COMPETITION AND INNOVATION IN THE SWEDISH PHARMACEUTICAL MARKET

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Chapter 1

Introduction and Summary

Introduction and Summary of Essays

This thesis consists of four essays dealing with topics related to the pharmaceutical market. Two main themes can be discerned in these essays. The first is how competition is affected by regulations, which is the focus of essays one and three. The second theme is the relationship between innovation, on the one hand, and markets success and pharmaceutical expenditures on new innovative drugs on the other, which is the focus of essays two and four. Some very general observations can be made. The first, relating to the first theme, is that regulations may decrease competition in some markets and sometimes have effects contrary to those intended by the policy makers. The second observation is that new innovative drugs seem to have a large impact on the pharmaceutical market by opening up new markets and driving an increase in pharmaceutical expenditures.

The purpose of the first essay is to compare the pricing of new pharmaceuticals in the Swedish market where prices are regulated, with the results of Lu and Comanor [1998] who studied the pricing of new pharmaceuticals in the US market. A data set of all New Chemical Entities launched in Sweden between 1987 and 1997 is collected. The same regressions as in Lu and Comanor [1998] are then run on these data. In line with their results, introductory prices are found to depend on the degree of therapeutic innovation. The average relative launch prices are, however, higher in Sweden. Contrary to the results on the US market, the real prices for NCEs fall substantially over time for all classes of therapeutic innovation. Furthermore, contrary to the results of Lu and Comanor [1998][*], we find no effect of the number of branded substitutes on either introduction prices or price dynamics. Our results indicate that price regulation discourages the use of penetration strategies and decreases price competition between brand name drugs.

The second essay addresses the question how new innovative drugs gain market shares when introduced in the market. It is assumed that new innovative drugs can differ from existing drugs in both a vertical and a horizontal quality aspect. In the vertical quality aspect, all patients will agree that higher is better. For example, more efficacy and fewer side effects are preferred by everyone to less efficacy and a larger number of side effects. The horizontal aspect, on the other hand, allows for differences in preferences. For example, some side effects may be ranked differently by different patients. A model explicitly dealing with these two quality aspects is analyzed with respect to markets shares, prices and competition. The implications from this model are tested on data from the Swedish pharmaceutical market. Vertically differentiated drugs are found to gain larger market shares, command higher prices, and be less sensitive to substitutes than drugs that are only horizontally differentiated. One implication may be that a regulated market with price insensitive consumers, ceteris paribus, is more conducive to the most innovative drugs than to less innovative ones, since competition in prices is more important for the latter class of drugs.

The third essay studies the effect of the reference pricing system on generic entry in markets where brand name pharmaceuticals lose patent protection. The hypothesis is that the

[*] Lu, Z. J., and W. S. Comanor [1998] "Strategic Pricing of New Pharmaceuticals" *Review of Economics and Statistics* 80(1), 108-118.

reference pricing system may increase price competition in some markets to such an extent that entry is deterred if it entails sunk costs. A sample of brand name drugs including drugs that lost patent protection both before and after the reference pricing system is compared and a model of the probability of generic entry is estimated, where the presence of a reference pricing system is one of the explanatory variables. According to these estimates, it seems as if the likelihood of generic entry after patent expiration was reduced by half after the introduction of the reference pricing system. On basis of this result, an attempt is made to measure the effect of the deterred entry on the net savings of the reference pricing system. It seems as if savings due to lower prices caused by the introduction of the reference pricing system were outbalanced by higher prices in markets with deterred entry. Increasing competition without simultaneously reducing the sunk costs of entry may thus turn out to be an example of ineffective competition policy.

The fourth essay investigates how the growth in pharmaceutical expenditures is determined. A theoretical model of growth in pharmaceutical expenditures is analyzed and the role of new innovative drugs for growth in Swedish pharmaceutical expenditures is studied empirically. The result from the theoretical model is that the potential driving forces of the steady state growth in expenditures are inflation in introductory drug prices, the inflow of new innovative drugs and the increase in underlying demand. The result from the empirical study is that introductory prices have been stable during the period studied but that new innovative drugs have opened up new markets and increased the number of drugs consumed. An important conclusion is that the change in the drug price index is of little importance for growth in pharmaceutical expenditures in steady state. Under current trends, it might be necessary to decrease the access to new innovative drugs if the steady state growth rate is to be reduced.

Chapter 2

Essay I: Pharmaceutical Pricing in a Regulated Market

Pharmaceutical Pricing in a Regulated Market*

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Abstract

We compare how new pharmaceuticals are priced in the price regulated Swedish market with the pricing of new pharmaceuticals in the US market, as studied by Lu and Comanor [1998]. We collect a data set consisting of all New Chemical Entities (NCEs) launched in Sweden between 1987 and 1997, and test the same models as Lu and Comanor [1998]. In line with their results, we find that introductory prices depend on the degree of therapeutic innovation. The average relative launch prices are, however, higher in Sweden.

Further, contrary to the results from the US market, Swedish real prices for NCEs fall substantially over time for all classes of therapeutic innovation. Also contrary to the findings of Lu and Comanor [1998] we find no effect of the presence of branded substitutes on either introduction prices or price dynamics. Our results indicate that the price regulation discourages the use of penetration strategies and decreases price competition between brand name drugs.

*We thank Magnus Johannesson for his advice and comments. We have also benefited from comments and discussions with Tore Ellingsen, Ulf-G. Gerdtham, and Bengt Jönsson.

1 Introduction

The rapid increase in pharmaceutical expenditures in many countries (see e.g. Abbott [1995] and Besley and Gouveia [1994]), has generated much interest in the pricing of pharmaceuticals. It is sometimes argued that the presence of patent protection and third-party financing could lead to excessive prices, and therefore many nations have some form of expenditure regulation. One example is price caps, which are currently gaining in popularity with regulatory agencies and government institutions. However, the use of price caps as a means to curb pharmaceutical expenditures is the subject of some controversy. Opponents of price (cap) regulation argue that this may adversely affect incentives to develop new and better products, since producers are not adequately reimbursed for the massive investments needed to bring new drugs to the market. This standpoint is taken by many in the United States where no such regulation exists, (see e.g. Danzon [1997]). It has also been maintained that price caps are not even effective in curbing pharmaceutical outlays (Abbott [1995] and Danzon and Chao [2000]).

In order to evaluate the effects of price regulations and to resolve the controversies surrounding pharmaceutical prices, we believe that further empirical work is desirable. In this paper, we take a step in this direction, performing a basic comparison of pricing patterns in a market with regulated prices with a market where prices are not regulated. More specifically, we consider how the pricing strategies of pharmaceuticals in Sweden relate to the pharmaceutical pricing in the US market using identical explanatory variables.

There have been a number of empirical studies on the pricing of new patented drugs in the US market. Reekie [1978], in a seminal study, examined the introductory prices of new chemical entities (NCEs) launched in the US between 1958 and 1975. He found that the introductory price (relative to existing substitutes) depended on the degree of therapeutic advance, i.e. the price premium was larger for drugs offering important therapeutic gains compared to drugs offering minor therapeutic gains. Reekie [1978] also found that prices tended to increase faster for drugs introduced at lower prices compared to drugs with higher launch prices.

The pricing pattern observed by Reekie is consistent with the observation made by Dean [1969], who distinguished between two pricing strategies for new products: skimming and penetration. A skimming strategy involves setting a relatively high introductory price to skim off the highest willingness

to pay, and then lowering the price. Penetration is the opposite strategy: lower introductory prices followed by increased prices as demand picks up. Dean [1969] argued that skimming strategies are more often used for products offering major advantages over existing products, and that penetration strategies are used for products that offer only marginal improvements over existing products.

Recently, Lu and Comanor [1998] (henceforth LC) performed a study of 144 NCEs introduced in the US between 1977 and 1987.[1] The principal motive of their paper was to explore and quantify the demand side determinants for NCE prices. In their view, therapeutic value and market structure are the main explanatory variables for NCE pricing. This is in contrast to the more established supply side arguments often used in the debate over pharmaceutical prices.

LC classified the new pharmaceuticals into three different classes of therapeutic gain, depending on whether the drugs represented a major, a minor, or no improvement over existing drugs. Introductory prices for drugs representing important therapeutic gains were on average about three times higher than those for existing substitutes, whereas new drugs that offered little therapeutic gains were launched at about the same price as existing substitutes. The real prices for drugs representing important therapeutic gains were relatively stable over time. However, for drugs representing small improvements the real prices increased substantially. These results are thus consistent with Dean's [1969] observation of skimming and penetration strategies. LC also found that the presence of branded substitutes had a clear negative effect on both introductory prices and price changes over time.

LC concluded that competitive forces play an important role in the US pharmaceutical market, and hypothesized that an introduction of price regulations may discourage penetration strategies.

The purpose of the present study is to compare the outcome in a (price) regulated market with the results in the US market by performing the same tests as in LC. To do so, we examine a data set consisting of all NCEs launched in Sweden between 1987 and 1997, and estimate the same models as in LC. In line with their results, we find that introductory prices reflect the degree of therapeutic innovation. Contrary to the results in the US market, the real prices for NCEs fall substantially on average over time for all classes of therapeutic gain, so the price cap regulation rules out the use

[1] In their study, the term New Molecular Entities (NME) is used.

of penetration strategies. More interestingly, we find no evidence of branded substitutes having any effect on either introductory prices or price dynamics. It therefore appears that price competition between pharmaceutical brands is indeed less pronounced under price cap regulation.

The remainder of this paper is structured as follows. We first give a brief description of the pharmaceutical market in Sweden. Then we informally discuss some of the hypotheses that the regulatory constraint provides and put these in relation to the findings in LC. We continue with a description of the estimated models and the data, then with a presentation of the results. The final section offers a concluding discussion.

2 The pharmaceutical market in Sweden

In Sweden, a substantial fraction of the pharmaceutical consumption is subsidized by the government. For pharmaceutical products that are included in the public insurance program, the state will fully reimburse individual consumption exceeding some fixed amount per annum.[2] If pharmaceutical producers wish to have their products reimbursed through this system, prices must be set by the appropriate government agency. Prior to 1993, prices were determined by the National Corporation of Swedish Pharmacies (NCSP) after negotiations with the producers. The NCSP is government-owned and monopolizes the retailing of all pharmaceuticals in Sweden. When the NCSP was in charge of the price negotiations, firms were not allowed to sell their products until the prices were agreed upon. If the NCSP and a firm were unable to reach an agreement about the price, the firm could apply to engage the Medical Products Agency (MPA)[3] as a mediator. In 1993, the National Social Insurance Board (NSIB) replaced the NCSP as the government agency responsible for administering the drug benefit scheme. Since that time, participation in the public insurance program has been optional, so producers are allowed to market their drugs outside the program and set prices freely. However, since consumption outside the benefit program must be financed completely out-of-pocket, producers have rarely exercised this option. The objective of the NSIB is to determine pharmaceutical prices so as to:

[2]Presently, this amount is SEK 1800 (approx. USD 200). Although the co-payment schedule has changed somewhat over the time for our sample (1987-1997), the state financed part has always been large.

[3]The MPA is roughly the Swedish equivalent of the FDA in the US.

- ensure a consistently high level of public health;
- ensure that a sufficient range of pharmaceutical products are available at reasonable prices;
- support an efficient production of pharmaceuticals;
- encourage the research and development of new pharmaceuticals.[4]

Furthermore, when setting the launch price for a new product, the regulating agency should consider the medical merits and the health economic value of the product, the price in comparable countries,[5] and the price (and reimbursement cost) for related treatments (pharmaceutical or other). The health economic value represents the societal benefit the new drug brings in terms of savings for the total reimbursement bill (e.g., through effects on other products comprised in the benefit schedule), savings on social insurance due to reduced sick leave, health care savings in the form of a reduced number of physician visits, and also savings due to a reduced amount of care outside the direct health care sector (e.g. home care).

The manufacturer is responsible for providing the regulating agency with the relevant information about the drug.[6] This information should also contain, apart from the above, forecasts of sales in Sweden the first two years after launch, and predicted sales at a steady state level.

Once an introductory price has been set, it cannot be raised within the two first years after launch. Thereafter, applications for price increases for the whole product line, but not individual products, are considered once per year. As a general rule, the producer may increase prices within some specified margin and is granted some leeway for individual products in the basket. For instance, price increases on certain products may be allowed if the producer lowers prices on other products in the basket.

Since 1993, the reference pricing system has been used in Sweden. This system applies when the patents for brand name pharmaceuticals have expired and there are generic substances in the market. If generic alternatives are available, the reimbursement scheme allows full coverage for products

[4]These points are in accordance with the 1990 Transparency Directive of the European Union.

[5]Most notably other northern European countries.

[6]The regulating agency has no means of conducting investigations of its own, but must rely on the information supplied by the applicant or outside sources.

that cost no more than 1.1 times the lowest priced generic pharmaceutical. If consumers want brand drugs priced above this level, they have to pay the differential out-of-pocket.

3 Preliminary discussion

3.1 The US and Swedish markets

LC argue that demand factors explain well the determinants for NCE prices in the US, and their findings are in line with what standard economic theory predicts. In particular, they find that therapeutic advantage has a positive effect on relative launch prices since willingness to pay increases in quality. Also, pharmaceuticals that are mainly intended for chronic conditions command on average lower relative launch prices than drugs primarily intended for acute conditions. Moreover, the former display a pattern of increasing prices over time, so there is evidence that penetration pricing is being used for chronic drugs. This is expected since chronic drugs are to a large extent repeat purchase items, and the appropriate strategy for pricing such goods is by a penetration scheme: low initial prices in order to attract a consumer base whose loyalty can be exploited when the producer increases prices later.

Furthermore, LC find substantial evidence that the presence of brand name substitutes has a negative effect on relative introduction prices. This is also expected: even though brand name products are all patented they may still have similar therapeutic properties and functions. Therefore, prescribing physicians have more products to choose from in treating a given condition.

Finally, LC find that on average the presence of generic competition among the brand name substitutes has a *positive* effect on relative launch prices for NCEs. LC report conflicting evidence on the effect of generic entry on NCE prices from earlier studies, i.e. Caves et. al. [1991], Frank and Salkever [1995], and Grabowski and Vernon [1992]. One explanation for the positive price effects offered both in Frank and Salkever [1995] and in LC, is that it may be more profitable for a brand name producer to focus on satisfying the inelastic segment of demand when generic drugs enter the market. In this instance, other brand name producers may follow suit and increase their prices too. In short, LC conclude that the demand factor variables they consider explain both launch prices and price dynamics in the American pharmaceutical market.

We expect some of the effects that LC describe to be present also in the Swedish data. However, given the broad regulatory policy objectives stated above, it is not obvious how the two markets compare given the same explanatory variables. For example, the price regulation in Sweden makes it difficult for firms to raise the price of one of their products without simultaneously lowering prices on other products. Consequently, we do not expect to observe penetration strategies. Instead, we are more likely to observe constant or falling real prices over the whole range of NCEs in the sample, although it is conceivable that the prices of less therapeutically advanced drugs fall less than those of more innovative drugs.

As far as launch prices are concerned, it is reasonable to expect that therapeutically advanced drugs are rewarded with premia by the regulator as compensation for high R&D outlays. Although the regulator could argue that, given that these costs are sunk, it would be rational to offer the producer marginal cost coverage only. Such behavior, however, is not in line with the regulator's objective to "encourage the research and development of new pharmaceuticals". Also, producers would be hesitant to supply the Swedish market with their products in case they were not sufficiently compensated.[7] Hence, we expect similar patterns as in LC. However, we do not expect any major differences between drugs intended for acute and chronic drugs since penetration pricing is not really an option for the producers.

LC argue that the market structure, or, more specifically, the nature of competition, is a strong candidate in explaining both launch prices and price dynamics. In particular, the existence of more branded substitutes has depressing effects on NCE launch prices. In the regulated environment, however, the market structure may not reflect price setting to the same extent so the relationship between prices and the number of substitutes is less clear-cut. On the one hand, the presence of branded substitutes provides the regulator with more bargaining power to keep prices low by exercising "yardstick regulation". On the other hand, in the interest of the public health the regulating agency has a commitment to ensure the availability of a variety of horizontally differentiated products. For any given level of demand, each product then risks obtaining a smaller market share so the regulator compen-

[7]It can be said that the Swedish market is very small in an international perspective so given the sunk costs, any price above marginal cost should be accepted by the producers. However, there are additional costs associated with the marketing of a new drug, e.g. training of pharmaceutical consultants, promotion campaigns, etc. Therefore, the option of not supplying the drug may be seriously weighed.

sates them by allowing higher prices. Consequently, the strong connection between NCE prices and brand substitutes observed in the American data may be less pronounced in the Swedish data.

As mentioned above, there is mixed empirical evidence of the relation between prices on new pharmaceuticals and the presence of generic competition among the branded substitutes. Here, we have no reason to believe that the presence of generics among the brand name substitutes should affect the NCE prices in any systematic way. The ambiguous effects from branded competition are expected to be present here also. Furthermore, brand name substitutes with generic competitors tend to be older drugs located further away from the NCE in product space than newer brands without generic competition. Therefore we expect a very weak link between NCE prices and generic competition in our sample.

4 Empirical analysis

4.1 Equations and variables

We now proceed with the estimation of the LC model on the Swedish data. We consider the following two models:

$$(1) \qquad LWRIS = \alpha_0 + \alpha_1 A + \alpha_2 B + \alpha_3 ACUTE + \alpha_4 LNS + \alpha_5 \left\{ \begin{array}{c} DG \\ LG \end{array} \right\} + \varepsilon,$$

and:

$$(2) \qquad \begin{aligned} LRATIO \;=\; & \beta_0 + \beta_1 A + \beta_2 B + \beta_3 ACUTE + \beta_4 DALP + \\ & \beta_5 DBLP + + \beta_6 DCLP + \beta_7 LNS + \beta_8 \left\{ \begin{array}{c} BG \\ LGS \end{array} \right\} + \delta, \end{aligned}$$

where:

- $LWRIS$ denotes the logarithm of the ratio of the launch price of an NCE to the weighted average price of existing brand name substitutes;

- *LRATIO* is the logarithm of the ratio of the real price (CPI deflated) of a new drug four years after launch to its real introductory price;
- *A* and *B* are dummy variables that take the value 1 if an NCE is *A*(*B*) classified and zero otherwise;
- *ACUTE* indicates whether an NCE is used primarily for an acute condition;
- *LNS* denotes the logarithm of 1 plus the number of existing brand name substitutes at the time of launch;
- *DG* indicates whether an NCE had generic competition among its brand name substitutes at the time of launch;
- *LG* denotes the logarithm of 1 plus the percentage of substitutes that had generic rivals at the time of launch;
- *BG* indicates whether or not an NCE has a generic rival four years after launch, when there was none at launch;
- *LGS* is the logarithm of the ratio of the percentage of brand name substitutes that had a generic rival after four years to the same percentage at the time of NCE launch, (expressed as whole numbers plus 1);
- *DALP*, *DBLP*, and *DCLP* are interactive variables equaling the product of *LWRIS* and the variables indicating whether the NCE is classified as *A*, *B*, or *C*, respectively.

These models are in effect identical to the ones estimated in LC, and therefore provides a framework for comparing the results in the two different markets.

4.2 The data

The data we use consist of all NCEs approved by the Medical Products Agency (MPA) in Sweden between 1987 and 1997. In total the MPA approved 335 NCEs in this time period. Of these NCEs, we excluded 89 from the present analysis either because they were never marketed in Sweden, or

because a price had not yet been set on the NCE at the time of this analysis. Our data set thus includes a total of 246 NCEs.

No official rating of therapeutic advance is available for pharmaceuticals in Sweden. As a part of this research project, a rating was carried out by pharmacologists connected to the MPA, (see Beermann and Rosén [1999]). Beermann and Rosén had access to all relevant NCE information from the MPA and collaborated with the agency to determine the rating. The purpose was to provide a rating of the therapeutic advance for all NCEs approved between 1987 and 1997, according to how the NCE was judged by the MPA at the time of approval. They classified the NCEs according to the FDA rating system that was used also in the study by LC. These classes are:

- *A*- Important therapeutic gain: Drug may provide effective therapy (by virtue of greatly increased efficacy or safety) for a disease not adequately treated or diagnosed by any marketed drug, or provide markedly improved treatment of a disease through improved efficacy or safety (including decreased abuse potential),

- *B*- Modest therapeutic gain: Drug has a modest but real advantage over other available marketed drugs; for example, somewhat greater effectiveness, decreased adverse reactions, more convenient route of administration, etc., and

- *C*- Little or no therapeutic gain: Essentially duplicates in medical importance and therapy for one or more existing drugs.

In addition to rating the new NCEs according to therapeutic advance Beermann and Rosén [1999] also classified the drugs according to type; that is, whether a drug was indicated primarily for treatment of acute illnesses or chronic conditions.

Beermann and Rosén used the WHO Anatomic Therapeutic Classification (ATC) system to define substitute drugs (ATC Index with DDDs (Defined Daily Dosage), [1997]). The ATC system is divided into 14 anatomical groups (e.g. Heart and Circulation). Each anatomical group is divided into main therapeutic groups, and then into therapeutic subgroups that are further divided into chemical/therapeutic subgroups (e.g. HMG-Co A reductase inhibitors). The chemical/therapeutic subgroups are finally divided into groups according to chemical substance. For example, a chemical substance

is the cholesterol lowering drug Simvastatin that belongs to the HMG-CoA reductase inhibitors chemical/therapeutic subgroup.

We defined close substitutes as drugs in the same chemical/therapeutic subgroup that share the same indication.

This is similar to the definition used by LC, and for most of the new NCEs substitutes were defined in this way. In the event that an NCE did not have any substitute in the same chemical drug class, the substitute was defined as the drug that was most commonly prescribed for that indication in the year before the introduction of the NCE.

For Class *A* drugs it is often difficult to define substitute drugs, since many of these compounds are intended for indications not previously treated by any marketed drug (see the above definition of class *A* drugs). In the ranking of therapeutic advance according to the FDA classification scheme, Beermann and Rosén [1999] therefore divided the class *A* drugs into:

(*i*) drugs that lacked a substitute drug at the time of introduction (drugs for indications not previously treated by drugs), and

(*ii*) drugs with substitute drugs at the time of introduction (drugs providing markedly improved efficacy or safety over existing drugs).

Out of the total 246 NCEs in this study, there were a total of 8 class *A* drugs with substitutes and there were 28 class *A* drugs without substitutes. Naturally, the drugs without substitutes could not be included in the analysis of relative introductory prices since their relative prices could not be defined.

In order to estimate relative prices between NCEs and substitutes comparable dosages need to be defined. For this purpose we used the Defined Daily Doses (DDD) system recommended by the WHO for studies of drug use (ATC Index with DDDs). A DDD is defined as the average daily dose of a drug used by an adult for treatment of the main medical indication of the drug. Official DDDs were available for about two-thirds of the drugs in our sample and were used in these cases. For the remaining drugs daily dosages were based on the recommended average daily dosages in FASS (Pharmaceutical Specialities in Sweden), a widely used medical reference book that contains instructions/recommendations on the appropriate use of all drugs in Sweden. When recommendations regarding dosages were not sufficiently specific or not available in FASS, we consulted clinical pharmacologists (Beermann and Rosén) for the appropriate daily dosages. When doses were given in amount per square meter (e.g. for creams and lotions) or amount per kg body weight, the daily doses were based on one square meter and 70 kg, respectively.

Some pharmaceuticals are available in more than one form of administration. For example, the same drug can be taken as a pill or a fluid. As a rule we calculate the price for tablets when these were available. If there was no tablet, we chose the administration form of the package containing the largest number of daily dosages.

We based all prices on the official retail prices of drugs in Sweden.[8] These prices are set once a year and are reported in FASS. We estimated a price per daily dose for all NCEs and all substitute drugs. We estimated the average price for existing substitutes as the weighted average of the price of all substitutes, with the market shares in the year before the introduction of the NCE as weights. We collected data on substitute quantities from SDM (Swedish Drug Market (1987-1997), a database containing the quantities of all drugs sold on the Swedish market graciously provided by the Swedish Association of the Pharmaceutical Industry. We then adjusted all prices to 1997 prices using the official consumer price index produced by the Statistical Yearbook of Sweden [1999].

[8]In Sweden the price is independent of the buyer (which is not the case in e.g. the US).

5 Results

5.1 Summary statistics

Table 1 summarizes some statistics on relative introductory prices for 218 NCEs introduced between 1987 and 1997 (excluding the 28 A class drugs without substitutes).

Table 1: Relative Introdutory Prices

Class	Relative Introductory Price					Substitutes[a)]	
	N	Median	Mean	Std	Range	I	II
A							
Acute	5	1.43	1.59	0.56	1.10 – 2.55	1	0
Chronic	3	10.97	9.40	4.88	3.93 – 13.30	1	0
Combined	8	2.04	4.52	4.83	1.10 – 13.30	1	0
B							
Acute	30	1.64	3.75	4.96	0.17 – 19.28	4.11	0.03
Chronic	42	2.55	3.92	4.77	0.09 – 20.32	3.80	0.17
Combined	72	2.25	3.86	4.85	0.09 – 20.32	3.93	0.11
C							
Acute	63	1.26	2.16	3.09	0.04 – 16.70	4.40	0.12
Chronic	75	1.13	2.18	3.54	0.12 – 26.17	4.49	0.18
Combined	138	1.16	2.17	3.33	0.04 – 26.17	4.45	0.15

[a)] Subheadings I and II denote the average number of branded substitutes, and the fraction of substitutes with generic competition, respectively.

On average, relative launch prices increase with the degree of innovation. The average relative launch price is 2.2 for C drugs, 3.9 for B drugs and 4.5 for A drugs. The median relative launch prices are substantially lower than the mean, indicating that prices are highly skewed with a few relatively high priced NCEs. The median relative launch prices reveal patterns similar to the average prices, however. The only exception is that the median launch price decreases somewhat for A drugs compared to B drugs. This result should be interpreted with some care given that there are only eight A drugs (with substitutes) in the sample. For drugs in classes B and C, the average relative launch prices are about the same for acute and chronic drugs. For A drugs the relative launch prices are lower for acute drugs than for chronic drugs, but again this comparison is highly limited by the small number of A

drugs.

The number of branded substitutes at introduction decreases with the degree of therapeutic innovation. The average number of branded substitutes at introduction is 1 for A drugs, 3.7 for B drugs and 4.5 for C drugs. The fraction of branded substitutes with generic competition at introduction of the NCE also decreases with the degree of therapeutic innovation. For A drugs, none of the branded substitutes face generic competition whereas 15 percent of the branded substitutes for C drugs face generic competition.

In Table 2 we show some summary statistics about the inflation adjusted change in the price of NCEs four years after introduction. This comparison includes all the NCEs in our database with a follow-up time of at least four years (N=149).

Table 2: Ratios of Inflation Adjusted Prices 4 Years after Introduction

Class	Ratios of Inflation Adjusted Prices 4 Years after Introduction					Substitutes[a)]	
	N	Median	Mean	Std	Range	I	II
A							
Acute	16	0.78	0.83	0.28	0.52 – 1.65	0.31	0
Chronic	12	0.75	0.73	0.12	0.44 – 0.91	1.57	0
Combined	28	0.77	0.78	0.21	0.44 – 1.65	0.90	0
B							
Acute	20	0.93	0.90	0.33	0.34 – 2.05	2.75	0.10
Chronic	26	0.82	0.84	0.13	0.64 – 1.10	2.46	0.12
Combined	46	0.86	0.86	0.24	0.34 – 2.05	2.60	0.11
C							
Acute	42	0.89	0.89	0.29	0.40 – 2.51	4.58	0.13
Chronic	33	0.79	0.81	0.10	0.64 – 1.07	4.03	0.14
Combined	75	0.84	0.85	0.23	0.40 – 2.51	4.33	0.14

[a)]Subheadings I and II denote the average number of branded substitutes, and the fraction of substitutes with generic competition, respectively.

The average real price decreases over time for all classes of drugs: for A drugs the average real price decline is 22 percent, for B drugs it is 14 percent, and for C drugs the average real price decline is 15 percent. There is thus a tendency for a larger price decline for A drugs compared to B and C drugs. There is also a tendency for a greater decline in prices for chronic drugs compared to acute drugs. The range of price changes for the

individual drugs is wide, with some drugs more than doubling in price and some decreasing to a third of the introductory price.

5.2 Regression results

Table 3 shows the regression results of the determinants of relative introductory prices (Equation 1).

Table 3: Regression Analysis of Determinants of Relative Introductory Prices

Variable	Regression Equations[a)]		
Constant	0.485*** (2.895)	0.486*** (2.886)	0.486*** (2.889)
A	0.920** (2.446)	0.920** (2.483)	0.921** (2.442)
B	0.463*** (2.988)	0.463*** (2.980)	0.462*** (2.978)
Acute	−0.197 (−1.371)	−0.197 (−1.351)	−0.200 (−1.375)
LNS	−0.124 (−1.239)	−0.124 (−1.138)	−0.119 (−1.125)
DG		0.004 (0.019)	
LG			−0.077 (−0.153)
N	218	218	218
R2	0.082	0.083	0.083
R2ADJ	0.065	0.061	0.061
F	4.794***	3.817***	3.822***

[a)]Numbers in parentheses are t-values. *Significance at the 10 % level. **Significance at the 5 % level. ***Significance at the 1 % level.

The variable for class A drugs is statistically significant at the 5 percent level and the variable for class B drugs is significant at the 1 percent level. Moreover, both have the expected signs. This strongly suggests that A and B drugs are launched at higher relative prices than C drugs. The coefficient for A drugs is also, as expected, higher than for B drugs, but this difference between A and B drugs is not significant. The variable for acute drugs is

negative but not significant. The variable for the number of branded substitutes is also negative and insignificant. The extent of generic competition on the market does not show a significant effect either. The explanatory power of the regression equations for introductory prices is low with an R-square value of 8 percent.

Table 4 reports the results for the determinants of the real price change four years after introduction.

Table 4: Regression Analysis of Rates of Change of Real Prices

Variable	Determinants of Real Price Changes[a)]					
Constant	−0.202*** (−4.813)	−0.203*** (−4.811)	−0.201*** (−4.782)	−0.175*** (−3.039)	−0.174*** (−3.000)	−0.168*** (−2.900)
A	−0.138*** (−2.624)	−0.138*** (−2.625)	−0.140*** (−2.671)	−0.126 (−0.855)	−0.130 (−0.880)	−0.137 (−0.934)
B	0.032 (0.726)	0.033 (0.750)	0.031 (0.722)	0.003 (0.040)	0.004 (0.050)	0.005 (0.059)
Acute	0.069* (1.856)	0.068* (1.840)	0.064* (1.739)	0.076* (1.932)	0.077* (1.943)	0.075* (1.900)
DALP				−0.008 (−0.330)	−0.008 (−0.320)	−0.008 (−0.314)
DBLP				−0.001 (−0.039)	−0.001 (−0.081)	−0.003 (−0.196)
CDLP				−0.009 (−0.762)	−0.009 (−0.761)	−0.010 (−0.871)
LNS	−0.020 (−0.872)	−0.016 (−0.621)	−0.011 (−0.476)	−0.008 (−0.090)	−0.014 (−0.539)	−0.010 (−0.395)
BG		−0.023 (−0.356)			−0.032 (−0.468)	
LGS			−0.280 (−1.175)			−0.313 (−1.280)
N	128	128	128	149	149	149
R2	0.093	0.096	0.104	0.094	0.095	0.104
R2ADJ	0.064	0.059	0.067	0.049	0.043	0.053
F	3.567***	2.862**	3.138***	2.089**	1.845*	2.041**

[a)]Numbers in parentheses are t-values. *Significance at the 10 % level. **Significance at the 5 % level. ***Significance at the 1 % level.

We estimated the equations both with and without the interaction terms between relative introduction prices and the drug classification. The reason for this is that we may include the A class drugs that had no substitute drug at the time of introduction.

The variable for class A drugs is negative and highly significant, whereas the variable for class B drugs is positive but insignificant. This indicates that prices for A drugs decline faster over time than prices for B and C drugs, but that there is no significant difference between B and C drugs. The variable for acute drugs has a positive coefficient, but fails to be significant at the 5 percent level. The variables for generic competition and brand name competition have no significant effect on the change in prices over time. Likewise, the interaction variables between drug classification and relative introductory price are insignificant. The explanatory power of the regression equations is low with an R-square value of about 10 percent.

6 Concluding remarks

The main purpose of this paper was to compare NCE pricing outcomes in a regulated market (Sweden) with those reported from a market without price regulation (US). In accordance with LC we found that introductory prices depend on the degree of therapeutic innovation. The patterns were similar in both studies, but the average relative introductory prices were higher for all classes of drugs in the regulated market.

The inflation-adjusted price change over time differed substantially between the studies. In the present analysis, real prices declined over time for all classes of drugs. This result is in contrast to the substantial price increase that was reported for C drugs in the US.

Compared to the US market, the Swedish market is thus characterized by higher relative launch prices and falling real prices over time. This pattern of high relative launch prices and declining real prices over time is in line with what one might expect from the price cap regulation in Sweden. Although penetration pricing was not observed for any of the classes of drugs, there was a small tendency for the prices of class A drugs to fall more than the prices of class B and class C drugs. This was the only similarity with the US market in pricing patterns over time.

Contrary to the results in LC there was also a tendency for real prices of acute drugs to fall less over time than those of chronic drugs. LC also

found that branded substitutes had a substantial negative effect on both introductory prices and price changes over time, and that the extent of generic competition tended to increase the relative launch prices. We found no significant effect of the number of substitutes, branded or generic, neither on the relative launch prices nor on the price changes over time.

We note that the NCE samples used in the Swedish and American studies are taken in different time periods. The samples are roughly of the same length but the present sample starts some ten years after the one used in LC. This discrepancy may have some effect on the validity of the comparison.

The differences in price behavior between the US and the Swedish markets suggest that the competitive forces at work in the two regimes are different. Pricing decisions seem to play a major role in the US, whereas it is difficult to see from the Swedish data that prices are as important strategic variables in the regulated market. Clearly, price caps limit the possibilities to use certain pricing strategies which then naturally do not appear in the Swedish data. It generally appears that some of the pricing constraints imposed by the regulator offset some disciplinary effects that market forces bring. The high variance in introductory prices and the lack of price effects from branded competition in the Swedish market are examples of this

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Chapter 3

Essay II: Innovativeness and Market Shares in the Pharmaceutical Industry

Innovativeness and Market Shares in the Pharmaceutical Industry*

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Abstract

We analyze the pharmaceutical market with a model of horizontal and vertical product differentiation. The implications from the model are tested on data from the Swedish pharmaceutical market. We find that vertically differentiated drugs gain larger market shares, command higher prices, and are less sensitive to substitutes than drugs that are only horizontally differentiated.

1 Introduction

Pharmaceutical producers are bringing more and more sophisticated drugs to the market, contributing to the quality of life of millions of patients. This, however, is occurring at rising cost, as reflected in the shares of national GDPs devoted to pharmaceutical expenditures. In most countries, there is extensive government involvement in public reimbursement schemes reflecting a concern that pharmaceutical products be efficiently provided to citizens. The associated price regulations stemming from these schemes are an example of how decision makers try to control the rising costs caused by increasing consumption of medical drugs. Meanwhile, there is a general awareness of the trade-off between controlling costs and providing proper incentives for

*We have benefitted from discussions with Tore Ellingsen, Ulf-C. Gerdtham, Magnus Johannesson, and Bengt Jönsson.

to explore how incentives for R&D are provided on the pharmaceutical market. In this paper, we ask how the introduction of new innovative drugs is rewarded through market shares and prices in the Swedish market.

Earlier research on the economics of the pharmaceutical market has focused mainly on three topics: behavior at generic entry after patent expiration, pricing policies and price sensitivity of pharmaceuticals, and the effectiveness of promotion outlays. In the first category the literature has addressed questions concerning various barriers to entry, price competition, and factors that determine entry. Examples in this category are Grabowski and Vernon [1992], Frank and Salkever [1997] on pricing and barriers to entry, and Scott Morton [1999] on factors that determine generic entry. Reekie [1978] and Lu and Comanor [1998] analyzed pricing strategies as a function of product innovativeness. Ellison et al. [1997] studied the price sensitivity of generic and therapeutic substitutes, and Mortimer [1997] considered the influence of insurance on prescription patterns. The effectiveness and importance of advertising and promotion was analyzed by Berndt et al. [1995], and earlier by Hurwitz and Caves [1988].

Recent work has offered new perspectives on the pharmaceutical market. For instance, Berndt et al. [1999] investigated the existence of network effects in the antiulcer market, and Stern and Trajtenberg [1998] used micro data to study physicians' prescription behavior. Lichtenberg [1998] studied creative destruction in the pharmaceutical market, measuring the effect of new drug introductions on the sales of old drugs. Lichtenberg's results suggest that the most innovative drugs increase aggregate sales one-to-one, while less innovative new drugs decrease the sales of old drugs more than they increase aggregate sales.

Unlike earlier work that was limited to generic pharmaceuticals or particular submarkets, this paper considers the direct interplay between innovativeness, prices, and market shares for new innovative pharmaceuticals in many submarkets. We hope to shed some light on the most important variables which determine how a new innovative pharmaceutical is rewarded in the market. We focus on the differentiation aspect of the good, a factor which we believe is fundamental for understanding how new innovative drugs capture market shares. More specifically, we assume that new innovative drugs are differentiated from each other both in vertical and horizontal dimensions. Along the vertical dimension, pharmaceuticals differ in their general medical efficacy, whereas the horizontal dimension measures how the drugs cater to idiosyncratic tastes or needs. We provide an analysis of this in a model and

test its implications on Swedish quarterly data. We consider New Chemical Entities (NCEs) in 55 therapeutic categories with observations ranging over a twelve-year period. Our main result is that the more innovative and vertically differentiated drugs capture larger market shares and higher prices compared with the less innovative drugs that are only horizontally differentiated. The market shares of the vertically differentiated drugs also seem less sensitive to the number of substitutes. We also conjecture that more innovative drugs capture larger market shares when consumers are insensitive to prices. If prices are regulated in such an environment, relative prices must be set differently in order to maintain the same incentives as in the unregulated setting.

The paper is organized as follows. After a discussion of the pharmaceutical market, we present an address model of product differentiation in the spirit of Hotelling. We proceed with a description of the data and an empirical analysis of some of the implications we derive from the model. Finally, we conclude by summarizing the main results.

2 The pharmaceutical market

It is sometimes argued that while there is nothing fundamentally unique about the pharmaceutical market, many features present in other industries are combined and exaggerated.

At the very heart of the industry is a heavy focus on research and development. Bringing a new therapeutic drug to the market is a lengthy and costly process: the average time period between the scientific conception and the marketing of a new drug is reported to be about ten years in the US, and the associated average cost is nearly 300 million USD.[1] The primary reasons are the stochastic nature of new drug development and the rigorous safety regulations imposed on the industry. For every new pharmaceutical brought to the market, tens of thousands of molecular structures have been screened. An overwhelming majority of the candidate compounds will fail and be discarded on the way, leaving only a tiny subset for further testing first on animals and then on humans.[2] Once the required testing is complete, and the developing firm has a marketable end product, the manufacturer must

[1] *The Economist* [1998], Schweitzer [1997].

[2] On average, only 1 out of 10 000 molecules that enter the initial screening process is actually developed into a drug. (*The Economist* [1998])

obtain approval from the regulatory authorities to start selling the drug. If the drug is approved the firm usually initiates an intense marketing to boost demand. The pharmaceutical industry spends, on average, about the same share of its revenues on marketing as it does on research (Comanor and Schweitzer [1995]). This figure is matched only in certain markets for sophisticated electronic components. Hence, the industry is extreme also in this sense.

The demand side is also atypical. The final consumer (the patient) does not usually choose the specific product, or even treatment. Instead, a better informed agent (the physician) makes the choice for the consumer. In addition, the physician may be constrained in her choice of products due to third party payment and other regulations. The high degree of insurer involvement is particular to the pharmaceutical market, and to the health industry in general.

Pharmaceuticals are fairly specialized products, and individuals respond idiosyncratically to different drugs. Therefore individual consumers may not agree on the ranking of a given pharmaceutical in relation to others, although there is consensus over the general efficacy or therapeutic benefit of the drug. The individual reaction to a certain brand (e.g. with regard to the nature and intensity of its side effects) is often hard to predict ex ante. For this reason, pharmaceuticals are, to a high degree, experience goods whose benefits must be judged after consumption.

It is natural to assume that the process leading to a good match between an individual consumer and a drug is perceived as a cost by the patient. Individuals are adverse to exposing themselves to unwelcome side effects that may result from consuming new pharmaceuticals. The consumer (and in some sense also the prescribing physician) is thought of as making a "consumption investment" in a given drug which will increase the differentiation relative to the ex ante.

Therefore we suggest that if an individual has found a good or even acceptable match, he will be reluctant to try a new drug even if the new drug is expected to be slightly better. In other words, an individual who switches between brands will incur an additional cost.

As mentioned above, we have chosen to concentrate on the product differentiation aspect of pharmaceutical drugs. We contend that therapeutic drugs are well suited for the traditional story of horizontal and vertical product differentiation. This literature stems from the seminal contributions of Launhardt and Hotelling and has been elaborated by numerous others. The

basic idea is that pharmaceuticals provide some degree of therapeutic advantage or general medical efficacy, which constitutes the vertical component of the products. All individuals (patients and/or physicians) agree on the ranking of the products in this respect. That is, all individuals prefer a higher medical efficacy product to a lower efficacy product, all else being equal, implying that they would choose the former over the latter. In addition, there is a horizontal dimension representing the individuals' idiosyncratic tastes for products. In our framework we assume that various pharmaceuticals may be ranked differently by individual consumers, even when they have the same medical potency to treat a certain condition. The reason is that some individuals may experience more severe side effects from certain pharmaceuticals than other individuals, or simply that they prefer a certain profile of side effects over another. This horizontal component therefore suggests that they would not necessarily prefer the same drug if prices were equal.

The market for anti-depressants is a pharmaceutical submarket with both horizontal and vertical product differentiation, and here serves as an example. In this market, there are two predominant types of pharmaceuticals, the tricyclic drugs and the Serotonin inhibitors, SSRIs. The tricyclic drugs belong to an older class of anti-depressants. These drugs increase the production of neurotransmitters of which low levels are associated with depression. The SSRIs belong to a newer generation of drugs. Instead of increasing the production of some neurotransmitters, these inhibit the uptake of a certain neurotransmitter, serotonin.

It has not been scientifically ascertained that the SSRIs are on average more effective in providing relief or treating depression than the older tricyclics. The main contribution of the SSRIs is the reduced probability of adverse side effects and generally less severe side effects. The first of the SSRI drugs (Prozac®) was therefore not classified as an *A* drug (important therapeutic gain) according to the FDA classification system, but as a *B* drug (modest therapeutic gain). Due to the reduced probabilities of side-effects, the SSRIs are vertically differentiated from the tricyclics. There is also inter-brand horizontal differentiation (within the SSRI group and within the tricyclics group), and intra-brand differentiation (between the two groups). For example, Prozac® is horizontally differentiated from the other SSRIs in that it has the longest half-life. This characteristic is attractive for individuals who sometimes forget to take their medication, but it is a disadvantage to those who occasionally experience adverse reactions. SSRIs are horizontally

differentiated from tricyclics in that they produce certain side effects (such as gastrointestinal disease) with higher probability than the tricyclics, but there is a (much) lower probability for a wide range of other symptoms. For this reason, some patients may have a nonpecuniary reason to prefer a tricyclic drug to an SSRI drug, even though SSRIs are generally perceived as more advanced and innovative.[3]

The Swedish pharmaceutical market In the Swedish pharmaceutical market consumers are largely subsidized, and prices are determined in a regulated environment. Until 1993, pharmaceutical prices were determined in negotiations between producers and the National Corporation of Swedish Pharmacies (NCSP). The NCSP is a state-owned company that monopolizes the retailing of all drugs in Sweden. In 1993 a government agency, the National Social Insurance Board (NSIB), assumed the role of the NCSP in the negotiations with the pharmaceutical industry. The regulatory rules also changed slightly, so that from 1993 a producer need only negotiate a price with the NSIB if it wants consumers to be reimbursed for its products within the national pharmaceutical benefit scheme[4]. Prices are set annually, but both producers and the agency may initiate re-negotiations in cases where there are wide discrepancies between the anticipated and the actual performance of their products. In the present sample there are few cases of drastic price changes, however. In most cases real prices decline slightly over time. We think of the outcome as the result of a one-shot bargaining process between two equally potent parties. Both parties consider the price levels in comparable countries and seem reluctant to deviate from the norm in the European Union, not least because of the potential effects of parallel import. Once the initial price is agreed upon, the price path is normally corrected only so that the price falls just below the CPI, unless the drug performs very unexpectedly.

Pharmaceutical consumption in Sweden is financed in three different ways. The cost of prescription drugs is shared between the NSIB and the patient. The patient pays a decreasing fraction of her consumption out-of-pocket up to a certain level, above which pharmaceuticals are entirely covered

[3] An excellent review on the medical properties of anti-depressants is provided in the paper "Pharmaceutical Innovations and Market Dynamics: Tracking Effects on Price Indexes for Anti-depressant Drugs" by Berndt et al. [1996].

[4] A producer may opt not to do this and set prices independently.

by the NSIB via federal taxes. This scheme is re-initiated annually so that once the consumers have reached the level where co-payment stops, they pay nothing for additional pharmaceutical consumption for the remainder of that year[5]. Pharmaceuticals that are sold to and consumed in hospitals are financed by the regional authorities, which organize and provide most of the health care in Sweden. Finally, prescription-free, over-the-counter pharmaceuticals are paid for by consumers alone.

Physicians in general have little direct incentive to prescribe the most cost-effective pharmaceuticals. However, they may have indirect incentives to take account of their prescription costs. For example, some hospitals have pharmaceutical boards supervising the prescriptions and the use of drugs. These boards try to influence physicians to make more cost-effective decisions. Physicians may also be concerned about the costs borne by the patient as a result of the prescription, or about the general costs for taxpayers. Whether physicians' incentives to prescribe cost-effective drugs are strong enough to have an important impact on prescription patterns is still largely an open question. (For a study on the prescription behavior of Swedish physicians, see Lundin [2000]).

3 The theoretical framework

3.1 Assumptions

In order to examine the effect that innovativeness has on market shares we adopt a simple address model of product differentiation. In this class of models, stemming from the classic work of Hotelling [1929], it is assumed that there are J products located in some characteristics space W and that consumers have preferences defined on this set. The utility for an individual $i \in I$ is then a function $u_i(\mathbf{w}, \mathbf{p})$ of his address in relation to the products and the prices $\mathbf{p} \in \mathbb{R}^J$ charged by the suppliers. The individuals are distributed over the set W according to some distribution Φ. The consumers are often assumed to have inelastic demand for exactly one product, so a strategy for a consumer i is a decision vector $\mathbf{d}_i : W \times \mathbb{R}^J \to \{0,1\}^J$ with $\sum_{j \in J} d_{ij} = 1$. All firms[6] $j \in J$ are assumed to maximize profits $\pi_j(\mathbf{w}, \mathbf{p})$ by choosing location and price. A firm strategy would then be a pair (w_j, p_j) in some prescribed

[5]This level is SEK 1800, or approximately USD 180.

[6]Each firm produces exactly one product, so j denotes both product and producer here.

order. A Nash equilibrium for this game, if it exists, will then give rise to an expression for the market share for all firms $j \in J$,

$$M_j = M_j\left(\mathbf{w}^*, \mathbf{p}^*, \Phi\left(\mathbf{w}^*\right), J\right) \ , \tag{1}$$

which will be in the focus of our attention in the empirical analysis.

We will here consider a simplified version of a setup used by Economides [1993]. In his model, firms play a multi-stage game by choosing whether or not to enter and then choosing location, quality, and price. Here we simply focus on the price game, taking all other variables as given. That is, we consider J firms exogenously located on $W = H \times V$ where H is a circle of unit circumference, and where $V = \{0, v\}$ with $v > 0$. A firm location is then a pair $(h, v) \in W$ which has been determined outside the game. The first component, $h \in H$, represents the *variety* and the second component, $v \in V$, represents product *quality*. We think of H as the horizontal dimension over which individuals have idiosyncratic preferences, and V denotes the vertical dimension over which the individuals have the same preference ranking. In our framework a pharmaceutical product is then identified by these two dimensions, where the variety caters to individual specific needs, and quality is simply the overall medical potency or efficacy of the drug. That is, at given prices, more quality is preferred to less by all individuals, but some individuals may prefer one certain variety over others. The firms maximize profits by choosing a price $p_j \in \mathbb{R}_+, \forall j \in J$ given a vector $\mathbf{w}$ of locations. We assume that all firms have identical marginal costs, normalized to zero. The consumers are distributed on H rectangularly so Φ is simply the Lebesgue measure on the unit interval. The utility function for an individual i, located at x_i, purchasing from supplier j, located at $w_j = (h_j, v_j)$ is given by

$$u_i\left(w_j, p_j, \alpha, t\right) = v_j - t\left|h_j - x_i\right| - \alpha p_j \ , \tag{2}$$

where t is a transport cost and where α is a parameter measuring consumer price sensitivity. The transport cost is, as usual, interpreted as the utility loss an individual incurs by consuming a non-ideal product, and it is the same across all individuals. The parameter α measures the weight the consumer puts on prices in their choice of pharmaceutical. We first consider the case where consumers attach some importance to prices, that is when $\alpha > 0$. For reasons of comparison we also consider the case where $\alpha = 0$, that is when the price has no influence whatsoever on consumer choice. This is intended to reflect the case where pharmaceutical expenditures are completely tax

financed and when prices are set by a regulator. In this setting the consumers only choose an optimal action, whereas the firms take no action. We begin by describing the equilibrium of the price game.

3.2 Equilibrium

In line with Economides we restrict attention to localized competition strategies which leave each firm with positive demand. A firm j then faces demand $D_j(\mathbf{p}, \mathbf{w}, J)$:

$$D_j = \frac{\alpha(p_{j+1} + p_{j-1} - 2p_j) + 2v_j - v_{j+1} - v_{j-1} + t(h_{j+1} - h_{j-1})}{2t}, \quad (3)$$

where z_j is the location of a consumer indifferent between suppliers j and $j+1$. Each firm $j \in J$ then solves the maximization program:

$$\max_{p_j} [\pi_j(\mathbf{w}, \mathbf{p}) = p_j D_j(\mathbf{p}, \mathbf{w}, J)] .$$

This gives rise to the J equilibrium equations

$$\mathbf{A}\mathbf{p}^* = \mathbf{y} + \mathbf{B}\mathbf{v} , \quad (4)$$

where

$$\begin{aligned} \mathbf{A}_j &= (0, .., 0, -1/4, 1, -1/4, 0, .., 0) \\ y_j(\mathbf{h}) &= t(x_{j+1} - x_{j-1})/4\alpha \\ \mathbf{B}_j &= (0, .., 0, -1/4\alpha, 1/2\alpha, -1/4\alpha, 0, .., 0) \end{aligned} \quad (5)$$

are the jth rows of $\mathbf{A}$, $\mathbf{y}$, and $\mathbf{B}$, respectively. As Economides points out, the matrix $\mathbf{A}$ is circulant[7] and may be inverted as long as its column sum is different from zero. The equilibrium price is then given by

$$\mathbf{p}^* = \mathbf{A}^{-1}[\mathbf{y} + \mathbf{B}\mathbf{v}] . \quad (6)$$

If we make the simplifying assumptions that (1): the firms are placed equidistantly on H and (2): that there is only one producer of quality $v > 0$, say j,

[7] A matrix is circulant if each row is equal to the preceding upper row moved one step to the right.

we have that

$$
\begin{aligned}
p_j^* &= \tfrac{t}{2J\alpha} \textstyle\sum_{j \in J} a_{jk}^{-1} + \tfrac{a_{jd}^{-1}}{2\alpha} v \\
p_{j\pm1}^* &= \tfrac{t}{2J\alpha} \textstyle\sum_{k \in J} a_{j+1k}^{-1} - \tfrac{a_{j+1d}^{-1}}{4\alpha} v \\
p_{j\pm n}^* &= \tfrac{t}{2J\alpha} \textstyle\sum_{k \in J} a_{j+nk}^{-1}, \text{ for } n > 1 \ ,
\end{aligned}
\tag{7}
$$

where a_{jk}^{-1} is the kth element in sum of the jth row in $\mathbf{A}^{-1}$, and where a_d^{-1} is the diagonal element in $\mathbf{A}^{-1}$. The assumption of equidistantly located producers provides a clearer link between the idea of horizontal product differentiation and the number of substitutes in the market. This simplification enables us to let the number of firms J serve as a measure of variety competition on the circle H. In the empirical analysis the number of substitutes will serve as a variable for the degree of horizontal differentiation.

Since the matrix $\mathbf{A}$ is circulant, $\mathbf{A}^{-1}$ has the properties that the row sum is the same across rows and that the diagonal elements are the same. Let $\beta = \sum_{k \in J} a_{jk}^{-1}$ for all j and let γ be the main diagonal entry of $\mathbf{A}^{-1}$. The equilibrium prices are then given by:

$$
\begin{aligned}
p_j^* &= \tfrac{1}{2\alpha} \left(t\beta/J + \gamma v \right) \\
p_{j\pm1}^* &= \tfrac{1}{2\alpha} \left(t\beta/J - \gamma v/2 \right) \\
p_{j\pm n}^* &= \tfrac{1}{2\alpha} t\beta/J, \text{ for } n > 1 \ .
\end{aligned}
\tag{8}
$$

From these expressions we see how location affects optimal prices for the different firms. The high quality producer j sets the highest equilibrium price, as expected. Also, prices are decreasing in the number of firms J. Furthermore, the effects of the (localized) competition pushes down the equilibrium price for a low quality producer that is located next to a high quality producer. This is so since the lower quality producers that are placed immediately next to the high quality producer do not have the same variety advantage as competitors farther away on the circle. The scope for variety competition is more limited and therefore firm $j's$ immediate neighbors must price more aggressively than other lower quality suppliers.

The equilibrium market shares are given by:

$$\begin{aligned} M_j &= \tfrac{1}{J} + \tfrac{2v(4-3\gamma(J))}{8t} \\ M_{j\pm1} &= \tfrac{1}{J} + \tfrac{4v(\gamma(J)-1)}{8t} \\ M_{j\pm2} &= \tfrac{1}{J} - \tfrac{v\gamma(J)}{8t} \text{ , for } n > 1 \text{ ,} \\ M_{j\pm n} &= \tfrac{1}{J}, \text{ for } n > 2 \text{ ,} \end{aligned} \tag{9}$$

where we must impose that $v < 8t/J\gamma$, so the quality premium cannot be too large.[8] Since the rows in $\mathbf{A}$ sum to less than unity, γ is decreasing in J (and approaching 1 from above). The condition that γ be less than 6/5 is also met for all J, implying that the high quality producer will enjoy the largest market share of all producers.

Interestingly, the firms with the smallest market shares are not the immediate neighbors of a high quality producer, but instead the neighbors $j+2$ and $j-2$, one slot farther away. The producers closest to the high quality supplier must set a more competitive price than the other lower quality producers. Hence, the neighboring producer closest to him in turn, $j+2$, will yield some market share for this reason. In fact, due to the more intense price competition between firms j and $j+1$, the immediate neighbors of a high quality producer will gain a larger market share than all other firms (except the high quality supplier). Also, we note that a high quality producer loses less market share relative to a lower quality producer when the number of firms increases. This would imply that the high quality producer is less sensitive to competitors than lower quality producers are. If we compare the profits accruing to the different producers we find that

$$\pi_j(\mathbf{p}^*) \geq \pi_{j+n}(\mathbf{p}^*) \geq \pi_{j+1}(\mathbf{p}^*) \geq \pi_{j+2}(\mathbf{p}^*) \text{ ,} \tag{10}$$

indicating that the high quality producer enjoys the highest profit, whereas the least preferred slot is the one next to the immediate neighbor of the high quality producer.[9]

[8] This is to ensure that no firm gets zero demand in the restricted set of equilibria that we consider.

[9] The middle inequality is valid as long as $t \leq \frac{\beta+(\gamma-1)\left(v^2J^2\gamma-2\beta vJ\right)+2vJ}{4\beta}$, which is likely to hold, especially for large J.

3.3 Case where $\alpha = 0$

In the case where consumers are indifferent to prices, the only relevant variable is product location. Here we assume that firms take no action and simply offer their products given their locations in W. The consumers now choose the pharmaceutical that maximizes gross benefit given their location. If we assume rectangular Φ on H as above, the following market shares will result:

$$\begin{aligned} M_j &= \tfrac{1}{J} + \tfrac{v}{t} \\ M_{j\pm1} &= \tfrac{1}{J} - \tfrac{v}{2t} \\ M_{j\pm n} &= \tfrac{1}{J} \ , \text{ for } n > 1 \ . \end{aligned} \tag{11}$$

The distribution of market shares is slightly different than in the former case. As before, the high quality producer j will enjoy the largest market share but this share is larger than when firms set prices optimally. Also, producer $j's$ larger market share comes at the expense of the immediate neighbors', $j+1$ and $j-1$, market shares. All other $J-3$ producers get an equal market share of $1/J$. Clearly, the absence of price as a strategic variable will cause some consumers closer to $j+1$ and $j-1$ to now prefer product j, which they did not prefer when the net benefit was the decision criterion. Since they cannot respond by lowering prices, producers $j+1$ and $j-1$ will lose market shares compared to the above. The firms $j+2$ and $j-2$ are not affected by the competitive pricing of firms $j+1$ and $j-1$, respectively, and therefore now enjoy the same market shares as the other lower quality producers have. Of course, we cannot determine which of the two "regimes" $\alpha > 0$ or $\alpha = 0$, is preferred by the different producers since we had assumed an exogenous regulatory price.

3.4 Remark

In view of the admittedly highly stylized model above, we expect certain features to be present in the subsequent empirical analysis. Firstly, we expect that innovative drugs will command higher prices on the average and gain larger market shares than do the lower quality producers. Also, the idea that most low quality producers will be relatively more sensitive to an increased number of competitors than will the high quality producer, is consistent with the theory.

This outcome is expected to be more pronounced in the case where consumers are fully reimbursed for their pharmaceutical expenditures.

4 Empirical analysis

Data The data consist of quantities sold and price quotes for a set of NCEs introduced in Sweden between 1987 and 1997. Each NCE has been labeled with an indicator B and C representing the therapeutic advantage that the NCE offers over existing substitutes.

Quantities We have defined quantity as the number of daily dosages sold during a given period of time. We use the quantities for daily dosage in accordance to the Defined Daily Doses (DDD) system recommended by the WHO for studies of drug use (ATC Index with DDDs, [1997]). A Defined Daily Dose denotes the average daily dose of a drug used by an adult for the treatment of the main medical indication of the drug. Official DDDs were available for about two-thirds of the drugs in our NCE sample, and we used them in these cases. For the remaining drugs, we based quantities for daily dosages on the recommended average daily dosages in FASS (Pharmaceutical Specialities in Sweden 1988-1998), a reference book widely used by physicians in Sweden. When recommendations regarding dosages were not sufficiently specific or not available in FASS, we consulted pharmacologists for the appropriate quantities. In some cases however, it was not possible to establish an average daily dose since the use of the drug is too varied.

NSIB provided the data on quantities sold (measured as DDD per substance, whenever an official DDD was available) over the period 1996-1999:2. In order to obtain the relevant data for the period 1987-1995, however, we estimated the price per DDD for each NCE and approximated the number of daily dosages sold per quarter with the ratio between the sales revenue and the estimated price per daily dose. The prices of pharmaceuticals sold in Sweden are reported in FASS and the prices for pharmaceuticals sold by the NSIB are the same regardless of purchaser.[10] As a rule, we have chosen to calculate the price for tablets when these were available; if they were not, we chose the administration form of the package containing the largest

[10]We do not face the problems caused by multi-tariffs or price discrimination common in the US that make it difficult to determine the price of a pharmaceutical.

number of daily dosages. NSIB provided us with data on the sales of substances 1987-1999:2 defined as revenues per quarter. It should be noted that of the B and C drugs introduced on the Swedish market between 1987-1997, we were not able to analyze all empirically. In order to include an NCE drug in the analysis we needed data on prices per DDD or sales in DDDs for all substitutes. Since the data on sales and quantities were on the ATC code (Anatomic Therapeutic Classification, see below) level, we had to exclude all markets where at least one substitute drug had generic competition. However, there are three markets where we were able to obtain prices and quantities for generic competitors for some drugs in 1998 and 1999. For this reason there are three drugs with observations only in the second and third year. (This is the reason why the number of observations reported in tables 2 and 3 is larger for the second year than for the first year).

Definition of markets We have defined the therapeutic markets using the World Health Organization (WHO) Anatomic Therapeutic Classification (ATC) system. The ATC system is divided into 14 anatomical groups (e.g. Heart and Circulation). Each anatomical group is divided into main therapeutic groups, and then into therapeutic subgroups that are further divided into chemical/therapeutic subgroups (e.g. HMG-Co A reductase inhibitors). The chemical/therapeutic subgroups are further divided into groups according to chemical substance. An example of a chemical substance is the cholesterol-lowering Simvastatin that belongs to the HMG-CoA reductase inhibitors chemical/therapeutic subgroup.

We define a competitor or substitute to an NCE as a pharmaceutical within the same chemical therapeutic subgroup sharing the main indication. In some cases there are no competitors in the same therapeutic group as the NCE at the time of market entry. In some of these cases, pharmacologists have indicated certain pharmaceuticals outside the chemical therapeutic subgroup which may be considered as substitutes. We define the market share of an NCE as the number of daily doses sold during a given period of time divided by the total number of daily doses sold of the NCE and its competitors combined.

There are several caveats with this definition of a market. First, pharmaceuticals outside the market as we have defined it, may be prescribed to certain patients for the same indication for which the NCE is intended. Therefore, this definition will underestimate the actual market. Second, drugs that

are within the same chemical therapeutic subgroup and that share the same indication may be prescribed to some patients with other indications. This will overestimate the actual market size in our definition. For these reasons, the market shares as we have calculated them are necessarily approximations of the true market shares.

Therapeutic classes No official rating on therapeutic gain for pharmaceuticals is available in Sweden. We have therefore used the rating system constructed by pharmacologists (see Beermann and Rosén [1999]). Beermann and Rosén [1999] classified all NCEs introduced in Sweden between 1987 and 1997 according to the FDA rating system used in the US. This system contains three different classes of therapeutic advantage.

- *Class A:* Important therapeutic gain: Drug may provide effective therapy (by virtue of greatly increased efficacy or safety) for a disease not adequately treated or diagnosed by any marketed drug, or provide markedly improved treatment of a disease through improved efficacy or safety (including decreased abuse potential).
- *Class B*: Modest therapeutic gain: Drug has a modest but real advantage over other available marketed drugs; for example, somewhat greater effectiveness, decreased adverse reactions, more convenient route of administration, etc.
- *Class C*: Little or no therapeutic gain: Essentially duplicates in medical importance and therapy for one or more already existing drugs.

We have excluded class A drugs in our empirical study since they rarely have well-defined substitutes.

Variables The following variables are included in the subsequent analysis.

- M_t is the market share of an NCE obtained at time t where $t \in \{1, 2, 3\}$ indicates the first, second, and the third years after launch.
- B indicates whether the NCE is a class B drug.
- C indicates whether the NCE is a class C drug.

- SUB_t is the number of substitutes at period t. If a substitute has been in the market for less than four of the quarters during the period, its contribution to the number of substitutes is calculated as the number of quarters divided by four.

- $PRATIO$ is the price of the NCE divided by the weighted average price of the number of substitutes at the time of introduction.

Econometric model In our model pharmaceuticals are differentiated by price, the vertical quality dimension indicated by the classification of the drug (B or C), and the presence of a horizontal dimension approximated by the number of therapeutic substitutes in the market.

To see whether the location in product space will influence the relative price of a new drug, we first regress the price ratio on the B indicator variable, the number of substitutes and the number of substitutes multiplied with a dummy for a B classified drug respectively. The latter variable is included in order to detect systematic differences between B and C drugs with respect to how they are affected by the number of substitutes. The regression equation is

$$(1) \qquad \log PRATIO = \alpha_0 + \alpha_1 B + \alpha_2 \log SUB_1 + \alpha_3 B \log SUB_1 + \varepsilon \ .$$

We then regress the variable for the market shares on the number of substitutes and the indicator variable for a B drug. Since prices are determined by the location in product space in our model, we exclude this variable in the second regression. We expect that the price and market shares are determined by the same factors. The price sensitivity of physicians may also be low due to a lack of pecuniary incentives.[11] The second regression equation therefore provides information on how the new pharmaceutical's exogenous location in product space determines market success. We expect a vertically differentiated (B) drug to be more successful in terms of gained market share than a C drug. This difference is influenced by the degree of horizontal differentiation. If the vertical quality is valued more by consumers than the horizontal aspect we should expect B classified drugs to take large market

[11] The price ratio is far from significant at any conventional levels when it is included in the regression.

shares irrespective of the number of substitutes. The pharmaceuticals in class C, on the other hand, would be more sensitive to horizontal differentiation.

To test the degree of product differentiation we regress the market shares for the first four quarters for each $t \in \{1, 2, 3\}$ combined on the number of substitutes and the dummy for B classified drugs.

$$(2) \qquad \log M_t = \beta_0 + \beta_1 B + \beta_2 \log SUB_t + \upsilon_t \ .$$

In order to detect if there are any systematic differences between B drugs and C drugs with respect to how they are affected by the number of substitutes, we also regress the equation above with an added variable for the B dummy multiplied with the number of substitutes.

$$(3) \qquad \log M_t = \delta_0 + \delta_1 B + \delta_2 \log SUB_t + \delta_3 B \log SUB_t + \xi_t \ .$$

5 Results

When we run regression (1) we find that the B indicator variable is positively correlated with the log of the price ratio ($\log PRATIO$), and that the variable for the number of substitutes ($\log SUB$) is negatively correlated with the log of the price ratio. The results are summarized in table 1 below.

Both the B indicator variable and the interaction variable for the number of substitutes are significant at the 10 percent level. The coefficient of the interaction variable for the number of substitutes of B drugs is quite insignificant and indicates that there is no difference between the way the prices of B drugs and C drugs are affected by the number of substitutes. Even though the degree of significance is low, the results are consistent with the hypothesis that product differentiation has an influence on prices. A vertically differentiated product is expected to command a higher price when it enters the market, and we also expect that a larger number of substitutes will affect prices adversely. We cannot tell whether the correlations between differentiation and prices are due to a market pricing strategy by the firms, whether the differentiation has affected the bargaining position of the firms vis-à-vis the regulating authorities, or both. The fact that the price variable is far from significant when it is included in regression (3) may indicate that prices play a minor role in determining the market success of the drug. If this

Table 1: Regression 1: Price ratio and product differentiation.

	logPRATIO[a)]
Constant	0.430** (2.068)
B	0.503* (1.701)
logSUB1	−0.373* (−1.697)
BlogSUB1	−0.009 (0.002)
N	83[b)]
F-test	3.910***
R2	0.129
R2adj	0.096
Breusch-Pagan	6.619*
RESET	0.656

[a)]Results in the regression are corrected for heteroscedasticity. Numbers in parentheses are the t-values of the coefficients. The RESET-test is conducted with the predicted value raised to two, three and four. *Significance at the 10% level, ** significance at the 5% level and *** significance at the 1% level. [b)]There are two fewer observations in the price regression (1) compared to the market shares regression (2). This is because two drugs lacked well-defined relative prices per DDD, but their market shares were zero.

is the case, the price is not likely to be an important variable in the market strategy but rather a result of the bargaining game between the firm and the regulating authorities. A higher quality and a smaller number of substitutes may strengthen the threat of the firm's withholding a drug from the market.

In the second set of equations, where we regress the log of the market share ($\log M$) on the number of substitutes and the B indicator variable for the first three periods, we find that all variables are significant at the 1 percent level or lower. The B indicator variable has the expected sign, and vertically differentiated class B pharmaceuticals seem on average to gain larger market shares than the class C pharmaceuticals. This is further supported by the descriptive statistics presented in table 4.

The first year in the market, the average market share of a B drug is 33 percent compared with 10 percent for a C drug. The corresponding figures

Table 2: Regression 2: Market shares, therapeutical rating, and number of substitutes.

	logM1[a)]	logM2	logM3
Constant	−2.605*** (−8.947)	−1.315*** (−3.743)	−1.587*** (−6.125)
B	1.392*** (3.410)	2.051*** (3.716)	1.10*** (3.087)
logSUB	−1.780*** (−4.113)	−2.017*** (−4.118)	−1.420*** (−3.217)
N	85	88	78
F-test	17.94***	18.30***	10.72***
R2	0.304	0.301	0.222
R2adj	0.287	0.285	0.202
Breusch-Pagan	9.04**	6.14**	24.15***
RESET	2.62	1.36	1.40

[a)]Results in the regressions are corrected for heteroscedasticity. Numbers in parentheses are the t-values of the coefficients. The RESET-test is conducted with the predicted value raised to two, three and four. *Significance at the 10% level, ** significance at the 5% level and *** significance at the 1% level.

for the second and third years are 44 percent and 46 percent for class B pharmaceuticals, and 18 percent and 22 percent for class C pharmaceuticals, respectively. The number of substitutes is slightly smaller for B drugs than for C drugs, 1.6, 1.8, and 1.9 compared with 2.1, 2.3, and 2.3, for the first, second, and third years, respectively. The variable for the number of substitutes is negative, as expected, and lends support to the hypothesis that a larger degree of horizontal differentiation obstructs market penetration. The intercept is larger in the regression equations for the second and third years compared to the first year. The average market shares increase between the first and second years and seem to stabilize in the third year. In the last period both the B indicator variable and the number of substitutes have a smaller impact on the variable for average market share. This is indicated in the smaller coefficients of the B and $\log SUB$ coefficients. Also, the R-square value decreases from 0.30 in the second regression to 0.22 in the third

Table 3: Regression 3: Testing the difference in effect from the number of substitutes on the market share of B drugs and C drugs, respectively.

	logM1[a)]	logM2	logM3
Constant	−2.309***	−1.04**	−1.311***
	(−6.781)	(−2.597)	(−4.316)
B	0.714	1.241*	0.239
	(1.532)	(1.892)	(0.570)
logSUB	−2.262***	−2.408***	−1.802***
	(−4.023)	(−3.984)	(−3.214)
BlogSUB	1.557*	1.508	1.441**
	(1.983)	(1.563)	(2.002)
N	85	88	78
F-test	13.30***	12.91***	8.15***
R2	0.330	0.316	0.248
R2adj	0.305	0.291	0.218
Breusch-Pagan	9.185**	6.854*	29.439***
RESET	1.304	0.982	0.680

[a)]Results in the regressions are corrected for heteroscedasticity. Numbers in parentheses are the t-values of the coefficients. The RESET-test is conducted with the predicted value raised to two, three and four. *Significance at the 10% level, ** significance at the 5% level and *** significance at the 1% level.

regression. A possible explanation for this is that consumer learning about the new drug and the producers' marketing efforts become more important over time relative the initial product space location.

Finally we add the variable with the B dummy multiplied with the number of substitutes in order to determine whether there are any systematic differences in how B and C drugs are affected by the number of substitutes. For all three periods, the coefficient is of nearly the same magnitude as that of the coefficient of the log SUB variable, but with the opposite sign. In the first period the coefficient of the interaction variable is very close to being significant at the 5 percent level. During the second period it falls short of being significant at the 10 percent level, and for the third period it is significant at the 5 percent level. It thus seems that there are differences in the

Table 4: Average market shares and number of substitutes.

	Year 1[a)]	Year 2	Year 3
Market share			
B drugs	0.33 (0.31)	0.44 (0.31)	0.46 (0.34)
C drugs	0.10 (0.16)	0.18 (0.22)	0.22 (0.25)
Number of substitutes			
B drugs	1.6	1.8	1.9
C drugs	2.1	2.3	2.3

[a)] Numbers in parentheses are standard deviations for market shares.

way the market share of a B drug is influenced by the number of substitutes compared with a C drug, and that a class B drug seems to be much less affected.

The data is afflicted with heteroscedasticity. For this reason t-values are estimated based on White's heteroscedasticity consistent covariance matrix whenever the Breusch-Pagan test is significant.

6 Discussion

In the preceding analysis we focus on pharmaceuticals' location in product space as the major determinant of pricing and market success. We assume that each therapeutic market consists of a unit circumference circle where each consumer demands one variety. We interpret the number of substitutes as a measure of competition in the sense that more substitutes improve the match between a consumer and a certain pharmaceutical. This implies that it is more difficult for a new brand to establish itself the larger the number of substitutes. This, however, presupposes that the potential scope for differentiation (or the possibility to locate farther away from the competitors) is the same across markets. This is clearly a simplification. Some markets have a larger potential for differentiation than others, and therefore a larger number of substitutes. The strength of the local monopoly enjoyed by each variety

naturally depends on the number of potential niches. Certain illnesses affect homogeneous groups of patients while others affect more heterogeneous parts of the population. For example, while prostate cancer is a disease afflicting elderly men only, depression may strike a person of any age and of either sex. It might be the case that elderly men react more homogeneously to side effects than the more diverse part of the population that suffers from depression. Therefore, the potential to gain substantial market power may be lower for products intended for the former condition, given the same number of substitutes. If there were a way to control for this heterogeneity, we would get a clearer picture of how the number of substitutes affects the degree of competition.

Another caveat concerns the assumption of exogenous product location. Even though it is difficult for a firm to determine exactly where a product will be located, it is nevertheless true that some markets may be more prone to differentiation than others. If the scope for product differentiation increases the opportunities to make profits within a market, which is likely, this will increase the R&D efforts to locate on these markets. Product differentiation may also be endogenous in another and more subtle way. Although some drugs are very similar with respect to efficacy and side effects, their attributes may be emphasized ex post in the marketing of the drug. Consumers may therefore perceive differences between pharmaceuticals that are founded in factors beyond the physical product. If product differentiation is endogenous in some of these ways, the number of substitutes will not correspond to the actual competition in therapeutic markets. However, given the complexities of the pharmaceutical market we believe that the simplifying assumption of exogenous product differentiation is necessary.

7 Summary and policy implications

The location in product space seems to influence both prices and the market success enjoyed by new innovative pharmaceuticals. Vertically differentiated class B drugs are priced higher and capture a larger market share than C classified drugs, which are only horizontally differentiated. There is some evidence that the number of substitutes existing in the market affects the price of a drug relative to the existing substitutes for both B and C drugs. A plausible explanation is that the bargaining position of the firm vis-à-vis the regulating authorities, and thereby the price level, is influenced by the

perceived innovativeness of the drug. However, the price relative to existing substitutes does not seem to have any important effect on the captured market share. This might lend support to the hypothesis that the prescribing physicians in Sweden are rather insensitive to prices. We find that the degree of horizontal differentiation interpreted in terms of the number of existing substitutes adversely influences the market share captured by a new pharmaceutical. However, this effect seems to be more pronounced for C drugs than for B drugs.

Our results indicate that the more innovative B classified drugs are better rewarded than the less innovative C drugs. Further, there is no evidence that horizontally differentiated C drugs have any important effect on the market shares that the more innovative B drugs capture.

The empirical findings in this paper basically conform with the predictions of our model of product differentiation, suggesting that this approach might be valuable for further research in this area.

Two cases of our model with product differentiation were discussed: One with price sensitive consumers and price as a strategic variable, and one without price sensitive consumers. In the latter case the more innovative drugs tended to capture larger market shares. This observation should be taken into consideration by regulators who set prices administratively. In a market with price-insensitive consumers, innovative drugs can have lower prices but still be as profitable as if they were priced freely in a market with price-sensitive consumers. Less innovative drugs lose out the most in markets with regulated prices and price insensitive consumers.

Expenditures may also be affected by the price sensitivity of consumers. Since more innovative drugs take larger market shares in the absence of price sensitivity and usually receive higher prices than less innovative drugs, expenditures in price-insensitive markets may be more strongly affected by new innovations.

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Chapter 4

Essay III: Generic entry before and after reference prices

Generic entry before and after the introduction of reference prices

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Abstract

This paper studies the effect of the reference pricing system on generic entry in markets where brand name pharmaceuticals lose patent protection. I find the likelihood of generic entry after patent expiration to decrease, after the introduction of the reference pricing system. According to my estimates savings due to increased competition in markets affected by the reference pricing system may have been outbalanced by higher prices, due to less competition in markets where the reference pricing system led to deterred entry.

1 Introduction

A number of countries have introduced reference pricing systems in order to increase price competition in the pharmaceutical market. Under reference pricing, the reimbursement level is based on the cost of the cheapest drug in a class of medically equivalent drugs. If the patient wants to buy a more expensive drug in this class he must pay the price differential out of his own pocket. The reference pricing system has mostly been applied to brand name drugs and their generic substitutes. A number of case studies of markets where the reference pricing system has been applied find that the average price level on these markets decreases (Jönsson [1994] and Danzon[1996]). On the basis of these results, many have drawn the conclusion that reference pricing systems are effective against increasing pharmaceutical expenditures.

This paper analyzes the effect of the reference pricing system on generic entry, after patent expiration of brand name drugs. The hypothesis is that the reference pricing system reduces prices after generic entry, to such an

extent that generic entrants are unable to recoup their sunk costs in some markets. Hence, generic entry is deterred and certain brand name drugs are protected from generic competition when their patents expire, which leads to higher prices on these markets than would have otherwise been the case. The reference pricing system may thus be less effective in decreasing overall drug expenditures than is commonly believed.

Whether the reference pricing system actually decreased generic entry is tested through a comparison of the number of generic entrants in 1998 for drugs which experienced patent expiration between the years 1992-1997, and generic entry in 1992 for a second group of drugs that experienced patent expiration between 1986-1991. Since the reference pricing system was proposed in 1992, the comparison makes way for a natural experiment.

The results from the empirical analysis indicate that generic entry was nearly reduced by half after the introduction of the reference pricing system. This supports the hypothesis that the reference pricing system decreased the profitability of generic entry to such a degree that entry was deterred in some markets. Based on the result that generic entry was nearly reduced by half after 1992, the forgone savings due to deterred entry are estimated. According to these estimates, the savings that the reference pricing system caused in markets with generic entry after 1992 were outbalanced by forgone savings due to deterred entry in other markets. The long-run effect in terms of reduced pharmaceutical expenditures may therefore be non-existent. This result has interesting implications for competition policy, as it demonstrates that policies increasing competition between firms in some markets may imply that fewer firms will take up competition with incumbents in these markets. To have a lasting effect on competition, policies must also focus on reducing the sunk costs associated with entry.

The remainder of this paper is structured as follows. First, a background is given which summarizes some of the main results on competition between generic and brand name drugs. This is followed by a description of the Swedish pharmaceutical market. Then, the possible effects of the reference pricing system on competition and entry are discussed in the framework of the theoretical literature on potential and actual competition. After this, the data and the empirical test are described and the impact of the reference pricing system on pharmaceutical expenditures is estimated. Finally some conclusions are drawn.

2 Background

Markets where brand name drugs are challenged by generic competitors have been studied by a number of economists since the 1970s. One important reason for such an interest in a specific set of markets is the supposedly anomalous behavior exhibited by patients and doctors. Even though most experts would agree that generic drugs are medically equivalent to brand name drugs, brand name drugs tend to keep large market shares despite markedly higher prices. Schwartzman [1976], reported that antibiotics was the only market where generic competition had a significant impact; similar findings were also reported by Bond and Lean [1977] and Statman [1981]. In a later study, Hurwitz and Caves [1988] noted that the market shares captured by generics were not significantly affected by the price differential to the original drug. Instead, the price differential seemed to increase slowly over time as the number of competitors increased, a phenomenon later analyzed by Frank and Salkever [1992]. They found that it was rational for the pioneering firm to raise its price at the introduction of generic competition, if the market was segmented and less price sensitive consumers were loyal to the brand name drug. A slightly different explanation to the phenomenon of higher prices in response to entry was put forward by Perloff et al [1996]. They analyzed a model of product differentiation where brand name drugs are perceived to be spatially differentiated from each other. When a new drug enter the market, the firm with the brand name drug gives up a part of the market to the entrant and raise the price for consumers with strong preferences for its product.

The observation that cheaper generics often fail to reduce the prices of brand name drugs has been taken as evidence that the pharmaceutical market does not function in a proper, competitive way. This has urged some economists to study the generics market in greater detail, in order to track down the mechanisms that keep the prices of brand name drugs up, and if possible, to find policy measures that can increase the competitiveness of these markets.

Most studies conducted on markets where brand name drugs experience patent expiration are old. The incentives for generic competition and selection of cheaper alternatives have increased in the 1990s, due to cost containment efforts and attempts at improving the cost-effectiveness in the health services. Therefore, studies seeking to explain prices and market shares for generics in terms of the reimbursement system and the incentives to make

cost-effective choices among patients and physicians are of special interest. Hellerstein [1998] studied the prescription behavior of physicians, in the US and how it was affected by differences in reimbursement system. She found some physicians to be more likely to prescribe generic drugs than others. Surprisingly, she found no evidence that these differences were caused by the reimbursement system. Mortimer [1997] examined how the demand for prescription drugs was influenced by different kinds of insurance. The self-paid sector was least price elastic, while the managed care sector was found to be most price elastic.

On the Swedish market, prices are regulated and patients are insured by the state for pharmaceutical expenses and they are only required to pay a part of this cost. However, the part paid by patients has increased during the 1990s and the reference pricing system has been introduced. A few studies have focused on prices and price competition in the Swedish pharmaceutical market, encompassing both the years before and after the introduction of the reference pricing system.

Aronsson et al [1998] used data from 1972 to 1996 for 13 substances, where the originator was subject to generic competition, and they found the price of the originator to be affected by generic competition. The higher the price of the original product relative to the average price of the generic substitutes, the larger the decrease in the market share of the original product. Another finding was that the impact of generic competition varied between different markets, but the model did not explain these differences. They also found evidence that the introduction of the reference pricing system influenced the prescription behavior of physicians, their price sensitivity doubled.

Lundin [1999] conducted a detailed study of physicians' prescriptions in the Swedish municipality Tierp. The data set contained all prescriptions for seven substances dispensed from two pharmacies. Lundin could identify the prescribing physicians, the patients and the date of prescription. He estimated a model where it was assumed that the physician considered the effects on the patient's health as well as the financial consequences of the prescription decision. For this reason, the price differential between an originator and a generic drug to be paid by the patient and the insurance respectively was considered. The model also allowed for brand loyalty, where this effect was decomposed into a drug specific, a patient specific and a physician specific effect. A dummy was included in order to capture the effect of the reference pricing system.

Lundin found support for the hypothesis that preferences and habits

played an important role in the drug choice. Furthermore, physicians seemed to be more prone to break their habits and prescribe generics when the patient had to pay a larger part of the cost out of his own pocket. Another result was that the reference pricing system increased the likelihood of prescribing a generic drug, notwithstanding the coinsurance rate.

Bergman and Rudholm [2001] studied the effects on prices in the Swedish market when brand name drugs lose patent protection. In particular, they analyzed whether brand name drugs used limit pricing in response to the introduction of potential competition. According to their estimates, prices fell by 2-3 percent in response to patent expiration, thereby supporting their hypothesis, and another 5 percent for each new competitor. They also showed that the reference pricing system had a strong negative effect on the prices of brand name drugs.

Scott Morton [1999] examined the entry choices of generic pharmaceutical firms. She found that these firms were more likely to enter markets similar to other markets from which they had experience. They were also more likely to enter large markets, markets for drugs against chronic conditions and drugs with large hospital sales.

3 The Swedish pharmaceutical market

Prices of pharmaceuticals are regulated in Sweden. Until 1993, pharmaceutical prices were determined in negotiations between manufacturers and the National Corporation of Swedish Pharmacies (NCSP). The NCSP is a state-owned company with a monopoly on the retail of all drugs in Sweden. When the NCSP handled the price negotiations, firms were not allowed to sell their products until the prices had been agreed upon. If the NCSP and a firm were unable to reach an agreement, the firm could apply to engage the Medical Products Agency as an arbitrageur to determine a price, as a regulator of last resort (the Medical Products Agency is responsible for the approval of all drugs in Sweden). In 1993, the National Social Insurance Board (NSIB) took over the role of the NCSP. The regulation also changed slightly and since 1993, a firm must negotiate a price with the NSIB only if it wants consumers of its drug to be reimbursed by the drug benefit scheme. If a firm does not want reimbursement, the price can be set freely. Prices are set annually, but firms may initiate re-negotiations in cases with large discrepancies between the anticipated and the actual performance of their products.

The instructions for the price negotiations are stated in the NSIB statute book. These guidelines are somewhat vague, but optimally, when setting the price of a product, the NSIB should consider a number of factors: expected sales, therapeutic advantage of existing drugs (or other alternative treatments), prices in comparable countries, health economic benefits such as quality-adjusted life-years (QALYs), estimated savings in social security expenditures, the reduction of other forms of health care (e.g. hospital care, care at home), and estimated number of reduced sick days. The price negotiation is initiated by a firm submitting a bid, often accompanied by a cost report and the estimated sales, and in some (but far from all) cases, a health economic evaluation of the product's merits. The NSIB evaluates the data and makes a counter offer based on the information from the firm. The firm is required to provide all pertinent information about the drug on which the NSIB can base its counter offer/decision. That is, the NSIB has no means of conducting any investigations of its own, but must rely on the firm report or outside sources.

The regulatory mechanism employed in Sweden can be interpreted as a form of price cap regulation, where the goal is to have approximately constant real prices over time. An exception is prices for generic drugs. In 1992, the government proposed the reference pricing system which was introduced on January 1, 1993. Brand name drugs and their generic counterparts are included in the system if they are considered therapeutically equivalent and have the same administration form. If the patient buys a drug that is more than 10% more expensive than the cheapest substitute in the category, he must pay the difference out of his own pocket.

4 Theory

In their paper "Potential competition, actual competition and economic welfare" [1988] Dasgupta and Stiglitz criticized the view, that potential competition in many cases suffices to establish efficiency, even in the presence of large non-convexities; a view which had been purported by some Chicago economists such as Grossman [1981] and Baumol, Panzar and Willig [1982].

Dasgupta and Stiglitz show, with a number of examples, that even with small sunk costs associated with entry, potential competition may not be effective in ensuring efficiency or zero profits. The simplest example to illustrate their argument is a market with Bertrand competition and a small

sunk cost to enter. Since there are no mark-ups in this market, there is no possibility to recover sunk costs and hence, no entry will take place. In the case of a market with product differentiation, there is a mark-up but the sunk cost of entry may still be prohibitive. A general principle emerging after the exploration of a large variety of models is that the more competitive a market is after entry, the less effective is potential competition as a disciplinary device. More precisely, they conclude that the larger the elasticity of substitution between two goods in a market, the smaller need the sunk cost to be to deter entry.

The discussion of potential competition is highly relevant for the pharmaceutical market. Patents for drugs are valid for a limited period of time in order to limit the profits accruing to the pharmaceutical industry and to transfer the surpluses to consumers. However, even though the expiration of patents make it possible for other firms to produce generics of the brand name drug, prices has not always decreased as much as expected due to a real or imagined difference in quality and product line. This has stimulated policymakers to implement policies to increase price competition or to regulate the prices of brand name drugs. One example is the reference pricing system which increases the elasticity of substitution between brand name drugs and their generic competitors, by letting the consumer pay the whole price differential out of his own pocket, if this differential is larger than 10 %. If we are concerned with Dasguptas' and Stiglitz' observation that the more competitive a market is, the lower the sunk cost of entry must be for entry to occur, we may have to reconsider these measures. Policies that are only concerned with the competitiveness of markets ex-post entry and not with sunk costs, may end up deterring entry and protecting the monopoly position of the incumbent. A similar argument can be applied to markets that have been disciplined by price regulations that set a ceiling on the prices of brand name drugs. If brand name drugs are perceived as better than their generic counterparts by a sufficiently large segment of the market, a regulation that reduces the price of the incumbent brand name drug may force the producer of the generic to lower its price even further to capture market shares. In some cases, this level may be too low to finance necessary sunk costs of entry and the average price level of the substance will be higher with than without price regulation.

4.1 Market size and the occurrence of entry

The cost saving effects of the reference pricing system does not only depend on whether it deters entry but also in which markets entry is deterred. If entry is deterred mainly in small markets, reference prices will, to a large extent, reduce pharmaceutical expenditures. However, if entry is mainly deterred in markets above the average size where entry occurs without reference pricing, the net negative effect on pharmaceutical expenditures may be much smaller or even positive. In theory, generic entry can thus be affected by market size in various ways.

Marketing and distribution networks Usually, the incumbent firm has invested a great deal of money in its brand name product through marketing.(The pharmaceutical industry spends more on marketing than on R&D (The Economist [1998]). This investment may affect the costs of entry in a significant way. The higher the degree of brand loyalty in the market, the more spending on marketing might be needed for a generic drug to be considered by prescribing physicians. Besides the cost of marketing a new generic drug, there are costs associated with setting up production and a distribution network. These kinds of costs are usually increasing with the size of the market. However, it is not clear a-propri whether they increase faster, at the same rate or slower than the size of the market.

Entry deterrence Another reason why costs of entry may vary with market size is suggested by Ellison and Ellison [2000]. They argue that incumbents will take actions to deter entry in intermediate, but not in very small markets or very large. In very small markets entrants will not be able to recoup sunk costs and entry deterrence is unnecessary. In very large markets a small market share suffices for the entrant to recoup its sunk costs and entry deterrence will be too difficult. Ellison and Ellison find some support in their data that incumbents do indeed take considerable entry deterrent actions in intermediate sized markets.

The degree of price competition and the size of the market There may also be reasons for price competition to be stiffer in larger markets

due to the behavior of physicians and policies to make physicians more cost conscious. For example, physicians may be more aware of prices for drugs in categories where they prescribe large volumes. Furthermore, more information is usually available for large categories of drugs. In every county council, there are pharmaceutical committees that recommend drugs for physicians to prescribe. These committees usually draw up lists of drugs which mainly focus on the drugs that sell most. If marketing is more prevalent in large markets, this might make physicians more aware of prices. Large markets may thus be less profitable per unit sold than smaller markets.

5 Data

The data set contains information about patent expiration dates, sales volumes and the existence of generic competitors. Patent expiration dates have been supplied by LIF (Swedish Association of the Pharmaceutical Industry). Sales volumes per substance have been collected from the National Corporation of Swedish Pharmacies (NCSP) and the number of generic competitors in the relevant years have been obtained from FASS (Pharmaceutical Specialities in Sweden) ([1992] and [1998]).

6 Empirics

To test the hypothesis that the reference pricing system has affected the occurrence of entry when brand name drugs lose their patent protection, two samples of drugs that have lost patent protection are compared. The first sample contains drugs that lost patent protection between 1986 and 1991. The second sample contains drugs that lost their protection between 1992 and 1997. Firms are assumed to have acted on the information available in 1992, i.e. that the government would introduce the reference pricing system. The observations in the first sample are assigned with an indicator variable 0 and those in the second sample with an indicator variable 1. The market size is associated with the possibilities for profits and is therefore expected to be associated with the likelihood of entry. For every observation, there is a variable for the log of sales in 1998 Swedish crowns (SEK) in the year of the count of the number of generic entries. The log variable is tested, since the impact of extra sales on entry may be expected to increase less, the larger is

the market. There are also dummy variables for the number of years after patent expiration that the count of generic entries took place. An interaction variable between the sales in crowns is included to see whether the reference pricing system has different effects on markets of different sizes.

There is a binary variable for the occurrence of generic entry that takes the values, zero or one. Generic entry is counted for the first sample of drugs in 1992 and for the second sample in 1998.

Variables,

RP : A dummy variable taking the value of 1 when there is a reference pricing system and 0 otherwise.

$LogMarket$: The log of the sales of the brand name drug and its generic competitors at the year of the count of the number of generic competitors.

$RP * LogMarket$: An interaction variable. The RP dummy times the $LogMarket$ variable.

$DYears2$, $DYears3$... : Dummies for the number of years after patent expiration.

6.1 Empirical strategy

A logit model is estimated to test the effects of the reference pricing system. This binary model is employed to test whether there is an effect from the reference pricing system on the probability of generic entry.

As a baseline, the generic entry is modeled as a function of market size, the number of years after patent expiration and the existence of a reference pricing system. Then, I include the interaction between the reference pricing system and market size.

6.2 Results

In the six-year period before the introduction of the reference pricing system, 53 substances lost patent protection. The average and median market sizes for these drugs were 29 million and 7.8 million crowns, respectively. Of these 53 substances, 17 experienced generic entry and the average number of

Table 1: Descriptives

	Before RP	After RP
Number of markets	53	48
Average market size	$29 Million SEK$	$40 Million SEK$
Markets with entry	17	8
Average number of entrants	1.9	2.4
Average size of markets with entry	$63 Million SEK$	$48 Million SEK$

entrants in these markets was 1.9. The average size of a market where entry had occurred was 63 million SEK in 1992.

In the six-year period after the introduction of the reference pricing system, 48 substances lost patent protection. The average and median market sizes for these drugs were 40 million and 8.5 million SEK, respectively. 8 substances experienced generic entry and the average number of entrants was 2.4. The average size of a market where entry had occurred was 48 million SEK in 1998. The smaller average size of the market is probably a result of the increased price competition due to the reference pricing system. As a comparison, the average market size the year before patent expiration for these drugs was 72 million SEK or 67 % of this market.

The average size of a market that did not experience entry after patent expiration increased from 12.8 million SEK in 1992 to 40 million SEK in 1998. The value of the market for drugs that lost patent protection between 1992 to 1997 was 1900 million SEK in 1998 and the segment that had experienced generic entry was worth 382 million SEK, or 20 % of this market. The drugs that lost patent protection between 1986 and 1991 were worth 1473 million SEK in 1992. The segment that experienced generic entry in 1992 was worth 1012 Million SEK.

In the baseline model, the RP variable is negative and significant at the 5%-level. The $LogMarket$ variable is positive and significant at the 1%-level. The dummy variables for years fail to be significant at any conventional levels. When the interaction variable $RP*LogMarket$ is included in the analysis, the coefficients and significance levels largely change magnitudes and degrees of significance. The interaction variable is significant at the 10%-level, thereby indicating that the reference pricing system might have a larger negative impact on entry in large markets. However, the correlation between the RP variable and the interaction variable indicates the presence of collinearity.

Table 2: Logit analysis

	Model 1	Model 2
Constant	−7.77***	−12.4***
	(0.0021)	(0.0037)
RP	−1.20**	8.34
	(0.031)	(0.12)
RP*LogMarket		−0.58*
		(0.076)
LogMarket	0.46***	0.75***
	(0.0017)	(0.0033)
D2YEAR	−1.23	−1.51
	(0.20)	(0.14)
D3YEAR	−0.62	−0.72
	(0.49)	(0.44)
D4YEAR	0.71	0.53
	(0.44)	(0.58)
D5YEAR	0.069	−0.038
	(0.94)	(0.97)
D6YEAR	−0.30	−0.51
	(0.77)	(0.63)
Log-likelihood	−45.7	−44
N	101	101

Notes: Values in parenthesis are p-values. *Significant at the 10% level, ** significant at the 5% level and *** significant at the 1% level.

6.2.1 Discussion of results

There is some evidence that the introduction of the reference pricing system decreased entry after patent expiration. The number of brand name drugs that experienced generic entry after patent expiration was reduced by half compared to the six years preceeding the reference pricing system. There is also evidence that the size of the market has a large positive impact on the likelihood of entry. This is reasonable since a larger market makes it less difficult to recoup the sunk costs of entry. An interaction between market size and the reference pricing system was also included to see whether the reference pricing system affected markets of different sizes differently. However, the results regarding such an interaction are difficult to interpret. There seems to be a large degree of collinearity between the variable for the reference pricing system and the interaction variable. The sign of the interaction variable gives some very weak support to the hypothesis that the reference pricing system might have been more effective in deterring entry in large markets. The small number of cases with generic entry after the introduction of the reference pricing system is a further reason for caution in the interpretation of the interaction variable.

7 Estimation of the forgone savings due to deterred entry

In this section, I estimate the forgone savings due to the entry that might have been deterred when the reference pricing system was introduced and compare that figure with the savings that the reference pricing system did entail. Supported by the results in the previous section, the estimate will be based on the assumption that generic entry after patent expiration was reduced by half, after the introduction of the reference pricing system.

The introduction of the reference pricing system had three major effects on expenditures. The first is the influence on the average price level in the markets where reference prices have been applied. The second is the potentially deterrent effect on generic entry into markets where patents have expired. The third is the effect on market shares and prices of drugs that are substitutes to the drugs for which the patents expired. The last effect is the most difficult to estimate, since it requires information on cross-price elasticities. For this reason, I will make my estimate under the assumption that the quantities consumed of the substances for which the patents have expired, are unaffected by prices. I also assume that there are no effects on prices or quantities consumed of drugs of other substances that may be used for the same indications. The first two effects are estimated below:

1. The effect on prices of brand name drugs and generic drugs from the introduction of the reference pricing system was analyzed by Marcusson and Weiner [1994]. They estimated the savings due to lower prices for drugs that were included in the reference pricing from the start to be SEK 305 million, which equals 25 % of the sales of these drugs in 1992, that is, before the reference pricing system was implemented. (Note that the drugs that were included in the reference pricing system in 1993 were already subject to generic competition. This means that the reference pricing system had an additional price decreasing effect to that which was caused by already existing generic competition).

The sales of drugs that lost their patent protection in 1992 to 1997 amounted to total sales of SEK 580 million, based on the year preceeding the patent expiration. Without the reference pricing system, it is assumed that these sales would have decreased in volume to SEK 410 million.(See paragraph 2 below). The reference pricing system is assumed to have added another 25 % in savings to these sales. That is, the savings from the reference

pricing system are SEK 100 million for the drugs that lost patent protection between 1992 and 1997.

2. To estimate the forgone savings in markets with deterred entry, a hypothetical decrease in average prices for substances with generic competition before the introduction of the reference pricing system is required. This hypothetical decrease is obtained by using two calculations on the markets for generic drugs in 1990. Using Gunnarson's estimate of the effect of generic competition on brand name drug prices (Gunnarsson [1991]) and the share of generic drugs of total sales in 1990 (Nilsson et. al [1998]), it seems as if brand name drugs responded to generic competition by reducing prices by 5 %.(Indirect savings). Furthermore, according to estimates by Nilsson et. al [1998], the direct savings from the use of cheaper generics were reduced average prices for these substances by another 16 %. Combining both indirect and direct effects, generic entry seems to have reduced the average prices for substances that lost patent protection by about 20 %. Under the assumption that generic entry would have taken place in additional markets with a sales volume of SEK 580 million and that generic entry without the reference pricing system would reduce prices by 20 %, the forgone savings due to deterred entry are estimated at about SEK 120 million.

It seems as if the savings from the reference pricing system in markets with generic entry after patent expiration are outbalanced by losses of savings in markets where entry was deterred. Thus, the only effect of the reference pricing system on aggregate expenditures seems to have been a one shot saving on the drugs that were included in the system during its implementation. Furthermore, the cost saving effect of the reference pricing system may decrease over time, as the market shares for the drugs initially included in the system decrease, due to the introduction of new and more advanced drugs.

This is a rough estimation and there are some caveats. First, the reference pricing system is assumed to have had the same effect on markets with drugs that lost patent protection after 1992 as on markets included in the system from the start. However, it is possible that drugs that entered after 1992, when the reference pricing system was implemented, had a different pricing strategy compared to the drugs entering before 1992. Second, incumbents may have changed their pricing strategy in response to expected entry. Third, changes in reimbursement levels during the period studied may have changed the way generic competition affects markets not included in the reference

pricing system.

8 Concluding remarks

According to early estimates, the initial effects of the introduction of the reference pricing system in Sweden were decreased pharmaceutical expenditures of about SEK 305 million, due to lower prices. As old drugs are replaced by newer and more advanced ones the importance of the initial effect of the reference pricing system will decrease. Therefore, the consequences for drugs that lost/will lose patent protection after the introduction of the reference pricing system will gain in importance for the long-run effect on pharmaceutical expenditures.

This paper finds empirical support for the hypothesis that generic entry decreased after the introduction of the reference pricing system. Only half as many brand name drugs experienced generic entry after the reference pricing system compared to the rate of entry before its introduction. A comparison between an estimate of the savings in markets that experienced generic entry after the introduction of the reference pricing system with an estimate of the hypothetical savings that might have taken place without the reference pricing system due to a higher degree of generic entry, indicates the net effect on expenditures to be about zero. That is, the reduced prices due to the reference pricing system when generic entry takes place are approximately outbalanced by foregone savings in markets where entry is deterred.

An explanation of the observed decrease in entry is that the reference pricing system has sharpened competition ex-post entry in markets for generic drugs to such a degree that it has become difficult to recoup sunk costs of entry in some markets. This has interesting implications for competition policy as it demonstrates that measures increasing competition ex-post entry without simultaneously decreasing the sunk costs of entry may be ineffective.

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Chapter 5

Essay IV: Innovative Drugs and the Increase in Pharmaceutical Expenditures

Innovative Drugs and the Increase in Pharmaceutical Expenditures

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Abstract

This paper investigates how the growth in pharmaceutical expenditures is determined. A theoretical model of the growth in pharmaceutical expenditures is analyzed and the impact of new innovative drugs on the growth of Swedish pharmaceutical expenditures is studied empirically. The result from the theoretical model is that the potential driving forces of the steady state growth in expenditures are inflation in introductory drug prices, the inflow of new innovative drugs and the increase in the underlying demand. The result from the empirical study is that introductory drug prices have been stable during this period but that new innovative drugs have opened up new markets and increased the drug consumption. An important conclusion is that the change in the drug price index is of little importance for the growth in pharmaceutical expenditures in steady state. At present, it might be necessary to reduce the access to new innovative drugs if the steady state growth rate is to be reduced.

1 Introduction

Expenditures on pharmaceuticals have been increasing in most OECD countries during the 1990*s*. Between 1990 and 1996, expenditures on pharmaceuticals expressed as a percentage of GDP increased, on average, by 67 % (Andersson and Poullier [1999]). This should be compared with the 1980*s*, when expenditures on pharmaceuticals were almost constant for this group of countries. (OECD Health Data [1998]). The increase in expenditures has motivated policy makers in a number of countries to take measures in order

to limit the pharmaceutical bill. Meanwhile, the industry and some economists have signalled the risk for negative consequences for R&D incentives, if such measures are driven too far (Scherer [1993]).

The purpose of this paper is to isolate the factors determining the rate at which pharmaceutical expenditures grow and empirically investigate which factors have been driving expenditures in Sweden since the late 1980*s*. A simple model is provided where the growth of pharmaceutical expenditures is analyzed with variables such as the introduction of new drugs, the price structure, underlying demand and the rate of substitution between new and old drugs. It is shown that an inflation in the introductory prices of new drugs, a continual increase in the underlying demand and an increase in the supply of new innovative drugs are the only factors that can increase pharmaceutical expenditures in steady state. Other changes, such as an increased inflation in the prices of existing drugs and an increased rate of substitution will only have a level effect in the transition from one steady state to another. The empirical study of the pharmaceutical expenditures in Sweden covers the period 1987 to 1998. The *NCEs* introduced in this period have been rated according to their innovativeness. The extent to which new drugs of different degrees of innovativeness replace old drugs and expand markets is studied and the average introductory prices for these new drugs, weighted by their sales volumes, are calculated. The results suggest that the sales of innovative *NCEs* introduced during this period has quite a small effect on the sales of already existing drugs. Instead, the more innovative drugs seem to have captured new patient groups and complemented, rather than substituted, old treatments. An increase in the demand for old drugs also seems to have affected costs. There is no evidence of an increase in the inflation of introductory prices. Thus, it seems as if the increase in pharmaceutical expenditures in this period is primarily caused by the introduction of new innovative drugs. The results suggest that the strong focus on pharmaceutical prices in the debate on the growth in pharmaceutical expenditures is misdirected. They also shed some light on the fact that pharmaceutical expenditures seem to grow irrespecive of whether the drug price index is increasing or decreasing.

The paper is structured as follows. First, I discuss the different factors that can influence the level of and the change in pharmaceutical expenditures. I then present some earlier studies on pharmaceutical expenditures, followed by a theoretical discussion where I analyze different factors influencing pharmaceutical expenditures through a simple model of the change

in pharmaceutical expenditures. Finally, the empirical findings of this paper are presented and some concluding remarks are made.

2 Which are the determinants of pharmaceutical expenditures?

Expenditures on pharmaceuticals are determined by the structure of the pharmaceutical market. Supply and demand interact through a filter of regulations to determine prices and quantities consumed. A number of important factors influencing both the demand and the supply side should be taken into consideration. I first list the direct causes and then discuss possible underlying causes.

Direct causes The change in drug expenditures between two periods can be described as follows:

$$E_{t+1} - E_t = P^1_{t+1}X^1_{t+1} - P^1_t X^1_t + P^2_{t+1}X^2_{t+1} - P^2_t X^2_t + P^3_{t+1}X^3_{t+1}$$

The factors that increase expenditures can be read directly out of this formula. Ceteris paribus, there is the price effect, the quantity effect and the substitution effect.

Price effect:

1. Prices P^1 and P^2 of the existing stock of pharmaceuticals, $X^1$and X^2, are increasing.

Quantities:

2. The quantities of the existing drugs X^1 and X^2 are increasing.
3. The new drug X^3 attracts new patients.

Substitution:

4. There is a substitution from the cheap old drug X^1 to the more expensive old drug X^2.
5. The new drug X^3 takes market shares from the less expensive drugs, X^1 and X^2.

Underlying causes

Price effect:

- If competition in the pharmaceutical market is hampered by industry concentration or other factors, pharmaceutical companies may increase their prices. Given that consumers do not choose to greatly reduce their consumption in response to higher prices, this may lead to increased aggregate expenditures.

- Patent lengths play an important role in price formation. When the patent of a drug expires, there is room for generic entry. Typically, generic entrants are priced below brand name drugs. There is evidence that, in many cases, the price of brand name drugs increases in response to generic entry. The effect of generic entry is, however, that the average price for the substance decreases (Frank and Salkever [1997], Caves et. al [1991]). In Europe, where many countries apply reference pricing to drugs with generic substitutes, prices have been significantly reduced for this class of drugs (WHO [1996]). As the number of drugs off patent increases over time, a downward pressure on drug prices and expenditures might be expected. This argument hinges on the assumption that the market share of off-patent drugs increases over time. If the stock of drugs consumed is continually upgraded due to the introduction of new drugs, there will be no such effect.

- Increased costs in the production of pharmaceuticals and costly R&D may also lead to higher prices and increased expenditures. If prices are regulated, a price increase may be due to a strengthened bargaining position for the pharmaceutical industry; companies might refuse to introduce new drugs in countries where price regulation is perceived to be too stiff.

Quantities:

- There has been a change in the health care system from in-hospital care to open care. Since open care uses more pharmaceuticals than in-hospital care, this might be an important reason for the increase in quantities. However, this change itself is likely to be a result of technological change. As more effective pharmaceutical treatments become

available, patients can be treated with drugs instead of in-hospital care, for example the new and more effective medicines for controlling heart disease. Preventing heart attacks reduces the number of people in need of in-hospital care. (Lichtenberg [1996]). The fact that the change in Swedish pharmaceutical expenditures follows a pattern similar to those in other countries also suggests that the explanation goes beyond organizational change.

- There is a strong correlation between the income level in a country and the share of GDP that is spent on health care (Anell, Jönsson and Persson [1998]). If incomes rise, we should expect more spending on pharmaceuticals.

- The degree to which the government reimburses patients for their pharmaceutical expenditures affects aggregate drug expenditures. A larger degree of co-payment discourages the consumption of pharmaceuticals (Soumari et. al [1987]).

- Old people utilize pharmaceuticals to a larger extent than young people. As a larger fraction of the population joins the elderly cohorts, it is reasonable to expect a growth in the demand for pharmaceuticals. However, this has a rather slow impact on expenditures, and there is no dramatic change in the age-structure of the population. According to Carlsson [1999], the increase in real pharmaceutical expenditures due to the aging population in Sweden is only 0.6 % per year.

- If the access to health care increases, the number of physician consultations are likely to increase. This may lead to an increase in the notification of diseases and hence, a larger number of prescriptions dispensed. New technology may also increase the likelihood of notification.

- During the product life of a drug, the pharmaceutical industry seeks new fields of application in order to enhance the potential market of its drug. This means that old drugs attract new patients over time.

- When drugs become available over the counter, demand might increase due to higher availability.

- As the pharmacological experience of drugs become more sophisticated over time, the perceived safety of a larger number of drugs increases which may also increase the demand for these drugs.

- In some cases, new innovative drugs makes it possible to treat conditions which could not previously be treated. This opens up new markets and increases the total number of drugs consumed. Improved drugs with less/lower side-effects and a higher degree of efficacy may also attract new patients who found existing treatments too risky.

Substitution:

- Some drugs have long product cycles and the sales of drugs increase slowly over a number of years. This may be particularly true for drugs intended for chronic conditions. Patients have good reasons to be brand loyal. The efficacy and side effects of drugs are different for different people. If a patient is risk averse and has found a drug which works well, he should not shift to a new drug even though the expected effects of the new drug are higher ranked than those of the old drug. For this reason, new drugs will be mostly consumed by newly diagnosed patients. For conditions with a long duration, it may take several years before a new drug has reached the peak of its sales. If drugs have a profile of constant prices over time and new and more expensive drugs capture markets from older drugs, there will be a substitution of drugs in the existing assortment that may keep up a growth in drug expenditures long after the introduction of a new drug.

- The willingness to pay is higher for improved drugs compared to existing substitutes. For this reason, new innovative drugs tend to be priced above existing substitutes. (Lu and Comanor [1998], Ekelund and Persson [1999]). When improved drugs are introduced and older and less expensive drugs are replaced, the new drugs cause higher aggregate expenditures.

3 Earlier studies

Ulf Gerdtham et. al ([1993] and [1998]) conducted two studies on the rise of pharmaceutical expenditures in Sweden. In these studies, the authors divided

the increase in expenditures for the periods 1974 – 1991 and 1990 – 1995 into three components; a change in prices, larger quantities consumed and a residual. The residual was interpreted as the increase in expenditures due to a change in prescription patterns towards more expensive drugs.

During the first period 1974 to 1991, the increase in real expenditures of 67 % was accompanied by a decline in the price index of 30 %, an increase in consumed quantities of 11 % and an increase in the residual of 115%. In the second period, 1990 to 1995, real expenditures increased by 50 %. The decline in the price index was 9 %, quantities increased by 27 % and the residual increased by 30 %.

The department of health (DoH) in the UK and the Intercontinental Medical Statistics (IMS) both studied the growth in expenditures for 25 selected products on the UK market between 1993 and 1994. Due to slightly different measurement techniques, the estimated increases were 12.5 % and 13.5 %, respectively. The IMS found the main reasons for the increase to be a larger number of prescribed items and a shift towards more expensive drugs. The DoH which separated the two effects found the shift towards more expensive drugs to be the most important of the two factors.(Office of Health Economics [1997]).

Ulf Gerdtham et. al [1995] have conducted a study to see which structural factors influence the different levels of drug expenditures in different countries. One of the most important factors was the reimbursement system. If a country increased the government coinsurance rate by 10 %, pharmaceutical expenditures were estimated to increase by 2 – 3 %. Capitation as a way of financing doctors and the existence of budget ceilings also had significant and strong effects. In the open care, budget ceilings tended to decrease pharmaceutical expenditures by 12 %, while they increased in-hospital care expenditures by around 16 – 18 %.

4 Model

There are several reasons to believe that there are regularities in the evolution of pharmaceutical expenditures. For example, price formation is determined by the regulatory regime, which is likely to remain quite stable over time. It is therefore reasonable to expect that prices evolve according to a relatively stable pattern. If prices, for example, start to increase at a quicker pace, this might be due to a shift of regime. The same way of reasoning can be applied

to the rate of innovations. The incentives for research and the probabilities of drug discoveries are likely to be quite stable over time. However, a shift in the incentives and probabilities for discoveries of breakthrough drugs may be due to a change in the safety regulations or new technologies, such as combinatorial chemistry. Another factor is the demographic influence on the increase in quantities consumed. As the population grows older and, on average, becomes less healthy, more drugs will be consumed. This growth may correspond to a constant factor.

Starting from the hypothesis that there are regularities in the functioning of the pharmaceutical market regarding key factors such as prices and the inflow of new innovative drugs, it is possible to theoretizise about a steady-state or an equilibrium growth in pharmaceutical expenditures.

If key variables are changing according to some rule or principle the resulting growth rate when all these factors are determined by a set of constant rules may be considered as a steady state growth. In such a framework, a change in price setting or in the speed of new drug introductions will move the drug market from one steady state to another.

To model pharmaceutical expenditures, it is necessary to structure the formula:

$$E_{t+1} - E_t = P^1_{t+1}X^1_{t+1} - P^1_t X^1_t + P^2_{t+1}X^2_{t+1} - P^2_t X^2_t + P^3_{t+1}X^3_{t+1}$$

For this purpose, the mechanisms describing the changes in drug expenditures are modeled. It is postulated that there are steady states where key variables grow at constant rates from period to period. The key variables are the prices of the existing assortment, introductory prices, the number of new drugs introduced and the increase in the underlying demand.

Price changes over time The price pattern is highly dependent on the regulatory system. In Europe, prices tend to be tightly regulated. Some sort of price-cap regulation is a common scheme in many countries, that is, a pattern of constant or falling real prices over time is imposed for most drugs. The measured rate of changes in drug prices is therefore constant or negative. However, if introductory prices increase at a sufficient rate, costs will increase at given quantities. In fact, markedly higher launch prices constitute the optimal response to the implementation of a price-cap regulation under conditions of rapidly changing demand (Abbot [1994]).

In countries with a less regulated market for pharmaceuticals, the observed price pattern may be quite different. Some firms employ a so-called penetration strategy, that is, drugs are introduced at prices below the existing substitutes at the time of entry. When they have captured part of the market, prices are increased in order to profit from brand loyal consumers (Lu and Comanor [1998]).

The rate of price changes can be described by a number raised to the power of the number of periods, s, the drug has been on the market θ^s. $\theta > 1$ if prices are increasing over time and $\theta < 1$ if they are decreasing.

Introductory prices Introductory prices may also change over time. Since changes in introductory prices are not captured by changes in the drug price index, their effect on aggregate expenditures may be difficult to track down. It is also difficult to tell whether the quality adjusted price is increasing or decreasing (Frank et. al. [1998]). New drugs tend to be more advanced than old drugs and a higher price per unit is not necessarily a higher price related to effect (Cutler et. al. [1998]). However, the issue here is not whether the cost-effectiveness of drug use is increasing or decreasing but to study the determinants of aggregate expenditures. For this reason, I am only concerned with the real price of a daily dose of a new drug. The introductory price in period t is ρ raised to the power of t, ρ^t if ρ has remained constant since the first period where ρ can be larger, equal or less than one, depending on whether introductory prices are increasing or decreasing over time.

Substitution When new drugs enter the market, a fraction of the old drugs are replaced. The replacement ratio can be affected by a number of factors. The number of new drugs introduced in every period n and the innovativeness z of new drugs are likely to be of special importance. Depending on how drug expenditures are financed, the price of new drugs may be relevant. Other factors such as the reimbursement level and health care routines may also have effects and can be summarized in the parameter l. Let $0 \leq a(n, z, l) \leq 1$ be the fraction of old drugs that are replaced. A larger number of new drugs n should increase the share of old drugs that are replaced in every period, due to stiffer competition $a'_n(n, z, \rho^t, l) \geq 0$. The effect of an increased innovative height z is ambiguous $a'_z(n, z, \rho^t, l) \lesseqgtr 0$. On the one hand, more innovative drugs might mean stiffer competition with existing

drugs, on the other hand, the new innovations may cater specifically for the needs of previously untreated patients. A higher introductory price should decrease the rate at which new drugs replace old $a'_{\rho^t}(n, z, \rho^t, l) \leq 0$. A decrease in the reimbursement rate or a reform making the health care system more sensitive to drug prices, might make it more difficult for expensive new drugs to capture market shares $a'_l(n, z, \rho^t, l) \geq 0$.

Market expansion A new drug may also attract new patients and expand the market. This expansion can be expressed as a percentage, b, of the old quantities. It is reasonable to expect a larger number of drug introductions, n and the innovative height, z to have a positive impact on the total number of patients treated $b'_n(n, x, z) \geq 0$, $b'_z(n, z, x) \geq 0$. In the long run it will be more difficult to expand the market as the number of treatable diseases increase. The size of the expansion as a percentage of the existing market x is expected to be decreasing $b'_x(n, z, x) \leq 0$.

Ageing population, etc. A number of factors can increase the number of drugs consumed; factors such as an aging population or a shift from in-hospital care to open care were mentioned above. These factors, determining the overall rate at which drugs are prescribed, are captured in the growth variable g. $1 + g = G$.

In order to analyze a model with the above variables, a drug is only assumed to exist for two periods. This is a simplifying assumption which approximates the fact that the market shares of old drugs usually shrink over time. The model begins in a hypothetical first period where n, θ, ρ are constant and $b'_x(n, x, z) = 0$. Drug expenditures evolving from period one with the first introductory price being one will be:

Period 0:

$$E_0 = 1$$

Period 1:

$$E_1 = G(a(n)\rho + (1 - a(n))\theta + b(n)\rho)$$

Period 2:

$$E_2 = G^2((1-a(n))(1+b(n))\rho\theta + a(n)(1+b(n))\rho^2 + (1+b(n))b(n)\rho^2)$$

Period 3:

$$\begin{aligned} E_3 &= G^3(a(n)((1+b(n)) + (1+b(n))b(n))\rho^3 + (1-a(n))((1+b(n)) + \\ &\quad (1+b(n))b(n))\theta\rho^2 + (1+b(n) + (1+b(n))b(n))b(n)\rho^3) \end{aligned}$$

etc.....

To obtain the rate at which drug expenditures are increasing in steady state, the following division is performed:

$$\frac{E_{t+1} - E_t}{E_t} = G\rho b(n,x) + G\rho - 1$$

The preceding analysis lends itself some conjectures about the factors driving the growth in expenditures. The rate of the price change θ has no effect on the growth rate of expenditures in steady state, due to the ongoing creative destruction. If a drug will only survive on the market for a certain number of periods, the prices drugs have reached after a certain number of periods may be constant over time. The only effect of a change in the price pattern is a level effect. The magnitude of this level effect depends on the market shares captured by a drug during its different stages of the product-cycle.

The growth rate in steady state is also independent of the rate at which new drugs capture market shares. When expenditures are compared between two periods, the drugs with the largest market shares will have the largest impact on this difference. In steady state, these drugs are always from two different and subsequent periods. Whether the drugs with the largest influence are "young" or "old" may have a level effect but not a growth effect.

When introductory prices are increasing, the average price of drugs will increase irrespective of the price pattern over time and as a consequence, so will costs. Hence, introductory prices have a growth effect on expenditures. There is also an obvious effect from the rate at which the size of the market is expanding; as more drugs are consumed, expenditures increase. The first

factor increasing the size of the market is drugs for new indications or drugs with better effects making them more attractive to patients. However, in the model above, I have assumed the percentage increase of the drug market to be constant, irrespective of the market size. A more realistic assumption in the long run would be that $b'_x(n,z,x) < 0$. The second important effect, increasing the growth in expenditures, is the increase in underlying demand due to factors such as an ageing population. If the population converges to an equilibrium age distribution, the growth rate effect from increased quantities may even out. Therefore, the growth in introductory prices seems to be the most important factor for determining the long-run growth in expenditures.

5 Data

In order to analyze the role played by new innovative drugs for rising pharmaceutical expenditures, I have collected data on pharmaceutical sales in Sweden. The sales are added on different levels, the level of the individual *NCE* drug, and categories of drugs classified in the ATC-system. The ATC-system is a coding system with five levels (WHO [1997]). The categories studied are therapeutic groups and subgroups, which represent the second and third levels in the classification system. The first level defines on which organ or system in the body the pharmaceutical acts and the second level defines the class of illnesses treated with the drugs in the category. The third level indicates a more specific diagnosis or pharmacological principle. For example: N06 is a second level classification and includes all psychoanaleptic drugs, while N06A are antidepressants. The data has been supplied by the National Corporation of Swedish Pharmacies (NCSP). The data set contains sales in Swedish crowns (SEK) per quarter for each substance, with an individual ATC-code for the years 1987 – 1998. Sales have been adjusted to reflect the 1998 price level. (Statistical Yearbook of Sweden [1999]).

The *NCEs* are rated according to therapeutic novelty. There is no official rating on therapeutic gains for pharmaceuticals available in Sweden. However, clinical pharmacology experts Rosén and Beerman [1999] have constructed a rating system for *NCEs*, introduced on the Swedish market 1987 – 1997. The classification has been conducted according to the FDA rating system used in the US, which consists of three classes of drugs:

- Class *A*: Important therapeutic gain: Drug may provide effective ther-

apy (by virtue of greatly increased efficacy or safety) for a disease not adequately treated or diagnosed by any previously marketed drug, or provide markedly improved treatment of a disease through improved efficacy or safety (including decreased abuse potential).

- Class B: Modest therapeutic gain: Drug has a modest but real advantage over other available marketed drugs; for example, somewhat greater effectiveness, decreased adverse reactions, more convenient route of administration, etc.

- Class C: Little or no therapeutic gain: Essentially duplicates in medical importance and therapy for one or several already existing drugs.

It is important to note that each drug is classified relative to the existing substitutes at the time of introduction. For this reason, a C-classified drug which is introduced after an A-classified drug may be as medically advanced as the A-classified drug. Since the purpose of this paper is to study the effect of innovativeness on pharmaceutical expenditures after 1987, drugs which are classified C relative to an A-classified or a B-classified drug within the same chemical/therapeutic sub-group are considered as A and B drugs, respectively, relative to the drugs introduced before 1987. With this definition, 122 A-, 99 B- and 114 C-classified drugs were registered between 1987 and 1997.

6 Descriptive statistics

In the period studied, 1987−1998, real expenditures on pharmaceuticals doubled. The most notable change was the sales of *NCEs* introduced between 1987 and 1997 that had grown to 8.8 billion in 1998. Of these 8.8 billion, 3.92 billions came from drugs categorized A relative to the 1987 stock of drugs, 2.74 billion for B-drugs and 2.14 billion from C drugs. (1998 prices). It thus seems as if the *NCEs* caused most of the increase in expenditures, with the most innovative drug contributing the most to expenditures. However, to get a more accurate picture, the effect of *NCEs* on the sales of old substances must be taken into account. In those therapeutic subgroups where no entry of *NCEs* occurred, sales increased from 2.82 to 3.76 billion SEK (1998 prices), or by 33.6 %. This figure is surprising since the prices of old drugs

decrease over time. A closer look at the data discloses that the increase in the expenditures on old drugs is, to a large extent, explained by three outliers; Estrogens (+227 million crowns), Nicorette (+232 million crowns) and asthma medicines with inhalers (R03B-) +373 million crowns. In the case of asthma inhalers, technological improvements have lead to a substitution from old inhalers to newer and more expensive ones. Since the data set only includes *NCEs*, this substitution is not captured by the empirical analysis. The increase in Nicorette sales is also attributable to factors outside the theoretical framework. In the period studied, Nicorette became available as an OTC-drug, which is most likely to be the cause of the increase together with higher taxes on cigarettes. Without these three categories, expenditures on old drugs would have increased by 4 % only. Some of the drugs in the old-category were introduced just before 1987, and may have larger sales volumes in 1998 compared to 1987. For most old drugs expenditures are decreasing, which is probably due to a general decrease in prices and quantities. Due to the large impact of the three outliers, it is difficult to tell how drugs in the categories experiencing *NCE* entry would have increased without entry. In the therapeutic subgroups where *NCEs* were introduced, sales decreased from 7.16 billion crowns to 6.62 billion crowns (1997 prices), which corresponds to a reduction by 8 %. The difference between the change in sales for old drugs that didn't experience *NCE* entry and those that did indicates the replacement effect when new drugs enter the market.

7 Introductory prices

The Swedish price regulation can be described as a price-cap regulation restricting prices and revenues, that is, the regulating authorities consider expected sales quantities when setting prices. There seems to be an implicit goal for the profit. If actual sales deviate greatly from expected sales, the regulating authorities may initiate renegotiations. If sales are larger than expected, for example, prices will be adjusted downwards. The instructions for the National Social Insurance Board (NSIB) also state that the health economic and medical value of a drug should be taken into consideration, so that more valuable drugs are admitted higher prices. To determine whether introductory prices have been increasing, it is necessary to control for quantities sold and the innovativeness of a drug. If drugs are priced higher in real 1997 prices at a given innovative height and quantities sold, there is

evidence that introductory prices are indeed increasing over time. The test is designed such that $\ln p$, (the log of the inflation adjusted price per ddd in the 1997 price level), is run against the $\ln q$, where q is the number of daily doses sold during the drug's first four quarters in the market, the innovative classification i.e. A, B, C and a continuous variable, *year*, which takes on value one for 1987, and value two for 1988 and so forth.

$$\ln p = \ln q + A + B + year + \epsilon$$

Variables $\ln q$, A, B are significant with the expected signs. The *year* variable falls short of being significant and the coefficient is very small. This indicates that real introductory prices are unaffected or very marginally affected by the time variable, indicating that the Swedish regulatory authorities have kept the reward for innovative drugs constant over time, see table 1.

Table 1: Regression 1: Introductory prices over time

	LNpratio
Constant	9.474***
	(22.55)
lnq	−0.579***
	(−18.92)
A	1.36***
	(6.09)
B	0.90***
	(4.56)
year	0.01
	(0.37)
N	231
F	119***
R2	0.679
R2adj	0.673

Notes: Numbers in parentheses are the t-values of the coefficients. *Significance at the 10 % level, **Significance at the 5 % level, ***Significance at the 1 % level. Since many of the original 335 drugs were registered but never marketed and since some drugs were marketed but failed to gain a market share, only 231 drugs are included in the regression.

8 Substitution or new prescriptions?

To study the effect of the introduction of *NCEs* on pharmaceutical expenditures, a regression is run to estimate the extent to which *NCEs* of different degrees of innovativeness have replaced the sales of old drugs. The regression

is run on two levels, with sales divided between therapeutical groups and subgroups. For these two levels, sales are calculated in terms of crowns spent. A difference between the two levels may indicate that drugs of a certain innovative height have a more extensive effect on drug use than its therapeutical subgroup. For every group, the change in sales of old drugs and the sales of $NCEs$ introduced between $1987 - 1997$ in this category is calculated. The sales are divided among, A, B and C drugs, relative to substances introduced before 1987. The regression is run on the following equation:

$$Chold = \beta_1 + \beta_2 A98 + \beta_3 B98 + \beta_4 C98 + \epsilon$$

where:

- Chold is a variable for the change in sales for old drugs in a group between 1987 and 1998.
- $A98$ is a variable for the sales in 1998 of A-classified drugs in a group.
- $B98$ is a variable for the sales in 1998 of B -classified drugs in a group.
- $C98$ is a variable for the sales in 1998 of C-classified drugs in a group.

8.1 Results

For both regressions, the coefficient for A drugs is about -0.08 and falls short of being significant.(See table 2). Since the A drug class includes drugs that are intended for illnesses which previously remained untreated, the small negative impact on the sales of old drugs is not surprising. The effect of B drugs is more puzzling, these have a small but significant negative effect on the sales at the therapeutical subgroup level. When the groups are extended, it is natural to expect an increase in the negative impact since some of the drugs may affect sales outside their therapeutic group. For example, more effective antidepressants may decrease the demand for sleeping pills, since sleeping problems are one of the symptoms of depression. However, the negative effect is smaller and insignificant for B drugs at the therapeutic group

Table 2: Regression 2: Change in drug expenditures when new drugs are introduced

	$\text{Chold}_{subgroup}$	Chold_{group}
Constant	$9 * 10^{6*}$	10^{7}
	(1.919)	(1.333)
A	−0.080	−0.085
	(−1.295)	(−−1.440)
B	−0.140**	−0.070
	(−−2.139)	(−1.243)
C	−0.352	−1.052**
	(−0.954)	(−2.194)
N	158	55
F	3.199**	4.589***
R2	0.058	0.209
R2adj	0.040	0.164

Notes: Numbers in parentheses are the t-values of the coefficients. *Significance at the 10 % level, **Significance at the 5 % level, ***Significance at the 1 % level.

level, which might be due to the sample being smaller on the therapeutic level. If there is one indication, it is that B drugs have a limited effect on the sales of old drugs within the same therapeutical subgroup. For C drugs, both the extent of the effect and its significance increases when the level is changed from therapeutical subgroup to therapeutical group. One reason may be that C drugs are closer substitutes to existing drugs than A and B drugs, and therefore take larger market shares from existing drugs. C drugs seems to decrease the sales of old drugs one by one. They do not seem to contribute to the increase in pharmaceutical expenditures.

The coefficients in the regressions can be used to estimate the effects of the introduction of new drugs on the increase in drug expenditures. Since the second regression captures most of the effects on the sales of old drugs, these coefficients are used to calculate the replacement effects of A and C drugs. For B drugs, using the coefficient obtained from the first regression seems more reasonable since it is significant. The coefficient is also expected to increase when the regression is run at the group level, which makes the coefficient from the first regression seem more reliable. It should also be noted that there is no significant correlation between the B and the C drug in either the first or the second regression. Furthermore, the coefficient for B drugs should be higher than the coefficient for A drugs. The net contribution

to expenditures from each class of *NCEs* is estimated, and calculated as the total sales (1998) of each class of drugs minus the coefficient from the regressions, times the total sales.(See table 3).

Table 3: Effects on expenditures

	Sales 1998	Old drugs	Net contribution
A	3963 million	−337 million	3626 million
B	2740 million	−384 million	2356 million
C	2140 million	−2251 million	−111 million

9 Discussion

The results from the model indicate that rising introductory prices or expanding markets due to new innovative drug introductions, and an increase in underlying demand are the potential driving forces for steady state expenditure growth. Since introductory prices remained constant over time, the only remaining factors are new drug introductions and an increase in the underlying demand. The empirical results indicate that the effects on aggregate sales of innovative A and B drugs are quite large. These drugs seem to expand markets more than they replace old drugs. The net contribution of sales from these drugs in 1998 is somewhere around SEK 6 billion. This is to be compared with the increase of about SEK 1 billion in the sales of old drugs in therapeutical subgroups where no new entries occurred. The latter increase is most likely to be caused by new innovative forms of administrating drugs, exemplified by inhalers for asthma medicines. The increase in expenditures for old drugs in categories where new innovative drugs entered is estimated to have been SEK $2-3$ billion without these entries, that is, new innovative drugs introduced in 1987 – 1997 made up 60 % (net) of the total increase of SEK 10 billion between 1987 and 1998. There are two possible reasons for the increase in the underlying demand for old drugs. First, a new drug usually reaches its peak in sales after many years. Some drugs called "old drugs" in the above categorization might have been on a higher sales level in 1998 compared to 1987, since they were regarded as new innovative drugs in at least some of the years studied. To some extent, the increase in the sales of old drugs may also have been driven by new indications.

Innovations in the future The Swedish market is undoubtly being transformed by the introduction of new innovative drugs. It seems as if most of the *NCE* introductions during the studied period have reached new patient groups, which is reflected in the large increase in quantities sold in the period 1990 – 1995, compared to 1974 – 1991. (Ulf Gerdtham et. al ([1993] and [1998]). Whether the growth in pharmaceutical expenditures will continue at the same pace depends on the nature of the technological progress in the pharmaceutical industry. If the same mechanisms that have been driving the increase in pharmaceutical expenditures in the past decade are to create another doubling of expenditures in the next decade, the supply of new innovative drugs must continue to increase. The question is whether this development is likely.

The rate at which new innovative drugs are introduced is determined both by technological change and incentives. New technological advances in gene therapy and combinatorial chemistry may decrease the costs of developing a new drug as well as increase the likelihood of major discoveries at given research efforts. However, technological advances may also have adverse effects on incentives for innovative research. Improvements in combinatorial chemistry, for example, are expected to decrease the time it takes for competitors to develop a similar, but patentable, substance after the introduction of a new drug. The effects of technological change is therefore ambiguous.

In the past few decades, the cost of developing a new drug has increased. Hansen [1979] studied 67 products that entered clinical testing between 1963 and 1975 and found an average R&D cost of $138 million, which should be compared with measures from the period 1970 – 1982, DiMasi et.al., [1991] and Myers and Howe [1997]. Their measures range from $312 to $459 million. Despite these increases of R&D costs for US firms, the number of *NCEs* approved has been constant and there is no discernible drop in industry profitability. This indicates that the introduction of new drugs may increase profitability, either due to a possibility for firms to charge higher prices or an increased market for new drugs. The results in this study indicate the latter effect to be important.

10 Concluding remarks

The growth in pharmaceutical expenditures has motivated policy makers in a number of countries to consider measures for reducing pharmaceutical costs.

Ideally, the measures taken or proposed should be evaluated on the basis of their impact on welfare and not primarily on their effect on aggregate costs. However, the beliefs about the driving forces for expenditures influence the perception of their welfare effect, they also form expectations about the effects of policy measures as well as the prognoses of future costs. In this paper, I have identified three factors that can drive the long-run growth of pharmaceutical expenditures in steady state, increasing introductory prices, an increase in the underlying demand for pharmaceuticals and new innovative drugs. There is no evidence that introductory prices are increasing in Sweden. The last two factors were found to be the most important for the growth of Swedish expenditures. Drugs incorporating significant medical advances introduced in $1987-1997$ increased pharmaceutical expenditures one-to-one and drugs incorporating moderate but real medical advances increased pharmaceutical expenditures by nearly as much. These two groups of drugs were estimated to have contributed to about 60 % of the increase in pharmaceutical expenditures. Drugs incorporating marginal medical advances were not found to make a net contribution to pharmaceutical expenditures. The second most important factor seems to be a general increase in the number of prescriptions. New indications for old drugs, a long product cycle and an increase in the underlying demand may be the causes. New technologies for the administration of drugs, such as asthma inhalers, also have an effect. However, these effects are not explicitly dealt with in the regressions. An interesting result from the theoretical model is that the price change in the existing assortment of drugs, i.e. the price index, is not a determinant of the steady state growth rate of pharmaceutical expenditures. This may explain the paradox that pharmaceutical expenditures are increasing at approximately the same rate in the Swedish pharmaceutical market as in the US market, even though the price index is increasing in the US, while it has been decreasing in real terms in Sweden.

If current trends continue, the number of new drugs introduced will be the main cause for the increase in pharmaceutical expenditures. However, for pharmaceutical expenditures to keep growing at the same rate, it is necessary for new drugs to expand the market by an increasing number of patients. Such a development can only be sustained in the long run by accelerating pharmaceutical innovations, which makes it likely that the growth in pharmaceutical expenditures will level out at some point.

Under current trends, there seems to be little scoop for decreasing the growth rate of pharmaceutical expenditures, without making the access to

new innovative drugs more difficult. Methods such as the reference pricing system or measures to make prescribers more cost conscious, will only have level effects.

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