in larger package sizes) and as general sales (in smaller package sizes) in the UK.

7.5.4 Other Types of Product Differentiation within a Molecule Market

The cases in this thesis analyse the effect of product differentiation on purchasing efficiency. An addition type of product differentiation that is not included in these analyses as a result of not existing in the omeprazole and paroxetine retail molecule markets is form. That is, some molecules are available in the retail pharmacy market in the form of pills, liquids, creams, nasal inhalers, etc. Studying the effect that this type of product differentiation has on purchasing efficiency within a molecule would be another interesting dimension of competition to explore.

7.5.5 Competition within a Therapeutic Class

These studies contribute to the literature by delving into pharmaceutical competition within the molecule market. However, it would also be interesting to research competition within the broader therapeutic market. There is already a body of literature that has studied the degree of competition between in-patent drugs. Specifically, these studies have found that despite entry of competing drugs (i.e. me-too drugs), first entrant (i.e. breakthrough drugs) prices continued to increase in real terms (CBO, 1998). Meanwhile, me-too drugs tend to enter at prices lower than the first entrant into the therapeutic class; however, once they gain brand recognition, they increase their prices substantially, usually at rates that far surpass the price increases of breakthrough drugs (Lu and Comanor, 1998). Thus, competition at the therapeutic class level is characterized by product differentiation in the form of quality and branding (Kanavos, Costa-Font and McGuire, 2007). The result is that both prices and therapeutic efficacy (i.e. quality) must be taken into account in this model of competition. Moreover, in order to differentiate their products in the therapeutic market, firms also heavily invest in promotional spending. Promotional spending is therefore a significant factor that should also be taken into account when analyzing competition in this third sphere (Danzon and Chao, 2000).

This above literature models competition between two patented molecules within a therapeutic class. However, to date, no studies have analyzed the degree of competition between off-patented drugs and patented drugs in the same therapeutic class. If generic entry causes patients to switch from a patented drug of one molecule to generic drugs of another molecule, then this may be another way in

which generic entry reduces costs (in addition to reducing the expenditures on that molecule itself).[81] This could be the case in Germany, where, under their new therapeutic reference pricing scheme, certain drugs of differing molecules have been classified into the same reference pricing group. Studying competition between off-patent drugs and in-patent drugs of differing molecule would also be interesting in the case of the OTC omeprazole switch in the USA, where some patients may have switched to a different PPI after their health plan delisted omeprazole in order to avoid the OTC omeprazole costs. Thus, it could be that an OTC switch for one drug actually caused a competing patented drug to gain market share. It is important to note, however, that similarly to the scenario of studying competition between in-patent molecules, discussions on the purchasing efficiency implications of competition between off-patent and in-patent drugs within a therapeutic class would need to account for these molecules' quality differences, possibly through methods of cost-effectiveness analyses.

7.5.6 Assessing the Effects of the Most Recent Regulatory and Market Changes in these Study Countries

These studies had access to data during the 2000q1-2005q1 period. Thus, in some of these study countries, there have been significant pharmaceutical policy changes since this study period. As the methodology chapter discusses in more detail, Germany introduced a therapeutic reference pricing scheme for certain molecules in 2005q1. In addition, France introduced a molecule-level referencing pricing scheme in 2003, although omeprazole and paroxetine were not included in it. The effect of France's reference pricing system may be similar to Germany's molecule-level reference pricing system that is reflected in these studies, although this depends on the extent to which other regulations such as distribution chain mark-ups influenced price competition as well. In Germany, the therapeutic reference system may not have had a significant effect on the price of omeprazole since it was the first drug in its class, and therefore probably the lowest price in the PPI therapeutic class, making it the reference price setter. However, for paroxetine, since it was not the first in its class, the introduction of the therapeutic reference price system may have resulted in lower paroxetine prices. The effect of the therapeutic

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[81] While the implication of substitution away from patented molecules could imply lower costs for payors, it could also imply less ability for manufacturers to recoup R & D costs.

reference pricing system would also depend on the way in which the prices were calculated and the degree of standardization across different strengths and molecules.

In addition to assessing the effects of the recent policy changes, it would also be interesting to study the effects of recent market changes. For example, generic versions of omeprazole OTC were approved for marketing by the FDA and the MHRA in 2008. Thus, it would be interesting to analyse the degree of price and market share competition amongst OTC omeprazole products.

7.5.7 A Qualitative Analyses on the Industrial Organization of Competition Within Molecule Markets

The methodology chapter and the studies themselves relate models of industrial organization to the relevant dimensions of competition between these off-patent products. Specifically, under the assumption that generic pharmaceutical manufacturers do not face increasing marginal costs of production, the study on competition amongst generics assumes a Bertrand-like model of competition, where generic manufactures engage in a form of price competition that is diluted by product differentiation and other bottlenecks in the market, including regulations. In the case of competition between the original brand and generic manufacturers within strength segments of a molecule, this study assumes a Market Harvesting/Experience Goods model of market share competition, whereby the original brand manufacturers keep flat (or increase) their relatively high prices and accept that they will retain the brand loyal segment of the market, while forgoing the price sensitive portion of the market to generics. Finally, the case on competition between the prescription and OTC market segments of a molecule researches the extent to which competition may be partially based on price (where there is evidence that some degree of market share competition does exist), which may reflect Bertrand-like competition.

In conclusion, these cases test for the nature and degree of competition between differing segments of a molecule market under the assumption that while competition between the original brand and generics may resemble a Market Harvesting/Experience Goods model, competition amongst generics is more likely to resemble a Bertrand model. In these cases, results from quantitative analyses are used to generate hypotheses on the way in which manufacturers of the same molecule compete—i.e. on the industrial organization of these dimensions of competition. It would therefore be interesting to conduct a more thorough analysis

on the industrial organization of these types of competition by surveying strategists who work for a wide range of pharmaceutical manufacturers across a number of countries on the extent to which they predetermine how much they want to sell and set their prices accordingly (resembling Cournot competition), despite facing fairly flat marginal costs of production, versus the extent to which they strive for the highest market share possible by basing their prices on other competitive prices in the market (resembling Bertrand competition). This qualitative information could then add to the quantitative findings from these studies to generate entirely new industrial organization theories, to the extent that the pharmaceutical industry does not conform to these existing theoretical models.

7.6 Conclusion

In conclusion, findings from this thesis show that competition within the off-patent omeprazole and paroxetine molecule markets exists at a micro-level in these study countries. Despite products appearing homogeneous in nature, manufacturers are able to prevent Bertrand competition by maximizing their prices in certain regulatory environments, such as reference pricing in Germany and price caps in France. In regulatory environments that are relatively free market oriented, such as the US and the UK, a larger degree of price competition exists. However, even in these environments, evidence shows that generic manufacturers are able to differentiate their products by altering strength, formulation, package sizes and in some cases, by receiving approval to market their products over-the-counter.

In addition, evidence shows that original brand manufacturers may retain a larger degree of market power than the passive market harvesting strategy suggests. In all four study countries, they benefit from locating their products in less common strength markets, where there appears to be less competition from generics. In certain cases, the original brand manufacturer may also be able to retain a large share of the molecule market post patent expiry by marketing their drug OTC or introducing a line-extension.

The effect of these regulations and product differentiation strategies is that off-patent molecule markets exhibit a lesser degree of price competition than economic theory might predict, resulting in an enhanced Bertrand-like model which results in ranging prices and unevenly distributed market shares. This, then, may result in purchasing inefficiencies for purchasers. To the extent that policymakers

are able to encourage a greater degree of price competition, as explored in this thesis, and to the extent that purchasers are able to improve purchasing efficiency, the opportunity for additional cost savings in off-patent molecule markets is ripe. These savings could then assist policymakers in making more optimal resource allocations, particularly during times of economic distress.

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APPENDIX A: PHARMACEUTICAL POLICIES OVERVIEW IN STUDY COUNTRIES

The USA: A Relatively Free Market Approach to Pharmaceutical Cost Containment

In the USA the Food and Drug Administration (FDA) is responsible for approving pharmaceutical products for marketing. Historically, once a drug has been granted permission to be market in the USA, it has automatically been covered by the majority of third party purchasers, without any formal evaluation of cost-effectiveness or a drug's relative therapeutic benefit. However, in the past decade both public and private purchasers have introduced mechanisms to contain the cost of drugs by encouraging lower cost, generic, products.

Pharmaceutical spending and cost containment measures in the USA are as varied as the country's insurance system. As of 2006, 44% of pharmaceutical expenses were paid for by private health insurers, while 34% were paid for by the government and 22% were paid in the form of patients' out-of-pocket expenses. The majority (53%) of government's pharmaceutical expenditures came from Medicare in 2006, with the next largest source of public funds (26%) coming from Medicaid. The rest of government pharmaceutical expenditures were sourced through programs such as the Veteran's Administration and the Federal Employees Health Benefit. The share of public expenditures that comes from Medicare increased from 7% in 2005 to 53% in 2006 as a result of the Medicare Part D implementation, which provides prescription drug coverage to the elderly and disabled (Kaiser Family Foundation Prescription Drug Trends Fact Sheet, 2008).

Unlike most countries in Europe, there are no centralized regulations that seek to contain pharmaceutical expenditures. Instead, separate payors leverage their market power in various ways in order to improve efficient purchasing. The majority of Americans (59% in 2007) obtain their health insurance coverage through their employers. As of 2007, 60% of employers were offering health insurance to their employees, with almost all plans including a prescription drug benefit (Kaiser Family Foundation Prescription Drugs Trends Fact Sheet, 2008). The administration of employers' prescription drug benefits is often outsourced to pharmaceutical benefit managers (PBMs), who negotiate discounts and rebates with manufacturers in exchange for increasing that drug's market share amongst its beneficiaries. Of the

portion of the population that receives its health benefits through their employers, 75 % were subject to a formulary structure in 2007 (up from 27% in 2000), which integrates cost-sharing with 3 or 4 tiers. Generics are usually placed on the first tier, which has the lowest cost-sharing requirement, while preferred branded drugs (which includes either branded drugs of significant therapeutic value that have no generic equivalents or branded drugs that offer significant rebates) are placed on the second tier and non-preferred drugs on the third tier, which has the high cost-sharing requirement. Over time, the tiered copayments have been increasing, with the average preferred drug copayment increasing from $15 in 2000 to $25 in 2007 and the average non-preferred drug copayment increasing from $29 in 2000 to $43 in 2007 (Kaiser Family Foundation: Prescription Drug Trends Fact Sheet, 2008). Thus, PBMs use formularies to contain pharmaceutical expenditures by negotiating rebates and discounts with manufacturers and retail pharmacies respectively and by shifting a portion of the costs to patients

Because rebates/discounts are part of private, proprietary negotiations between PBMs and manufacturers/pharmacies, the extent of savings is not made public. As a result, it is impossible to calculate the effective price (list price minus rebate/discount) that PBMs actually pay for pharmaceuticals. The list price in the USA is often based on a concept called the Average Wholesale Price (AWP). The AWP is not what the name suggests, however. Rather than being the average price at which wholesalers sell to retailers, the AWP is a published "list price," which the manufacturer suggests to the wholesaler. In practice, manufacturers sell their drugs to wholesalers at a significantly discounted rate (off of AWP), which also allows wholesalers to sell their drugs to retailers at a discounted rate (off of AWP) as well, while still retailing a percentage for profit. In practice, the AWP is a benchmark that is used in negotiating prices in the USA. One report suggests that the actual price charged by the manufacturer to the wholesaler is 20% less than the AWP, on average, which the wholesaler then marks-up approximately 2-4% before selling to pharmacies (USA Department of Health and Human Services, 2000).

Because pharmacies pay less than AWP in most cases, PBMs are often able to negotiate a percentage off of the AWP—the pharmacy discount. They also usually include a fix-rate payment called the dispensing fee, which averaged $2.50 in the late 1990s (USA Department of Health and Human Services, 2000). The intention of this dispensing fee was to cover pharmacists' operating costs where

negotiated discounts were significant. In general, the ability of PBMs to negotiate discounts with pharmacies depends on a number of economic factors such as how large and powerful the PBMs is versus how large and powerful the pharmacy network is. Industry experts claim that the payments to pharmacies for most brand name drugs and for some (roughly 25%) of generic drugs in the late 1990s was in the range of AWP minus 13 to 15 percent plus a $2.50 dispensing fee. For the other 75% of generic drugs, PBMs are often only willing to reimburse pharmacies at the cost of the lowest priced generic equivalent sold by that pharmacy. This report, however, does not offer any information on the average number of generic equivalents that a pharmacy stocks. Thus, the MAC system would presumably achieve lower prices for the PBM in cases where pharmacies stock multiple generic equivalents versus one or two. Under this pricing system, called the maximum allowable cost, the payment to pharmacies reportedly averaged AWP minus 50 to 60 percent (USA Department of Health and Human Services, 2000). In addition, the PBMs sometimes offered higher dispensing fees for generics in order to encourage generic substitution. (The majority of states in the USA gave pharmacists the right to substitute generic drugs in the 1980s, around the same time that the Hatch Waxman Act encouraged generic entry by allowing generic manufacturers to prove bioequivalence to the original brand rather than conduct their own clinical trials.)

In addition to the pharmacy discount, PBMs negotiate rebates directly with manufacturers. The size of the rebate depends on the bargaining power of the manufacturer. For example, a manufacturer of a drug that is innovative and has no close substitutes is less likely to give a large rebate than the manufacturer of an original brand drug that has multiple generic substitutes. These rebates may come in various forms, such as a fixed payment from the manufacturer to the PBM for each prescription dispensed, or a specific sum of money once the market share of the drug has increased to a certain target. In an attempt to quantify the savings that PBMs and health plans make from manufacturer rebates and pharmacy discounts, the General Accounting Office found that Blue Cross/Blue Shield paid $1.4 billion in pharmaceutical expenditures for the Federal Employees Health Benefits Program, compared to the $1.9 billion in expenditures that they would have paid had they not contracted with the PBM. Of the $505 million in savings, 21.2% was attributable to manufacturer rebates and 52.3% was attributable to retail or mail-order pharmacies discounts. The other savings was attributable to MAC reimbursement for generics,

prior authorization programs, etc. This savings translated into an average retail pharmacy discount of 14% off of AWP and an average manufacturer rebate of 5-6% off of AWP (USA General Accounting Office, 1997). Notably, the manufacturer rebate may have been slightly higher to the extent that the full savings were not passed on from the PBM to Blue Cross Blue Shield. However, contractual terms between health plans and PBMs usually require that 70-90% of the rebates are passed on to the health plan (USA Department of Health and Human Services, 2000). Despite these requirements, PBMs often also receive addition manufacturer rebates that are not tied to specific drugs, such as rebates in return for the PBMs promoting the manufacturers' drugs to physicians, etc. These rebates are even more difficult to estimate, although some experts believe they can even exceed the value of the drug-specific rebates discussed above (USA Department of Health and Human Services, 2000).

In addition to PBMs leveraging the purchasing power of their beneficiaries, various payors have formed purchasing pools, which combine the purchasing power of multiple health plans in order to negotiate higher rebates and discounts. For example, there are purchasing pools in which multiple states combine their Medicaid and state employees' programs to achieve better prescription drug prices.

Medicare is the federal health plan that covers seniors (aged 65 and older) and the disabled, representing 15% of the population in 2008 (Kaiser State Health Facts, 2008). It did not provide prescription drug coverage until 2006. Thus, prior to 2006, roughly three quarters of seniors obtained drug coverage separately through supplemental plans or employee retirement benefits, while the remaining quarter of seniors had no drug coverage. Since the start of 2006, however, all Medicare beneficiaries have been entitled to prescription drug coverage (90% of which had coverage as of 2008), which the federal government has outsourced to hundreds of private prescription drug and Medicare Advantage plans (which includes the private administration of all health benefits) (Kaiser Family Foundation, 2008). As a result, the covered drugs and accompanying cost-sharing requirements range (within a stipulated framework) for Medicare drug beneficiaries. Their commonality, however, is that most of them are subject to formulary (tiered prescription drugs with progressive co-pays) arrangements similar to employees in private health plans. In fact, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, which established Medicare part D, made it illegal for the federal government to

directly negotiate prices with pharmaceutical manufacturers. Thus, if policymakers were to want a more centralized form of pharmaceutical cost containment for Medicare, they would first need to change legislation.[82]

After Medicare, the next largest government health insurance program is Medicaid, representing 13.2% of the population. Medicaid is the public health insurance program for the low-income that is funded by both federal and state revenues. States receive matching dollars that are progressively higher for lower-income states. State Medicaid programs must cover a comprehensive set of health benefits, including prescription drugs, although they are at liberty to determine their own eligibility rules, payment arrangements to providers and cost-sharing structure (within certain parameters). Under federal law, pharmaceutical manufacturers are obligated to provide rebates to the Medicaid program. Under the Medicaid Best Pricing rule, for branded, patented drugs, manufacturers must offer Medicaid the lower price of either the best price in the private market or 15.1% off the average manufacturer price. For multisource original brand and generic drugs, manufacturers must offer 11% off the average manufacturer price. In addition to these mandatory rebates, some states have pursued additional rebates, called Supplemental Rebates. In this case, the Federal government agrees to allow state Medicaid programs to achieve higher rebates (through negotiating or creating state laws) than they would under Federal law, without forcing manufacturers to extend these rebates to other states or the federal government. As of 2006, about 75% of state Medicaid programs had introduced preferred drug lists and prior authorization programs (under which physicians must obtain authorization from the payor before prescribing a non-preferred drug); 70% had negotiated supplemental rebates; 60% had Maximum Allowable Cost programs for off-patent drugs (a program in which the payor only reimburses up to a certain amount for each drug, molecule-level reference pricing policies in Europe); 25% had joined multi-state purchasing pools, and 20% had created limits on quantities dispensed per prescription (Kaiser Family Foundation: Prescription Drug Trends, 2008).

The largest rebates given to public payors in the USA, however, are through the Federal Supply Schedule (FSS). Under the Veterans' Health Care Act of 1992, the Veterans' Administration negotiates prices directly with manufacturers, which

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[82] Various democrats have attempted this, but have not succeeded.

must be supplied to the VA, Department of Defense, the Public Health Service and the Coast Guard, which together comprised only 1.1% of the insured population in 2007 (Kaiser State Health Facts, 2007). The prices for brand name drugs must be at least as low as the best price sold in the private market, and no more than 76% of the average manufacturer price—the federal ceiling price. In practice, however, they are reported to be even lower than these stipulations. Specifically, one government study states that average FSS prices are more than 50% below the average manufacturer price (USA Department of Health and Human Services, 2000). Some explanations offered as to why the VA has been able to achieve such low prices include the fact that the VA only comprises such a small percentage of the insured population, that the VA is well skilled in price negotiation and that manufacturers want to ensure that their products are marketed in these federal facilities and agencies, where many physicians receive part of their training (USA Department of Health and Human Services, 2000).

Finally, the last federal rebate program is the 340B program, which manufacturers must comply with in order to participate in the Medicaid program. Under the 340B program, pharmaceutical companies provide community health centers and disproportionate share hospitals (hospitals that treat a disproportionate share of Medicaid/low income patients) with discounted prices.

The remaining share of the population—15.3% in 2007—in the USA is uninsured, and therefore has no prescription drug coverage (Kaiser State Health Facts, 2007). In addition to not having drug coverage, uninsured individuals in the USA face higher pharmaceutical prices than third party purchasers due to their inability to negotiate discounts with retailers. One study found that in 1999, the price for the average uninsured individual was approximately 15% higher than the price for the average insured individual (the majority of which was paid for by the third party purchaser (USA Department of Health and Human Services, 2000). Thus, it is not surprising that this population is often forced to go without needed medications as a result of facing the full and relatively high cost of drugs. A survey of nonelderly adults shows that the uninsured are twice as likely as the insured to not fill a prescription (45% versus 22%) or to cut pills or skip doses (38% versus 18%) (Kaiser Family Foundation: Prescription Drug Trends, 2008). Even patients who do have insurance in the USA are forced to reduce their cost-sharing burden by requesting generic drugs at the pharmacy, purchasing discount drugs over the

internet, switching to over-the-counter medications, buying drugs in larger quantity and pill splitting, using mail-order pharmacies, and taking advantage of manufacturers' or governments' assistance programs. Specifically, purchases of mail-order pharmaceuticals in the USA rose 54% from 2003 to 2007, increasing from 13% of total prescription sales in 2003 to 16% in 2007 (Kaiser Family Foundation: Prescription Drug Trends, 2008).

Finally, another way in which individuals sometimes attempt to save on the cost of drugs is by purchasing drugs from Canada. Until recently, such a practice was illegal due to safety concerns and uncertainties surrounding how importation or reimportation (reimporting drugs that were made in the USA and exported to other countries at lower prices than they would be sold in the USA) could distort manufacturers' pricing and supply incentives. (Specifically, the concern was that manufacturers could respond to importation by restricting the supply of drugs in other countries and/or could increase the price of their products in other countries to match USA prices.) However, the government usually turned a blind eye when individuals (often the elderly) crossed the border to buy drugs, and in 2006, new legislation made it legal for USA residents to transport up to a 90-day supply of prescription drugs from Canada to the USA. Although the percentage of drugs imported from Canada was small during this study period (.3% in 2003), the absolute dollar value ($700 million in 2003) still constituted a large market (Kaiser Family Foundation: Prescription Drug Trends, 2008).

France: A tighter regulatory approach to pharmaceutical cost containment based largely on negotiation and price controls

Figure 2-1 is a diagram of the pharmaceutical regulatory process in France. There are three different avenues through which a pharmaceutical company can obtain an authorization to market its product in France—a centralized procedure through the EMEA (European Agency for the Evaluation of Medicinal Products), a decentralized procedure of mutual recognition whereby France must accept a marketing authorization from another country and a national procedure through the French Agency for the Medical Safety of Health Products (AFSSAPS). All procedures require that the manufacturers' demonstrate quality, safety and efficacy, similarly to receiving approval from the FDA.

Once a manufacturer has received marketing authorization for its product, the Transparency Committee is responsible for determining whether it should be put on the positive list of reimbursable drugs, which is required for coverage by the statutory health insurance system. The decision of whether or not the product should be prescription-only or available OTC is first made by the Transparency Committee, followed by a review of whether or not the drug should be reimbursed, which is based on the rating of its "improvement on the medical benefit" (the ASMR rating) (OBIG, 2006). According to a recent report (OBIG, 2006), the ASMR rating is based on the following scale:

ASMR 1: significant therapeutic value

ASMR 2: significant improvement in terms of efficacy, and/or reduction of adverse effects

ASMR 3: modest improvement in terms of efficacy, and/or reduction of adverse effects, as compared with existing products

ASMR 4: minor improvement of benefit (e.g. user-friendliness, small interaction risk), as compared with existing products

ASMR 5: no therapeutic improvement of benefit, as compared with existing products (still recommended for reimbursement)

ASMR 6: negative opinion regarding inclusion into reimbursement

Drugs that receive an ASMR rank of 1-5 are deemed reimbursable, while a drug that is ranked ASMR 5 is not. OTC versus prescription status is independent of the rank that a drug receives. Thus, OTC products can be on the positive list of reimbursed drugs, although medicines approved for self-use in France are sometimes referred to as "useless" drugs by the press and the government since they have received the lowest ASMR rank (Kanavos and Gemmill, 2005). As a result, OTC products are sometimes not valued by the public in France to the extent that they are in countries like the USA.

Once a drug has received its ASMR rank and has been put on the positive list of reimbursed drugs, the Transparency Committee must then decide on a reimbursement rate for the drug. As of 1999, the manufacturers must provide information on the medical service rendered (SMR) by their product in accordance with the following criteria:

- The effectiveness of the drug and its possible side effects

- Its place in the therapeutic process, in relation to the alternative therapies available
- The seriousness of the condition in question
- The curative, preventative or symptomatic properties of the drug
- Its importance in terms of public health (Sandier, Paris and Polton, 2004)

A score of (A) means that the Transparency Committee has deemed the medical service of a product to be "major or considerable," which is usually the case with non-substitutable medicines that treat life-threatening or disabling conditions. The reimbursement rate for these products is 100%. A score of (B) is given to drugs that make a moderate impact, usually by treating serious conditions (but are not as vital as category A). These drugs are reimbursed at a rate of 65%. Drugs that are classified into category (C) often treat the symptoms of illnesses that are not as serious, such as common acute conditions. These are reimbursed at a rate of 35%. After five years on the positive list, drugs' SMRs must be re-evaluated since its place in the therapeutic process may have changed. Drugs that were previously on the positive list before 1999 were also subject to this evaluation process for the first time. As a result, for 617 drugs, the reimbursement rate dropped from 65% to 35% for drugs that were determined to be of low medical value, including some drugs from therapeutic categories such as anti-fungals, antiseptics, anti-acne, anti-histamines and gastro-oesophageal reflux (Kanavos and Gemmill, 2005). In addition, 84 of the drugs on the positive list were de-listed, including drugs from categories such as antacids, anti-bacterials, expectorants, etc (Kanavos and Gemmill, 2005).

Once the Transparency Committee has evaluated a drug for reimbursement status, it then passes the information its used in determining the SMR and ASMR ranking to the Comite' Economique des Produits de Sante (CEPS). Drugs with an ASMR ranking of I-III and an assumed projected turnover of less than 40 million Euros in the third year have the price notification scheme option or the traditional price negotiation option. Under the price notification scheme option, the manufacturer must propose a price that is consistent with other large European markets (CEPS, 2005), which the CEPS then has 15 days to decide whether or not to accept (for a five year period). In addition to proposing a price, the manufacturer must forecast sales for the first four years, which, if exceeded, require pay-backs. The CEPS may reject the price proposal, in which case the traditional price

negotiation procedure is followed. Although the price notification procedure was intended to enable the pricing of innovative pharmaceuticals in France to be more consistent with other markets (OBIG, report), in practice most manufacturers still opt to negotiate prices, although the use of the price notification procedure seems to be increasing. Specifically, in its first year, Abbott's protease inhibitor Kaletra was the only product to initiate the price notification system. In 2003, manufacturers of two new products chose to pursue the traditional price negotiation route instead, although eight drugs entered into the price notification procedure in 2004 (OBIG, 2006). (It is not necessarily surprising that some manufacturers preferred the price negotiation route, as drugs with ASMR rankings of I or II were usually allowed higher prices in negotiations anyways (OBIG, 2006).)

Under the traditional negotiations route between manufacturers and CEPS, prices are based on the Transparency Commission's determination of the drug's improvement in medical service rendered (ASMR), the price of similar drugs on the market, the forecasted sales/volume and the expected conditions of use (CEPS, 2005). Once approved, if the actual sales/volume exceeds the forecasted sales/volume, then manufacturers may face penalties in the form of pay-backs/rebates to the government, price reductions or even having their drug de-listed. These rebates are often significant, amounting to 454 million Euros in 2003 (CEPS, 2005).

The cost containment procedures (e.g. price negotiations, limited reimbursement rates) described above apply primarily to patented pharmaceuticals. However, one policy that has applied equally to branded drugs and generics is price cuts. Over the past five years, France has used price cuts to contain the costs of innovative drugs, drugs with minor therapeutic benefits and generics (OBIG, 2006). Specifically, drugs determined to have low medical benefits (i.e. low SMRs), faced an average price cut of 20% over a three year period between 2000 and 2003 (Kanavos and Gemmill, 2005). In addition, at the start of 2006, price cuts of 15% were introduced for original brand drugs and their generic equivalents with further 10% and 4% cuts planned for original brand and generics respectively (OBIG, 2006).

Another way in which pharmaceutical policies in France have changed over the past five years is in the shift toward generics. In 1999, the generic market share in France was only 2% and generic prices were capped at 30% lower than the original brand drug (Sandier, Paris and Polton, 2004; Kanavos and Gemmill, 2005).

However, in 2003, the law on financing the social security system authorized the introduction of a reference price system for a select group of drugs. As is the case with reference price systems in other countries, the government sets a specific price that it will reimburse for each group of drugs. In the case of France, this is calculated as the average generic price in each reference group, where the generic prices are capped at 30-40% of the original brand price at the time of patent expiration (Kanavos and Gemmill, 2005). If a manufacturer prices its drug above this reference price, then patients must pay the difference between the price and the reference price. This reference pricing system in France applies only to certain drugs that are off-patent. Originally in 2003, 29 molecules were chosen, which corresponded to 61 different groups of generic drugs and 71 reference prices, since in some cases there were multiple different dose and/or formulation combinations for the same molecule (CEPS, 2005). The criterion for a drug being included in this first wave of reference prices was a generic penetration of between 10% and 45% (based on penetration rates in April 2003). However, the second wave of 11 additional molecules that were included in June 2005 was based on generic penetration rates of 60%. Notably, the original intention was to include 18 additional molecules in the second wave. However, the government spared some of these drugs, possibly because they showed signs of strong rates of generic penetration (Kanavos and Gemmill, 2005).

A government report evaluated the effect of the reference pricing system on the pharmaceutical prices and expenditures for the relevant drugs in the first year of implementation. It found that in 70% of cases, the original brand manufacturers immediately reduced their prices to the reference prices. In only one case, the original brand manufacturer pursued the generics paradox strategy of increasing its price (CEPS, 2005). There is also evidence that despite the original brand price reductions, generic penetration doubled from roughly one quarter in 2003 to one-half in 2004 (CEPS, 2005). Thus, the reduction of original brand prices did not crowd out an increase in generic penetration. Moreover, it was estimated that net of the sales taxes on pharmaceuticals, the lower original brand prices resulted in a cost savings of 25 million Euros in 2003, and the reduction in generic prices an additional 7 million Euros (CEPS 2005).

There have been a number of attempts in France to encourage physicians to prescribe generic products. In 1997, an agreement between the social health insurance and doctors' associations introduced a program called "reference doctors,"

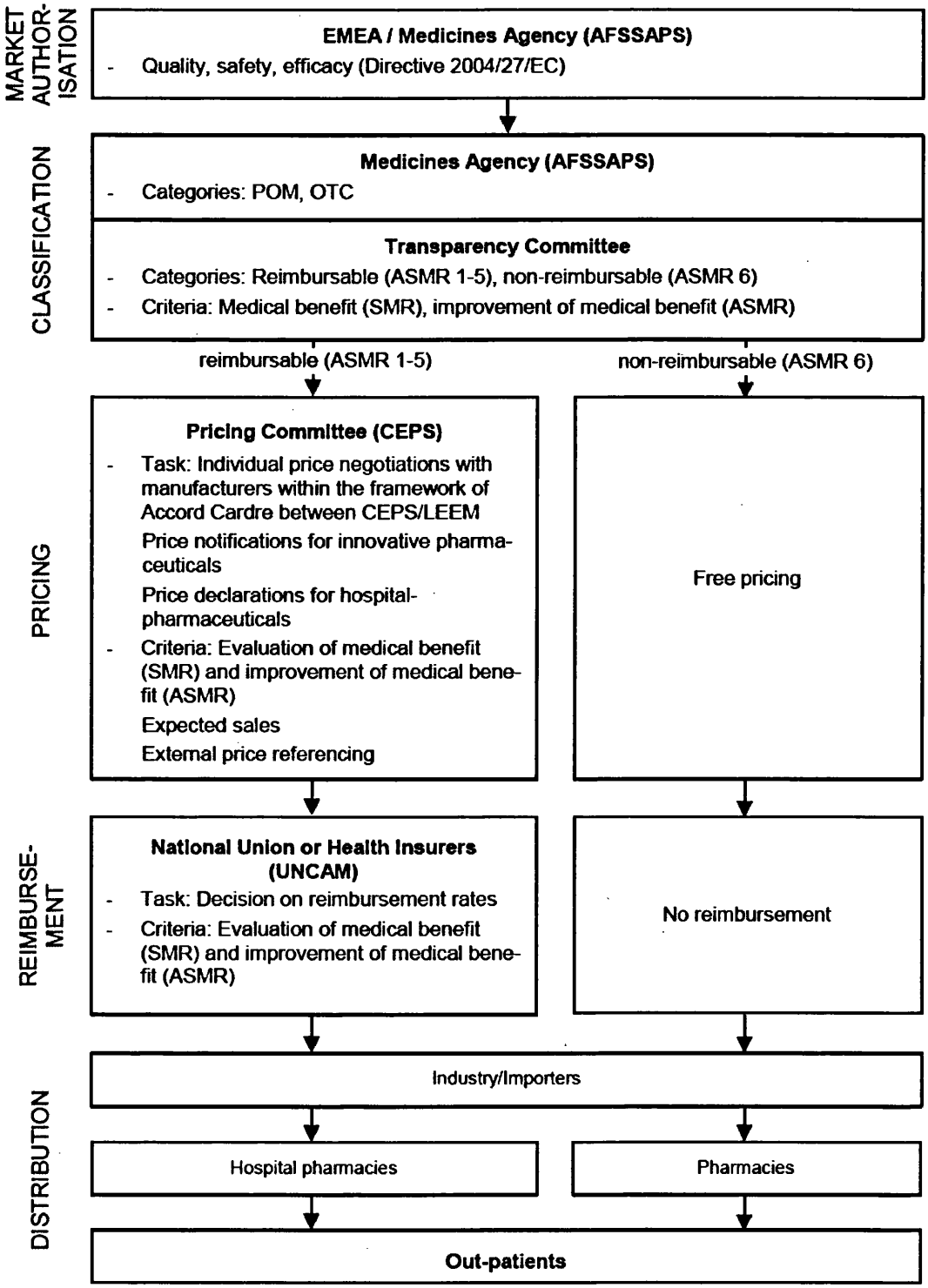
(also called the French "gate-keeper" system) in which participating doctors agreed to prescribe less expensive pharmaceuticals for 15% of their prescriptions in exchange for an annual fee per patient. In 2002, this program was revised to target generic prescribing more aggressively by increasing the annual fee in exchange for physicians committing to prescribe by the international non-propriety name (INN) or a specific generic for at least 25% of their prescriptions (OBIG, 2006). Consistent with this program, it was first made legal in 2002 for physicians to prescribe a drug by its generic name instead of its brand name (Kanavos and Gemmill, 2005).

In addition, there have been a number of policy changes that target pharmacists in an attempt to increase generic use. There are tight regulations surrounding pharmacies in France. Mail order and internet sales of pharmaceuticals are prohibited, as is the ownership of pharmacy chains. In 1999, a Decree made it legal for pharmacists to substitute branded medicines for generics, which the pharmacist association agreed to do in at least 35% of cases. In return for meeting this target, pharmacists were guaranteed a generic profit margin that was at least equal to the brand equivalents (Sandier, Paris and Polton, 2004). Another policy change targeting pharmacists was the move from a linear mark-up scheme to a two-scale regressive mark-up scheme in 1999 and the addition of a third scale in 2004. As a result, the current mark-up framework is 26.1% for drugs between 0 and €22.90, 10% for drugs between €22.91 and €150 and 5% for drugs greater than €150. There is also a flat rate of €0.53 that is given to pharmacists. Additionally, for generic drugs that are not part of the reference price system, the pharmacists are allowed to mark-up the same amount that they would for the original brand equivalent (OBIG, 2006). This negates any financial incentive that pharmacists would have had to dispense original brand drugs over generics. Similarly, the wholesale mark-up scheme is also regressive in an attempt to encourage generics: 10.3% for drugs between €0 and €22.90, 6% for drugs between €22.91 and €150 and 2% for drugs between €150. In addition to the wholesale and retail mark-ups, there is a value-added tax of 2.1% for reimbursable pharmaceuticals and 5.5% for nonreimbursables. This compares to the standard VAT of 20.6% (OBIG, 2006). Finally, pharmacies and wholesalers are permitted to negotiate discounts. For pharmacies, the discounts are not to exceed 2.5% of the original brand manufacturer prices and 10.74% of the generic manufacturer prices. Thus, this is yet another example of a policy that encourages the use of generics.

Unlike in the USA, pharmaceutical cost sharing in France is not heavily utilized as a cost containment mechanism (either in the form of revenue raising or in reducing demand). There are no flat prescription co-payments in France, although in theory, cost-sharing rates are high for the drugs that are not reimbursed (representing over half of all pharmaceuticals marketed in France) and for drugs that are only reimbursed at 35% and 65% (OBIG, 2006). However, in practice the majority of the population has supplementary insurance called Mutuelles, which covers these cost sharing requirements. In addition, patients who have serious diseases and/or disabilities are exempt from cost-sharing requirements, which represents roughly 12% of the population (CEPS, 2005). Finally, the introduction of the reference price system theoretically exposes patients to a greater share of pharmaceutical costs, where drugs are priced above the reference price. However, because most patients in France are not accustomed to having to share in pharmaceutical costs, evidence shows that patients are rarely willing to pay the difference (between the reference price and the actual price), which effectively reduces the market share of drugs above the reference price down to almost zero. This explains the above finding that the majority of original brand manufacturers reduced their prices to the reference price in 2003.

Finally, parallel export has been a common practice in France due to its relatively lower patented drug prices (in contrast with parallel importing, which is used as a cost containment mechanism in the USA, Germany and the UK). However, the introduction of the price notification system may result in patented prices aligning more closely with other major pharmaceutical markets, thereby reducing the practice of parallel exporting in France. Figure 2-1 summarises pharmaceutical regulations in France as of 2006.

Figure 0-1 Pharmaceutical Regulations in France, 2006



Note: The ASMR rating (reimbursement status) is independent from the prescription status (POM and OTC).
Source: ÖBIG 2006

Germany: A relatively free market approach to pharmaceutical cost containment, combined with reference pricing

Similarly to France and the USA, the criterion for marketing authorization in Germany is safety and efficacy. There are three ways a manufacturer can receive marketing authorization—through the EMEA, through the mutual recognition process in the EU (by obtaining marketing authorization in one of the other relevant countries first, in which case the Federal Institute for Pharmaceuticals and Medical Devices can only deny the transferred approval if there is a threat to the public's safety) and through Germany's national Federal Institute for Pharmaceuticals and medical Devices. One report claims that since the national process only requires demonstration of a marginal therapeutic benefit, using a small sample, many active substances of "merely minor modifications rather than real product innovations" are approved (Busse and Riesberg, 2004). The result is that the German pharmaceutical market consists of many presentations (i.e. strength/form/package size permutations) for a given molecule, which resulted in more than 9,449 presentations, of which 90% related to only 2,300 molecules (Busse and Riesberg, 2004).

Once a manufacturer has received marketing authorization for its drug, it may price feely and in most cases, is covered by the sickness funds. (The caveat to this free market approach is the reference pricing system, discussed below.) Until the 2003, the only drugs that were excluded from reimbursement for adults were those that treated "trivial" diseases, such as common colds, laxatives and motion sickness, and inefficient pharmaceuticals, such as certain combination drugs (OBIG, 2006; Kanavos and Gemmill, 2005). Thus, many over-the-counter drugs were covered. As a result, there was a large OTC market in Germany, amounting to €922 million OTC sales in 2002, which accounted for 21% of the total pharmaceutical purchases that year (Busse and Riesberg, 2004).

However, the 2004 SHI Modernization Act excluded the majority of OTC drugs from coverage, while retaining coverage of 36 specific OTC drugs that treat serious conditions (OBIG, 2006). In addition, coverage of most OTCs was also retained for children under the age of 12. In addition to OTCs and the original exclusions of trivial and inefficient drugs, "lifestyle" drugs, such as drugs that increase sexual drive, appetite suppressants and hair restorers, were also put onto the negative list in 2004 (OBIG, 2006). At the same time that most OTC drugs were

delisted, the distribution chain margins were also liberalized for these drugs, allowing pharmacies to price OTC drugs freely.[83] Meanwhile, the 36 OTC drugs that retained coverage are subject to the distribution chain regulations and the reimbursement system (i.e. the reference price system), similarly to the covered prescription medicines.

Unlike many other countries in Europe, Germany allows its manufacturers to set their own prices, independent of the prices in other countries. Rather than engaging in the practice of external reference pricing, as France partially does in the CEPS negotiation, Germany has become one of the countries that is most referenced by other EU countries. For this reason, manufacturers often set high prices in Germany so that they influence prices upwards in other markets (OBIG, 2006). However, despite allowing manufacturers to price freely, Germany still retains the authority to indirectly control pharmaceutical prices by mandating rebates and/or freezing prices. In 2003, there was a compulsory manufacturer rebate of 6%, payable to the sickness funds. Additionally, the 2004 SHI Modernization Act levied a 16% rebate on the manufacturer price of products that were not part of the reference price system (i.e. patented products) until the implementation of the reformed reference price system in 2005, after which point the rebate decreased to 6% (IMS World Markets). Finally, generics and original brand equivalents were subject to manufacturer rebates of 10% in May of 2006, with the exception of drugs that were already priced 30% below the reference price (OBIG, 2006). In addition to mandated rebates, there have been number of manufacturer price freezes. From January 1, 2003 to December 31, 2004, patented drugs' manufacturer prices were frozen at the October 1, 2002 price level. In addition, the Act on Economic Provision with Pharmaceuticals introduced a manufacturer price freeze for all medicines (at the November 1, 2005 level) from May 1, 2006 to March 31, 2008 (OBIG, 2006).

In addition to controlling pharmaceutical expenditures through rebates, price freezes and a negative list of coverage exclusions, Germany has a strong history of encouraging generic drug use. It is most well-known for its longstanding reference

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[83] Interestingly, one study found that this liberalization of the OTC distribution chain resulted in higher OTC prices (Germany HiT). One possible explanation for this may be that at the same time these OTC mark-ups were liberalized, these drugs were also delisted, resulting in only the price insensitive portion of the market purchasing these drugs (since the cost to a patient increased from the stipulated co-payment to the full cost of the drug itself).

price system, whereby a maximum reimbursement price is set for a group of drugs, requiring patients to pay any excess in price above the reimbursement price. Until the 2004 SHI Modernization Act, the reference price system applied only to off-patent drugs at the molecule level, grouping together all original brand drugs and their generic equivalents. The effect of this reference price system was that generic penetration (% of the total pharmaceutical market, in volume) increased from 10.9% in 1981 (prior to the reference price system, which was introduced in 1989) to 55.2% in 2004 (OBIG, 2006). As of 2003, 61% of prescriptions in Germany and 37% of total pharmaceutical expenditures were for reference priced medicines (Busse and Riesberg, 2004). Thus, until 2004, patented drugs were excluded from the reference price system, and reimbursed in full (with the exception of the mandated rebates).

One of the most significant changes in the 2004 SHI Modernization Act was the creation of therapeutic reference price groups, often referred to as Jumbo groups. Under this revised system, there are three different reference groups. Reference group 1 combines drugs of the same molecule into one group (i.e. the old reference price system). Reference group 2 combines drugs of different molecules, but similar therapeutic mechanisms, such as Proton Pump Inhibitors. Reference group 3 combines drugs of different therapeutic classes that treat the same condition, such as heartburn/reflux. The Federal Association of Sickness Funds is responsible for calculating the reference prices for these respective groups.

This new system represents a significant departure from previous pharmaceutical policy in Germany in that all patented prescription drugs that were covered by the sickness funds used to be excluded from the reference price system and reimbursed in full. Under the new regulations, however, patented drugs that are determined to be "without significant therapeutic advantage" have been included in groups 2 and 3 of the reference price system (OBIG, 2006). The new German Institute for Quality and Efficiency in Health Care (Institut for Qualitat und Wirtschaftlichkeit im Gesundheitsweserr, IQWiG) is responsible for evaluating drugs' therapeutic advantages and determining whether or not the drug should be part of the reference price system. Notably, it does not base its evaluations on cost-effectiveness criteria, but rather on the relative therapeutic benefit of drugs, as well as the drug's safety profile. If it decides that the drug is in fact "innovative" and is therefore therapeutically superior to all other drugs on the market, it excludes it from the reference price system and the drug is reimbursed in full by the sickness funds.

If, however, it decides that the drug is not therapeutically superior to its peers (e.g. so called "me-too" drugs), then it includes it in the reference price system, under which the drug is only reimbursed at its group's reference price. Thus, under this system, some patented drugs may be grouped with generics of other molecules, which are likely priced significantly lower than the patented drug, thereby influencing the reference price downwards, and resulting in the patented drug manufacturer being reimbursed at a relatively small fraction of its desired price. Not surprisingly, this policy is controversial, and has been adamantly opposed by most of the pharmaceutical industry.

IQWiG conducted its first evaluations on whether to include products into the reference pricing system in 2004, after which point the Federal Healthcare Committee, which is responsible for forming the actual reference groups, announced the first therapeutic reference groups. Effective on August 2004, statins, sartans, triptans and proton pump inhibitors became the first "jumbo" reference groups, with the goal of the German government being to eventually include 70-80% of all drugs in the reference pricing system (Decision Resources, 2005). Manufacturers of patented drugs in these classes have to reduce their prices to the reference price level in order to avoid a collapse in market share since most patients are not prepared to pay both the flat-rate pharmaceutical co-payment and the portion of the drug's price in excess of the reference price. As a result, few drugs in Germany are priced above the reference price (Kanavos and Gemmill, 2005). One exception was in the case of Pfizer's Sortis (atorvastatin). Because the prices of patented drugs in Germany are often reference by other EU countries, Pfizer refused to lower the price of its Sortis, which was still on patent, and which it claimed was therapeutically superior to other drugs in its class. Consistent with the claim that Sortis was therapeutically superios, a survey found that 58% of German physicians would have prescribed Sortis had it not been priced above the reference price. However, only 3% continued to prescribe Sortis despite its price premium (Decision Resources, 2005). The result was a "disastrous collapse" in Sortis' market share in Germany (Decision Resources, 2005).

Finally, regulations stipulate that group 1 reference prices not exceed the highest price in the lowest third of the reference group prices (OBIG, 2006). Legislation does not dictate how the reference prices are calculated for groups 2 and 3. However, in practice, different strengths of a group of drugs have received their

own reference prices. There has been some discussion of introducing daily cost of therapy limits as part of the reference pricing system (Decision Resources, 2005). If this were to happen, this could significantly alter the pharmaceutical market in Germany by reducing the current multitude of drug presentations for each molecule.

In addition to containing pharmaceutical expenditures through price cuts and freezes, and by expanding the reference pricing system, the SHI Modernization Act increased patient pharmaceutical cost-sharing. In 2003, before the new regulations, patients paid between €4 and €5 for a covered drug, on top of any difference between the reference price and the actual price (if the actual price was higher than the reference price). The 2004 SHI Modernization Act increased these cost-sharing requirements to 10% of the pharmacy retail price, with a minimum fee of €10 and an out-of-pocket maximum of 2% of a person's annual gross income. Similarly to before 2004, this is also in addition to any additional cost-sharing through the reference price system (Busse and Riesberg, 2004).

Germany also has a history of targeting physicians' spending and prescribing patterns in order to achieve efficient purchasing. During the 1993-2001 period, physicians were subject to pharmaceutical spending caps, above which they were legally liable to return a percentage of money to the sickness funds. However, this practice proved difficult to enforce, so in 2001, this system was abolished in favour of a more consensual process in which regional physicians' associations and the associations of sickness funds negotiate annual budgets, which do not contain mandatory pecuniary penalties, but do play a significant role in the contractual process. Both individual physician and regional spending targets are negotiated. The individual physician spending target is set according to the average physician prescribing costs per patient per year within each region. If physicians exceed their target by more then 25%, he/she may have to pay back a portion of the difference (usually the overspent amount minus 115% of the target) to the sickness funds. At the regional level, guidelines are set which encourage generic prescribing and parallel imports. In some cases, bonuses are offered to physicians that meet these regional targets. As a result of these pharmaceutical spending budgets and the reference price system, physicians in Germany were prescribing generic drugs in 75% of possible prescriptions in 2003. This was one of the highest generic prescribing rates in the EU in 2003 (Busse and Riesberg, 2004).

In addition to giving physicians the incentive to prescribe generics, pharmacists in Germany have also been targeted in the quest for pharmaceutical cost containment. As of February 2002, pharmacists have been required to substitute a generic for an original brand drug, unless the physician opposed it. Between July 2002 and August 2003, pharmacists were required to substitute in the case of 184 out of 680 molecules that had generic versions, which comprised 35% of the prescriptions in the generic market and 29% of generic market sales (Kanavos and Gemmill, 2005). The price range for generic substitution was calculated as the average price of the three most expensive and the three cheapest available generics (OBIG, 2006). The SHI Modernization Act of 2004 attempted to make the mandatory substitution consistent with the reference price system by ensuring that the reference prices were set below the substitution price line.

In addition to pharmacists having the authority to substitute generics, regulatory changes have also attempted to encourage substitution of low cost generics by reforming the wholesale and pharmacist mark-up allowances. Prior to 2003, pharmacists margins were digressively scaled, which gave pharmacists the financial incentive to dispense the most expensive products (although the absolute mark-up allowance was reduced shortly before 2004). However, the SHI Modernization Act of 2004 reformed pharmacists' margins to a flat-rate payment of €8.10 per prescription, plus a fixed margin of 3% of the wholesaler price. The Act also created regressively scaled margins for reimbursed OTC products, ranging from 68% for products in the €0.0 - €1.22 price range to 30% for products in the €35.95 - €543.92 price range. This replaced the old digressively scaled margins prior to 2004. Non-reimbursed OTC medicines are not subject to regulated margins as of 2004, but rather can be priced freely by the manufacturers, wholesalers and retailers. As part of the distribution chain regulatory changes, the 2004 Act also regressively scaled wholesaler margins for prescription-only medicines and reimbursable OTC medicines. Finally, Germany also levied a 16% valued-added tax onto its pharmaceuticals, which increased to 19% in 2007. Although this percentage is relatively low, compared to the VAT in other EU countries, it is a relatively high VAT for pharmaceuticals since most countries apply a lower VAT to pharmaceuticals than other products (Busse and Riesberg, 2004).

Similarly to the manufacturer rebate, pharmacies and wholesalers have also been required to give rebates. The pharmacy rebate rose from 5% until 2002 to 6%

in 2003 and changed to a flat rate of €2 per prescription-only drug after the SHI Modernization Act of 2004. As of 2005, however, the rebate is negotiated between the Federal Association of Sickness Funds and the Federal Association of Pharmacists' Organizations. In 2003, the total rebate amount from manufacturers, wholesalers, and pharmacists amounted to €3.1 billion (11.6% of pharmaceutical sales). However, pharmaceutical expenditures still grew by 2% during this period (Busse and Riesberg, 2004).

In addition to attempting to contain pharmaceutical costs by encouraging the purchase of more efficient drugs, the SHI Modernization Act of 2004 liberalized many of the rules for pharmacies in Germany. Prior to 2003, pharmacy chains were not permitted. However, as of 2004, pharmacists may own up to four pharmacies, which must be in the same or nearby county (Busse and Riesberg, 2004). In addition, as is discussed above, the majority of OTC products can now be priced freely (although they are not reimbursable). The purchase of pharmaceuticals via the internet is also now allowed. From January 2004 to July 2004, roughly 600 pharmacies took advantage of this new allowance by obtaining licenses to engage in e-commerce (Busse and Riesberg, 2004). The other component to the pharmacy market liberalization in 2004 was the allowance of mail order prescription and OTC drugs. In order to obtain a medicine via the mail, a patient must first send the prescription into a pharmacy. He pharmacist then sends the medication to the patient and the bill to the sickness fun. In theory, the patient must still make the co-payment, although the logistics behind how this happens are not clearly set out in the Act (Kanavos and Gemmill, 2005).

Finally, parallel trade has been a significant component of pharmaceutical cost containment in Germany. In 2000, pharmacists were required to substitute branded products with the imported equivalent whenever the imported version was at least 10% cheaper. As a result, the market share of imported pharmaceuticals rose from 1.8% in 1998 to 5.8% in 2001. However, the SHI Modernization Act of 2004 stipulated that imported prices be at least 15% (instead of 10%) cheaper in order to be substituted, which resulted in a decrease in parallel trade (OBIG, 2006).

The UK: A relatively free market approach to pharmaceutical cost containment combined with free market incentives

In the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) is responsible for approving the market authorisation of pharmaceuticals, based on the criteria of safety and effectiveness. In addition, like the FDA and most other pharmaceutical regulatory bodies, the MHRA continues to monitor the safety of drugs that are already on the market. The MHRA has three classification categories for drugs marketed in the UK—prescription-only medicines (POM), OTC pharmacy-only medicines (P) and OTC general sales (GS) medicines. The prescription only medicines can only be obtained through a prescription from a physician, while the pharmacy-only medicines sit behind the counter in pharmacies, where patients must request the medicine from the pharmacist. There are no restrictions for the general sales medicines, however, which may be sold at food stores and other retail outlets. Between 1999 and 2002, the MHRA approved the switch of about 50 medicines, largely for reasons of cost containment (OBIG, 2006).

The majority of OTC (both behind-the-counter and general sales status medicines) are not covered by the NHS. However, almost all prescription-only medicines in the UK are covered by the National Health Service. The exceptions are in the case of the Black List and the Grey List. The Black List is comprised of medicines such as diet pills, vitamins and herbal preparations. While the NHS does not cover medicines on the Black List, physicians may prescribe these medicines to NHS patients who are willing to pay the full price out-of-pocket (OBIG, 2006). There is also a Grey List, which consists of medicines that the NHS only covers for specific indications and patient groups. Like Black Listed drugs, physicians can still prescribe the medicine to patients who are not eligible, but are willing to cover the full cost of the drug. The Grey List is small, and consists mostly of substances that treat erectile dysfunction.

The vast majority of drugs that are not placed on the Black List or Grey List are covered, unless they receive a negative recommendation by the National Institute of Clinical Efficacy (NICE). The National Institute of Clinical Efficacy is an institute that employees health economists who evaluate the clinical efficacy and resource implications of new medicines. Thus, it operates independently from the NHS in its decisions. In practice, NICE tends to recommend that physicians

prescribe a drug if it costs less than $30,000 per quality adjusted life year, although this threshold is not official. Recently, NICE announced the decision to increase the $30,000 threshold for drugs that extend life (by at least 3 months, according to evidence) for patients with less than two years to live (BBC, 2009). NICE's negative decisions are meant to be binding, although the pharmaceutical industry and patient groups have the right to appeal the decision. Some healthcare policymakers criticize NICE as a rationing tool. However, in practice, NICE makes few negative recommendations.

The operation of NICE has also become a model for many other countries that are interested in introducing cost-effectiveness evaluations into their pharmaceutical policy. That isn't to say, however, that there aren't inefficiencies in the practice of NICE itself. NICE's evaluation of a new drug does not begin until the drug has received a marketing license from the MHRA. It then usually takes at least a year to complete the evaluation, during which time many physicians are hesitant to prescribe the drug in the event that it receives a negative evaluation, a problem referred to as "NHS blight" (The Royal College of Physicians of Edinburgh).

There are two different pharmaceutical policy schemes in the UK—one for branded drugs and one for generics. Notably, off-patent branded drugs used to be included in the PPRS scheme, but were shifted to the generic policies scheme in 2005. The scheme for on-patent brand drugs is called the Pharmaceutical Pricing Reimbursement Scheme (PPRS). The aims of the PPRS are to:

> Secure the provision of safe and effective medicines for the NHS at reasonable prices, promote a strong and profitable pharmaceutical industry capable of such sustained research and development expenditure as should lead to the future availability of new and improved medicines, and encourage the efficient and competitive development and supply of medicines to pharmaceutical markets in this and other countries. (OFT, 2007)

There are two components to the PPRS, profit controls and price controls. Under the profit control requirement, firms must repay any excess profits to the DH beyond a set maximum level of profits that they are allowed for their branded drugs. In practice, however, the difficulties in the DH assessing profitability (due to an increasingly global cost base and a high level of intangible capital) have resulted in negligible profit payments during the 1999-2004 scheme. Instead, the price controls

component of the PPRS is the strongest mechanism for containing costs. Under the price controls component, pharmaceutical manufacturers may freely set prices for their new medicines. However, price increases may be restricted. In addition, the renegotiation of the PPRS scheme, which is conducted every five years, often includes stipulated price cuts. The 1999-2004 scheme included a price cut of 4.5%, which produced annual savings of roughly £260 million. The 2005 scheme's price cut was increased to 7%, which was estimated to produce annual savings of £370 million. Under these price cut stipulations, manufacturers are only required to reduce the weighted purchased price of all of their drugs by the stipulated amount, so have the freedom to vary the prices of individual drugs.

In 2007, the Office of Fair Trade released a report that criticizes the PPRS and suggests a new system of patented drug pricing. In this report, they claim that the prices of branded drugs in the UK are significantly lower than in the USA, but higher than the price of branded drugs in all other European comparator countries, except for Ireland and Germany. The advantages to the scheme are that it allows for the quick introduction of new drugs, a quick and easy savings mechanism through price cutting, low administrative costs and the economic and therapeutic benefits (i.e. innovative medicines) of a profitable pharmaceutical industry. However, they claim that the disadvantages outweigh these advantages. The disadvantages to the price cuts are that they are not based on the value of drugs, may hurt smaller companies since they have a smaller portfolio of drugs to vary prices between and that a circular game of price cut anticipation may result, whereby drug companies anticipate the price cuts by introducing higher prices in the first instance and the DH anticipates this strategy by introducing larger price cuts. The disadvantages to the profit control component are: 1) free prices do not reflect therapeutic value, so do not provide companies with the right investment incentives, 2) companies do not have the incentive to invest in the UK because R&D allowances apply globally, not just R&D incurred in the UK. In response to these critiques, the OFT proposed a new ex-post value based pricing scheme for branded drugs, whereby maximum prices are set according to the clinical benefits of a new drug, relative to an appropriate comparator (OFT, 2007). Whether the DH will take any of the OFT suggestions is still undetermined.

In the majority of cases, generic prices in the UK are determined by the generic manufacturers and wholesalers. Specifically, the Department of Health sets a

reimbursement price for each molecule of a given strength that is based on reported manufacturer and wholesaler prices (The Drug Tariff, 2005). The exception was in the case of drugs that were subject to the Maximum Price Scheme from 1999 to 2005, under which the price of products that were in danger of supply shortages were capped at the level set by the manufacturer. This ensured that the NHS would not experience high price increases for drugs such as antibiotics. In 2006, this Maximum Price Scheme was replaced with a new policy that requires manufacturers of drugs that may be in short supply to obtain authorisation from the Department of Health for a price increase. In addition, to monitor the supply, manufacturers must submit quarterly information on generic medicines income revenues, cost of purchases and volume transactions.

Because the Drug Tariff prices are based on manufacturer and wholesaler prices, retailers are able to negotiate significant discounts during the procurement process. As a result, the Drug Tariff includes a clawback, through which the NHS is able to recoup a percentage of the savings from the discounts in the distribution chain. The NHS intentionally leaves a portion of the discounts for the pharmacists in order to provide pharmacists with the incentive to negotiate further price reductions. This is implemented through the Prescription Pricing Authority, which adjusts pharmacists' payments accordingly. The clawback ranges from 5.93% to 12.52% and depends on the volume of prescriptions dispensed on a monthly basis (Kanavos, 2007). Smaller pharmacies (i.e. pharmacies with smaller volumes) have a smaller percentage clawed back since they cannot reap the benefits of economies of scale. Information on the level of discounts has been obtained through a survey called the 'discount (margin) inquiry,' which uses prices from a sample of 300 pharmacies in order to determine the clawback (OBIG, 2006). Notably, chain pharmacies have been excluded from this survey, although they are still obligated to pay the clawback (Kanavos, 2007). The justification for this is that since chain pharmacies can leverage their purchasing power to negotiate larger discounts, including their discount information in the clawback calculation would result in a higher clawback that would hurt smaller pharmacies. However, on the flip side of the coin, the result of not including chain pharmacies in the clawback calculation is that they are able to retain a larger share of the discounts they negotiate than smaller pharmacies. In an attempt to ensure that the NHS is paying a fair price for medicines, all manufacturers

and wholesalers are now required to submit information on average prices, net of discounts offered. This information is publicly available.

As is discussed above, wholesale and generic retail margins are not controlled for generic medicines. For generic medicines, in addition to the share of the discount margin they are able to retain (less the clawback), pharmacists are also compensated on a fee-for-service principle, whereby they are remunerated the net ingredient cost of the pharmaceutical, which is listed in the Drug Tariff, as well as a dispensing fee of £0.9 per dispensed medicine (OBIG, 2006). For branded medicines, the PPRS limits the wholesale margin/discount to 12.5% off the NHS price. The wholesaler is free to pass on a portion of this margin to the pharmacists. Thus, in practice, the wholesaler margin is significantly below the capped 12.5%. According to the British Association of Pharmaceutical Wholesalers, on average 9% of the 12.5% margin is passed on to pharmacists, leaving wholesalers with a 3.5% margin (OBIG, 2006). There is no VAT on pharmaceuticals in the UK, with the exception of OTC pharmaceuticals, non-reimbursed private prescriptions and pharmaceuticals sold in hospital pharmacies, which are subject to the standard VAT rate of 17.5%.

On April 1 2005, a new contractual framework was introduced for pharmacists, through which their roles were widened. As of 2005, pharmacists in the UK can train to independently diagnose and prescribe a wide range of medicines to patients. Granting pharmacists this degree of responsibility is unique to the UK within the European Union. (Certain medicine classes, such as narcotics, remain the sole control of physicians.) While the initial treatment of patients is still meant to remain with the physicians, pharmacists may use diagnostic and prescribing skills to monitor the ongoing care of patients with chronic conditions. In return for such services, pharmacists are now reimbursed for the range and quality of services they provide rather than reimbursement being solely based on the volume of medicines they dispense. In addition to diagnosing and prescribing, examples of additional pharmacists' services include smoking cessation counselling and blood pressure checks (Kanavos and Gemmill, 2005). Thus, the strengthening of relationships between pharmacists and patients increases pharmacists' responsibilities as well as patients' responsibilities over their own health.

As part of the 2005 reform, the DH is also in the process of permitting the practice of on-line and mail-order pharmacies. Currently, on-line and mail-order pharmacies are only allowed to operate if they also have a "bricks and mortar" store,

through which the patient can receive professional services. However, under this new regulations, on-line and mail-order stores can operate without "bricks and mortar" branches as long as they continue to provide full professional services.

The one responsibility that pharmaceutical policy has not given to pharmacists in the UK is that of generic substitution. That is, if a physician prescribes a drug by its brand name, the pharmacists cannot dispense a generic equivalent. This differentiates the UK from most other countries in the European Union and the USA. Instead, pharmaceutical policy in the UK encourages the physicians to prescribe by the INN International Nonpropriety Name (INN). One of the ways some Primary Care Trusts incentivize physicians to prescribe this way is by offering them a percentage of their budgets surpluses for reinvestment into practice services and facilities (OBIG, 2006). As a result, in 2004, roughly 80% of prescriptions in the UK were written by the INN. The pharmacist may then choose to dispense whichever product (of that given strength/molecule combination) it choose. Since pharmacists' margins from generic medicines are usually significantly higher than the margins from brand name medicines, pharmacists are more apt to dispense a generic version of a drug when it is prescribed by the INN (Kanavos 2007). Thus, of the 80% of prescriptions that were written by the INN, 55.4% were dispensed generically. The majority of the other 44.6% were likely still on patent (Kanavos, 2007).

In addition to prescribing by the INN, there are multiple other ways in which the UK seeks to improve cost-effective prescribing. As is mentioned above, NICE recommendations are binding. This is taking into account in the determination of the prescribing budgets that the PCTs set, which cover regional spending on primary care over a three year period and is adjusted for by the local area's morbidity patterns and socioeconomic status. Individual physicians also receive performance reports from the Prescription Pricing Authority on their prescribing and expenditure profiles, compared with local and national averages. Benchmarking is also used through the Indicative Prescribing Scheme, which evaluates physicians' prescribing costs. Despite these benchmarking practices and soft money financial incentive mechanisms, there are not explicit financial sanctions for physicians who overspend their prescribing budgets. Finally, physicians in the UK use a computerized decision support system called PRODIGY (Prescribing Rationally with Decision Support in General Practice) which assists their prescribing decisions.

As another pharmaceutical cost containment measure, patients are required to pay a fee for each prescription. The amount—£6.50 in April 2005—increases each year by the British Consumer Price Index. However, roughly half of the UK population is exempt from having to pay the prescription fee (OBIG, 2006), including the following groups of people:

- All people aged 60 years or older
- Children under 16 years old
- Full-time students aged 16,17 and 18 years
- Pregnant women and women who have had a child in the previous 12 months
- Individuals who need medications pertaining to the disablement of war
- Individuals who have certain chronic medical conditions
- Individuals from households that receive income support, pension credit guarantee credit, or income-based jobseeker's allowance tax credit where income is £15,050 pounds per year or less (Kanavos and Gemmill 2005).

As a result of these exemptions and the fact that these populations consume a disproportionate share of the total prescriptions in the UK, only about 15% of dispensed prescriptions incur a prescription charge (Kanavos and Gemmill 2005). Thus, the prescription fee in the UK acts more as a revenue raiser from a population of people with means than as a mechanism through which to curb demand.

Similarly to Germany, parallel trade plays a significant role in the UK pharmaceutical market. Roughly 90% of pharmacists in the UK stock and dispense parallel trade pharmaceuticals (OBIG, 2006). Since the NHS reimburses parallel trade pharmaceuticals at the same Drug Tariff price as pharmaceuticals sourced domestically, pharmacists are able to reap significantly larger profit margins on these lower priced imports. Moreover, while the clawback does apply to these imported pharmaceuticals, the practice of allowing pharmacists to retain a percentage of these margins still incentivizes them to dispense the parallel traded product over domestically sourced products. As a result, parallel imports in the UK account for 15-20% of all NHS pharmaceutical sales (OBIG, 2006).

APPENDIX B: OTC REGULATIONS IN THE USA AND THE UK

OTC Regulations in the USA

The prescription and OTC drug markets face similar regulatory standards in the USA in that they both must be approved by the U.S. Food and Drug Administration (FDA) and deemed to be safe and effective for their intended use. There are, however, some significant differences in the OTC market, and its regulatory standards. For one, whereas the distribution of outpatient prescription drugs is limited to retail pharmacies (including mail order pharmacies), consumers may purchase OTC drugs in local grocery stores, wholesale food stores (e.g. Kosko), mass merchandisers (e.g. Walmart), mail order outlets and pharmacies. These channels amount to roughly 750,000 retail outlets in the USA, compared to 55,000 retail pharmacies (Consumer Healthcare Products Association). Another difference between prescription and OTC medicines is that the FDA regulates direct-to-consumer advertising for prescription drugs, whereas the Federal Trade Commission regulates DTC advertising for OTC medicines, similarly to other consumer products.

The process of making a prescription-only medicine available in the OTC market is called a Rx-to-OTC switch. Since 1976, close to 90 ingredients or dosage strengths have made the Rx-to-OTC switch, which translates to over 700 OTC products (FDA, 2005). The FDA's Center for Drug Evaluation and Research (CDER) has an office of Nonprescription Drugs that is responsible for the review of these switch applications, and for medicines seeking entry into the OTC market straight away (without first being available with prescription).

As is mentioned in the above section on the cost of applying, OTC applications in the USA must demonstrate that the medicine has an established safety and efficacy record, and that the patient is capable of proper selection and de-selection. In order to demonstrate this, the FDA requires studies of patients' understanding of the OTC labelling before authorizing the switch. In addition to label comprehension studies, actual use studies must be submitted whenever OTC safety and effectiveness is in question (e.g. often in the case of a molecule that has not yet been approved OTC) in order to show whether consumers will behave appropriately. The reason for these requirements may be because the USA does not have the pharmacy-only category that the UK and many other European countries

have. Consequently, they do not have the option of putting drugs behind the counter in order to ensure that pharmacists give first time users a proper explanation. This lack of professional intermediary therefore requires that extra safety precautions are used, such as these studies. Thus, because OTC medicines are not supervised by physicians or pharmacists in the USA, there is a wider margin of safety that is required for OTC medicines, than for prescription medicines.

For example, the FDA has shown a degree of receptiveness to approving an OTC switch for Merck's Mevacor by being willing to reconsider the switch application three times, once in 2000, again in 2005, and most recently in 2008. In the most recent review, the FDA's preliminary report stated that OTC Mevacor would be "a reasonably safe and effective option," provided consumers are able to adhere to the guidelines. However, the actual use studies showed that one quarter of people would take the pill, even though they weren't high enough risks to make it worth risking the medication's side effects, while 30% of patients who were high enough risks to require physician supervision reported being willing to switch to the OTC version (Kaiser Daily Health Policy Report, 2007). Thus, the FDA eventually rejected the application on the grounds that with the current labelling, consumers may not be able to safely and effectively direct their own care, (Neergaard, 2008) and since the USA does not have a pharmacy category, it did not have this middle ground option.

Once a manufacturer files an OTC switch application, the FDA sets up an advisory committee of physicians, pharmacists, and academic researchers, which makes a recommendation to the agency after determining whether a drug is safe and effective, and whether consumers are capable of managing that drug on their own. An advisory committee is not convened for an Rx-to-OTC switch in cases where the switch product is in a line of similar products already switched, where there are no new or outstanding issues, and where the decision to switch the first in the line of these similar products was presented to the advisory committees and the advisory committee recommended approval.

In theory, the CDER aims to approve OTC applications within 10 months. However, in practice, the timeframe depends on the application in question. In some cases, the FDA may request additional data on safety, effectiveness or use. In addition, the FDA requires labelling revisions, which may take time. Thus, the case-

specific feedback during the review process sometimes results in the approval process taking longer than intended.

Technically, regulations allow any interested party to petition the FDA to switch a medicine to OTC status. However, in practice, the FDA deems that the original brand manufacturer knows the most about its molecule since it filed the original new drug application (NDA) in order to receive prescription status. As a result, the final decision of whether to apply for a switch (especially if a drug is still on patent) usually rests with the original brand manufacturer. This was seen when WellPoint, a health insurer, petitioned the FDA to switch loratadine, certirizine and fexofenadine. Although WellPoint was still responsible for providing evidence on the safety of the drug in the OTC market, the FDA ultimately deferred to the original brand manufacturers before making a final decision. Thus, only loratadine was switched in November 2002, in an attempt by Schering-Plough to avoid the impending generic competition.

Theoretically, the FDA can also initiate a switch. The only example of this was in 1982, when the FDA initiated a switch for metaproterenol, a medicine that treats asthma. However, because of a lot of negative criticism, the FDA rescinded its application shortly after it was filed. There are also unresolved questions as to how the FDA should use proprietary data, what regulations would give the FDA the authority to initiate an application, and what sort of review process would be appropriate in such a case. Thus, in practice, the FDA has refrained from initiating switches for other products.

Once a medicine is approved for OTC status, the same molecule can continue to be marketed as a prescription product if the OTC version is marketed at a lower dose and/or has been approved for a different use. Following approval, the USA also sometimes grants OTC market exclusivity of 3 years, as it did in the case of Prilosec (discussed further below). This is often done to compensate the applicant for the costly OTC safety studies that were performed as part of the application process. Market exclusivity therefore seems less likely in cases where extensive studies were not required, or where the studies where performed by a third party. Such was the case with the loratadine switch; since WellPoint was responsible for providing the safety evidence, Schering-Plough was not granted market exclusivity following the switch approval. As a result, generic equivalents were allowed to enter the OTC market immediately following the approval. Finally, if the switch is made by the

original brand directly following patent expiration, then it is also possible that the FDA may extend the patent for an extra 3 years, which would both prevent generic entry in the prescription market and give the original brand manufacturer a significant first mover advantage in the OTC market.

In recent years, the FDA has announced that it hopes to increase annual switches by 50%, and is currently targeting drugs that are available OTC in countries outside of the USA (Cohen, Paquette and Cairns, 2005). Potential switch therapeutic categories include oral contraceptives, asthma, osteoporosis, hypertension, and high cholesterol. As part of this process, the FDA has indicated that it will supplement its studies on label comprehension with evidence from foreign countries (IMS Health Intelligence, 2005). This possible willingness to consider data from foreign countries in the approval process signifies a shift in the regulatory culture of switching drugs to OTC status. Moreover, there is also some discussion on the possibility of introducing a behind the counter category in the USA, which was discussed 30 years ago, but dropped (IMS Health Intelligence, 2005).

OTC Regulations in the UK

The regulatory body in the UK that is responsible for overseeing switches to the OTC market is called the Medicines and Healthcare Regulatory Agency (MHRA). When necessary, the MHRA consults with a group called the Committee on the Safety of Medicines, which is similar in function to the FDA's Advisory Committee. Thus, the regulatory agency structure is similar in the UK and the USA. One significant difference, however, is that in accordance with the Medicines Act of 1968 and Directive 2001/83/EC, there are three different categories for medicines in the UK. Like the USA, there is a prescription only medicines (POM) category in the UK. The OTC category, however, is divided into two subgroups, pharmacy (P) and general sales list (GSL). A drug in the UK that has pharmacy status is only available with the supervision of a pharmacist and therefore can only be sold at pharmacies, whereas a drug with general sales list status may be sold in all retail stores, including supermarkets.

Similarly to the USA, the principle criteria the MHRA uses in deregulating a drug from prescription only status is safety. In order to demonstrate safety, the applicant must supply user testing of patient information leaflets (PILs). These tests must demonstrate that the information in the patient leaflet is accessible and

understandable to the population of people who are most likely to use the medicine. However, the switch regulations in the UK are unlike the USA's in that the applicant does not need to conduct an actual use study that demonstrates patients' abilities to properly select and deselect the OTC version. Instead, the applicant may be allowed to extrapolate from evidence on the medicines' safety in the prescription-only market, especially in circumstances where the drug is known to have few side effects, where the OTC version is a lower dose than the prescription only version and/or where the target OTC population is a subgroup of the target prescription-only population (MHRA). Once an application has been filed, the MHRA opens up the switch process to public consultation so that other stakeholders (e.g. physician groups, etc.) may comment on the safety of the drug in question. Notably, if the application is eventually approved, the new legal status (of P or GSL) will only apply to that one product; all other products of the same molecule must obtain their own marketing authorization if they too seek a new legal status.

Similarly to the USA, pharmaceutical manufacturers (both original brand and generic manufacturers), third parties and the MHRA itself may initiate a switch. In practice, however, a third party must obtain the support of a company that actually manufacturers the product in order to achieve approval. However, it does not need to be the original brand manufacturer. Moreover, since few safety studies are required, relative to the USA, the costs of applying may be relatively low, which could in turn make it easier for generic manufacturers to file an application. As a result of these relatively low costs of applying, the UK may also be less likely grant P or GSL market exclusivity to the applicant. However, each subsequent competitor must file their own application in order to receive its own market authorization license.

In addition, in 2004, Article 54 of Directive 2004/27/EC amended Directive 2001/83/EC by requiring that countries grant one year of data protection following the approval of a switch application (MHRA). This effectively means that any safety evidence that was provided by the manufacturer that initiated the switch cannot be used by the MHRA in the approval of a subsequent application by a different manufacturer for a year following the approval (of the initial switch). Subsequent applications must therefore be self-sufficient in achieving approval. Thus, while this does not confer market exclusivity for the manufacturer that initiates the switch, it may in practice slow down the entry of competitors, especially to the extent that the approval process is not quick.

Similarly to the USA, the approval time for OTC switches varies on a case by case basis. The MHRA classifies switch applications into one of three categories: 1) the standard procedure, which is for changes in package size and an extension of an existing indication within authorized use, 2) the variation procedure, which is for follow on products and 3) the complex procedure, which is for the switch of a drug in a therapeutic class that is not yet available OTC, or drugs that have new indications, routes of administration, patient groups or strengths (MHRA). Switch applications that proceed through the standard procedure route are often not referred to The Committee on the Safety of Medicines, and therefore usually have short approval times of around 120 days. Meanwhile, switch applications that proceed through the complex procedure route usually require committee approval, which takes approximately six weeks, increasing the total approval time to 180 days. Other factors that may vary approval times include the length of the public consultation process, and whether the applicant decides to appeal a negative recommendation.

Following The Medicines for Human Use and Medical Device (Fees and Miscellaneous Amendments) Regulations 2002 (SI 2002/542), separate marketing authorisations and licenses are required for products of the same molecule that have a different legal status. As a result, the MHRA requires that these products also have different brand names. An exception is where the only difference in products is the package size, in which case the same brand name can be used. This means that if a molecule is available as both POM and P status (and likewise for P and GSL), but has differing strengths and/or target different populations, then the products must be sold under different brand names, even if the manufacturer of the products is the same. The MHRA's rationale for this is that safety concerns could arise if the products are sold under the same name (MHRA), presumably because patients could mistake them as being intended for the same use.

Similarly to the USA, manufacturers typically initiate switches in the UK. However, in 2001, the MHRA came up with a list of medicines that it deemed eligible to be switched from POM to P status. It also drafted a strategic framework under which such switches could occur, which included protocols that identify target populations (for the OTC eligible medicines) and training programs for pharmacists and their staff (MHRA). Thus, there is evidence that a cultural shift is also happening within the MHRA, with regulators becoming more supportive of switches.

A primary example of this increasing support for P to POM switches was seen in 2004, when the MHRA approved a 10mg dosage form of Merck & Company's simvastatin for POM status, known as Zocor Heart Pro in the UK. In this case, Merck initiated the switch, and the MHRA approved it on the grounds that POM availability of the 10mg low-dose version would open up a new, preventative market for low risk patients. This low dose version was previously not available to this low risk population of patients under the NHS. Thus, NHS coverage of the medium to high strength simvastatin still remained under the prescription only category. This case was especially symbolic of the MHRA's increasing willingness to expand the pharmacy OTC market, as high cholesterol is a chronic disease that has serious implications for a patients' long term health. The seriousness of this disease category is therefore a double-edged sword. On the one hand, allowing patients who are at risk of high cholesterol to be responsible for their own selection and deselection of medicine could have serious consequences in the event that patients are not able to accurately do so and pharmacists do not provide sufficient guidance. Even where pharmacists do provide accurate guidance, OTC availability means that patients are still able to purchase statins without ever having had a cholesterol test. (Availability of OTC drugs for such a serious illness could also be especially risky, given the fact that the MHRA does not require actual OTC use studies, and therefore does not have a strong sense for how the target population in the OTC market will actually behave.) On the other hand, the potential long term health benefits resulting from increased access to preventative cholesterol lowering drugs could also be significant, as clearly stated by the British Heart Foundation, which found that a 10mg daily statin dose would reduce heart attack risk by 27% for people at risk (Sipkoff, 2004).

Thus, evidence shows that both the USA and the UK have become more receptive to over the counter switches with medicines that treat chronic diseases.