

Who's Doing What in Pharmaceutical R&D?¹

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I. Introduction

The research effort undertaken by firms is driven by a multiple set of factors and incentives. The debate in the theoretical literature has focused the attention on “technology push” versus “demand pull” theories, the former considering the exogenous effect of science on technological change, while the latter regarding market growth and size as unique determinants of the decision to invest in R&D. Both theories tell only part of the story. The decision to invest in R&D, and therefore the rate and direction of technological progress, is the result of the interplay between the advances spanning from basic science², institutional variables, and economic factors, namely market growth and size (Dosi, 1982, 1988).

Despite the theoretical attention and importance attached to this issue, little empirical evidence is provided on the role of demand and science in affecting the rate of technological progress.

In this paper we investigate the pharmaceutical industry, where R&D has clear implications for the welfare and health of the population, and both patient needs and technological progress play a fundamental role in the innovation process. We ask what drives pharmaceutical R&D investments in specific therapeutic submarkets. To address this question it is essential to map the research effort of firms (both established pharmaceutical firms and new biotechnology firms) and public research organizations in terms of the epidemiological characteristics and the severity of the disease targeted by their R&D projects. Moreover, we take into consideration the nationality of the main corporations performing R&D in the pharmaceutical industry, with clear implications for the recent debate viewing Europe as a “free rider” on US innovations.

Scientific opportunity, assessment of the market potential and of the resources needed for development, and medical needs have been identified as the major drivers of the pharmaceutical decisions to invest in R&D (Crogham and Pittman, 2004).

Assessing medical needs

The identification of medical needs is still plagued with technical problems and by the fact that a widely accepted definition of need is still missing. In addition, to assess the need of a specific drug

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² That are in turn affected by technological progress (see Rosenberg, 1982).

in a given area it is necessary to analyse a complex set of epidemiological and economic data. How to compare a new treatment for a rare disease with high level of mortality with a new drug for more common diseases causing major disabilities? This trade-off is not easily resolved and more rigorous methods for assessing health needs are still to be developed (Crogham and Pittnam, 2004). In addition, when dealing with developing countries' needs, insufficient information about the number of patients, the effectiveness of existing products, and patient access makes it difficult for companies to identify priority markets (Webber and Kremer, 2001). In an analysis comparing medical needs, as measured by the burden of disease as disability adjusted life years, on the one side, and the industry response, proxied by the number of drugs in development on the other side, Crogham and Pittman (2004) provide unambiguous examples of both too many drugs for some conditions and too few or none at all for others, infectious diseases being the clearest example of failure to develop drugs when there is need (see also Trouillier *et al.*, 2001).

Building on Science

Scientific opportunity, regarded as the single most important factor that explains much of today's portfolio of drugs, is related to the knowledge of the basic mechanisms associated with the disease under study, allowing the identification of many potential molecular targets for exploration and new drug candidates. Indeed, advances in basic science have vastly expanded research opportunities: the number of drug targets has risen from 500 to more than 5,000 in recent years (Cockburn, 2004).

Market assessment and the analysis of resources required are directly linked to the expected profitability of the research project and therefore to the incentives provided to firms for undertaking research in that specific area. In particular, orphan drugs and drugs targeted to the needs of the African and South East Asian countries have little potential markets associated with little expected revenues, therefore attracting a little fraction of R&D efforts.

The role of market size

Acemoglu and Lin (2003) investigate the effect of potential market size on the entry of new drugs and pharmaceutical innovations (as measured by the FDA approvals of new drugs³). Their findings support the existence of an economically and statistically significant response of the introduction of new drugs to market size. Exogenous changes in market size, i.e. changes in the number of patient in a specific therapeutic category driven by the US demographic trends, significantly affect the introduction of new drugs (both generic and branded products) in a therapeutic category. The authors measure the potential market size for various drug categories according to the age distribution of their users at a given point in time, and then trace changes in potential market size driven by changes in demographics (holding the age profile of consumption of various drug categories constant over time).

³ The authors also use patents as a proxy for innovation, but the relationship between market size and innovation is weaker when this measure is employed in the regression.

Coherently with this study, Kremer (2002) argues that pharmaceutical R&D on health problems specific to poor countries is inadequate. The author reports data from WHO (1996) showing that less than 5 percent of global health R&D undertaken by private industry in 1992 was spent on diseases specific to less developed countries. Moreover, the characteristics of the market and the habits and behaviour of the targeted population make drugs available in developed countries often unsuitable for use in less developed countries, due to high prices, acquired resistance, or delivery and stock conditions. Research on vaccines, which are typically much more feasible to deliver than drugs in developing countries, is fairly limited (Kremer, 2002).

Additional evidence on this issue is provided by Troullier *et al.* (2002), who found that only 1% of the new chemical entities marketed between 1975 and 1999 were for tropical diseases and tuberculosis.

The WHO-IFPMA Working Group has undertaken a detailed investigation of the levels of public and private R&D targeted to the main infectious diseases affecting the world. Malaria and tuberculosis have been identified as the major diseases having insufficient product R&D, even though presenting scientifically tractable targets⁴ (WHO-IFPMA, 2001).

The genome sequencing of the human malaria and tuberculosis parasites can scientifically spur research in this area (Malcolm *et al.*, 2002).

Institutional settings

Public policy and initiatives play a significant role in pushing R&D for the development of drugs targeted to small markets, as it is the case for developing countries and rare diseases. Given the specific features of these markets, government interventions are needed to remove the major barriers for undertaking R&D in these areas. Particularly (see Webber and Kremer, 2001), the lack of the understanding of some diseases, coupled with the complexity of the science and technology involved, makes the prospect of finding new medicines and vaccines uncertain and therefore highly risky. In addition, poor expected market returns, plagued with insufficient information about the number of patients, the effectiveness of existing products and patient access, create doubt that returns will cover investments. DiMasi, Hansen and Grabowski (2003) estimated that the average out-of-pocket cost per new drug is US\$ 403 million (2000 dollars). In this respect, even though different analyses have produced different estimates, no doubt is cast on the high R&D investment required for drug development.

In addition, many existing products needed by people in developing countries are not being purchased by patients, health care facilities, governments, or nongovernmental organizations due to weakness in country-level physical, medical, financial and political infrastructure. A real danger exists that even if new products are developed, they will not be purchased and made available to those who need them. Also, the industry fears that intellectual property protection will be

⁴ The Group also identified African trypanosomiasis, Chagas disease, leishmaniasis, lymphatic filariasis, onchocerciasis and schistosomiasis as requiring additional R&D. Existing products for African trypanosomiasis, Chagas disease and leishmaniasis (all caused by kinetoplastid protozoa) are mostly parenteral in use, need multiple administrations, have serious side effects and are increasingly becoming compromised by acquired resistance (WHO-IFPMA, 2001).

inadequate. The most famous example is the case of praziquantel for the treatment of schistosomiasis, developed by Bayer and E. Merck whose supply was able to meet only a fraction of global needs (Reich and Govindaraj, 1998).

Push and pull mechanisms, respectively providing direct funding for research and improving the likelihood of a return on investments by creating or securing a market, are being proposed to attract the pharmaceutical industry to invest or reinvest in specified areas (for a critical review of the different mechanism see Webber and Kremer, 2001), and various public-private partnerships have been established, combining respective capacities and resources (Troullier *et al.*, 2001).

Even though much work remains to be done, various examples exist suggesting that the right set of incentives can be provided.

Finkelstein (2003) examines three discrete policy changes that increased the demand-side incentives to develop new versions of vaccines against six infectious diseases (hepatitis B, influenza, polio, diphtheria-tetanus, measles-mumps-rubella, and pertussis). By affecting the reimbursement of costs of vaccination, these policies affected the profitability to developing those vaccines, and turn out to be associated with a significant increase in the number of new vaccine clinical trials for the relevant diseases⁵.

Lanjouw and Cockburn (2001) examine the effect of the dramatic increase in patent protection following the GATT agreement. The peculiar characteristics of the market affected by the patent reform provide a unique setting for checking the effect of patent protection on innovative effort. The authors find some evidence of an increase in research targeted to tropical diseases, particularly malaria⁶, during the mid- to late 1980s even though this appeared to have levelled off in the 1990s. The US Orphan Drug Act (ODA) of 1983 was effective in promoting research to develop drugs for rare diseases in the US, and resulted in a large increase in orphan drugs introduction during the 1990s. Also evidence is provided of growth in consumption and increases in longevity for individuals with less common conditions, as compared to more common conditions, and these effects are significantly related to the Orphan Drug use for the condition (Lichtenberg and Waldfogel, 2003).

Biotechnology companies have undertaken the bulk of research in this area. As of 2000, biotechnology companies had sponsored 70% or the more than 900 orphan-designated projects in the US, and 50% of all approved biotechnology products had orphan drug status (Kettler and Marjanovic, 2004).

It is tempting to suggest a policy for pushing research targeted to tropical diseases resembling the ODA. Tropical diseases are certainly a niche market (as it is the case with orphan drug markets),

⁵ The author is unable to detect evidence of an investment response at earlier stages, as measured by pre-clinical trials or patent filings, that represent more of an attempt to develop fundamentally new technologies.

⁶ However, not all tropical diseases have attracted attention. For example they find no evidence of increased research activity targeting leprosy, causing about 4,000 death in 2001 (75% in South East Asia. WHO, 2002). Leprosy has a smaller estimated market than the cost of developing a drug and was therefore not an interesting prospect for a private firm without public subsidies (Lanjouw and Cockburn, 2001).

and biotechnology firms have demonstrated their ability to successfully advance a niche market strategy⁷ (Kettler and Marjanovic, 2004).

However careful thinking has to be made on the applicability of orphan-type legislation for pushing drug development for tropical diseases (Troullier et al., 1999; Troullier et al., 2002).

Indeed the benefits to tropical diseases spanning from the US ODA have been limited, and there's a presumption that this will be the case also in Europe. The seven-year market exclusivity has been the most significant incentive and the ODA has often been viewed as a mechanism to obtain seven years of exclusive marketing rights, especially for new biotechnology products (Trouiller et al., 1999). This clause implies a liberty of pricing, that are indeed extremely high for orphan drugs, that is incompatible with the economic and social situation of most developing countries with low purchase power and lack of a social security system (Trouiller et al., 1999; 2002).

Against this background, our descriptive evidence points to the fact that R&D in pharmaceuticals (as measured by the number of R&D projects for the development of a new drug) is mostly undertaken by US institutions, and to the leading role of US biotechnology companies and, to some extent, of public research organizations in targeting orphan diseases or diseases that are specific to the African regions. The research activity for the development of new drugs of public research organizations is almost non-existent in European countries, and this is true also when we look at biotechnology firms. This has implication for the development of the Orphan Drug legislation, currently under development in the European countries.

Clearly a different set of incentives is placed on firms (both biotechnology and pharmaceutical firms) as compared to public research organizations, which respond differently to profit incentives.

The paper proceeds as follows. The next section describes the data. Section III present evidence of the difference in the probability of success associated with the different characteristics of the selected indications. Section IV presents a broad map of pharmaceutical R&D efforts in Europe and the US, focusing on infectious diseases, their burden, and existing pharmaceutical products (drugs for prevention – vaccines – and treatment) and aims at analysing the research effort undertaken by the firms in diseases affecting developing countries. Section V presents an econometric model aimed at understanding the factors driving pharmaceutical research in specific areas. Section VI concludes the paper.

II. Description of the data

⁷ Research by biotechnology firms is indeed also driven by other concerns. Lerner (1995) takes into consideration the influence that litigation costs have on the patenting behaviour of the new biotechnology firms. His analysis is driven by the conjecture that the fear of costly litigation is leading to distortions in the pattern of innovative investments, particularly for small firms. Indeed, the analysis provides evidence that biotechnology firms with high litigation costs are less likely to patent both in subclasses with many previous awards by rival biotechnology firms, and in subclasses where firms with low litigation costs have previously patented, rendering niche market with low levels of current research an attractive alternative for biotechnology firms.

Data are drawn from a proprietary database⁸ comprising information about the economic and scientific activity of the private and public organizations active in the bio-pharmaceutical industry all over the world. The database covers information about the different stages of the innovative activities of the surveyed institutions from the patenting activity through commercialisation and marketing of their compound, including sales in major countries.

The analysis that follows is based upon detailed information on more than 17,000 pharmaceutical R&D projects worldwide for from 1990 up to 2005. For each of them the organization that originated the new pharmacologically active compound (leading institution) is distinguished from the organization(s) that were entitled of further development (licensors). Moreover, the entire project development history is traced from the starting date: patents filed; collaborative agreements; project status; preclinical and clinical data and outcomes; registration and market launch, together with information about the national location of experimentation and commercialisation. Also detailed information about the compound under development, comprising its preferred names and synonyms, pharmacological actions, therapeutic indications, ATC classes, and in case of commercialisation, the trade names are reported.

Project indications were evaluated on the basis of several parameters, in order to be describe and assess their characteristics. We considered the disease outcome, presence of organ damage or complication, etiology, chronicity, and diffusion⁹. As a result we are able to classify the diseases in terms of their severity, particularly we considered three aspects in absence of therapy: the outcome, distinguishing diseases that are life threatening, the presence of organ damage, and the possibility of developing complications.

In addition, we distinguished diseases with multifactorial or unknown etiology from diseases caused by a single factor, likely to be more easily targeted, as a proxy for the difficulty associated with the search of an active compound. WHO data have been cross linked to R&D projects in order to take into account the epidemiological characteristics of the disease too. Finally, we classified diseases based on their geographical spread to single out African diseases and, more in general, diseases affecting Less Developed Countries (LDC).

Finally, as a first proxy for market size and the strand of revenues associated with the compound, we considered two dummy variables: the first indicating projects targeting chronic diseases¹⁰, that

⁸ www.databiotech.com

⁹ The main source for the disease information has been Braunwald et al. (2001). Other information has been found in e-medicine reviews from the disease database (<http://www.diseasedatabase.com>). For diffusion data, information has been drawn from the “rare disease database” referred to by the FDA, and available at the internet address: <http://rarediseases.about.com/cs/orphandrugs/a/122103.htm>.

¹⁰ We have considered chronic a disease with one or more of the following characteristics: permanent, leaves residual disability, is caused by non reversible pathological alteration, requires special training of the patient for rehabilitation, or may be expected to require a long period of supervision, observation or care. In the analysis we included a dummy variable where 0 stands for acute, 1 for chronic.

involve treatment for longer time, and the second indicating projects targeting rare diseases, i.e. diseases with limited prevalence¹¹.

Under this perspective, we also built a variable measuring market size for each indication in 1995. We considered sales data in the US¹² in 1995 at the ATC3 level. In order to compute the variable, we built a mapping from project indication to ATC3 classes. We then considered market size associated to each indication (MKTSIZE) as total US sales in the matched ATC3 class(es) in 1995. Moreover, since firms operating in market with a lower level of competition are expected to be able to gain higher prices for innovative compounds, we include among the regressor the level of market concentration (MKTCONC), computed as the Herfindahl index of concentration in the matched ATC3 class in 1995.

This provides us a unique possibility to characterize the R&D efforts undertaken by biopharmaceutical companies and institutions over the last twenty years.

III. The characteristics of targeted therapeutic markets

First we aim at assessing the difference in success probabilities where R&D projects are classified according to the characteristics of the targeted disease. We argue that, besides firm capabilities in selected therapeutic market, projects targeting different diseases have inherently different probability of success. Studies addressing the probability of success of R&D projects in the pharmaceutical domain find substantial differences across therapeutic categories (see, e.g. Danzon, Nicholson, Pereira, 2005; Adams, Brantner, 2003). The availability of information about the characteristics of the disease target in terms of outcome, potential market size, etiology, emergence of complication and organ damage allows us to move a step forward and to analyze how the underlying characteristics of the targeted diseases affect the probability of success (see also Arora, Gambardella, Magazzini, Pammolli, 2006).

The analysis will help us explaining the productivity slowdown in the pharmaceutical industry that has been documented by the empirical literature (Mervis, 2005; Pammolli and Riccaboni, 2007). Despite increasing R&D expenditures in the pharmaceutical industry, the number of new molecular entities launched on the market is stable and much lower than the figure at the beginning of the Nineties.

Exploiting the potential of our database, we measured the dynamics of attrition rates in the stages involved in drug development over the Nineties. We considered terminated projects and distinguished two possible outcomes: success and failure. Since, we consider phase-specific

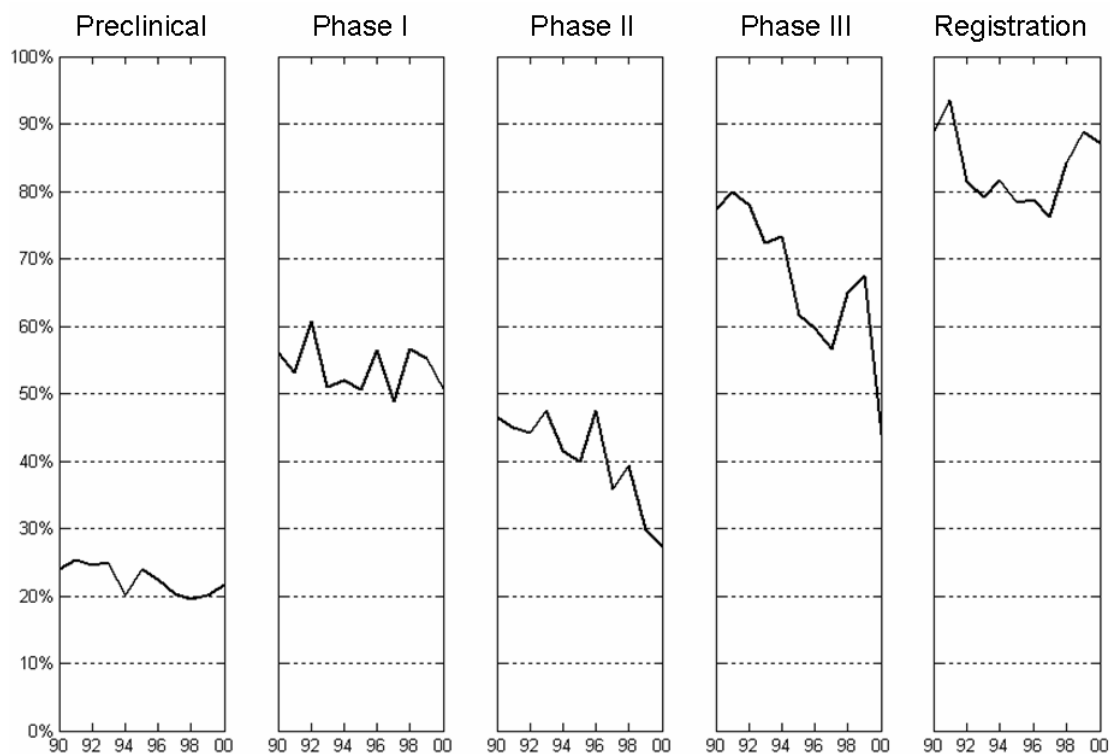
¹¹ An orphan or rare disease is generally considered to have a prevalence of fewer than 200,000 affected individuals in the United States. Certain diseases with more than 200,000 affected individuals are included, but subpopulations of these conditions may be less than the prevalence standard for rare disease. Given the small market size of drugs and other products designed to treat rare diseases, they are likely to offer little or no profit to the manufacturer. To foster their development, the “Orphan Drug Act” (1983) allows drug companies to take tax deductions for about three-quarters of the cost of the clinical studies (FDA, 1999), with an implied reduction of cost for development.

¹² We plan to extend this variable and also consider sales in the European markets.

attrition rates, for each phase involved in drug development, success is defined as a transition from one phase of drug development to the next one, while a project is considered to be failed if it's been discontinued, suspended or it is stated to be no longer in active research.

Figure 1 reports the share of successful projects over the total number of projects entering in any given phase of R&D in a certain year, where the x-axis represents the year of entry into the stage considered in each subplot.

Figure 1. Trends in probability of success for R&D projects



Estimation of attrition rates is complicated by the fact that the process of drug development is particularly long. 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 (12.3 months for completing Phase I, 26.0 months for Phase II, and 33.8 months for Phase III). Using a more comprehensive dataset, Abrantes et al (2003) states that for drugs that successfully passes through all three phases of clinical development, the average time in the process (not including any time spent between phases) amounts to 8 years. The time required for the assessment involved in each stage does not allow us to produce a sound estimation of the probability of success for projects that started a given phase after the year 2000. However, we assume that projects that entered preclinical or clinical trials before 2000 and have not yet moved on are failed.

Figure 1 shows that during the Nineties, the attrition rate of pharmaceutical R&D projects has increased, especially in clinical trials II and III. In clinical trials II, the probability of success has dropped from almost 1/2 to less than 1/3 while projects that started phase III in year 2000 have a probability of success that is almost one half than projects that entered phase III ten years before.

Against this background, Table 1 shows the average probability of success of R&D projects, classified according to the characteristics of the targeted disease. In this case, we considered as successful the R&D projects that ended with a market launch.

Clear-cut differences exist in the rate of success of R&D projects targeting indications with different characteristics.

R&D projects targeting lethal diseases have a lower probability of success, as well as projects targeted to pathologies causing complications and organ damages. Diseases with multifactorial or unknown etiology have a lower probability of success. The same holds for R&D projects targeted to rare diseases.

Moreover, we have classified the indication according to their potential market size (computed using the information on matched ATC3 classes). We considered a classification according to the percentiles of the distribution of sales for each indication in 1995. Particularly, we distinguish (i) indications among the top 10% according to market size, (ii) indications with market sales between the 75th and the 90th percentile, (iii) indications with market sales between the 50th and the 75th percentile, and (iv) indications with sales below the median. Top sales indications have a lower probability of success (11.99%) than indications with market sales between the median and the 90th percentile. Indications with market sales below the median have a lower probability of success than the intermediate group. In the case of top-sales indication, the lower expected probability of success is offset by the prospect of larger rewards, therefore pushing the research efforts in these areas.

On the contrary, smaller markets (below the median size) have both smaller rewards in case of success, and lower probability of success, leading to lower expected returns.

Table 1. Average probability of success, according to the characteristics of the targeted disease

Characteristic of the targeted disease	Probability of success (%)
Not lethal	21.00
Can be lethal	17.62
Always lethal	16.51
No organ damage	24.51
Causes organ damage	16.33
No complications	26.21
Causes complications	17.49
Unknown etiology	20.35
Unifactorial etiology	21.36
Multifactorial etiology	17.22
Acute	19.89
Chronic	17.58
Rare	36.20
Diffused	16.96
Top 10% indication (sales)	11.99
75-90 percentile	17.95
50-75 percentile	17.52
Below the median	13.72

IV. Mapping current R&D efforts

In this section we aim at characterizing current effort in R&D within the pharmaceutical industry. We consider only active projects at July 2005, and undertaken by established pharmaceutical companies (EPC), dedicated biotechnology firms (DBF), and public research organizations (PRO).

Table 2 reports the number of R&D projects, distinguishing originated and developed projects. Almost 50% of active projects are undertaken in the US, whereas European companies and institutions have originated/are developing 30% of active projects. Besides that an important difference emerges between the structure of the European and the US research environment. The difference is more pronounced if we look at the characteristics of Japanese projects.

Public research organizations (PRO) have a smaller role in Europe vis-à-vis the US. US PROs originated 16.0% of active projects, versus a figure of 6.5% for European PROs. As expected numbers are smaller in case of developed projects, since PROs often lack the capabilities, resources, and incentives to get a new product on the market.

Overall, EPCs play a more important role in Europe with respect to the US, where also DBF originates and develops a large share of new compounds.

Results are consistent with a different organization of the research activities in the Europe and the US (see Owen-Smith, Riccaboni, Pammolli, Powell, 2002). Large differences exist within the European boundaries, where in Sweden DBF originated 89.8% of R&D projects, whereas in Italy the figure reduces to 29.1%.

Table 2. Current R&D effort, by nationality and institution type of originator and developer

	Total		PRO		DBF		EPC	
	No.	%	No.	%	No.	%	No.	%
originated projects								
USA	3685	49.0%	589	63.5%	2542	55.6%	554	27.4%
	100.0%		16.0%		69.0%		15.0%	
EU-25	2297	30.5%	150	16.2%	1388	30.4%	759	37.5%
	100.0%		6.5%		60.4%		33.0%	
Japan	439	5.8%	24	2.6%	18	0.4%	397	19.6%
	100.0%		5.5%		4.1%		90.4%	
Other	1101	14.6%	165	17.8%	621	13.6%	315	15.6%
	100.0%		15.0%		56.4%		28.6%	
Total	7522	100.0%	928	100.0%	4569	100.0%	2025	100.0%
	100.0%		12.3%		60.7%		26.9%	
developed projects								
USA	3552	47.2%	379	61.1%	2388	55.9%	785	29.8%
	100.0%		10.7%		67.2%		22.1%	
EU-25	2290	30.4%	94	15.2%	1243	29.1%	953	36.2%
	100.0%		4.1%		54.3%		41.6%	
Japan	501	6.7%	22	3.5%	15	0.4%	464	17.6%
	100.0%		4.4%		3.0%		92.6%	
Other	1179	15.7%	125	20.2%	624	14.6%	430	16.3%
	100.0%		10.6%		52.9%		36.5%	
Total	7522	100.0%	620	100.0%	4270	100.0%	2632	100.0%
	100.0%		8.2%		56.8%		35.0%	

Reading key:

number of projects	as % of total by column
as % of total by row	

Next, we focus on R&D projects targeting diseases that are typical of LDCs, distinguishing by company location (showing that the overwhelming majority of R&D projects relevant for LDCs are performed in the US) and by institutional type (showing that in this segment public research organizations and new biotech companies play an important role).

Every infectious disease is unique. For some, products exist and are accessible. For many, products exist but there are problems with access, affordability or acquired drug resistance. Product R&D is underway looking for compounds targeting some diseases, but it has yet to deliver. In other instances, limited product R&D is underway because the scientific basis for rational study is insufficient. In other cases limited product R&D is underway not because of scientific barriers but because industry doubts that returns would cover the cost of the investment and support ongoing R&D (WHO-IFPMA, 2001).

This section focuses on current efforts targeting diseases that are prevalent in Africa: gonorrhea; HIV infection; diphtheria; pertussis; measles; tetanus; meningitis; malaria; poliomyelitis.

Table 3 summarizes the number of R&D projects addressing African diseases, by nationality of originators and developers and their typology: Public Research Organizations (PROs), Dedicated Biotechnology Firms (DBFs), and Established Pharmaceutical Companies (EPCs).

The bulk of projects are originated and developed in the US, whereas the contribution of the European companies to this research is fairly low. An important difference emerges between Europe and the US in this respect. The US biotechnology firms and public research organizations play an important role in originating and developing new compounds targeting African pathologies, whereas the role of these firms in Europe is rather limited (the exception being Sweden). In Europe, a prominent role is played by the established pharmaceutical corporation, originating and developing the larger part of projects targeting African diseases. In sum, the US effort is significantly above the world average, while European and Japanese institution, especially DBF, are less active in the field of African diseases.

Table 3. Number of R&D projects on Africa's diseases (AD), by nationality and institution type of originator and developer (1980-2004)

	Total		PRO		DBF		EPC	
	No.	%	No.	%	No.	%	No.	%
projects originated								
USA	822	56.8%	239	61.8%	369	74.7%	214	37.9%
	100.0%	+1.1%	29.1%	-0.0%	44.9%	+0.9%	26.0%	+1.7%
EU-25	338	23.4%	65	16.8%	73	14.8%	200	35.4%
	100.0%	-1.3%	19.2%	-0.5%	21.6%	-2.0%	59.2%	-0.4%
Japan	86	5.9%	17	4.4%	-	-	69	12.2%
	100.0%	-2.2%	19.8%	-1.9%	-	-4.9%	80.2%	-2.0%
Other	200	13.8%	66	17.1%	52	10.5%	82	14.5%
	100.0%	+0.6%	33.0%	+1.4%	26.0%	-0.2%	41.0%	+0.4%
Total	1446	100.0%	387	100.0%	494	100.0%	565	100.0%
	100.0%		26.8%		34.2%		39.1%	
projects developed								
	No.	No.	No.	%	No.	%	No.	%
USA	762	762	184	57.0%	356	71.1%	222	35.7%
	100.0%	100.0%	24.1%	-0.5%	46.7%	+0.6%	29.1%	+1.1%
EU-25	383	383	64	19.8%	85	17.0%	234	37.6%
	100.0%	100.0%	16.7%	+0.8%	22.2%	-1.6%	61.1%	0.0%
Japan	85	85	17	5.3%	-	-	68	10.9%
	100.0%	100.0%	20.0%	-1.6%	-	-5.2%	80.0%	-2.1%
Other	216	216	58	18.0%	60	12.0%	98	15.8%
	100.0%	100.0%	26.9%	+1.4%	27.8%	+0.1%	45.4%	+0.4%
Total	1446	1446	323	100.0%	501	100.0%	622	100.0%
	100.0%	100.0%	22.3%		34.6%		43.0%	

Reading key:

number of projects	as % of total by column
as % of total by row	% with respect to Δ as Rest of the World*

* This figure is the difference between relative effort within the country (number of projects in the country targeting AD as a % of the total number of project undertaken in the country) and the relative effort in the Rest of the World. The figure is in bold if the difference is statistically different from zero at the 5% level.

V. Econometric Model

To better understand the evolution of firms' R&D efforts in the last decade, in this section we move to analyze the dynamics of R&D project portfolios over time. The analysis will also prove to be useful for understanding the slowdown in R&D productivity that is characterizing the pharmaceutical industry.

According to standard economic theory, firms will enter markets that are expected to provide high profits and good prospects of market growth, whereas the presence of barriers to entry will decrease the likelihood of a firm entering the market. We aim here at analysing the likelihood of entry of firms into previously unexplored (by the firm) therapeutic markets, as a function of the characteristics of the targeted pathology, controlling for firm capabilities, both at the firm level and at the therapeutic market levels.

Our dependent variable is a dichotomous variable indicating whether a possibility of entry has been exploited during the 1995-2005 period. We compare corporation activities in therapeutic markets in 1995 or earlier to their activities after 1995. The year 1995 has been selected by looking at the data on new drug introduction over time. Indeed, after the year 1996 a decreasing number of new molecular entities has been introduced worldwide and current trends do not seem to reverse (see Pammolli and Riccaboni, 2007).

The data are organized in a matrix form, where rows represent firms ($i = 1, \dots, n$), and columns represent indications ($j = 1, \dots, K$). Each cell contains the number of active projects of firms i in market j . We build two different matrices: the first one contains the count of projects started before 1995, whereas the second consider the period 1996-2005. The comparison of the two matrices gives information about the entry strategies carried out by the firms across the indications. Entry is recorded in case a firm is observed not to operate in a therapeutic market before 1995, and to have originated at least one project in that area before 2005.

Coupled with the empirical evidence presented in Section 3, the analysis can help in interpreting the current trends in R&D productivity in the pharmaceutical industry.

Following the models employed in the literature studying the entry decision of firms into industries (see Sembenelli and Vannoni, 2000; Merino and Rodriguez, 1997), let $y^*(i,j)$ be the variables representing the propensity of firm i to enter market j (contingent upon not operating in market j).

The entry behaviour of firms can be modelled as follows:

$$y^*(i,j) = f(x(i), w(j), z(i,j)) + e(i,j)$$

where $x(i)$ is a vector including the set of variables describing the characteristics of firm i , $w(j)$ represents the characteristics of market j , and $z(i,j)$ is the vectors of variables describing characteristics of firm i and market j . $y^*(i,j)$ is not observed. We observe a dichotomous variable

$y(i,j)$ which assumes the value of 1 if firm i entered market j in the period 1996-2005, i.e firm i was not operating in market j prior to 1995 and it started¹³ a new R&D project after 1995.

The model is estimated via conditional logit, in order to explicitly consider the correlation among the choice of a firm to operate into different markets (Chamberlain, 1980). As a drawback, the effect of firm specific variables (firm-invariant) cannot be estimated. However, the focus here is on market characteristics affecting innovation, where we control for firm characteristics.

At the indication level, the main variables in our regression represent the characteristics of the disease in terms of etiology, outcome, chronicity, diffusion, organ damage, complications, market size and concentration. We also included the success share on projects terminated before 1995. In case no projects had been terminated for an indication before 1995, a value of zero is assumed, and a dummy variable is creating for indicating this information.

Finally, we considered the number of previous collaboration with firms operating in the area (as a licensee).

Our universe of observation is the set of pair indication-corporation with zero projects entering preclinical or clinical stages before 1995. All corporations starting at least one project in the time period 1996-2005 have been included in the analysis.

When information about preclinical and clinical trials are considered, in the time period 1996-2005 there have been 9,486 new entries, measured as firms entering therapeutic markets (indications) in which they were not active in 1995 or at an earlier date (for a total of 12,420 new R&D projects).

The tables that follow report the intensity of entry into therapeutic markets classified according to their characteristics. The “possibility of entry” is defined as a combination of corporation-market with no active projects in 1995 or at an earlier time. “Actual entry” is the number of the corporation-market combinations (with zero projects before 1995) that registered one or more projects in preclinical or clinical development after 1995.

We report the average probability of success of the R&D projects according to the characteristics, in terms of etiology, chronicity, etc. of the targeted disease, presented in Section 3.

¹³ The date of beginning of the project is taken equal to the date of preclinical, when this information is available, otherwise we considered the earliest information into clinical trials.

Table 4. Diseases classified according to etiology, intensity of entry

	Possibility for entry	Actual entry	Intensity %	Avg Probability of success
Unknown etiology	41,562	451	1.09	20.35
Monofactorial etiology	237,688	1,756	0.74	21.67
Multifactorial etiology	464,428	7,279	1.57	17.22
Acute	245,713	1,839	0.75	19.89
Chronic	495,875	7,625	1.54	17.58
Not lethal	210,199	1,630	0.78	21.00
Maybe lethal	398,708	5,118	1.28	17.62
Always lethal	134,771	2,738	2.03	16.51
No organ damage	291,618	2,117	0.73	24.51
Organ damage	452,060	7,369	1.63	16.33
No complications	100,089	496	0.50	26.21
Complications	643,589	8,990	1.40	17.49
Rare	175,338	1,206	0.69	36.20
Widespread	568,340	8,280	1.46	16.96
Top 10% indication	59,094	2,358	3.99	11.99
75-90 percentile	101,027	1,244	1.23	17.95
50-75 percentile	141,552	1,391	0.98	17.52
Below the median	304,464	2,274	0.75	13.72

The results show that firms have more intensely started projects targeted to:

- diseases with multifactorial or unknown etiology;
- chronic diseases;
- diseases that are always lethal or that can be lethal if not treated;
- disease causing organ damage and complications;
- more diffused diseases (rare diseases provide lower expected returns, nonetheless they have a higher probability of success).

Given, the lower probability of success for R&D projects targeting this group of diseases, this result provide support to the view that the slowdown in pharmaceutical R&D productivity is driven by difficulty of the most important therapeutic indications, and not by lack of effort. As far as market size is concerned, firms more likely pursue compounds targeting top-sales indication, where the intensity of entry decreases with the dimension of the market associated to project indication.

Finally, we considered an econometric model that aims at modelling the entry choices of firms into therapeutic submarkets. Table 5 presents conditional logit estimates, where we take into account the correlation of choices undertaken by the same firm into different market.

The model CLOGIT1 refers to firms that were active before 1995, CLOGIT2 consider firms that were not active before 1995, whereas CLOGIT3 consider all firms.

As far as the characteristics of the compound are concerned, the estimated coefficients confirm previous descriptive results (Table 4). The Table also reports marginal effect for model CLOGIT3, assuming that fixed effect is zero. The figure gives the change in the probability of entry,

corresponding to a change in the independent variables. For dummy variables, the figure report the effect on the probability of a change in the variable from 0 to 1.

As for the difficulty of the R&D project, as proxied by the characteristics in terms of etiology of the targeted disease, diseases with multifactorial or with unknown etiology, are more likely to be pursued by the firms. In addition firms are more likely to start a project targeting a disease causing complication or organ damage, or that can be lethal. As a result, it seems that firms are undertaking research effort in areas where diseases are more severe and difficult to tackle.

Moreover, previous probability of success for the selected indication has a negative impact on the probability of entry, i.e. the higher the probability of success of R&D projects targeting the selected indication and started before 1995, the lower the probability a new firm will start targeting the project. The effect is larger for indication with no available information before 1995.

Looking at the incentives that are related to market size, all the variables we considered point to the fact that firms respond to market incentives in devising their research strategies. Particularly, firms are less likely to tackle rare diseases, whereas they are more likely to consider chronic diseases, providing revenues for longer times. The coefficient of market size is positive and statistically significant: diseases with larger market attract more entry. The coefficient of market concentration is also positive and statistically significant. Less concentrated markets are less affected by (price) competition, giving the innovator the possibility of higher rewards for innovation, in case a better (more effective and with lower side effects) drug is launched on the market.

Table 5. Results of econometric estimates

	LOGIT1	LOGIT2	CLOGIT1	CLOGIT2	CLOGIT3	marginal effects (CLOGIT3)
RARE	-0.7602 (0.0674)***	-0.8983 (0.0785)***	-0.7791 (0.0677)***	-0.8510 (0.0512)***	-0.9027 (0.0787)***	-0.1516
CHRONIC	0.2566 (0.0441)***	0.5155 (0.0482)***	0.2702 (0.0447)***	0.3914 (0.0327)***	0.5227 (0.0485)***	0.0766
MULTI-ETIO	0.4249 (0.0469)***	0.4451 (0.0503)***	0.4415 (0.0474)***	0.4581 (0.0345)***	0.4494 (0.0505)***	0.0659
UNKN-ETIO	0.6099 (0.0848)***	0.3884 (0.0938)***	0.6090 (0.0866)***	0.4979 (0.0634)***	0.3831 (0.0945)***	0.0472
COMPLICATION	0.4927 (0.071)***	0.7133 (0.0875)***	0.5073 (0.0716)***	0.5971 (0.0551)***	0.7194 (0.0878)***	0.1178
ORGANDAMAGE	0.7061 (0.0482)***	0.907 (0.0544)***	0.7331 (0.0488)***	0.844 (0.0361)***	0.9192 (0.0546)***	0.1358
LETHAL	0.1035 (0.0476)**	0.2019 (0.0521)***	0.112 (0.0482)**	0.1483 (0.0352)***	0.2044 (0.0523)***	0.0291
INDSUCCPRE95	-0.9039 (0.0674)***	-1.2431 (0.0764)***	-0.9366 (0.0681)***	-1.0848 (0.0506)***	-1.2547 (0.0768)***	-0.1740
INDNOINFOPRE95	-1.9243 (0.0943)***	-1.7359 (0.1082)***	-1.9112 (0.0946)***	-1.6304 (0.069)***	-1.7454 (0.1084)***	-0.3398
MKTSIZE	5.5125 (0.2279)***	7.1210 (0.1904)***	6.0282 (0.2372)***	6.9525 (0.149)***	7.3291 (0.1941)***	1.0167
MKTCONC	0.4598 (0.0775)***	0.9102 (0.0795)***	0.4833 (0.0786)***	0.7101 (0.0557)***	0.9237 (0.08)***	0.1281
NPRJ	0.0105 (0.0005)***					
HERF	-0.7040 (0.0621)***					
PRESUCC	-0.0100 (0.0690)					
NOINFO	-0.3211 (0.0426)***					
PREAGREEMENT	1.4626 (0.0689)***		1.3742 (0.0735)***			
Constant	-4.8474 (0.099)***	-6.523 (0.1093)***				
N	158120	259974	143239	397961	254722	
Pseudo R2	0.1045	0.1122	0.1041	0.1133	0.1347	
Log likelihood	-15454.679	-16062.303	-12789.309	-26194.624	-13211.499	

*** p-value < 0.01; ** p-value < 0.05; * p-value < 0.10

VI. Summary and Conclusions

This paper has exploited a unique data set in order to assess the real distribution of R&D effort, both in terms of targeted diseases/therapeutic indications and in terms of the geographical location of the performing institutions. The overwhelming majority of R&D projects relevant for LDCs are performed in the US, with an important role played by both the public research system and the new biotech companies. The paper has produced a detailed representation of the current distribution of effort, coming to some relevant implications in terms of political economy, regulation, and trade relations.

Even though preliminary, our analysis reveals the existence of a “fishing-out” effect in pharmaceutical R&D. As time goes by, firms have increasingly targeted diseases with multifactorial or unknown etiology, chronic or lethal diseases, pathologies causing organ damage and complications, widespread diseases.

Since R&D projects targeting complex diseases have a lower probability of success, this is by far the most important cause of the pharmaceutical R&D productivity slowdown of the last decade. Provided that unmet medical needs induces higher attrition rates while the set of technological opportunities is expanding, pharmaceutical companies have to figure out new organizational forms to boost their R&D effort and selective capabilities in order to cope with growing risk of failure and guarantee a constant rate of arrival of new molecular entities to the market.

The analysis opens avenues for further research. Even though the conditional logit model allows to control for correlation among the choices of the same firm over time, different specification of the error term should be considered.

In addition, we do not consider in this paper the issue of unvalidated target, i.e. the exploration of mechanisms of action targeted by no drug approved at the time the drug being examined entered Phase II (Aghazadeh, Arnold, Beaver, 2005). Once a new mechanism of action is identified, firms start to build compounds in order to tackle the associated pathology. High competition and rapid advances in molecular biology and for the understanding of the biological root of major pathologies has forced companies to base their decisions uniquely on the most recent discoveries and projections, even if no compound relying on the same mechanism of action has reached the market (as an example consider current research around the p38 mitogen activated protein kinase, see Magazzini, Pammolli, Riccaboni 2006). In this respect, research is highly uncertain, since there is no clue about the validity of the underlying mechanism of action for targeting the selected pathology.

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