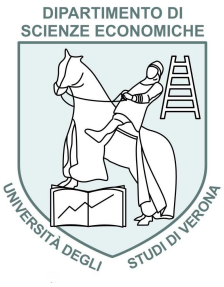

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The productivity crisis in pharmaceutical R&D

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"Should we invest money in this well? If so, how much should we risk and how much of the risk should we share with others?"
Grayson, 1960, p. 3

Abstract

We analyze the decline of R&D productivity in pharmaceuticals and its determinants. Since the molecular biology revolution, science has dramatically expanded the set of plausible therapeutic targets. However, innovation has become more difficult to achieve, and attrition rates of R&D projects have increased, especially in late-phase clinical trials. We show that the R&D productivity slowdown is associated with a higher concentration of R&D investments in high-risk domains, corresponding to unsolved therapeutic needs and unexploited biological mechanisms. We compare the strategies of European and US companies, finding differences in the composition of R&D portfolios, but no evidence of any productivity gap.

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1. Introduction

Innovation is becoming more difficult in many industries. Empirical accounts of the returns from innovative activities across a wide range of sectors show accumulating evidence of a long-term decline in R&D productivity (Griliches 1990, Kortum 1993, Kortum 1997, Jones 1995, Lanjouw and Schankerman 2004, Jones 2009).

The fall in research productivity has been ascribed to diminishing returns in the "knowledge production function". As market opportunities grow, incentives to undertake R&D activity increase, but research productivity declines due to stiffer competition to exploit such market opportunities (Kortum 1993). Alternatively, some scholars have advanced the hypothesis that the R&D effort has exhausted the easy targets, raising the bar for research success (Everson 1993, Segerstrom 1998): even if the innovation opportunities are not a finite set and keep growing with R&D and advances in basic science (Drews 1998, Cockburn 2006), new research opportunities also contribute to increase the complexity of R&D (Jones 2009).

In recent years the R&D productivity challenge has become particularly difficult in pharmaceuticals. The cost for developing a new drug has increased, as have total R&D expenditures (DiMasi *et al.*, 2003). Between 1998 and 2008 the output of new molecular entities (NMEs) has dropped by nearly 50% and attrition rates have increased sharply, especially in late-phase clinical trials (Mervis 2005, Pammolli and Riccaboni 2008). It has been argued that radical technological changes, such as the genomic revolution, have widened the gestation lag between investments in new research tools/organizational models and outcome, reducing R&D productivity in the short term. The number of NMEs is an imperfect measure of the research outcomes, as it does not reflect quality changes in R&D output. This caveat notwithstanding, there is a growing concern about the causes and consequences of the research drought experienced by the industry.

In this paper we analyze the recent trend in attrition rates in pharmaceutical R&D. We show that the decline in R&D productivity within the industry cannot be fully explained by the forces of demand and competition,

and we document an increasing focus of research activities on difficult and complex research areas characterized by a low probability of success. Apparently, the simplest problems have already been solved, and researchers are left with more difficult challenges, while the number of options that can yield viable therapies grows, raising the cost of exploring and developing new treatments.

The paper proceeds as follows. The next Section describes the data employed in the analysis. Section 3 characterizes the productivity crisis of the pharmaceutical industry at the global level, looking at changes in phase-specific attrition rates and development times. We provide evidence of a shift in investment decisions toward projects with low probability of success. After characterizing the global trends, Section 4 focuses on the comparative performance of US and European pharmaceutical industries. Section 5 concludes.

2. Data and Methods

Research productivity is typically measured as the ratio of R&D outputs to inputs. However, measuring research inputs and outputs in pharmaceuticals is difficult, as the innovation process builds on multiple and heterogeneous sources of knowledge, involves significant knowledge spillovers and lasts several years. The measurement problem is exacerbated by the growing division of innovative labor that spans different countries, as well as public and private research organizations (Orsenigo, Pammolli, Riccaboni, 2001; Owen-Smith, Riccaboni, Pammolli and Powell 2002). As a result, when assessing the productivity of pharmaceutical innovation efforts, the analysis needs to rely on different measurements and to look at a wide set of indicators and statistics.

Our analysis builds on the PHarmaceutical Industry Database (PHID) maintained by the Fondazione CERM (Competitiveness, Regulation, and Markets). The database draws from and integrates several sector-specific datasets providing information about innovation efforts and market activities of firms and institutions operating within the pharmaceutical industry. All in all, the database allows one to fully assess and characterize the major dimensions of

the pharmaceutical innovation and market efforts. PHID includes full text of more than 200,000 pharmaceutical patents applied for since the early Seventies. It reports detailed information about R&D projects directed to the development of more than 30,000 compounds, along with information on contractual relations; sales figures on about 160,000 pharmaceutical products (both branded and generics) sold in major markets from 1996 to 2008.[5]

The analysis undertaken in this paper exploits the information on R&D projects started from the year 1990, where PHID reports the timing of major milestones in development, from patent filing through preclinical and clinical trials until an R&D project is terminated (failure), or a new drug is commercialized (success). For each compound, we know the therapeutic indications being researched, distinguishing whether biotechnology tools have been employed in development, as well as the name of the institutions (both private firms and/or public research organizations) involved in development, along with their role in the project (originator/licensor vs. developer/licensee). We collected complementary information about company history and technological background, in order to distinguish pharmaceutical firms from new biotechnology firms that have entered the market since the Seventies and apply biotechnology tools and methodology for the drug development process. Finally, each therapeutic indication has been classified by a pharmacologist for its severity (whether lethal or not, whether causing organ damage or complications), etiology, chronicity, and patient population.

In the next Section, we document the slowdown of R&D productivity, both in terms of attrition rates and stage length. To understand the drivers of the observed dynamics, we focus on the changes in the composition of the research portfolio over time, showing that drug development efforts are more intensely directed toward complex pathologies. The analysis is based on project counts, where a R&D project is defined as the research directed to the testing and assessment of a compound for a well-defined therapeutic target.[6]

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[5] The database has been extensively analyzed in Pammolli and Riccaboni (2008).

[6] If a compound is tested for more than one indication, one project is counted for each indication (see also Arora *et al.*, 2009).

Drug development performance is assessed by looking at phase-specific success rate, within four years by phase start.[7] In addition, the length of the development stage is measured looking at the timing from patent filing to market launch.[8]

In order to understand the dynamics underlying the R&D productivity slowdown, we map the evolution of R&D efforts. As the main driver of research investments, the expected profitability of an innovation project can be computed as the product of the probability of market launch *times* the value of expected sales. Accordingly, we link each project to its "expected" probability of success (POS), measured as the (overall) average success rate of previous compounds targeting the same pathology, and to information about market sales.[9] The potential market size is measured by sales and standard units sold at the ATC3 level in major international markets (EU-15, US, and Japan) over the period 1996-2008.

Finally, we compare the performance of US versus Europe in pharmaceutical R&D. The nationality is defined according to the location of the originating firm/institution.[10]

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7 Analysis is limited to R&D projects entering trials from 1990 to 2004. Estimation of attrition rates is complicated by the fact that the process of drug development lasts several years. Based on a survey of ten large pharmaceutical companies, DiMasi et al. (2003) estimated the mean time from phase I to submission of an NDA or BLA with the FDA to be about 6 years. Using a more comprehensive dataset, Abrantes et al (2003) states that for drugs that successfully pass through all three phases of clinical development, the average time in the process amounts to 8 years. Therefore phase-specific attrition rate are taken into account, allowing us to consider a four-year cut off and also analyze more recent dynamics. We expect the four-year cut off to introduce minor bias in the reported attrition rates, since the vast majority of successful projects pass to the next stage within four years: 93% (preclinical), 86% (clinical I), 82% (clinical II) , 75% (clinical III).

8 The data for the analysis is limited to patented products launched in the US and EU-15 market.

9 Two complementary classification systems are employed in order to characterize the therapeutic market. In one classification, we consider the therapeutic indication written in standard terms, e.g. inflammation, cancer. This classification focuses on the clinical symptoms for which the drug is being tested. We also employ the Anatomical Therapeutic Classification (ATC) in the analysis, in order to group drugs with the same therapeutic and pharmacological activity. The ATC is hierarchical, where the first level identifies the organ or system on which the drug acts, grouping together, e.g. all drugs related to the central nervous system or to the cardiovascular system. At lower level, the chemical, pharmacological, and therapeutic characteristics of the drugs are also taken into account. At the third digit (ATC3), classes are defined by grouping all drugs with the same therapeutic and pharmacological characteristics.

10 US-EU collaborative research efforts are classified in a separate group.

3. The Growing Complexity of Pharmaceutical R&D

Since the mid Nineties, pharmaceutical R&D productivity has experienced a downturn. From 1998 to 2008 the number of NMEs has decreased sharply, whereas attrition rates, development times and R&D expenditures have increased (Abrantes-Metz, Adams and Metz 2006, Adams and Van Brantner 2006, Pammolli and Riccaboni 2008, David, Tramontin and Zemmel 2009, DiMasi and Faden 2009).

Exhibit 1 shows that the share of failed projects over the total number of projects entering any given stage of R&D (phase-specific attrition rates) has increased, especially in phases II and III of clinical trials (see also Mervis 2005, Pammolli and Riccaboni 2008). The probability of success in each stage involved in drug development has dropped over time. At the same time, the average development length (ADL), from patent filing to product commercialization, is longer for younger products. By taking into account the time from patent filing to market launch of patented compounds in the US and EU-15, ADL is increasing from 9.7 years for products launched before the Nineties to 13.9 for products launched in the year 2000 or later (Magazzini, Pammolli, Riccaboni, 2009).

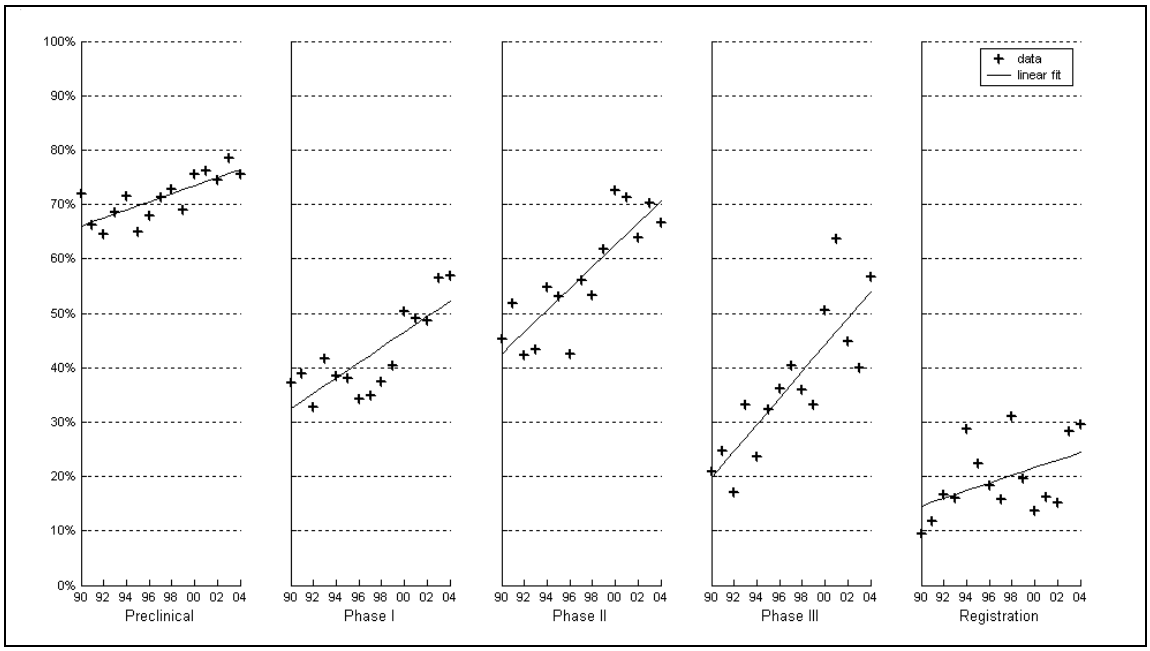

Exhibit 1: Trends in attrition rates of drug development projects, trials in the United States, Europe and Japan, 1990-2004

We explore the determinants of the increase in attrition rates and development times, by taking into account the portfolio choices of private and public research institutions. We assess the expected probability of success (POS) and potential market size of each compound. We classify POS in three levels (low/medium/high)[11] and we distinguish small and large markets[12]. Exhibit 2 shows the number and distribution of R&D projects before and after 2000. The proportion of projects with a lower expected POS is increasing. Globally, the

[11] In case of previously unexplored markets for which we are not able to compute the expected POS we set it equal to zero since we consider them to be extremely high risk projects. Low probability markets are those with a success rate lower than 5%, medium probability are in the range 5-10%, and high probability markets are those with an expected POS that exceeds 10%.

[12] The average level of sales over the observed time frame at the ATC3 is considered and we set a threshold at 2.2 billion dollars average value per year, roughly corresponding to the median sales level. We run sensibility tests by using the number of standard units sold instead of sale figures as well as different thresholds always reaching similar results.

share of projects targeting high-risk markets has grown from 80.87% in the Nineties to 83.37% after the year 2000. Since 2000, the share of R&D projects targeting larger markets with a lower POS has increased more than 12 percentage points, from 41.97% of the total number of projects started over the period 1990-1999 to 54.47% in 2000-2007. Research is more intensely directed toward larger and riskier targets/markets.[13]

Annex I further dissects this analysis taking into account the characteristics of the targeted therapeutic market. Projects using biotechnology tools are also taken into account.

Simple economic reasoning can provide a rationale for the observed shift toward riskier, larger market targets (see Acemoglu, Linn 2004). At each stage of drug development, firms evaluate the biological activity of each compound and its prospect for success (expected POS), along with development costs (linked to development times) and expected revenues (linked to the size of the patient population). Potential market size is a key determinant of profits: the larger the patient population, the larger the sales, the larger the incentives to undertake research in the area. At first thought, also POS exert a positive influence on incentives to innovate: holding the value of sales constant, higher POS is reflected in higher "expected" revenues. However, a countervailing effect is also in place, as sales value is the product of sales volume and price, which itself depends upon a large number of factors, such as the regulatory framework, the quality of the compound, and the intensity of competition. Intuitively, a lower POS translates into a lower expected number of competitors and, therefore, weaker and slower competition and higher expected revenues, and this effect seems to prevail on the basis of observed data. Larger and riskier markets are the ones providing higher expected revenues, therefore larger incentives to undertake research activities.

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[13] It is important to note that the enactment of legislation intended to encourage development of orphan drugs has provided incentives to undertake research in small markets, where expected revenues do not allow compensation of R&D expenditures. There is evidence of an increase in focus on rare disease. Moreover, advances in understanding the mechanisms underlying diseases are increasingly creating opportunities to differentiate products by matching sub-group of patients to specific "personalized drugs" (Trushaim *et al.,* 2007).

	Expected Probability of Success (POS)			
Market Size	**Low**	**Medium**	**High**	**Total**
		All projects, 1990-99		
Small	6,436 (38.90)	1,698 (10.26)	468 (2.83)	8,602 (51.99)
Large	6,943 (41.97)	739 (4.47)	260 (1.57)	7,942 (48.01)
Total	13,379 (80.87)	2,437 (14.73)	728 (4.40)	16544 (100)
		All projects, 2000-07		
Small	4,560 (28.91)*	1,387 (8.79)*	360 (2.28)*	6,307 (39.98)*
Large	8,592 (54.47)*	599 (3.80)*	277 (1.76)	9,468 (60.02)
Total	13,152 (83.37)*	1,986 (12.59)*	637 (4.04)*	15,775 (100)

Note: * to identify statistical differences in the over-time comparison (5% level of significance)

Exhibit 2: Number of R&D projects (% over total in parenthesis) by expected POS and targeted market size; before and after 2000; US, European, and Japanese trials

4. Who is More Productive in Pharmaceutical R&D? US versus Europe

A recent study comparing European firms' research productivity in pharmaceuticals with US firms' productivity pointed to superior performance by European firms (Light, 2009). Here, we perform a thorough analysis of the performance of US firms and institutions vis-à-vis Europe.

First we compare the success rates of research projects initiated by American and by European firms and institutions (Exhibit 3). The analysis is based upon 18,481 projects led by firms/institutions headquartered in the US, and 12,206 projects led by firms/institutions headquartered in Europe. US projects show higher success rates in early clinical trials, while European projects are more likely to succeed in downstream drug development stages.

	Probability of success					
	Preclinical	**Clinical I**	**Clinical II**	**Clinical III**	**Registration**	**Clinical trials**
Phase start	**(a)**	**(b)**	**(c)**	**(d)**	**(e)**	**(b) x (c) x (d) x (e)**
	US projects: 18,841 projects					
1990-1994	31.46	64.94	56.53	71.96	83.52	22.06
1995-2000	28.66	65.81	49.62	60.90	75.25	14.96
2000-2004	23.46	48.93	34.18	50.75	76.90	6.53
	European projects: 12,206 projects					
1990-1994	32.02	54.25	51.31	68.00	88.08	16.67
1995-2000	33.14	59.97	44.78	65.08	80.91	14.14
2000-2004	25.02	45.84	29.69	53.94	84.44	6.20

Exhibit 3: R&D projects started between 1990 and 2004: probability of success by development stage, US vs. Europe

In the first half of the Nineties, the success rate of US projects in clinical trials was 4.29 percentage points higher than the European rate. Since then, the decline in success rates has closed the R&D productivity gap between the US and Europe. In ten years, the US probability of success across the different stages of clinical trials has fallen from 22.06% down to 6.53% (-15.53 percentage points), while in Europe the decline in the probability of success has been less pronounced, from 16.67% to 6.2% (-10.47 percentage points).

Exhibit 4 shows that the effort by US companies in low POS markets has grown by 2.51 percentage points, from 82.17% (pre 2000) to 84.68% (after 2000), whereas the corresponding figure for European companies has grown by 3.76 percentage points (from 78.39% to 82.15%, still below the US figure). US companies and institutions were responsible for about half of the R&D projects undertaken from 1990 to 2008 (52.03% in 1990-99, 51.26% in 2000-08).[14]

[14] Even though the share of projects run by US and European institutions slightly changes over time, the trend is not significant at customary level of significance.

	Expected Probability of Success (POS)			
Market Size	**Low**	**Medium**	**High**	**Total**
US-originated projects, 1990-99				
Small	3,324 (37.40)	852 (9.60)	232 (2.61)	4,409 (49.61)
Large	3,979 (44.77)	370 (4.16)	130 (1.46)	4,479 (50.39)
Total	7,303 (82.17)	1,223 (13.76)	362 (4.07)	8,888 (100)
US-originated projects, 2000-07				
Small	2,396 (27.47)*	666 (7.63)*	192 (2.20)*	3,254 (37.30)*
Large	4,991 (57.22)*	328 (3.76)	150 (1.72)	5,469 (62.70)
Total	7,387 (84.68)*	994 (11.40)*	342 (3.92)*	8,723 (100)
European-originated projects, 1990-99				
Small	2,245 (40.81)	579 (10.53)	212 (3.85)	3,036 (55.19)
Large	2,067 (37.57)	273 (4.96)	125 (2.27)	2,465 (44.81)
Total	4,312 (78.39)	852 (15.49)	337 (6.13)	5,501 (100)
European-originated projects, 2000-07				
Small	1,781 (31.14)*	565 (9.88)*	137 (2.40)*	2,483 (43.42)*
Large	2,917 (51.01)*	212 (3.71)	107 (1.87)	3,236 (56.58)*
Total	4,698 (82.15)*	777 (13.59)*	244 (4.27)	5,719 (100)

Note: shaded cells compare US and EU share and identify the largest share (if difference is significant at 5% level)
The asterisk (*) identifies statistical differences in the comparison over-time (5% level of significance)

Exhibit 4: Number of R&D projects (% over total in parenthesis) by expected Probability of Success (POS) and targeted market size, before and after 2000, US vs. Europe

In 2000-2007, 57.22% of US projects have been directed toward markets which combine low POS and large size, whereas the portfolios of European companies appears to be more balanced (51.01% high risk/high payoff targets).

Exhibit 4 shows that the composition of the R&D portfolio of US enterprises is twisted toward therapeutic areas featuring lower POS. All in all, the higher POS that has been characterizing the European efforts might be driven by a different composition of the research portfolio in terms of riskiness of the research ventures. To test whether Europe has a higher probability of success in drug development, a simple probit regression model is set forth (Light, 2009).[15] The regression includes a dichotomous dependent variable, equal

[15] Here, the overall POS from preclinical to market is considered. The sample covers all R&D

to one if the project successfully reaches the market, and zero otherwise, i.e. we take into account the factors affecting the probability of market launch for R&D projects entering the preclinical stage. Furthermore, as market launch is not equivalent to market success, and the simple count of NMEs (or simple calculation of the proportion of successful R&D projects) is not apt at measuring the quality and innovativeness of drugs, we also check for the value of sales, where we consider as the dependent variable the sales of NMEs in the first two years after product launch,[16] both in terms of value and number of standard units sold.[17] Results of the analysis are reported in Exhibit 5.

The main variable of interest is a dummy variable identifying the projects started by European enterprises:[18] A positive and statistically significant coefficient indicates that European firms and institutions have a higher probability of market launch than US enterprises (larger profitability of innovations in the case of sales regression). The regression framework allows us to compare the R&D and market performance of firms and institutions operating across the Atlantic, taking into account the different composition of their research portfolio in terms of disease characteristics and research methodology. Particularly, we control for the characteristics of the targeted disease (lethal, organ damage, complications, etiology, chronicity, diffusion) and for the research approach (whether biotechnology tools are employed or not) by means of a full set of dummy variables. Time dummies (defined on the basis of the calendar year when the project is started) are introduced to accommodate the decreasing trend in R&D productivity and the evolution of sales. In addition, we

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projects started within the industry between 1990 and 2007, which involve US and European companies and public research organizations (PROs) among the institutions that first started the project. Ongoing projects are not considered in the analysis.The total number of projects considered in the analysis is 18,735.

16 A full account of product value would take into account the total sales of the product over the life cycle. Such an effort is hindered by data availability. We only have data over a fixed time frame, shorter than the effective product life. This approach fails to take into account product turnover and competition by generics, which is stronger in the US with respect to the European countries (Gambardella, Orsenigo, Pammolli, 2000; Pammolli and Riccaboni 2008).

17 As sales data are only available from July 1996, the sample is reduced and we take into account products launched for the first time over the years 1996-2006 by a European or US institution. The sample size is reduced to 353 NMEs launched in at least one of the countries considered in the analysis.

18 "EU originator": the variable equals 1 if the enterprise that started the project is located in Europe, otherwise it is located in the US.

check for type of sponsoring institution. Two dummy variables are considered in the analysis for projects originated by biotech firms and PROs (the reference category comprises projects started by pharmaceutical companies),[19] and, when analyzing the probability of success of R&D projects, we also run separate regressions specifically comparing pharmaceutical companies and biotechnology firms operating on the two sides of the Atlantic (Arora *et al*., 2009).

[19] A dummy variable for projects originated by more than one type of institution or by more than one geographic group is also considered in estimation. This is done in order to control for projects co-sponsored by US and European institutions. The focus is on the comparison of the US versus the European system of innovation, therefore no direct control for within-country collaboration is included. The issue of licensing is nonetheless important. The advent of biotechnology opened up the avenue for large collaborative efforts between small biotechnology companies, lacking the resources and capabilities for the large clinical trials, but highly skilled in the early development stages, and large pharmaceutical companies, required to acquire knowledge in the new field of research. The question whether this has been beneficial to the industry has not been resolved yet. In Annex I, we show that projects employing biotechnology tools and methods have a lower probability of success. However, it is not clear whether this is due to higher organizational complexity of the licenses or to the higher risk that characterizes collaborative ventures. Are efforts directed toward biotech methods less productive per se? Or the effect is driven by a larger share of agreements behind the figure? No definitive answer is provided at date (Zeckhauser, 1996; Pisano, 1997, 2006; Guedj, 2005; Danzon *et al*., 2005; Arora *et al*., 2004, 2009), and answering it is beyond the scope of this paper. We take a complementary perspective here and look at the characteristics of the therapeutic markets selected for development, also controlling for the industrial structure of the two systems.

	Probability of Success (POS)					Sales Value (log)				Sales Quantity (log)			
Sample /Markets	**All projects**	**All projects**	**All projects**	**Pharma only**	**Biotech only**	**All markets**	**All markets**	**EU-15 market**	**US market**	**All markets**	**All markets**	**EU-15 market**	**US market**
EU originator	.1928*	-.0148	-.0115	.1081	-.2576*	-.7353**	-.9742**	-.8010*	-.3117	.3467	-.3465	-.0446	.0401
	(.1067)	*(.0887)*	*(.0867)*	*(.1039)*	*(.1373)*	(.2973)	(.3206)	(.4264)	(.3452)	(.4531)	(.4053)	(.4882)	(.4846)
Biotech/PRO originator	no	yes	yes	no	no	no	yes	yes	yes	no	yes	yes	yes
Target & R&D dummies	no	no	yes	yes	yes	no	yes	yes	yes	no	yes	yes	yes
Time dummies	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Number of obs.	18,735	18,735	18,214	8,464	7,202	353	332	253	298	353	332	253	298
R-squared	.0257	.0606	.0910	.0585	.1025	.0890	.1366	.1711	.1343	.0751	.3439	.3339	.3219

Robust standard errors in parenthesis (clustered by firms)

** denotes p-value < 5%; * p-value < 10%.

Exhibit 5: The determinants of R&D and Market performance: comparing Europe and US

Even though, as argued by Light (2009), at a first glance European firms seem to have higher success rates vis à vis US firms, the difference fades away as soon as we take into account the composition of the R&D portfolios. Straight comparison of the US and European performances seem to reveal a higher probability of success (i.e. market launch) for projects started by European firms and institutions. After controlling for differences across research areas, there is no significant gap between European and US enterprises in term of drug development performances. Unconditional differences (i.e. differences arising when no controls are taken into account) are rather driven by the higher propensity of US organizations toward novel R&D methodologies and riskier therapeutic endeavors. The result holds true even if the regressions only consider pharmaceutical firms. On the contrary, when only the small biotechnology firms are included in the regression, European firms exhibit lower POS than their US counterparts, even if the coefficient is only marginally significant.

When sales data are taken into account, the market value of US innovations is on average higher than the value of European ones. This result holds true in all model specifications. When we remove the price effect by considering the number of standard units sold, again we do not find any significant difference between European and the US enterprises. In order to avoid spurious results driven by price differentials between the US and Europe, we also compare total sales *within* each region. Interestingly, the result is not driven by the higher prices that characterize the US market. Rather, it seems to reflect differences in quality of European and US innovations. When only EU sales are considered, the result holds true, whereas statistical significance vanishes when only US sales are considered.

5. Concluding thoughts

Drug development is increasingly difficult, as low-hanging fruit have been picked and the threshold for new discoveries rises.

The molecular biology revolution has expanded the number of viable therapeutic opportunities. The progress of the scientific frontier has ushered in growing specialization and division of innovative labor throughout the World.

Innovation in pharmaceuticals is a cumulative process, and markets where the probability of success is high are those in which effective compounds are already available for testing and improvements. However, both private and public payers discourage incremental innovation and investments in follow-on drugs in already established therapeutic classes, mostly by the use of reference pricing schemes and bids designed to maximize the intensity of price competition among different molecules. In established markets innovative patented drugs are often reimbursed at the same level as older drugs.

As a consequence, R&D investments shift toward new therapeutic classes, in which uncertainty and difficulty are high. Our data show that this reorientation of investments explains most of the decline in productivity in pharmaceutical R&D, measured in terms of attrition rates, development times, and the number of new chemical entities launched.

To a large extent, the productivity slowdown in the pharmaceutical sector appears to be a global phenomenon, induced by the combination between demand incentives and the difficulty of developing innovative drugs in areas of strong technological uncertainty and high unmet therapeutic need.

Still, our analysis in this paper confirms the existence of important differences in the organization of national systems of innovation and regulation in pharmaceuticals. In the United States, established pharmaceutical companies, biotech firms and other institutions collaborate across multiple therapeutic areas and stages of the development process. In contrast, large pharmaceutical corporations still play a dominant role in Europe (see also Owen-Smith et al., 2002; Pammolli, Riccaboni 2008). The larger presence of newly entered biotechnology firms in the US, largely geared toward exploratory research rather than exploitation of known compounds and mechanisms of action, makes the US system more oriented toward riskier research areas and markets (i.e. chronic and lethal diseases).

At first glance, the European research system is characterized by a higher probability of market launch for compounds entering the preclinical stage.

However, if the characteristics of the research portfolio are taken into account, the advantage of European firms and institutions vanishes. Rather, biotechnology firms in the US are more successful (i.e. have a higher probability of launching a compound in the marketplace) than European ones.

By controlling for the portfolio characteristics of the research investments, we do not find support for the claim of an R&D productivity differential between the US and Europe. Moreover, simple count of projects (or NMEs) fails to take into account the sales potential of each compound. When we take into account sales (both values and quantities) of "global" compounds launched in the marketplace, we document that the average market value of successful compounds by US companies tends to be higher than European ones.

In the long run, for both Europe and the US, the rate and direction of pharmaceutical innovation will be affected by the interplay between patterns of technological change, drug approval regulations, patent law, and demand incentives.

Even in new therapeutic areas, the early availability of information on biological targets and the information disclosure conveyed by patents induce intense competitive dynamics in R&D, amplify the intensity of price competition well before patent expiry (Lichtenberg, Philipson, 2002), and reduce effective patent life even for breakthrough drugs (Pammolli, Magazzini, Riccaboni 2009).

Against this background, both in Europe and in the US the new political economy of the industry seems to be looking for a framework within which to reconcile public and private incentives and balance the most critical tradeoffs between the goals of financial sustainability for payers and the goals of therapeutic innovation. Policies must evolve to account for the new difficulties and risks of pharmaceutical innovation, and to preserve an environment in which companies are encouraged to contribute to the global public good of pharmaceutical innovation by continuing to invest under conditions of strong uncertainty.

To be sure, the size and productivity of public science institutions, regulatory rigor and efficiency, as well as legislation and incentives specific to orphan and neglected diseases, will continue to be key in orienting and sustaining industrial innovation in pharmaceuticals. The evidence presented in

this paper documents the increasing difficulty of pharmaceutical R&D and a key question for the future is how to design incentives that can encourage innovation and investment. As it gets harder to develop the next generation of drugs, a legislation to enhance market exclusivity and patent protection might contribute to improve private incentives to invest.

Annex I. Further dissecting POS

This Annex presents additional evidence about the trends of increasing R&D effort towards areas with a lower POS.

We further classify R&D projects according to the characteristics of their therapeutic targets. As in Exhibits 2 and 4 in the text, we split projects started before and after the year 2000, and then grouped them according to the characteristics of the targeted disease, distinguishing projects employing biotechnology tools for drug development.

Exhibit A.1 provides additional evidence that a growing effort has been allocated toward therapeutic markets with a lower POS. More research projects are targeting lethal diseases, from 24.13% in the Nineties to 31.29% since 2000 (+7.16 percentage points). Research directed to chronic diseases has moved from 81.54% to 85.80% (+4.26%). Also, the share of projects employing biotechnology tools for drug development has increased from 12.03% to 14.77%.

However, there is also evidence that the share of projects directed to diseases causing organ damage and diseases with multifactorial etiology has decreased by 4.60 and 1.08 percentage points respectively. The number of projects targeting rare diseases has increased significantly, following specific legislations in major pharmaceutical markets.[20]

[20] Focusing on the countries included in the analysis, the US Orphan Drug Act of 1983 has effectively spurred the development of orphan drugs in the US (Yin, 2008). Similar provisions have been introduced in Europe from the year 2000, and Japan has introduced special provisions for orphan drugs since the year 1993.

Targeted Therapeutic Mkt	POS	percentage over total 1990-99	2000-08	Δ
Monofactorial etiol.	15.06	13.94	14.83	+0.89*
Unknown etiol.	11.58	3.89	4.08	+0.19
Multifactorial etiol.	9.58	82.17	81.09	-1.08*
Rare	21.08	7.47	11.90	+4.43*
Widespread	9.64	92.53	88.10	-4.43*
No organ damage	15.55	20.78	25.38	+4.60*
Organ damage	9.11	79.22	74.62	-4.60*
Acute	12.48	18.46	14.20	-4.26*
Chronic	10.00	81.54	85.80	+4.26*
Not lethal	14.28	13.83	12.96	-0.87*
Maybe lethal	10.06	62.04	55.75	-6.29*
Always lethal	9.24	24.13	31.29	+7.16*
Not Biotech	15.16	87.97	85.23	-2.74*
Biotech	8.42	12.03	14.77	+2.74*

Note: * to identify differences in time statistically significant at the 5% level

Exhibit A.1: Average success rate and distribution of R&D projects by therapeutic target and research methodology; US, European, and Japanese trials

When we distinguish according to the location of the originating corporation, focusing on the comparison between European and US enterprises, US firms and institutions are more active in research on lethal diseases than European firms, as well as on research employing biotechnology tools (Exhibit A.2).[21] Even though the share of biotech projects almost doubled from 9.53% to 14.08% in Europe, the difference between the two regions is still significant along this dimension. On the contrary, European and US research efforts are now aligned when comparing diseases causing organ damage. The number of projects targeting rare diseases has increased significantly, following specific legislation in the US and, to a lesser extent, in Europe.

[21] A set of tests has been performed in order to check whether the differences over time and across country at a given point in time are statistically significant (a 5 percent level is considered). See note at the bottom of the Table. With few exceptions, differences arise both over time and when comparing US and EU shares.

From 1990 to 1999, European efforts were more intensely targeting multifactorial diseases, but the difference is no longer statistically significant when share in 2000-08 are compared. The share of projects targeting diseases with unknown etiology is now larger in Europe with respect to the US.

Targeted Therapeutic Mkt	POS	United States 1990-99	United States 2000-08	Δ	Europe 1990-99	Europe 2000-08	Δ
Monofactorial etiol.	15.06	15.12	15.61	0.49	13.23	13.83	0.60
Unknown etiol.	11.58	4.07	3.77	-0.30	4.42	4.70	0.28
Multifactorial etiol.	9.58	80.81	80.61	-0.20	82.34	81.47	-0.87
Rare	21.08	8.22	12.83	4.61*	6.70	11.09	4.39*
Widespread	9.64	91.78	87.17	-4.61*	93.30	88.91	-4.39*
No organ damage	15.55	19.47	25.29	5.82*	22.61	25.77	3.16*
Organ damage	9.11	80.53	74.71	-5.82*	77.39	74.23	-3.16*
Acute	12.48	17.48	13.45	-4.04*	19.60	14.06	-5.54*
Chronic	10.00	82.52	86.56	4.04*	80.40	85.94	5.54*
Not lethal	14.28	13.75	12.66	-1.09*	14.75	13.81	-0.94
Maybe lethal	10.06	60.20	53.88	-6.32*	64.39	58.15	-6.24*
Always lethal	9.24	26.05	33.46	7.41*	20.86	28.04	7.18*
Not Biotech	15.16	85.52	84.35	-1.17*	90.47	85.92	-4.55*
Biotech	8.42	14.48	15.65	1.17*	9.53	14.08	4.55*
Average POS	10.54	11.05	5.98		15.20	7.76	

Note: in the column Δ the "*"identifies the differences in time (statistically significant at the 5% level)
Note: shaded cells identify statistical significance in the comparison of US and EU shares
(The larger value is identified when statistically different at the 5% level)

Exhibit A.2: Average success rate and distribution of R&D projects by therapeutic target and research methodology

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