

R&D Productivity, Spillovers and Effective Patent Life

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Abstract

We develop and test a model to investigate the effect of increasing R&D complexity on the effective patent life and incentives to innovate. Our model predicts the erosion of patent life and shrinking of product lifetimes in the presence of parallel R&D with spillovers and correlated R&D market portfolios. The model is tested in the context of the worldwide pharmaceutical industry. We analyze the dynamics of the timing from patent filing to market launch, the period of market exclusivity from product launch to the entry of a new in-patent product, and sales erosion from between-patent competition by the later in-patent products within the same market. Our results show that the effective patent term has declined three months every year since the beginning of the Nineties. In addition, substantial sales erosion well before patent expiry characterizes the pharmaceutical industry, along with increased competition by generic producers after patent expiry.

Keywords: Patent value, Innovation, R&D competition.

JEL Classification: D23; D83; O34; O31; L13.

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1 Introduction & Background

Research productivity – as typically measured by the patent-R&D ratio – has declined steadily across different industries and countries (Griliches 1990, Kortum 1993, Kortum 1997, Jones 1995, Lanjouw et al. 2004). By 1990 the number of patents produced per US researcher had fallen to just 55% of its 1970 level, with even steeper declines in Europe (Everson 1984, Everson 1993). Kortum (1997) found that the number of researchers has increased by nearly 5% each year since the beginning of the Fifties, while patents per researcher have been diminishing. The fall in research productivity can be ascribed to the growth of markets opportunities which increase private returns to R&D and thus reduce research productivity through stiffer competition in the research sector (Kortum 1993). However, even with constant market opportunities, innovation exhaustion and increasing complexity of R&D implies decreasing R&D productivity (Everson 1993, Kortum 1993, Segerstrom 1998). Moreover, rising costs of dealing with the patent systems could possibly led researchers to patent fewer of their inventions (Griliches 1990). Lanjouw et al. (2004) find that adjusting for a rise in patent quality accounts for some of the variation in research productivity at the sector level, with the notable exception of the pharmaceutical industry where there was especially fast growth in R&D.

As it is widely recognized, patents play a prominent role in the pharmaceutical industry. Mansfield (1986) found that, absent patent protection, 60 (65) percent of pharmaceutical inventions would not have been developed (commercialized). A study by Levin et al. (1987) estimates that patents raise imitation costs of new drugs by about 40 percent. According to survey of the US manufacturing firms in 1994, patents are the most effective tools to protect property rights and prevent rivals from copying pharmaceutical innovations (Cohen et al. 2000). Arundel and Kabla (1998) discuss similar results for Europe.

The value of pharmaceutical patents has been growing in time since the R&D costs for new drug have increased at a compound annual rate of 7.4% above general price inflation during the Eighties (DiMasi et al. 2003) and keep growing at the same pace in the following decade (Pammolli and Riccaboni 2008). A significant share of the rising R&D expenditures is related to the cost of compounds aban-

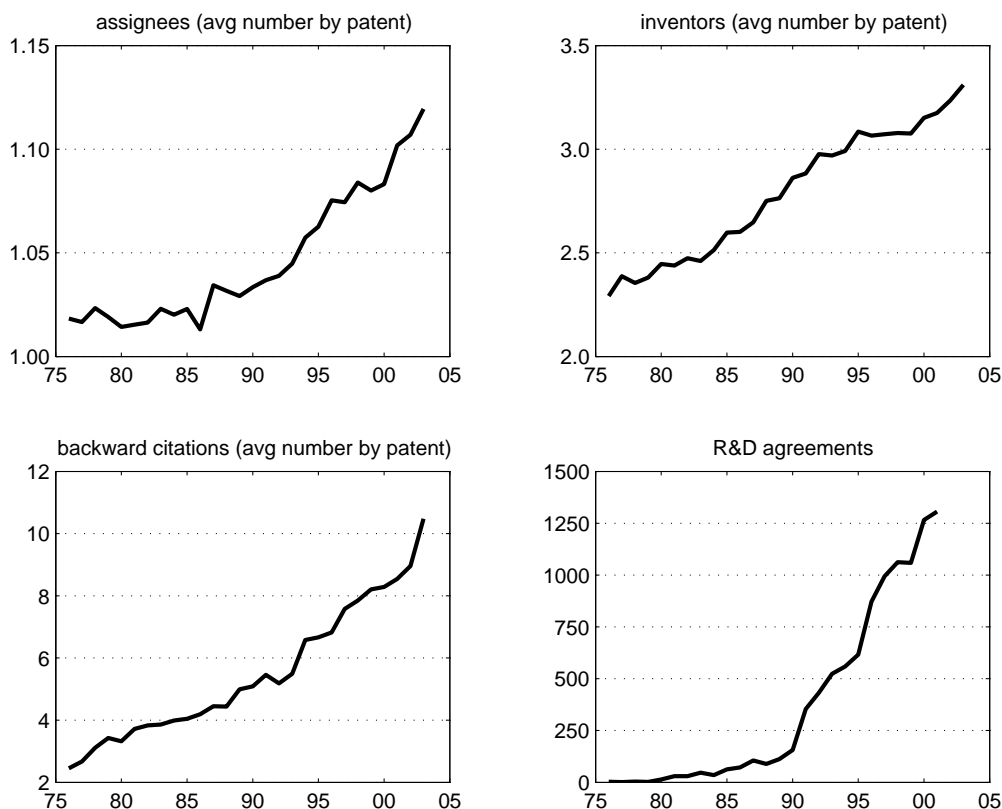


Figure 1: The increase of the average number of inventors and R&D organizations per patent and the total number of R&D licensing agreements in pharmaceuticals

done in clinical trials. Over the last thirty years, despite the exponential growth of public and private R&D expenditures, the rate at which the pharmaceutical industry has generated New Chemical Entities (NCEs) has been substantially stable. In the Nineties, the probability of success in clinical phase II (III) halved from about 50% (80%) to 25% (40%) (Mervis 2005, Pammolli and Riccaboni 2008). Among the possible causes of the productivity slowdown, the growing complexity of R&D in pharmaceuticals plays a prominent role. As shown in Figure 1, the average number of inventors, assignees and backward citations per patent, as well as the number of licensing agreements all have soared since mid-Seventies.

Higher attrition rates imply a longer gestation lag before market approval of new drugs and shrinking Effective Patent Life (EPL). In addition to that, the R&D productivity slowdown has been complemented by increasing market turnover.

The interval between the commercial introduction of a new (patented) product and the time when entry by later competitors begin has been shrinking (Bayus 1998). Agarwal and Gort (2001) find that the average time-span has declined from almost 33 years at the end of XIX century down to 3.4 years in 1967-86. According to DiMasi and Paquette (2004), the period of marketing exclusivity of a breakthrough drug in a new class has fallen from 10.2 years in the Seventies to 1.2 years in the late Nineties. Notably, the vast majority of follow-on drugs were in clinical trials prior to the approval of the first-in-class compound. In such an environment of parallel R&D where future innovators are a competitive threat the statutory life of a patent may be irrelevant. The EPL as measured by the expected time until a patented product is replaced in the market is considerably shorter than statutory life. Mansfield (1984) reports that 60% of patents are effectively terminated within 4 years. Accordingly, Levin et al. (1987) show that almost all patents are duplicated in 5 years. Hutt (1982) reviews the main studies concerning the pharmaceutical industry, all of which report a sharp decline in EPL from 1966 to 1981. The EPL of the NCE drugs approved by FDA in 1980 and 1981 was about 7 years, far below than the nominal patent life. More recently, Andersson and Hertzman (1993) show a sharp decrease of EPL in Sweden from 12.3 years in 1965 to 8.3 years in 1988, despite the extension in the nominal patent term due to Sweden's entry into the European Patent Convention. Using European and US data, Bottazzi et al. (2001) find that after 7 years from launch the sales of a patented drug converge toward the average sales of the therapeutical submarkets it belongs to. In a different research setting, working on patent renewal data in Germany, Lanjouw et al. (2004) show that more than 50% of the patents are abandoned in ten years. Thus we can conclude that EPL depends on both R&D attrition rates and follow-on patented product competition.

Several scholars have addressed optimal patent breadth in the context of one-time innovation, where broader patents permit a shorter patent life (Klemperer 1990, Gallini 1992, Denicolo 1996, O'Donoghue et al. 1998). Broader patents increase static inefficiencies, but with a shorter life the inefficiencies terminate sooner. In quality-ladder models new products outpace previous ones with temporary monopoly power, while within patented product differentiation and limited patent breadth we observe between-patent competition. Coherently with this view,

Lichtenberg and Philipson (2002) maintain that the innovator's returns in the US pharmaceutical industry are not only eroded at patent expiry as a result of generic competition (within-patent competition), but also during the patent life by the introduction of similar products under different patents (between-patent competition). The authors show that the innovator's returns erosion from between-patent competition appears to be at least as large as from within-patent competitors.

Against this background, in this paper we aim at analyzing the effect on the market value of patents of increasing R&D complexity and parallel R&D in the context of the pharmaceutical industry. The market value of inventions is decomposed into the EPL and the sales turnover due to follow on products before and after patent expiry.

In Section II we outline a simplified model of the relationship between R&D complexity, knowledge spillovers and EPL. Section III describes the data and the indicators used. In Section IV we explore how the determinants of the market value of pharmaceutical inventions in the last fifteen years. The final Section concludes.

2 The basic model

In this section we analyze market portfolios of R&D projects that would emerge under competition among rival research units (Dasgupta and Maskin 1987) in a domain characterized by a decline in the rate at which firms launch innovative (patented) products due to increasing R&D complexity. We investigate the joint effect of the slowdown of R&D productivity, also due to more stringent requirements of regulatory authorities for market approval, and accelerated product turnover upon the effective patent life (EPL) of innovative products.

As in Cabral (1993), we assume that the process of getting a new product into the market consists essentially of two stages: first, the R&D race to discover and patent a new product candidate and second, to pass through a testing phase – such as clinical trials for pharmaceutical products – and get it approved for marketing. Then, patented products that successfully pass the trials compete in the final market.

In the first stage firms choose a research trajectory and define the features of the candidate product thus defining the degree of correlation among the success

probabilities of R&D projects. At the end of the R&D race successful firms patent their product candidates and decide if to move it into the trial phase. The duration of the trial phase is purely stochastic with a given instantaneous probability of success. If research projects follow different research trajectories the correlation of R&D market portfolios is nil. In this case even with perfect patent protection there could be several companies holding different “complementary ” patented products competing in the final market. By reducing the patent breadth products can share some features. Thus more firms can share the same research trajectory by partially differentiating product characteristics, that is to say they can develop analogous products. We index by β the degree of dissemination of technological knowledge allowed by the patent (i.e. knowledge spillovers). Thus $(1 - \beta)$ with $(0 \leq \beta \leq 1)$ is a measure of patent breadth (Denicolo 1996). When $\beta = 0$ there is maximum protection against spillovers and firms can only take different independent R&D trajectories. If $\beta > 0$ firms can share the same trajectory provided that their candidate products are sufficiently differentiated.

We assume there are $k(t)$ mutually exclusive research trajectories to be investigated at time t and the probabilities of success along different trajectories are independent. In order to be authorized for commercialization a product must successfully pass through the trial phase. Each firm spends a fixed (sunk) set up cost R for each R&D race and get a patent plus an R&D cost $c > 0$ per unit of time in clinical trials. All firms in the industry share the same R&D technology. Thus, without loss of generality, we set $R = 0$ and assume that the patent is issued at the beginning of the trial phase and last T periods. In the trial phase, every firm which hold a patent and spend c until product launch is successful in discovering the next marketed product with instantaneous probability $\lambda/k(t)$, where $k(t)$ is the number of research trajectories at time t and λ is the instantaneous probability of success along each trajectory. On the one hand, by assuming, as in Segerstrom (1998), that R&D starts off being equally difficult in all markets and that R&D difficulty grows in each industry as firms do more R&D ($\partial k(t)/\partial t > 0$) due to the proliferation of ex-ante equally plausible research hypothesis (trajectories) we obtain a result similar to the R&D exhaustion (or fishing-out) effect. On the other hand, in the context of the pharmaceutical industry a decrease of λ can substantiate more stringent regulatory requirements for product launch. Indeed, after

the 1962 Kefauver Harris Amendment to the Federal Food, Drug and Cosmetic Act, pharmaceutical firms are required to prove improved efficacy as compared to commercially available treatments.

The patent market exclusivity period is therefore of random duration: it starts with product launch and ends whenever rival firms launch a patented drug in the same market (between-patent competition) or the patent expires. We apply three different measures of the Effective Patent Life (EPL).

Absent between-patent competition, EPL is simply given by the difference between patent term and the duration of the testing phase. In such a case EPL_1 corresponds to the market life of patented products (Hutt 1982). In presence of between-patent competition, the EPL_2 is the expected time until a patented product is replaced in the market or, more precisely, the patented product interarrival time (O'Donoghue et al. 1998). Finally, since new products do not completely replace pre-existing ones as in quality-ladder models, in the following we shall consider the effect of between patent competition in terms of product market share turnover (EPL_3).

If we interpret, as usual, the social payoff V as the present value of a perpetual flow of benefits, then the expected patent value is given by

$$V = \int_0^{\infty} v e^{-rt} dt = \frac{v}{r} \quad (1)$$

where v is the expected social value of innovation per unit of time and r is the discount rate. Assuming, for the sake of simplicity that the patentee can capture the entire social surplus while the patent is valid, a patent lasting $T < \infty$ periods provides the following return

$$EPV = \int_0^T v e^{-rt} dt \equiv v(1 - e^{-rT})/r = v\tau \quad (2)$$

where τ is the normalized patent length. By assuming an exponential distribution for the patented product arrival times equation 2 becomes

$$EPV = \int_0^T v e^{-(\lambda/k+r)t} dt \quad (3)$$

where λ/k indexes the instant probability of success (product launch) of a stochas-

tic process and $L = k/\lambda$ is the corresponding expected product interarrival time.

In the following we analyze the EPV in the case of patent exclusivity, parallel R&D and market portfolios with independent and correlated R&D projects.

2.1 CASE I. Patent exclusivity regime without spillovers

We start from the “the winners take all” hypothesis which corresponds to the case in which the probability of success in the testing phase is so low as compared to the patent length that there is no chance of between-patent competition. Moreover, we consider perfect patent breadth (no spillovers: $\beta = 0$). In this case there is no overlapping patent terms and each product experience a temporarily monopoly on the final market.

A firm start the trial phase at time $t = 0$. The firm payoff s is negative in each period before product launch $s = -c$, where c is the R&D cost per unit of time in the trial phase, and positive after product launch: $s = v$. In the post launch patent exclusivity regime the firm capture the per-period benefit of the innovation (v) until patent expiry (T). Let’s assume that the instantaneous probability of success of the trial is λ/k with $k = 1$ thus the expected duration of the trial phase is exponentially distributed with mean $L = 1/\lambda$.

DEFINITION 1: The effective patent life equals the period of product market exclusivity $EPL_1 = T - L$ (Hutt 1982).

A firm will start the trial phase if the expected payoff of undertaking trials is positive:

$$v(T - L) - cL > 0 \tag{4}$$

or

$$v/c > L/(T - L) \tag{5}$$

by considering that $L = 1/\lambda$

$$v/c > \frac{L}{\lambda T - L} \tag{6}$$

since $T > L$ the ratio on the left is always positive. Moreover the patent exclusivity condition ($T < 2L$) implies $v > c$ and it is equivalent to say that $v(T - L)/n - cL <$

0 or

$$v/c < \frac{n}{\lambda T - 1} \quad (7)$$

with $n > 1$. In case of n coexisting patented products each taking the same share of total value v (or having the same probability to be first to launch and get the patent) the expected payoff is negative. This is the classic incentive failure the patent system is meant to address. In this case the patent proscribes innovation and guarantees an innovator the full net social return on R&D expenditures.

Let's now analyze the effect of a decrease in the instantaneous probability of success λ/k where $k > 1$ substantiate multiple alternative R&D trajectories. In this case equation 4 becomes

$$v/c > \frac{k}{\lambda T - k} \quad (8)$$

Thus, *ceteris paribus*, if the R&D difficulty increases in time due the proliferation of research trajectories (higher k) or increasing difficulties in the testing phase (lower λ), such as increasing regulatory requirements in clinical trials of pharmaceutical products, the expected number of launches will decrease and potentially the condition in equation 8 could be no more satisfied.

A proportional patent term extension can dynamically restore the R&D incentives, as well as an increase in v or improvements in the R&D technology (i.e. a decrease of c). Let define $\tau = 1 - e^{-(r+\lambda/k)T}$ where T is the patent life, λ/k is the instantaneous probability of success and r is a common discount rate. Analogously we define $\beta(T) = (1 - e^{rT})/r$. Thus the expected payoff is given by

$$EPV = \beta(T)v - \frac{(c+v)\tau}{r + \lambda/k} \quad (9)$$

As T goes from 0 to infinity, τ ranges from 0 to 1 and can be seen as the "normalized" expected patent length. Thus an increase in the expected length of the pre-launch R&D phase can be counterbalanced by a corresponding extension of the normalized patent length τ .

In sum, we can state the following proposition

PROPOSITION 1: An increase in the number of R&D trajectories of $k > 0$ implies a reduction of the EPL_1 of $D = \frac{(c+v)\tau}{r + \lambda/k}$ which reduces to kL in the simplified

discrete case in which $c = r = 0$ and $v = 1$. In such a case a dynamic patent term extension of $\Delta T = +kL$ can restore the EPL_1 .

2.2 CASE II. Between-patent competition without spillovers

In the case in which condition in equation 7 does not hold more than one company decide to enter the testing phase (parallel R&D) and possibly compete in the final market (between-patent competition). We still assume that the probability of success of different R&D projects are statistically independent. In other words, different firms decide to move to the testing phase along different R&D trajectories. Firms are free to enter into the testing phase and all firms have the same R&D technology (same per-period cost $c > 0$). As before the instantaneous probability of success is λ/k where $k \geq 1$ is the number of independent R&D trajectories. We start from the case $k = 1$. Let l_1 be the arrival time of the first patented product into the market and l_2 be the arrival time of the second product. If the two stochastic processes are Poisson processes with the same instantaneous probability of success λ we have

$$Pr(l_2 > l_1 + t | l_1 = 0) = e^{-\lambda t} \quad (10)$$

for $t > 0$ independently of l_1 . Similarly we can define the inter-arrival times of subsequent products $l_3, l_4, \dots, l_i, \dots, l_m$. Products arrivals are independent of each other and interarrival times have an exponential distribution with mean $L = 1/\lambda$. In the previous section we have considered the case $L < T < mL$ with $m > 1$. Now we pass to describe the case in which $T > mL$ and thus we observe overlapping patent terms and between-patent competition.

DEFINITION 2: We define $EPL_2 = l_{i+1} - l_i$ as the expected patented product interarrival time that is to say the expected time until a patented product is replaced in the market (O'Donoghue et al. 1998).

Conditional on successful innovation, the payoff depends on the number of innovations competing in the same market. For the sake of simplicity, we can assume that if m firms are simultaneously present with a patented product in a given market each get an equal share $s = v/m$ of the social payoff v (or equivalently if the patent has perfect breadth and more firms make the discovery, they have the

same probability to get the patent). If each innovation is drastic and occurs in a homogeneous good market with linear demand function $P(Q) = aQ$ by normalizing to 0 post innovation marginal costs the aggregate output will be $Q = \gamma a$ with γ ranging from 1/2 (perfect collusion) to 1 (Bertrand competition). Thus profits with m competing firms will be $s(m) = \frac{1}{m}\gamma(1 - \gamma)a^2 \leq v/m$ with $v = a^2/4$. We start by considering the upper limit $s = v/m$ (Denicolo and Franzoni 2003). Next, we can suppose that the first firm to develop a product makes great inroads into the market and thus reaps a large share of the rents from the invention also by means of rent-seeking strategies (first mover advantage). If the first product to market controls a share of the social surplus which approaches unity, we are back in “the winner takes all” scenario. In such a case we must consider a decay of the expected payoff based on the order of arrivals $v(i) = v(i - 1)q$ where $q = v(i)/v(i - 1)$ is likely to be less than unity in the case of first mover advantage but can be positive in quality-ladder dynamics when new products outpace previous ones (temporary monopoly power).

DEFINITION 3: We define $EPL_3 = EPL_1(\sum_{i=1}^m (1 - \frac{1}{i}q^{i-1}))$ where m is the number of in-patent competitors, and q is the average sales erosion due to the entry of follow-on products.

In the next section, we will estimate the empirical value of q in the pharmaceutical industry and show that as an average $q \leq 1$ even in the long-run (strong first mover advantage).

Firms will keep entering until expected profit are dissipated. The total number of firms that will enter the market, m , satisfies

$$\frac{v(T - mL)q^m}{m} - mcL = 0 \quad (11)$$

by rearranging we obtain

$$v/c = \frac{m^2L}{(T - mL)q^m} \quad (12)$$

In the case $m = 1$ this condition boils down to equation 4. The higher is the first mover advantage q the fewer firms will enter the market. The relationship between the probability of success λ/k and the number of products in the market is the following

$$\lambda/k = \frac{(v + c\frac{m}{q^m})m}{vT} \quad (13)$$

In the case of $c = 0$, $k/\lambda = kL = T/m$, an increase of k implies a proportional decrease in the expected number of product arrivals. The presence of R&D costs $c > 0$ and market power $q < 1$ implies $\partial m/\partial \lambda < 0$. However, the increase in the number of R&D trajectories k can be compensated by a proportional restoration of the patent term T . It should be notice that, contrary to the monopolistic regime, equation 11 implies that a lower probability of success induces and increase in the expected payoff of the last entrant. This is true for all entrants. Figure 2 shows the expected payoff of the first and second product into the market as a function of k with $c = r = 0$ and $q = 1$. Conditioned upon successful entry, an increase of the R&D complexity k will benefit the successful firms by selecting out potential follow on products. For the first entrant this holds up to $kL = T/2$. For higher values of k we are back to the monopolistic regime (CASE I) and a further decrease of R&D productivity exerts a negative effect on the R&D incentives to the point that a firm expected payoff turns negative and it will not invest in the trial phase.

In sum, in the case of parallel R&D and independent research projects, an increase of k will shift the expected launch date of each product but it will delay the arrival of the follow up products too. Since the EPL will increase from L to kL and the expected payoff will grow. Late comers and firms that spent too much time in the first phases of the R&D process will be selected out while conditioned upon entry product will experience a longer EPL. Thus the following proposition holds

PROPOSITION 2: Ceteris paribus, in a high λ regime an increase in the number of R&D trajectories of $k > 0$ implies an increase of the EPL_2 conditioned upon product launch.

2.3 CASE III. Between-patent competition with knowledge spillovers

We pass now to consider the case of high λ markets in which condition of equation 11 holds for $m > 1$ and parallel R&D projects can be correlated since patent

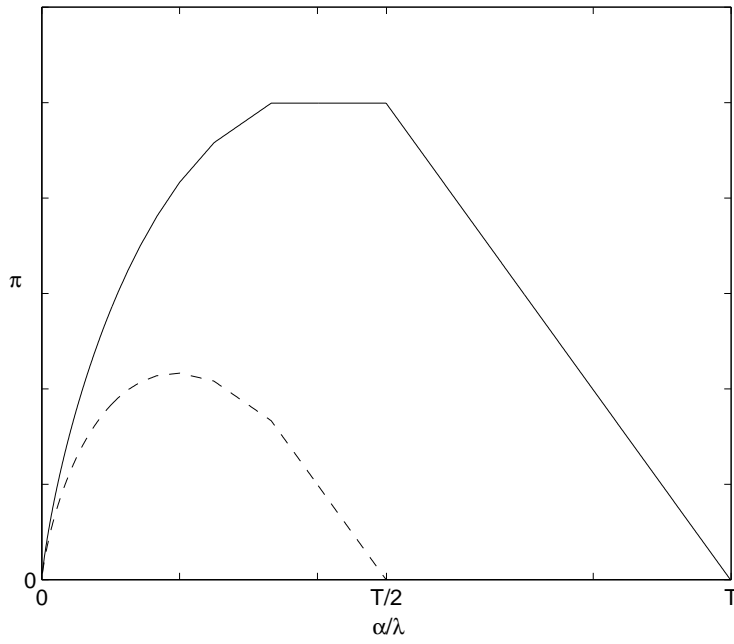


Figure 2: Expected payoff for the first (full line) and second entrant (dashed line) as a function of the expected arrival time kL with $c = r = 0$ and $q = 1$. By increasing the number of R&D trajectories k the expected payoff will increase up to the point that the product is selected out.

breadth is not perfect ($\beta > 0$). At the beginning of the R&D race firms choose the R&D trajectory and the n properties of the patented product. If patent protection is not perfect they can decide to take the same trajectory and share a fraction β of the characteristics of products. Firms who decide to share βn properties of their products with the others can either refer to them in scientific publications (common knowledge), cite other patents or license-in some of them. In the empirical session of this paper we will evaluate different ways in which product portfolios turn out to be correlated in the pharmaceutical industry. In this section we discuss the effect of knowledge spillovers on EPL. In the trial phase each of the n th properties of a product are tested. The test of each feature has an instantaneous probability of success $\lambda(n)$. Since the sum of two independent Poisson processes is still a Poisson process the expected probability of arrival of two products that share βn properties are correlated. Let's start from the case in which two firms develop a product each with one common property out of two: $P_1 = (A, B)$ and $P_2 = (A, C)$ (either A is common knowledge, or one of them cite the other patent, or firm 2 license the patent of product 1 for a different application (C) or vice versa). In this case the patent breadth index $\beta \geq .5$. Now they both move into the testing phase. In the first (second) phase feature one (two) is considered. If $A(t)$, $B(t)$ and $C(t)$ are independent Poisson processes with rates $\lambda(a)$, $\lambda(b)$ and $\lambda(c)$, then $A(t) + B(t)$ and $A(t) + C(t)$ are Poisson processes with rates $\lambda(a) + \lambda(b)$ and $\lambda(a) + \lambda(c)$, and $Cov(A(t) + B(t), A(t) + C(t)) = Var(A(t)) = \lambda(a)$ so the correlation coefficient of the two products is $\lambda(a)/sqrt((\lambda(a) + \lambda(b))(\lambda(a) + \lambda(c)))$. Now we can generalize to the case of n product characteristics of which β are in common. We assume for simplicity that each test have the same probability of success λ . The expected duration of the trial phase is given by the Erlang distribution

$$f(t; n, \lambda) = \frac{\lambda^n x^{n-1} e^{-\lambda t}}{(n-1)!} \quad (14)$$

with mean $n/\lambda = nL$ and variance n/λ^2 . In the case $n = 1$ the distribution simplifies to the exponential distribution while the Gamma distribution generalized the Erlang distribution in the case of real n . On the one hand, the increase of duration of the pre-launch R&D phase we modelled by assuming that the number of research trajectories (k) and product features and required tests (n) are increasing

in time. On the other hand, the probability of success of R&D projects are cross correlated whenever a fraction $\beta > 0$ of the features of a portfolio of R&D projects are shared. Thus, back to the two product example above, since they share $\beta = 1/2$ of their properties, the expected interarrival time between the first and the second product is $(1 - \beta)nL$ which corresponds to the conditional probability of success of the second product given that the first one have already been successful. Conditioned upon first arrival, increasing levels of β can counterbalance the growth of n and k . Figure 3 shows the effect of increasing n on β . If $n/\lambda > T/2$ only one product is on the market (CASE I) with $\beta = 0$. If $c = 0$ the two firms will be indifferent about the value of β . However, if $c > 0$ each of the firm will prefer a positive correlation among the projects: the first project will delay its expected arrival time (and cost) due to n while the follower can anticipate her arrival time by choosing $\beta > 0$. As demonstrated by Dasgupta and Maskin (1987) in the winner-takes-all scenario and two point distributions (CASE I) the R&D market portfolio consists of projects that are too highly correlated .

Cabral (1993) shows that even if we relax the winner takes all condition but the process by which a product gets chosen involves some degree of ex-ante uncertainty (i.e. the outcomes of the trial phase) and/or firm's products are substitutes and firms can avoid pure price competition by means of collusive or Cournot solutions as well as non-price competition through first mover advantages and marketing expenditures firms will select more correlated R&D projects. Bulut and Moschini (2006) show that firms that can opt for trade secrets as a IPR protection instrument select less correlated market R&D portfolios. However, this results does not apply to our model due to the presence of a purely stochastic phase after the selection of the R&D protection instrument. Clearly, if the probability of being imitated is higher than the launch probability the trade secrecy option is not viable.

In sum, the following proposition define the relationship between R&D spillovers and the EPL

PROPOSITION 3: in a high λ regime with $\beta > 0$, growing R&D complexity (higher n and/or k) and non-price between patent competition firms will select too correlated R&D projects and the EPL_3 will decrease.

In the next section we will test propositions 1-3 and measure the evolution of the effective patent life in the pharmaceutical industry over the last fifteen years.

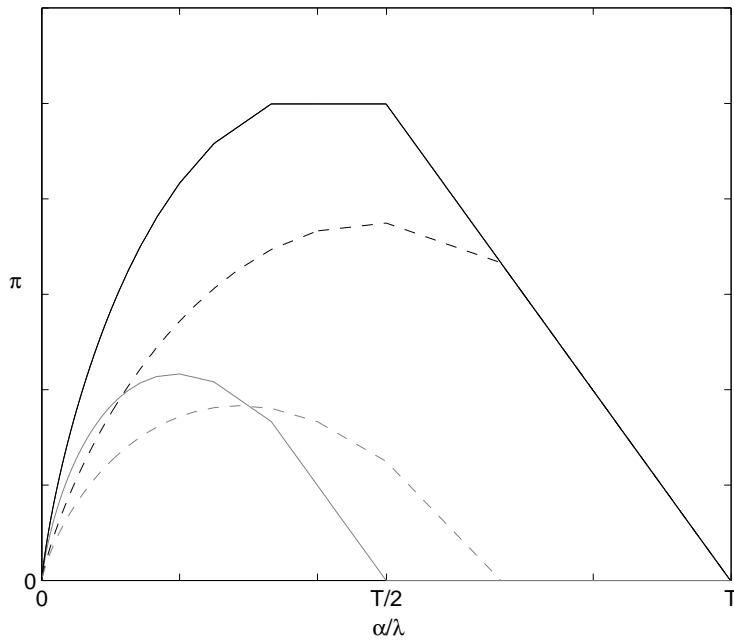


Figure 3: Expected payoff for the first and second entrants as a function of n/λ with $\beta = 0$ (full lines) and $\beta = .5$ ($c = r = 0, q = 0$). By increasing n/λ above $T/2$ only one product is left on the market with $\beta = 0$. However, by choosing a higher level of β the second product can restore its expected payoff. Since each firm does not know ex-ante the sequence of arrivals

3 The Effective Life of Pharmaceutical Patents

Empirical analysis are based on the PHID database maintained by the CERM Foundation in Rome. The PHID dataset combines data on market sales of pharmaceutical products in major international markets with information about new drug development, R&D and innovation¹.

For each product launched in the US and EU-15 countries, we are able to track patent information, the publications related to each molecule, and market sales from 1996 to 2008. Analysis focuses on patented products.

First, we consider the time from patent filing to launch of the product on the market (EPL_1). Then, we analyze the evolution of in-patent competition over the last decade taking into account the time span between the launch of the drug and the entry of a new patented competitor in the same market (EPL_2), as well as the timing from patent expiry to the entry of the first (unbranded) generic product. Overall, the analysis provides a full account of the dynamics of competition facing an innovator, i.e. between-patent competition, by the production of close substitute covered by different patents, and within-patent competition spanning from production of the same compound by generic producers (Lichtenberg and Philipson 2002). Standard methodology for survival analysis is employed², along with models that study penetration dynamics.

In order to properly assess the length of the market exclusivity period, it is essential to devise a definition of the market that correctly classify products that are close substitutes for treating the same pathology. We chose to define the market as the compounds within the same 4th digit Anatomical Therapeutic Classification (ATC4), analyzing the between patent competition of drugs belonging to the same chemical, therapeutic, and pharmacological characteristics. Even though not perfect, given the available information, this is the best approach for the identification of therapeutic substitution, and it is widely adopted by the antitrust authorities to identify relevant pharmaceutical markets worldwide.

There is an important difference between modeling time from patent filing to product launch, and modeling time from product launch to entry of a later in-

¹See Appendix A for a detailed description of the dataset and the information contained therein.

²See Appendix B for details.

patent competitor (or from patent expiry to generic competition). Our sample is built starting from in-patent products launched in the US and European countries, so the time from patent filing to product launch is observed for each compound. In this case, the main dynamics over time can be captured by a simple average of observed time lags classified according to the year of product launch. On the contrary, the time to follower/generic entry is only observed *only if* a later in-patent/generic competitor effectively enters the market during the observation period of our database. If entry is not observed before 2008, it may well occur at a later time, still to be realized. In statistical terms, the observation on time to later in-patent/generic entry is censored. In this case, dynamics over time cannot be captured by taking averages of observed time spans, because at more recent times only faster entries are observed, causing a downward bias in averages computed on observed entries. On the contrary, the censoring in the data is fully accounted for in a regression framework.

3.1 Measuring R&D complexity and spillovers

In order to test the predictions of our model, measures of research complexity and knowledge spillovers have been devised.

Various measures of spillovers have been proposed in the literature relying on the information contained in patent citations. If patent i cites patent j , this is taken as an indication of knowledge flows between j and i as well as communication between inventors in the cited and the citing patent (Jaffe et al. 2000, Jaffe and Trajtenberg 2002). Accordingly, we define a dummy variable equal to 1 when the innovator compound cites previous patents in the same market (ATC4)³. Besides patents, we also devise a measure of relatedness of two molecules on the basis of the information contained in publications. We look at co-occurrences in scientific publications, i.e. we define a dummy variable equal to 1 if there is at least one

³Regressions have also been undertaken by considering the spillover dummies built looking at follower information (both building on patents and publications). However, sample size is reduced due to the fact that only compounds actually experiencing the entry of a later patent can be considered in the analysis (the censored durations, i.e. those products not experiencing entry, cannot be included). Analysis of the dynamics in EPL does not change substantially. Therefore, we prefer to build the variables by looking at the characteristics of the innovative compound.

publication where the innovator compound is mentioned together with previous molecule(s) available within the same ATC4. On the basis of our model, we expect compounds with knowledge spillovers to experience shorter entry lags.

Furthermore, we consider the order of entry of each compound (computed on the basis of observed entry for all the time periods available), where later products can enjoy a wider pool of knowledge and wider spillovers, and therefore experience faster entry⁴.

On the other side, no standard measure is available for *complexity*. The concept is multifaceted and it can be defined taking into account different aspects of drug development. Drug development is becoming more *complex*, as inferred from the dramatic decline in productivity that is characterizing the industry.

First, regulatory requirements for clinical trials are becoming more stringent, and a wider set of information need to be provided in order to get marketing approval. As an example, over the period 1977-1980 about 38,044 pages were need for approved new drug application. The figure increased to 90,650 in 1989-1992 and can now run 100,000 pages or more⁵. Unfortunately, no data is available about this issue and a time trend is included in the regressions in order to capture the increasing regulatory requirements.

Besides increased complexity on the regulatory side, the inherent nature of drug development process is becoming more difficult. A number of important evolutionary trends have fundamentally reshaped the pharmaceutical industry in the past thirty years, strengthening the interactions between basic science and product development, with advances in physiology, pharmacology, enzymology, cell biology and later molecular biology strongly affecting the patterns of technological development (Gambardella 1995, Henderson et al. 1999). The connectedness of drug development to its scientific underpinnings has increased the range of scientific opportunities available to players in the industry, leading firms to rely on alternative approaches for targeting the same pathology, leading firms to contribute to the validation and extension of such results, therefore increasing the uncertainty surrounding the drug development process. In order to measure this dynamic, we

⁴Available empirical studies of the patterns and dynamics of research productivity in the pharmaceutical domain point to the presence of large knowledge spillovers in this industry (Henderson and Cockburn 1996, Magazzini et al. 2009).

⁵Source: Pharmaceutical Research and Manufacturers of America.

rely on a measure based on the (log) number of different biological targets that are considered by successful and unsuccessful R&D projects in our database. We assume that the broader the set of biological targets (mechanisms of action), the higher the level of uncertainty of the compounds targeting the pathology.

Moreover, the advent of biotechnology has led deep organizational shifts that have forced companies to rely on a wide network of collaborations in order to access the different resources and capabilities needed in the drug innovation process, but that are widely dispersed across a variety of different actors (Arora and Gambardella 1994, Orsenigo et al. 2001). Accordingly, Pammolli and Riccaboni (2008) show that the average number of patent assignees, as well as the average number of patent inventors is increasing over time, along with the number of R&D agreements. In order to capture these dynamics, a dummy variable identifying licensed compounds will be included in the analysis.

3.2 EPL_1 : Increasing time to marketing approval

Table 1 reports the average time (in months) from filing of the patent to product launch, grouping compounds on the basis of the launch year of the product, along with the p-values of the t-tests comparing average lags in subsequent decades. Particularly, we distinguish products launched in 1989 or before (≤ 1989), products launched between 1990 and 1999 (199Y), products launched in 2000 or later (200Y).

With few exceptions⁶, the timing from patent filing to product launch is increasing over time and differences are statistically different from zero⁷.

Dynamics over time are also assessed by means of a regression framework, where the dependent variable is the time from patent filing to product launch. In order to be consistent with the analysis undertaken in the next section, the sample is restricted to products launched over the period 1993-2007.

Increasing regulatory requirements over time are captured by a time trend, built on the basis of the launch year of the product. The uncertainty surrounding the

⁶See the cases of Finland and USA for products launched in 2000 or later with respect to the Nineties.

⁷As a complementary account, the time from product launch to patent expiration is decreasing over time, reducing the time where the firms are allowed to recoup investments in R&D.

Country	Average time to market (months)			t-test (p-value)	
	≤ 1989	199Y	200Y	$T_{8Y} = T_{9Y}$	$T_{9Y} = T_{0Y}$
Austria	118.5	147.0	161.9	<0.001	0.012
Belgium	119.8	164.9	177.2	<0.001	0.082
Denmark	117.1	142.2	161.6	<0.001	0.004
Finland	107.7	138.0	139.1	<0.001	0.851
France	130.3	152.7	189.1	<0.001	<0.001
Germany	120.5	155.1	180.2	<0.001	<0.001
Greece	77.9	120.0	158.6	<0.001	<0.001
Ireland	111.6	135.7	150.0	<0.001	0.055
Italy	90.0	134.0	172.7	<0.001	<0.001
Luxembourg	93.7	128.5	154.4	<0.001	<0.001
Netherlands	111.0	137.9	158.5	<0.001	0.002
Portugal	99.6	139.0	164.1	<0.001	0.001
Spain	114.4	150.0	161.6	<0.001	0.029
Sweden	114.5	138.6	160.4	<0.001	<0.001
UK	124.5	147.7	179.4	<0.001	<0.001
USA	141.0	158.5	167.7	0.008	0.184

Note: " ≤ 1989 " / " $8Y$ " refers to products launched before the year 1989.

"199Y" / " $9Y$ " refers to products launched over the period 1990-1999.

"200Y" / " $0Y$ " refers to products launched in the year 2000 or later.

Table 1: Average time (months) from patent filing to product commercialization, by launch year of the product; p-value of t-test for equality of the means in different periods

proper target for each therapeutic market is measured relying on the information about biological targets linked to the targeted indication (Science).

Under a different perspective, we also look at the effect of organizational complexity with the inclusion of a dummy variable identifying the products where the patent assignee is different from the company that markets the compound, i.e. the product is marketed/developed under a license with the original patentee. We expect licensed compounds to have longer development times, due to more complex organization of the development process, involving research/marketing contracts between the original innovator and the licensee(s).

Disease characteristics are also considered as control variables, as available literature shows different development times for compounds targeting different

indications (Abrantes Metz et al. 2004). We considered three aspects in absence of therapy, and devised three dummy variable. “Lethal” equal 1 if the disease is always lethal absent therapy, “Organ damage” characterizes those pathologies causing permanent organ damage (not lethal), and “Complication” identifies the diseases causing complications (not causing organ damage and not lethal). As a result, three different level of severity can be identified. Moreover chronicity is considered, where “Chronic” equals 1 if the products is directed towards chronic pathologies.

Country fixed effects are included in all specifications.

Results are reported in Table 2.

Moreover, in order to reduce unobserved heterogeneity, we exploit the classification of therapeutic substances undertaken by the US Food and Drug Administration (FDA). The FDA distinguishes standard review from priority review, on the basis of the therapeutic potential of the compound. A product that provides significant improvement compared to the existing products in the treatment, diagnosis, or prevention of a disease is granted a priority review. On the contrary, standard review is granted to drugs showing therapeutic qualities that are similar to those of products already available on the market. Empirical accounts of the factors affecting approval times consistently show that more important drugs are developed and approved more rapidly than less important drugs (Dranove and Meltzer 1994, Olson 1997)⁸. Accordingly, Model 5 only consider products that have been granted a priority review in the US. A negative coefficient is expected in the regression of the timing from patent filing to product launch due to the regulations and institutions supporting the review of those compounds.

All the proposed measures of complexity (trend, science, license) have a positive effect on the timing from patent filing to marketing, and results are robust when we restrict the sample to more important drugs (granted priority review).

The disease characteristics are overall statistically significant, where disease causes complication are linked to longer time spans, whereas the reverse is true for lethal diseases. Compounds for chronic conditions exhibit shorter time from patent to launch on the market, and this might be explained in terms of simpler

⁸Priority reviews are usually also granted the fast track program, entailing closer communication with the FDA during development, and accelerated development.

Variable	Model 1	Model 2	Model 3	Model 4	Model 5 ^(a)
Trend	0.0141*** (0.0013)	0.0132*** (0.0013)	0.0128*** (0.0013)	0.0141*** (0.0013)	0.0147*** (0.0025)
Science		0.0334*** (0.0071)	0.0297*** (0.0071)	0.0700*** (0.0083)	0.0871*** (0.0183)
License			0.1549*** (0.0106)	0.1551*** (0.0105)	0.2341*** (0.0211)
Outcome				-0.1224*** (0.0314)	-0.4011* (0.2052)
Organ damage				-0.0275 (0.0299)	-0.2940 (0.2045)
Complications				0.0659** (0.0326)	-0.2066 (0.2035)
Chronic				-0.1144*** (0.0330)	-0.0532 (0.1237)
Constant	5.028*** (0.0218)	4.891*** (0.0389)	4.833*** (0.0388)	4.809*** (0.0091)	4.368*** (0.2874)
Country FE	yes***	yes***	yes***	yes***	yes***
$\ln(\sigma)$	-0.7787*** (0.0088)	-0.7841*** (0.0090)	-0.8002*** (0.0090)	-0.8124*** (0.0091)	-0.6979*** (0.0154)
κ	0.6238*** (0.0222)	0.6258*** (0.0226)	0.6343*** (0.0226)	0.6568*** (0.0232)	0.5548*** (0.0402)
Log lik	-5396.00	-5137.87	-5032.18	-4976.74	-1873.61
N	7,660	7,345	7,345	7,345	2,427

^(a) Only priority reviews included in the sample

Standard errors in parenthesis.

*** statistically significant at 1% level; ** at 5%; * at 10%

Table 2: Survival analysis: time from patent filing to product launch; Gamma hazard function

access to patient population required for drug assessment.

The lengthening of the time from patent filing to product launch is the main component of the characterized dynamics in EPL. From the Nineties, the drug development process has increased, on average, about 22 months. Different dynamics characterize the European countries and the US, the latter experiencing a lengthening far below the average increase in research time of the European countries (average increase for the US is 9.2 months versus an average of 22.5 for EU-15 countries). The US result is consistent with previous empirical account of the timing of clinical development and approval in the US show that FDA reforms aimed at speeding the review process have been effective (Carpenter et al. 2003, Keyhani et al. 2006). We are not aware of similar studies undertaken on European data.

The lengthening of the research process is driven by different concurrent effects: more stringent regulatory requirements on the authority side, the advent of biotechnology and the shift in organizational set up of the drug development process, along with the increasing complexity inherent in drug discovery.

3.3 EPL_2 : Market exclusivity & spillovers

When turning to the analysis of the time lag from the launch of an in-patent product to subsequent in-patent launch within the same market, we have to take into account the fact that time lags are censored, as in more recent times only faster entry are observed. Therefore computing the average time lag at different time frames would provide a misleading picture for more recent times, where for younger products shorter average time lag to follower entry are computed as later entry will be observed at future times. A regression framework (survival analysis) allows us to fully address this issue.

We model the factors affecting the time lag (in months) between the launch of each products over the period 1993-2007 and the entry of the next in-patent within the same market as defined by the ATC4 classification, i.e. the “market exclusivity” time⁹.

⁹In the paper, we take into account the length between pairs of subsequent launches in the same ATC4, referring to the innovator as the first product in the pair and follower to the second one entering the market. The first product needs not to be the first compound launched in the ATC4, rather it could have been considered “follower” in the previous analyzed pair.

Time span	% still under market exclusivity
1 year	77.75
4 years	47.27
8 years	32.91
10 years	28.81

Table 3: Survival function estimates (Kaplan-Meier): % still under market exclusivity at selected time span from innovator launch

The changes in the average (log) time to follower entry are modeled as parametric shift captured by a time trend included in x_i (where the time trend is defined on the basis of year of product launch). Products launched over the period 1993-2007 are taken into account¹⁰.

First, Table 3 presents the Kaplan-Meier estimates of the share of innovators enjoying market exclusivity after selected years from launch. Coherently with Mansfield (1984), about 50% of patents experience competition by a substitute products within 4 years. The share reduces to 28.81% if we consider time span of 10 years from innovator launch.

Kaplan-Meier estimates by groups of products defined on the basis of the launch year reveal that time to market exclusivity is longer for younger products¹¹. As increasing complexity is delaying the entry of products, also the entry of the follower is expected to occur at a later point in time, increasing the market exclusivity time.

Our interest is in understanding how knowledge spillovers can shape the dynamics of market exclusivity. As a first approximation, we look at the dynamics of entry that characterize products with different order of entry. As discussed in Section 3.1, later products can enjoy a wider pool of knowledge and wider spillovers, and therefore we expect them to experience faster entry. Indeed, the pharmaceutical industry has been largely characterized as one with large knowledge spillovers (Henderson and Cockburn 1996, Magazzini et al. 2009). The intuition is confirmed by observed pattern of time lengths to subsequent entry, whose smoothed

¹⁰The choice is driven by the availability of sales data.

¹¹Average median time to the follower entry is about 4 years, therefore products launched after 2005 are not reported in the graph.

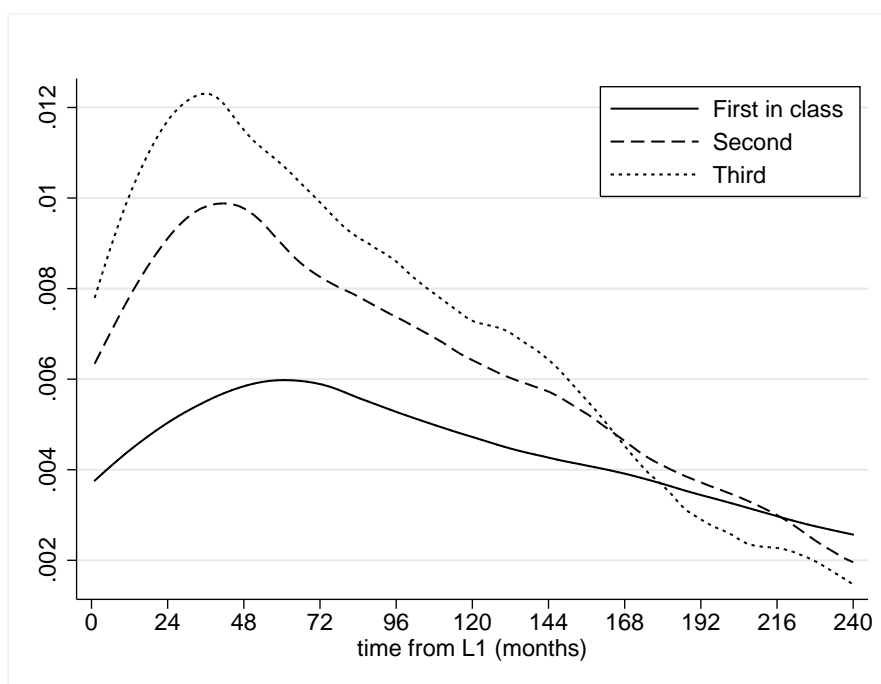


Figure 4: Smoothed hazard estimates (Kaplan-Meier), by order of entry

estimated hazard (Kaplan Meier estimates) is reported in Figure 4.

When a product is the first to enter the market (“First in class”), the hazard of entry of a later in-patent competitor is lower at earlier times from launch with respect to the second and third product in the class. The hazard of follower entry at earlier time is increasing as the order of entry increases.

In order to dig further into this issue, a regression model is considered that takes into account the (log) time between market entry and the launch of the next in-patent competitor in the same market (ATC4).

The main variables of interest are the ones capturing knowledge spillovers.

Market and disease characteristics are included in the regressions as controls. Particularly, we consider the market concentration at the time the innovator compound is launched (as defined by the Herfindahl index of concentration at the ATC4 level), as well as market size (measured by the logarithm of sales value), and the market share of the innovative firm within the same ATC4 before launch of the new product (Experience). As we expect concentrated markets to attract

lower entry, we expect market concentration to have a positive impact on the market exclusivity time. On the contrary, market size is expected to have a negative impact on market exclusivity, as larger markets attract higher entry. Pre-launch market share of the innovator is included to take into account the possibility of a deterrent effect, where the fear of costly litigations leads to distortions in the pattern of innovative investments. Available evidence shows that this is indeed the case for smaller firms¹². Analogously, the share of self-citations to the innovator patent is considered as a proxy for appropriability of the research trajectory underlying the development of the product (up to the time of product launch), employed in the literature as a measure of the cumulative nature of the innovation and the “increasing returns” property of knowledge accumulation, in particular within a narrow field or technology trajectory. The higher the share of self citations a patent receives, the stronger the competitive position of the firm/institution in that particular technology, making it able to capture a higher share of the knowledge spillovers created by previous research (Hall et al. 2000). Therefore, slower entry by competitors is expected, i.e. the expected sign of this variable is positive.

As far as disease characteristics are concerned, we include the dummy variables aimed at capturing the severity of the disease.

Country dummies are included in all specifications, even though when market controls are introduced in the regressions, they are no longer statistically significant. When the time trend (built on the basis of the launch year of the innovator compound) is not considered in the analysis, time dummies are included in the regressions (still, built on the basis of the launch year of the innovator compound).

Table 4 reports the estimated coefficients, and Figure ?? provides a graphical inspection of how Model 1 and Model 7 fit the data.

When included one at a time, the variables related to the spillover effects are all negative and statistically significant, where products with larger spillovers experience faster entry (Model 1-3). The effect of the measure of spillovers built on patents is weaker, and loses statistical significance when the spillover variables

¹²An empirical account of the patenting behavior of the biotechnology firms shows that biotechnology firms with high litigation costs are less likely to patent both in subclasses with many previous awards by rival biotechnology firms, and in subclasses where firms with low litigation costs have previously patented, rendering niche markets with low levels of current research an attractive alternative for biotechnology firms (Lerner 1995).

Variable	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6 ^(a)	Model 7
SP(patent)	-.1767*** (.0554)			.0146 (.0558)	.0302 (.0565)	.0373 (.0684)	.0105 (.0666)
SP(publ)		-.5590*** (.0420)		-.3929*** (.0472)	-.3764*** (.0490)	-.3816*** (.0616)	-.3482*** (.0602)
Order of entry			-.0720*** (.0055)	-.0488*** (.0062)	-.0507*** (.0063)	-.0487*** (.0077)	-.0556*** (.0075)
Trend					.0078 (.0053)	.0200** (.0082)	.0253*** (.0081)
Science					-.0736** (.0299)	-.0202 (.0367)	.2151*** (.0420)
License					.2409*** (.0420)	.3128*** (.0508)	.3568*** (.0498)
Concentration						.3060* (.1661)	.2539 (.1630)
Size (log)						-.0189** (.0096)	-.0122 (.0095)
Experience						.2994 (.2645)	.1353 (.2587)
Self-cits.						.1130 (.0811)	.1420* (.0793)
Lethal							-.3280** (.1422)
Org.Damage							.3771*** (.1356)
Complicat.							.5547*** (.1508)
Chronic							-1.092*** (.1776)
Constant	3.599*** (.1261)	3.920*** (.1280)	4.010*** (.1295)	4.108*** (.1299)	4.323*** (.1586)	4.199*** (.2132)	3.977*** (.2592)
Country FE	yes***	yes***	yes*	yes**	yes***	yes	yes
Launch Y. FE	yes***	yes***	yes***	yes***	no	no	no
$\ln(\sigma)$.5392*** (.0136)	.5215*** (.0137)	.5186*** (.0140)	.5120*** (.0140)	.5127*** (.0146)	.5193*** (.0137)	.4930*** (.0199)
κ	-.1695*** (.0553)	-.1330** (.0539)	-.1068*** (.0538)	-.0995*** (.0534)	-.0573 (.0549)	.0000 -	.0580 (.0650)
Log-lik	-11475.6	-11392.7	-11396.4	-11361.5	-10949.4	-7716.7	-7623.4
AIC	23017.1	22851.4	22858.9	22792.9	21946.8	15467.8	15285.3
N	7790	7790	7790	7790	7470	5551	5551

Note: standard errors in parenthesis.

*** statistically significant at 1% level; ** at 5%; * at 10%

^(a) lognormal hazard function employed, due to convergence problems with the Gamma specification.

Table 4: Survival analysis: time from innovator launch to follower entry; Gamma hazard function

are all included in the regression (Model 4). On the contrary, the measure of spillover built on publications and the order of entry are negative in all the model specifications.

When the variables capturing complexity are included in the regressions, two contrasting effects emerge. On the one side, the time trend (a proxy for increasing regulatory requirements over time) and the dummy license (as a proxy for organizational complexity) are positive and statistically significant. On the other side, complexity on the research side exerts a negative impact on the time from market launch to competitor entry. This pattern can be explained by taking into account the effect of Science on the drug development process. For more complex pathology, we expect a higher reliance of the drug discovery and development process on the advances in the realm of scientific knowledge. The convergence at the level of scientific explanation leads to a proliferation of a priori hypothesis on plausible research trajectories, and parallel R&D development (Orsenigo et al. 2001), also enhancing the correlation between firms' portfolio of R&D projects and speeding up the process of competitive entry. However, statistical significance vanishes when controls at the level of pathology are included in the regression (Model 7).

The dummy variables describing market characteristics are jointly significant, and it is interesting to note that products targeting diseases causing organ damage or complications (not always lethal) experience slower entry, whereas the reverse is true for compounds targeted to chronic diseases. Results about chronic diseases and diseases causing complications are coherent with results in Table 2.

Overall, the time span from compound launch to the entry of subsequent competitor is non-decreasing over time. The spillover variables point to a significant effect in the pharmaceutical industry, leading to a shrinkage of the market exclusivity times. This is consistent with the previous account of the characteristics of R&D competition in the pharmaceutical domain, that have highlighted the presence of significant knowledge spillovers.

3.4 Between-patent competition

Finally, we look at the intensity of between-patent competition starting from the time when the following in-patent competitors enters the market. The analysis

relies on a simple model of technological substitution, where penetration of the new technology is expressed as a (non-decreasing) function of time. These models have been largely employed for forecasting purposes, rather we are interested in understanding the rate at which the follower product steals market shares to the previous innovator, and whether this pattern has changed over time.

We adopt the original framework developed by Fisher and Pry in the early Seventies (Fisher and Pry 1971), where we let f_{1t} be the market share of innovator at the time t and f_{2t} be the market share of competing (younger) technology¹³. We set to 0 the time when the period of market exclusivity for the innovator product ends with the entry of the next in-patent compounds (as the two compounds belong to the same market, it is assumed that they compete for the treatment of the same pathology, i.e. they are close substitutes). As quarterly sales data are available time is measured in quarters from follower launch. Penetration is measured as a function of the ratio f_{2t}/f_{1t} . Both sales values and quantities are considered. In addition, the dynamics that characterize the ratio of prices p_{2t}/p_{1t} are also considered, where p_{jt} represents the price of product j ($j = 1, 2$).

As a preliminary descriptive account of the main dynamics characterizing between-patent competition (in terms of sales and pricing strategy), Figure 5 represents the median values of the sales (value and quantity) and price ratios for each product in our database, along with the 40th and 60th percentiles.

After about twenty quarters (five years) from the launch of the competing product ($j = 2$), median ratio between sales market share of follower and of the older innovator is about 0.7 when we look at sales values and 0.6 when we look at sales quantity. In our model we considered the upper bound of equal market shares for the old innovative compound and the new one; in most cases, the younger innovation does not reach the sales value of the original innovator. This is consistent with evidence of brand loyalty within the pharmaceutical domain (Scherer and Ross 1990, Schmalensee 1982).

Median values of the ratio of prices show that follower price is higher than the

¹³As sales and price figures are only available from July 1996, the sample is further reduced and only takes into account products launched over the time period covered by the sales data. Moreover, only products where the entry of a substitute in-patent compounds is actually observed can be considered in the analysis. Furthermore, in order to avoid spurious results, the regression (15) is only run if at least 10 observations (10 quarters after entry) are available.

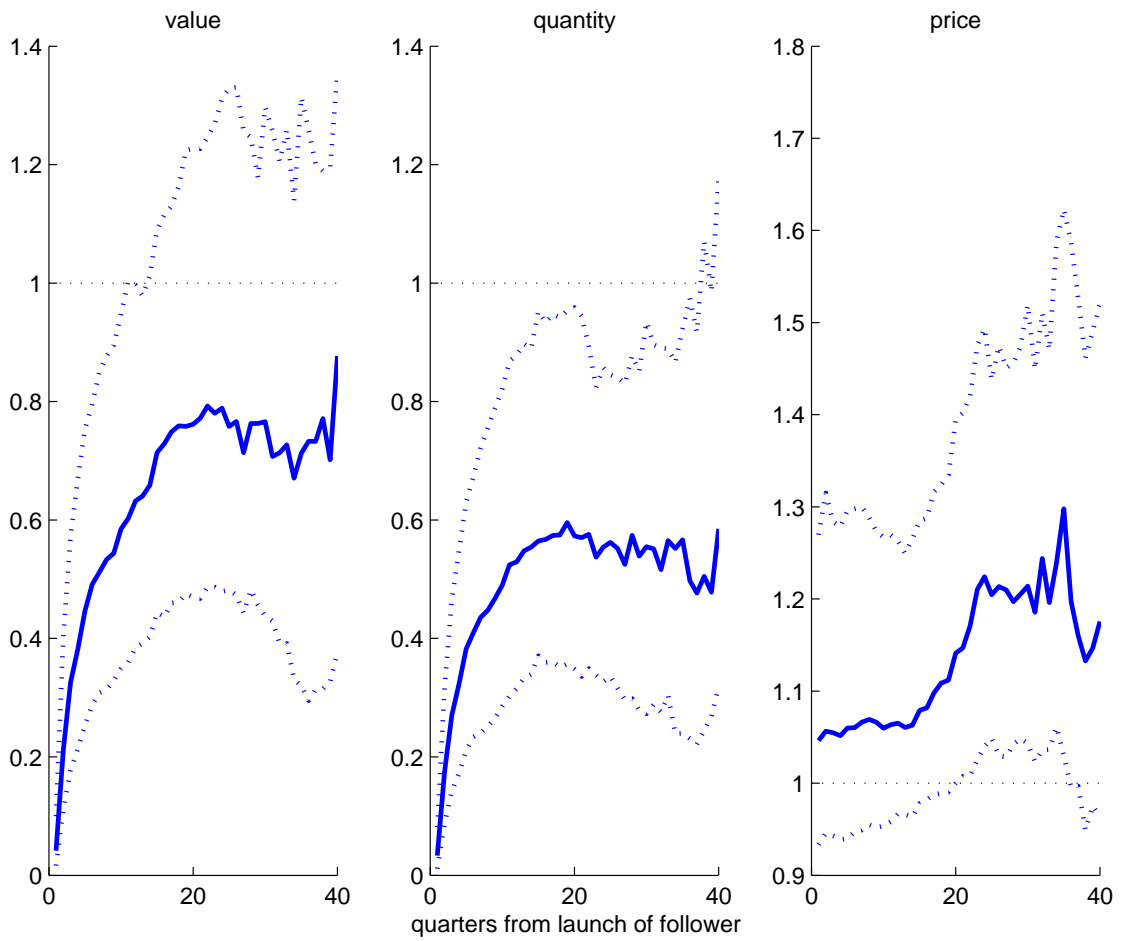


Figure 5: Sales (value) of follower / sales of first innovator

price charged by the innovator, also explaining the lower penetration in the case quantities are considered. The result is consistent with the model by Perloff et al. (1996), where the price of follower product can be above the price under market exclusivity in a wide range of cases (both under collusive behavior and Bertrand competition).

In order to dig further into the drivers of follower penetration, we employed the original formulation in (Fisher and Pry 1971) and considered the following regression for each innovator-follower in our database (both in values and quantity):

$$\ln(f_{i2t}/f_{i1t}) = \alpha_i + \beta_i t + u_t \quad (15)$$

For each product, we consider the value of β_i , i.e. the product specific erosion due to follower entry. The higher the value of the estimated β_i , the faster the erosion of sales due to follower entry. In order to check the appropriateness of the linear specification, a Ramsey test (RESET) has been carried over (with a quadratic form holding under the alternative hypothesis). The linearity of the model cannot be rejected¹⁴ in about 50% of cases. Finally, average values of the estimated β_i have been considered, grouping the products according to the launch year of the innovator/“first” compound (see Table 5).

No significant dynamics emerge in the analysis of penetration of follower compound over time. Estimated β_i s are rather constant when looking at the dynamics characterizing average and median values. The pattern is confirmed by the test comparing the average values of the estimated β_i , that is only marginally significant (p-value > 0.01) when comparing the products (innovator) launched over the years 1998-2002 to 2003-2008. No difference emerges when comparing the median values.

On the contrary, the median value of the ratio of price is lower in more recent years, where follower prices are equal to the price of the innovator compound, whereas over the period 1993-2002, follower entry was 5% higher with respect to innovator price.

¹⁴Statistical significance set at the 1% level.

Launch year of innovator	N	All compounds		Restricted sample	
		Average estimated β_i	Median estimated β_i	Average estimated β_i	Median estimated β_i
SALES VALUE					
1993-1997	752	0.0584	0.0565	0.0421	0.0405
1998-2002	738	0.0698	0.0609	0.0555	0.0478
2003+	168	0.0892	0.0510	0.0905	0.0451
QUANTITY					
1993-1997	752	0.0590	0.0553	0.0429	0.0380
1998-2002	738	0.0694	0.0611	0.0563	0.0463
2003+	168	0.0905	0.0551	0.0992	0.0613
MEDIAN PRICE RATIO, 1st YEAR					
1993-1997	1117	1.0469			
1998-2002	1264	1.0402			
2003+	600	0.9952			

Table 5: Average and median value of estimated β_i , over launch year of innovator/“first” compound

3.5 Patent life erosion over the last 15 years

On the basis of our model and the results reported in the previous sections¹⁵, we compute an estimate of the average number of months in the exclusivity stage lost as an effect of the reduction in EPL for selected countries.

Results are summarized in Table 6, where we separately consider the two definitions previously employed in the literature (EPL_1 : months from patent filing to market launch, and EPL_2 : months from market launch to the entry of the next in-patent competitor), along with our definition (EPL_3) that also takes into account the dynamics in sales value following the entry of the next in-patent competitor.

On the one side, EPL_1 assumes that full market exclusivity is enjoyed from market launch to the end of the patent protection. Accordingly, one month lost for drug development correspond to one eroded month of effective patent life. If this definition is applied, countries have lost on average 1.7 months per year over

¹⁵Median estimated survival times are considered. In the case of the time from patent filing to product launch Model 3 (Table 2) is considered, whereas Model 5 (Table 4) is considered to compute the time span from product launch to the entry of the next in-patent competitor.

Country		EPL_1	EPL_2	EPL_3
EU-15	Launched in 1993	105.9	46.9	93.8
	Launched in 2007	80.5	48.2	73.7
	$\Delta_{(EPL_{07}-EPL_{93})}$	-25.3	+1.2	-20.1
	Avg. Δ	-1.7	+0.1	-1.3
USA	Launched in 1993	95.7	47.7	85.5
	Launched in 2007	70.6	44.1	64.9
	$\Delta_{(EPL_{07}-EPL_{93})}$	-25.1	-3.6	-20.6
	Avg. Δ	-1.7	-0.2	-1.4
Total	Launched in 1993	105.2	47.0	93.2
	Launched in 2007	79.9	48.1	72.4
	$\Delta_{(EPL_{07}-EPL_{93})}$	-25.3	+1.1	-20.9
	Avg. Δ	-1.7	+0.1	-1.4

Table 6: Eroded patent life (months), 1993-2007

the period 1993-2007.

On the other side, EPL_2 assumes that innovator sales are eroded when the next in-patent competitor enters the market. If this definition is applied, patent life would be actually rather stable over time. (increasing complexity is counter-balanced by spillovers).

The assumptions underlying EPL_1 and EPL_2 are not suited for describing the dynamics of the pharmaceutical industry. Neither market exclusivity is not enjoyed from market launch to patent expiry, due to the entry of in-patent competitors, nor sales are driven down to zero when entry by competitors occurs. Rather, if the value of patent protection for the “first” in class compound at market launch (corresponding to market sales) is normalized at 1, the entry of the next (“second”) in-patent competitor would erode sales of $1/2\bar{q}$. When the next (“third”) in-patent competitor enters the market, sales are further reduced, and, according to our model, sales reduction would be equal to $1/3\bar{q}^2$. Following this line of reasoning market sales would be, on average, reduced by $1/J\bar{q}^{J-1}$ after the entry of the J -th competitor.

By taking into account the average time from patent filing to market launch (EPL_1), and the time from market launch to the entry of the next in-patent competitor (EPL_2), we are able to infer the average number of competitors entering

the market during the period of patent protection¹⁶. Accordingly the normalized value of sales for products entering a market in country c is computed as:

$$EPL_3(c) = \sum_{J=1}^{J(c)} \left(1 - \frac{1}{J} \bar{q}(c)^{J-1} \right) \quad (16)$$

with $J(c)$ is the number of in-patent competitors allowed for by country-specific estimates of EPL_1 and EPL_2 , and $\bar{q}(c)$ is the country-specific average erosion due to competitor's entry after EPL_2 months.

Overall, patent life has decreased 1.3 months per year for European countries and 1.4 per year for the USA. Over the studied period, patent life has been eroded about 20 months, posing concerns regarding the incentives for undertaking R&D activities on the side of the firms (Lanjouw and Schankerman, 2004).

3.6 Post-expiry dynamics: generic competition

The model does not take into account the dynamics characterizing the innovator sales after the patent expires. We let market share of innovator equal to zero at patent expiration, assuming instantaneous entry of generic producers, fostering vigorous price competition in the market place. Actually, this is not always the case, and markets with different characteristics experience different levels of entry. As a result, the value of a patent does not end with patent expiry, rather it may well extend beyond patent expiry, especially for small markets (Scott Morton n.d., Hudson n.d.). Moreover, the dynamics of price competition and the diffusion of generic products after patent expiry vary significantly across countries. Available evidence shows that both generic penetration and the impact on prices competition are linked to the extent of price regulation (Danzon and Chao 2000, Magazzini et al. 2004).

In this section, we analyze and assess the dynamics characterizing generic competition, looking both at the time span from patent expiry to first generic entry and whether the pattern of generic penetration has changed over time. Only un-branded generics are taken into account and we focus on the pattern of competition

¹⁶We consider a time span of 20 years from patent filing to patent expiry.

between branded and unbranded products containing the same molecule, checking whether and how this has changed over time.

As a preliminary account, the diffusion of generic drugs is increasing in the US and across European countries (see Figure 6). Even though, when measured using value, the market shares of generic products has a comparable level in Europe and the US, quantity shares reveal a larger diffusion of unbranded products in the US (the prototype example of unregulated market). The difference between the two measure is driven by the price differential of generic products in the European countries with respect to the US, where European countries experience unbranded product prices that are larger than the prices in the US for the same compound (Pammolli and Riccaboni 2008).

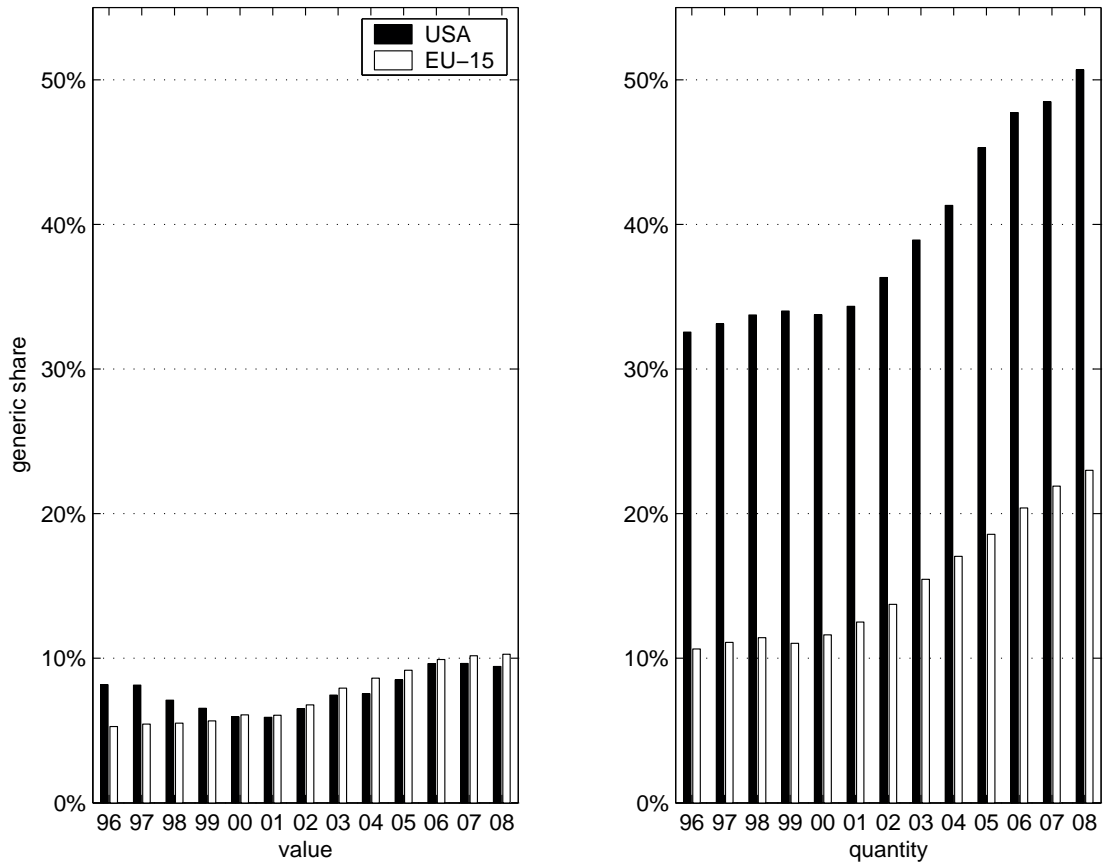
Table 7 reports the estimated coefficient of the survival analysis taking into account the time span from patent expiry to the entry of the first (unbranded) generic product. In this case we adopt a narrower definition of market, grouping all products with the same molecule¹⁷. In the words of Lichtenberg and Philipson (2002), dynamics of within-patent competition are taken into account. We look both at the speed of entry and at branded sales erosion due to generic entry. Due to data limitation only products experiencing patent expiration over the period 1996-2008 are considered in the analysis.

As a preliminary account Figure 7 depicts the Kaplan-Meier estimate of the survival function grouping the products according to the year of patent expiry. Two time periods are considered, before and after the year 2000. The graph clearly shows that the entry of generic producers is becoming faster and more likely over time.

Estimated ancillary parameters of Model 1 would be consistent with the exponential hazard function, as well as with the Weibull and log-normal specification. On the basis of AIC, the Weibull specification is preferred for the analysis.

The trend variable is built considering the time of patent expiration. The coefficient is negative and statistically significant in all specification, pointing to faster entry of unbranded products over time. Innovator products with standard FDA review also experience faster entry with respect to priority reviews, and this

¹⁷Multi-molecule products are excluded from the analysis, for the difficulty in the identification of the time of patent expiration.



Note: July-December considered for the year 1996; January-June considered for the year 2008.

Figure 6: Generic (unbranded) market share: EU-15 versus the US

Variable	Model 1	Model 2	Model 3	Model 4
	Gamma	Weibull	Weibull	Weibull
Trend (expiry)	-.0792*** (.0168)	-.08464** (.0178)	-.0923*** (.0182)	.01594 (.0321)
Lethal			.9698*** (.3023)	.3714 (.3987)
Org.damage			.6695** (.2759)	.1063 (.3803)
Complication			.3772 (.3427)	-.4140 (.4304)
Chronic			-.1930 (.3954)	.1780 (.4406)
Size				-.5214*** (.0512)
Concentration				-.6429** (.3218)
Constant	6.266*** (.6863)	6.251*** (.2333)	5.793*** (.4735)	9.594*** (.7035)
Country FE	yes***	yes***	yes***	yes***
$\ln(\sigma)$	-1.052 (3.101)	-.1489*** (.0535)	-.1521*** (.0536)	-.1721*** (.0571)
κ	3.515 (10.90)	1.000 -	1.000 -	1.000 -
Log. lik.	-1179.8	-1183.5	-1161.1	-897.6
AIC	2397.5	2403.0	2366.3	1843.3
N	2,066	2,066	1,965	1,795

Table 7: Survival analysis: time from patent expiry to unbranded generic entry; Gamma/Weibull hazard function

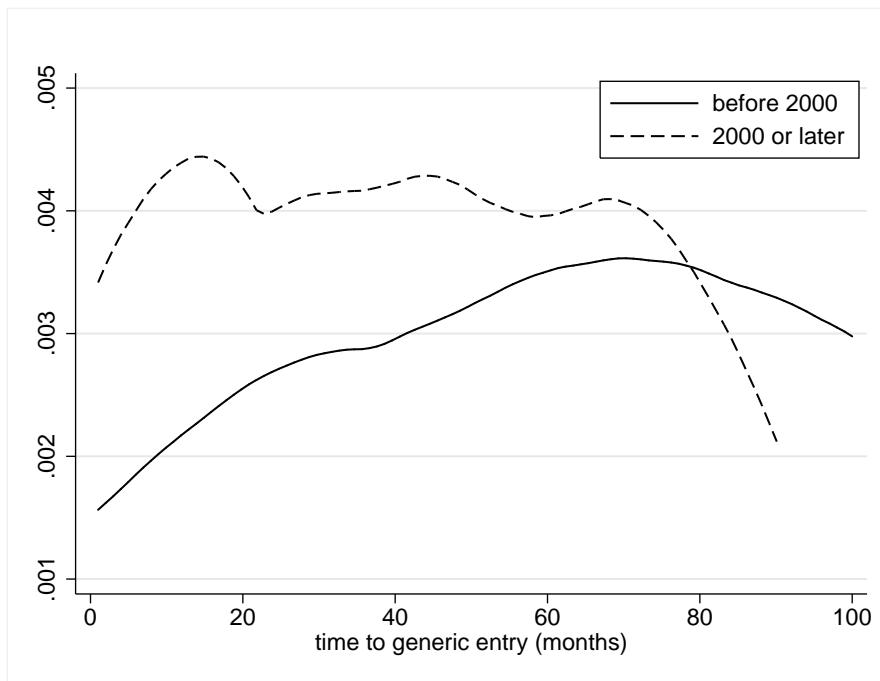


Figure 7: Smoothed hazard estimates (Kaplan-Meier): time from patent expiry to (unbranded) generic entry, by year of patent expiry

might be due to stronger brand loyalty for newer treatments. We include a full set of controls aimed at taking into account the characteristics of the targeted disease. Coherently with previous account of the likelihood and speed of generic entry, the chronic dummy loses statistical significance when market controls are included in the regressions (Bae 1997). Only the dummy variables indicating diseases causing complications and with unknown etiology turn out to be statistically significant and they both point to a negative effect of these variables.

As far as market characteristics are concerned, we include the size of the market (in quantities) and concentration (as measure by the Herfindahl index) in the quarter preceding patent expiration. Coherently with previous studies¹⁸,

Country FE are included in all regression and they turn out to be statistically significant.

Overall, the entry of generic producer is becoming faster over time.

Next we adopt the Fisher-Pry framework, described in Section 3.4, in order to assess the level of substitution of unbranded products over branded alternatives. Figure 8 describes the evolution of the ratio of generic to branded sales (both in quantity and value) and the ratio of prices.

After 20 quarters (5 years) generic producers have gained about 30% market share in terms of value and 28% in terms of quantity. Generic prices are about 75% of branded prices at launch, and the ratio decreases over time. This effect can be driven by a decrease in branded prices when generic share starts to be substantial¹⁹.

Then, we consider the Fisher-Pry regression (15) taking into account the ratio between generic and branded sales. Table 8 shows average values and median values of the estimated coefficients grouped according to the time of patent expiration of the original compound.

Statistical testing²⁰ confirm the trends highlighted in the table, where no difference seems to exist in terms of branded sales erosion due to generic entry over the

¹⁸See, e.g., Scott Morton (n.d.) and Bae (1997).

¹⁹Analysis of US data over the Eighties shows that many brand-name originators keep increasing their prices after generic entry (Caves et al. 1991, Frank and Salkever 1997). This is not the case for European countries, where originator prices either stay constant or decreases after patent expiration (Magazzini et al. 2004).

²⁰We considered both a t-test of mean equality and non parametric testing checking the equality of median values.

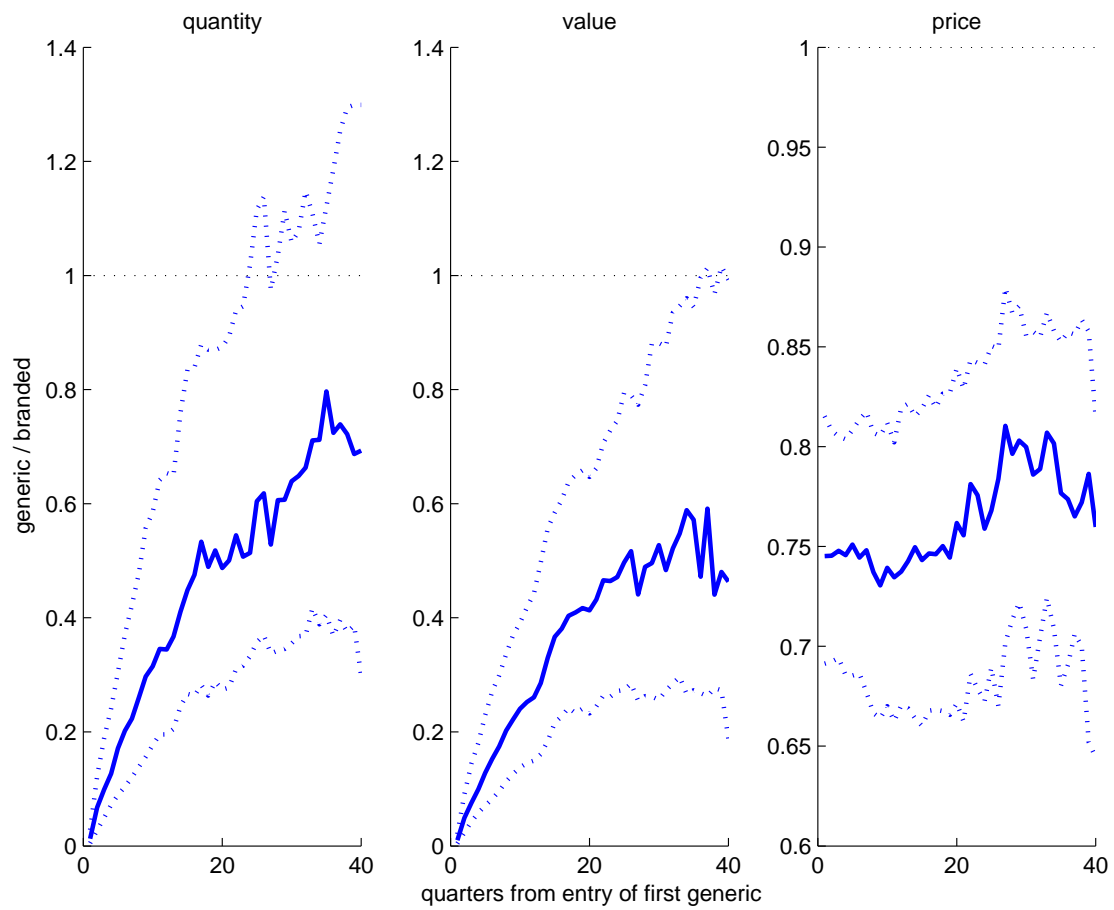


Figure 8: Penetration of generic producers and pricing strategy: sales value, quantity and prices (line: median; dotted lines: 40-th and 60-th percentiles)

Launch year of innovator	N	All compounds		Restricted sample	
		Average estimated β_i	Median estimated β_i	Average estimated β_i	Median estimated β_i
SALES VALUE					
1996-1999	160	.1538	.1238	.1354	.0952
2000-2003	288	.1499	.1210	.1423	.1087
2004-2008	163	.2231	.1546	.2206	.1556
QUANTITY					
1996-1999	160	.1656	.1361	.1701	.1384
2000-2003	288	.1611	.1265	.1698	.1368
2004-2008	163	.2345	.1628	.2140	.1612
MEDIAN PRICE RATIO, 1st YEAR					
1996-1999	170	.7684			
2000-2003	344	.7426			
2004-2008	240	.7118			

Table 8: Average and median value of estimated β_i , over launch year of innovator/“first” compound

period 1996-1999 and 2000-2003. On the contrary, generic penetration is faster for products with patent expiration over the period 2004-2008, with respect to previous periods. The difference can be explained by looking at price dynamics, where price competition induced by generic producers is becoming more substantial. Generic to branded price ratio is 71.18% over the period 2004-2008, smaller than the corresponding figures for the previous periods (respectively, 76.84% for products experiencing patent expiration in 1996-1999, and 74.26% over the period 2000-2003).

4 Concluding Remarks

The pharmaceutical industry is a textbook example of a science based sector characterized by high cost, highly uncertain and easily imitable inventions for which patent protection assures appropriability thus providing incentives for innovation. In the early Nineties, studies have testified the sharp decrease of EPL, as measured as residual patent life from product launch, over the 70s-80s. In more recent years,

studies have analyzed the dynamics of branded products within the same market, showing that competition from later patents is substantial and may be much larger than competition spanning from patent expiry and the entry of generic producers. A full account of the dynamics of EPL in recent years is lacking, even though patent reform is one of the main headings of the policy agenda.

We develop a simple model to investigate the effect of increasing R&D complexity on the EPL and incentive to innovate. Our model predicts the erosion of EPL and shrinking of product lifetimes in presence of parallel R&D with spillovers and correlated R&D market portfolios. The model is tested in context of the worldwide pharmaceutical industry, exploiting a comprehensive dataset on innovative activities and market sales in major European countries and the US. First, we consider the time from patent filing to launch of the product on the market. Then, we analyze the evolution of competition characterizing the in-patent products over the last decade taking into account the time span between the launch of the drug and the entry of a new patented competitor in the same market. Finally, even though not directly taken into account in our model, we study the timing from patent expiry to the entry of the first (unbranded) generic product.

Interestingly enough, the time lag from patent filing to product launch is increasing over time and it is shorter for products providing significant therapeutic advantages, and for compounds subject to a licensing agreement (where the company marketing the compound is not the patent holder).

Consistently with the developed model, results provide evidence of significant spillovers in the pharmaceutical industry. When taking into account the time lag from the innovator launch to the entry of a later competitor, the hazard of entry of a new in-patent competitor is significantly higher for follower compounds. The hazard of entry at earlier time is increasing with the order of entry of the product in the market. Later products are able to enjoy larger knowledge spillovers from previous entry.

Overall, the effective patent term has declined 1 year every 4 years since the beginning of the Nineties (analysis cover the period 1993-2007), with significant differences between the European countries and the US. The EPL erosion turns out to be mostly an European phenomena. The US result is consistent with previous empirical account of the timing of clinical development and approval in the US

show that FDA reforms aimed at speeding the review process have been effective.

In addition we show that, once patent expires, sales erosion (both in value and quantity) from (unbranded) generic producers is becoming stronger in recent years.

Our findings have implications for the current debate about patent term restoration rules, particularly for the pharmaceutical industry, largely relying on patents as a means for the protection of intellectual property rights. Particularly, fixed patent term restoration rules, such as the Hatch-Waxman Act, are only partially effective in counterbalancing the erosion of patent value, with important implications on the incentive to undertake R&D efforts.

A Description of the data

The CERM database combines several sector-specific proprietary datasets concerning R&D activity, collaborations and final drug markets with data from public sources, as well as companies, confidential information, and press releases. As a result, the database provides a unique source for studying the innovative activities and the patterns of competition, both on the R&D side and on the market, faced by the private actors and public institutions in the pharmaceutical industry.

A.1 Patents and publications

The information available in patent applications and scientific publications are exploited to measure technological and scientific capabilities of firms and institutions involved in drug development.

The database covers the full set of patents at the US patent office and at the European patent office from 1978 to December 2008, as well as WIPO data from 1978 to August 2008. A wide set of information is available for each patent. For the purpose of this study we stress the availability of the application and grant dates, and of the assignee name(s). For the US patents, information is also available about backward and forward citations. In this respect, a major effort has been undertaken in order to standardize assignee names, allowing us to track patents belonging to same corporation. As a result, we are able to distinguish self-citations and citations by other companies.

As far as the publications are concerned, information are extracted from PubMed, a service of the US National Library of Medicine²¹, including over 18 million citations from MEDLINE and other life science journals for biomedical articles from 1948. Data are updated to September 2008. Ad hoc queries have been performed in order to select the publications mentioning the compounds included in our analysis.

²¹See <<http://www.ncbi.nlm.nih.gov/pubmed/>>.

A.2 Drug development projects

The CERM database reports information about more than 17,000 R&D projects all over the world carried over since the 1980s.

The whole development history of each project is monitored, reporting information from patent filing to eventual launch on the market, the firm(s) involved in its development and their role (distinguishing developer/licensor from licensees), and the therapeutic area and biological mechanism of the compound being developed. Also the country where trials are conducted is reported.

Information in the R&D data have been exploited to compute the number of R&D trajectories targeting a given disease, by joining the information on the therapeutic area targeted by each compound and the biological targets considered for drug development.

A.3 Sales data

Sales data of all pharmaceutical products for the EU-15 countries and the USA are available (quarterly) over the period July 1996 – June 2008. Sales data are measured both in value²² and quantity²³, along with information about the 4th digit Anatomical Therapeutic Classification (ATC4), the corporation that holds marketing rights to the compound, the launch date, and molecule(s). With few exceptions²⁴, data are available both at the retail and hospital level, but for the purpose of our analysis, we considered aggregated data over the two channels for each country.

Sales information have been exploited for the analysis of the time lag from in-patent product launch to the entry of a new in-patent compound (the time from

²²Original data are expressed in sterlings where a constant exchange rate has been applied for conversion. The analysis presented in this paper employ nominal values. Results do not change if the GDP deflator (extracted from OECD data) is applied and real values are considered.

²³Quantity are expressed in standardized number of doses. For example, in the case of solid products, the standard dose is a capsule or a tablet, for liquid products, it is a spoonful. The measure allows for comparison of products with different routes of administration.

²⁴We cover the retail segment only for Greece, Ireland, Luxembourg, and Portugal. In the case of Denmark, and Sweden it is not possible to distinguish between the two channels. Spain hospital data are only available from the year 1999. However, given the nature of our analysis, we claim that these limitations won't affect our results.

L_1 to L_2 in our model), as well as to understand the intensity of between- and within-patent competition.

A.4 Linked information & controls

Information about the patent(s) protecting the compound is available on a country basis, reporting the filing date and the expected time of patent expiry. As a result, we are able to assess the time lag from patent filing to product launch on the market.

Even though country patents are available, in order to recover information about backward and forward citations (essential for the assessment of the level of spillovers), the US patent number needs to be considered²⁵. However, as protecting the same compound, patents in different countries belong to the same family, and information about spillovers in the US can be taken as a (imperfect) proxy for worldwide spillovers.

Product names have been matched to the database “drugs@FDA” provided by the US Food and Drug Administration (FDA)²⁶, and we considered the information about the therapeutic potential of the compound. Particularly, FDA distinguishes standard review from priority review, where compounds granted a priority review are those providing significant improvement compared to existing products in the treatment, diagnosis, or prevention of a disease. On the contrary, standard review is granted to drugs showing therapeutic qualities that are similar to those of products already available on the market. To the best of our knowledge, such information is not available for European countries, leading us to consider FDA data and extend FDA classification to the same compound when launched in the European countries.

Finally, we exploit the information provided by an evaluation of diseases developed with the help of a pharmacologist, aimed at describing and assessing every pathology. The evaluation is based on several parameters²⁷ such as the outcome

²⁵As mentioned in the previous sections, citations are only available for patents at the USPTO.

²⁶See <<http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/>>.

²⁷The main source for the disease information was Braunwald et al. (2001). We also drawn from e-medicine reviews in the disease database at the internet address <<http://www.diseasedatabase.com>>.

(whether lethal in absence of therapy), the presence of organ damage or complication, and chronicity²⁸. The developed dummy variables allow us to control for disease characteristics, where the information about the outcome, organ damage and complication is important for understanding the severity of the disease.

B Basic notions of survival analysis applied to the estimate of EPL

Standard methodology for survival analysis will be employed to study the dynamics that have characterized: (i) the time lag from patent filing to product launch (testing phase); (ii) the time lag from product launch to the entry of the following in-patent competitor (patent/market exclusivity); (iii) the time lag from patent expiry to the entry of the first unbranded product²⁹.

Analysis starts with the specification of the probability that the event that changes the compound state³⁰ will occur between two time periods, conditional on not having occurred at the beginning of the selected time frame. For explanation purposes, let us consider the time L when the innovator product is launched. The instantaneous probability of market launch at time t can be defined as:

$$\lambda(t) = \lim_{\Delta t \rightarrow 0} = \Pr(t \leq L < t + \Delta t | T > t) / \Delta t. \quad (17)$$

We let the hazard function depend on a set of characteristics of the product under study: i.e. we consider $\lambda(t, x_i)$, the hazard function of product i with characteristics x_i . Estimation is performed using STATA.

As the baseline specification, survival analysis usually employs the exponential

²⁸A chronic disease is defined as showing one or more of the following characteristics: permanent, leaves residual disability, is caused by non reversible pathological alteration, requires special training of the patient for rehabilitation, or may be expected to require a long period of supervision, observation or care.

²⁹Also *branded* generic products can enter the market after patent expiration. Only unbranded generics are considered in the analysis, as these introduce vigorous price competition in the market place (Magazzini et al. 2004).

³⁰In our case: (i) product launch (L_1) makes the product leave the testing phase; (ii) entry of later in-patent competitor (L_2) makes the product leave the market exclusivity stage; and (iii) the first unbranded product enters the market (after patent expiration).

distribution, where the hazard of experiencing the exit state is constant over time. In order to take into account the departures from this specification that characterize our data, we consider various models customarily employed in duration analysis and selected the best representation on the basis of the Akaike Information criterion (AIC). Also graphical inspection of the overall fit of the model is undertaken by using Cox-Snell residuals. A generalized gamma distribution³¹ has been selected for the analysis of the time lag between patent filing and product launch, and for the time from first innovator launch to the launch of the later competitor. On the contrary, analysis of the time lag from patent expiration to the entry of the first generic relies on the exponential distribution.

The use of the generalized gamma distribution allows great flexibility in the shape of the hazard function, and it includes, as special cases, the Weibull distribution, the exponential distribution, and the lognormal distribution. The distribution is customarily employed for modeling waiting times.

The estimated model takes into account the factors affecting the relevant (log) time length, i.e. (i) the log of the testing stages, (ii) the log of the market exclusivity time, and (iii) the log time to generic entry. In order to interpret the results, a positive coefficients means that a unit increase in the corresponding variable causes a delay in the time of drug launch/entry of the follower. The reverse is true when the coefficient is negative.

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³¹We also experimented with other distribution, i.e. Weibull, Gompertz, and considered the Cox regression model where no distribution is imposed on the baseline hazard. Results, available from the authors upon request, are broadly consistent with those provided in the paper. The choice of the Gamma can be also justified if thinking about the process characterizing drug development. Suppose that product successful launch takes place in p stages (i.e. clinical trials). At the end of phase I (t_1) the first success occurs; after that phase II begins and the second success occurs at time t_2 . Product launch occurs at the end of the p -th phase. The inter-arrival time is $L = t_1 + t_2 + \dots + t_p$. If t are independently exponentially distributed the distribution of L is then called the Erlangian distribution. By replacing parameter p with the continuous parameter we obtain the gamma distribution.

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