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R&D, Within and Between Patent Competition in the Pharmaceutical Industry

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Abstract

We analyse the consequences of the increasing complexity of R&D on within- and between-patent competition in the pharmaceutical industry. The intensity of competition is measured by jointly considering the timing from market launch to patent expiry, the strength of between-patent competition as well as competition introduced by generic producers. A simple model is proposed that predicts the shrinking of product lifetimes in the presence of correlated parallel R&D projects and market portfolios. The model is tested using data on pharmaceutical products sold in Europe and in the US. Based on our model we are able to estimate the impact of R&D complexity and relatedness among R&D portfolios on the value of innovative drugs.

Keywords: Patent value, innovation, R&D competition, pharmaceutical industry.
JEL Classification: D23; D83; O34; O31; L13.

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1 Introduction

The pharmaceutical industry is facing a R&D productivity crisis (Cockburn, 2006, Pammolli *et al.*, 2011): the costs of developing a new drug and total R&D investments have been increasing (DiMasi *et al.*, 1991, DiMasi *et al.*, 2003, Adams and Van Brantner, 2006), as has the failure rate of candidate drugs in clinical trials (Mervis, 2005, Pammolli and Riccaboni, 2008). Conversely, the number of new molecular entities launched on the market has remained virtually flat, whereas blockbusters patent expiries has lead to a drop in sales of more than $100bn (the so-called "patent cliff") (Kelleher, 2009, Jack, 2012).

Although this may seem a recent industry-specific phenomenon, empirical accounts of the returns from innovative activities have been accumulating sound evidence about the long-term decline in the productivity of the R&D effort across sectors and countries (Griliches, 1990, Kortum, 1993, 1997, Jones, 1995, Lanjouw et al., 2004, Jones, 2009).[1] Increasing market opportunities, stiffer competition, and the increasing burden of knowledge are considered as the main causes of the decline in R&D productivity (Everson, 1993, Kortum, 1993, Segerstrom, 1998, Lanjouw et al., 2004, Jones, 2009).

In this paper, we take a new look to the evolution of R&D competition and final market dynamics in the pharmaceutical industry. Namely, we develop a comprehensive analysis to measure the intensity of competition for innovative drugs that, besides, statutory patent life and follow-on competition, takes into account the erosion of sales due to the entry of generic producers after patent expiry.

In the literature, there has been many attempts to quantify the extent of innovation and competition in the pharmacetical industry along different directions. Dranove and Meltzer (1994) took into account the development time of new molecular entities introduced since 1950s (up to 1986) and found an increasing time lag from first international patent filing to FDA approval. Using more recent data, DiMasi *et al.* (2003) show longer time from the start of clinical testing to submission of new drug applications with the Food and Drug

[1] By the 1990s, the number of patents produced per US researcher had fallen to 55% of its 1970 level, with even steeper declines in Europe (Everson, 1984, 1993). Kortum (1997) found that the number of researchers has increased by nearly 5% each year since the beginning of the 1950s, while patents per researcher have been diminishing.

Administration (FDA) for compounds first tested in humans between 1983 and 1994 with respect to previous analysis (DiMasi *et al.*, 1991).[2] The erosion of patent life induced by longer clinical trials and the expansion of regulatory burdens have been documented by several studies (Hutt, 1982, Andersson and Hertzmant, 1993, Dranove and Meltzer, 1994, Abrantes Metz *et al.*, 2004). R&D and market competion are closely related. It has been found that he gap between the commercial introduction of a new (patented) product and the arrival of later competitors has been shrinking (Bayus, 1998). Thus, measuring residual market value of innovative drugs as the time-span between product launch and patent expiry (or time to first generic entry) only provides an upper bound to effective patent value. Rather, we should also consider the expected time until a patented product is replaced on the market. Agarwal and Gort (2001) find that the average time-span from market launch to competitor entry has declined from almost 33 years at the end of the 19th century to 3.4 years in 1967-86. According to DiMasi and Paquette (2004), the time lag between the introduction of breakthrough drug (first-in-class compounds) and follow-on new drugs has fallen from 10.2 years in the 1970s to 1.2 years in late 1990s. Mansfield (1984) reported that 60% of patents are effectively terminated within 4 years. Accordingly, Levin et al. (1987) showed that almost all patents are duplicated in 5 years. 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, the expected value of innovative products is a function of both time-to-market and follow-on competition. Also, after patent expiration, the time period from innovator's market launch to generic entry has been shrinking (Grabowski and Kyle, 2007). Besides erosion of innovators' returns by generic competition after patent expiry (*within-patent competition*), competitive forces are active during patent life too, between similar products under different patents (*between-patent competition* – see Lichtenberg and Philipson, 2002).

Our goal in this paper is to integrate different measures of patent value in a unified and coherent framework. First, we set the boundary of the in-patent market regime for between-patent competition by measuring the residual patent life of pharmaceutical products, i.e.

[2]However, the effect is counterbalanced by a decrease in the timing of FDA approval associated with the implementation of the 1992 Prescription Drug Use Fee Act (DiMasi *et al.*, 2003).

the timing from market launch to the end of statutory patent life. Second, we analyse the competition induced by follow-on competitors and generic producers. As in Lichtenberg and Philipson (2002), we consider two dimensions: (i) the timing of entry, and (ii) the sales erosion conditionally upon entry.

Our contribution to the literature is twofold. First, we account for the patterns of within and between-patent competition both in Europe and the US, whereas the previous literature focuses on the US. Second, we identify the key drivers of the the timing and intensity of market competition in the pharmaceutical industry. Based on our estimates, we quantify the impact of different regimes in terms of composition of R&D portfolio on the intensity of market competition.

Our findings have some relevant policy implications on the current debate on the disclosure of clinical trials data in Europe and the US (Rodwin and Abramson, 2012). Based on our results, we show that by increasing the correlation of R&D portfolio, holding complexity constant, competition is increased with an implied reduction in the value of innovative drugs. By granting full access to clinical trial results, we expect an increase in the relatedness of R&D projects, and the value of innovative drugs is reduced up to 14%, of which 10% is due to decrease of between-patent competition, before the patent expires. The effect is found to be larger in the US with respect to European countries.

The paper proceeds as follows. Section 2 describes a simple model of the relationship between R&D complexity, competition and the value of innovative pharmaceutical products. Section 3 illustrates data and methodological approach. Section 4 tests the predictions of our model in the context of the pharmaceutical industry. The final Section concludes.

2 R&D and market competition in the pharmaceutical industry

The degree of competition between innovative drugs is influenced by a differentiated set of factors. On the one hand, R&D complexity and the growing burden of knowledge induces

longer gestation lags before market approval. On the other hand, the strength and intensity of follow-on market competition (both by new patented drugs and generic producers) can substantially reduce the market value of patented drugs. In this respect, the extent and strength of patent protection play a central role in protecting innovators' returns.

In this section, we take a broader view to analyse the combined effect of R&D complexity, market competition and patent breadth. We measure the extent of competition as the effective patent life (EPL) of innovative products taking into account the duration of clinical trials as well as sales erosion caused by the entry of in-patent and off-patent competitors.

We analyse market portfolios of R&D projects which would emerge under competition among rival research units (Dasgupta and Maskin, 1987). As in Cabral (1993), we assume that the process of getting a new product into the market consists essentially of two stages: (1) the R&D race to discover and patent a new product candidate, and (2) a testing phase, such as clinical trials for pharmaceuticals, to have the product approved for marketing. At the end of the R&D race, successful firms patent their product candidate and decide whether to move it into the trial phase. Thus, patent coverage lasts T years from the beginning of the trial phase (set at $t = 0$). Clinical trials are required before the regulatory authority approves marketing of new drugs. Clearly, a product launched after L years of trials has a residual patent life of $T - L$ years.

The outcome of clinical trils can be represented as a stochastic process, due to strong uncertainty about safety and effectiveness of drugs in humans.[3]. Specifically, clinical trials are modelled as Poisson processes with instantaneous probability of success λ. We consider a technology space consisting of k independent R&D trajectories (Sutton, 1998) or lines of research (Aghion *et al.*, 2008). In the first stage, a firm must choose an R&D trajectory. When firms opt for different R&D trajectories, R&D market portfolios are totally uncorrelated. However, firms may be working along the same R&D trajectory, developing chemically related drug candidates (Dasgupta and Maskin, 1987, Sutton, 1998). Along the same R&D trajectory, patented products are allowed to share some features (but not all) depending on the extent of patent coverage. Thus, more firms can follow the same research trajectory by

[3]Sutton (1998) described it as a "lottery game".

partially differentiating product characteristics, that is to say, they can develop analogous products.

We assume that products have a finite number of features n, to be tested. Thus, if two analogous products share m features, they will have the same probability of success in $m < n$ trials. In such a simple stochastic set-up, the patent market exclusivity period (i.e., the time until an innovative product experience competitor's entry) is of random duration: it starts at product launch (L_i) and ends whenever rival firms launch a patented drug on the same market (L_{i+1}) (between-patent competition), or the patent expires ($T < L_{i+1}$) and generic drugs are allowed to enter (within-patent competition).

With perfect patent protection, analogous products are ruled out and there is no between-patent competition, so that the residual patent life is simply given by the difference between the patent term and the duration of the testing phase.

In case of between-patent competition, the strength of between-patent competition is related to the the expected time until a patented product is replaced in the market or, more precisely, the patented product inter-arrival time (O'Donoghue *et al.*, 1998). In this framework, "the winner takes all" hypothesis corresponds to the case in which the probability of success in the testing phase is so low compared with the patent length that there is no chance of between-patent competition and/or there is perfect patent breadth and firms choose different R&D trajectories. In such a case, there are no overlapping patent terms and each product has a temporary monopoly on the final market. A firm starts 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 captures the per-period benefit of the innovation (v) until patent expiry (T) and 0 afterwards. With a single R&D trajectory, the expected duration of the trial phase is $L = 1/\lambda$, and a firm will start the trial phase if the expected payoff of undertaking trials is positive: $v(T - L) - cL > 0$ or

$$v/c > \frac{1}{\lambda T - 1} \tag{1}$$

Since $T > L$ the ratio on the left is always positive.[4]

The more alternative and equally plausible research trajectories there are, the lower the instantaneous probability of success λ/k. In the case of $k > 1$, equation (1) becomes:

$$v/c > \frac{k}{\lambda T - k} \tag{2}$$

Thus, *ceteris paribus*, if R&D complexity increases due to the proliferation of research trajectories (higher k) or increasing difficulties in the testing phase (lower λ), the expected number of new product launches will decrease.[5] We may conclude that increasing R&D complexity (higher k) implies longer clinical trials and therefore a contraction of the residual patent life.

When we measure competition by looking at residual patent life, we assume that full market exclusivity is enjoyed from market launch to the end of the period of patent protection, implicitly only allowing competition by generic producers. Instead, between-patent competition is substantial, causing an erosion of innovator's sales, well before patent expiry (Lichtenberg and Philipson, 2002, DiMasi and Paquette, 2004).

We now consider the most interesting case in which more than one company enters the testing phase (parallel R&D) and may compete in the final market (between-patent competition). In this case, the probability of success of different R&D projects may be statistically independent if firms decide to move to the testing phase along different R&D trajectories. Conversely, firms which choose the same lines of research may have correlated R&D portfolios.

Let us start with the case of perfect patent protection (thus, firms follow different R&D

[4]For u competing products, the patent exclusivity condition implies that

$$v/c < \frac{u}{\lambda T - 1}$$

thus, in case of coexisting products, each taking the same share of total value v, the expected payoff turns negative. This is the classic incentive failure which the patent system is meant to address. In this case, the patent proscribes innovation and guarantees innovators the full net social return on R&D expenditures.

[5]In the case of a discount rate $r > 0$, if we define $\tau = 1 - e^{-(r+\lambda/k)T}$ and $\eta(T) = (1 - e^{rT})/r$, the expected payoff becomes:

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

As T goes from 0 to infinity, τ ranges from 0 to 1 and may be seen as the "normalized" expected patent length.

trajectories). Let L_i be the arrival time of the patented product i on the market and L_{i+1} be the arrival time of the follow-on product. Since trials are Poisson processes with the same instantaneous probability of success λ, then it is well-known that inter-arrival times are independent and exponentially distributed with mean $L = 1/\lambda$. Therefore, in the markets where the arrival of follow-on competitors is expeced before patent expiry, we might observe overlapping patent terms and between-patent competition. Conditional upon successful innovation, the payoff depends on the number of products competing in the same market. For the sake of simplicity, we can assume that if J firms are simultaneously present with a patented product in a given market, each obtain an equal share $s = v/J$ of payoff v.[6]

With parallel R&D and independent research projects an increase in the number of trajectories k will shift the expected launch date of each product, thus reducing the expected payoff. However, the proliferation of R&D trajectories will delay the expected arrival of follow-up products from L_i to kL_i for all candidate products. Late-comers and firms which spent too much time in the first phases of the R&D process will be selected out whereas, conditional upon entry, products will have a longer residual patent lifes. Thus, we can state that, *Ceteris paribus*, in a high λ regime and perfect patent protection, an increase in the number of R&D trajectories k implies an increase of the time before the arrival of follow-on competitors.

Lastly, let us consider the case of markets with correlated parallel R&D projects (patent breadth is not perfect). At the beginning of the R&D race, firms choose the R&D trajectory and the features of their candidate drugs. With imperfect patent protection, firms can choose the same lines of research and share a fraction $m < n$ of product features. In the trial phase, each of the n product features is tested. Each test has a given instantaneous probability of success λ_n. Since the sum of two independent Poisson processes is still a Poisson process, the expected probability of arrival of two products which share properties are correlated

[6]This is equivalent to saying that, if the patent has perfect breadth and more firms make the discovery, they have the same probability of obtaining the patent. If innovation is drastic and occurs in a homogeneously good market with linear demand function $P(Q) = aQ$, by normalizing post-innovation marginal costs to 0, the aggregate output will be $Q = \gamma a$, with γ ranging from 1/2 (perfect collusion) to 1 (Bertrand competition) (Denicolo and Franzoni, 2003). Thus, profits with J competing firms will be $s(J) = \frac{1}{J}\gamma(1-\gamma)a^2 \leq v/J$ with $v = a^2/4$. Here we consider the upper limit $s = v/J$.

(Dasgupta and Maskin, 1987).[7]

When products share $0 < \beta \leq 1$ of their features, the expected inter-arrival time between the first and second product is $(1 - \beta)nL$, which corresponds to the conditional probability of success of the second product, given that the first one has been successful. Conditional upon first arrival, increasing levels of product relatedness (β) can counterbalance the growth of k. As demonstrated by Dasgupta and Maskin (1987), in "the winner takes all" scenario and two-point distributions, the R&D market portfolio consists of projects which are too highly correlated. Cabral (1993) shows that the result holds even if we relax "the winner takes all" condition. Correlated R&D projects will arise in case of ex ante uncertainty (i.e., about the outcomes of the trial phase) and/or when firm's products are substitutes, and firms can avoid pure price competition by collusive or Cournot solutions as well as non-price competition through first mover advantages and marketing expenditures. When $c = 0$, firms will be indifferent about the value of β, however, for positive c, each firm will prefer correlated R&D projects. Summing up, in a high λ regime, with $0 < \beta \leq 1$ and high R&D complexity (high k) firms will select correlated R&D projects and between-patent competition will be stiffer, due to R&D correlation (Dasgupta and Maskin, 1987).

All in all, the proliferation of research trajectories (k) implies longer trials and patent inter-arrival times. Conversely, the presence of correlated R&D projects reduces the time between the arrival of patented products. The increasing burden of knowledge, in the presence of imperfect patent protection and R&D spillovers, should thus reduce the market value of innovative products.

Since new products developing along the same R&D trajectories are imperfect substitutes (like analogous drug candidates) they do not completely displace pre-existing ones. Hence, in our empirical analysis, we consider the effect of between-patent competition in terms of product market share turnover, weighting the time from market launch to the end of the statutory life of the patent according to the market share left after the entry of follow-on

[7]Let us consider, as an example, the case in which two firms develop a product with two features, of which one is in common: $P_1 = (A, B)$ and $P_2 = (A, C)$. Next, they both move into the testing phase. In the first (second) stage, feature one (two) is tested. If trials are independent Poisson processes with rates λ_a, λ_b and λ_c, then L_1 and L_2 are Poisson processes with rates $\lambda_a + \lambda_b$ and $\lambda_a + \lambda_c$, and $Cov(A+B, A+C) = Var(A) = \lambda_a$, so that the correlation coefficient of the two products is given by $\lambda_a / \sqrt{(\lambda_a + \lambda_b)(\lambda_a + \lambda_c)}$.[8]

products competing in the same market. In addition, the level of competition induced by generic producer after patent expiry is analysed.

3 Data and Methods

Our empirical investigation is based on the PHarmaceutical Industry Database (PHID) maintained at IMT Lucca, Italy. PHID 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 patterns of competition, both on the R&D side and on the market, faced by private actors and public institutions in the pharmaceutical industry.

In our analysis we consider products launched in the US and the EU-15 countries. For each compound, the database track country-specific patent information (including the date of patent filing and patent expiry), the scientific publications related to the compound,[9] and the evolution of market sales from July 1996 to June 2008 in EU-15 countries and the United States.[10]

The analysis will take into account the timing of within- and between-patent competition, as well as their intensity. In particular, we study the time of exposure to generic producers, first by making the simplifying assumption that generic entry occurs at patent expiration (that is, we analyse how R&D complexity and parallel R&D affect the drug development process and therefore the time from market launch to the end of statutory patent life), and then by taking into account the hazard of entry and sales erosion by generic producers. In order to characterize between-patent competition, we first rely on a survival analysis that explore the determinants of the time span from market launch to follow-on competition.

[9]Information about scientific publications was extracted from PubMed, a service of the US National Library of Medicine, including over 18 million citations from MEDLINE and other life science journals for biomedical articles from 1948. See <http://www.ncbi.nlm.nih.gov/pubmed/>.

[10]Sales data are measured in both value and quantity together with information about the 4th digit Anatomical Therapeutic Classification (ATC4), the corporation which holds marketing rights to the compound, the launch date, and the compounds(s) involved.

Next, we investigate the patterns of sales erosion from branded competitors. Finally, the competition induced by generic producers at patent expiry is taken into account.

As a first step to our analysis, it is essential to devise a definition of the relevant market in which products are substitutes to treat a given pathology. In the analysis of between-patent competition, we define the market according to the 4-digit Anatomical Therapeutic Classification (ATC4), grouping together compounds targeted to the same pathology and exploiting the same mechanism of action (Danzon and Furukawa, 2006).[11] Instead, a finer level is considered for the analysis of within-patent competition, which typically occurs at the level of specific compounds. Therefore, generic substitution by products with the same compound is considered.

3.1 Timing and intensity of competition

In order to characterize the dynamics of between- and within-patent competition, we take into account both (i) the timing from market launch to the entry of follow-on competition, and the timing from market launch to the entry of generic producers; (ii) the intensity of competition as characterized by sales erosion conditional on entry.

Survival analysis is employed to study the factors affecting the residual patent life, as well as time to follow-on and generic entry. To measure the intensity of between-patent competition, we rely on a simple model of technological substitution, in which penetration of the new technology is expressed as a (non-decreasing) function of time (starting from the

[11] The Anatomical Therapeutic Classification (ATC) groups drug products on the basis of the therapy, with the anatomy as the main organizing theme. The classification is hierarchical and, at the first digit, compounds are grouped according to the organ or system on which they act; at the second digit, classes are formed according to their pharmacological and therapeutic action. The third digit groups together all compounds with the same therapeutic and pharmacological characteristics, whereas, at the fourth digit, also chemical characteristics are considered. For example, at the first digit, class A refers to compounds targeted to the alimentary tract and to metabolism with drugs used to treat acid related disorders classified in A02. The third digit further distinguishes between antiacids (A02A), drugs for peptic ulcer and gastro-oesophageal reflux disease (A02B), and other drugs for acid related disorders (A02X). At the fourth digit, class A02B further distinguishes H2-receptor antagonists, prostaglandins, proton pump inhibitors, combinations for eradication of Helicobacter pylori, and other drugs for peptic ulcer and gastro-oesophageal reflux disease. As an example, an analysis of competition dynamics in the class of H2-receptor antagonists is reported in Berndt *et al.* (1995). With few exceptions, also in the analysis of follow-on drug development undertaken by DiMasi and Paquette (2004), the therapeutic class is identified on the basis of ATC4. The four-digit markets are thus a more accurate level to analyse product competition.

time when the following in-patent competitor enters the market) (Fisher and Pry, 1971).

Let $s(1,t)$ be the market share of the innovator at time t and $s(2,t)$ the market share of competing (follow-on) technology. We set at $t = 0$ the time when the period of market exclusivity for the innovator product ends with the entry of the next in-patent compounds.[12] Penetration is measured as a function of the (log) ratio $q(t) = s(2,t)/s(1,t)$, and it is assumed to evolve as the following function of time (Fisher and Pry, 1971):

$$\ln[s_i(2,t)/s_i(1,t)] = \theta_{0i} + \theta_{1i}t + u_{it} \tag{3}$$

with θ_{1i} measuring the erosion of product i due to follower entry (entry of product $i+1$). The higher the value of the estimated θ_{1i}, the faster the erosion of sales due to follow-on competition.[13]

The regression results are then exploited to devise a measure of market exclusivity which appropriately accounts for the level and patterns of between-patent competition following the entry of competitors' products. That is, we value each month from product launch to patent expiry on the basis of expected market competition. We assign the value 1 to every month before the entry of the next in-patent competitor, and then the value of one additional month of patent life is weighted on the basis of the intensity of competition. The measure of market exclusivity (in-patent) is defined as follows:

$$ME_{in} = \sum_{t=1}^{T-L_1} D(t < L_2 - L_1) + D(t \geq L_2 - L_1) P\left(\frac{1}{1+\hat{q}_t}\right)$$

with L_1 and L_2, respectively, the time of entry of the innovator and the time of entry of the next follow-on competitors, T the statutory patent life,[14] $\hat{q}_t = \exp(\hat{\theta}_0 + \hat{\theta}_1 t)$, $D(z) = 1$ if z is true, and $P(a) = p_e \times a + (1 - p_e)$ with p_e equal to the probability of experiencing follow-on competition.

[12] 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 substitutes.

[13] The coefficient θ_{1i} will be written as a function of product and market characteristics.

[14] As a result, $T - L_1$ represents the residual patent life after the innovator's launch, and $L_2 - L_1$ is the interarrival time before follow-on competition.

So far, we made the simplifying assumption that at patent expiration generic producers enter the market fostering Bertrand competition and driving down prices to marginal costs. However, this might not be the case and the value of the patent extends beyond patent expiry (Hudson, 2000). Thus, in order to consider a measure of market exclusivity that also takes into account post-expiry dynamics, we take into account the timing and intensity of generic competition. Analogously, using the Fisher-Pry set up, we study the penetration dynamics of generic products as compared to branded products after patent expiration:

$$\ln[s_m(G,t)/s_m(B,t)] = \theta_{0m}^G + \theta_{1m}^G t + u_t \tag{4}$$

where $s_m(G,t)$ represents the total sales of generic producers, $s_m(B,t)$ represents the total sales of branded products in market (molecule) m. Time is measured in quarters from the year of patent expiry. The higher the value of the estimated θ_{1m}^G, the faster the erosion of branded sales due to generic entry.

By combining the in-patent and off-patent periods, we define the following measure of market exclusivity (in- and off-patent, total):

$$ME_{tot} = ME_{in} + \sum_{\tau=1}^{120} P\left(\frac{1}{1+\hat{q}_\tau}\right) \times P_G\left(\frac{1}{1+\hat{q}_t^G}\right) \tag{5}$$

with $\hat{q}_\tau = \exp(\hat{\theta}_0 + \hat{\theta}_1(T - L_1 + \tau))$, $\hat{q}_\tau^G = \exp(\hat{\theta}_0^G + \hat{\theta}_1^G \tau)$, $P(a) = p_e \times a + (1 - p_e)$ with p_e equal to the probability of experiencing follow-on competition, and $P_G(a) = p_G \times a + (1 - p_G)$ with p_G equal to the probability of experiencing generic competition.[15] ME_{tot} is thus equal to ME_{in} plus the value accruing after patent expiration.

3.2 Measuring R&D complexity and parallel R&D

For each drug development project, PHID monitors both the therapeutic market toward which the compound is targeted and the biological mechanisms of action of the drug can-

[15] A fixed time frame of 10 years (120 months) after patent expiration is considered. We also experimented using different time frame with no difference in the results.

didates.[16] A number of important 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 evolution of technology (Gambardella, 1995, Henderson *et al.*, 1999, Pammolli *et al.*, 2011). The connectedness of drug development to its scientific underpinnings has increased the range of scientific opportunities available to players in the industry, leading to a proliferation of alternative approaches for targeting the same pathology (Drews, 2000, Hopkins and Groom, 2002, Drews, 2003, Overington *et al.*, 2006). We claim that the larger the number of available approaches, the more complex is the research surrounding the pathology, as a clear path for the treatment has still to be identified. Accordingly, the level of R&D complexity k is proxied by the (log) number of the differing biological targets which are considered by R&D projects in the preclinical stage.[17]

We also exploit the information developed with the help of a pharmacologist, aimed at describing and assessing disease complexity.[18] The evaluation is based on several parameters such as outcome (whether lethal if therapy is not provided), any organ damage or complication, the etiology (distinguishing multifactorial etiology, monofactorial etiology, and diseases with unknown etiology). We argue that the complexity of the disease is higher for lethal diseases or diseases causing complications and organ damages, as well as for diseases with unknown or multifactorial etiology (Pammolli *et al.*, 2011).[19]

We devise a measure of product similarity (β) based on the content of scientific publications and patents. If two compounds are jointly mentioned in a scientific publication, they should share some features. Thus, we measure β by looking at co-occurrences in publications. In particular, we define a dummy variable equal to 1 if there is at least one publication in which the innovator compound is mentioned together with compound(s) available within

[16] As an example, for the treatment of glaucoma, various approaches have been pursued including prostaglandin agonist, 5HT antagonist, alpha adrenergic agonist. PHID allows us to distinguish compounds using the different research approaches. The information is available for different therapeutic indications.

[17] Indeed, in our data, markets in which a higher number of biological mechanisms is explored are also characterized by a lower probability of success.

[18] The main source for disease information was Braunwald *et al.* (2001). We also drew information from e-medicine reviews in the disease database at the <http://www.diseasedatabase.com>.

[19] In some specification of the model, we also include dummy variables that identify ATC1 classes in order to check robustness of the estimated coefficients.

the same market (ATC4). Ad hoc queries were performed in PubMed in order to select publications mentioning the compounds included in our analysis.[20]

We also considered information in patent citations and build on the idea, well-established in the literature, that if patent A cites patent B, it means that patent A contains a piece of knowledge patent B is building upon, leading us to claim that the two patents need to share some features (Jaffe and Trajtenberg, 2002, Fontana *et al.*, 2009). A dummy variable is considered, equal 1 if the innovator compound cites previous patents in the same market (ATC4).

On the basis of our model, we expect a negative effect of these variables on the time span between innovator launch and competitor entry.[21]

DiMasi and Paquette (2004) show that later entrants tend to enter the market sooner (that is, the time from first-in-class to the second follow-on drug is longer than the timing from the second to the third follow-on drug). Accordingly, the order of entry of each compound (computed according to observed entry for all the time periods available) is also included in the regressions of between-patent competition.[22]

3.3 Additional control variables

We consider additional variables as controls in the analysis of R&D and market competition. Since it has been shown that concentrated and smaller markets attract lower entries (Acemoglu and Linn, 2004), market size is taken into account to control for the attractiveness of different market opportunities. Moreover, market concentration at the time when the innovator compound was launched (as defined by the Herfindahl index of concentration at ATC4 level) and the market share of the innovative firm within the same ATC4 before launch of the new product are added to the regressions to control for market power and experience, respectively. The pre-launch market share of the innovator is also included, to take into account the possibility of a deterrent effect, where the fear of costly litigation leads to distortions

[20]Data were updated to September 2008.

[21]These two variables are obviously not included in the analysis of within-patent competition, as there is complete correspondence between the molecule in the branded products and that in generic drugs.

[22]Also this variable is not included in the analysis of within-patent competition.

in the pattern of innovative investments. Available evidence shows that this is indeed the case for smaller firms (Lerner, 1995). 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. The higher the share of self-citations a patent receives, the stronger the competitive position of the firm/institution in that particular technology (Hall *et al.*, 2000). Therefore, slower entry by competitors is expected, i.e., the expected sign of this variable is positive.

A description of the variables included in the analysis is provided in Table 1.

**** TABLE 1 ABOUT HERE ****

4 Competition in the pharmaceutical industry

Before turning to the analysis of between- and within-patent competition, we characterize the dynamics of drug development process, and the corresponding period of patent coverage of innovative compounds. The life of pharmaceutical patents can be decomposed in two periods: (a) the time from patent filing to market launch (i.e. the timing of product development and clinical testing); (b) the time from market launch to the end of statutory patent life (see Figure 1). For every compound, our database report both the launch date and the date of patent filing and expiry (including patent extensions, if any) at the country level. Accordingly, country-specific information are taken into account.[23] In Figure 1 we distinguish products launched before 1990, products launched in the 1990s and products launched in 2000 or later.[24]

**** FIGURE 1 ABOUT HERE ****

Figure 1 shows that the timing from patent filing to market launch is increasing over time, with a corresponding decrease in the residual patent life (and therefore, faster exposure to the

[23]If the same compound is launched in two different countries, it is treated as two (not independent) records in the dataset.

[24]The duration analysis presented in Section 4 (Tables 2 and 4) only considers products launched over the period 1993-2007, that is 6,644 country-products. For some analysis (e.g. results in Figure 1) we extend our dataset to include compounds launched before 1993 (10,757 country-products).

competition by generic producers).[25] All differences over time are statistically significant at the 5 percent level, with the exception of the time of compound R&D in the US for product launched over 1990-99 as compared to 2000-08. All in all, Figure 1 provides evidence of a decrease in residual patent life driven by an increase in the timing of product development.

Table 2 reports the results of a survival analysis in which the dependent variable is the time (months) from product launch to patent expiry in each country. Among the independent variables, the number of biological targets is used to proxy R&D complexity, together with dummy variables for disease characteristics. Country fixed effects (Country Dummies) and time dummies are included in all specifications.

**** TABLE 2 ABOUT HERE ****

Consistent with theoretical predictions, the number of R&D trajectories negatively affects the timing from product launch to patent expiration. The result holds true when the variables describing the disease characteristics and market dummies are included in the analysis. The coefficients for the measures of disease complexity (that is, whether lethal, causing organ damage or complications, and the etiology) are broadly coherent with predictions: the coefficient for lethal diseases is negative, but it lacks statistical significance; patents protecting drugs that may cause organ damage or complications record lower residual patent life; patents associated to drug targeted to diseases with monofactorial etiology exhibit longer residual patent life. The order of entry has a positive effect; however, this is not statistically significant when market dummies are included in the regression.

We next consider the analysis of the expected time between product arrivals, as measured by the time lag (in months) between the launch of each product and the entry of the next

[25]Note that, for the US, our estimates of the residual patent life for products launched before the year 1989 are coherent with data provided by Dranove and Meltzer (1994). For more recent times, DiMasi *et al.* (2003) reports a total time of about 11.9 years from initial synthesis of a compound to FDA approval, therefore including human clinical trial, preclinical and the discovery stage. However, comparison with our results is complicated by the fact that pharmaceutical firms apply for patent protection during the preclinical stage (Danzon *et al.*, 2007). Still, we get longer estimates of successful completion than DiMasi *et al.* (2003), and the difference might be due to the different set of organizations included in the analysis (DiMasi *et al.*, 2003 only consider data from large pharmaceutical firms, whereas both large and small organizations are included in our analysis).

in-patent in the same market (ATC4).[26]

Table 3 reports the Kaplan-Meier estimates of the share of innovators enjoying market exclusivity after selected years from launch. Matching the results of Mansfield (1984), we find that about 1/2 of patents undergo competition by substitute products within 4 years. This share increases to 70% when we consider a time-span of 10 years from innovator launch. We run a set of regressions to understand the role of R&D complexity and product similarity on market exclusivity (see Table 4).

**** TABLE 3 ABOUT HERE ****

The regression model takes into account the time between market entry and the launch of the next in-patent competitor in the same market. Country and time dummies are included in all specifications.

**** TABLE 4 ABOUT HERE ****

The variable identifying project relatedness (both in patents and scientific publications) has a negative and statistically significant effect: more similar products experience faster entry, providing support to our theoretical predictions. Consistently with DiMasi and Paquette (2004) the order of entry has a negative and statistically significant effect.

Estimated Models 3-5 also include in the regressions the measure of R&D complexity and additional controls. The number of R&D trajectories has a positive effect on the time lag to follow-on entry, but the coefficient is only marginally significant, when market controls are included in the analysis (Model 5). Products targeted to diseases causing organ damage or complications experience slower entry of follow-on competitors, whereas, when diseases with monofactorial etiology are considered, the entry of follow-on competitors is faster. Sign of the estimated coefficients are broadly consistent with our predictions in Proposition 2, that is, lower R&D complexity leads to faster entry of follow-on competitors. In most cases,

[26]We analyse the time span between pairs of subsequent launches in the same ATC4, referring to the innovator as the first product in the pair and the follower as the second one entering the market. The first product need not be the first compound launched in the ATC4, but may have been considered a "follower" in another pair.

statistical testing fails to reject the null hypothesis that the single coefficient is equal to zero; however, coefficients are jointly statistically significant in Model 5.[27]

The market and firm control variables introduced in Model 5 have the expected sign, although they are not statistically significant.

Overall, correlation of R&D portfolios play a significant role in the pharmaceutical industry, leading to a shrinkage of market exclusivity times. Conversely, milder support is provided to the prediction that increasing R&D complexity lead to a longer market exclusivity time, however this prediction holds only when there is no R&D correlation. Even if the coefficients of the "R&D complexity" variable have the expected sign, they are jointly significant at the 1% level only in Model 5.

The interarrival time only provides a partial picture of the intensity of between-patent competition, and it is important also to analyse sales erosion spanning from follow-on products. Analysis is carried out by relying on the model of technological substitution proposed by Fisher and Pry (1971).

As described in the previous section, let $s(1,t)$ be the market share of the innovator at time t and $s(2,t)$ the market share of competing (follow-on) technology.[28] The time $t = 0$ corresponds to the entry of the next in-patent compounds. Quarterly sales data are available, so time is measured in quarters from the follower launch. Penetration is measured as a function of the ratio $q(t) = s(2,t)/s(1,t)$.

As a preliminary descriptive account of the main dynamics characterizing between-patent competition (in terms of sales and pricing strategy), Figure 2 shows the median values of sales (value and quantity) and price ratios for each product in our database, together with 40th and 60th percentiles.

**** FIGURE 2 ABOUT HERE ****

[27] The p-value of the joint test undertaken on the "complexity" variables (R&D trajectories, lethal, organ damage, complications, and monofactorial etiology) is less than 5%.

[28] As sales and price figures were only available from July 1996, the sample is further reduced and now only comprises products launched over the time period covered by the sales data. In addition, only products for which the entry of a substitute in-patent compounds was actually observed can be considered in the analysis.

We find evidence of a strong first mover advantage. After about twenty quarters (five years) from the launch of the competing product ($j = 2$), the median ratio between sales market share of the follower and the older innovator is about 0.7 for sales values (0.6 for quantities sold). In our model, we examined the upper bound of equal market shares for the old innovative compound and the new one. Empirically, in most cases, the younger innovation never reaches the sales value of the original innovator, consistent with evidence of brand loyalty within the pharmaceutical field (Scherer and Ross, 1990, Schmalensee, 1982, Sutton, 1998).

The median values of the price ratios show that the follower price is higher than the price charged by the innovator, also explaining the lower penetration when quantities are considered. The result is consistent with the model of Perloff *et al.* (1996), in which the price of a competing product may be above the price under market exclusivity in a wide range of cases (both collusive behavior and Bertrand competition).

Result of the Fisher-Pry regression (3) are reported in Table 5. A fixed effect panel data model is employed for estimation. The coefficient θ_{1i} is written as a linear function of compound and market characteristics. As these are fixed over time for each product, it is not possible to identify the effect of those variables on the average of the dependent variable (that is, whether these variables affect θ_{0i}), however it is possible to identify whether penetration dynamics (as captured by θ_{1i}) are different on the basis of those observable characteristics of the compounds and of the market.[29] Besides the variables used in the survival analysis, we include the age of the compound in the regressions, in order to test whether sales erosion has become faster over time. The higher the value of the estimated θ_{1i}, the faster the erosion of sales due to follow-on competition. The introduction of the interaction terms between t and product/market characteristics allows us to assess the variables that significantly affect the penetration dynamics.

**** TABLE 5 ABOUT HERE ****

[29]This is accomplished by including in the model interactions between t and the variables of interest.

According to our estimates, younger products experience faster erosion: the coefficient of the interaction between t and product age ($t\times$Product age) is negative, and statically significant. Also, drugs targeted to markets with a larger number of R&D trajectories experience slower sales erosion. As for the correlation of projects, products citing previous patents experience faster sales erosion, whereas no significant effect is detected when correlation is measured trough co-occurrence in scientific publications. Finally, erosion is faster in larger markets.

4.1 Generic competition and post-patent expiry dynamics

We now analyze off-patent competition between generic producers and branded (patented) products,[30] looking both at the time span from patent expiry to first generic entry and whether the pattern of generic penetration has changed over time.[31]

Figure 3 reports the hazard function of the time to generic entry from the year of patent expiry. Compounds are grouped on the basis of the year of patent expiry,[32] and we show that the entry of generic producer is becoming faster over time (Grabowski and Kyle, 2007). Products whose patent has expired after the year 2000 are more likely to experience generic entry soon after patent expiration as compared to products whose patent has expired in the previous time period.

**** FIGURE 3 ABOUT HERE ****

Table 6 reports the estimates of a survival model, where the dependent variable is the time from patent expiry to generic entry, and we consider the effect of the disease dummies and market characteristics at the time of patent expiration.[33]

**** TABLE 6 ABOUT HERE ****

[30] When we referring to generic products, we are considering *unbranded* generics. PHID does not allow us to identify branded generic products.

[31] In this section, the relevant market is defined grouping compounds with the same molecular entity.

[32] We restrict our analysis to molecules with patent expiry over the years 1993-2007. The set of compounds considered in the analysis is therefore different from the one in previous section, in which we were taking into account innovator products *launched* over the same time period.

[33] A Weibull survival distribution has been considered for the analysis.

Results show that generic entry is faster (the time from patent expiry to generic entry is shorter) in larger and more concentrated markets, whereas the reverse is true for lethal diseases, as well as diseases causing permanent organ damage and with monofactorial etiology. However, the effects of the disease dummies is not robust to the inclusion of the market (ATC1) dummy variables, with the exception of compounds targeted to diseases with monofactorial etiology. Besides time to generic entry, it is important to analyse the erosion of sales spanning from generic competition.

Analogously to the study of between-patent competition, we rely on the Fisher-Pry model to study the penetration dynamics of generic products. Figure 4 shows the median ratio of generic sales to branded sales after patent expiry. After about 5 years, the ratio of generic sales to branded sales equals 1/2, that is generic products hold about one-third of total market sales. Price competition is substantial, with price of generic products being about 75 percent of the average price of branded products.

**** FIGURE 4 ABOUT HERE ****

Table 7 reports the results of the estimate of the Fisher-Pry regression for the case of generic producers, as in equation (4). The higher the value of the estimated θ_{1m}^{G}, the faster the erosion of branded sales due to generic entry. In this regression we consider the interaction between the years since patent expiry and t,[34] trying to understand whether younger products experience faster sales erosion by generic producers (see also Grabowski and Kyle, 2007). We also include the interaction with disease and market characteristics considered in the previous regression.

**** TABLE 7 ABOUT HERE ****

Conditional on entry, the erosion of sales of branded products due to the entry of generic producers is substantial, and it is faster for products experiencing patent expiry in more

[34] Again, all regressions include interactions between t and country dummies to allow for different dynamics at the country level.

recent years. As for the disease and market characteristics, these have a limited impact on sales erosion.[35]

All in all, our results indicate stronger competition due to generic entry in the recent years.

4.2 The role of complexity and parallel R&D

Building on the estimates obtained in the previous sections, we compute the predicted market exclusivity time according to the different definitions proposed in this paper, and highlight the differences between the US and EU-15 countries.

Table 8 reports the computed value of residual patent residual patent life (RPL), and market exclusivity considering the period before patent expiry (ME_{in}) and including competition by generic producers (ME_{tot}). RPL and the time from innovator entry and follow on competition have been computed according to the Models estimated in Table 2 and Table 4 (respectively, Model 2 and Model 3 have been considered in the computations). Sales erosion from between- and within-patent competition has been computed on the basis of the Fisher-Pry regressions reported in Table 5 (Model 4) and Table 6 (Model 2). We considered average values for all the variables included in the regressions, and changed the level of R&D complexity (trough the number of trajectories and the share of lethal diseases), and R&D correlation (baseline, corresponding to the average value of R&D correlation in patents and publications; full correlation both in patents and publications; no correlation nor in patents neither in publications).

Results show that by increasing R&D complexity, the RPL decreases, as well as ME_{in}. On the contrary, an increase in ME_{tot} is observed, as the result of decreasing competition by generic producers.

The level of correlation of compounds has an effect on market exclusivity: higher correlation implies shorter interarrival times between the innovator and the follow on competitors, therefore reducing ME_{in} and ME_{out}. In particular, setting full correlation of R&D com-

[35] Conditional on entry. However these variables have an impact on the timing of generic entry (see Table 6).

pounds decreases the value of innovative drugs of about 14% when all countries included in the analysis are considered. Of this figure, 10% is due to decrease of between-patent competition, before the patent expires. The result has implications on the current debate on the disclosure of clinical trials data in Europe and the US. By fully disclosing clinical trial results, an increase in the correlation of R&D project portfolio is expected, implying changes in the pattern of competition and therefore in the value of innovative drugs. The effect is found to be stronger for the US with respect to European countries. Also, by comparing the values of ME_{in} and ME_{out} for the United States and Europe, we observe a higher competition induced by generic producers in the United States as compared to Europe after patent expiration.

5 Concluding remarks

The role of patent protection in the pharmaceutical industry is largely debated searching for a balance between incentives to R&D, market contestability and competition.

In this paper we develop a simple model to examine the effect of increasing R&D complexity and correlation of R&D portfolio on market turnover. We predict the erosion of market exclusivity times and shrinking of product lifetimes in the presence of parallel R&D and correlated R&D market portfolios. The model is tested exploiting a comprehensive dataset on innovative activities and market sales in major European countries and the US.

After the completion of the human genome project, there has been a sharp increase in the number of potential targets for new cures. Given that unexplored new targets had to be validated (or discarded), the proliferation of R&D trajectories has lead to longer R&D trials in the first place, thus reducing the market life of pharmaceutical patents. Since all companies experience the same negative shock in R&D productivity, the arrival of follow-on products should also be delayed. Counterbalancing this effect, the presence of correlation in project portfolios, as measured through co-occurrence in scientific publications and patent citations, translates into shorter periods of market exclusivity. In face of increasing R&D uncertainty, firms tend to focus on a subset of research trajectories, thus selecting correlated R&D projects.

Overall, our results show that increased R&D complexity and relatedness among compounds increase competition, thus reducing the value accruing to innovative drugs.

The analysis reveals interesting differences in the patterns of competition in Europe *vis-á-vis* the US. First, the residual patent life is longer in the US than in Europe. This might explain by longer clinical trials in the US or by delayed launches in the European countries. When between-patent competition is considered, the value of innovative compounds is similar in Europe and the US, leading us to claim that sales erosion due to follow-on competition is stronger in the US as compared to Europe. Also, when the competition in the off-patent segment of the market is taken into account, the value of innovative products is higher in Europe than in the US, due to the stronger competition introduced in the US by generic producers at patent expiration.

Increasing competition has two opposite effect on residual patent life and total value, as increasing R&D complexity reduces residual patent life and increases the value of innovative drugs, especially when the off-patent market is taken into account.

This paper also contributes to the recent debate on the potential consequences of disclosing full information of clinical trials, which is undergoing both in Europe and in the US. While it is unclear whether disclosing clinical trial results would affect the probability of success in drug development, our analysis reveals that it has strong implications on the value innovative drugs. The increased information that would become available on the features of investigational compounds would push correlation of R&D portfolios, thus reducing the value of innovative compounds. The effect would be stronger in the US than in Europe.

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	Between-patent competition		Within-patent competition	
Variable	Mean	Standard Deviation	Mean	Standard Deviation
R&D trajectories	4.422	.7175	–	–
Lethal	.3037	.4599	.2331	.4228
Organ damage	.5710	.4950	.6351	.4815
Complications	.0882	.2836	.0998	.2998
Monofactorial Etiology	.0673	.2505	.0272	.1628
R&D correlation	.7313	.4433	–	–
Order of entry	2.717	2.127	–	–
Concentration	.0771	.1684	.0588	.2092
Market size (log)	6.411	3.431	5.411	3.172
Experience	.0226	.1085	–	–
Self-citations	.2092	.3146	–	–

Table 1: Descriptive statistics of the variables included in the analysis of between- and within-patent competition

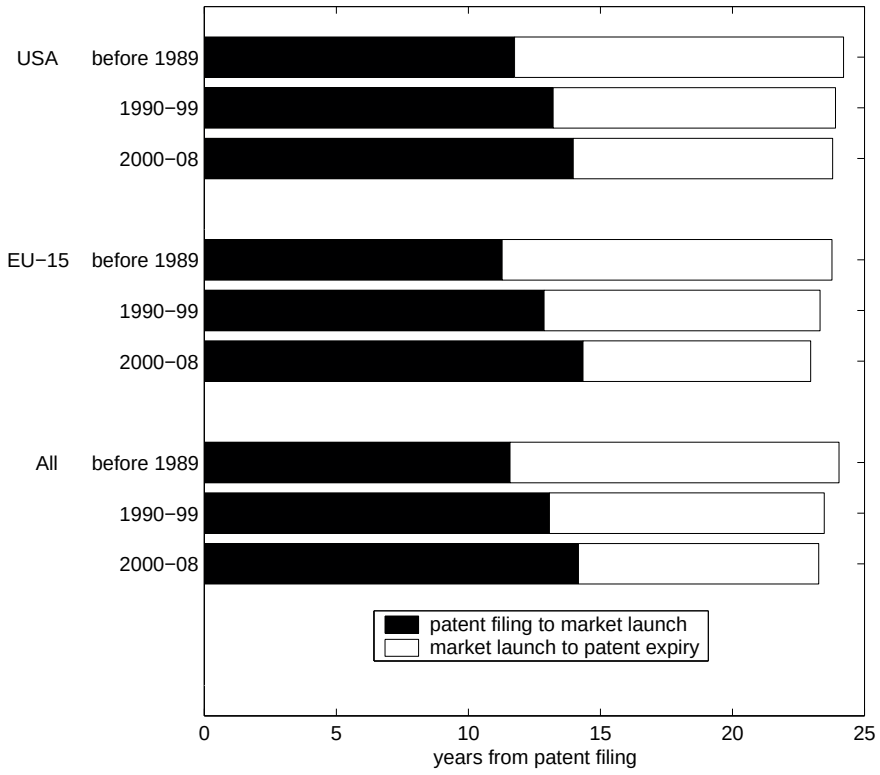

Figure 1: Decomposition of patent life: (a) from patent filing to market launch; (b) from market launch to patent expiry, by year of product launch.

Variable	Model 1	Model 2	Model 3
R&D trajectories	-.0457**	-.0495***	-.0486**
	(.0182)	*(.0182)*	*(.0201)*
Lethal	-.0241	-.0286	-.0369
	(.0521)	*(.0535)*	*(.0521)*
Organ damage	-.0876*	-.0850*	-.0825*
	(.0480)	*(.0497)*	*(.0455)*
Complications	-.1479***	-.1487***	-.1160**
	(.0514)	*(.0522)*	*(.0468)*
Monofactorial etiology	.0868**	.0881**	.1378***
	(.0371)	*(.0378)*	*(.0425)*
Order of entry		.0105**	.0063
		(.0042)	*(.0041)*
Constant	5.148***	5.119***	5.036***
	(.0908)	*(.0940)*	*(.1006)*
Time Dummies	yes***	yes***	yes***
Country Dummies	yes***	yes***	yes***
Market Dummies	no	no	yes***
σ	.3351***	.3367***	.3245***
	(.0159)	*(.0156)*	*(.0149)*
κ	1.652***	1.632***	1.691***
	(.0792)	*(.0767)*	*(.0773)*
Log lik	-4606.6	-4596.1	-4481.8
N	6,644	6,644	6,644
AIC	9287.2	9268.1	9065.6

Robust standard errors in brackets.

(adjusted for clustering at market level).

Statistical significance: *** 1%; ** 5%; *10%

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

Time-span	percentage of products still under market exclusivity
1 year	77.19
4 years	46.01
8 years	31.50
10 years	27.49

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

Variable	Model 1	Model 2	Model 3	Model 4	Model 5
R&D correlation	-1.052***	-.9255***	-.9479***	-.9369***	-.9615***
(publ.)	*(.1460)*	*(.1458)*	*(.1082)*	*(.1387)*	*(.1696)*
R&D correlation	-.5841***	-.5409***	-.5312***	-.5201***	-.5110***
(patents)	*(.1104)*	*(.1112)*	*(.1082)*	*(.1069)*	*(.1339)*
Order of entry		-.1171***	-.1122***	-.0811***	-.1194***
		(.0276)	*(.0284)*	*(.0278)*	*(.0321)*
R&D Trajectories			.0897	.0889	.1914**
			(.0824)	*(.0878)*	*(.0962)*
Lethal			.1027	-.0420	-.0077
			(.2285)	*(.2445)*	*(.3068)*
Organ damage			.3842*	.0793	.4585
			(.2016)	*(.2286)*	*(.2905)*
Complications			.7540**	.6521*	.7978**
			(.3044)	*(.3162)*	*(.3911)*
Monofactorial etiology			-.2551	-.2984	-.3656
			(.2133)	*(.2216)*	*(.2367)*
Concentration					.2311
					(.2372)
Size (log)					-.0004
					(.0206)
Experience					.1935
					(.3583)
Self-cits.					.0678
					(.2064)
Constant	4.303***	4.786***	4.098***	4.351***	3.852***
	(.2830)	*(.3373)*	*(.5540)*	*(.5970)*	*(.6259)*
Time Dummies	yes***	yes***	yes***	yes**	yes***
Country Dummies	yes***	yes***	yes***	yes***	yes**
Market Dummies	no	no	no	yes***	no
σ	1.575***	1.566***	1.555***	1.538***	1.567***
	(.0242)	*(.0375)*	*(.0386)*	*(.0406)*	*(.0491)*
Log-lik	-9,591.6	-9,542.9	-9502.5	-9427.4	-6681.9
AIC	19,249.2	19,153.8	19,083.1	18,958.8	13,447.7
N	6,644	6,644	6,644	6,644	4,942

Robust standard errors in brackets (adjusted for clustering at the market level).

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

Table 4: Survival analysis: time from innovator launch to follower entry; Log-Normal hazard function.

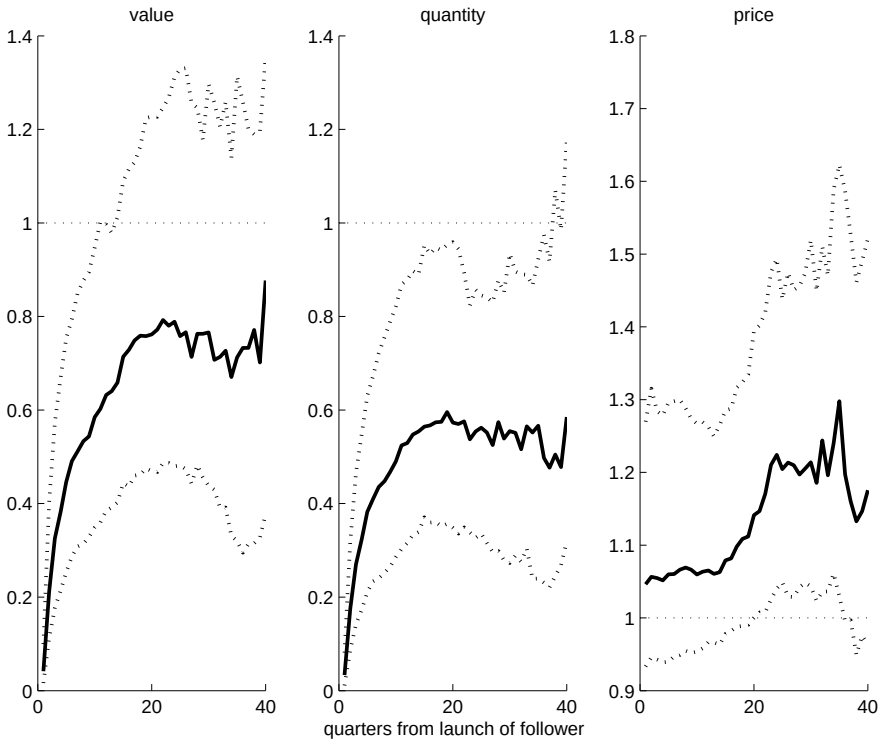

Figure 2: Sales (value) of follower / sales of first innovator.

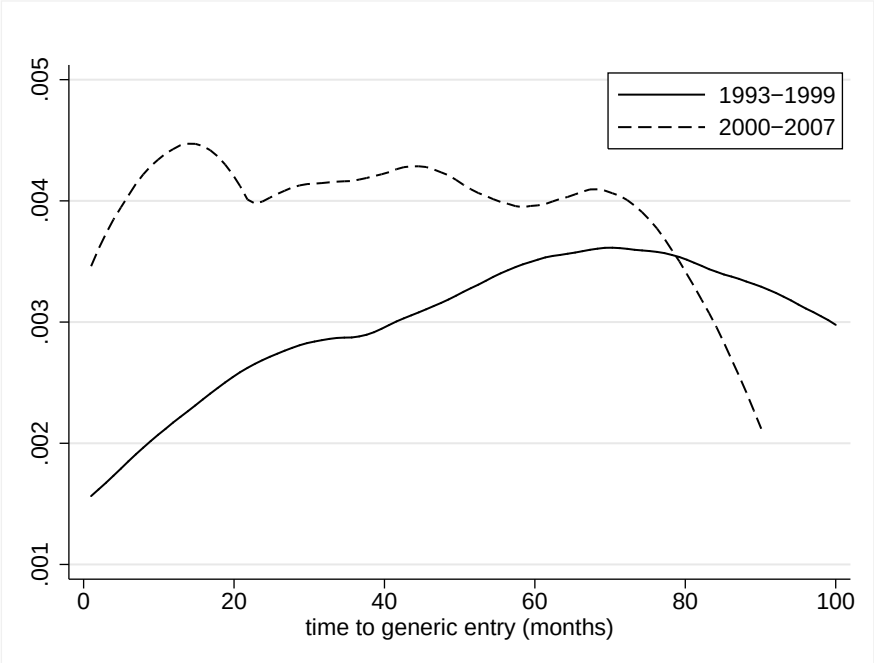

Figure 3: Hazard of generic entry after patent expiry, compounds grouped on the basis of the year of patent expiry

Variable	Model 1 (value)	Model 2 (value)	Model 3 (value)	Model 4 (value)	Model 5 (value)	Model 6 (quantity)
t	.0434***	.0877***	.0743***	.0991***	.1278***	.1188***
	(.0102)	*(.0146)*	*(.0194)*	*(.0254)*	*(.0351)*	*(.0335)*
t×Product age		-.0039***	-.0031***	-.0026**	-.0063***	-.0069**
		(.0009)	*(.0011)*	*(.0012)*	*(.0019)*	*(.0019)*
t×R&D correl. (publ.)			-.0032	.0034	.0145	.0139
			(.0073)	*(.0081)*	*(.0105)*	*(.0104)*
t×R&D correl. (patents)			.0192***	.0207***	.0155**	.0199***
			(.0058)	*(.0060)*	*(.0074)*	*(.0074)*
t×Order of entry			.0025	.0031	.0014	.0017
			(.0021)	*(.0022)*	*(.0026)*	*(.0026)*
t×R&D Trajectories				-.0103**	-.0125**	-.0101**
				(.0047)	*(.0052)*	*(.0051)*
t×Lethal				.0176	.0111	.0041
				(.0135)	*(.0196)*	*(.0185)*
t×Organ damage				.0134	.0073	.0011
				(.0122)	*(.0194)*	*(.0178)*
t×Complications				.0119	.0066	.0062
				(.0135)	*(.0197)*	*(.0184)*
t×Monofactorial etiology				.0247**	.0153	.0223*
				(.0107)	*(.0115)*	*(.0117)*
t×Concentration					-.0214	-.0170
					(.0226)	*(.0232)*
t×Size (log)					.0021*	.0027**
					(.0013)	*(.0013)*
t×Experience					.0377	.0263
					(.0239)	*(.0239)*
t×Self-cits.					.0061	.0119
					(.0089)	*(.0090)*
Constant	-1.385***	-1.408***	-1.405***	-1.421***	-1.401***	-1.421***
	(.0289)	*(.0283)*	*(.0293)*	*(.0293)*	*(.0315)*	*(.0312)*

Note: All regressions include interactions between t and country dummies.

Table 5: Result of the Fisher-Pry regression; sales erosion from between-patent competition.

Variable	Model 1	Model 2	Model 3
Lethal	.8545***	.6038***	-.1207
	(.1863)	*(.2102)*	*(.2177)*
Organ damage	.8621***	.6235***	-.1234
	(.1737)	*(.1992)*	*(.2034)*
Complications	.4764**	.2368	.0711
	(.2037)	*(.2385)*	*(.2280)*
Monofactorial etiology	.7655**	.7617**	1.018***
	(.3326)	*(.3483)*	*(.3433)*
Size (log)		-.5588***	-.5782***
		(.0307)	*(.0301)*
Concentration (HHI)		-.4579***	-.4539***
		(.1529)	*(.1472)*
Constant	4.6735***	9.5390***	10.371***
	(.2459)	*(.4327)*	*(.4610)*
Time Dummies	yes***	yes***	yes***
Country Dummies	yes***	yes***	yes***
Market (ATC1) Dummies	no	no	yes***
p	.8211***	.8611***	.9291***
	(.0247)	*(.0281)*	*(.0298)*
Log lik.	-3296.7	-2322.6	-2133.4
N	3835	3259	3259
AIC	6663.4	4713.1	4362.7

Table 6: Time from patent expiry to generic entry, Weibull survival function.

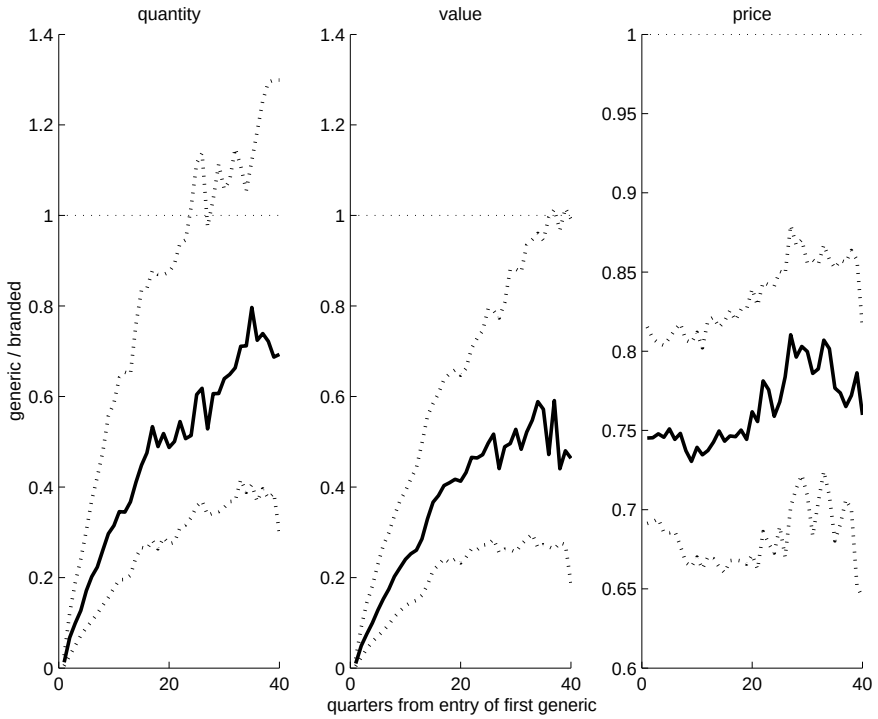

Figure 4: Penetration of generic producers and pricing strategy: sales value, quantity and prices (line: median; dotted lines: 40-th and 60-th percentiles)

Variable	Model 1 (value)	Model 2 (value)	Model 3 (value)	Model 4 (value)	Model 5 (quantity)
t	.0756***	.1285***	.1627***	.0895**	.1706***
	(.0155)	*(.0235)*	*(.0278)*	*(.0437)*	*(.0381)*
$t\times$Years since patent expiry		-.0062***	-.0075***	-.0072***	-.0087***
		(.0020)	*(.0023)*	*(.0024)*	*(.0023)*
$t\times$Lethal			-.0047	.0023	-.0121
			(.0200)	*(.0207)*	*(.0232)*
$t\times$Organ damage			-.0285**	-.0229	-.0279*
			(.0143)	*(.0151)*	*(.0163)*
$t\times$Complication			-.0313**	-.0257	-.0352**
			(.0153)	*(.0159)*	*(.0166)*
$t\times$Monof.etiology			.0181	.0284	.0324*
			(.0188)	*(.0186)*	*(.0175)*
$t\times$Size (log)				.0063	.0038
				(.0040)	*(.0029)*
$t\times$Concentration				-.0058	.0031
				(.0162)	*(.0155)*
Constant	-2.939***	-2.965***	-2.923***	-2.946***	-2.648***
	(.0570)	*(.0607)*	*(.0645)*	*(.0655)*	*(.0637)*

All regressions include interactions between t and country dummies.

Table 7: Result of the Fisher-Pry regression, sales erosion from within-patent competition

		R&D correlation								
		baseline	no correl.	full correl.	baseline	no correl.	full correl.	baseline	no correl.	full correl.
R&D trajectories		**United States**			**Europe**			**All countries**		
baseline	RPL	117.09	117.09	117.09	112.09	112.09	112.09	112.40	112.40	112.40
(mean)	ME_{in}	103.03	117.00	90.80	102.03	111.55	92.37	102.09	111.90	92.27
	ME_{tot}	149.89	182.67	128.54	163.18	191.10	141.21	162.35	190.57	140.42
low	RPL	118.86	118.86	118.86	113.79	113.79	113.79	114.10	114.10	114.10
(1st quartile)	ME_{in}	103.04	117.49	90.70	102.70	113.18	92.72	102.73	113.45	92.59
	ME_{tot}	148.17	181.19	127.59	161.72	190.87	139.98	160.88	190.26	139.20
high	RPL	114.40	114.40	114.40	109.52	109.52	109.52	109.82	109.82	109.82
(3rd quartile)	ME_{in}	101.98	114.00	90.96	100.97	109.20	92.06	101.03	109.50	91.99
	ME_{tot}	151.79	183.42	130.39	165.35	191.37	143.51	164.50	190.87	142.69
Lethal	RPL	114.80	114.80	114.80	109.91	109.91	109.91	110.21	110.21	110.21
diseases	ME_{in}	101.16	114.00	87.95	100.60	109.33	89.98	100.63	109.63	89.85
	ME_{tot}	145.70	181.49	124.42	158.06	190.10	135.75	157.29	189.56	135.04

Table 8: Predicted values of RPL, ME_{in}, and ME_{tot} for different values of R&D complexity and project correlation.

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