Brand-loyalty in pharmaceuticals: Evidence from the international literature

Panos Kanavos, PhD

and

Eri Nikou, MSc

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Abbreviations

ANDA : Abbreviated New Drug Application

CBO : Congressional Budget Office (USA)

DDD : Defined Daily Dose

DTCA : Direct To Consumer Advertising

FDA : Food and Drug Administration (USA)

GDP : Gross Domestic Product

HTA : Health Technology Assessment

IMS : Intercontinental Medical Statistics

INN : International Non-proprietary Name

IQWiG : Institute for Efficiency and Health Care Quality

KFF : Kaiser Family Foundation

NSAID : Non-Steroidal Anti-Inflammatory Drug

OECD : Organisation for Economic Cooperation and Development

OTC : Over The Counter

PE : Patent Expiry

PPI : Proton Pump Inhibitor

PhRMA : Pharmaceutical Research and Manufacturers of America

R&D : Research and Development

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Executive summary

1. Brand-loyalty theory has often been used in the health economic and pharmaceutical literature to explain the price-insensitivity of originator drug after the expiration of the patent and the entry of generics in the market. It has also been used to explain the preference for a particular branded medicine over another in therapeutic markets that are patent protected.
2. There are differences in the definition and perception of brand loyalty as it applies in pharmaceuticals and as it applies in marketing science. According to marketing science, a necessary and sufficient condition for brand-loyalty to exist is the presence of brands. In this context, a consumer is regarded as loyal when he shows a preference and buys a particular brand in a product category, because he believes that this brand offers the right product features, images or level of quality at the right price, giving him satisfaction.
3. This is slightly different to the situation that prevails in the pharmaceutical market place. Brands do exist in pharmaceuticals, but pharmaceutical markets display certain peculiarities, which call for an adaptation of the brand loyalty paradigm in this industry.
4. Prescription medicines cannot be purchased without doctors' prescription or pharmacists' authorisation and endorsement. Equally, the number of prescription medicines is very large and it is very difficult even for health care professionals to know all of them and there is no drug that is absolutely safe. Whereas brands are created through advertising, the advertising of prescription medicines directly to the public is prohibited in most countries and only detailing to health care professionals is allowed, although in an era of free access to information patients can acquire information about new treatments and medicines without much restriction. As a result, brand loyalty in pharmaceuticals increasingly applies to both physicians as well as to patients. Finally, the pharmaceutical sector is subjected to intense regulation pertaining to safety, quality, efficacy and, increasingly, cost-effectiveness by regulatory authorities, prior to medicines becoming available for human use. This further stimulates the creative branding process.
5. The peculiarities of the pharmaceutical sector mean that whereas from an industry perspective there is a powerful desire to create strong and lasting brands, in reality, this is subject to significant constraints for a number of reasons. First, health insurance frequently requires physicians to prescribe by INN rather than by brand-name. Second, it is unlikely that the physician will try the product himself, therefore, s/he relies on feedback about the action of the medicine from the patient or from the observation of the patient's medical tests. Third, there is a separation

between patients and prescribers. Patients can neither buy a prescription drug from the shelf of the store nor can know and judge the reactions and side effects of a continuously increasing and different variety of prescription drugs.

6. Although brand loyalty exists and frequently underwrites consumer (and proxy-consumer) behaviour in pharmaceutical markets, in practice it is very difficult to measure it with a significant degree of accuracy.
7. Nevertheless, two aspects of brand loyalty arise in pharmaceutical markets as a result of the pharmaceutical market structure and intellectual property rights protection. The first relates to brand loyalty in the context of competition at therapeutic class level within in-patent markets and accounts for the effect of product differentiation among close substitutes. The second relates to brand loyalty in the context of competition post-patent expiry and the extent to which pharmaceutical markets become genericised after the entry of generic competitors, the speed at which this occurs and whether the patent-expired originator brand retains a certain market share.
8. In branded in-patent markets, the extent to which a particular brand can maintain (significant) market share in the face of competition from other products in the same therapeutic category can be perceived as evidence of brand loyalty. Evidence exists from the statins class, whereby products entering the markets of France, the UK, the Netherlands and Germany first enjoyed "first mover advantages" and commanded higher prices than their competitors. When all statins were on the market, prices were not affected downwards and the market was divided out to the key players in this therapeutic class. Products therefore, compete on "quality", namely the attributes of their respective products, and, through that they create the brand loyalty to the respective consumers.
9. Whereas branded products may enjoy a degree of monopoly power through patent protection when first entering a market and are therefore in a position to develop brand loyalty of their own, the extent of substitutability and whether it is close among the products in the class, may erode some of the price advantages these products may have on the market. Highly substitutable products with little product differentiation among them are more likely to display poor brand loyalty Therefore, product differentiation is a necessary, but not a sufficient condition for clear brand loyalty advantages.
10. Brand-loyalty has also been used on a number of occasions in the health economic literature as an explanation for the price insensitivity of originator drug when its patent expires and generics enter into the market. Although cheaper versions of the originator drug are available the originator drug does not lose completely either its market share or its increased level of price, a fact that is being explained by the literature as brand-loyalty. This persistence of innovator drug against generic competitors could be connected with factors such as the

following: the existence of insurance coverage, the absence of financial incentives for doctors, patients' perceptions about generic drugs linking these with originator brand loyalty, issues around bioequivalence, the absence of substitution laws and financial incentives for pharmacists, the existence of strict regulation of price and reimbursement of drugs, the use of line-extensions, advertising and the market success of originator drugs.

11. The existence of insurance coverage for prescription medicines seems to be one factor that explains the persistence of brand-name drugs over generic equivalents. Pharmaceutical markets are often characterised by price inelastic demand because of extensive medical insurance moral hazard. Moral hazard is reflected in two instances: in that many patients dislike talking about cost with their doctor, and in their feeling that generic prescriptions are a strategy to reduce cost at the expense of patient quality of care.

12. Physicians are key decision-making agents for drug consumption and prescription medicines typically require a physician's prescription to be dispensed. In this context, branded medicines (whether branded generics or brand originator drugs) also seem to be preferred by doctors. Contributing factors for this include the non-existence of strict budgets or other financial measures restricting the freedom to prescribe the drug of choice. Additionally, physicians may often have doubts about the bioequivalence or therapeutic equivalence of generics in relation to their brand-name alternatives, although this is currently less the case.

13. In some countries, particularly lower income countries with weak regulatory regimes, prescribing a brand or the originator, is frequently the best choice for the patient. Finally, physicians may show an element of habit pushing patients to consume what they are used to (i.e. a brand) rather than a generic. Finally, physicians may prefer brand names because they may be familiar only with the brand-name of specific drugs and unaware of the correspondence between generic and brand-name drugs, thus continuing to prescribe the latter even when generic drugs are available for all the above reasons. This is largely dependent on the nature of training physicians receive once at medical school.

14. Patients' reservations about the use of generic medicines –particularly unbranded generics- has often led to conflict between them and their primary care physician, as physicians as well as pharmacists often find that patients have doubts about generic equivalence and show preference for (innovator) brand named medicines. More frequently than not, generic medicines can differ in appearance from their branded equivalents and in cases in which more than one generic drug is available, they may differ from each other. Not only may the colorants and excipients vary, but the size, shape and delivery formulation of the generic product also may differ considerably from the branded product.

These differences can cause anxiety and confusion in patients, especially in the elderly and occasionally result in a patient inadvertently taking two formulations simultaneously. There is evidence that patient preferences can also be a barrier to increased generic substitution. Patients may perceive brand-name products as being of higher quality compared to generic products. Frequently, patients with chronic diseases more often showed a negative attitude towards generic drugs, confirming assumptions from different authors that chronically ill patients perceive the consequences and risks of generic substitution as more serious and have more fear of health loss.

15. The system of pricing and reimbursement that is in operation in every country can provide an explanation about the persistence of brand name drugs against non-brands. It is easier for generics to enter in markets that have liberal pricing regimes than command and control regulation of pharmaceutical prices. Generic entry has a negative effect on originators prices' in countries with free pricing such as the US and those with free pricing subject to moderate regulations such as the UK, Germany and Canada, but none or even a positive effect in countries with strict price or reimbursement regulation such as France, Italy and Japan. Thus, the existence of strict regulations is one more reason for the persistence of branded drugs over non-brands. Finally, despite the increase in market entry of generic drugs, which was facilitated by Bolar provisions and explicit legislative acts, line extensions introduced for an original brand helps the original's price be rigid despite generic entry.
16. One of the fundamental hypotheses surrounding brand-loyalty is that it might contribute to drug adherence. This particular angle of the issue has not been explored explicitly in the literature, but what has been explored is the relationship between generic substitution and adherence. Yet, research shows that the link between generic substitution and adherence to medicines is weak although consumers tend to re-use those medicines that have already worked for them, and are reluctant to try medicines that they have not tested before and may not suit them. Finally, after discontinuation of brand-name coverage, patients were found more likely to use less medication, stop medications, and not start medications.

1. Introduction

Since the mid-1990s, expenditures on prescription medicines have grown faster than other major components of the health care system, in most OECD countries. As a result, prescription drug costs have risen as a proportion of total health care costs (**Table 1**). In the USA, the Kaizer Family Foundation (KFF) attributed 42% of the spending increase experienced between 1997 and 2002 to increased utilization, 34% to shifts in the mix of drugs used (from older and cheaper medicines to newer and more expensive medicines), and 25% to price inflation of existing drugs (Hong et al 2005). Most OECD countries have introduced an array of cost containment measures in order to curb high expenditure growth rates, improve efficiency, reduce wasteful resource use, whilst at the same time aiming to maintain or improve quality. Policies have included the wide use of health technology assessment in assessing value of pharmaceutical innovations, the encouragement of generic medicines use through various means (at prescribing, dispensing or cost-sharing level), and the targeting of physician prescribing behaviour through an array of financial and non-financial incentives. Yet, little evaluation exists of whether these policies have achieved their objectives. Very frequently additional measures are introduced on an ad hoc basis and without due consideration given to interactions between policies or measures. This may impact the range of services or goods offered to patients or their availability.

In this environment, the emphasis on quality in health care is critical, as health insurance systems (both public and private) are accountable to their members for the quality of services they provide. Patient perceptions about the quality of goods and services they receive are also important and there is greater emphasis on this in recent years. Based on perceptions about quality, patients form beliefs about the nature of goods and services they receive, which, in turn enables them to shape loyalty towards providers, services or goods that deliver the highest quality to them. Pharmaceuticals are no exception to this.

In this study, the marketing science conceptual framework is used to analyse what brand-loyalty is according to marketing science and explore whether marketing theories provide a suitable framework for explaining brand loyalty in pharmaceutical markets. In addition, the paper explores the available evidence on innovator drug price movements in the face of brand and/or generic competition. Finally, the study discusses whether adherence to prescription medicines can be influenced by brand-loyalty itself or is affected by additional factors, such as generic substitution, among others.

In the following sections, we present the data and methods employed in the literature search and provide the definition of brand-loyalty according to marketing science. Subsequently, we discuss the main characteristics of the pharmaceutical industry that differentiate this sector from all the other industries, and the extent to which brand-loyalty can be applied in pharmaceutical markets. We describe and analyse the factors that may influence brand loyalty in pharmaceutical markets, both in-patent and off-patent, as well as examine how brand-loyalty is used in the health care literature and try and explain if it somehow influences patient adherence to prescription medicines. In the final section, we summarise the key findings and draw the main conclusions.

Table 1

Health and pharmaceutical spending in selected OECD countries, 1995 - 2005

Country	Total expenditure on health as % of GDP			Total expenditure on pharmaceuticals and other non-durables per capita, (at US$ exchange rate)			Total expenditure on pharmaceuticals and other non-durables as a % of total health expenditure		
	1995	**2000**	**2005**	**1995**	**2000**	**2004**	**1995**	**2000**	**2005**
Canada	9.2	8.9	9.9e	252	330	537e	13.8	15.9	18.2
France	9.4	9.2	10.5e	451	418	676e	17.6	20.3	18.9e
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	8.1e	217	220	447e	19.2	21.3	22.8e
United Kingdom	7.0	7.3	8.4d	209	276	430	15.3	16.4	16.6
United States	13.3	13.3	15.3	325	535	752	8.9	11.7	12.3

Note: e=estimate.

Source: OECD Health Data, 2007.

2. Methods

This paper is based primarily on secondary sources, notably literature review, but also relies, in part, on primary data handling and reporting. Primary data handling has included the analysis of IMS pricing and sales data sources for certain product categories (statins and ACE I inhibitors, in particular). With regards to secondary sources, in order to identify the relevant literature, searches in MEDLINE and Thomson databases for English-language literature for the January 1980 –August 2007 period were conducted using one or combinations of the following terms:

(a) Brand loyalty;

(b) Drug(s);

(c) Medicine(s);

(d) Pharmaceutical(s);

(e) Brand-name;

(f) Generic(s);

(g) Adherence;

(h) Compliance;

(i) Concordance;

(j) Generic substitution;

The above terms were used to identify peer review papers investigating the factors influencing brand-loyalty, compliance and their intersection. The number of studies per term is shown on **Table 2**. In addition to the above, books, internet sources, published reports, other secondary sources as well as grey literature were used, where appropriate to collect further material on the subject.

Table 2

Total number of studies per keyword, January 1980 – August 2007

Term	Number of peer review studies
Brand loyalty	43
Drug(s)	726,329
Medicine(s)	398,183
Pharmaceutical(s)	178,264
Brand name(s)	580
Generic medicine(s)	13,969
Adherence	44,645
Compliance	77,280
Concordance	14,130
Generic substitution	368

Source: The authors from Medline & Thomson, August 2007.

From the above search, 120 studies according to the relevance with the topic were selected for review along with relevant publications from the reference lists of articles identified in the initial database search, in total 200 studies. The relevance of a study was mainly identified by studying the abstract of each.

No study was found that examine solely the effect of brand-loyalty on adherence to prescription medicines, but a number of studies were identified to be examining the phenomenon of brand loyalty as it applied to competition primarily in off-patent markets. The evidence is summarised in the sections that follow. As discussed above, the study period for this review was January 1980 to August 2007. Where appropriate, a few studies were included which

were to be published in 2008 but were relevant to the subject matter of the review and made available at the authors' discretion.

3. Brand loyalty

3.1 What is a brand?

The American Marketing Association defines a brand as "… a name, term, sign, symbol, or design, or a combination of them, intended to identify the goods or services of one seller or group of sellers and to differentiate them from those of competitors" (Kotler, 2000,p.404).

A brand can be a name, trademark, logo or other symbol and it is essentially a seller's promise to deliver a specific set of features, benefits and services consistently to the buyers (Kotler 2000). According to the trademark law, the seller has exclusive rights to the use of the brand name in perpetuity and this is the main difference among brands and other assets, such as patents and copyrights which have expiration dates.

A brand is composed of the name, the packaging, the product itself and its features, the experience of the product, the advertising and promotion. The name is a vital component because markets are very crowded and competitive so differentiation is a necessary element for the product life-cycle. A powerful brand provides remarkable competitive differentiation, crosses the borders of countries and markets and prohibits rivals to copy. The name of the product alone can build a relationship with customers and can enhance the preference and loyalty of the consumers as "… words have the power to inspire, to motivate and to trigger a call to action" Robins (2006). Product packaging can either speed up customer's selection when a customer is accustomed to a specific package, or attract customers due to colour and shape. The product itself and its features are easily used and understood respectively. Also, the experience of the product should be pleasant and satisfactory offering to the customer short enough satisfaction so as to suggest the product to others. Advertising and promotion portray the brand, bring its value to life and connect the product with the audience's feeling and desires.

Brands have different degrees of power and value in the marketplace. One extreme case is brands which are not recognized by most buyers. There are also brands with (a) a fairly high degree of brand awareness; (b) a high degree of brand acceptability; (c) a high degree of brand preference; and (d) a high degree of brand loyalty.

3.2 What is brand loyalty and what are its determinants?

A distinction needs to be made between *repeat purchasing behaviour* and *brand-loyalty*. Repeat purchasing behaviour is the actual re-purchasing of a brand, therefore, it encapsulates the behavioural aspect of this action. In addition to that, brand-loyalty includes that behaviour's sources or antecedents. This means that the "reason" occurs before the behaviour.

Brand-loyalty is a consumer's preference to buy a particular brand in a product category. This preference exists because consumers perceive that the brand offers the right product features, images, or level of quality at the right price. This perception becomes the basis for a new buying habit. In essence, in an initial phase consumers will make a trial purchase of the brand and, after satisfaction is obtained, will tend to form habits and continue purchasing the same brand because the product is safe and familiar.

Consumers can have different degrees of loyalty to specific brands. According to their brand-loyalty status buyers can be divided in four categories:

i) *hard-core loyals*: who buy one brand all the time within a product category;

ii) *Split-loyals*: who show a preference for two or three brands within a product category;

iii) *Shifting loyals*: who switch from one brand to another; and

iv) *Switchers*: who show no preference to any brand, they choose which brand they will buy in a given shopping trip depending on relative prices of the products.

Markets can have different numbers of the four types of buyers. A brand-loyal market is one with a high percentage of hard-core brand loyal buyers such as the toothpaste market and the beer market (Kotler 2000).

For brand-loyalty to exist there must be experiential branding. The need of experiential branding has been emphasized in that "… experiential branding creates a unique relationship in which consumers and brands connect from an emotional and individual perspective not just physically or visually. This experience results in positive purchase decisions and strengthens brand loyalty. If that experiential connection with consumers can be captured, it is likely that they will talk about a particular brand and reinforce it constantly to everyone they know. If this connection is translated to the store shelf that brand can become a part of their life" Glass (2004).

Favourable brand attitudes are the determinants of brand-loyalty. Consumers must be satisfied with the product in order to develop loyalty to it. If companies want to convert occasional purchasers of their products into brand-loyal ones, habits must be reinforced. Consumers must be reminded of the value, the satisfaction and the benefits of their purchase so as to be encouraged to continue purchasing the same product in the future.

In order to encourage repeat purchases, the use of advertising is critical not only prior to but also after the sale. Advertisements generate brand awareness and promote initial purchases at the first stage of the product life-cycle. In later stages of a product's life, advertisements shape and reinforce consumer attitudes; as a result, these attitudes mature and convert into beliefs, which are necessary to be reinforced until they develop into loyalty. Thus, advertisements have the power to reinforce consumers' perception and behaviour. Giddens (2002) suggests that it is easier to re-enforce behaviours

than to change them and the sale is just the beginning of an opportunity to turn the purchaser into a loyalist.

4. The concept of Brand Loyalty in pharmaceuticals

4.1 The nature of prescription medicines, R&D, marketing, DTCA[1], regulation and government intervention

Property rights are conveyed to the owner of a brand; trademark law protects all elements that enhance the recognisability of a product, which, in the case of pharmaceuticals may relate, among others, to the name used for a specific medicinal preparation. Brand names lead to ownership rights and, potentially also, to enhanced market share, as manufacturers are keen to use them as identifiers for product sold and establish a long-term relationship between the brand and its users.

Although brands are recognized as valuable strategic assets little evidence seems to exist that the pharmaceutical industry takes long-term brand building seriously. Perhaps this is due to the characteristics of the industry which is with the exception of the over-the-counter (OTC) sector completely different from any other. More specifically, the nature and special features of prescription medicines separating prescribers and consumers, the excessive spending on research, the agile sales and marketing activities, the absence until recently of direct-to-consumer advertising[2] (DTCA), as well as regulation and government intervention, are factors that differentiate this industry from all others and are discussed in the following paragraphs.

Firstly, demand for prescription medicines is unusual because the consumer is typically not the one who decides on which product to consume and most often not the one paying for it. Indeed, the purchase of prescription drugs involves a multistage process as firstly, a physician writes a prescription, secondly, a pharmacist dispenses and substitutes whenever possible, a patient consumes and possibly pays a share of the cost, and in most cases, a third-party payer pays most of the cost. This drug purchasing process is characterized by the existence of information asymmetries between doctors and patients and uncertainty about drug effectiveness. As medical knowledge

[1] Direct to consumer advertising.
[2] And which still is forbidden in Europe.

is complex, the information held by the doctor regarding the consequences and possibilities of treatment is very much greater than that of the patient.

As most drugs differ both in their effectiveness and their incidence of side effects across patients, uncertainty is another element of drug consumption. Since patients are not informed and lack information about which treatment is most effective and suitable under every disease condition, they depend on physicians who diagnose, suggest and in most cases prescribe a treatment. Thus, access to complete information and prescription rights are restricted to health care professionals.

Secondly, the pharmaceutical industry has invested significant resources in R&D activities. R&D spend varies widely from one drug to the next and often depends on the type of drug being developed, the possibility of failure and whether the drug is based on a new molecule not used before in any pharmaceutical product or is a modification of an existing drug. Research is increasingly directed to chronic rather than acute health care problems and medications for chronic use have accounted for an increasing share of the major new drug introductions Grabowski and Vernon (1990). The development of a new drug is a long and expensive process. DiMasi et al (2003) estimated the average cost of developing an innovative new drug to be more than $800 million in 2000 US$, including the costs of projects that have failed and the value of foregone alternative investments. Also, the same study reports that it takes about 12 years to develop an innovative new drug and if an estimate of the cost per approved new drug for R&D conducted after approval is added the total R&D cost is almost US$900 million. Although total spending on R&D activities has tripled since 1990, the number of breakthrough innovative medicines approved by regulatory authorities such as the US FDA each year has not shown a comparable upward trend (CB0 2006). Manufacturers devote a growing share of R&D resources to incremental improvements of existing drugs rather than in discovering new molecular entities. From 1998 to 2003 of 487 drugs that were approved by the FDA 67 (14%) were actually new compounds likely to be improvements over older drugs (Angell 2004).

Additionally, this industry has been heavily criticized that it invests mainly on extensive sales and marketing activities and not on real research. On the other hand, the launch of several products each year requires that physicians be informed about the new introductions on a continuous basis and this is done by marketing. Not too infrequently, the marketing activities by pharmaceutical companies are the only source of succinct and valid information readily available to health care professionals in a timely fashion. Pharmaceutical companies have spent more on marketing and sales promotion than on anything else (Brekke, 2006; Collier, 2002). According to the Pharmaceutical Research and Manufacturers of America (PhRMA), 35% of the industry members' personnel in 2000 were in marketing. When a new drug comes into the market, the primary marketing goal is to generate awareness of a previously-unavailable treatment for a medical condition and medical professionals work towards this direction. The long-term desire is to generate a degree of brand awareness, a degree of differentiation based on quality and the attributes of the particular product marketed (known in the economics literature as "vertical product differentiation") and even brand-loyalty among physicians, that extends beyond the time of patent expiration to when generics are available and stops when the drug is replaced by another more powerful innovative drug.

Moreover, DTCA of prescription medicines was prohibited until recently in nearly all countries. Advertising of prescription medicines to the public is still prohibited in all countries of the European Union, although this ban has recently been under review. By contrast, the U.S.A, New Zealand, Bangladesh and South Korea allow advertising of prescription medicines directed at patients. Pharmaceutical companies in the U.S.A. spent $2.47billion on DTCA activities for prescription drugs in 2000 (Mintzes et al, 2002). DTCA is a controversial practice and there are arguments for and against it. Advantages are that it gives consumers information about treatment options and better knowledge of the risks of medication, may increase adherence to drug therapies, can motivate the public to pursue lifestyle changes *in lieu* of

prescription drugs, and may help to increase public awareness, early diagnosis and treatment of serious diseases such as hypertension, diabetes, cholesterol and depression and aids patient-doctor discussions (Harker and Harker, 2007; Woloshin et al, 2001). On the other hand, disadvantages of DTCA are that it might inappropriately increase patient demand for specific and costly medicines, increasing simultaneously risks as patients do not have so much information about drugs as manufacturers or physicians, and this demand might adversely affect the physician-patient relationship leading to less than satisfactory health outcomes, causing physicians to waste valuable time during encounters as well (Brekke and Kuhn, 2006).

Finally, the prescription medicines sector which brings about 90% of global revenue for the pharmaceutical industry is highly regulated and subject to government intervention. As knowledge increased and pharmaceuticals began to become effective for a vast area of previously untreatable symptoms and diseases, the industry prospered. However, as the market expanded, so did restrictions on product claims and the communication of information. Few industries in the industrialized world are subject to so intense regulatory control as the pharmaceutical industry. Every product produced for the prescription market is subject to intense scrutiny and testing required by regulatory authorities. The direct cost of these clinical trials is high, but the indirect costs in terms of time and cost both for patients and manufacturers are even higher. In addition to regulating quality, efficacy and safety, governments regulate drug prices and product reimbursement status as a means of exerting control on pharmaceutical public spending. Finally, mandatory Health Technology Assessments (HTAs) with new medicines having to prove their cost-effectiveness in relation to a valid alternative treatment is another form of government intervention.

4.2 The pharmaceutical marketing environment

Large multinational pharmaceutical companies are research intensive and are investing heavily both in basic as well as developmental research. The recent wave of mergers, such as that of Pfizer with Warner-Lambert and the one of Glaxo Wellcome with SmithKline Beecham, has created companies with annual sales in excess of $22 billion and $25 billion respectively (Blackett and Robins 2001). However, these big businesses have only a small fraction of the total global pharmaceutical market. Such a competitive environment would bring about many innovative products, all battling to gain supremacy for the company marketing them. In consumer markets, the more intense the competition is, the more important is the need for strong brands. Whereas from an industry perspective there is a powerful desire to create strong and lasting brands, in reality, this is subject to significant constraints. The reasons for that are outlined below.

First, in most countries there are pressures from health insurance on physicians to prescribe by the generic name rather than by brand-name, as an attempt to control continuously increasing pharmaceutical cost. Moreover, Hemminki et al (1984) found that physicians cannot remember all the different names of the drug, namely chemical, generic and trade-name, and this problem is greater for general practitioners who handle a big variety of patients and drugs.

Second, the selection of the prescription medicine by the physician is seen as a totally rational evidence-based choice. However, it is unlikely that the doctor will try the product himself, so usually relies on feedback about the action of the medicine from the patient or from the observation of the patient's medical tests.

Third, there is a separation between patients and prescribers. Patients can neither buy a prescription drug from the shelf of the store nor can know and judge the reactions and side effects of a continuously increasing and

different variety of prescription drugs.[3] Existing regulatory controls can be seen as a barrier to enter the market, but which stimulate the creative branding process.

Fourth, the fact that ensuring market access and maximising market share are so important means that this industry is sales rather than marketing driven. According to Blackett and Robins, 50% to 70% of a company's promotional budget will be spent on the sales force and this means is universally regarded as the most effective promotional tool, although this may be changing in the future in payor-dominated environments. In the US health care environment sales forces are numbered in thousands of medical representatives, whereas in some countries each medical representative may have 50 or more doctors to call on.

Finally, advertising in the pharmaceutical industry, directly to consumers is disallowed in extensive parts of the world (with the notable exception of the US, where Direct-To-Consumer-Advertising – DTCA is allowed), and, therefore, the ability to reach customers directly is slightly compromised. Whereas it is allowed to promote new medicines to physicians through detailing campaigns and provision of information material, such campaigns and the expenditure they result in from an industry perspective, are increasingly being scrutinised by governments and are subject to restrictions or/and taxation.

For all the above reasons, a branded medicine may have limited opportunities for continuous and sustainable revenue creation post-patent expiry. Adding to them, the strong competition in each therapeutic category which works as an extra barrier to entry and the fact that volume of an innovator drug, but in many cases even prices, can fall when the period of patent protection expires, these opportunities seem to be even more restricted. Extending patent life or exclusivity for a drug can be further safeguarded by switching certain aspects of it OTC or by launching line

[3] Although, as discussed later, patients do not always need a prescription to acquire a prescription medicine.

extensions. However, these moves are not without barriers due to safety, and regulatory issues.

5. Brand loyalty and pharmaceutical policy

5.1 Methodological underpinnings

Importantly, although brand loyalty exists as a concept and probably underwrites consumer (and proxy-consumer) behaviour in pharmaceutical markets, in practice it is very difficult to measure it with a significant degree of accuracy.

Nevertheless, two aspects of brand loyalty arise in pharmaceutical markets as a result of the pharmaceutical market structure and intellectual property rights protection. The first relates to brand loyalty in the context of competition at therapeutic class level within in-patent markets and accounts for the effect of product differentiation among close substitutes. The second relates to brand loyalty in the context of competition post-patent expiry and the extent to which pharmaceutical markets become genericised after the entry of generic competitors, the speed at which this occurs and whether the patent-expired originator brand retains a certain market share. Both aspects are explored in the sections that follow.

5.1.1. Brand loyalty and product differentiation

While much attention has been given to the demand side of the market, with extensive literature available on the influence of co-payments on consumption level (Gregson, 2005), less attention has been paid to the supply-side. On this side of the market the literature has tended to concentrate on issues such as (a) the returns to the R&D process (Danzon & Towse, 2003), (b) the estimation of the impact of competition between generics and branded goods on product price (Lexchin, 2004; Grabowski and Vernon, 1992) and (c) the impact of regulation on products and their market prospects (Danzon et al, 2005).

The general issue of market structure and pricing within the branded product market has received little attention. Branded products may enjoy a degree of monopoly power through patent protection when first entering a market. Lu and Comanor (1998) found, however, that of over a hundred products analysed during the late 1970s and 1980s in the U.S. market, 90 per cent had close substitutes. More generally, the degree of substitutability across products varies substantially being at its highest where differences in chemical structure are minimal and a general class effect holds. To that end, products within the same therapeutic class may be similar, but differentiated with regards to some of their attributes, which make them unique to individual patients.

The behaviour of the pharmaceutical market is, therefore, country - and product - specific. One should expect markets for drugs to be heterogeneous, with the heterogeneity resulting from the extent of product differentiation within each therapeutic market. Yet, surprisingly, very limited research has been undertaken on the degree of competition within a particular class of drug and in particular the degree of substitutability or complementarity that exists across products within the same class. Whilst there is a growing literature on the influence of generic competition after patent expiry there is little work on the influence of competition across a therapeutic class within patent protection. Lu and Comanor (1998) found significant pricing differentials accounting for therapeutic advantage, which correlated inversely with the degree of substitutability. The number of branded substitutes had a significant and substantial negative effect on the introductory price of new drugs. As the number of substitute drugs increased from one to two there was an average 38 per cent decline in the ratio of the new drug price to the average existing market price, while increasing the number of substitutes from two to three led to a 19 per cent decline in this ratio. Moreover, the impact of substitution was not limited to the introductory market price effect, subsequent price changes were also found to be affected by the degree of substitution.

Danzon and Chao (2000) considered, within a larger range of hypotheses, the effect of substitution across a therapeutic class and the first-mover advantage on product price. The results with respect to therapeutic substitutes were inconclusive. Although there was evidence of lower price adoption for successive entrants into a therapeutic class the regression results were difficult to interpret because of potential endogeneity and omitted variables problems. No evidence was found of competition within therapeutic class in North America but a small negative effect was detected on price in France, Italy, Germany and the UK. As competitive effects on price were not found in France and Italy with respect to generics it was concluded that the therapeutic class effect may be merely indicating the use of reference pricing in these two countries. Ellison et al (1977), concentrating on the demand for four cephalosporins (prescribed as anti-infection agents) found that there were relatively high cross-price elasticities between generic substitutes but small and not universally significant elasticities between therapeutic substitutes.

Given that a major justification for the monopoly power enjoyed under patent in the branded product market is that it creates appropriate incentives to stimulate further R&D within individual pharmaceutical companies, investigation of the degree to which this power may be eroded through quantification of substitutability across products is obviously important.

Overall, whereas branded products may enjoy a degree of monopoly power through patent protection when first entering a market and are therefore in a position to develop brand loyalty of their own, the extent of substitutability and whether it is close among the products in the class, may erode some of the price advantages these products may have on the market. Therefore product differentiation is a necessary, but not a sufficient condition for clear brand loyalty advantages.

5.1.2. Brand loyalty and the effect of patent expiry

The residual market share retained by the originator drug post-patent expiry and post-generic entry, demonstrates –in principle- clearly the existence of brand loyalty. From an international perspective, access to generic medicines has been facilitated over the past quarter of a century. In the USA, the 1984 Hatch-Waxman Act was enacted to streamline the way for easier and less costly market entry of safe and effective generic drugs. This Act eliminated the duplicative tests that had been required for a generic medicine to obtain approval from the US Food and Drug Administration (FDA), requiring only that manufacturers demonstrate "bio-equivalence" to an already approved innovator drug. The improvements in the review procedures were expected to save patients and health care systems billions by reducing the time for approving new generic drugs and increasing competition with innovator drugs. However, innovator drugs historically have been able to maintain high prices even after patent expiration, a phenomenon called the "generic paradox", that was connected with first-mover advantages, namely, first movers have natural product differentiation advantages that permit them to charge high prices and retain substantial market shares even after the entry of generic competitors, because consumers have more information about innovator's quality. Prior to 1984, the price rigidity of the patent-expired brand-name drugs was explained by barriers to entry, as both pioneer drugs and their generic versions had to document proof of safety and efficacy and thus only few generic drugs were able to enter the market. Cook (1998) reported that for 13 major drugs with patents expiring between 1990 and 1993, 11 experienced generic entry within 2 months of patent expiration whereas, only 2 of the top 13 drugs with patents expiring between 1976 and 1982 had generic entry within 1 year of patent expiration. Also, Kermani (2002) reported that prior to implementation of the Act only 35% of top-selling drugs had generic competitors, whereas nowadays almost all do. This is due to the fact that, the act created the vehicle of an Abbreviated New Drug Application (ANDA), reducing the burden of proof of safety and efficacy for generics.

This reduction of regulatory barriers to entry should have promoted price rivalry with little threat to consumer safety, since generics are very similar to formulations already approved. However, although the number of generic entries has increased, empirical studies report no evidence of such price rivalry; rather price of brand-name drugs were maintained or in some cases, went up after the expiration of their patent (Frank and Salkever 1992; Grabowski and Vernon 1992; Wagner and Duffy 1988). This price rigidity of patent-expired brand-name drugs is well recognized and this phenomenon has puzzled economists and policy makers who had expected price rivalry from the easier entry of generic competitors following the 1984 Act. Whereas the phenomenon of the generic paradox has been explored in the US environment, recent evidence has suggested that it may be present in some European settings (Vandoros & Kanavos, 2008).

Traditionally, brand-loyalty is the only explanation for the price rigidity of patent-expired innovator drugs to generic entry. According to the brand-loyalty explanation, patent-expired brand-name drugs show price rigidity because a sufficient number of price-insensitive customers continue to buy brand-name drugs despite the availability of affordable generics. However, the use of the brand-loyalty theory in the pharmaceutical literature is not correct as the nature of prescription medicines is quite different from other consumer products.

5.2. Brand loyalty in in-patent markets

Bearing in mind the measurement issues surrounding brand loyalty in pharmaceuticals, it can be argued that brand loyalty in in-patent markets may be measured by the degree of individual products to maintain a positive market share over time, particularly as competition increases following the introduction of competitor brands. Brand loyalty in this context is related to a particular brand product's actual efficacy, based on clinical trial results, and effectiveness in community use. It is also related to the perception by an

individual patient that the product in question delivers (therapeutic) benefit associated with minimal side effects through personal experience with the product.

In branded in-patent markets, therefore, the extent to which a particular brand can maintain (significant) market share in the face of competition from other products in the same therapeutic category can be perceived as evidence of brand loyalty. This can be examined with reference to any particular therapeutic product class; the example offered in this paper relates to the statins market in 4 European countries (UK, Germany, France, and The Netherlands). Examining the determinants of competition in the statins market involves testing whether the market quantity delivered of the leading product on the market is determined by own price and by the prices of the other statins following entry.

Figure 1 presents the market shares for each of the five statins on the market in the four specified countries over the 1991 to 2002 period. Pravastatin and simvastatin were the first to enter, almost simultaneously, the markets in all four countries. From this preliminary evidence it would appear that the products entering these markets first enjoyed "first mover advantages" and commanded a higher price than their competitors. One stylized fact is that these two first entrants share the individual markets between them almost equally, with the exception of the UK where simvastatin was the market leader with approximately 60% market share. Over time, and as other entrants come into the market, market shares tend to converge, with approximately the same market share for each of the five statins. This resembles the long-run equilibrium outcome, which would evolve if each firm adopted a Cournot strategy with quantity setting, taking the market quantities of competing products as given. Equilibrium quantities at the product level are, therefore, assumed to be inversely related to the number of therapeutic competitors. In turn, this suggests that there may be high complementarity or substitutability among statins and this is tested for below. Of course the model

is not pure Cournot as this would imply that there is product homogeneity whereas product branding induces some degree of product differentiation.

Figure 2 examines prices of all statins from 1992 onwards. Price differentiation across the various markets is evident. Simvastatin was priced higher than pravastatin in Germany and France, whereas pravastatin was priced higher than simvastatin in the UK. Figure 2 also suggests that the entry of additional statins post-1995/1996 did not affect prices of the first two statins (pravastatin and simvastatin) adversely. Prices of followers (atorvastatin, fluvastatin, and cerivastatin) are everywhere close to or below the incumbent statins, with the exception of cerivastatin and atorvastatin in Germany, which entered at a price higher than that of one of the market leaders (simvastatin) and maintained this price difference over time. As expected the general trend given from Figure 2 is clear, we do not generally observe any downward pressure on prices as competitors enter the markets, with the possible exception of the Netherlands and even here only with respect to one product, indicating the lack of importance of price competition in this market. This is consistent with the general Cournot strategy[4] with a product

[4] Cournot competition is an economic model used to describe an industry structure in which companies compete on the amount of output they will produce, which they decide on independently of each other and at the same time. In this model, firms do not compete on price. It is named after Antoine Augustin Cournot (1801-1877) after he observed competition in a spring water duopoly. It has the following features: (a) there is more than one firm and all firms produce a homogeneous product, i.e. there is no product differentiation; (b) firms do not cooperate, i.e. there is no collusion; (c) firms have market power, i.e. each firm's output decision affects the good's price; (d) the number of firms is fixed; (e) firms compete in quantities, and choose quantities simultaneously; (f) the firms are economically rational and act strategically, usually seeking to maximize profit given their competitors' decisions. An essential assumption of this model is that each firm aims to maximize profits, based on the expectation that its own output decision will not have an effect on the decisions of its rivals. Price is a commonly known decreasing function of total output. All firms know *N*, the total number of firms in the market, and take the output of the others as given. Each firm has a cost function. Normally the cost functions are treated as common knowledge. The cost functions may be the same or different among firms. The market price is set at a level such that demand equals the total quantity produced by all firms. Each firm takes the quantity set by its competitors as a given, evaluates its residual demand, and then behaves as a monopoly.

differentiation model described above, whereby incumbents and new entrants compete on "quality", or the attributes of their respective products such as branding and marketing.

5.3 Brand loyalty in off-patent markets

According to marketing science brand-loyalty does not seem to exist in the prescription drug segment as these drugs do not have an infinite market life, but they are replaced by new medicines. Also, consumers do not buy them freely from the shelf, but must have a prescription from a qualified physician, not even can persuade friends to consume the same drugs, as in most of the cases people do not have the knowledge either to compare health conditions or to compare drug effects, side-effects and reactions with other medicines that they might consume for other health problems that they face. Yet, the brand-loyalty paradigm can be adapted and used to explain what is happening in pharmaceutical markets before and after patent expiry.

In particular, brand-loyalty has also been used on a number of occasions in the health economic literature as an explanation for the price insensitivity of originator drug when its patent expires and generics enter into the market. Generic medicines typically contain the same active ingredient(s), in the same or similar dosage forms and routes of administration and should meet the same standards in terms of quality with the innovator drug, whereas they may differ in characteristics, such as shape, scoring configuration, release mechanisms, packaging and colours (Verbeeck et al 2006). Being essentially copies of originator drugs, generics have lower prices than original drugs and can offer significant savings to patients (if patients pay significant proportion of their drug costs out-of-pocket) and to health care systems. According to Lexchin (2004) generics are 25%-50% cheaper than originator brand-name drugs. King and Kanavos (2002) reported even greater price differences between 20-90% based on more detailed separation in terms of countries. Although cheaper versions of the originator drug are available the originator

drug does not lose completely either its market share or its increased level of price, a fact that is being explained by the literature as brand-loyalty. This persistence of innovator drug against generic competitors could be connected with factors such as the following: the existence of insurance coverage, the absence of financial incentives for doctors, patients' perceptions about generic drugs linking these with originator brand loyalty, issues around bioequivalence, the absence of substitution laws and financial incentives for pharmacists, the existence of strict regulation of price and reimbursement of drugs, the use of line-extensions, advertising and the market success of originator drugs.

5.4. Moral hazard

The existence of insurance coverage for prescription medicines seems to be one factor that explains the persistence of brand-name drugs over generic equivalents. Pharmaceutical markets are often characterised by price inelastic demand because of extensive medical insurance, where this exists. Since individuals only pay a small amount of the medical cost, when they are ill, prices seem to have a limited impact not only on the choice of whether or not to consume a drug, but also on the choice between a brand-name versus a generic equivalent. In reality, because of the existence of insurance, patients may tend to over-consume medical care as they do not bear the full cost of provision; this is the moral hazard problem and seems to be favouring the consumption of branded medicines even further (Lundin 2000). Patients as well as physicians do not necessarily have the incentive to invest in low-cost treatments as long as insurance companies are willing to pay the cost of prescriptions; this is frequently taking place regardless of these medicines' unbranded generic or brand-name status. In many countries, the marginal cost of treatment does not have to be covered by the patient. The moral hazard is reflected in two instances: in that many patients dislike talking about cost with their doctor, and in their feeling that generic prescriptions are a strategy to reduce cost at the expense of patient quality of care. Given this extensive insurance coverage, consumer demand is price inelastic and consumers do not

care about the cost of drug they consume, as they pay only a small amount of pharmaceutical cost, giving branded medicines the opportunity to remain on the market and continue to command a (significant) market share.

5.5. Generics, brands and perceptions: Physicians and physician prescribing

Physicians are key decision-making agents for patient drug consumption and prescription medicines typically require a physician's prescription to be dispensed.[5] In this context, branded medicines (whether branded generics or brand originator drugs) also seem to be preferred by doctors. Contributing factors for physicians to opt for branded medicines are that no strict budgets or other financial measures restricting the freedom to prescribe the drug of choice are in force. Additionally, physicians may often have doubts about the bioequivalence or therapeutic equivalence of generics in relation to their brand-name alternatives, although this is currently less the case. However, in some countries, particularly lower income countries with weak regulatory regimes, prescribing a brand or the originator, is frequently the best choice for the patient. Finally, physicians may show an element of habit pushing patients to consume what they are used to (i.e. a brand) rather than a generic.

Hellerstein (1998) found that almost all physicians prescribe both types of drugs (brands and generics) to their patients, but some physicians are more likely to prescribe generic drugs while others are more likely to prescribe trade-name drugs. The reason why some physicians are more likely to prescribe the former rather than the latter and the other way around is largely unexplained, but could largely be attributed to the dual agency problem. Since physicians do not generally benefit financially from the prescription choice that they make for their patients, it might seem that physicians should act as

[5] Although phenomena of dispensing a prescription medicine without a prescription have been observed in many European – including EU – countries, including Spain, Italy, Greece, Bulgaria, Romania; prescription drug dispensing without a prescription is rampant in developing and middle income countries; in these environments, the key decision making agent is often the pharmacist, not the physician.

perfect agents for their patients, prescribing only those drugs that the patient would choose if patients were the decision-making agents. However, there are costs to the physician associated with prescribing drugs and physicians may not act as perfect agents for their patients. These costs can take many forms, one of which is the costs of collecting information on the availability and efficacy of generics and the price differential between generics and trade-name drugs. After the patent on a trade-name drug expires it may take time for information to diffuse about the existence and name of the generic. In addition, a risk averse physician may not prescribe a generic until its efficacy is established. Brennan and Lee (2004) found that a physician was willing to prescribe brand-name medications when the problem was clinically significant, insisting on generic drugs only when the problem was relatively clinically insignificant. Also, studies found that doctors believe that brand-names can not be replaced by generics in specific conditions as generics are not therapeutically interchangeable (Meredith, 2003; Drummond, 1997; Dong et al, 1997; Banahan & Kolassa, 1997; Motola & DePonti, 2006; Pereira et al, 2005). Moreover, individual doctors are usually more risk-averse, less sensitive to cost and creatures of habit so they continue to prescribe brand-name drugs even when less expensive generics exist.

Generic drug manufacturers do very little advertising, while information about new trade-name drugs is widely disseminated formally through advertising the published results of drug efficacy studies. It may therefore be much more costly for a physician to learn about the introduction of new generic drugs. Finally, prescribing physicians adhere to guidelines issued or regulatory measures imposed by health insurance organisations, such as the requirement to prescribe generically, or to observe a fixed budget for prescribing. In this way, prescribing physicians do not only act as agents to their patients, but also as agents to health insurers. Indeed, fixed budgets to physicians provide an incentive to contain costs, which, in turn, encourages generic prescribing and vice versa.

Another survey of a national sample of family physicians was undertaken by Bower and Burkett (1987) to investigate several aspects of attitudes and prescribing patterns related to generic drugs. Of the respondents to 317 of 501 questionnaires, 62.5 percent of physicians said they had enough confidence in generic drugs to prescribe them in their practices, but only 26.9 percent said they actually prescribed mostly generics. The authors found that the habit of prescribing mostly generic drugs was more common among family physicians who were residency-trained, who relied least on drug company representatives and who were regular readers of the New England Journal of Medicine. Also, the ability to recognize all ten generic names included in the survey tool was found to be highest among these same groups of physicians and also among those who relied least on journal advertisements and those who were regular readers of the Medical Letter, a publication providing information on medicines, whereas respondents who said that they relied a great deal on drug company representatives for information had relatively impaired ability to recognize all ten generic names included in the survey tool and were much less likely to prescribe generic drugs in their practices. Physicians who said that they relied a great deal on advertisements in journals were also less likely to recognize all ten generic names on the list. In the same survey, respondents indicated that their most important sources of information on new drugs are journal articles and recommendations from colleagues, with almost one half of respondents indicating that they rely " a great deal" of these sources, whereas almost 30 percent of respondents do not rely on journal advertisements at all and over 90 percent of respondents rely to some extent on information from drug company representatives and 93 percent use drug samples in their practice.

Hellerstein (1998) and Temin and Kolassa (1995) reported that doctors have little knowledge of actual drug prices. Despite large expenditures on advertising in the industry, promotion information seldom reports actual prices. The fact that physicians do not know the costs of the drugs they prescribe suggests that they cannot be fully price sensitive and they can only estimate the magnitude of cost savings from generics and it is quite costly to collect this

kind of information, as generic manufacturers do very little advertising and promotional activities of innovator companies seldom report actual prices of drugs, respectively.

Steinman et al (2007) found that physicians referred to medications by their brand-names more frequently than by their generic-names even when generic versions were available because brand-names are often more memorable than generic-names and easier to pronounce as they have in many cases on average 1.5 fewer syllables than their generic counterparts. Finally, physicians may prefer brand names because they may be familiar only with the brand-name of specific drugs and unaware of the correspondence between generic and brand-name drugs, thus continuing to prescribe the latter even when generic drugs are available for all the above reasons. This is largely dependent on the nature of training physicians receive once at medical school.

5.6. Generics, brands and perceptions: Patient perspective

Patients' reservations about the use of generic medications –particularly unbranded generics- has often led to conflict between them and their primary care physician, as physicians as well as pharmacists often find that patients have doubts about the equivalence of the substituted drug [6] and show preference for (innovator) brand named drugs, helping the latter to retain their market share and price-level. Problems may arise at individual level when a brand-name drug is substituted for a generic equivalent, as patients may resist changing from a brand-name drug which they know well to a generic equivalent that may look different. Most physicians have "problem patients" or "difficult patients", whereas recent evidence suggests that at between 20%-30% of consumers believe that generic prescription drugs are both less safe and effective than their branded equivalents. Patients' perception of risk was found to be dependent on the severity of the medical condition for which a treatment was administered. For instance, only 14.2% of patients with cough

[6] Often this skepticism comes from the physicians themselves, who, in turn, influence the views of patients.

and cold symptoms stated that generic drugs were riskier than their branded counterparts, compared with 53.8% of patients with a heart condition.

As elderly people represent a substantial segment of the population accounting for ~25% of all prescription drugs and 40% of all over-the-counter (OTC) medications consumed in OECD countries, special attention is given to this part of population. Individual pharmacokinetic variation is of particular importance in the elderly because many suffer from 1 or more chronic medical conditions and are often receiving several concomitant drugs. In addition, physiologic changes associated with age may affect drug absorption, distribution, metabolism and excretion. Consequently, there are concerns that there may be differences in drug pharmacokinetic properties in this patient population that might not be detected in younger, healthier subjects. It is, therefore, likely that generic substitution could adversely affect elderly patients and, as such, it should be carefully monitored in the geriatric population.

Generic drugs can, at times, differ in appearance from their branded equivalents and in cases in which more than one generic drug is available, they may differ from each other. Not only may the colorants and excipients vary, but the size, shape and delivery formulation of the generic product also may differ considerably from the branded product. These differences can cause anxiety and confusion in patients, especially in the elderly and occasionally result in a patient inadvertently taking two formulations simultaneously.

There is evidence that patient preferences can also be a barrier to increased generic substitution (Mott, 2002). Patients may perceive brand-name products as being of higher quality compared to generic products. In one study in a British general practice, 46% of the patients questioned stated that they were dissatisfied when confronted with a drug change to a generic prescription (Dowell et al, 1995). However, according to a study in New Jersey (McGettigan et al, 1997), nearly all patients agreed to use a generic substitute if the doctor approved of such a substitution. A negative view on generic drugs was also more frequently expressed by older people and independently, chronically ill patients, due to prejudice that inexpensive drugs “must” be of inferior quality.

In a study based on prescriptions in a US Midwestern community (Mott and Kreling 1998), generic substitution occurred significantly more often for acute than for chronic conditions. In many studies, patients with chronic diseases more often showed a negative attitude towards generic drugs, confirming assumptions from different authors that chronically ill patients perceive the consequences and risks of generic substitution as more serious and have more fear of health loss (Ganther and Kreling, 2000). Himmel et al (2005) reported that between 12% and 13% of the patients in their study having some experience of generic substitution showed a lower efficacy or side effects, whereas Brennan and Lee (2004) report the extreme case of a patient believing to be allergic to generic medications. Federman et al (2007) found that older patients of generalists, and, to a greater extent of cardiologists, often use brand-name drugs when generic equivalents are available. All the above factors show that patients' fear and doubts about safety and bioequivalence of generics lead them to prefer branded medicines.

5.7. Generics, brands and perceptions: The robustness of bioequivalence and implications for generic substitution

A significant factor that explains the persistence of originator drugs is that the issue of generic substitution of branded products still remains controversial. Much of the current debate focuses on perceived problems with the design of bioequivalence studies and a number of important issues have been identified. First, it is apparent through clinical experience that a measure of average bioequivalence is not necessarily sufficient to ensure bioequivalence for wide and narrow therapeutic index drugs, such as digoxin and for drugs with high levels of variability in their pharmacokinetics, such as PPIs. Second, the exclusive use of normal and healthy volunteers in bioequivalence studies has often been criticized. Third, the use of single doses is a point of contention. Finally, other problematic issues pertinent to generic substitution include consumer perception of risk (as discussed in the previous section), differences in product and packaging appearance and differences in excipients.

Several outstanding issues and concerns undermine patients' and health care providers' confidence in generic products. Many of these concerns arise from the fact that the development of generic products does not require large or extensive trials in patients for claimed indications. This fact has led to the belief that generic products are potentially inferior to their branded counterparts. Public confidence was further undermined following the generic drug scandal in the United States in 1987, in which US Food and Drug Administration (FDA) approval of a number of generic drug products was shown to be fraudulent.

In 1992, attempts were made to re-establish the credibility of the generic drug market with the introduction of legislation that enforces stricter monitoring of product quality and bioequivalence. Despite this legislation, the debate over the appropriate circumstances in which to substitute a brand-name product with a generic alternative still has not been resolved.

Meredith (2003) reported that the use of a single regulatory limit for all drugs has been criticized and is especially of concern with regard to drugs with a narrow therapeutic index, that is, drugs for which a relatively small change in systemic concentration can lead to marked changes in pharmacodynamic response, such as digoxin and carbamazepine. Similarly, when the therapeutic window is wide such as in the case of oral antibiotics, antacids, antihistamines, vitamins and certain analgesics, variations in pharmacodynamic response may not have crucial effects on clinical outcomes. There is also concern over whether bioequivalence equates to comparable clinical efficacy and tolerability.

The development of a brand-name formulation requires the demonstration of its pharmacokinetics, efficacy and tolerability in normal and healthy subjects and in the target patient population. However, the development of a generic equivalent only requires the demonstration of its bioequivalence with the brand-name product in normal and healthy subjects. It is assumed that bioequivalence in this population will equate to bioequivalence in the overall patient population and to comparable clinical efficacy and tolerability, despite this not being an established fact.

A further criticism of current bioequivalence studies is that they extrapolate bioequivalence in normal and healthy subjects to all patient populations. However, drug pharmacokinetic properties in healthy individuals may not accurately predict the pharmacokinetic properties observed in patient subgroups. In addition, bioequivalence studies routinely involve single doses of a drug. The findings of these single-dose studies are used to predict the results of multiple-dose use. However, there are a number of concerns with this convention. First, most drugs are not administered as single doses and require maintenance of a steady state to achieve therapeutic benefit. Second, the serum concentration reached at steady state is generally higher than that achieved after a single dose in studies in healthy volunteers. Third, single-dose studies give no indication of the possible effects of accumulation of active metabolites that may occur with continuing treatment. Finally, in recent studies omeprazole sodium formulations were found not to be bioequivalent because of differences in the quality of their enteric coating (Elkoshi, 1997; Elkoshi, 1999).

Current bioequivalence requirements may not be sufficient for drugs that exhibit a high degree of variability in pharmacokinetic variables. Drugs such as verapamil hydrochloride and nadolol exhibit high levels of variability in their pharmacokinetic profiles and this has been demonstrated to complicate the assessment of bioequivalence. In 1986 the Pharmaceutical Manufacturers Association (PMA) proposed that the use of a single regulatory acceptance range for all drugs should be replaced by an individualized drug-by-drug approach in which the regulatory authorities would determine the acceptance limits at the time of the branded drug's patent expiry. Clinical practice has also revealed a number of different drug classes for which bioequivalence issues warrant caution in generic substitution: cardiovascular agents, anticonvulsant agents, psychotropic agents, nonsteroidal anti-inflammatory drugs (NSAIDs) and levothyroxine sodium.

In several therapeutic categories, potential risks of generic substitution are thought to exist: modified-release formulations, low-dose oral

contraceptives and other hormonal therapies and proton pump inhibitors (PPIs). For example, Dong et al (1997) reported that generic levothryroxine preparations are often not recommended because of widespread concern about the tharapeutic equivalence of less costly generic products. However, it is controversial whether different brands of levothyroxine are therapeutically interchangeable and bioequivalent because variations in thyroxine levels have been observed in patients taking either generic or brand-name preparations. Thus, the substitution of generic drugs for brand-name products is highly controversial and often is met with suspicion by health care providers and patients, because of many unresolved issues around bioequivalence, giving to the innovator drug the advantage to remain in the marketplace.

In the 1970s and the 1980s, the absence of substitution laws and financial incentives for pharmacists are two additional factors that explain the persistence of branded medicines versus (unbranded) generics. The growth of the generic industry was supported by pharmacists who welcomed the opportunity to exercise professional judgement during the medication-dispensing process. Physicians originally opposed to this movement in many countries, but, increasingly, generic substitution has been accepted and formed a key thrust of reform in pharmaceutical policy in many European countries and the USA in the 1990s. Although, legislation differs considerably among countries and among different US states, it is still possible to dispense a brand, even when a generic is available; for instance, by placing “no substitution” on the prescription, doctors can ensure that in special circumstances, the branded formulation is dispensed. In the United Kingdom, the National Health Service distinguishes between generic prescribing and generic substitution in general practice. The former refers to the decision made by a physician to prescribe by International Non-proprietary Name (INN), whereas the latter refers to the fact that the pharmacy can substitute a brand-name formulation with a generic formulation. The UK law does not permit generic substitution in general practice, except in emergency cases or under strict regulation by the appropriate hospital, whereas generic prescribing is compulsory. Pharmacists

are authorized in most countries to substitute between generically equivalent products to fill the prescription.

In order for pharmacists to promote generic substitution they must be reimbursed in such a way not discourage them from dispensing the cheapest drug. Flat fees per prescription or fixed percentage margins do not necessarily provide an incentive for pharmacists to dispense generic drugs, as in the former case pharmacists receive the same amount for dispensing a brand-name drug as for a generic equivalent and in the latter they receive more for dispensing a brand medicine. By contrast, regressive margins do provide such an incentive, although in both cases, pharmacy remuneration policy by health insurance must be viewed in tandem with the discounts offered to pharmacies by generic manufacturers. These discounts are thought to be more prominent to pharmacy chains than to individual community pharmacies (Kanavos, 2006; Kanavos and Taylor, 2007). Thus, the absence of substituting rights or financial incentives or both for pharmacists can explain the persistence of innovator drugs in the off-patent pharmaceutical markets.

5.8. Pricing and reimbursement

The system of pricing and reimbursement that is in operation in every country can provide an explanation about the persistence of brand name drugs against non-brands. Although each country has its own unique system for regulating pharmaceutical prices, countries can be separated in those that regulate prices or reimbursement rates of pharmaceuticals (France, Italy, Spain and Japan), those that do not, such as the USA and Germany[7], and a mixed group (the UK, Germany[8], the Netherlands, Sweden and Canada). The evidence from the literature suggests that it is easier for generics to enter in markets that have liberal pricing regimes than command and control regulation

[7] For innovator drugs only. This is changing as assertions regarding pricing premia for new innovator drugs will be subjected to cost-benefit analysis by the Institute for Efficiency and Health Care Quality (IQWiG), that advises the Joint Cttee which decides on reimbursability of new pharmaceutical products.

[8] Includes off-patent sector with the implementation of reference pricing.

of pharmaceutical prices. For example, the US and Germany do not impose price ceilings on new pharmaceuticals whereas France, Canada, the Netherlands, Denmark and Italy have various regulatory arrangements that control prices of new medicines and France and Italy the price of generics as well (King & Kanavos, 2002). Danzon and Chao (2000) found that generic entry has a negative effect on originators prices' in countries with free pricing such as the US[9] and those with free pricing subject to moderate regulations such as the UK, Germany and Canada, but none or even a positive effect in countries with strict price or reimbursement regulation such as France, Italy and Japan. Thus, the existence of strict regulations is one more reason for the persistence of branded drugs over non-brands.

In addition, Bae (1997) found that there is a negative relationship between originator drug sales revenue and the time to generic entry. Entries of generics tend to be slower for drugs that have either very few or a very large number of competing brands in the marketplace. Also, drugs that primarily treat chronic conditions tend to enter faster than those primarily treating acute illnesses. It was also found that the generic industry is targeting large-revenue products and chronic drug markets whereas entry of a generic drug is influenced by the existing branded substitutes in the marketplace.

Greater stability of demand seems to be a factor that attracts generic entry more to the chronic disease drugs than to the acute drugs. Thus, originator drugs have in same cases the ability to retain market shares as they do not face competition from generics.

Investment in advertising activities seems to deter competition and extends the life originator brands, as manufacturers seek to differentiate their products in order to maximize their lifetime value. Hence, through life cycle management, branding appears to be an appealing path to follow. (Over-) investment in advertising can deter generic market entry under certain

[9] Although this must be compared with contradictory evidence regarding the generics paradox which suggests that that originator drug prices are not necessarily affected by the entry of generic medicines, as discussed in previous sections to this report.

conditions. Hurwitz and Caves (1988) and Rizzo (1999) found that brand-name advertising decreases the price-elasticity of demand in the pharmaceutical industry, because it increases brand-loyalty and both studies concluded that brand-name advertising inhibits generic market entry. Similarly, Konigbauer (2007) incorporated both the goodwill effect of advertising and the decreased price-sensitivity and concluded that generic market entry can be deterred by over-investing in advertising. Overall, advertising can deter competition from generic equivalents after patent expiration.

Apart from the above reasons, Hong et al (2005) proposed an alternative explanation for the continued price rigidity of patent-expired brand-name prescription drugs; despite the increase in market entry of generic drugs, which was facilitated by Bolar provisions and explicit legislative acts, such as the 1984 Drug Price Competition and Patent Term Restoration Act in the USA, line extensions introduced for an original brand helps the original's price be rigid despite generic entry. Study hypotheses were to test whether market entries of new-product extensions are associated with market success of original brand-name drugs before generic drug entry and whether original brand-name drugs exhibit price rigidity to generic entry only when they are extended. A line extension is a variation of an existing product; this variation can be a new formulation of an existing product or a new modification of an existing molecular entry. Since the extension has the market exclusivity that the original brand has lost and its demand is elastic to changes in the original's price, the brand owner would change the original's price to support the demand for the extension. Thus, the original's price would become rigid with the entry of generic versions, but it would be sensitive to the entry of extensions. This study provided an explanation for the continued price rigidity of patent-expired brand-name drugs despite the increased market entry of generic competitors. It also provided some support for the alternative explanation to brand loyalty that a new product-line extension introduced for an original brand helps the original price be rigid despite the entry of generics.

5.9 The Demand-side: Brand loyalty and adherence

5.9.1 Adherence and its determinants

The issue of adherence with medical treatment and particularly with consuming medicines have received considerable interest in the health economics literature. Although "compliance" is the most useful key world in searching the literature, the term has over the years come under attack and has been replaced by terms such as "adherence" and, more recently, "concordance". *Compliance* suggests that the doctor knows best, *adherence* gives a more active role to the patient whereas *concordance* refers to the outcome of the encounter between the doctor and the patient. In this study all these terms are used interchangeably.

It is not easy to identify the noncompliant patient. However, previous studies provide some indication of several factors that are known to affecting adherence with medication. These factors are classified in the following five categories:

(a) treatment-related;

(b) disease-related;

(c)patient-related;

(d) physician-related; and

(e) environment-related.

The nature of the medicine, the duration, complexity, cost and side-effects of the medication are categorized as treatment-related factors. Jones et al (2003) found greater adherence to oral than to inhaled controller asthma medications. Many studies found compliance to be negatively related with length of treatment. It has been estimated that about 50% of patients prescribed long-term medication for chronic diseases do not fully comply with prescribed regimens. This proportion is remarkably consistent across diseases as epilepsy, arthritis, diabetes, hypertension, schizophrenia and asthma (Perkins, 2002; Christensen, 1978, among others). In contrast, studies

indicate that the level of adherence in short-term medications for acute conditions such as antibiotic treatments and nebulised medications and pancreatic enzymes, is relatively high (80-95%) and moderate (65%-80%) respectively.

Numerous studies have shown that the complexity of the medication, as indicated by the number of drugs to be consumed, the daily dose frequency, and the nature of the dosage forms employed, are negatively correlated to compliance (Christensen, 1978). Complex medications contribute to patient non-compliance because they are confusing and inconvenient (Kulkarni et al, 2006). Also, compliance decreases as the incidence and severity of side effects and the cost of treatment increase (Huskamp et al, 2003; McDonald et al, 2002; Shrank et al, 2004). Poor compliance has also been reported in patients with a lack of insight and awareness of their illness and in those who believed that medicine should be taken only when they were feeling ill. Several studies have tried unsuccessfully to relate compliance with patient characteristics (McDonald, 2002). However, compliance does not seem to relate with patient age, sex, race or education (Weingarten and Cannon, 1988).

The communication between physician and patient is assumed to affect patient compliance and some studies have examined the dynamics of this relationship on medicine taking. Patient non-compliance could be attributed to inadequate communication and information, whereas when patients are given more and better information about their medicines their compliance was found to have significantly improved (Conrad 1985). Studies also indicate that the lack of social support is consistently related with non-adherence (Oehl et al, 2000; Nose et al, 2003) and in the case of specific diseases such as mental illnesses related risk factors include the stigma of mental illness and living alone (Oehl et al, 2000).

5.9.2 Does brand loyalty contribute to drug adherence?

One of the fundamental hypotheses surrounding brand-loyalty is that it might contribute to drug adherence. This particular angle of the issue has not been explored explicitly in the literature, but what has been explored is the relationship between generic substitution and adherence.

Research shows that the link between generic substitution and adherence to medicines is weak. For example, generic substitution does not affect adherence to antihypertensive drugs (van Wijk et al, 2006), although this may not hold for other classes of medicines. Indeed, research has found that medication utilization by asthmatic patients may vary with ease of drug administration, efficacy and tolerability but not exclusively because of the use of brand versus generic versions (Jones et al 2003). Rates of persistence to the use of lipid-lowering medicines also vary with choice of agent prescribed, co-morbidity and socioeconomic status, despite universal coverage of prescription drug costs but there is little indication brand versus generic treatments result in differences I use (Avorn et al, 1998).

In principle, consumers should stay loyal to the benefit of medication and its contribution to health rather than being loyal to a particular brand. Yet, there is some indication that patients prefer brand-name pharmaceuticals instead of generics in the off-patent pharmaceutical market. Evidence suggests that consumers tend to re-use those medicines that have already worked for them, and are reluctant to try medicines that they have not tested before and may not suit them (Klemperer, 1995).

Generic substitution occurs significantly more often for acute than for chronic conditions and is frequently not accepted by higher income and older patients. Patients with chronic diseases have shown more often a negative attitude towards generic drugs, confirming assumptions from different authors that chronically ill patients perceive the consequences and risks of generic substitution as more serious and have more fear of health loss (Himmel et al, 2005). Also, patients with higher income and older patients were found to prefer brand-name prescription medicines than generic, although findings are not always consistent across studies (Nair et al, 2002).

Finally, after discontinuation of brand-name coverage, patients were found more likely to use less medication, stop medications, and not start medications (Tseng et al, 2006). The same study found that the participants most at risk for decreasing medication use in association with discontinuation of brand-name drugs were those who were younger and who had lower income. The therapeutic classes most affected by decreased medication use, when an involuntary switch from brand-name generic to generic-only drug coverage occurred, included drugs for treating hyperlipidemia, ulcer or reflux, pain or inflammation, asthma or emphysema, allergies, depression, stroke, infection, hypertension and osteoporosis or hormone therapy.

6. Conclusions of the evidence on brand loyalty in pharmaceuticals

Brand-loyalty theory has often been used in the health economic and pharmaceutical literature to explain the price-insensitivity of originator drug after the expiration of the patent and the entry of generics in the market. It has also been used to explain the preference for a particular branded medicine over another in therapeutic markets that are patent protected.

There are differences in the definition and perception of brand loyalty as it applies in pharmaceuticals and as it applies in marketing science. According to marketing science, a necessary and sufficient condition for brand-loyalty to exist is the presence of brands. In this context, a consumer is regarded as loyal when he shows a preference and buys a particular brand in a product category, because he believes that this brand offers the right product features, images or level of quality at the right price, giving him satisfaction.

This is slightly different to the situation that prevails in the pharmaceutical market place. Brands do exist in pharmaceuticals, but pharmaceutical markets display certain peculiarities, which call for an adaptation of the brand loyalty paradigm in this industry. Importantly, prescription medicines cannot be purchased without doctors' prescription or pharmacists' authorisation and endorsement. Equally, the number of

prescription medicines is nowadays very large that it is very difficult even for health care professionals to know all of them and there is no drug that is absolutely safe. Whereas brands are created through advertising, the advertising of prescription medicines directly to the public is prohibited in most countries and only detailing to health care professionals is allowed, although in an era of free access to information patients can acquire information about new treatments and medicines without much restriction. As a result, brand loyalty in pharmaceuticals increasingly applies to both physicians as well as to patients. Finally, the pharmaceutical sector is subjected to intense regulation pertaining to safety, quality, efficacy and, increasingly, cost-effectiveness by regulatory authorities, prior to medicines becoming available for human use. This further stimulates the creative branding process.

The peculiarities of the pharmaceutical sector mean that whereas from an industry perspective there is a powerful desire to create strong and lasting brands, in reality, this is subject to significant constraints for a number of reasons. First, health insurance frequently requires physicians to prescribe by INN rather than by brand-name. Second, it is unlikely that the physician will try the product himself, therefore, s/he relies on feedback about the action of the medicine from the patient or from the observation of the patient's medical tests. Third, there is a separation between patients and prescribers. Patients can neither buy a prescription drug from the shelf of the store nor can know and judge the reactions and side effects of a continuously increasing and different variety of prescription drugs.

Although brand loyalty exists and frequently underwrites consumer (and proxy-consumer) behaviour in pharmaceutical markets, in practice it is very difficult to measure it with a significant degree of accuracy.

Nevertheless, two aspects of brand loyalty arise in pharmaceutical markets as a result of the pharmaceutical market structure and intellectual property rights protection. The first relates to brand loyalty in the context of competition at therapeutic class level within in-patent markets and accounts for the effect of product differentiation among close substitutes. The second

relates to brand loyalty in the context of competition post-patent expiry and the extent to which pharmaceutical markets become genericised after the entry of generic competitors, the speed at which this occurs and whether the patent-expired originator brand retains a certain market share.

In branded in-patent markets, the extent to which a particular brand can maintain (significant) market share in the face of competition from other products in the same therapeutic category can be perceived as evidence of brand loyalty. Evidence exists from the statins class, whereby products entering the markets of France, the UK, the Netherlands and Germany first enjoyed "first mover advantages" and commanded higher prices than their competitors. When all statins were on the market, prices were not affected downwards and the market was divided out to the key players in this therapeutic class. Products therefore, compete on "quality", namely the attributes of their respective products, and, through that they create the brand loyalty to the respective consumers.

Whereas branded products may enjoy a degree of monopoly power through patent protection when first entering a market and are therefore in a position to develop brand loyalty of their own, the extent of substitutability and whether it is close among the products in the class, may erode some of the price advantages these products may have on the market. Highly substitutable products with little product differentiation among them are more likely to display poor brand loyalty Therefore, product differentiation is a necessary, but not a sufficient condition for clear brand loyalty advantages.

Brand-loyalty has also been used on a number of occasions in the health economic literature as an explanation for the price insensitivity of originator drug when its patent expires and generics enter into the market. Although cheaper versions of the originator drug are available the originator drug does not lose completely either its market share or its increased level of price, a fact that is being explained by the literature as brand-loyalty. This persistence of innovator drug against generic competitors could be connected with factors such as the following: the existence of insurance coverage, the absence of

financial incentives for doctors, patients' perceptions about generic drugs linking these with originator brand loyalty, issues around bioequivalence, the absence of substitution laws and financial incentives for pharmacists, the existence of strict regulation of price and reimbursement of drugs, the use of line-extensions, advertising and the market success of originator drugs.

The existence of insurance coverage for prescription medicines seems to be one factor that explains the persistence of brand-name drugs over generic equivalents. Pharmaceutical markets are often characterised by price inelastic demand because of extensive medical insurance moral hazard. Moral hazard is reflected in two instances: in that many patients dislike talking about cost with their doctor, and in their feeling that generic prescriptions are a strategy to reduce cost at the expense of patient quality of care.

Physicians are key decision-making agents for drug consumption and prescription medicines typically require a physician's prescription to be dispensed. In this context, branded medicines (whether branded generics or brand originator drugs) also seem to be preferred by doctors. Contributing factors for this include the non-existence of strict budgets or other financial measures restricting the freedom to prescribe the drug of choice. Additionally, physicians may often have doubts about the bioequivalence or therapeutic equivalence of generics in relation to their brand-name alternatives, although this is currently less the case. In some countries, particularly lower income countries with weak regulatory regimes, prescribing a brand or the originator, is frequently the best choice for the patient. Finally, physicians may show an element of habit pushing patients to consume what they are used to (i.e. a brand) rather than a generic. Finally, physicians may prefer brand names because they may be familiar only with the brand-name of specific drugs and unaware of the correspondence between generic and brand-name drugs, thus continuing to prescribe the latter even when generic drugs are available for all the above reasons. This is largely dependent on the nature of training physicians receive once at medical school.

Patients' reservations about the use of generic medicines –particularly unbranded generics- has often led to conflict between them and their primary care physician, as physicians as well as pharmacists often find that patients have doubts about generic equivalence and show preference for (innovator) brand named medicines. More frequently than not, generic medicines can differ in appearance from their branded equivalents and in cases in which more than one generic drug is available, they may differ from each other. Not only may the colorants and excipients vary, but the size, shape and delivery formulation of the generic product also may differ considerably from the branded product. These differences can cause anxiety and confusion in patients, especially in the elderly and occasionally result in a patient inadvertently taking two formulations simultaneously. There is evidence that patient preferences can also be a barrier to increased generic substitution. Patients may perceive brand-name products as being of higher quality compared to generic products. Frequently, patients with chronic diseases more often showed a negative attitude towards generic drugs, confirming assumptions from different authors that chronically ill patients perceive the consequences and risks of generic substitution as more serious and have more fear of health loss.

The system of pricing and reimbursement that is in operation in every country can provide an explanation about the persistence of brand name drugs against non-brands. It is easier for generics to enter in markets that have liberal pricing regimes than command and control regulation of pharmaceutical prices. Generic entry has a negative effect on originators prices' in countries with free pricing such as the US and those with free pricing subject to moderate regulations such as the UK, Germany and Canada, but none or even a positive effect in countries with strict price or reimbursement regulation such as France, Italy and Japan. Thus, the existence of strict regulations is one more reason for the persistence of branded drugs over non-brands. Finally, despite the increase in market entry of generic drugs, which was facilitated by Bolar provisions and explicit legislative acts, line extensions introduced for an original brand helps the original's price be rigid despite generic entry.

One of the fundamental hypotheses surrounding brand-loyalty is that it might contribute to drug adherence. This particular angle of the issue has not been explored explicitly in the literature, but what has been explored is the relationship between generic substitution and adherence. Yet, research shows that the link between generic substitution and adherence to medicines is weak although consumers tend to re-use those medicines that have already worked for them, and are reluctant to try medicines that they have not tested before and may not suit them. Finally, after discontinuation of brand-name coverage, patients were found more likely to use less medication, stop medications, and not start medications.

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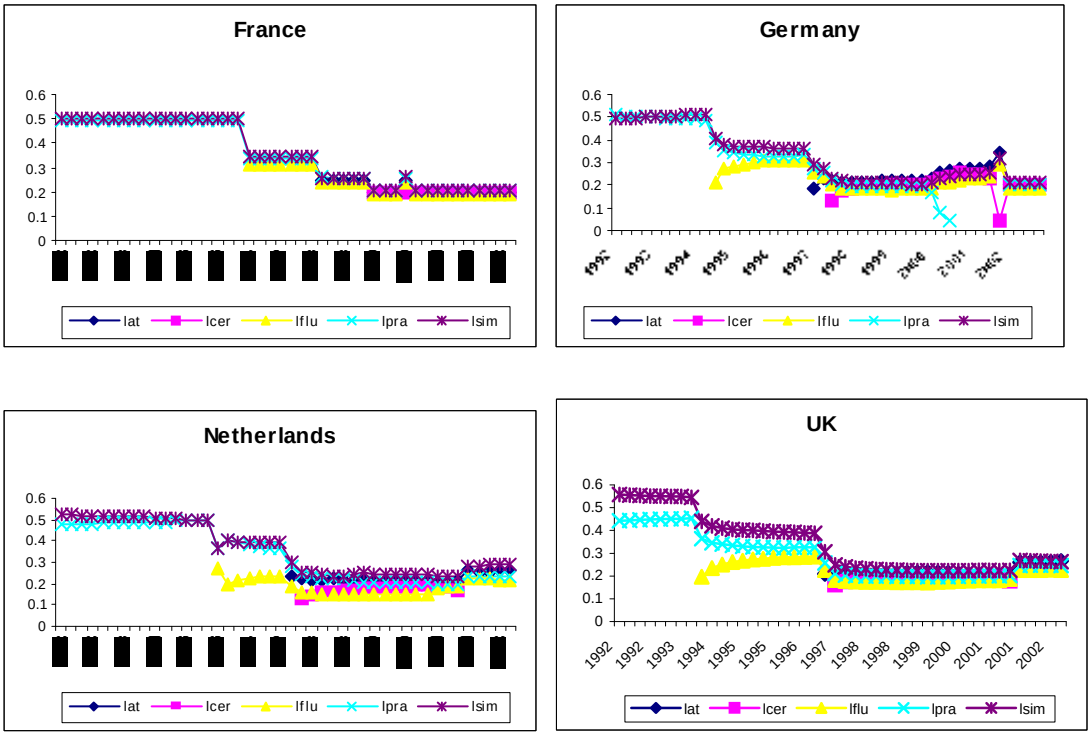
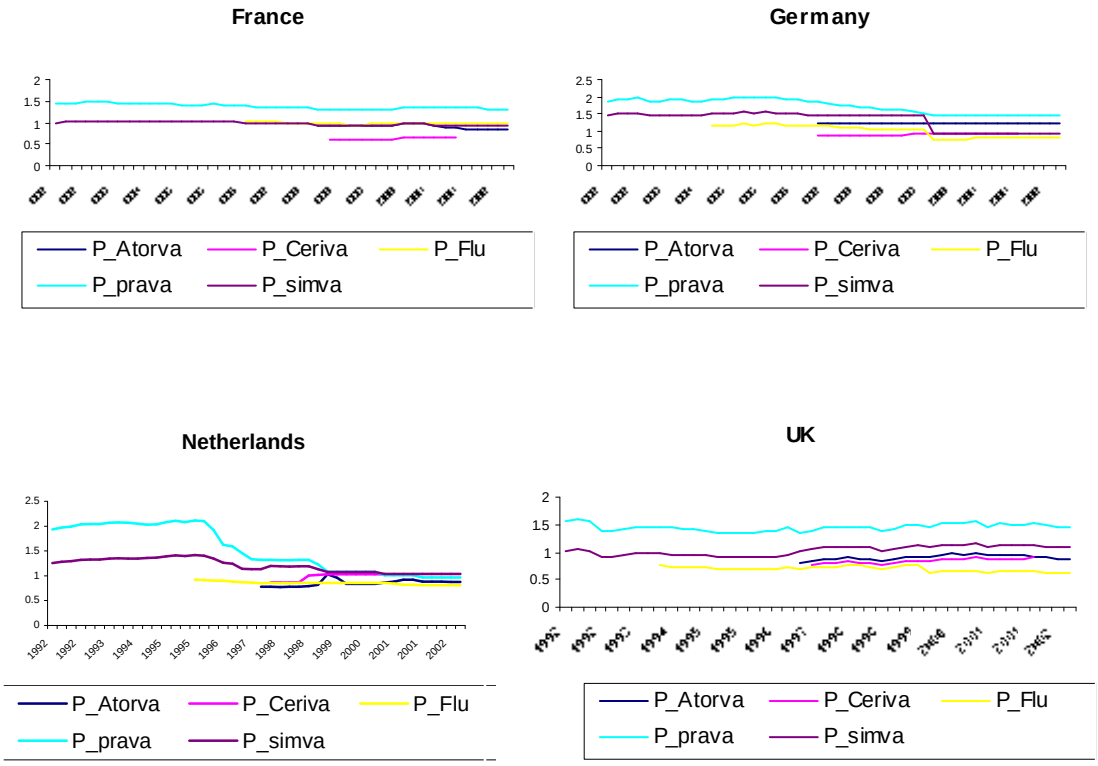
Figure 1
Market shares of statins in selected EU countries, 1992 - 2002



***Source**:* The author from IMS.

Figure 2
Prices of statins in four European countries (adjusted by pack size and DDD), 1992 - 2002



Note: Atorva = atorvastatin; Ceriva = cerivastatin; Flu = fluvastatin; Prava = pravastatin; Simva = simvastatin.
Source: The author from IMS.

Table 3
Generic penetration on patent expiration in the USA: Evidence from18 drugs

	At date of entry (%)	One year after generic entry (%)	Two years after generic entry (%)
Average brand name price index	**100%**	**107%**	**111%**
Average generic price index	**100%**	**78%**	**65%**
Average ratio of generic price to brand name price	**61%**	**46%**	**37%**
Average generic market share in units	**9%**	**35%**	**49%**
Brand name market share in units	**91%**	**65%**	**51%**

Source: Grabowski and Vernon, *American Economic Review*, 1988.

Table 4

Impact of (generic) competition in ACE inhibitors – effect on branded drug sales and prices

	UK	Netherlands	France	Germany
Sales	-77% overall -86% for top presentations	-51% overall -92% for top presentations	-51% overall -67% for top presentations	-69% overall -98% for top presentations
Prices (02-first year of PE)	+21% for top presentations; two presentations discontinued	-30%, -46%, & -40% for top presentations	+ 1.1% & +1.2% for top two presentations	-64%, -74% & -38% for top three presentations

Source: Kanavos & Srivastava, 2007.

Table 3

Penetration and pricing of generics in Europe in relation to the branded medicine: the effect of brand loyalty revisited

	Average penetration after 4 years (%)	Differential between reference price and generic after 4 years (%)
UK	**55%**	**80%**
Netherlands	**35%**	**50%**
Germany	**45%**	**30%**
France	**5-15%**	**30%**
Italy	**5-15%**	**25%**
Spain	**5-15%**	**25%**