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Patent Value and R&D Competition

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Abstract

This paper aims at characterizing the dynamics of R&D competition within the pharmaceutical domain, focusing on the role of patent disclosure, the extent of uncertainty, and role of scientific advances. Following the empirical literature in the economics of innovation, we employ patents as a proxy for innovations and patent citations as a measure of knowledge utilization and spillovers. Pharmaceuticals are a unique setting in this respect, given the characteristics of the innovation process, that make patents an important means for appropriating returns from R&D. All in all, the analysis provides evidence that in the pharmaceutical industry research advances through a process of trial-and-error, where both successes and failures set the ground for subsequent innovations. The disclosure of the information about new compounds or new mechanisms of action play an important role in this industry fostering R&D efforts and competition in identified therapeutic markets in the search for new marketable products building both on failures and successes. The outcome of this process is highly uncertain and building on a success provides no certainty about the outcome of the search. Indeed, discontinued patents building on previous failures exhibit a higher citation rate. We also contribute to the debate about the relevance of citation in measuring patent value by looking at the relationship between patent citations and product sales.

1 Introduction

The pharmaceutical industry faces continued criticism over the productivity of R&D spend and in particular over the value of "me too" innovation. There is a lack of understanding of the nature of scientific advance in medicine and the extent of uncertainty (in terms of project failure) of R&D work in a therapy area.

This paper – which is part of a larger on-going research project on the properties of R&D competition in pharmaceuticals – looks at the features of the learning process that characterizes the actors operating within the pharmaceutical domain. This industry represents a unique framework for studying issues related to innovation and innovative activities, given its strong roots into the realm of scientific knowledge, the important role played by patents as a means for protecting economic returns from R&D (in exchange of the full disclosure of the characteristics of the innovation), the high level of competition and its distinctive industry structure, where actors with different ethos, especially with regard to information sharing and disclosure, and different capabilities coexist and have created a wide network of collaborations[1].

Strong linkages exist between drug development and the scientific advances in the "Open Science", leading firms to dissect and analyze an increasing number of techniques, trajectories and exploration strategies (Orsenigo, Pammolli and Riccaboni 2001). Basic science constantly feed the innovation process in pharmaceuticals, leading firms to seek within a common pool of knowledge. Despite that, research investments across firms are weakly correlated, after removing the common effect due to exogenous shocks (Henderson and Cockburn 1994). This pattern notwithstanding, knowledge spillovers play a significant role in pharmaceutical research and competing projects exhibit complementary patterns, as rival research results are positively correlated with firm productivity (Henderson and Cockburn 1994, Henderson and Cockburn 1996).

Against this background, we build on a comprehensive dataset about the innovative activity of pharmaceutical and biotechnology firms, including R&D project level data, patents, citations, and collaborations, and explore the nature of technological advances and of the underlying technological (learning) regime, shaping the industrial patterns of innovative activity (Nelson and Winter 1982, Winter 1994, Malerba and Orsenigo 1993, Breschi, Malerba and Orsenigo 2000).

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[1]See, e.g., Powell, Koput and Smith-Doerr (1996)

The literature has analyzed the pattern of successes over time, finding evidence of low serial correlation in the introduction of successful products within families of chemically related compoounds at the firm level (Sutton 1998). Analogously to the economic value of findings and non-findings spanning from basic research, we claim that the learning process within the pharmaceutical domain builds both on R&D successes and failures (David, Mowery and Steinmueller 1992).

Given the high relevance of patent for protecting pharmaceutical innovations (Cohen, Nelson and Walsh 2000, Arundel and Kabla 1998), research efforts are proxied using patents, whereas knowledge utilization and spillovers are measured by looking at the pattern of patent citations[2]. The key assumption is that a citation made to a previous patent denotes a knowledge transfer from the cited patent to the citing one[3]. Patents rule out direct imitation of the innovative compound or process, nonetheless the information disclosed trough patents expand the knowledge frontier and can provide rivals useful insights into new chemical and pharmacological properties of compounds or mechanism of action, eventually fostering research for new patentable compounds or processes. Two competing processes can be at work here. On the one side, patenting may guarantee the innovating firm an advantaged position in the industry. On the other side, the disclosure of a breaktrough innovation trough patenting may be the source of new technological opportunities for the firms operating in the same industry, providing information the rivals can build upon. Generally, empirical results support both types of effect, depending on the appropriability and complementary asset regimes (McGahan and Silverman 2006).

Our analysis reveals that technological competencies are accumulated building both on successfully developed compounds and on failures. On the one side, it is not surprising that marketed products play an important role in guiding subsequent research efforts of both the innovating firm and its rivals. On the other side, also failures, i.e. compounds that do not pass trough all the stages involved in drug development, due, for example, to lack of effectiveness or toxicological effects, substantially spur rival innovative efforts. Actually patents whose knowledge base also comprises failures by rival firms have higher relevance as measured by the number of life-time

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[2]See Jaffe and Trajtenberg (2002) and the literature referenced therein.

[3]We are aware that patent citation count is only a noisy proxy of the relevance of the knowledge disclosed, since citations might be included for strategic purposes or added by firm's lawyers or by patent examiners (Alcacer and Gittelman 2004). However, survey evidence shows that, even if noisy, patent citations are indicative of knowledge spillovers and communication among inventors (Jaffe, Trajtenberg and Fogarty 2000).

received citations.

The distinction between leadlike and druglike compounds is useful in interpreting our results. At the early stages of drug development, firms identify lead structures, i.e. compounds that typically exhibit sub-optimal target binding affinity, but with relatively simple chemical features, well-established structure-activity relationship, good properties in terms of absorption, distribution, metabolism, and excretion, and a favorable patent situation, making them good starting points in medicinal chemistry efforts (Oprea, Davis, Teague and Leeson 2001). Even though they will never reach the market, a large number of subsequent development builds on their structure.

In the pharmaceutical technological paradigm (Dosi 1988), firms need to be able to master knowledge from many different sources when searching for new molecules with optimal target binding affinity properties. First basic scientific knowledge about the relationship between chemical structures and physical properties, then technological capabilities and previous experience, built on the basis of both its failures and successes, and of failures and successes of rival firms. The analysis presented in the paper shows that knowledge about failed compounds play an important role in guiding subsequent research efforts, both within and outside the originating firm boundaries.

The paper is organized as follows. Section 2 describes the features of the drug development process, which is characterized by high uncertainty, low cumulativeness, and by a large presence of knowledge spillovers. Section 3 describes the data and the methods used in this study. Section 4 presents the empirical results, discussed in Section 5, also drawing implications in terms of efficiency of the research efforts at the sector level.

2   The Drug Development Process

When talking about the innovation process and its dynamic properties, the pharmaceutical industry is a peculiar one in many respects.

The pharmaceutical industry is a textbook example of a "science-based" sector (Pavitt 1984), where innovation, both in the form of new therapeutic products and improvements of existing products (in terms of better delivey, reduced side effects, or improved efficacy) is jointly driven by advances in the field of applied sciences and in the knowledge about bacterial, animal and human processes led by the scientific community. Innovation is, in turn, the fundamental source of firm competitiveness and profitability.

However, the pharmaceutical R&D process involve high costs, long development times, and it is subject to high uncertainty. The innovative process of drug development evolves linearly through well-defined stages. When a firm discovers a potentially active substance a patent is applied for preventing firm's rivals from copying the new compound or technology. Even if important, the patent is only the first step in a lengthy process for the development of new drugs, not always ending with a product that can be commercialized on the market. First, preclinical trials are aimed at assessing the safety of administering the compound to human, and then clinical trials are carried over for assessing its safety and effectiveness in targeting the selected indications. Only in case all the stages are successfully passed, the new compound can be registered and then marketed, allowing the firm to recover the R&D costs necessary for its development. Studies based on US trials report an average time of 6/8 years from the start of clinical testing to submission of a new drug application or a biological licensing application (DiMasi, Hansen and Grabowski 2003, Abrantes-Metz, Adams and Metz 2004). Pre-approval costs are estimated to be over 800 million US (2000) dollars (DiMasi et al. 2003, Adams and Brantner 2006). Besides development times and out-of-pocket expenditures, cost estimates takes into account the significant share of R&D projects is abandoned due to the emergence of toxicological effects or to the lack of effectiveness in treating the targeted disease. US Food and Drug Administration (FDA) estimates that only a small percentage of the discovered compounds lead to a marketable product: among the compounds selected for human clinical trials, 70% passes Phase I, while the share of successful compounds is significantly reduced in the case of Phase II and Phase III, respectively 33% and 25-30% (Trenter 1999). Even if a product successfully reaches the market, firms do not suspend the monitoring activity to check the emergence of side effects or new toxicological evidence that might eventually lead to the withdrawal of the product from the market[4].

In addition, the pharmaceutical R&D process is characterized by a large presence of R&D spillovers. Larger firms enjoy higher productivity rates not only for economies of scale, but also for economies of scope spanning from a high level of diversification in the R&D activity that allow firms to capture internal and external knowledge spillovers (Henderson and Cockburn 1996).

As a result, firm competitive advantages both on the R&D and market

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[4]On the positive side, monitoring side effects (emerging also during clinical trials) might also produce evidence suggesting new application of a compound, the most striking example being Viagra (Kling 1998).

side, are quickly eroded over time. In an analysis of the patents related to the memory-enhancing agents (MEA), a "tree-plane" model of technological development is presented. The authors identify the central technology plane, containing patents related to MEA, and its precursor and successor technology planes, containing respectively the earlier, cited research, and the patent protecting the new applications or variations of the MEA central technology. The three planes are populated by different sets of institutions, showing that firms other than the central MEA innovator are able to catch the new technological opportunities (Narin, Smith jr. and Albert 1993).

On the market side, empirical evidence suggests that having a leading product in a therapy class is not a predictor of the likelihood of having a leading (in house originated) product in the next generation of therapies for that disease. Sutton (1998) analyzed the top 50 selling drugs in 1960, 1973, and 1986, focusing on the patterns of entry of new drugs. The analysis shows few instances where firms have been able to mantain their leading position in the submarket, pointing to a low degree of serial correlation in success. Rather, market shares are likely eroded by rivals, introducing the large majority of chemically related compounds that have followed the introduction of a top-selling product.

Evidence based on the US market dynamics shows that the reduction in the present discounted value of the innovator's return from between-patent competition, i.e. from new drugs introduced in the same therapeutic category, appears to be at least as large as the reduction from within-patent competition, induced by generic producers at patent expiration, and may be much larger (Lichtenberg and Philipson 2002).

All in all, entry and competition in R&D is higher in pharmaceuticals than in other sectors.

These features, coupled with ease of imitation of pharmaceutical compounds, make patents an important means for protecting innovations and, as a result, a good measure of the research effort in the pharmaceutical domain[5].

We exploit the information provided by patents and patent citations, as

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[5]Results from the Carnegie Mellon Survey, about the nature and strength of the appropriability conditions in the US manufacturing sector, administered in 1994, show that the drug industry is the one where patents received the highest score as an effective mechanism for protecting property rights (Cohen et al. 2000). In addition, 100% of respondents stated one of the reasons for patenting product innovations rely in preventing rivals from copying the innovation. Based on a different survey about the patenting activity of the largest European firms, Arundel and Kabla (1998) report a high propensity to patent in pharmaceuticals: the combined rate for both product and process innovations is higher than 50% in this industry.

a proxy for research efforts and knowledge diffusion, in order to characterize the dynamic nature of the innovation process in pharmaceuticals.

When using patent-based indicators for measuring technological change is important to recognize the fact that "the quality of the underlying innovation varies widely from patent to patent" (Scherer 1965), meaning that innovations differ substantially in terms of their technological and economic impact. The first empirical account of the heterogeneity in the private value of patents was based on information about the renewal fees of European patents (Pakes 1986, Schankerman and Pakes 1985, Schankerman and Pakes 1986), confirming that the distribution of patent value is highly skewed: a large amount of patents has a very low value, while the patents that provide important advances both in the technological and economic respects are quite few. Since then, various information regarding the patent documents have been used in the economic literature as a proxy for patent value, including the number of claims, the family size (i.e. the number of countries in which a patent application was filed on the innovation); the number of backward and forward citations; whether the patent was litigated and the years of renewal of the patent fees[6].

We exploit the citation-value (both technological significance and economic impact) relationship largely investigated by the empirical literature on innovation and supported by survey evidence, and focus on the pattern of citations received by a patent, as a proxy for knowledge utilization and diffusion (Jaffe and Trajtenberg 2002, Harhoff, Narin, Scherer and Vopel 1999, Jaffe et al. 2000).

3   Data and Methods

The analysis builds on a comprehensive dataset on the innovative activity undertaken within the pharmaceutical industry, including R&D project level data, patents, citations, and collaborations[7].

The database contains information about all pharmaceutical and biotechnology patents[8] granted by the USPTO since 1965, including backward and forward citations. Firm data at the level of specific R&D project worldwide in the last 25 years are also available. The database tracks the development history of about 16,400 R&D projects, starting from patent application

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[6]For a review see Lanjouw, Pakes and Putnam (1998); Hall, Jaffe and Trajtenberg (2001); Jaffe and Trajtenberg (2002).

[7]See www.databiotech.com.

[8]US patents in selected IPC and US classes are included in the database.

to the latest stage of drug development through preclinical, clinical development and commercialization. In case of aborted projects, the database reports the time when the firm announces that the research around the compound has been discontinued. By exploiting the information about the patents protecting the compound, the project data have been matched to patent data[9], including the number of forward citations up to May 2004, the application date, and the name of the assignee. Patent history is available for 49 per cent of the projects included in the database. In case a compound is marketed, the database reports the information about the trade name across different countries, allowing us to gather information about sales in the US market over the period January 1994-March 2005.

The matching of the different sets of data proved to be a formidable, large-scale task, that tied up a great deal of our research efforts for a long time, providing us a unique dataset that monitors R&D activities of pharmaceutical and biotechnology firms from patenting to eventual commercialization of the protected compound[10].

We further selected the patents associated to R&D projects of candidate drugs that were terminated either with a success, i.e. a product commercialised on the market, or with a failure, i.e. the project was discontinued due to the emergence of toxicological effects or to lack of effectiveness. The final database encompasses information about 2,000 R&D projects and their associated patents, entering into clinical trials from 1977 to 2002. Henceforth, we refer to marketed (discontinued) patents as the patent associated to marketed (discontinued) R&D projects.

Citation patterns of our sample of patents is compared with a sample of "matched" patents, for which our database reports no information about preclinical or clinical development. For each patent in our sample with known outcome (marketed or discontinued), a "matched" patent has been randomly selected[11] from the set of biopharmaceutical patents with the

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[9]For projects listing a patent granted by a patent office other than the USPTO, we considered the US patent in the same family as the one listed in the database. In case no US patent is identified, the project is not considered in the analysis. This choice has been driven by the fact our sources only provide citation data for US patents. Moreover, different patent examination procedures characterizes the the US and European patent offices, leading to large differences in the average number of citations per patent (Breschi and Lissoni 2004, Michel and Bettels 2001). Focusing only on US citations avoids the emergence of spurios results driven by different institutional settings.

[10]Old molecules and/or natural products, which do not have any associated patent have been omitted from the analysis.

[11]We have built three different "matched" samples in order to check the robustness of our results. Estimated coefficients across the three samples do not change substantially.

same application year, publication year, and IPC class as the focal (marketed or discontinued) patent considered for selection. By comparing the citation pattern of discontinued and marketed patents against the selected sample of "matched" patents, we will be able to ascertain the level of knowledge utilization and diffusion associated with each set and the related R&D competition dynamics.

Since the focus is on the pharmaceutical industry, only citations from subsequent patents in the pharmaceutical domain have been taken into consideration. We distinguish self-citations from citations made by other companies. Citations made by others have been proved to be a good proxy for knowledge spillovers (Jaffe et al. 2000), whereas self-citations are considered to be indicators of the cumulative nature of the technology and a measure of the extent to which innovators are able to reap the benefits of their own research (Hall et al. 2001).

First, we will employ the double-exponential function to model the citation lag distribution for marketed and discontinued patents, against the average biopharmaceutical patents (i.e. the sample of "matched" patents). The model provides a flexible framework for studying the process underlying the generation of citations, where an exponential process by which knowledge diffuses is combined with a second exponential process by which knowledge become obsolete (Jaffe and Trajtenberg 1996, Caballero and Jaffe 1993). Following Jaffe and Trajtenberg (1996), we model the likelihood that a patent granted in year T will cite a patent granted in year t as:

$$p(t,T) = \alpha \exp[-\beta_1(T-t)](1 - \exp[-\beta_2(T-t)])$$

where α is linked to the overall likelihood of receiving a citation, whereas β_1 and β_2 are indicators of, respectively, the rate of obsolescence of knowledge (i.e., the rate at which new knowledge replace the existing one) and the rate of diffusion of the knowledge related to the invention protected by the patent. It is not possible to separately identify the three parameters in the model. We allow the parameters describing the average citation intensity (α) and the rate of obsolescence (β_1) to vary as a function of attributes of both the cited and the citing patent (particularly, we distinguish marketed and discontinued patents from the sample of matched patents with no information about preclinical or clinical development), whereas the rate of diffusion (β_2) is considered constant across the patents with different outcome (marketed/discontinued/"matched"). By doing so, we implicitly assume that the three sets of patents we consider can differ in terms of average citation intensity and obsolescence rate, whereas the rate of diffusion of the information

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disclosed trough the patent is not affected by the outcome of subsequent development.

The analysis allows us to ascertain knowledge utilization and diffusion that is associated with marketed and discontinued patents with respect to the other patents issued within the biopharmaceutical domain.

Next, we run a regression where the dependent variable is the number of citations received by our sample of patents adjusted on the basis of the estimated citation lag distribution, in order to reflect life-time citations. The estimation aims at identifying the factors that affect the importance of the patent and of the associated innovation. We include among the regressors a set of dummy variables identifying cases where the patent is building on a previous failure or success and whether the patent is cited by subsequent successes/failures. Control variables for the characteristics of the technological classes (defined on the basis of the International Patent Classification, henceforth IPC), assignees and the patent-innovation itself are added.

The two sets of results will provide a clear picture of the dynamics underlying R&D competition in the biopharmaceutical domain. The estimation of the citation lag distribution function will allow us to show the dynamics associated with knowledge utilization and diffusion, whereas the regression analysis aims at disentangling the relationship between the productivity of knowledge and its sources.

Finally, we take into account the linkage between patent citations and the private value of patented innovations, as measured by the value of sales over the patent life. We model the total number of citations received by the patent as a function of total sales over a 20-year window from launch, obtaining an estimate for the elasticity of sales with respect to citations.

4   Empirical Results

4.1   Citations and project outcome

Figure 1 compares the observed and estimated citation lag distribution functions for marketed and discontinued patents, taking as a benchmark the citation lag distribution function of patents with no information about pre-clinical or clinical development. On the x-axis, the citation lag, i.e. the difference between the citing and the cited patent grant year, is reported. It represents the time elapsed from grant date. The y-axis depicts the (average) observed and estimated citation intensities, i.e. the likelihood that any patent will be cited by the patents granted x years apart (Jaffe and Trajtenberg 1996).
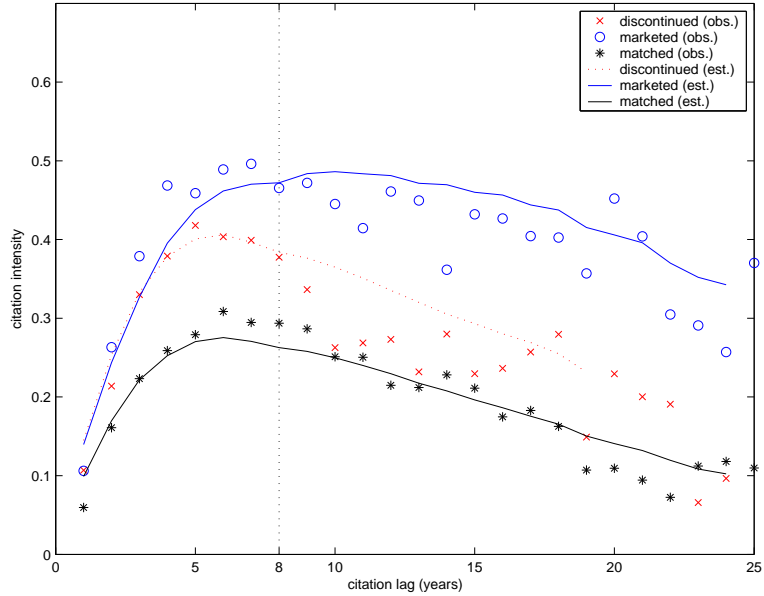
Figure 1: Observed and estimated average citation lag distribution

The observed citation lag distribution is computed as the ratio between the number of citations received by patents granted in year t from patents granted in year T and the theoretical number of potential citations:

$$p(t, T, o) = \frac{c(t, T, o)}{n(t, o)\, n(T)}$$

where t indicates the grant year of the cited patent, T is the grant year of the citing patent[12], and o represents the outcome of the associated R&D project (marketed or discontinued vs. matched patents). The potential number of citation is given by the number of citations that would have been observed if all patents granted in year T would have cited all patents granted in year t with outcome o (marketed/discontinued/"matched"), that is equal to the product of the number $n(T)$ of patents granted in the citing year and the number $n(t, o)$ of patents granted in the cited year with a known outcome o.

In order to estimate the theoretical citation lag distribution, we considered the following specification of the double-exponential function:

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[12]The citation lag is given by $T - t$.

$$p(t, T, o) = \alpha(t, T, o) \exp[-\beta_1(o)(T - t)](1 - \exp[-\beta_2(T - t)]).$$

We claim that the grant year of the citing and the cited patent[13] only affect the average citation intensity α, while the outcome of the project affect both the average citation intensity α and the rate of obsolescence β_1. Due to identification problems, the rate of diffusion (β_2) is considered constant over time and across the three sets of patents. Particularly, given the citation-value relationship widely documented by the empirical literature, we expect that marketed patents receive on average a higher number of citations with respect to discontinued patents. The model specification however allows us also to dig further into the dynamics of knowledge utilization and diffusion and to analyze the speed and extent to which existing knowledge is "picked up" in the case of failures and successes, as a proxy for the diffusion and utilization of the associated innovation. Estimates, reported in Table 1, are obtained by nonlinear least squares estimation, weighting each observation by $[n(t, o) \, n(T)]^{1/2}$. The lines depicted in Figure 1 are obtained by taking the average[14], for each lag, of the fitted values from Model 2.

The Figure also indicates the 8-year citation lag, which corresponds to the average length from patent application to termination of the project[15].

Coherently with previous literature showing that the number of citations received by a patent is positively associated to its value[16], citations turn out to be related to the outcome of the project. The observed and estimated distributions indicate that, on average, discontinued patents receive a number of citations that is lower than the number of citations received by patents associated to marketed projects (compare the values of the $\alpha^{discontinued}$ and $\alpha^{marketed}$ coefficients). However, both sets receive a higher number of citations than the average patent in the biopharmaceutical domain with no information about clinical or preclinical development. The estimate of the α coefficients associated to discontinued and marketed patents are higher than 1, indicating that patents associated to preclinical or clinical development,

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[13]As in previous empirical literature dealing with this model, convergence problem forbids the estimation of the model where all the cited-year effects are considered. The problem is solved by introducing the cited-year effects considering 5-year time periods.

[14]Both in the case of observed and estimated citation lag distributions, weighted averages are considered, where the weights are the same as the ones used in the estimation process.

[15]This is actually few months longer for marketed compounds, being equal to 7.8 years for discontinued R&D projects and to 8.3 years for marketed R&D projects.

[16]See Trajtenberg (1990); Lanjouw and Schankerman (1999); Harhoff et al. (1999); Jaffe et al. (2000); Trajtenberg, Henderson and Jaffe (1997); Jaffe and Trajtenberg (2002).

	Model 1	Model 2
$\alpha^{discontinued}$	1.264**	1.329**
	(0.182)	(0.111)
$\alpha^{marketed}$	1.309**	1.511**
	(0.158)	(0.108)
β_1	0.107**	0.084**
	(0.008)	(0.013)
$\beta_1^{discontinued}$	0.827**	1.049**
	(0.135)	(0.108)
$\beta_1^{marketed}$	0.554**	0.604**
	(0.087)	(0.077)
β_2	0.114**	0.248**
	(0.014)	(0.042)
Cited year effects	no	yes
Citing year effects	no	yes
R-squared	0.686	0.858

* statistically significant at 5% level.

Table 1: Results of the double-exponential estimation, dependent variable: citation intensity

irrespective of their outcome, are more likely to receive a citation than the average biopharmaceutical patent (taken as the reference category). The analysis shows that there exists a value associated also with discontinued patents: even though the compound associated with the patent will never reach the market, due to the emergence of toxicological problems or lack of effectiveness, the opened research trajectory is a source of information and insights for firms other than the original innovator.

It is interesting to note that within the first 5 years from patent grant, no significant difference is detected between discontinued and marketed patents, whereas starting from year 5 the two series start to diverge in a significant way. The analysis of the estimates of β_1 reveals an important difference between marketed and discontinued compounds in terms of knowledge obsolescence. Under this perspective, discontinued patents and the matched set of patents exhibit very similar dynamics (the β_1 associated with associated with discontinued patents is very close to 1, pointing to no differences between discontinued patents and the matched set of patents). On the contrary, the knowledge embedded in patents protecting marketable compounds becomes obsolete less quickly than the other patents in the biopharmaceu-

tical domain (the β_1 associated with marketed patents is lower than 1). Indeed, the citation intensity of marketed compounds is rather stable after commercialization, whereas the citation intensity of discontinued patents decreases substantially[17].

The maximal citation frequency for discontinued patents is earlier in time than the maximal citation frequency of marketed patents.

Our estimates are coherent[18] with the estimates of the Drugs and Medical sector presented by Hall et al. (2001). Moreover, an interesting pattern emerges in their results when comparing Drugs and Medical to other sectors. The citation lag distribution for this sector is more flat, whereas the citation lag distribution functions for the sectors of Computers and Communications, Electrical and Electronics, Chemical, and Mechanical have higher peak earlier in time. Knowledge in the Drugs and Medical sector diffuses less rapidly and takes a longer time to become obsolete. Important information about the protected compounds in terms of toxicological effects and effectiveness are revealed over time leading to a lengthier process of citation within this industry.

The disclosure of the information about the compound under study in patents and the advances in science sets the ground for a "race" for reaching the market, where competitors start exploring the new research arena pursuing parallel research trajectories even though the outcome is still highly uncertain. Competition on the R&D side in the pharmaceutical industry is substantial and firms entering the new research arena build both on future failures and successes.

The regression model presented in the following aims at adding new insights into the issue by looking at the relevance of the research building on failures and on successes, and of the research cited by future failures and successes.

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[17]Also note that the larger departures between the estimated and observed citation lag distribution in the case of discontinued patents is registered right after the average time for discontinuation. This might point to the fact that the termination of the research around a compound/mechanism of action is a major signal for rival firms that nonetheless regain interest after few years from the time of discontinuation and the citation intensity of discontinued patents is still higher than the citation intensity of the "matched" set of patents, also many years after discontinuation. On this issue, we mention the fact that we asked a pharmacologist to extensively inspect the patents citing discontinued projects in search of a reason for the citation, finding no instance of "negative" citations, rather citations refer to pharmacological action or the structure of the compound.

[18]With respect to Hall et al. (2001) results, our estimated β_2 coefficient is lower. This might be explained by the fact that we only consider citations by institution other than the original assignee, which can require a longer time span with respect to self-citations to manifest.

The dependent variable is the (log) number of citation received during the life time of the patent, where the observed citation frequency has been adjusted using the estimated coefficient of the citation lag distribution function[19] (Table 1).

The independent variables are listed in Table 2 and aim at capturing the characteristics of the cited patent, of the IPC class and of the patenting firm. Moreover by taking into account whether R&D projects associated to backward and forward citations have been discontinued or have successfully reached the market, we aim at contributing to the discussion about the productivity of R&D spillovers (Levin and Reiss 1988).

Few patents cited by or citing our sample of patents are associated to a R&D project with a known outcome. Particularly, we identify 9 per cent of patents building on a previous failure, and 10 per cent of patents building on a previous success. On the other side, 6 per cent of patents are cited by a future success, and 9 per cent by a future failure. This reflects the fact that pharmaceutical and biotechnology firms screen thousands of compounds but very few enter into preclinical and clinical stages of development.

As far as the characteristics of the technological class of the patent, we consider the number of firms active in the IPC class, and the Herfindahl index of concentration computed at the technology class level on the basis of patent counts.

Patents characteristics are measured using the indicators developed by Trajtenberg et al. (1997) on the basis of backward citations. We consider the share of self-citations in the patents (pt-selfc) that measures the extent to which benefits from research antecedents are appropriated by the firm and help in understanding whether the patent belongs to a research trajectory strongly rooted within the company. The index of originality of the patent (pt-orig) measures the breadth of its technological roots[20], whereas the importance of the previous patents cited by the patent under investigation is measured by pt-importb which takes into account the number of backward citations in the patents and the number of citations they receive[21]. The importance of scientific sources with respect to technological ones within the

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[19]Given the integer nature of the citation values, we set log(0)=0.

[20]The index is computed as an Herfindahl index of diversification, considering the share of backward citation in each IPC class. The closer pt-orig is to 1, the broader are the technological roots of the underlying research, i.e. they span many different IPC classes. The index is zero when all backward citations contained in the patent are classified within the same IPC class.

[21]The higher is the value of pt-importb, the higher is the number of backward citations contained in the patent and the citations they receive.

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Variable	Description	Mean	σ
failure	Dummy equal to 1 if the associated project is a failure	0.34	0.48
success	Dummy equal to 1 if the associated project is marketed	0.14	0.34
ipc-nimp	Number of firms operating in the same IPC class	112.75	125.33
ipc-conc	Concentration of the IPC Class (Herfindhal index)	0.09	0.19
pt-selfc	Share of self-citations of the patent*	0.15	0.30
pt-orig	Index of originality of the patent*	0.42	0.37
pt-science	Science Index*	0.32	0.34
pt-importb	Importance of cited patents*	89.44	484.36
pt-timeb	Average time lag*	5.38	4.41
ass-coree	Share of firm patent within the same technology class (IPC)	0.14	0.24
dbf	Dummy equal to 1 if the originating firm is a dedicated biotechnology company	0.14	0.35
pro	Dummy equal to 1 if the originator is a public research organization	0.13	0.33
bf	Dummy equal to 1 if the project-patent cites a previous failure	0.09	0.29
bs	Dummy equal to 1 if the project-patent cites a previous success	0.10	0.30
ff	Dummy equal to 1 if the project-patent is cited by a future failure	0.09	0.28
fs	Dummy equal to 1 if the project-patent is cited by a future success	0.06	0.25

* defined as in Trajtenberg et al. (1997).

Table 2: Description of the variables

patent is captured by pt-science, which is the ratio between the non-patent references and the total number of references (previous patents or previous scientific literature) listed in the patent. The closer to 1, the larger the scientific underpinnings of the research, relying more heavily on the scientific literature rather than on previous patents. Finally pt-timeb measures the time distance between the citing and the cited patents. The higher pt-timeb, the older the sources the patent builds upon.

As compared to the descriptive statistics reported in Trajtenberg et al. (1997), no difference emerges with respect to the value of pt-selfc. On the contrary, the average value of pt-timeb in our sample is lower, indicating younger sources for our sample of patents, whereas the values of pt-orig, pt-science, and pt-importb are higher. One important difference with the sample in Trajtenberg et al. (1997) relies in the fact that we only consider pharmaceutical patents, and citations are counted only within the pharmaceutical technological classes.

As far as the characteristics of the patent assignee are concerned, we take into account the share of firm patent within the same technology class (IPC), and two dummy variables indicating whether the patentee is a dedicated biotechnology company (dfb) or a public research organization (pro). The largest share of patents in our sample are assigned to pharmaceutical companies: 14 per cent of patents are assigned to dbf, and 13 per cent in the case of pro.

Results of the estimation of a censored regression model are reported in Table 3[22]. Cited year dummies are included in all the specifications. The Tobit estimation procedure has been preferred to simple regression due to the high incidence of patents receiving zero citations (27.28%).

Coherently with previous results and with the empirical literature supporting the use of citations received by a patent as a proxy for its value both in economic and technological terms (Trajtenberg 1990, Lanjouw and Schankerman 1999, Harhoff et al. 1999, Jaffe et al. 2000, Trajtenberg et al. 1997, Jaffe and Trajtenberg 2002), we find that patents associated to marketed R&D projects receive a higher number of citations than patents with no preclinical or clinical information. However, also discontinued patents receive a higher number of citations than our sample of matched patents (taken as the benchmark category), even though the estimated coefficient of the failure dummy is lower than the estimated coefficient of the success

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[22]We also aggregated the data at the project level, considering the citations to all the patents associated with a specific project. Results, available from the authors upon request, do not change substantially.

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	Model 1	Model 2	Model 3	Model 4
failure	0.578 *(0.056)***	0.561 *(0.057)***	0.424 *(0.055)***	0.376 *(0.060)***
success	1.294 *(0.076)***	1.270 *(0.078)***	1.036 *(0.076)***	1.062 *(0.084)***
ipc-conc	-0.350 *(0.146)***	-0.338 *(0.148)***	-0.263 *(0.141)**	-0.258 *(0.141)***
ipc-nimp	-.5E-3 *(.2E-3)***	-.5E-3 *(.2E-3)***	-.5E-3 *(.2E-3)***	-.5E-3 *(.2E-3)***
pt-selfc	-0.225 *(0.088)***	-0.228 *(0.093)***	-0.279 *(0.089)***	-0.281 *(0.089)***
pt-orig	-0.423 *(0.082)***	-0.403 *(0.083)***	-0.377 *(0.080)***	-0.381 *(0.080)***
pt-science	0.718 *(0.091)***	0.709 *(0.092)***	0.688 *(0.088)***	0.688 *(0.088)***
pt-importb	.4E-3 *(.5E-4)***	.4E-3 *(.5E-5)***	.4E-3 *(.5E-5)***	.4E-3 *(.5E-5)***
pt-timeb	-0.004 *(0.007)*	-0.007 *(0.007)*	-0.005 *(0.006)*	-0.005 *(0.006)*
ass-coree	0.184 *(0.110)**	0.186 *(0.110)**	0.240 *(0.106)**	0.238 *(0.106)***
dummydbf	0.560 *(0.080)***	0.570 *(0.081)***	0.538 *(0.078)***	0.540 *(0.077)***
dummypro	0.406 *(0.079)***	0.396 *(0.080)***	0.366 *(0.076)***	0.368 *(0.076)***
bf		0.125 *(0.094)*	0.081 *(0.091)*	-0.226 *(0.140)*
bs		0.215 *(0.085)***	0.027 *(0.083)*	0.118 *(0.124)*
ff			1.137 *(0.086)***	1.142 *(0.086)***
fs			0.994 *(0.105)***	0.986 *(0.104)***
bf*fail.				0.617 *(0.188)***
bf*succ.				-0.026 *(0.329)*
bs*fail.				-0.116 *(0.183)*
bs*succ.				-0.211 *(0.204)*
Constant	0.966 *(0.158)***	0.957 *(0.159)***	0.735 *(0.153)***	0.745 *(0.153)***
Log Likel.	-6880.51	-6739.59	-6600.79	-6594.30

** 5% level of significance; * 1% level of significance
Cited year (application) effects included in all regressions.

Table 3: Regression results. Dependent variable: ln(number of adjusted forward citations). Number of observation: 4,194.

dummy. Coherently with results reported in Table 1, discontinued patents receive a lower number of citations than marketed patents.

As far as the share of self-citations, the variable has a negative impact on the number of forward citations by firms other than the original assignee, supporting the claim that self-citations are indicative of the level of appropriability of research efforts. Being strongly rooted within the technological domain of the patent assignee significantly affects the number of citations subsequently received by firms other than the original innovator, i.e. the level of knowledge utilization outside the originating institution.

The estimated coefficients of pt-orig show that patents with sparse tech-

nological roots receive a lower number of citations by other firms. These are likely patents within narrow fields of application, therefore being relevant only to the firms and institutions working within the same technological domain.

Patents with predominance of scientific sources over technological ones contribute more heavily to subsequent research. This is not surprising within the biopharmaceutical domain, characterized by a strong link of innovative activity to its scientific underpinnings. Also patents building on an important (in the sense of highly cited) knowledge base are more often subsequently cited.

The estimated coefficients of pt-timeb, the average age of the sources the patent builds upon, is negative but not statistically significant. Competition in the pharmaceutical domain is substantial and the relevant knowledge base is rapidly evolving, pushing the innovating firms need to rely on the most recent advances and discoveries. Patents relying upon older knowledge bases have a low innovative content, and will be less often the basis of subsequent research. However, the age of the backward citations doesn't seem to affect significantly the number of forward patent references.

As far as the characteristics of the patent assignee are concerned patents by dbf and pro receive on average a higher number of citations. The former result is consistent with Hall, Jaffe and Trajtenberg (2000) who find that in the pharmaceutical sector smaller biotechnology firms are more likely to average a higher citation rate. As a tentative explanation for this phenomenon, we propose that this is due the growing division of innovative labor and the wide network of collaborations among the different actors involved in the drug development process that has come to characterized the pharmaceutical industry (Arora and Gambardella 1994, Powell et al. 1996, Orsenigo et al. 2001). The small biotechnology firms are highly specialized in the early stages of drug development, but they lack the resources and capabilities that are needed for the large clinical trials, therefore they are more likely to license-out their compounds to the large pharmaceutical companies with significant expertise with clinical trials. This is also true for public research organizations, strongly oriented toward basic science and the early stages of the innovation process in pharmaceuticals. As a result, dbf and pro patents are more likely to be the object of an alliance and the basis of subsequent research by firms other than the original innovators, leading to knowledge transfer from the original innovator to the company that licensed-in the compound and continues the research around it. Likely, the research undertaken by the licensee will give rise to new technological opportunities or compounds, and as a result the new innovation will certainly cite

the licensed patent, therefore increasing the number of citations received by competitors to dbf and pro patents.

The characteristics of the IPC class of the patent also exert a significant effect on the number of subsequent citations received by the patent. Patents in classes that are highly concentrated receive on average a higher number of citations. This result might be driven by the low incentives of firms other than the original innovators in pursuing research in classes where concentration on the technological side is high, i.e. the technological competences are bundled within a low number of firms. On the contrary, a higher number of firms in the technological class leads to a lower number of citations, *ceteris paribus*. Patents in crowded technological fields receive, on average, a lower number of citations, due to the larger number of different research trajectories pursued by different firms that can be the source of knowledge in subsequent developments.

Looking at the relevance of previous/future failures/success citing/cited by the patent, we note that patents that are subsequently cited by future failures and successes receive on average a higher number of citations. On the contrary, previous successes and failures do not have any statistically significant effect on the relevance of the patent for subsequent research[23], pointing to low cumulativeness of research and high uncertainty in the pharmaceutical domain. Building on a previous success doesn't assure to reach high levels of R&D productivity.

However, looking at the projects that entered into preclinical or clinical trials reveals that patents citing previous failures receive a higher number of citations than the base category. The composite effect is statistically significant for failed R&D project patents. This pattern might be the result of the process of trial-and-error at work within the pharmaceutical domain. The estimated coefficients support a role of failures in spurring technological competition in the pharmaceutical domain, being the basis of future research by other firms, which seems to reach higher levels of efficiency in pursuing the research, at least in terms of diffusion and utilization (as proxied by the number of received citations).

Overall the analysis reveals that the information contained in patents represent an important source of information for monitoring the R&D activities undertaken by the competitors and provide a spur to innovative efforts by other firms in related fields or in the same area of application of

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[23]The estimated coefficient of bs (a dummy variable equal to one if the project-patent cites a previous success) is positive and significant in Model 2, but the result is not robust to the inclusion of the ff and fs dummies.

the original patent.

4.2 Citations and sales value

We dig further into the citation-value relationship by looking at the strand of revenues associated to patented products. We considered the marketed patents in our sample and, by exploiting the information about the trade name of the compound in different market, we linked each marketed project (and its associated patent) to sales in the US market from January 1994 to March 2005. Analogously to the estimation of the citation lag distribution, we considered the double-exponential function in order to estimate the parameter of the function characterizing the product life cycle of the patented pharmaceutical products.

We considered the dynamics of market share within the ATC4 class over a 19-year time frame[24]. Figure 2 reports the observed and estimated sales dynamics starting from market launch, where we considered the evolution of market shares within the relevant therapeutic market, identified on the basis of the ATC4 class. Estimated coefficients are reported in Table 4.

	coeff.	s.e.	p-value
α	.3667	.0114	0.000
β_1	.0502	.0043	0.000
$R^2 = 0.4044$			

Table 4: Estimated parameters of the function describing the product life cycle (4,902 obs.)

Following the same procedure used in the case of the citation lag distribution function, the estimated coefficients allow us to compute weights that, applied to the value of sales over the observed time period, enable us to estimate the sales over a longer time span than the one observed in the data.

Computations allow us to study the relationship between total (computed) sales over the product life cycle and the total (adjusted) number of citations the patent protecting the compound receives. This has to be considered as a preliminary result, since we do not control for market size and characteristics, or for the level of competition. Nonetheless, available

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[24]The time span has been selected in order to resemble patent life. This has to be interpreted as a rough approximation, since effective patent life is shorter for pharmaceutical products, due to the time needed for drug development (Grabowski and Vernon 2000).
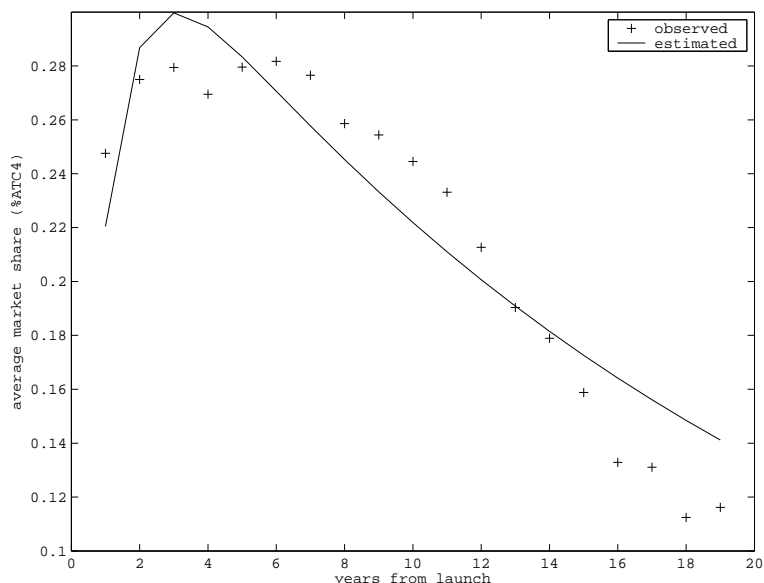
Figure 2: Observed and estimated sales distribution function

data allows us to characterize the citation-value relationship quite sharply looking at the strand of revenues associated to a patent during its life.

First, we consider simple correlation between sales and citations. Even though statistically significant at the 5% level, the magnitude of correlation coefficient is rather low: it is equal to 0.15 if calculated on adjusted values (both considering the first patent only or, in case of multiple patents protecting the same molecule, the sum of the citations received by all the patents), raising to 0.18 if log of variables is considered[25]. The scatter of the log of citations versus the log of sales is depicted in Figure 3.

Finally, we estimate a multiplicative model, where we consider the relationship between number of citations and total sales (estimated over the life-cycle). Let s_i be the total sales of the compound, and c_i the number of citations received by the patent (we considered both the citations received by the first patent covering the compound and the total number of citations for all the patents). We considered the following model (Cameron and Trivedi 2005):

$$E[s_i|c_i] = \exp[\gamma + \beta \ln(c_i)],$$

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[25]Variables deviate substantially from the normal distribution. The log-transformation is considered in order to reduce the departure.
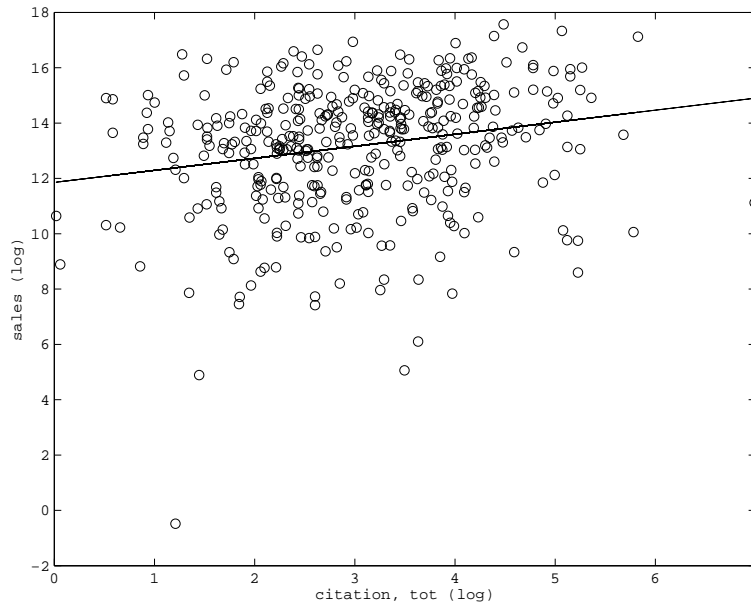
Figure 3: Log of citations versus log of product sales

estimated using nonlinear least squares (see Table 5). Given the specification of the model, β directly estimates the sales-citation elasticity.

	First patent	Total cits.
$\hat{\gamma}$	13.8407	13.5924
	(0.3067)	(0.2987)
$\hat{\beta}$	0.2899	0.3496
	(0.0827)	(0.0730)
N	396	397
R^2	0.2429	0.2606

Table 5: Model estimates: sales as a function of life-time citations

The reported R^2 is rather low, pointing to the fact that other factors need to be considered when analysing this relationship. Even though preliminary, results confirm the positive linkage between number of citations and private value of patents, documented in the empirical literature. A one percent increase in the number of citations correspond to a 0.30 per cent increase in total sales (market share within the relevant therapeutic market).

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5   Discussion and Policy Implications

This paper has looked at the nature of R&D competition in the pharmaceutical industry, a unique framework for studying issues related to innovation and innovative activities. Besides the importance of patents as a means for appropriating returns to R&D, as evidenced in surveys of firms in the manufacturing sectors in the US and Europe (Arundel and Kabla 1998, Cohen, Goto, Nagata, Nelson and Walsh 2002), a number of evolutionary trends has profoundly shaped the organization of innovative activities within the industry.

The industry has come to be the archetype of the "science-based" sector, where advances in basic knowledge about bacterial, animal and human processes provide a deeper understanding of the molecular and biochemical roots of specific diseases processes and of the mechanisms of pharmacological action of known and new substances, guiding the innovative activities of the actors involved in drug development. The advances in genomics, gene sequencing, transgenic animals have provided the industry a huge number of novel biological targets thought to be relevant to a vast array of diseases. As a result, firms likely pursue parallel research trajectories searching for compounds with binding properties around the same target.

Against this background, the paper has explored the learning process of the actors involved in the pharmaceutical domain, focusing on the learning processes by rival firms. Differently from previous studies, we also take into account the role of research failures in providing the ground for subsequent innovation.

Patent protection forbid direct imitation of the compound (or process), nonetheless rival firms may search around the original molecule and find a patentable variant that offer some advantages. Patent citation data allow tracking subsequent developments.

Coherently with previous literature showing the existence of a relationship between patent citation and (private and social) patent value, marketed patents receive a higher number of citations, and for a longer time span. No difference emerges between marketed and discontinued patents in the early stages of development, where the research outcome is still unknown. Differences in the citation lag distribution are driven by the post-outcome behavior, i.e. from the citations received after the successful product commercialization. In addition, we provide evidence of a positive relationship between market sales and citations.

However, our empirical analysis shows the existence of a set of discontinued compounds whose patent receives a high number of citations, also

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after the termination of the associated R&D project, i.e. they provide the basis for subsequent innovations, eventually also leading to compounds that successfully reach the market. This suggests the existence of a social value associated to discontinued project and to the diffusion of the associated information, in terms of new (and better) research trajectories exploring new therapies for treating a disease. Moreover the regression analysis shows that research building on rival failures has a wider impact on subsequent research, as measured by the number of life-time citations received by the associated patent.

The information disclosed through patents leads to an expansion of the knowledge frontier, that stimulate further R&D effort, both in terms of new patents and new firms entering the research arena. It may well happen that firms other than the original innovator are the first to reach the market, being able to pursue more effectively the new line of research.

In this perspective, the discussion about patent scope becomes crucial in this industry, where research is highly cumulative in nature and firms enjoy knowledge spillovers spanning from internal and, to some extent, from external R&D projects, pointing to a trade-off that cannot be easily resolved. This poses problems for the optimal design of patent law[26]. On the one side, it is necessary to fully reward early innovators for the technological foundation they provide to later innovators, but also later innovators should be rewarded adequately for their improvements and new products.

Too narrow patents would be ineffective as incentives to R&D (the main function of the patent system), whereas too broad patents would be an obstacle to the development of parallel research trajectories, which might be improved with respect to their predecessors in terms of side effects or delivery method. In addition, as shown in Scotchmer (1991) too broad patents might inefficiently inflate incentives for the first innovator, which might not be capable of efficiently pursuing all subsequent lines of research.

Coupled with the evidence about the social value of failures provided in this paper, the argument reinforces the argument of more public sponsorship for basic research (Scotchmer 1991).

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[26]See Scotchmer (1991) for a detailed discussion of the optimal patent scheme in the case of cumulative knowledge.

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