R&D in the Pharmaceutical Industry

A World of Small Innovations

Juan-José Ganuza[1] Gerard Llobet[2] Beatriz Domínguez[3]

[1]Universitat Pompeu Fabra

[2]CEMFI

[3]BBVA

Health Economics and the Pharmaceutical Industry – Toulouse
January 25-26, 2008

The Pharmaceutical Industry

- The pharmaceutical industry is unusual in several dimensions:
  - DEMAND:
    - A patient consumption is usually *induced* by his/her physician,
    - patients often do not pay all the cost of their medication, and
    - the incentives of the physicians and the insurer are not perfectly aligned.
  - SUPPLY:
    - Innovation is the main source of a firm's competitive advantage.
    - R&D represents around 20% of sales revenue (around 5 times the average of all manufacturing firms).
    - The value of an innovation is difficult to assess.

- According to a survey by the *National Institute for Health Care Management* (2002) in the 1989-2000 period:
  - Of the 1035 drugs approved by the FDA only 15 % were highly innovative, while 46% were minor innovations to existing compounds, and 11% showed no improvement.
  - Big improvements are becoming rare.

Type of Drug	1989-1994	1995-2000	1989-2000
Priority NMEs	17%	13%	15%
Standard NMEs	18%	22%	20%
Priority IMDs	8%	9%	8%
Standard IMDs	39%	50%	46%
Other Drugs	18 %	6%	11%

It has been argued that this trend towards small innovations might be due to the following two reasons:

1. The pressure from generic producers has induced firms to invest in minor modifications of existing compounds that are patentable and require few tests for approval.
    - In the U.S., for example, the Hatch-Waxman Act (1984) grants a patent extension of three years for INM and five for NME.
    - In some countries, dosage or compound modifications entitle firms to process patents.

   And this is the opinion of an unlikely source:

House, Episode 1-17
"Role Model"

2. Firms create variations of existing patented products which are in turn patentable. These follow-on innovations are despectively denoted as **me-too drugs**.

   - A typical example are cholesterol-lowering drugs (Statins). Started by Lovastatin, several firms introduced competing varieties such as simvastatin (Zocor), atorvastatin (Lipitor), pravastatin (pravachol), fluvastatin (Lescol) or rosuvastatin (Crestor).
   - Zantac was a follow-on of the anti-ulcer drug Tagamet. It is argued that Zantac did not outperform Tagamet, but it was successful due to clever marketing.

As Stiglitz (2006) writes,

> *Drug companies expend huge amounts of money coming up with drugs that are similar to existing drugs but are not covered by existing patents; even though these drugs might not be better than the existing ones the profits can be enormous. This may explain the seeming inefficiency of the big drug companies, which, despite huge total expenditures, have come up with relatively few drugs that are more than a minor improvements on previous drugs.*

This Paper

- This paper shows that the proliferation of these inefficiently small innovations might be associated to distortions in the patients' demand elasticity.
- These distortions might arise because the willingness to pay for the product is (for some) agents not related to the value of the product. Why?
  - Some patients may be *insured* and some other may not.
  - Some doctors may *internalize the social cost* of the prescription and others not.
  - Some doctors may *collude with pharmaceutical firms* to prescribe well-known and intensitively advertised drugs and others not.
  - Some doctors/patients may be uniformed about the real value of the innovation and they can overestimate it.
- In summary, the demand combines segments of different elasticities.

These characteristics are in line with the description of the pharmaceutical sector of Scherer(1993),

> *it is not too extreme an oversimplification to suppose that when generic substitutes exist, the world of drug buyers consists of two quite different groups – those that are price-sensitive and those who are not.*
>
> *When there is only one branded product, the pricing problem is straightforward. But once generic substitutes enter at much lower prices, the market is bifurcated, and the incumbent branded seller commonly finds it more profitable to desert the price-sensitive market than to reduce the prices quoted to price-sensitive customers.*

- As a result, firms might find profitable to focus on small innovations targeted to the non-price sensitive part of the demand.
- Hence, the excesive reward that firms obtain from small innovations reduces the incentives to invest in R&D.
- We also provide several extensions of the model:
    - We analyze the effect of different regulatory instruments.

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  - We endogeneize this lack of sensitivity as the result of the firm's marketing effort.
  - We extend the model to the case of competition in R&D.

The Ritalin Case

- Ritalin is the commercial name of Methylphenidate, patented by Ciba (now absorbed by Novartis) in 1954.
- It is used to treat children with ADHD (Attention-deficit hyperactivity disorder).
- Concerta was launched in 2000, a once-daily extended release form (as opposed to three times) of Methylphenidate.
- According to Consumer Reports, on November 2006 the monthly cost in the U.S. for a 20mg daily dosage was

Generic Methylphenidate	$ 31
Ritalin	$ 67
Concerta	$ 130

Related Literature

- Literature on Intellectual Property Rights (mainly patents) and the Return from Innovation (Scotchmer, 2004).
- Distortions in the Pharmaceutical Industry (Hellerstein, 1998).
- The effect of generic products (Frank and Salkever, 1992).

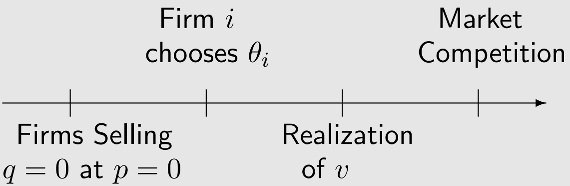
The Model

- A homogeneous (or generic) good of quality normalized to 0 is competitively produced with marginal cost 0 at zero price.
- Firm i can invest in R&D to create an improvement of size $v \in [0, 1]$.
- The improvement v is uncertain, and arises from the distribution $F(v, \theta)$, with density $f(v, \theta)$.
- Firm i can devote R&D effort θ at a cost θ.
- Assume that for $\theta' > \theta$, $F(v, \theta') < F(v, \theta)$ for all v.
  $\Longrightarrow$ Higher effort increases the expected improvement size.
- The improvement has a production marginal cost of 0.

The Demand

- A continuum of consumers (or patients) with unit demand.
- Consumers do not pay for the good, financed by an insurer.
- All consumers have the same utility $U(v) = v$ for the good.
- Consumer's demand is *induced* by their doctors.
- Two kinds of Doctors:
  - A proportion σ of doctors is **captured**. They behave according to
  $$U_C(v) = U(v) = v.$$
  - The remaining $1 - \sigma$ are **non-captured** and internalize the "social" cost of the product.
  $$U_{NC}(v) = v - p.$$
- The price is limited to be less than 1.

Timing of the Model



- Two Strategies for the improved product:
  - Target Inelastic Demand, or
  - Wider Coverage.

The First Best

- It is optimal that all consumers purchase the good, regardless of v.
- The optimal level of effort, θ^s is defined by

$$\theta^S = \arg\max_{\theta} \int_0^1 v f(v, \theta) dv - \theta.$$

The Market Equilibrium

- Firm i might maximize profits by either
  - selling to all consumers at price $p = v$, or
  - selling to only captured doctors at the maximum price, $p = 1$.

Lemma

For high quality improvements, $v \geq \sigma$ the optimal price is $p = v$ so that firm i sells to all patients. Otherwise, the optimal price is $p = 1$ and a proportion σ of patients buys the improved product.

- Profits can be written as

$$\Pi(v) = \begin{cases} 1 \times \sigma & \text{if } v < \sigma, \\ v \times 1 & \text{if } v \geq \sigma. \end{cases}$$

- The choice of effort of firm i corresponds to

$$\theta^*(\sigma) = \arg\max_{\theta} \int_0^{\sigma} \sigma f(v, \theta) dv + \int_{\sigma}^{1} v f(v, \theta) dv - \theta.$$

Proposition

The private optimal choice of effort is lower than the first best for all $\sigma > 0$. Moreover, the level of effort $\theta^*(\sigma)$ is decreasing in σ.

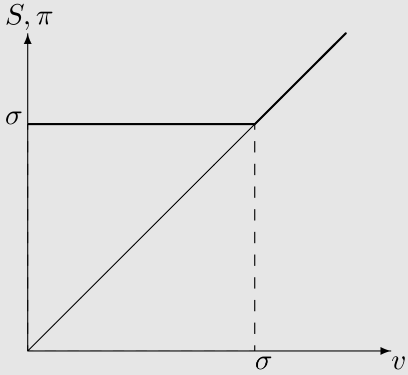


Figure: As in the following figures, for different realizations of v, the thin diagonal denotes social value S while profits corresponds to the thick line.

Interpreting the Result

- In the typical model of innovation, a monopolist obtains a share $\gamma < 1$ of the total value generated, by a fixed-size innovation, v. That is, $\pi = \gamma v$.
- If the cost of an innovation is K, some efficient innovations will not be undertaken. That is,

$$v > K > \gamma v = \pi.$$

- But when the size of innovation is endogenous, is the lack of rewards the cause of this inefficiency? Not necessarily.

- In our model, if $\sigma = 0$, $\gamma = 1$, the monopolist appropriates all the social surplus generated.
- However, when $\sigma > 0$ then $\gamma > 1$ for small innovations.
- Why do we still obtain underinvestment? The lack of sensitivity of the demand (captured doctors) provides insurance against low values of v.
- In this model, this intuition is represented by $\pi'(v) < 1$.

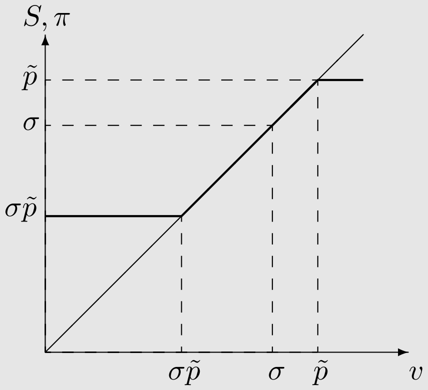
The Effect of Regulatory Instruments

Instrument	Some Countries that use them
Price Controls	Austria, Belgium, Luxembourg, Finland, France, Greece, Italy, Portugal, Spain, EU New Member States
Copayments	Germany, Finland, UK, Italy, Netherlands, Sweden, Poland
Reference Pricing	Denmark, Sweden, Germany, Netherlands

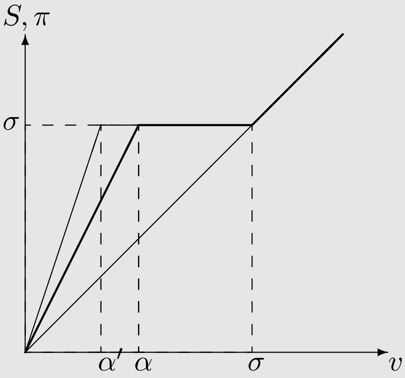
- In contrast with the conventional wisdom, instruments that reduce firm rents, to the extent that they also increase the demand elasticity, may elicit higher research effort.

In the context of our model:

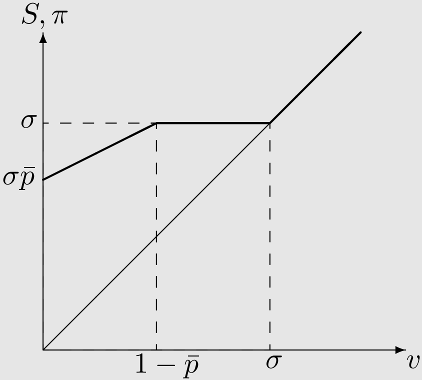
- *Price Controls:* They restrict the price that may be charged for low quality products... but also for high quality ones. The First Best cannot be achieved.

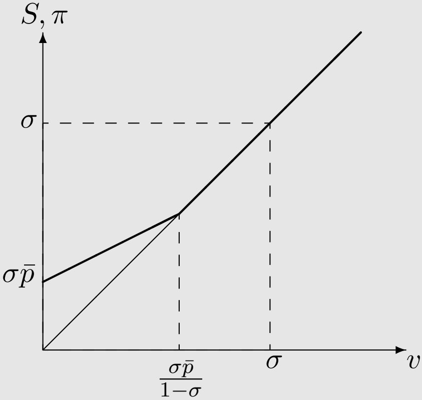


- *Copayments:* Patients need to pay a proportion α of the cost. It is less profitable to target low-quality products to captured doctors. A moderate copayment ($\alpha = \sigma$) might achieve the First Best, but θ is not monotonic in α.



- *Reference Prices:* Patients pay the part of the price that exceeds $\bar{p}$. The First Best can only be achieved without any insurance.

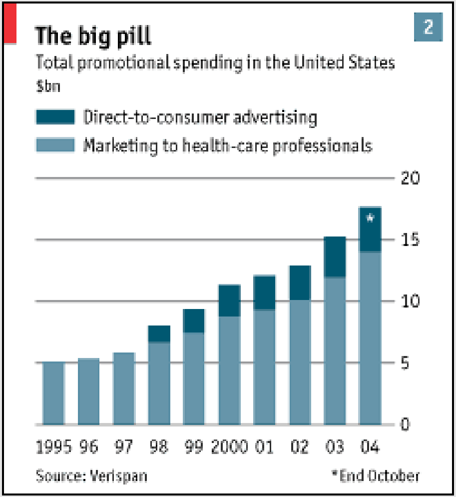




R&D and Marketing

Warning: this section is work-in-progress.

- Doctors may have their decisions *distorted* for several reasons:
  1. have different preferences,
  2. are captured **by pharmaceutical firms**,
  3. may lack information regarding v.
- The paper so fas has focussed on the first aspect
- In this section we argue that marketing may affect doctors' demand elasticity through the last two channels.

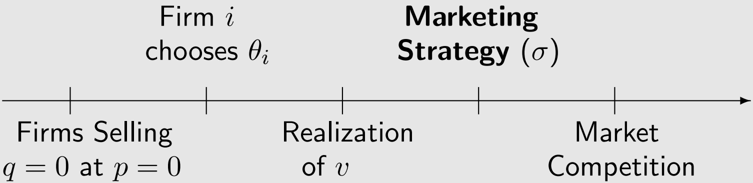

The big pill
Total promotional spending in the United States
$bn
Direct-to-consumer advertising
Marketing to health-care professionals
20
15
10
5
0
1995 96 97 98 99 2000 01 02 03 04
*
Source: Verispan
*End October
2

- Product marketing might be *informative* or *persuasive*.
- We assume all doctors are subject to marketing efforts. Some doctors receive an *informative message* and some doctors receive a *persuasive gift*.
  - We assume an informative message is free.
  - Persuading a proportion σ of doctors entails a cost $C(\sigma)$, increasing in σ.
- If a doctor is informed his utility becomes $U = v - p$.
- If a doctor receives a persuasive gift his utility becomes

$$U = v + s - p$$

where s includes estimation errors, the doctors' valuation for the gift, etc... drawn from a distribution $H(s)$ with density $h(s)$.

- The timing is as follows:



For a given v, the firm has two kinds of strategies:

1. Set $p > v$ and sell only to a proportion of persuaded doctors, with profits

$$\Pi_P(v) = \max_{p>v,\sigma} \; p\sigma(1 - H(p - v)) - C(\sigma).$$

where a finite p^* satisfies $(1 - H(p^* - v)) - ph(p^* - v) = 0$ and

$$\Pi'_P(v) = \sigma^*(v)p^*h(p^* - v) < 1$$

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where a finite p^* satisfies $(1 - H(p^* - v)) - ph(p^* - v) = 0$ and

$$\Pi'_P(v) = \sigma^*(v)p^*h(p^* - v) < 1$$

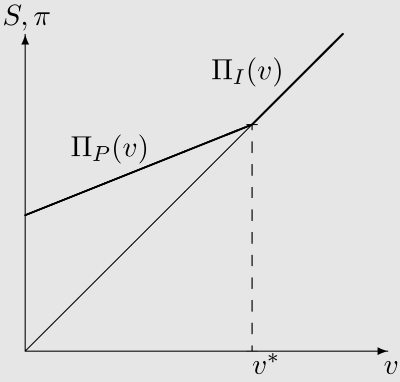
2. Set $p \leq v$ and sell to all informed, as well as a proportion of persuaded doctors,

$$\Pi_I(v) = \max_{p\leq v,\sigma} p\left[\sigma(1 - H(p - v)) + (1 - \sigma)\right] - C(\sigma).$$

Notice that this function is decreasing in σ and hence, it is optimal to inform all doctors $(\sigma^* = 0)$ and set $p^* = v$ with $\Pi_I(v) = v$.

- Hence, similar to the benchmark model, if $v^* = \Pi_P(v^*)$, then

$$\Pi(v) = \begin{cases} \Pi_P(v) & \text{if } v < v^*, \\ \Pi_I(v) & \text{if } v \geq v^*. \end{cases}$$



Proposition

If $\Pi_P(0) > 0$*, the R&D effort chosen by the firm, that solves*

$$\theta^M \in \arg\max \int_0^1 \pi_M(v) f(v,\theta) d\theta - \theta,$$

is lower than θ^S*.*

Competition

- How the results change when there is competition?
- To analyze the effects of this induced demand, we construct a setup in which the distortions associated to patent races do not arise.
- Consider two symmetric firms, 1 and 2.
- Each firm puts effort θ_i to obtain an improvement from the distribution $F(v, \theta)$.

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- Consider two symmetric firms, 1 and 2.
- Each firm puts effort θ_i to obtain an improvement from the distribution $F(v, \theta)$.
- The First Best can be easily characterized from the problem

$$\max_{\theta_1,\theta_2} \quad \int_0^1 \left\{ \int_0^{v_2} v_2 f(v_1,\theta_1) dv_1 + \int_{v_2}^1 v_1 f(v_1,\theta_1) dv_1 \right\} f(v_2,\theta_2) dv_2$$
$$-\theta_1 - \theta_2$$

- Assume that there are no increasing returns in innovation, so that both firms *should* put positive effort and $\theta_1^s = \theta_2^s = \theta^s$.

- To study the competitive solution, let's start with the case with $\sigma = 0$, so that there are no captured doctors.
- Given p_1 and p_2, doctors prefer good 1 to good 2 if

$$v_1 - p_1 \geq v_2 - p_2.$$

- In equilibrium, if, for example, $v_1 > v_2$, then $p_1 = v_1 - v_2$ and $p_2 = 0$. Profits would result in $\pi_1 = v_1 - v_2$ and $\pi_2 = 0$.
- The effort choice of firm 1 corresponds to

$$\max_{\theta_1} \int_0^1 \left\{ \int_{v_2}^1 (v_1 - v_2) f(v_1, \theta_1) dv_1 \right\} f(v_2, \theta_2) dv_2 - \theta_1.$$

Lemma

When $\sigma = 0$, in the symmetric equilibrium of the game $\theta_1^* = \theta_2^* = \theta^s$.

- When $\sigma = 1$ the firm with the highest quality will always sell, at a price of 1. Hence. the choice of effort corresponds to

$$\max_{\theta_1} \int_0^1 \int_{v_2}^1 f(v_1, \theta_1) dv_1 f(v_2, \theta_2) dv_2 - \theta_1 =$$

$$\max_{\theta_1} \int_0^1 (1 - F(v_2, \theta_1)) f(v_2, \theta_2) dv_2 - \theta_1$$

- Opposing forces mean that effort can be larger or smaller than in the first best.

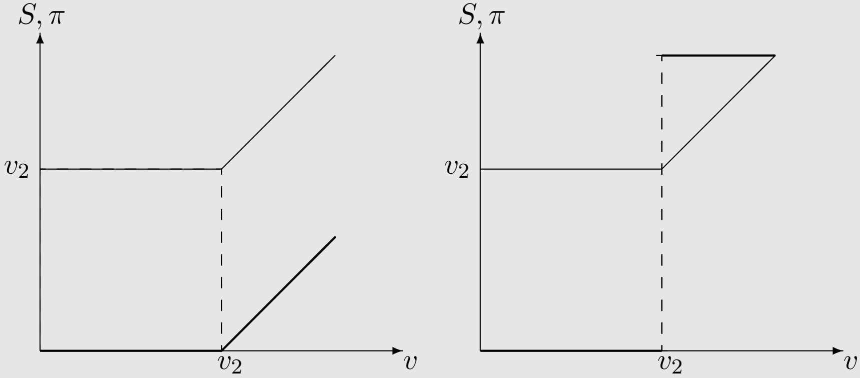

Figure: Profits of firm 1 and social welfare generated as a function of v_1 for a given value of v_2 when (i) $\sigma = 0$ and when (ii) $\sigma = 1$.

An Example

- Assume that $F(v, \theta)$ is a two-point distribution, where

$$v = \begin{cases} \underline{v} = \frac{1}{2} - x & \text{with prob } \theta_i^{\frac{1}{2}} \\ \bar{v} = \frac{1}{2} + x & \text{otherwise} \end{cases}$$

- The first best corresponds to

$$\theta_1^s = \theta_2^s = \theta^s = \left(\frac{\bar{v} - \underline{v}}{2 + \bar{v} - \underline{v}} \right)^2 = \left(\frac{x}{1 + x} \right)^2 .$$

- And when $\sigma = 1$, the maximization for firm 1 is

$$\max_{\theta_1} \; \theta_1^{\frac{1}{2}} \theta_2^{\frac{1}{2}} \frac{1}{2} + \theta_1^{\frac{1}{2}} (1 - \theta_2^{\frac{1}{2}}) + (1 - \theta_1^{\frac{1}{2}})(1 - \theta_2^{\frac{1}{2}}) \frac{1}{2} - \theta_1$$

  and in equilibrium $\theta_1^* = \theta_2^* = \frac{1}{16}$.
- Hence, there is excessive innovation if and only if $x < \frac{1}{3}$.

Concluding Remarks

- We have shown that the proliferation of inefficiently small innovations is consistent with the segmentation of the demand.
- Firms target small innovations to the more inelastic market segment. Hence, small innovations receive an excessive reward and this effect reduces the incentives to innovate.
- We interpret the segmentation of the demand as endogenous to the firm's marketing decisions.
- Contrary to the conventional wisdom, regulatory policies intented to reduced rents but that at the same time increase the demand sensitivity may enhance the incentives to innovate.
- Competition has in general an ambiguous effect. However, for risky projects underinvestment is likely to be the outcome.

Is there Evidence of this Behavior?

- The paper predicts higher prices and smaller innovations in markets in which the inelastic segments of the demand are more prevalent.
- Duggan and Scott-Morton (2006) provides supporting evidence.
- Using data from the top 200 prescription drugs in the U.S. for 1997 and 2002, it studies the effect that the Medicaid market share – which covers around 50 million people, and includes the cost of prescriptions – had on the final price of the product.
- The results show that
  - Drugs that apply to diseases that are more prevalent in patients covered by Medicaid have higher prices.
  - Regulation generates distortions in the product development decisions. The initial price that Medicaid pays is based on the average price of this product in the market but, over time, the price increases only according to inflation. $\longrightarrow$ Firms selling successful products release minor variations (for example, changes in dosage) which are considered new drugs to increase the price to Medicaid.

Future Research

- Embedding the features of the present model in a dynamic framework we can show that investment in R&D might decrease while at the same time marketing expenditures may raise.
- This behavior seems consistent with stylized facts regarding the recent evolution of these two variables.
- The rationale is as follows:
  1. Between the expiration of the patent, and the arrival of a new product, incumbent firms and generic producers, compete with an homogenous product.
  2. Persuasive marketing is a profitable short-run strategy in such a case.
  3. To the extent that present expenditures in persuasive marketing increase the futures effectiveness of such an strategy, firms might opt to reduce future investment (equivalent to a change from H to H').