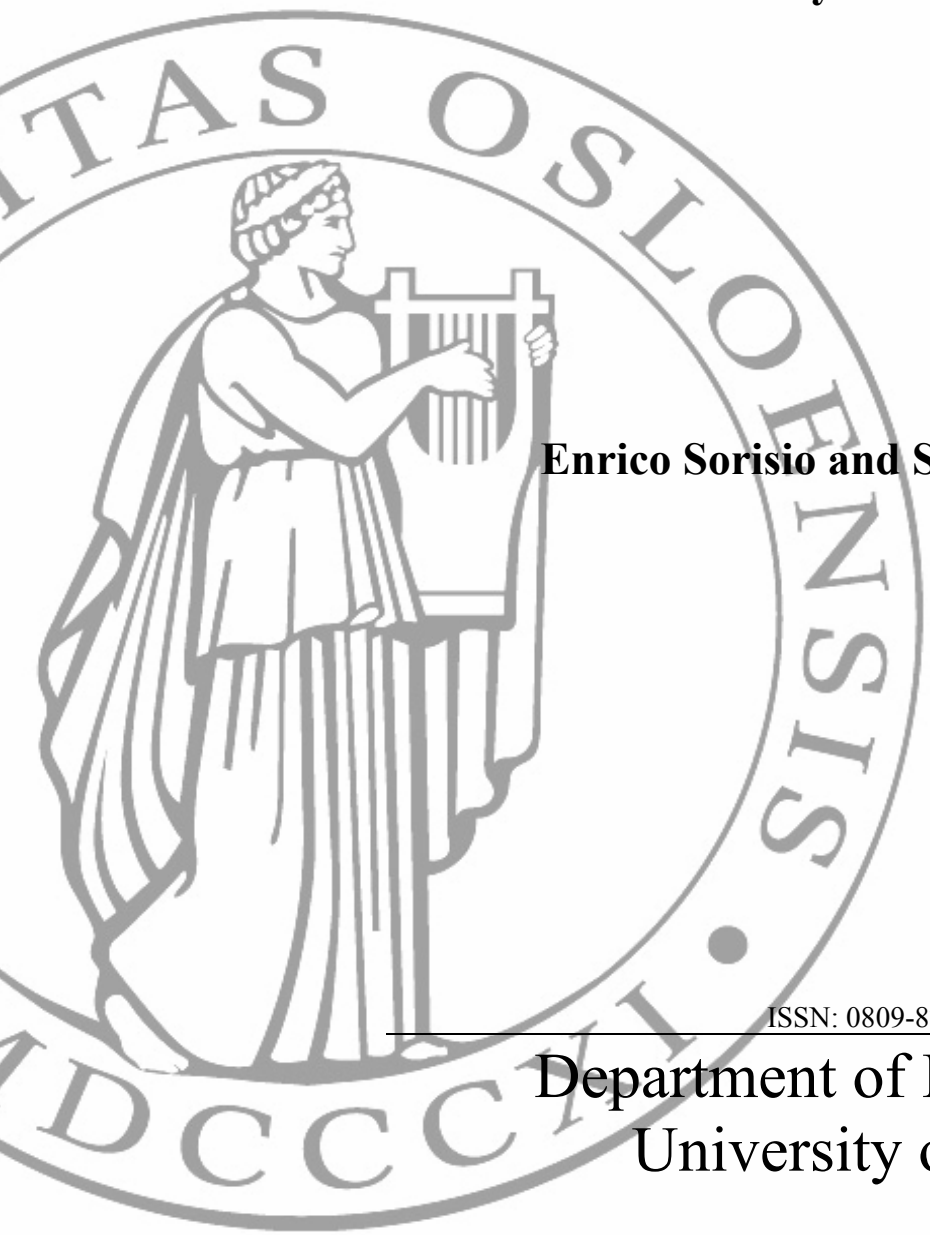
MEMORANDUM

No 12/2006

Innovation and market dynamics in the EPO market



Enrico Sorisio and Steinar Strøm

ISSN: 0809-8786

Department of Economics
University of Oslo

This series is published by the
University of Oslo
Department of Economics

P. O.Box 1095 Blindern
N-0317 OSLO Norway
Telephone: + 47 22855127
Fax: + 47 22855035
Internet: http://www.oekonomi.uio.no/
e-mail: econdep@econ.uio.no

In co-operation with
The Frisch Centre for Economic Research

Gaustadalleén 21
N-0371 OSLO Norway
Telephone: +47 22 95 88 20
Fax: +47 22 95 88 25
Internet: http://www.frisch.uio.no/
e-mail: frisch@frisch.uio.no

List of the last 10 Memoranda:

No 11	Hilde C. Bjørnland, Leif Brubakk and Anne Sofie Jore Forecasting inflation with an uncertain output gap. 31 pp.
No 10	Marina Della Giusta, Maria Laura Di Tommaso, Isilda Shima and Steinar Strøm What money buys: clients of street sex workers in the US. 31 pp.
No 09	Cathrine Hagem and Hege Westskog Distributional constraints and efficiency in a tradable permit market. 27 pp.
No 08	Hilde Bojer Resources versus capabilities: a critical discussion. 16 pp.
No 07	Erling Barth, Alexander W. Cappelen and Tone Ognedal Fair Tax Evasion. 28 pp.
No 06	John K. Dagsvik Justifying Functional Forms in Models for Transitions between Discrete States, with Particular Reference to Employment-Unemployment Dynamics. 40 pp.
No 05	Hild-Marte Bjørnsen and Erik Biørn The Joint Labour Decisions of Farm Couples:A Censored Response Analysis of On-farm and Off-farm Work. 50 pp.
No 04	Morten Henningsen Moving between Welfare Payments. The Case of Sickness Insurance for the Unemployed. 35 pp.
No 03	Rolf Golombek and Michael Hoel Endogenous technology and tradable emission quotas. 16 pp.
No 02	Jo Thori Lind Do the rich vote Conservative because they are rich?. 46 pp.

A complete list of this memo-series is available in a PDF® format at:
http://www.oekonomi.uio.no/memo/

09/05/2006

Innovation and market dynamics in the EPO market

by
Enrico Sorisio[1] and Steinar Strøm[2]

Abstract

We have estimated the demand of erythropoietin (EPO) on market data from the Nordic countries. Assuming that prices are set in a Nash-Bertrand game we determine the degree of competition in this Nordic market. We also report the impact of product innovation on welfare, e.g on consumer and producer surplus. The product innovation is the entry of Aranesp in the Nordic market. We find a positive effect related to the introduction of Aranesp in the EPO market. The high increase in consumer surplus however seems not to be accompanied by a great increase in producer surplus, whose growth is slight. Some time after the introduction of the innovation, the surplus growth does not seem to increase, it remains more or less the same (or decreases a bit). An important conclusion in our paper is that although there are few firms competing in the Nordic market for EPO, the estimated long run market power is low.

JEL Classification: C35, D43, I18, L11
Keywords: Discrete choice, demand for pharmaceuticals, monopolistic competition, EPO

[1] PharmaNess scarl; University of Turin

[2] University of Oslo; The Frisch Centre, Oslo; University of Turin

1. Introduction

Erythropoietin (EPO) is a recombinant protein that stimulates the production of blood red cells; it is used for the treatment of anemia related to chronic renal failure in dialysis patients, to increase the production of autologous blood in normal subjects, and to reduce the duration of anemia in patients treated with chemotherapy. Dispensing of EPO represents a strong advance in such therapies, also because it reduces the need of blood transfusions, with less risks of coming down with illnesses like viral hepatitis and AIDS.

The biotech drug market is very competitive. In recent years, biotech has claimed an increasing share of novel treatments approved by the US Food and Drug Administration (FDA); that trend is shifting (Lawrence, 2004). There are more new drugs or biologic applications coming from biotechnologies. The number of biotech drugs on the market that have sales over 1 billion USD per year is rapidly increasing. Recombinant therapeutic proteins still represent the main business sector of biotechnological drugs. Their development started in the '80s with the beginning of a lot of clinical studies and the launch of the first products. Recent estimations showed a market in constant growth, with worldwide sales of 32 billion USD in 2003, and expected sales of about 53 billion in 2010 (Pavlou and Reichert, 2004).

In this paper we study the demand and supply of erythropoietin in four Nordic countries, using an econometric model based on discrete choice and a random utility model. It measures the effect of price changes as well as the loyalty of patients and physicians to a drug. Our main aims are to estimate demand for EPO and to determine the degree of competition in this Nordic market. The main motivation for this paper is to analyze the impact of product innovation on market power and welfare, e.g. on consumer and producer surplus. The product innovation is the entry of Aranesp in the Nordic market.

We find a positive effect related to the introduction of a strong product innovation in the EPO market. The large increase in consumer surplus however seems not to be accompanied by a large increase in producer surplus, whose growth is slight. Some time after the introduction of the innovation, the total surplus tends to remain more or less the

same (or decreases a bit). Although there are only three producers in the Nordic market (after the entry of Aranesp), the estimated market power in the long run is rather low.

The paper is organized as follows. In the next two sections we give a brief review of literature and a description of the different EPO product and the global market. In Section 4 we present the econometric models and in Section 5 summary statistics of the sample follows. Estimates are given in Section 6 while Section 7 reports the result of the welfare analysis. Section 8 concludes.

2. A brief review of literature

Most of the literature on drug demand is based on the relationship between patient and physician, whose interaction influences the decision to prescribe and to take a certain medicine. Given the fact that the doctor acts as an imperfect, but interested agent of the patient, it is possible that the loyalty to a specific brand plays an important role, in other terms habits can often lead the physicians prescriptions or patients consumption (Stern and Trajtenberg, 1998).

Biotechnological-pharmaceutical R&D process takes a lot of time and is very complicated, an important role on this being played by regulatory authorities (Berndt et al., 2005). Drug development costs are constantly increasing both in general terms (DiMasi et al., 1991, DiMasi et al., 2003) and by therapeutic category (DiMasi et al., 2004). On the other hand pharmaceutical R&D productivity, often measured by the number of new products launched in the pharmaceutical markets, seems to decrease sensibly, varying from therapeutic category and being influenced by a long-term process of alliances, mergers and acquisitions (Danzon et al., 2004; Danzon et al., 2005). The sign and magnitude of this influence are however controversial. Scale, scope and spillover effects are other possible factors that can affect productivity (Henderson and Cockburn, 1996; Cockburn and Henderson, 2001).

Productivity of the biotech drug sector has been investigated in the last years, showing different trends depending on several factors or differentiating by therapeutic area or drug type (Reichert and Paquette, 2003; Reichert and Pavlou, 2004). The diffusion of pharmaceutical innovation and the demand for pharmaceuticals can be influenced by consumption externalities, advertising and scientific information (Azoulay, 2002; Battacharyya, 2005; Berndt et al., 2003).

The simple count of the number of new drugs (i.e. products) launched does not seem to provide an adequate measure in order to evaluate the social impact of product

innovations. Trajtenberg (1990) proposes a model of evaluation of the changes on welfare subsequent to product innovation, and in addition to this he aims to investigate the role of patents as indicators of innovation in a certain field. Incremental patient welfare caused by a certain innovation can increase due to concurrent introduction of other innovations, changes in the prices or other observed characteristics, and because of market withdrawal of existing drugs (Cleanthous, 2002). Patients' benefits arising from pharmaceutical innovation is also influenced by the problem of non-compliance with a specific therapy, and by the motives of physicians in their prescription behavior (Ellickson et al., 1999). All the references cited do not investigate the EPO market or any other biotechnological drug; hence the analysis of such markets can give further information on innovation and welfare in the pharmaceutical sector.

3. Description of the products and the market

Erythropoietins represent the biotechnological drugs class with the higher sales, about 10 billion USD worldwide per year. The first EPO products were introduced about 15-20 years ago. In the United States, the largest market worldwide, there was an initial monopoly of the product called Epogen (epoetin alfa) developed by Amgen, the world's largest biotechnology company and launched in 1989, with the therapeutic indication of anemia in patients with renal failure. Despite its patents expiration (2004/2009), it still holds a large part of the market shares. In 1995 a new product came out, called Procrit, originated by Amgen, that gave an exclusive license to a Johnson&Johnson (J&J) subsidiary, with indication for anemia in non-dialysis patients (e.g.: chemotherapy-induced anemia, therapeutic surgery). After the first monopoly phase, the market was characterized by market segmentation, in order to gain the highest profits. The reasons why Amgen decided to give a license to a potential competitor can be many: lack of productive capacity, better distribution and promotion network by J&J, or a strategic ex-ante decision in order to disincentive a potential big competitor to invest in research and development of similar products[3].

In 2002 Amgen launched Aranesp in the United States (darbepoetin alfa), a drastic product innovation, and a substitute of the existing products: it represented a strong technological advance because it showed longer half-life, needing less dosing (fewer injections than Epogen) and it is more powerful than epoetin alfa. It also allowed

[3] Many interesting arguments about licensing and R&D are discussed by Tirole, 1991, par. 10.8.

Amgen access to new anemia market segments (including both pre-dialysis and oncology patients). The cost effectiveness ratio of darbepoetin alfa is better than that of epoetin alfa (Amgen, 2002). Amgen holds the worldwide exclusive rights to Aranesp, excluding Japan and China, where Kirin marketed the product under a license agreement.

In markets outside US (especially Europe and Japan), the competition issues were slightly different: two products developed by two different firms were competing, and we did not observe a market segmentation. In 1988 Amgen launched its epoetin alfa product, sold under license by J&J and its subsidiaries under a variety of commercial names (Eprex, Erypo, Epopen, Epoxitin, Globuren, Espo…) whose therapeutic indication was the treatment of anemia. In sales analysis Eprex is often considerer equivalent to Epogen/Procrit; from a technological point of view they should be considered as different products, for they are manufactured by different companies in different facilities, using different methods and formulations. This could depend on different regulations to the drugs given by the main authorities (FDA in the US and EMEA in Europe). For the purposes of our analysis we could still consider them as the same product.

In 1988 the non-US markets also saw the launch of another EPO product, called Recormon (epoetin beta), whose indication was the treatment of anemia in patients with chronic renal failure; it was developed by Genetics Institutes and marketed in EU by Boehringer Mannheim, sold in Japan by Chugai (under the name Epogin). It has then been marketed by Roche, that acquired those companies. The product failed to enter the US market, but a new formulation has then been filed in the US for other diseases (haematological malignances). Later the product changed name to NeoRecormon, due to some incremental innovations. Finally, Aranesp was launched in Europe in 2001, some months before the launch in the US, gaining high market shares.

The existing products (in US and outside US) experienced a lot of relatively small incremental innovations mainly related to drug delivery, such as new formulations, longer time of action, different therapeutic indication broadening the uses of those drugs, etc… Those are typical strategies used by the big pharmaceutical companies in order to extend the patent protection over time. There are also signs that new big competitors are trying to enter the EPO market through the development of new products that will probably have a great impact on the EPO market in the next years[4].

[4] The first potential entrant is represented by Dynepo (epoetin delta), the equivalent protein of Amgen's erythropoietin, Epogen, which has been manufactured using Transkaryotic Therapies' (TKT) gene activation technology. The product received FDA approval in September 2001 for the

There are many other important issues about the high level of competition in the EPO market. Competition is not only expressed by R&D, price and marketing strategies, but it is also realized through the engagement of legal disputes over license and patent rights (Crespi, 2005)[5].

Another potential issue is the threat of biogenerics. In the US, with first patent expiration generic erythropoietin can be sold on the market. However a biogenerics competition is not to appear soon in the US market, due to a legal biogenerics approval to be established. Experts estimate that it will take about 5 years (from 2004) to have generic epoetin alfa on the US market (Dove, 2001).

Recently in Europe EMEA, the European regulatory agency issued a document about "biosimilar" (a new biological medicinal product claimed to be "similar" to an original reference medicinal product which has been granted a marketing authorisation in

---

treatment of anemia in patients with chronic kidney failure, and it was approved in March 2002 by the European Commission but has not been launched due to an ongoing patent dispute with Amgen and Kirin regarding the infringement of Epogen's patents. In 2001, the US District Court for the District of Massachusetts ruled that Dynepo infringed several patents associated with Amgen's Epogen, while the High Court of Justice in the UK produced a similar ruling. Recently, the House of Lords in the UK agreed to hear Kirin-Amgen's petition for an appeal in a patent infringement suit involving Dynepo. The decision to hear both companies' appeals follows a unanimous opinion of non-infringement from the UK Court of Appeal in favor of Aventis/TKT. Furthermore, a patent appeal is pending in the US.

Another candidate product is Roche's second-generation epoetin R744, which is currently developed as a potential treatment of chemotherapy-induced anemia. This is an advanced form of currently marketed erythropoietins and – together with the recent purchase of Chugai's erythropoietin business – shows the company's firm intention to expand beyond NeoRecormon and form a strong franchise with the potential to challenge Amgen's and Johnson & Johnson's market shares in hematology and oncology. Roche plans to file for approval in 2006 and launch the product in 2007. However R744 is not expected to effectively compete with the established market leaders in the erythropoietins market (J&J's Procrit and Amgen's Epogen and Aranesp). This, and the launch of new generations of erythropoietins such as Aventis's Dynepo, will sharpen the loss of market share of NeoRecormon in the long term.

[5] For example J&J tried to sell Procrit in US on the dialysis market, not included in the licence; in 2002 an arbitrator ruled that J&J breached the licence agreement, but denied Amgen's request to terminate the agreement. On the other hand J&J tried to demonstrate that Aranesp was only a new version of Epogen, claiming that they were entitled to rights over Aranesp for non-dialysis use as part of the licensing agreement covering Epogen. In 1998 Amgen won the dispute.

the Community), in which there are the guidelines concerning the scientific data to be provided to substantiate the claim of similarity used as the basis for a Marketing Authorisation Application (MAA) for any biological medicinal product, e.g.: medicinal products containing biotechnology-derived proteins as active substance, immunologicals such as vaccines, blood-derived products, monoclonal antibodies, etc (EMEA, 2004). Generics manufacturers are planning to market a generic version of epoetin alfa in Europe when EU patents will expire and there will be an approval process for biogeneric products, that is coming. Anyway it is difficult to produce biogenerics, because the production process is very complicated. In addition to legal and regulatory problems the biogenerics firms will thus face some technical problems.

4. The model

4.1 Demand side

In this study we present a formal model of demand and supply analysis, whose aims are to determine the factors that influence the choice of a drug in the EPO market, and to examine the changes in the choice induced by a product innovation in terms of social welfare.

In this model (based on Berry, 1994, Berry and Pakes, 2002, Razzolini, 2004, and Train, 2002) we assume a consumer represented by a couple physician-patient i=1,2,…,I maximizing their utility deriving from the consumption of a product j=1,2,…,J in a certain time period. Actually, because EPO is mainly used in connection with serious cancer therapy, the decision makers, the consumers, will be medical doctors working in hospitals. Because a hospital is facing more strict budget constraint than a GP/ patient, for whom a substantial part of the expenses is reimbursed by the government, we would expect the demand to be rather elastic.

Consumer utility is given by the following function:

(1) $U_{ij} = U(\varepsilon_{ij}, p_j, x_j, \mu_j, \alpha)$

where ε_{ij} represents unobserved individual/drug characteristics (also called the taste shifter), p_j is the drug price, x_j and μ_j are product characteristics, and α is the vector of demand parameters to be estimated. Consumer i chooses product j if:

(2) $U(\varepsilon_{ij}, p_j, x_j, \mu_j, \alpha) = \max_r U(\varepsilon_{ir}, p_r, x_r, \mu_r, \alpha); \forall r$

A very simple version of the utility function is given by a linear function with an additive error term, independently distributed among consumers and product characteristics:

(3) $$U(\varepsilon_{ij}, p_j, x_j, \mu_j, \alpha) = V_j(p_j, x_j, \mu_j, \alpha) + \varepsilon_{ij}$$

V_j is the representative utility and it measures the mean utility level derived from the consumption of product j, and ε_{ij} is the deviation from this mean level due to taste heterogeneity. In this model the only product attributes that are directly taken in consideration are price (p_j) and time spent (x_j) on the market for each drug. Using a fixed effect estimation procedure will capture other characteristics.

By assuming ε_{ij} to be independently, identically distributed extreme value (i.i.d. or type I extreme value) across individuals and products, the probability that consumer i will choose drug j is given by:

(4) $$\varphi_{ij} = \varphi_j = P(U_{ij} = \max_r U_{ir}) = \frac{\exp(V_j)}{\sum_{k=1}^{J} \exp(V_k)}$$

We observe that due to our assumption all consumers are observerable identical. The observed parallel to the probability that product *j* is chosen (eq. (4)) is the market share of the product. Because we only have access to aggregate data our observed variable will be the market share.

If we consider the incumbent product that entered into the EPO market (i.e. Eprex) as the base product, here denoted product no 1, and if we assume there is no outside good whose utility can be normalized to zero, the estimated market shares for product *j* and for Eprex (indexed with 1) at time t are:

(5) $$\varphi_{jt=} \frac{e^{\beta_{jt} p_{it} - \beta_{1t} p_{1t} + \mu_{jt}}}{1 + \sum_{k=2}^{J_t} e^{\beta_{kt} p_{kt} - \beta_{1t} p_{1t} + \mu_{kt}}}, \text{ for } j=2,\ldots J_t,$$

and:

(6) $$\varphi_{1t=} \frac{1}{1 + \sum_{k=2}^{J_t} e^{\beta_{kt} p_{kt} - \beta_{1t} p_{1t} + \mu_{kt}}}$$

where μ_{jt} can differ across alternatives and time and J_t are the number of products available at time t.

Dividing φ_{jt} by φ_{1t}, we get

$$(7) \qquad \ln\left(\frac{\varphi_{jt}}{\varphi_{1t}}\right) = \beta_{jt} p_{jt} - \beta_{jt} p_{1t} + \mu_{jt}.$$

Next we will assume:

$$(8) \qquad \beta_{jt} = \alpha_0 + \alpha_1 \cdot \frac{A_{jt}}{A_{1t}}, \ j=1,\ldots, J_t;$$

$$(9) \qquad \mu_{jt} = \tilde{\mu}_{jt} + \alpha_j$$

$A_{jt}=x_{jt}$ represents the time (in quarters) product j has been on the market. This variable should capture the habits of doctors and patients to choose the same product, irrespective of price. Thus it is considered as a measure of the brand loyalty: higher values of this variable lead to higher probability of that product to be chosen. Note that the highest value of A_{jt}/A_{1t} is 1, e.g. the period when the first branded product became available.

The parameter μ_{jt} is determined by two elements: $\tilde{\mu}_{jt}$ is a random i.i.d. term (white noise with zero expectation and constant variance), while α_j is a deterministic alternative specific coefficient, that represents attributes and aspects that remain constant over time.

The demand equation that will be estimated is then

$$(10) \qquad \ln\left(\frac{\varphi_{jt}}{\varphi_{1t}}\right) = \alpha_j + \alpha_0(p_{jt} - p_{1t}) + \alpha_1\left(p_{jt}\frac{A_{jt}}{A_{1t}} - p_{1t}\right) + \tilde{\mu}_{jt}.$$

4.2 Supply side

The supply side analysis model is based on the following hypotheses: producers maximize their profits and prices are determined in a Nash-Bertrand equilibrium. The expected profits is given by (A, p and α are vectors, and q_j is amount sold, the index for time t is suppressed):

$$(11) \qquad \Pi_j(p, A, \alpha, M) = p_j M\varphi_j(A, p, \alpha) - C_j(q_j) = (p_j - c_j)M\varphi_j(A, p, \alpha),$$

where M is the market size, the quantity sold of a certain drug is $q_j = M\varphi_j$, and we assume that marginal costs are linear and constant: $C_j = c_j \cdot q_j = c_j \cdot M\varphi_j$.

The first order condition for maximum of expected profit is given by:

$$M(p_j - c_j)\frac{\partial \varphi_j}{\partial p_j} + M\varphi_j = 0,$$

which – due the structure of the choice probability φ_j given in (5) – can be rewritten to yield:

$$(12) \qquad p_j - c_j = -\frac{\varphi_j}{\frac{\partial \varphi_j}{\partial p_j}} = \frac{-\varphi_j}{\beta_j \varphi_j (1-\varphi_j)} = \frac{1}{(-\beta_j)(1-\varphi_j)}; j = 1,2,,,J$$

As a measure of the market power of firm j in the Nordic markets for EPO, we will apply the Lerner index, which is defined as (reintroducing time t):

$$(13) \qquad L_{jt} = \frac{p_{jt} - c_{jt}}{p_{jt}}.$$

From (12) and 13), we get

$$(14) \qquad L_{jt} = \frac{1}{-\beta_{jt} \cdot (1-\varphi_{jt}) \cdot p_{jt}}$$

Because we expect β_{jt} to be negative, the Lerner index is positive. From the definition of this index, equation (13), we observe that under perfect competition where prices equal marginal costs the Lerner index equals 0. At the other extreme- monopoly - the price is at highest relative to marginal costs and by convention we set the Lerner index equal to 1 under monopoly. Thus the Lerner index varies between 0 and 1, that is between the outcomes of perfect competition and monopoly. In between these two extremes we have market structures with market powers less than under monopoly. From the structure of the choice probability, φ_j, we easily get that the own-price elasticity, denoted E_{jjt}, is given by $[\beta_{jt} \cdot (1-\varphi_{jt}) \cdot p_{jt}]$, and hence the Lerner index can be expressed as $L_{jt} = \frac{1}{-E_{jjt}}$. We thus see that in order to have value of the Lerner index between 0 and 1, the own-price elasticity has to be negative and numerically larger than 1. Actually, if the numerical value of the own-price elasticity is not larger than 1 at price optimum, then a Nash-Bertrand equilibrium in prices, given our assumptions so far, does not exist.

To model how the market power and market structure may evolve we will assume that the higher the max of the firm specific Lerner index is the higher is the chance is that new firms enter and presses down margin in all firms. This assumption seems to accord with what happened to the market after Aranesp entered the market. We will thus assume that the current index of market power, the Lerner index at time t, depends on the max Lerner index lagged one period, here specified as the following autoregressive stochastic process:

(15) $$L_{jt} = \lambda_j + \lambda_1 \max_r [L_{r,t-1}] + \eta_{jt} .$$

Here λ_j are firm specific fixed effects while λ_1 is coefficient that may or may not be less than 1; η_{jt} is assumed to be white noise. If the entry threat works and reduces the market power for the firms in the market, we will expect λ_1 to be less than 1. If so the max of the expected Lerner index gradually will converge towards a level denoted $\bar{L}$ and is given by

(16) $$\bar{L} = \frac{\bar{\lambda}}{1 - \hat{\lambda}_1}$$

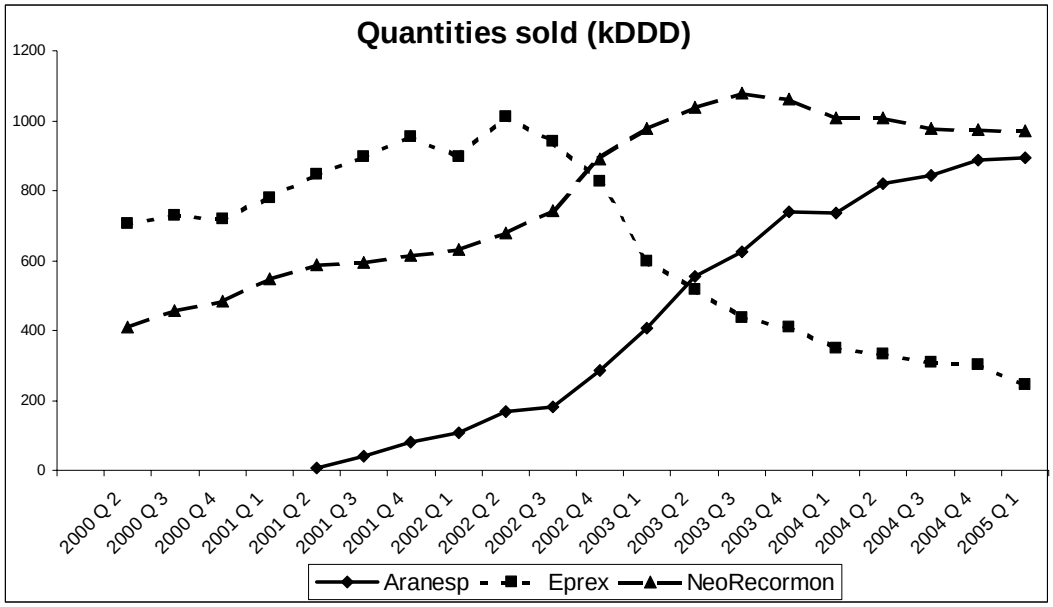
where $\bar{\lambda}$ and $\hat{\lambda}_1$ are the average of the estimated fixed effects and the estimate of λ_1, respectively.

5. Data and summary statistics

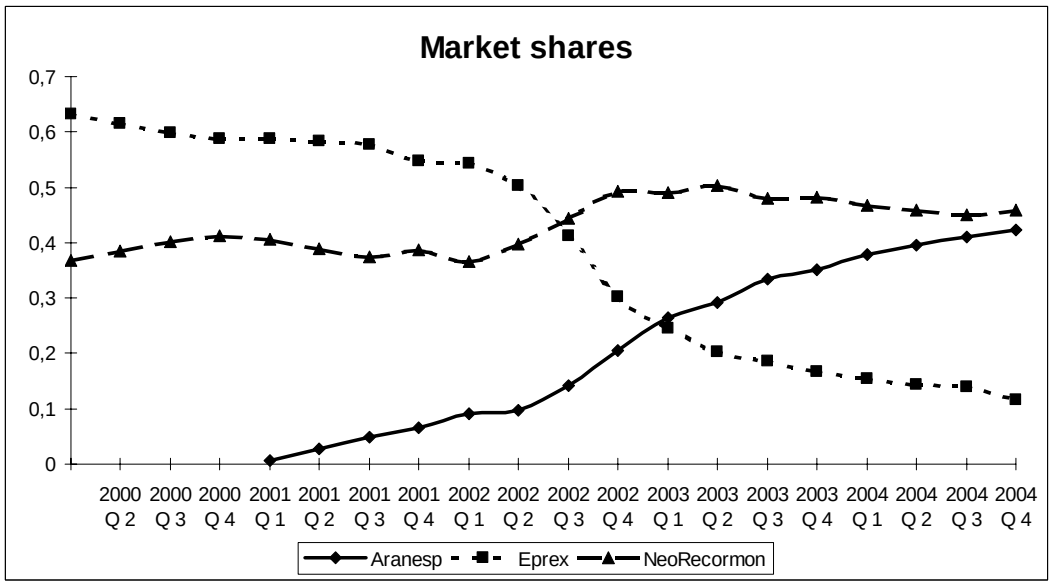
The dataset consists of market values (expressed in thousand euros) and quantity sold expressed in thousands defined daily doses (ddd) for each drug on the market included in the ATC codes related to EPO; data are available for each separate country (Denmark, Finland, Norway, Sweden), and they cover a five years period from the second quarter of 2000 to the first quarter of year 2005 included. During that period there are three products competing: Eprex, NeoRecormon and Aranesp; the latter is launched in Finland and Sweden in second quarter of 2001, and in Denmark and Norway in the third quarter of 2001.

Eprex is marketed by Johnson&Johnson, NeoRecormon by Roche and Aranesp by Amgen. Aranesp is a quite strong product innovation. Prices are expressed per ddd and deflated using national price indexes of each country, then converted into euro according the official exchange rates in each quarter. Market value is given by price multiplied by quantity sold.

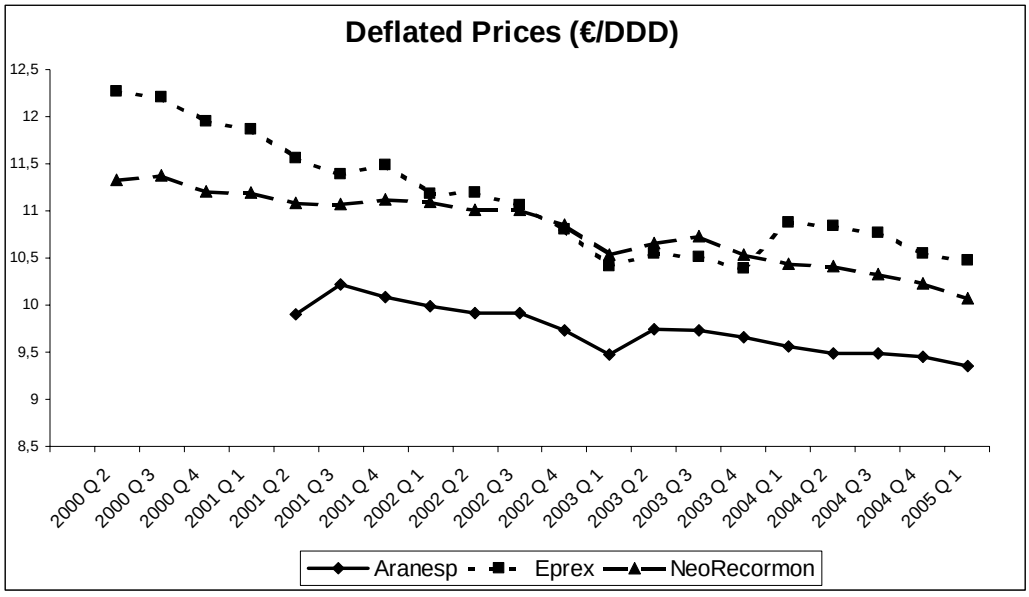
The following figure shows the quantities sold expressed in thousands ddd's in the four countries together. Note the reduction of sales of Eprex when Aranesp enters the market.



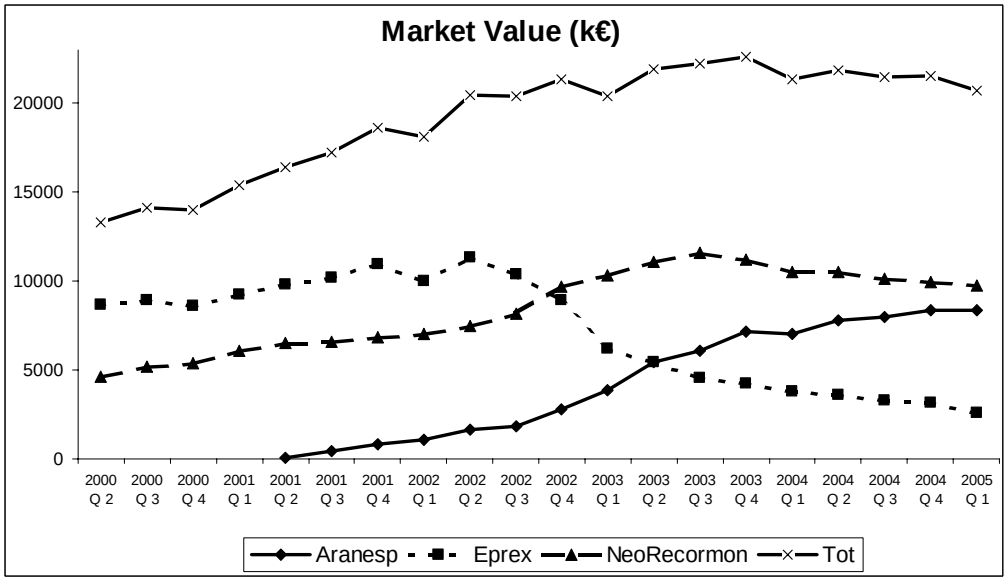
The descending market power of Eprex is also clear in the next figure, that shows the market shares of each product. On the other hand NeoRecormon shares are quite constant over time.



The next figure shows the deflated prices. There is a clear tendency to a decrease over time for each product. Aranesp has the lowest price.



The next figure gives the global sales in thousand euros for each product and the whole market.



Descriptive statistics for the sample used in our estimations are showed in Table 1.

Table 1. Descriptive statistics.

INDUSTRY VARIABLES (Nobs=56)	Mean	Std. Err.	Median	Std. Dev.	Min	Max
Market Value (€x1000)	6,848.84	430.15	7,088.15	3,218.93	82.18	11,565.79
X (DDDx1000)	641.59	39.82	693.15	298.01	8.30	1,077.40
P (deflated price)	10.61	0.10	10.54	0.73	9.35	12.27
Market shares	0.36	0.02	0.39	0.17	0.01	0.63
A (No. of quarters)	37.79	2.61	45.50	19.56	1.00	61.00
N (No. of firms)	2.86	0.05	3.00	0.35	2.00	3.00
NP (number of biotech drugs available)	35.52	0.71	38.00	5.34	27.00	43.00
PMA_{jt} (Brand cumulated no. of post marketing authorizations)	5.63	0.67	4.25	5.02	0.00	14.00
PMA_t (Industry cumulated no. of post marketing authorizations)	16.79	1.52	16.50	11.38	1.00	33.50
Q (quantity in dddx1000 of biotech drugs sold. excluding EPO)	32,941.35	431.20	32,710.10	3,226.78	25,873.70	38,585.20
EPREX (Nobs=20)						
Market Value (€x1000)	7,205.18	680.38	8,637.93	3,042.74	2,567.18	11,317.40
X (DDDx1000)	640.46	57.22	713.20	255.88	245.00	1,011.20
P (deflated price)	11.12	0.14	10.97	0.61	10.39	12.27
Market shares	0.39	0.05	0.46	0.20	0.12	0.63
A (No. of quarters)	51.50	1.32	51.50	5.92	42.00	61.00
PMA_{jt}	1.95	0.37	1.00	1.67	1.00	6.00
NEORECORMON (Nobs=20)						
Market Value (€x1000)	8,435.99	504.73	8,922.94	2,257.20	4,646.80	11,565.79
X (DDDx1000)	786.94	51.74	816.80	231.40	410.30	1,077.40
P (deflated price)	10.82	0.09	10.93	0.39	10.08	11.38
Market shares	0.43	0.01	0.43	0.05	0.37	0.50
A (No. of quarters)	47.50	1.32	47.50	5.92	38.00	57.00
PMA_{jt}	7.75	1.16	8.25	5.21	0.00	13.50
ARANESP (Nobs=16)						
Market Value (€x1000)	4,419.47	790.09	4,640.70	3,160.38	82.18	8,390.20
X (DDDx1000)	461.31	83.68	481.80	334.72	8.30	893.90
P (deflated price)	9.73	0.06	9.73	0.25	9.35	10.21
Market shares	0.22	0.04	0.23	0.15	0.01	0.42
A (No. of quarters)	8.50	1.19	8.50	4.76	1.00	16.00
PMA_{jt}	7.56	1.29	7.75	5.16	0.00	14.00

6. Estimates

6.1 Demand side

First we deflated the nominal values in the 4 countries using national price indexes (2000 Q2 = 100, sales are expressed in euro). Then we computed market shares, difference between prices and price-time and estimated the unknown coefficients in equation (10) above. Estimates are made with a fixed-effect regression.

Table 2. Estimates of the demand equation

Coefficients	**Estimates**	**Std. Err**.	**t-values.**
α_0	**-1.305316**	0.3506637	**-3.72**
α_1	**1.813934**	0.1136616	**15.96**
α_i (average)	**5.619583**	0.3415373	**16.45**
R-sq:	within = 0.8703 between = 0.7902 overall = 0.2220		
F test that all u_i=0: F(2, 43) =131.62 Prob > F = 0.0000			
No of observations: 48			

All pharmaceuticals have side effects. These side effects are likely to be known by the medical doctor, in particular among those working in hospitals. The less negative these side effects of a certain drug are, the more likely it is that this drug will be chosen. The consumer will be willing to pay a higher price for drugs with less negative side effects. The producer knows this. Hence drug with less negative side effects may get a higher price in the market. As econometricians we do not have this knowledge and we do not observe the side effects either (qualitative effects of the drugs). To us these side effects may be present in the random terms in the demand equations. Due to the pricing strategy of the firm a correlation may arise between the price and the error term in the demand equations. Ignoring this correlation when estimating the model may yield bias estimates and we would expect that price responses are underestimated. What we wrongly get as weak price responses may be due to the fact that mor expensive drugs are just bought because of some unobserved drug characteristics. In order to account for this possible endogeneity bias we have tried with instrumenting the price in the demand equation, using four instrumental variables (IV). The ideal instruments should be correlated with the price but not with the unobserved qualities of the drugs. The specification of the instrumental variables and the complete results of the IV-estimation are reported in the Appendix; the next table shows the result of the fixed-effect regression using all four IV together.

Table 3. IV-Estimates of the demand equation

Coefficients	**Estimates**	**Std. Err**.	**t-values.**
α_0	**-2.606865**	0.8078158	**-3.23**
α_1	**2.014828**	0.1790754	**11.40**
α_i (average)	**5.83535**	0.4093001	**14.26**
R-sq:	within = 0.8727 between = 0.7936 overall = 0.2229		
F test that all u_i=0: F(2, 43) =99.41 Prob > F = 0.0000			
No of observations: 48			

We observe that to instrument the prices matters lot with regard to the estimate of α_0. As alluded to above the price responses are strengthened when prices are instrumented. The estimates of the other coefficients are only slightly changed.

Price elasticities

To calculate own-price and cross-price elasticities we first note that

$$\beta_{jt} = \alpha_0 + \alpha_1 \cdot \left(\frac{A_{jt}}{A_{1t}} \right) \qquad \text{for j=2,3 (NeoRecormon, Aranesp)}$$

$$\beta_{jt} = \beta_j = \alpha_0 + \alpha_1 \qquad \text{for j=1 (Eprex).}$$

As noted above, the own-price elasticity is given by:

(17) $$E_{jjt} = EL\left[\varphi_{jt} : p_{jt} \right] = \beta_{jt} \cdot p_{jt} \cdot (1 - \varphi_{jt}) \qquad \text{for j=1,2,3}$$

Cross-price elasticities are given by:

(18) $$E_{jkt} = -\beta_{kt} \cdot p_{kt} \cdot \varphi_{kt} \qquad \text{for j,k =1,2,3, j}\neq\text{k}$$

Table 4. Own-price elasticities and cross-price elasticities.

	Own-price elasticity			**Cross-price elasticity**					
t	E11t	E22t	E33t	E21t	E31t	E32t	E12t	E13t	E23t
2000 Q 2	-2.55	-5.44	-	5.90	-	-	2.35	-	-
2000 Q 3	-2.65	-5.28	-	5.67	-	-	2.47	-	-
2000 Q 4	-2.71	-5.03	-	5.37	-	-	2.54	-	-
2001 Q 1	-2.76	-4.91	-	5.21	-	-	2.60	-	-
2001 Q 2	-2.69	-4.88	-25.23	5.04	17.39	11.56	2.55	0.03	0.04
2001 Q 3	-2.68	-5.00	-25.04	4.92	16.78	10.84	2.43	0.16	0.20
2001 Q 4	-2.74	-5.12	-23.77	4.88	16.44	10.30	2.35	0.28	0.36
2002 Q 1	-2.86	-4.98	-22.77	4.48	14.95	10.48	2.43	0.37	0.48
2002 Q 2	-2.88	-5.09	-21.68	4.43	14.63	9.67	2.28	0.51	0.65
2002 Q 3	-3.10	-4.81	-21.17	4.04	13.19	10.37	2.48	0.55	0.70
2002 Q 4	-3.59	-4.35	-19.46	3.22	10.40	11.26	2.73	0.78	1.00
2003 Q 1	-4.11	-3.84	-17.31	2.26	7.21	11.95	2.94	1.10	1.40
2003 Q 2	-4.50	-3.88	-16.26	1.85	5.85	11.88	2.96	1.45	1.84
2003 Q 3	-4.73	-3.80	-15.40	1.53	4.79	12.09	3.06	1.61	2.03
2003 Q 4	-4.78	-3.90	-14.19	1.37	4.25	11.16	2.86	1.83	2.30
2004 Q 1	-5.12	-3.83	-13.50	1.29	3.95	10.95	2.84	1.90	2.38
2004 Q 2	-5.18	-3.92	-12.67	1.18	3.59	10.45	2.75	2.03	2.54
2004 Q 3	-5.21	-3.93	-12.17	1.10	3.30	10.08	2.68	2.12	2.64
2004 Q 4	-5.12	-3.94	-11.69	1.04	3.10	9.65	2.60	2.19	2.72
2005 Q 1	-5.23	-3.80	-11.16	0.85	2.52	9.60	2.62	2.24	2.77
average	**-3.76**	**-4.49**	**-17.72**	**3.28**	**8.90**	**10.77**	**2.63**	**1.20**	**1.50**
std dev	**1.10**	**0.61**	**5.01**	**1.87**	**5.72**	**0.83**	**0.22**	**0.81**	**1.00**
min	**-5.23**	**-5.44**	**-25.23**	**0.85**	**2.52**	**9.60**	**2.28**	**0.03**	**0.04**
max	**-2.55**	**-3.80**	**-11.16**	**5.90**	**17.39**	**12.09**	**3.06**	**2.24**	**2.77**

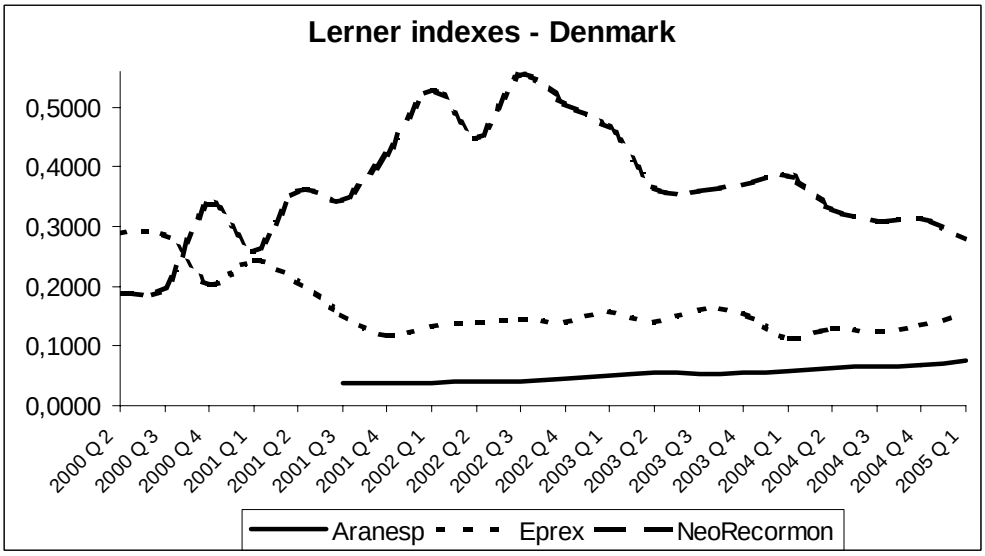
1:Eprex, 2:NeoRecormon, 3: Aranesp

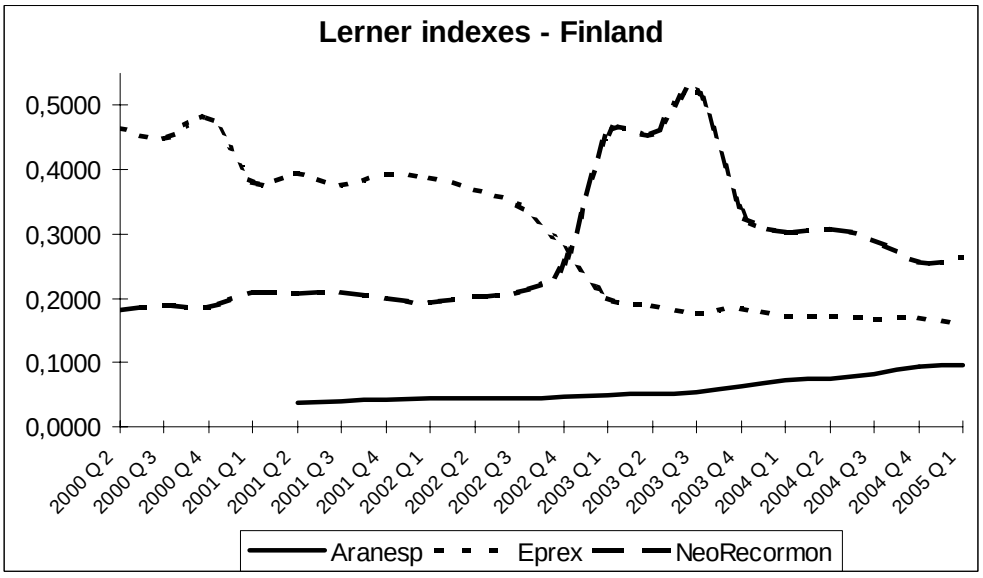
Direct price elasticities are negative as expected and sizeable. The (negative) own-price sensibility of Eprex increases over time, while the other products show an opposite trend. These changes over time are in part driven by the changes in the market shares and prices and in part by the loyalty effect captured by the variable A_{jt}. Aranesp is the most more price-responsive drug. Cross elasticities are all positive and sizeable. The impact of the price of Eprex on the demand of the two other products declines over time, while the other cross elasticities are increasing over time.

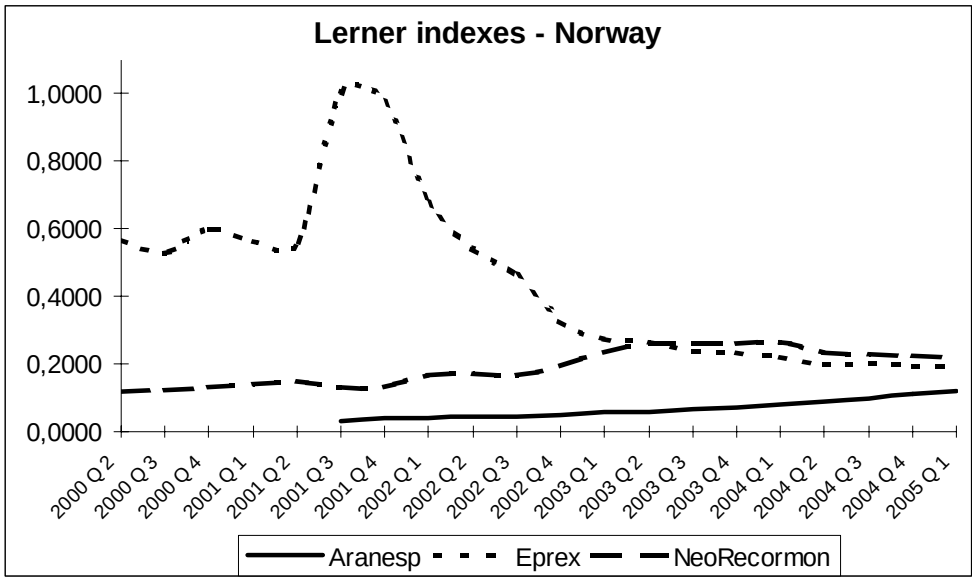
We observe that that all own-price elasticities are above 1 numerically, which is necessary for a Nash-Bertrand equilibrium in prices to exist.

6.2. Supply side

From the estimates of the demand side and from the formula for the Lerner index expressed as $L_{jt} = \frac{1}{-E_{jjt}}$ we computed the Lerner indices for the firms in each of the Nordic markets, i.e. for Sweden, Norway, Denmark, Finland. These indices are given in the figures below. Then we estimated equation (15) above separately for each of the Nordic markets. The results are given in Table 5 below.






Lerner indexes - Norway
1,0000
0,8000
0,6000
0,4000
0,2000
0,0000
2000 Q2
2000 Q3
2000 Q4
2001 Q1
2001 Q2
2001 Q3
2001 Q4
2002 Q1
2002 Q2
2002 Q3
2002 Q4
2003 Q1
2003 Q2
2003 Q3
2003 Q4
2004 Q1
2004 Q2
2004 Q3
2004 Q4
2005 Q1
Aranesp
Eprex
NeoRecormon

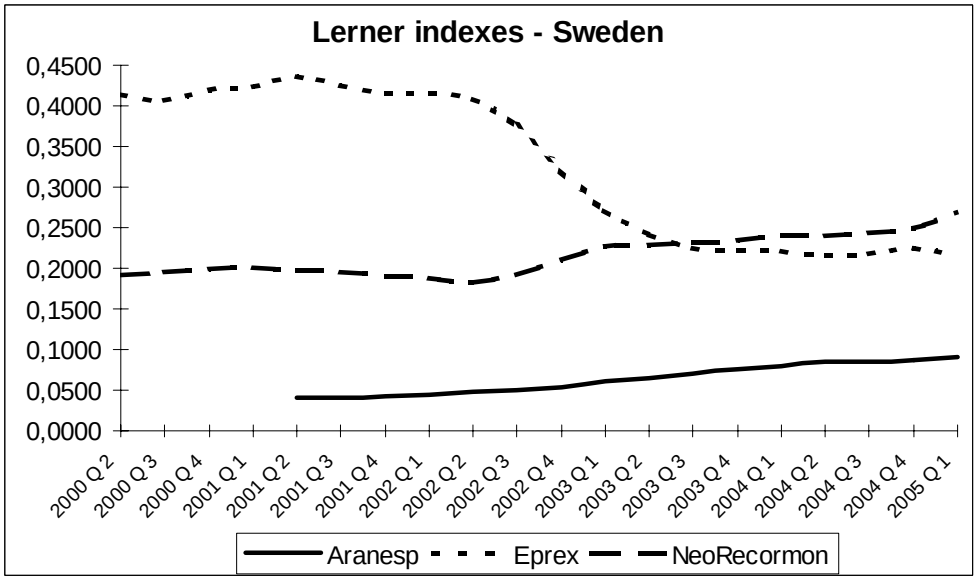

Lerner indexes - Sweden
0,4500
0,4000
0,3500
0,3000
0,2500
0,2000
0,1500
0,1000
0,0500
0,0000
2000 Q2
2000 Q3
2000 Q4
2001 Q1
2001 Q2
2001 Q3
2001 Q4
2002 Q1
2002 Q2
2002 Q3
2002 Q4
2003 Q1
2003 Q2
2003 Q3
2003 Q4
2004 Q1
2004 Q2
2004 Q3
2004 Q4
2005 Q1
Aranesp
Eprex
NeoRecormon

Table 5. Estimates of evolution of market power in the Nordic markets for EPO

Coefficients	Countries					
	Denmark			Finland		
	Estimates	Std err	t-values	Estimates	Std err	t-values
λ_1	**0.189531**	0.1035	**1.83**	0.1964	0.1703	1.15
λ_i (constant)	**0.133928**	0.041	**3.26**	**0.14185**	0.0653	**2.17**
Long-run	**0.1652**	-	-	**0.1765**	-	-
Coefficients	Norway			Sweden		
	Estimates	Std err	t-values	Estimates	Std err	t-values
λ_1	**0.198512**	0.0737	**2.69**	**0.2236**	0.0916	**2.44**
λ_i (constant)	**0.151812**	0.0402	**3.78**	**0.13404**	0.0315	**4.25**
Long-run	**0.1894**	-	-	**0.1726**	-	-

Results in bold are significant at a 5-10% confidence level. If we consider that the Lerner index reflects competition in the market, its calculated values seem to indicate that the Nordic market for EPO is rather competitive. The Lerner indexes in the long run in each country are similar, around 0.17-0.19; which imply that the market power in these markets are predicted to converge to values 17-19 percent above the perfect competitive outcomes.

The Lerner index values when all countries are taken together lead to similar results, as we note in the graph and table below.

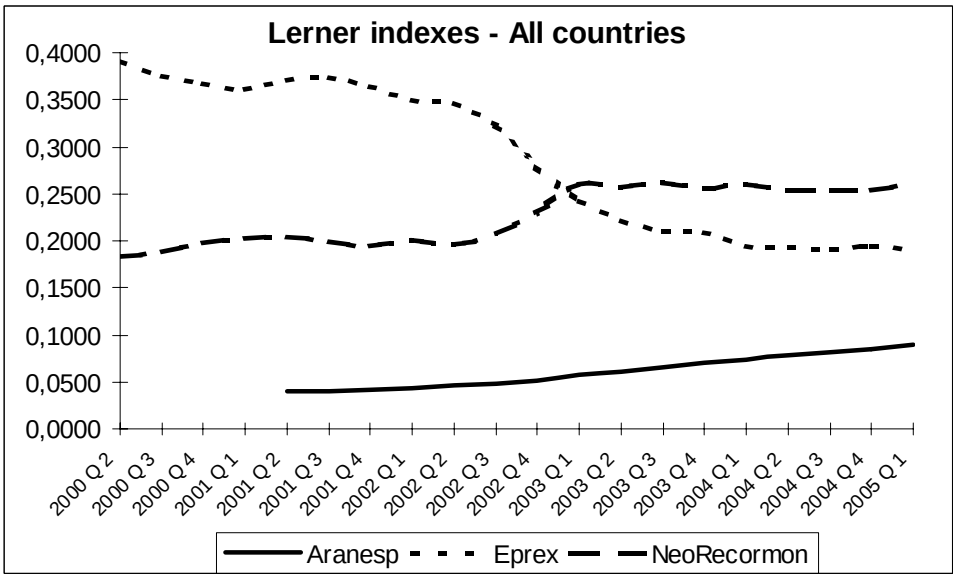


Table 6. Estimates of market power (all countries together)

Coefficients	All countries together		
	Estimates	Std err	t-values
λ_1	**0.2453**	0.1296	**1.89**
λ_j (constant)	**0.122**	0.0408	**2.98**
Long-run	**0.1617**	-	-

The estimate of the λ_1 coefficient is higher than the coefficients estimated for the single countries, while the firm specific constant is slightly lower. The long-run index converges to a value of about 0.16 (quite the same we observed in each country).

7. Welfare analysis

Using the results above we have measured the gains in social welfare arising from the product innovation, i.e. the entry of Aranesp, in EPO market. In order to calculate the expected surplus of the single consumer (here the representative consumer) we have employed the following formula (Trajtenberg, 1990):

$$(19) \qquad E[CS]_t = E[\max_r U(\varepsilon_{irt}, p_{rt}, x_{rt}, \mu_{rt}, \alpha); \forall r] = [\sigma \cdot \ln \sum_{j=1}^{J_t} \exp\left(\frac{V_{jt}}{\sigma}\right)] + C,$$

where: $\mathbf{-1/\sigma = \alpha_0}$ is the coefficient related to price difference, V_{jt} is the deterministic part of the utility, and C is an unknown constant term that represents the fact that the absolute

level of utility cannot be measured. In what follows we have set C so that the E[CS] equals zero in the second quarter.

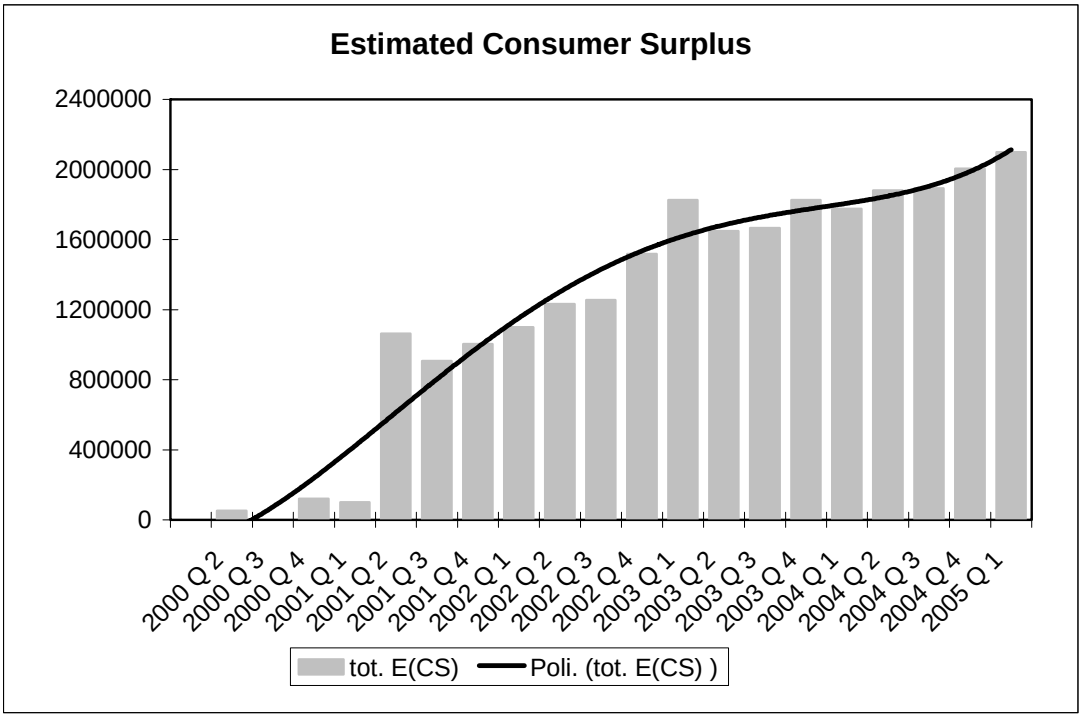
In order to get the total consumer surplus we need to determine the number of consumers for every quarter. It has been computed as the ratio between the number of ddd's sold in each quarter and the number of days of the quarter, thus obtaining the mean number of daily doses of the drugs sold every day, i.e. the mean number of patients (consumers) that take EPO every day. The total consumer surplus is simply given by the number of consumers times the expected consumer surplus for the representative consumer. We then have computed the change in the total consumers' surplus over time: $\Delta E(CS) = E(CS)_t - E(CS)_{t-1}$. The results are given in Table 7 below.

Table 7. Consumer surplus estimates. Euro

Q	Total E(CS)	ΔE(CS)
2000 Q 2	51,980	-
2000 Q 3	0	-51,980
2000 Q 4	121,254	121,254
2001 Q 1	100,148	-21,106
2001 Q 2	1,063,511	963,363
2001 Q 3	906,742	-156,769
2001 Q 4	1,002,229	95,487
2002 Q 1	1,098,943	96,714
2002 Q 2	1,232,139	133,196
2002 Q 3	1,254,337	22,198
2002 Q 4	1,517,437	263,100
2003 Q 1	1,824,610	307,173
2003 Q 2	1,647,418	-177,192
2003 Q 3	1,665,660	18,242
2003 Q 4	1,825,753	160,093
2004 Q 1	1,775,407	-50,346
2004 Q 2	1,879,688	104,281
2004 Q 3	1,892,090	12,402
2004 Q 4	2,004,967	112,877
2005 Q 1	2,098,066	93,099

From the moment the product innovation (Aranesp) enters the market (2001 Q 2) we observe a large increase in the consumer surplus: it becomes about 10 times greater then before. Then the surplus increases at lower rates (quite the same we observe during the quarters before the innovation) or slightly decreases; this probably means that the introduction of Aranesp is the only relevant factor in determining the surplus of the

consumers. The following graph shows the total consumer surplus in each quarter (bars) and its trend over time, represented by the polynomial curve (poli).



We have also computed the expected producer surplus, i.e. the expected profit in price equilibrium, and its changes over time. Due to the assumption that costs are linear, we could determine the profit of every producer (index j) in every country (index k) during the period from the second quarter of 2000 to the first quarter of 2005:

(20) $$E(PS_{jkt}) = L_{jkt} \cdot p_{jkt} \cdot ddd_{jkt}.$$

To obtain the total surplus of the producers we just nee to sum the figures by country and products together for every time quarter:

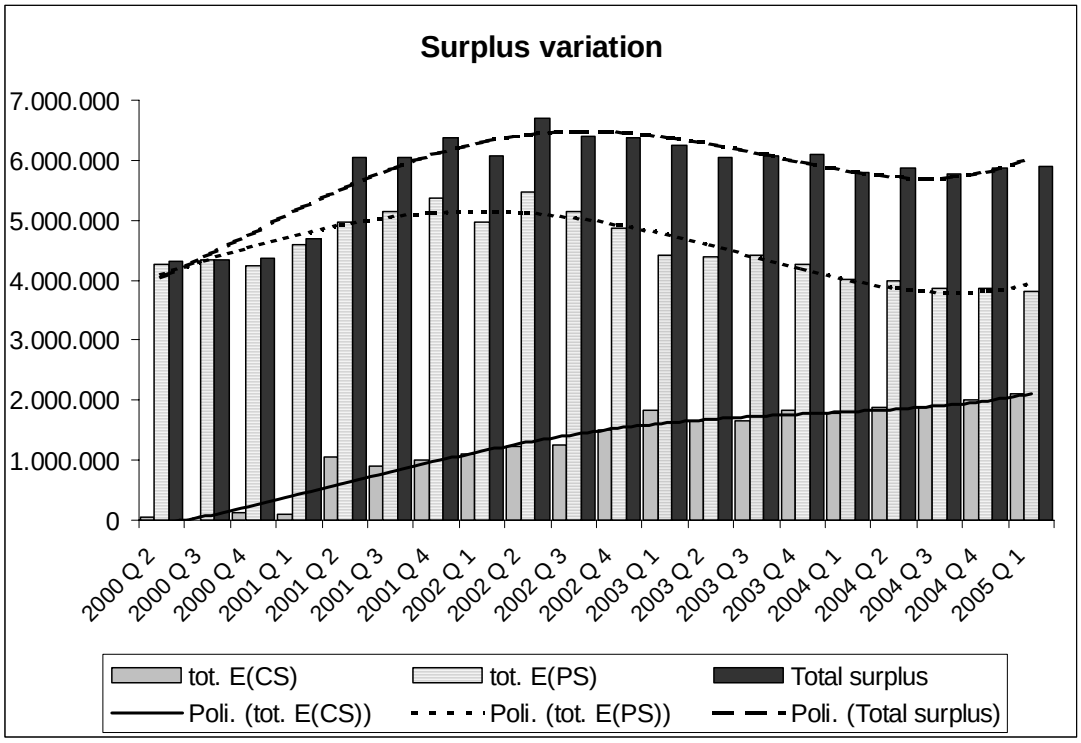
(21) $$E(PS_t) = \sum_{j=1}^{3} \sum_{k=1}^{4} E(PS_{jkt})$$

Results are summarized in the Table 8 and graph below:

Table 8. Producers surpluses and total surpluses

Q	Total E(PS)	ΔE(PS)	Total surplus (cons+prod)	Total surplus variation
2000 Q 2	4,256,591	-	4,308,571	-
2000 Q 3	4,344,780	88,189	4,344,780	36,209
2000 Q 4	4,248,672	-96,108	4,369,926	25,146
2001 Q 1	4,600,664	351,992	4,700,812	330,886
2001 Q 2	4,976,495	375,831	6,040,006	1,339,194
2001 Q 3	5,151,252	174,756	6,057,994	17,987
2001 Q 4	5,367,239	215,988	6,369,468	311,475
2002 Q 1	4,962,969	-404,270	6,061,912	-307,556
2002 Q 2	5,472,407	509,438	6,704,546	642,634
2002 Q 3	5,143,010	-329,397	6,397,347	-307,199
2002 Q 4	4,855,845	-287,165	6,373,282	-24,065
2003 Q 1	4,414,753	-441,092	6,239,363	-133,919
2003 Q 2	4,395,416	-19,338	6,042,834	-196,530
2003 Q 3	4,407,890	12,474	6,073,550	30,716
2003 Q 4	4,269,732	-138,158	6,095,485	21,935
2004 Q 1	4,013,626	-256,105	5,789,033	-306,451
2004 Q 2	3,987,988	-25,639	5,867,676	78,642
2004 Q 3	3,871,679	-116,309	5,763,769	-103,907
2004 Q 4	3,869,764	-1,915	5,874,731	110,962
2005 Q 1	3,808,817	-60,947	5,906,883	32,152

The following graph shows the variation of consumer, producer and total surplus over time, with their respective trends:



Aranesp enters the four markets in 2001 Q2 and Q3. The results show that there is a slight increase in producer surplus and the product innovation leads to the highest increase rates both in absolute and relative terms. The table shows also the sum of producer and consumer surplus and their variation over time. We observe an increase in this total surplus after the launch of Aranesp, but after some time has elapsed since the innovation we cannot see a clear trend of growth in total surplus. We can conclude that the introduction of the new product leads to considerably higher consumer welfare and brings more profits to the firms (but if we look at each firm we see that one of the incumbent looses market shares and profits, while others have gains) but the innovation does not seem to have a strong long term effect on the total surplus.

8. Conclusions

In this paper we have studied the demand and supply of erythropoietin in four Nordic countries. Our main aims have been to estimate demand for EPO and to determine the degree of competition in this Nordic market. We also have reported the impact of product innovation on welfare, e.g on consumer and producer surplus. The product innovation is the entry of Aranesp in the Nordic market.

We find a positive effect on consumer surplus of the entry of Aranesp. Some time after the introduction of Aranesp, the total surplus, expected consumer surplus plus expected producer surplus, remains more or less the same (or decreases a bit).

References

1. Amgen. Data From Study Shows Aranesp Dosed Every Other Week More Cost-Effective Than Epoetin Alfa For Treating Anemia In Chemotherapy Patients. 12-9-2002. http://www.amgen.com/media/pr.jsp?year=2002
2. Berndt,E.R., R.S.Pindyck, and P.Azoulay. 2003, Consumption Externalities and Diffusion in Pharmaceutical Markets: Antiulcer Drugs, *The Journal of Industrial Economics* LI, 243-270.
3. Berndt,E.R., A.H.B.Gottschalk, T.J.Philipson, and M.W.Strobeck. 2005, Industry Funding of the FDA: Effects of PDUFA on Approval Times and Withdrawal Rates, *Nature Reviews Drug Discovery* 4, 545-554.
4. Berry,S. 1994, Estimating Discrete Choice Model of Product Differentiation, *RAND Journal of Economics* 25, 242-262.
5. Berry, S. and Pakes, A. *The Pure Characteristics Discrete Choice Model of Differentiated Products Demand.* Working Paper, October 1, 2002.
6. Bhattacharyya, A. *Advertising in Specialized Markets: Example from the US Pharmaceutical Industry.* Working Paper, February 28, 2005.
7. Cleanthous, P. *Patient Welfare Implications of Innovation in the U.S. Antidepressant Market.* Working Paper, October 2002.
8. Cockburn,I.M. and R.M.Henderson. 2001, Scale and scope in drug development: unpacking the advantages of size in pharmaceutical research, *J.Health Econ*. 20, 1033-1057.
9. Crespi,R.S. 2005, Erythropoietin in the UK: a setback for gene patents?, *Nat.Biotechnol.* 23, 367-368.
10. Danzon, P. M., Epstein, A., and Nicholson, S. *Mergers and Acquisitions in the Pharmaceutical and Biotech Industries.* Working Paper, May 2004.
11. Danzon,P.M., S.Nicholson, and N.S.Pereira. 2005, Productivity in pharmaceutical-biotechnology R&D: the role of experience and alliances, *J.Health Econ*. 24, 317-339.

12. DiMasi,J.A., R.W.Hansen, H.G.Grabowski, and L.Lasagna. 1991, Cost of innovation in the pharmaceutical industry, *J.Health Econ*. 10, 107-142.
13. DiMasi,J.A., R.W.Hansen, and H.G.Grabowski. 2003, The price of innovation: new estimates of drug development costs, *J.Health Econ*. 22, 151-185.
14. DiMasi,J.A., H.G.Grabowski, and J.Vernon. 2004, R&D Costs and Returns by Therapeutic Category, *Drug Information Journal* 38, 211-223.
15. Dove,A. 2001, Betting on biogenerics, *Nat.Biotechnol.* 19, 117-120.
16. Edwards,M.G., F.Murray, and R.Yu. 2003, Value Creation and Sharing Among Universities, Biotechnology and Pharma, *Nat.Biotechnol.* 21, 618-624.
17. Ellickson,P., S.Stern, and M.Trajtenberg. 1999, Patient welfare and patient compliance: an empirical framework for measuring the benefits from pharmaceutical innovation, *NBER Working Paper Ser*ies #6890.
18. EMEA. 2004, Committee for Medicinal Products for Human Use: Guideline on Similar Biological Medicinal Products. http://www.emea.eu.int/pdfs/human/biosimilar/043704en.pdf
19. Grabowski, H. G. *Patents, Innovation and Access to New Pharmaceuticals*. Working Paper, July 2002.
20. Grimm,A.M., K.K.Flaharty, L.E.Hopkins, J.Mauskopf, A.Besarab, and P.H.Vlasses. 1989, Economics of epoetin therapy, *Clin.Pharm*. 8, 807-810.
21. Henderson,R.M. and I.M.Cockburn. 1996, Scale, Scope, and Spillovers: The Determinants of Research Productivity in Drug Discovery, *RAND Journal of Economics* 27, 32-59.
22. Lawrence,S. 2004, The biotech drug market, *Nat Biotechnol.* 22, 1496.
23. Malerba,F. and L.Orsenigo. 2002, Innovation and Market Structure in the Dynamics of the Pharmaceutical Industry and Biotechnology: Towards a History-Friendly Model, *Industrial and Corporate Change* 11, 667-703.
24. Pavlou,A.K. and J.M.Reichert. 2004, Recombinant protein therapeutics--success rates, market trends and values to 2010, *Nat.Biotechnol*. 22, 1513-1519.
25. Pavlou,A.K. and M.J.Belsey. 2005, The therapeutic antibodies market to 2008, *Eur.J.Pharm.Biopharm.* 59, 389-396.
26. Razzolini, T. *The Norwegian market for pharmaceuticals and the non-mandatory substitution reform of 2001: the case of enalapril.* [12/2004]. 2004. Oslo. University of Oslo, Department of Economics Memoranda.

27. Reichert,J.M. and C.Paquette. 2003, Therapeutic recombinant proteins: trends in US approvals 1982 to 2002, *Curr.Opin.Mol.Ther.* 5, 139-147.
28. Reichert,J.M. and A.K.Pavlou. 2004, Monoclonal Antibodies Market, *Nature Reviews Drug Discovery* 3, 383-384.
29. Reichert,J.M. 2004, New Biotechnology Therapeutics - Challenges for the industry, Bio in English 38-41.
30. Stern,S. and M.Trajtenberg. 1998, Empirical Implications of Physician Authority in Pharmaceutical Decisionmaking, *NBER Working Paper Series* #6851.
31. Takayama,M. and C.Watanabe. 2002, Myth of market needs and technology seeds as a source of product innovation — an analysis of pharmaceutical new product development in an anti-hypertensive product innovation, *Technovation* 22 (2002), 353-362.
32. Tirole,J., 1988, *The Theory of Industrial Organization*. (Cambridge, Mass.), The MIT Press.
33. Train,K.E., 2002, *Discrete Choice Methods with Simulation*. (Cambridge, Mass.), Cambridge University Press.
34. Trajtenberg,M., 1990, *Economic Analysis of Product Innovation.* (Cambridge, Mass.), Harvard University Press.
35. Werner,R.G. 2004, Economic aspects of commercial manufacture of biopharmaceuticals, *J.Biotechnol*. 113, 171-182.

APPENDIX – Estimates of the demand parameters with instrumental variables.

To reduce endogeneity problems we instrument the price difference variable (pricediff) of the first demand equation:

$$\ln\left(\frac{\varphi_{jt}}{\varphi_{1t}}\right) = \alpha_j + \alpha_0(p_{jt} - p_{1t}) + \alpha_1(p_{jt}\frac{A_{it}}{A_{1t}} - p_{1t}) + \tilde{\mu}_{jt}\,.$$

We computed four instrumental variables:

(1) NP_t:

the number of biotech products that are available in the Nordic pharmaceutical market at each time t: it can be considered a proxy of the impact of R&D in field of the biotechnologies for health;

(2) PMA_{jt}:

the cumulated number of post-marketing authorizations obtained by each product, they measure the impact of incremental innovations and could express some unobservable quality characteristics of the EPO products[6];

(3) PMA_t:

the cumulated number of post-marketing authorization for the whole EPO market, that is the sum of all brand authorizations in every quarter;

(4) Q_t:

quantity (expressed in thousand ddd per quarter) sold of all biotechnological drugs in the market excluding EPO products.

We have estimated the demand coefficients with all possible combinations of instrumental variables and related results are summarized in the following tables:

[6] The post-marketing authorizations are derived from the official data from EMEA, that reports every change in each drug after its commercialization. According to the importance given by the European regulation authority, to major changes we assigned a weight equal to 1, and to minor changes equal to 0.5. Data for Eprex are derived from FDA files.

Instrumented variable: (p_{jt} - p_{1t})								
Instrument(s)	NP_t		PMA_{jt}		PMA_t		Q_t	
Coefficients	Value	t stat.	Value	t stat.	Value	stat.	Value	t stat
α_0	-9.99108	-0.96	-5.2815	-2.55	-5.4824	-2.09	-5.0562	-1.69
α_1	3.3351	1.78	2.5098	6.12	2.5449	5.09	2.4703	4.45
α_j (constant)	7.05986	3.24	6.2784	8.32	6.3117	7.68	6.2411	7.67

Instrument(s)	NP_t; PMA_{jt}		NP_t; PMA_t		PMA_{jt}; PMA_t		NP_t; Q_t	
Coefficients	Value	t stat.	Value	t stat.	Value	t stat.	Value	t stat.
α_0	-4.04594	-2.90	-2.4821	-3.00	-5.2595	-2.55	-3.7529	-1.72
α_1	2.2936	8.03	2.0199	11.20	2.5059	6.15	2.2423	5.51
α_j (constant)	6.0737	10.61	5.8147	14.46	6.2748	8.35	6.0252	9.87

Instrument(s)	PMA_{jt}; Q_t		PMA_t; Q_t		PMA_{jt}; PMA_t; Q_t		NP_t; PMA_{jt}; PMA_t	
Coefficients	Value	t stat.	Value	t stat.	Value t	t stat.	Value	t stat.
α_0	-5.2813	-2.55	-5.4525	-2.09	-5.2407	-2.56	-2.7495	-3.23
α_1	2.5097	6.12	2.5397	5.12	2.5026	6.17	2.0668	11.06
α_j (constant)	6.2784	8.32	6.3067	7.72	6.2716	8.38	5.8589	13.89

Instrument(s)	NP_t; PMA_{jt};Q_t		NP_t; PMA_t; Q_t		**NP_t; PMA_{jt}; PMA_t; Q_t**	
Coefficients	Value	t stat.	Value	t stat.	**Value**	**t stat.**
α_0	-3.5939	-3.01	-2.3584	-2.99	**-2.6069**	**-3.23**
α_1	2.2145	8.90	1.9984	11.52	**2.0418**	**11.40**
α_j (constant)	5.9989	11.66	5.7942	14.76	**5.8353**	**14.26**