The productivity crisis in pharmaceutical R&D

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Abstract | Advances in the understanding of the molecular basis of diseases have expanded the number of plausible therapeutic targets for the development of innovative agents in recent decades. However, although investment in pharmaceutical research and development (R&D) has increased substantially in this time, the lack of a corresponding increase in the output in terms of new drugs being approved indicates that therapeutic innovation has become more challenging. Here, using a large database that contains information on R&D projects for more than 28,000 compounds investigated since 1990, we examine the decline of R&D productivity in pharmaceuticals in the past two decades and its determinants. We show that this decline is associated with an increasing concentration of R&D investments in areas in which the risk of failure is high, which correspond to unmet therapeutic needs and unexploited biological mechanisms. We also investigate the potential variations in productivity with regard to the regional location of companies and find that although companies based in the United States and Europe differ in the composition of their R&D portfolios, there is no evidence of any productivity gap.

Knowledge production function
A function that specifies the output of new ideas by an individual, a firm, an industry or the entire economy for all combinations of research and development inputs (labour and the existing stock of knowledge).

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doi:10.1038/nrd3405

Empirical accounts of the returns from innovative activities across a wide range of sectors provide accumulating evidence of a long-term decline in the productivity of research and development (R&D)[1–5]. This fall in productivity has been ascribed to diminishing returns in the knowledge production function. As science progresses, incentives to undertake R&D activity increase, but research productivity declines owing to greater competition in exploiting new market opportunities[2]. Some scholars have proposed that past R&D efforts have exhausted the easy targets, thereby raising the bar for research success[6,7]. However, even if innovation opportunities keep growing with advances in basic science[8,9], new research opportunities also contribute to the increase in the complexity of R&D[5,10].

In recent years, the R&D productivity challenge has become particularly difficult to overcome in the pharmaceutical sector[11,12]. The cost of developing a new drug has increased, as have total R&D expenditures[13], while the rate of introduction of new molecular entities (NMEs) has at best remained approximately constant[14] and attrition rates have risen sharply, especially in late-phase clinical trials[15–17]. It should be noted, however, that the number of NMEs is an imperfect measure of R&D outcomes, as it does not reflect changes in the quality of the output. In addition, the productivity crisis might be a temporary phenomenon, as radical technological changes, such as the genomic revolution, could initially increase the time lag between investment and outcome, thereby reducing R&D productivity in the short term[18]. Nevertheless, there is a growing concern about the causes and consequences of the innovation drought in the pharmaceutical industry.

Here, we analyse recent trends in attrition rates and development times in pharmaceutical R&D using data from the Pharmaceutical Industry Database (PhID) maintained at the IMT Institute for Advanced Studies Lucca, Italy[16]. The database draws from and integrates several data sets, thereby providing information about innovation and market activities of companies and institutions involved in pharmaceutical R&D in recent decades (BOX 1). We show that the decline in the productivity of pharmaceutical R&D cannot be fully explained by the forces of demand and competition, and we document an increasing focus of research activities in the development of selective drugs in complex research areas that are characterized by a low probability of success (POS). It seems that research efforts have been reoriented towards more difficult targets, while the number of options that can yield viable therapies has grown dramatically. Consequently, the cost of R&D of new drugs has risen.

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Box 1 | **The Pharmaceutical Industry Database**

The Pharmaceutical Industry Database (PhID), maintained by the IMT (Institutions, Markets, Technologies) Lucca, Italy, combines several sector-specific proprietary data sets regarding research and development (R&D) activity, collaborations and final drug markets. These data are collected from public sources and from companies (confidential information and press releases). Data collection started in 2000, financed by a grant from the Merck Foundation (EPRIS project). The PhID includes full text entries comprising more than 200,000 patent applications since the early 1970s (from the US Patent and Trademark Office, the European Patent Office and the World Intellectual Property Organization); detailed information about R&D projects spanning more than 28,000 compounds; 20,000 collaborative agreements; and sales figures on ~160,000 pharmaceutical products (both branded and generics) sold in the major markets (the United States, the 15 European Union countries (EU-15: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden and the United Kingdom) and Japan) between 1996 and 2008 (REF. 16). For each compound, information regarding the targeted therapeutic market, the timing of major development milestones, and the name and type of organizations involved is provided.

Targeted therapeutic market. Two complementary classification systems are used in the PhID. First, the therapeutic indication is written in standard terms (for example, inflammation or breast cancer); this classification focuses on the clinical symptoms for which the drug is being tested. Second, the Anatomical Therapeutic Chemical (ATC) classification is used. The ATC divides drugs into groups according to the organ or system on which they act and/or their therapeutic and chemical characteristics.

The first level of the ATC classification (ATC1) identifies the organ or system on which the drug acts; for example, all drugs related to the central nervous system or to the cardiovascular system. At the lower levels, the chemical, pharmacological and therapeutic characteristics of the drug are also taken into account. At the third level (ATC3), classes are defined by grouping all drugs with the same therapeutic and pharmacological characteristics. Each therapeutic indication has been classified by a pharmacologist for its severity, chronicity and patient population[20] (information has been complemented with e-medicine reviews from the Disease Database, and for rare diseases we drew on the US National Institutes of Health database of Rare Diseases and Related Terms).

Timing of major development milestones. Timing is from patent filing to preclinical and clinical trials (Phases I–III), registration and market launch. If the project fails to pass through all the stages of drug development, the time and development stage when the company announced termination of the project is reported.

The name and type of organizations involved. The companies and/or public research organizations involved, along with their role in the project (originator or licensor versus developer or licensee), are reported.

Measurements of R&D productivity

Research productivity is typically measured as the ratio of R&D outputs to inputs. However, measuring research inputs and outputs for 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 labour, the number of R&D collaborations and the number of private and public research organizations that span different countries[10,19]. As a result, the analysis of productivity of pharmaceutical R&D needs to rely on different measurements and to look at a wide set of indicators and statistics, which are included in the PhID (BOX 1).

We analysed R&D projects in the PhID that were started from 1990 onwards, for which we know the timing of major milestones in development from patent filing through to preclinical and clinical trials until termination (failure) or market launch (success). For each compound, information is available on the therapeutic indications being researched, the name and type of institutions involved (companies and/or public research organizations), along with their role in the project (that is, as originator or licensor versus developer or licensee). Each therapeutic indication has been classified by a pharmacologist for its severity, chronicity and patient population[20] (information has been complemented with e-medicine reviews from the Disease Database, and for rare diseases we drew on the US National Institutes of Health database of Rare Diseases and Related Terms). Finally, biologics have been distinguished from chemical entities.

The growing complexity of pharmaceutical R&D

First, we investigated attrition rates and phase lengths, and analysed the composition of research portfolios over time. The analysis is based on project counts, whereby a R&D project is defined as the research directed towards testing and assessing a compound against a well-defined therapeutic target.

Since the mid-1990s, pharmaceutical R&D productivity has experienced a downturn. From 1998 to 2008, the number of NMEs approved per year declined (although it has been roughly constant since 2005), whereas attrition rates, development times and R&D expenditures have all increased[9,14,16–18,21–24]. FIGURE 1 shows the dramatic growth in attrition rates — the proportion of failures out of the total number of projects entering any given stage of R&D — across all phases, but especially in Phase II and Phase III clinical trials. Estimation of attrition rates is complicated by the fact that the process of drug development lasts several years. According to recent estimates, the average time to pass through US clinical trials ranges from 6 years to 8 years[13,21]. We considered phase-specific success rates within 4 years from initiation of phase for R&D projects that entered clinical trials from 1990 to 2004 in Europe, the United States and Japan. We expect the time cut-off to introduce a minor bias in the reported attrition rates, as the majority of successful projects pass to the next stage within 4 years: 93% in preclinical, 86% in Phase I, 82% in Phase II and 75% in Phase III.

Overall, the POS for each stage of drug development has declined over time. At the same time, the average development time — from patenting to product commercialization — has increased for more recent products. By taking into account the time from patent filing to market launch in the United States and in the 15 European Union countries (EU-15: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden and the United Kingdom), the average time of development has increased from 9.7 years for products launched during the 1990s to 13.9 years for products launched from 2000 onwards.

To explore the causes of the increase in attrition rates and development times, we analysed R&D investment decisions. The potential pay-off for an R&D project can be calculated as the product of the probability of market launch multiplied by the potential market value of the compound. Accordingly, for each project we calculated the 'expected POS', that is, the average success rate (in reaching the market from the preclinical testing

New molecular entity (NME). A medication containing an active ingredient that has not been previously approved for marketing in any form in the United States. NME is conventionally used to refer only to small-molecule drugs, but the term is used here to include biologics as a shorthand for both types of new drug and also to new drugs in all the regions studied, rather than just those approved in the United States.

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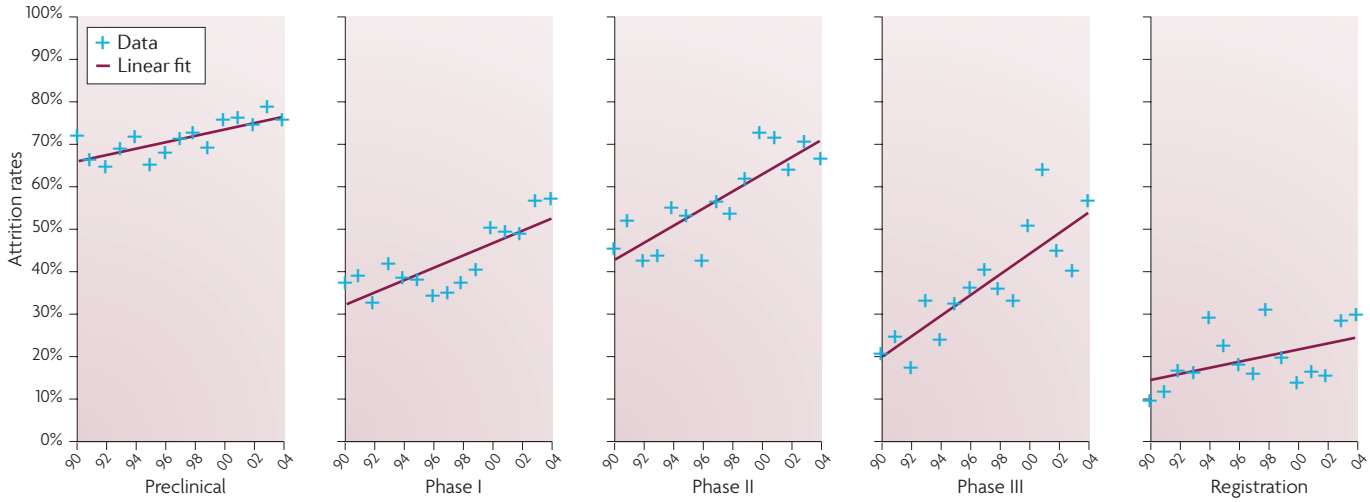

Figure 1 | **Trends in attrition rates of drug development projects.** Data are for projects started between 1990 and 2004 in the United States, Europe and Japan. Source: analysis of the Pharmaceutical Industry Database (BOX 1).

phase) of compounds targeting the same pathology. In the case of previously unexplored markets for which the expected POS is not available, we set it at zero, as we considered them as extremely high-risk projects[25]. Market size was measured by using the average value of sales per year per molecule in the major international markets (EU-15, the United States and Japan) from 1997 to 2007 (BOX 1). Only sales of branded drugs were considered.

TABLE 1 shows the distribution of R&D efforts, in terms of new R&D projects started, by broad therapeutic areas (Anatomical Therapeutic Chemical classes at the first level of disaggregation, ATC1; see BOX 1 for definition).

In particular, from 2000, the share of R&D projects in the ATC class of antineoplastic agents grew from 16.55 to 23.43% (+6.88%). Two other ATC classes attracted R&D projects: neurological (+1.09%) and alimentary tract and metabolism (+1.56%), whereas the share of R&D projects in the cardiovascular field experienced the strongest contraction (–4.57%). Interestingly, the ATC class of antineoplastic agents had both the highest potential sales and the lowest POS (TABLE 1).

We next analysed the effect of the changing composition of research portfolios on total R&D productivity. We calculated the number of R&D projects started in two time periods: 1990–1999 (t = 1) and 2000–2004 (t = 2). To account for the different lengths of the two time periods, we considered the average number of new projects started per year in each period (NP_1 and NP_2). For the projects started in each period, the expected number of NMEs is equal to the POS multiplied by the number of projects (NP). The aggregate POS is given by the average POS at the ATC1 level, weighted by the share of R&D projects in any ATC class. Accordingly, the change in the output of pharmaceutical R&D can be measured as shown in the equation:

$$\frac{NME_2}{NME_1} = \frac{POS_2}{POS_1} \times \frac{NP_2}{NP_1} = \frac{POS_2}{POS(1,2)} \times \frac{POS(1,2)}{POS_1} \times \frac{NP_2}{NP_1}$$

NME_1 is the expected number of NMEs produced by R&D projects started between 1990 and 1999, NME_2 is the expected number of NMEs generated by projects started between 2000 and 2004, and POS(1,2) is the POS obtained by applying the POS measured for each ATC class at time 1 weighted according to the distribution of R&D efforts at time 2. The first term on the right hand side of the expression — $POS_2/POS(1,2)$ — can be interpreted as the effect on R&D productivity of the change in the POS at the ATC level; the second term — $POS(1,2)/POS_1$ — measures the variation of R&D productivity due to the change in the composition of R&D efforts; the third term — NP_2/NP_1 — represents the change in the total number of R&D projects.

Based on this calculation, the expected change in R&D productivity is 0.48. In other words, every year, the number of expected NMEs generated by the projects started between 2000–2004 is less than one-half of the number of expected NMEs per year generated by R&D projects started between 1990 and 1999. Interestingly, the result is not driven by a decline of R&D productivity at the ATC level, as the calculated value of the $POS_2/POS(1,2)$ term is 0.92. Instead, it is the composition effect term $POS(1,2)/POS_1$ — which has a calculated value of 0.43 — driving the change. Indeed, the term representing the change in the number of projects is 1.21, as a consequence of the significant increase in the number of projects (NP_1 = 1,419; NP_2 = 1,716). Hence, without the reorienting of R&D efforts, R&D productivity would have remained almost constant.

FIGURE 2 shows the composition of R&D efforts at a finer level of disaggregation (ATC3; see BOX 1 for definition). As in TABLE 1, we computed POS, potential market sales and the percentage distribution of R&D projects by ATC3 class. The percentage distribution by POS and potential sales was calculated for the following:

- All R&D projects, 1990–2004 (D)
- R&D projects started in the 1990s (D_1)
- R&D projects started between 2000 and 2004 (D_2)

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Table 1 | **Average success rate, sales and share of the total number of R&D projects***

Anatomical Therapeutic Classification (ATC1)	Number of projects	Average sales (US$ million)	Average POS (%)	Percentage of total projects		
				1990–1999	2000–2007	Change‡
L: Antineoplastic and immunomodulating agents	6,566	105.3	1.80	21.77	29.77	+8.00
Including L01: Antineoplastic agents	5,094	92.0	1.29	16.55	23.43	+6.88
N: Nervous system	3,817	43.5	2.85	14.46	15.55	+1.09
B: Blood and blood-forming organs	822	72.9	3.81	4.11	2.38	–1.73
J: Anti-infectives for systemic use	4,737	82.4	3.92	18.85	18.41	–0.44
M: Musculoskeletal system	1,472	22.6	4.19	6.49	5.10	–1.39
A: Alimentary tract and metabolism	2,046	14.8	4.46	7.26	8.82	+1.56
R: Respiratory system	1,165	13.3	4.81	5.07	4.10	–0.97
C: Cardiovascular system	2,139	45.6	4.86	10.72	6.15	–4.57
D: Dermatologicals	859	4.4	6.64	3.63	3.13	–0.50
G: Genitourinary system and sex hormones	865	21.0	11.75	3.95	2.86	–1.09
Other (H+P+S)§	945	11.2	19.79	3.70	3.73	+0.04

POS, probability of success; R&D, research and development. *The top ten areas in terms of activity are defined according to the top level of the ATC system. ‡All differences are statistically significant (*P*-value < 5 %) except for class J and the residual class 'Other'. §H represents systemic hormonal preparations, excluding sex hormones and insulins; P represents antiparasitic products, insecticides and repellents; S represents sensory organs. Source: analysis of the Pharmaceutical Industry Database (BOX 1).

- R&D projects started by US organizations, 1990–2004 (D_{US})
- R&D projects started by European organizations, 1990–2004 (D_{EU})

Each panel in FIG. 2 depicts the POS on the *x* axis and the logarithm of potential sales on the *y* axis. On the vertical *z* axis of FIG. 2a we show the percentage distribution (*D*) of R&D projects by POS and potential sales level. The distribution of R&D efforts is clearly concentrated in the upper left hand corner of the plot (indicating high sales and low POS).

In FIG. 2b, the *y* axis shows the change in the percentage distribution of projects from 2000 onwards: D_2–D_1. As they are percentage changes, positive and negative variations sum to zero, as in the last column of TABLE 1. Positive values represent areas in which the research efforts have increased from 1990–1999 to 2000–2004, whereas negative values correspond to a reduction of research intensity. After 2000, there has been an increase in the high-risk, high-premium region of the R&D portfolio; more projects are targeted towards cancer, Alzheimer's disease, obesity, rheumatoid arthritis, Parkinson's disease and diabetes fields, and less efforts in the cardiovascular and anti-HIV fields.

FIGURE 2c compares R&D efforts by US and European companies. It plots the difference between the distributions of R&D efforts in the United States and Europe: D_{US}–D_{EU}. Positive values are R&D areas in which US companies are more active, whereas negative values are research fields in which European companies have more of a presence. Available data show that US R&D activities are more concentrated toward riskier and potentially larger markets.

The enactment of legislation in Europe and the United States intended to encourage development of orphan drugs has provided incentives to undertake R&D for rare diseases, for which the expected revenues would not traditionally have been expected to compensate for R&D expenditures owing to the small number of patients affected. Since the passing of these legislations, there is evidence of an increase in focus on rare diseases and an increase in the market value of new compounds[26,27]. Moreover, advances in understanding the molecular mechanisms of diseases generate opportunities to differentiate products by matching sub-groups of patients to specific 'stratified' drugs[28]. These trends are not in contradiction with our findings, since most of the orphan drugs are in large and increasingly differentiated ATC3 markets[29].

Simple economic reasoning can provide a rationale for the observed shift towards riskier[9] and larger market targets[30]. 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 regulatory hurdles) and potential revenues (linked to the size of the patient population and price levels). Potential market size is a key determinant of profits: the larger the patient population at a given price level, the larger the potential sales, and therefore the larger the incentives to undertake research in the area. At first glance, POS might also be anticipated to exert a positive effect on incentives to innovate: holding the value of sales constant, a higher POS is reflected in higher potential revenues. However, a countervailing effect is also in place, as sales value is the product of

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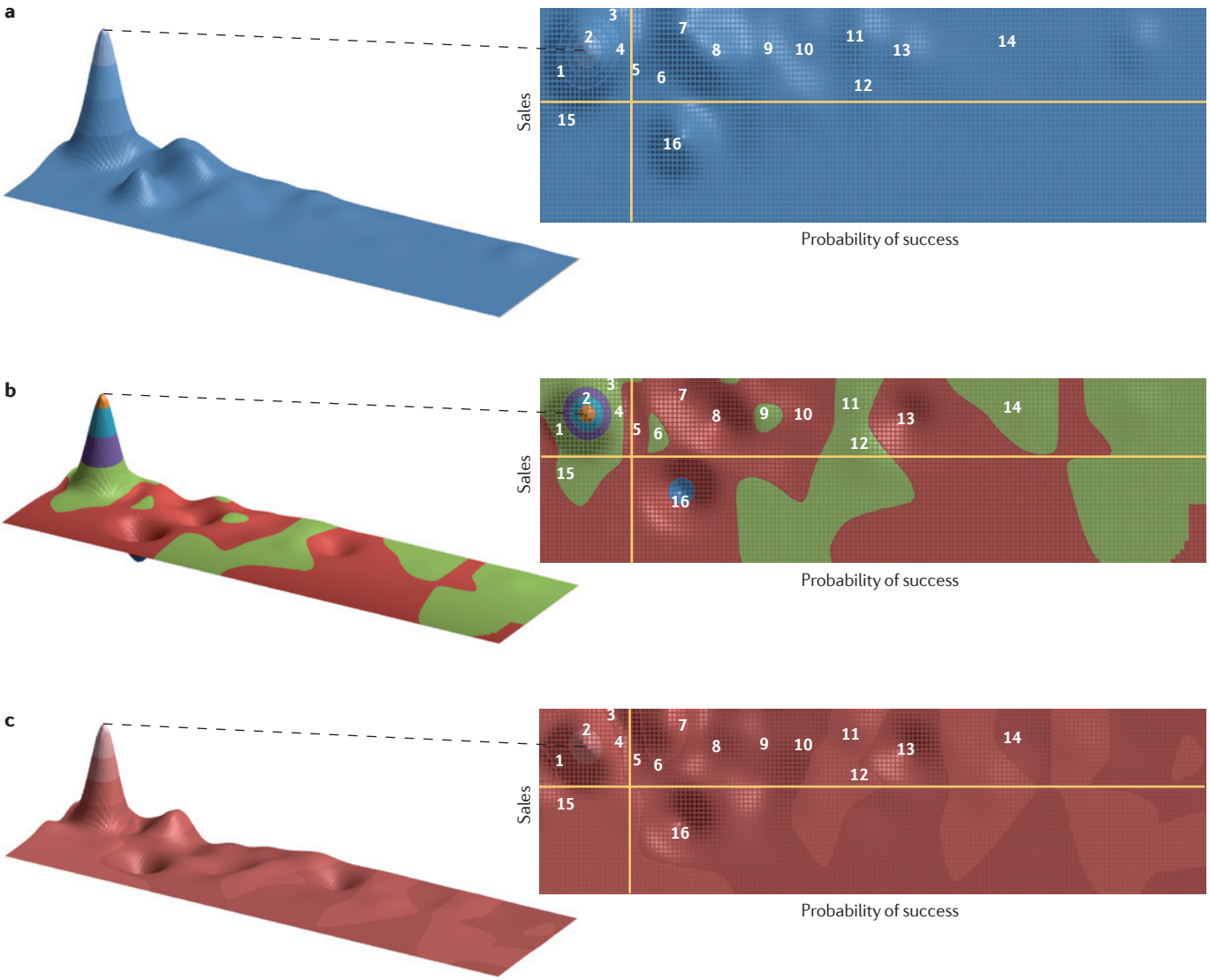

1	A08A: Anti-obesity	**10**	C04A: Peripheral vasodilators
2	L01X: Cancer, monoclonal antibodies	**11**	J05B: Antivirals, others
3	N07D: Anti-Alzheimer's drugs	**12**	N02B: Analgesics
4	M01C: Specific antirheumatics	**13**	C02A: Anti-adrenergic agents
5	C01B: Anti-arrhythmics	**14**	G04D: Urinary incontinence; B02D: Blood fractions
6	A10B: Diabetes, excluding insulin	**15**	A16A: Other alimentary tract and metabolism products
7	J05C: Anti-HIV	**16**	C06A: Cardiovascular, others
8	C01D: Vasodilators		
9	N04A: Anti-Parkinson's drugs		

Figure 2 | **The distribution of R&D projects by potential sales and probability of success.** In each panel, the probability of success (POS) is shown on the *x* axis and the logarithm of potential sales on the *y* axis. Two reference lines have been added at 2% POS (*x* axis) and US$10 million of average sales per year (*y* axis). A contour plot and a three-dimensional view of the same distribution are shown. **a** | The vertical axis shows the percentage distribution of research and development (R&D) projects by POS and potential sales level. The distribution of R&D efforts is concentrated in the upper left hand corner of the plot (indicating high sales and low POS). **b** | The vertical axis shows the change in the percentage distribution of projects from 2000 onwards. Positive values (peaks in the plot) represent areas in which the research efforts have increased from 1990–1999 to 2000–2004, whereas negative values (holes in the plot) correspond to a reduction of research intensity. Labels with the name of the ATC3 (see BOX 1 for definition) areas that experienced the largest variations have been added to the plot. After 2000, there has been an increase in the high-risk, high-premium region of the R&D portfolio. **c** | The vertical axis shows the difference between the distributions of R&D efforts in the United States and Europe. Positive values (peaks in the plot) are R&D areas in which US companies are more active, whereas negative values (holes in the plot) are research fields in which European companies have more of a presence. Available data show that US R&D activities are more concentrated towards riskier and potentially larger markets. Source: analysis of the Pharmaceutical Industry Database (BOX 1).

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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, into weaker and slower competition and higher expected prices and revenues. This effect seems to prevail on the basis of observed data: larger and riskier markets are the ones providing higher expected revenues, and therefore larger incentives to undertake research activities.

We further classified R&D projects according to the characteristics of their therapeutic targets. As before, we split projects that were started before and after 2000, and then grouped them according to the characteristics of the targeted disease, distinguishing projects utilizing biotechnology tools for drug development.

FIGURE 3 provides additional evidence that a growing effort has been allocated towards therapeutic markets that have a lower POS in recent years. First, research shifted towards developing drugs for chronic diseases (for example, Alzheimer's disease, chronic obstructive pulmonary disease, diabetes, obesity, depression, multiple sclerosis and rheumatoid arthritis), which have an average POS of 6.88%, compared with acute disease (average POS of 8.77%). This corresponds to a move from 81.54% of projects in the 1990s to 85.80% of projects in the period 2000–2007, which is an increase of 4.26%. Second, more research projects are targeting potentially lethal diseases (mostly cancer and some infectious diseases, such as tuberculosis), which have an average POS of 5.54% compared to non-lethal diseases (average POS of 9.72%). This corresponds to an increase from 20.86% of projects in the 1990s to 28.04% of projects in the period 2000–2007 (+7.18%).

In addition, the share of projects run by small organizations — defined here as having less than the mean number of R&D projects of an organization in the PhID, which is 14 — has expanded from 16.44% to 30.01% (+13.57%). The projects utilizing biotechnology tools for drug development have also increased from 22.80% to 26.49% (+3.69%). Finally, the number of projects targeting rare diseases (for example, rare cancers, lysosomal storage disorders and muscular dystrophy) has increased (+4.43%).

Overall, the increase in the number of R&D projects targeting specific cancers is the main driver behind the reorienting of the R&D effort during the past decade. US organizations have a larger share than European organizations in the most dynamic R&D fields, a trend that is discussed in more depth in the next section.

A comparative analysis: US versus Europe

Empirical accounts of the productivity differences between Europe and the United States provide mixed results. Several analyses have indicated that most innovative drugs have originated in the United States[31–33], whereas a recent study comparing research productivity in pharmaceuticals between US and European firms pointed to superior performance by European firms[34].

Cross-country comparisons of R&D productivity are traditionally based on the location of headquarters of the main research organization, which is typically the

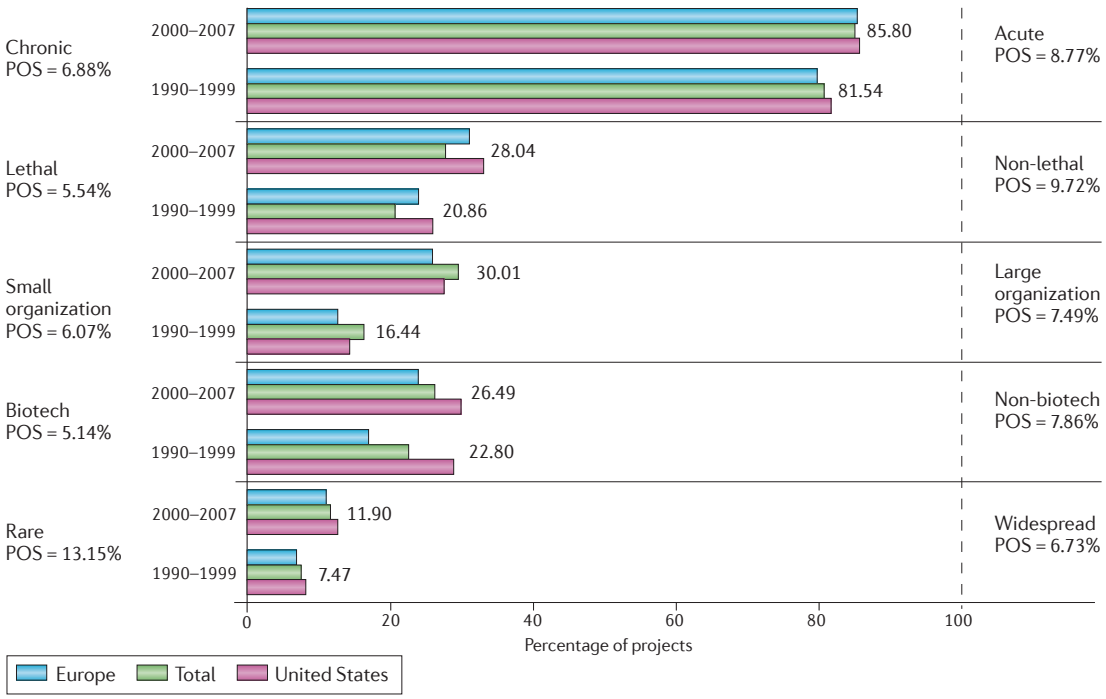

Figure 3 | **Average success rate and distribution of R&D projects according to the characteristics of the disease targeted, size of organization and research methodology.** Between the two time periods compared (1990–1999 and 2000–2007) there has been a shift towards research and development (R&D) projects with a lower probability of success (POS). Source: analysis of the Pharmaceutical Industry Database (BOX 1).

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Box 2 | **The R&D productivity of the top ten pharmaceutical companies**

Research and development (R&D) activities in the pharmaceutical industry are increasingly globalized, with the US research system playing a prominent role[19,45]. As a result, the location of the headquarters of an organization does not necessarily reflect the location of the innovative activities. Collaborative R&D projects should be treated separately, and the location of R&D laboratories should be considered. We used the share of patents invented by researchers located in Europe versus the United States as a proxy of the location of R&D (TABLE 2). Even if most of the top ten pharmaceutical companies still have a 'home country' bias in the location of R&D laboratories, companies such as Roche and GlaxoSmithKline have an approximately even distribution of R&D activities in Europe and the United States (see the table).

By considering the location of the headquarters only, the EU companies in the group seem to be more productive (TABLE 2), since they have launched four more new molecular entities (NMEs) in the period 2000–2007 (even if the sales of the NMEs in 2008 are higher for US firms). However, if Roche and GlaxoSmithKline are considered separately as global companies, firms with a balanced set of R&D activities in Europe and the United States turn out to be more productive in terms of number of NMEs launched per year.

Finally, we calculated the contribution of the US and EU research to the NMEs using the assumption that every patent inventor of a company contributes evenly to NMEs. By considering the location of inventors, the United States made the larger contribution to innovative drugs, as found in another study[33].

Company (location of headquarters)	Number of NMEs (brand names)*	Share of R&D	
		United States	Europe
AstraZeneca (United Kingdom)	2 (Faslodex, Iressa)	0.19	0.81
Sanofi–Aventis (France)	7 (Apidra, Abreva, Elitek, Ketek, Lantus, Uroxatral, Zemaira)	0.20	0.80
Novartis (Switzerland)	11 (Certican, Elidel, Enablex, Exjade, Galvus, Gleevec, Sebivo, Tasigna, Tekturna, Zelmac, Zometa)	0.26	0.74
Hoffman-La Roche (Switzerland)	10 (Actemra, Avastin, Bonviva, Fuzeon, Lucentis, Mircera, Pegasys, Tarceva, Tnkase, Xolair)	0.46	0.54
GlaxoSmithKline (United Kingdom)	7 (Abreva, Altabax, Arranon, Avodart, Cervarix, Lotronex, Tykerb)	0.53	0.47
Pfizer (United States)	13 (Chantix, Dynastat, Eraxis, Inspra, Lyrica, Relpax, Selzentry, Somavert, Sutent, Toviaz, Vfend, Geodon/Zeldox, Zyvox)	0.81	0.19
Johnson & Johnson (United States)	5 (Doribax, Invega, Prezista, Ortho Evra, Reminyl)	0.86	0.14
Merck & Co. (United States)	8 (Arcoxia, Cancidas, Gardasil, Invanz, Isentress, Januvia, Zetia, Zolinza)	0.88	0.12
Abbott (United States)	2 (Humira, Kaletra)	0.90	0.10
Bristol-Myers Squibb (United States)	5 (Baraclude, Ixempra, Orencia, Reyataz, Sprycel)	0.90	0.10

*Only NMEs launched for the first time in either Europe or the United States in the period 2000–2007 were considered. Withdrawn drugs have been omitted, as well as drugs whose original patent is held by another company. Source: analysis of the Pharmaceutical Industry Database (BOX 1).

firm that holds the patent, sponsors the clinical trial or launches an NME. However, as R&D activities are increasingly collaborative and globalized, particularly for larger pharmaceutical companies, looking only at the location of the headquarters can be misleading. To avoid spurious comparisons, we took a novel approach with respect to existing literature and defined the location of the organization on the basis of the location of innovative activities as measured through patents. Arguably, as patent protection is particularly important in pharmaceutical R&D, the location of patent inventors is a good proxy of the location of key research activities[35]. For research organizations with more than three R&D projects, we considered the share of patents with inventors located in either the United States or Europe over the period 1980–2004. For smaller companies, we assume that the share of R&D located abroad is negligible (companies with four to nine projects have only 5% of their patent inventors overseas). The share of R&D activities in Europe equals one if all patent inventors are based in Europe, whereas it equals zero if all inventors are in the United States (other regions have not been considered in our analysis, but their share in total pharmaceutical patenting is still relatively low). BOX 2 and TABLE 2 show the location of R&D activities for the top ten pharmaceutical companies.

To test the importance of the location of R&D activities on the POS of all companies and R&D institutions, a set of regressions is set forth (TABLES 3,4). We considered 18,735 R&D projects started by US or European companies and public research organizations between 1990 and 2007.

The first regression includes a dichotomous dependent variable, equal to one if the project successfully reaches the market, and zero otherwise. That is, we took into account the factors affecting the probability of market launch for R&D projects entering the preclinical stage (regression 1

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Table 2 | **R&D productivity of the top ten pharmaceutical companies**

R&D productivity	No. of NMEs*	Average per firm (per year)	Sales ($US millions)‡	Sales per NME	SU§ (millions)	SU per NME
Based on headquarter location						
Europe‖	37	1.06	15,958	431	1,560	42
United States	33	0.94	19,347	586	4,542	138
Based on share of R&D by company type, firms headquartered in Europe						
Mostly European	20	0.95	7,770	389	1,162	58
Global¶	17	1.21	8,188	482	398	23
Based on share of R&D by inventor location						
Europe	29	0.83	13,042	451	1,781	62
United States	41	1.17	22,263	542	4,3215	10

*Only new molecular entities (NMEs) launched for the first time either in Europe or the United States in the period 2000–2007 are considered. Withdrawn drugs have been omitted, as well as drugs whose original patent is held by another company. ‡Sales of NMEs in 2008. §SU = standard units of NMEs sold in 2008. ‖Sales of Zemaira not included. ¶'Global' companies are Roche and GlaxoSmithKline. Source: analysis of the Pharmaceutical Industry Database (BOX 1).

in TABLES 3,4). Ongoing projects are not considered. Furthermore, as market launch is not equivalent to market success, and the total of NMEs (or simple calculation of the proportion of successful R&D projects) is not a measure of their quality and innovativeness, we also assessed the value of sales; we considered the sales of NMEs in the first 2 years after product launch, both in terms of value and number of standard units sold as the dependent variable (regressions 2 and 3 in TABLES 3,4).

We compared the performances of European versus US organizations from two perspectives. First, location of R&D was defined as usual on the basis of the location of the headquarters (TABLE 3). In this case, the main variable of interest was a dummy variable identifying the projects started by European organizations: a positive and statistically significant coefficient indicates that European organizations have a higher probability of market launch than US enterprises (higher market value of innovations in the case of sales regression). The variable 'Europe' equals one if the headquarters of the organization that started the project is located in Europe and equals zero if it is located in the United States. In the case of projects originating from two or more organizations, the project is assigned either to European or US originators if no joint effort was detected. R&D projects carried out in collaboration between US and European organizations are treated separately, and a dummy variable is included in the regressions to control for joint research efforts.

Second, the location of R&D was assigned based on where patents have been invented (TABLE 4). Organizations whose share of patents invented in Europe is larger than two-thirds are classified as European. Organizations with less than one-third of patents invented in Europe are considered to be US-centred research organizations. A third category includes 'Global' R&D organizations with a share of patents invented in Europe in the range one-third to two-thirds. Accordingly, the regression includes two dummy variables: Europe and Global, while US projects are taken as a benchmark. We also considered different cut-offs for the three groups (that is, 25–75% and 40–60%) and results are broadly consistent.

The regression framework allowed us to compare the R&D and market performance of organizations, taking into account the different composition of their research portfolios in terms of disease characteristics and research methodologies. Particularly, we controlled for the characteristics of the disease targeted and for the research approach (whether or not it was a biotechnology project) by means of a full set of dummy variables. Time dummies (defined on the basis of the calendar year when the project is started) were introduced to accommodate both the decreasing trend in R&D productivity and the evolution of sales. In addition, we checked for the type of sponsoring organization. Two dummy variables were introduced for projects originated by biotechnology companies and public research organizations; the reference category comprised projects started by pharmaceutical companies. When analysing the POS of R&D projects, we ran separate regressions specifically comparing pharmaceutical companies and biotechnology companies operating in the United States or Europe.

Although at a first glance, European organizations seem to have higher success rates compared with US organizations, after controlling for the larger share of biotechnology companies and PROs in the United States and for differences in the composition of R&D portfolios (TABLE 3), there is no significant gap between European and US organizations in this respect. Unconditional differences (that is, differences arising when no controls are taken into account) are driven by the higher propensity of US organizations to focus on novel R&D methodologies and riskier therapeutic endeavours[31]. The lack of productivity differences between EU and US organizations in terms of POS of research projects is confirmed when location is defined according to the location of patent inventors, whereas global companies (operating on both sides of the Atlantic) show a better performance, confirming the results in BOX 2 and TABLE 2 for the full set of companies. Interestingly, as it seems that US organizations have higher success rates in early clinical trials and biotechnology projects, whereas European ones seem

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to have higher success rates downstream[16], global companies might better organize R&D activities according to local comparative advantages.

Global R&D companies are on average larger in terms of number of projects and compounds under development. Empirical accounts of the determinants of R&D productivity in the pharmaceutical industry suggest that size is indeed important[36–38]. However, controlling for size, firms with a global division of innovative R&D still seem to be more productive. By separating pharmaceutical companies from biotechnology companies, we noticed that global pharmaceutical companies showed a better performance, coherently with the results for the whole sample, whereas the difference lacks statistical significance when biotechnology companies are taken into account (maybe due to small numbers).

When sales data are taken into account, the market value of US-originated innovations was on average higher than the value of European ones (regression 2 in TABLES 3,4). This finding holds true in all model specifications. On the contrary, no difference is detected between institutions with global innovative activities and companies whose research is mostly based in the United States. In order to avoid spurious results driven by price differentials between the United States and Europe, we also compared total sales within each region[39]. Interestingly, the result was not driven by the higher price of drugs in the US market; rather, it seems to reflect differences in quality of European-originated and US-originated innovations. When only sales in the EU-15 market are considered, the result holds true, whereas statistical significance vanishes when only US sales are considered. In summary, as an average US organization takes more risk, when successful, they attain higher price premiums than the European organizations. When we remove the price effect by considering the number of standard units sold, we do not find any significant difference between European and US organizations, however defined (regression 3 in TABLES 3,4).

In summary, R&D productivity in pharmaceuticals seems to be higher for organizations that are able to exploit the international division of innovative labour. US companies tend to specialize in higher-risk, higher-pay-off markets, for which the price premium for innovative drugs is potentially larger.

Concluding thoughts

Pharmaceutical R&D has become increasingly challenging for various reasons, including the proliferation of plausible targets to pursue for therapeutic innovation resulting from advances in molecular biology, most of which are yet to be validated[40–43]. Innovation in pharmaceuticals is a cumulative process, and markets in which the POS is high are those in which effective compounds are already available. 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. Indeed, in established markets, innovative patented drugs are often reimbursed at the same level as older drugs. As a consequence, R&D investments tend to focus on new therapeutic targets, which are characterized by high uncertainty and difficulty, but lower expected post-launch competition[25]. Our empirical investigation indicates that this reorienting of investments accounts for most of the recent decline in productivity in pharmaceutical R&D, as measured in terms of attrition rates, development times and the number of NMEs launched.

Our analysis also 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, biotechnology companies and other institutions collaborate across multiple therapeutic areas and stages of the development process. By contrast, large pharmaceutical corporations still play a dominant role in Europe[16,19,44]. At first glance, the organizations with their headquarters based in European countries are characterized by a higher probability of market launch for compounds entering clinical development. However, when the composition of research portfolios is taken into account, the apparent comparative advantage of European organizations vanishes. By controlling for portfolio composition of research investments,

Table 3 | **R&D productivity by location of the company's headquarters***

R&D projects/ markets	Europe	Biotech/PRO; R&D portfolio	Time dummies	Number of observations	R-squared
Regression 1 — dependent variable: probability of success, baseline: US firm					
R&D projects: all	0.193‡ (0.107)	No	Yes	18,735	0.026
R&D projects: all	–0.012 (0.087)	Yes	Yes	18,214	0.091
Regression 2 — dependent variable: sales value (logarithm of $US), baseline: US firm					
Markets: all	–0.761‡ (0.306)	No	Yes	353	0.089
Markets: all	–0.974§ (0.321)	Yes	Yes	332	0.137
Regression 3 — dependent variable: logarithm of standard unit sold, baseline: US firm					
Markets: all	0.241 (0.457)	No	Yes	353	0.086
Markets: all	–0.347 (0.405)	Yes	Yes	332	0.344

PRO, public research organization; R&D, research and development; US, United States. *Robust standard errors in parenthesis (clustered by firms). ‡Denotes *P*-value <10%. §Denotes *P*-value <5%. Source of data: the Pharmaceutical Industry database (BOX 1).

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Table 4 | **R&D productivity by location of patent inventors***

R&D projects/ markets	Europe	Global	Biotech/PRO; R&D portfolio	Time dummies	Number of observations	R-squared
Regression 1 — dependent variable: probability of success, baseline: US firm						
R&D projects: all	–0.069 (0.098)	0.234§ (0.087)	Yes	Yes	18,735	0.094
R&D projects: pharma	0.039 (0.123)	0.290§ (0.088)	Yes	Yes	8,464	0.060
R&D projects: biotech	0.016 (0.236)	–0.234 (0.146)	Yes	Yes	7,202	0.101
Regression 2 — dependent variable: sales value (logarithm of $US), baseline: US firm						
Markets: all	–1.222§ (0.345)	–0.534 (0.400)	Yes	Yes	332	0.147
Markets: EU-15	–0.950‡ (0.484)	–0.186 (0.494)	Yes	Yes	253	0.178
Markets: US	–0.091 (0.332)	–0.589 (0.398)	Yes	Yes	298	0.143
Regression 3 — dependent variable: logarithm of standard unit sold, baseline: US firm						
Markets: all	–0.439 (0.424)	–0.962‖ (0.473)	Yes	Yes	332	0.346
Markets: EU-15	0.074 (0.509)	–0.366 (0.570)	Yes	Yes	253	0.334
Markets: US	–0.370 (0.571)	–0.416 (0.599)	Yes	Yes	298	0.323

EU-15, the 15 European Union countries (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden and the United Kingdom) ; PRO, public research organization; R&D, research and development; US, United States. *Robust standard errors in parenthesis (clustered by firms). ‡Denotes *P*-value <10%. §Denotes *P*-value <5%. ‖Denotes *P*-value = 0.08 when the 40–60% cut-off is considered. Source of data: the Pharmaceutical Industry database (BOX 1).

we do not find support to the claim of R&D productivity differences between US and European organizations, as classified according to headquarter location. These findings were confirmed by defining nationality on the basis of the location of the research teams (location of inventors). When we considered sales of compounds launched in the global marketplace, we found that the average market value of NMEs launched by US companies was higher than European ones. However, the focus on the comparison between Europe and the United States misses an important finding that emerges from our analysis: the most productive organizations in pharmaceutical R&D at present are global companies with innovative activities located on both sides of the Atlantic.

This result notwithstanding, the inherent uncertainty of pharmaceutical R&D has, in our view, so far not been effectively addressed through diversification by individual companies or through collaborative alliances. This uncertainty calls for a stronger reliance on precompetitive research at the early stages of drug discovery and development in the most relevant and challenging areas, as well as for greater international coordination and cooperation in market regulation.

The rate and direction of pharmaceutical innovation will continue to be affected by the interplay between patterns of technological change and market regulation. In our view, the value and cost of innovation should be assessed not only from a static efficiency perspective, but also from a dynamic one. From a static efficiency perspective, when two projects with the same potential market value but different POS values are compared, it is rational to drop the riskier project. However, such a perspective fails to take into account the dynamic effects of competition among different organizations on market value and the risk of R&D projects. First, if all the organizations choose to invest in therapeutic areas in which the POS is high, those markets will experience fierce price competition, also due to the incentives designed by regulators and institutional payers through reimbursement and pricing schemes. If payers do not recognize any premium for incremental innovation, it is rational for investors to aim to achieve market exclusivity in difficult areas, which are characterized by a low POS, rather than being forced to compete on price in a low-risk but highly crowded market. Second, the benchmark to measure the degree of risk is endogenous: at the aggregate level, the more firms invest in high-risk markets, the lower is the risk premium each of them has to pay to investors. Taken together, these two effects have pushed pharmaceutical companies to focus on high-risk, high-potential areas of activity.

In the near future, the evolution of the industry is likely to be shaped by evaluations that reflect the dynamic perspective. In particular, rigorous technological assessment exercises are increasingly being implemented in order to estimate the value of innovation to patients, the relative therapeutic merits of new drugs and their value for society. However, pricing, co-payment and reimbursement schemes should not introduce excessive penalties for incremental innovation, especially when it is the outcome of fierce R&D competition under conditions of strong uncertainty, started well before the launch of the first product on the market. This is an important point, as when uncertainty is high, parallel R&D along similar trajectories based on growing scientific understanding of complex diseases should not necessarily be considered as wasteful duplication or imitation. On the contrary, parallel R&D activities, failures and product launches are often the result of the underlying uncertainty. Establishing an environment in which the 'winner takes it all' could produce unintended consequences, contributing to increased market concentration and reducing the total amount of R&D effort.

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1. Griliches, Z. Productivity, R&D, and the data constraint. *Amer. Econ. Rev.* **84**, 1–23 (1994).
2. Kortum, S. Equilibrium R&D and the patent–R&D ratio: US evidence. *Amer. Econ. Rev.* **83**, 450–457 (1993).
3. Kortum, S. Research, patenting, and technological change. *Econometrica* **65**, 1389–1419 (1997).
4. Lanjouw, J. & Schankerman, M. Patent quality and research productivity: measuring innovation with multiple indicators. *Econ. J.* **114**, 441–465 (2004).
5. Jones, B. The burden of knowledge and the 'death of the reinassance man': is innovation getting harder? *Rev. Econ. Stat.* **76**, 283–317 (2009).
A parsimonious explanation for the increase in specialization and teamwork in pharmaceutical R&D.
6. Everson, R. Patents, R&D and invention potential: international evidence. *Amer. Econ. Rev.* **83**, 463–468 (1993).
7. Segerstrom, P. Endogenous growth without scale effects. *Amer. Econ. Rev.* **88**, 1290–1310 (1998).
8. Drews, J. *In Quest of Tomorrow's Medicines* 1–272 (Springer, Basel, 1998).
9. Cockburn, I. M. in *Innovation Policy and the Economy* Vol. 7 Ch. 1 (eds Jaffe, A. B., Lerner, J. & Stern, S.) 1–32 (The MIT Press, 2007).
A critical assessment of the productivity crisis in pharmaceutical R&D.
10. Orsenigo, L., Pammolli, F. & Riccaboni, M. Technological change and network dynamics: lessons from the pharmaceutical industry. *Res. Policy* **30**, 485–508 (2001).
11. Booth, B. & Zemmel, R. Prospects for productivity. *Nature Rev. Drug Discov.* **3**, 451–456 (2004).
12. Paul, S. M. *et al.* How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nature Rev. Drug Discov.* **9**, 203–214 (2010).
13. DiMasi, J., Hansen, R. & Grabowski, H. The price of innovation: new estimates of drug development costs. *J. Health Econ.* **22**, 151–185 (2003).
14. Munos, B. Lessons from 60 years of pharmaceutical innovation. *Nature Rev. Drug Discov.* **8**, 959–968 (2009).
15. Mervis, J. Productivity counts — but the definition is key. *Science* **309**, 726–726 (2005).
16. Pammolli, F. & Riccaboni, M. *Innovation and Industrial Leadership: Lessons from Pharmaceuticals* (Center for Transatlantic Relations, 2008).
This book contains an in-depth analysis of pharmaceutical productivity based on the PhID.
17. David, E., Tramontin, T. & Zemmel, R. Pharmaceutical R&D: the road to positive returns. *Nature Rev. Drug Discov.* **8**, 609–610 (2009).
18. Helpman, E. & Trajtenberg, M. in *General Purpose Technologies and Economic Growth* (ed. Helpman, E.) 85–119 (The MIT Press, 1998).
19. Owen-Smith, J., Riccaboni, M., Pammolli, F. & Powell, W. A comparison of U.S. & European university–industry relations in the life sciences. *Manage. Sci.* **48**, 24–43 (2002).
An in-depth comparative analysis of the US and European systems of innovation in the life sciences.
20. Braunwald, E. *et al. Harrison's Principle of Internal Medicine* 15th edn (McGraw-Hill, 2001).
21. Abrantes-Metz, R., Adams, C. & Metz, A. Pharmaceutical development phases: a duration analysis. *J. Pharma. Fin. Econ. Policy* **14**, 19–41 (2006).
22. Adams, C. & Van Brantner, V. Estimating the cost of new drug development: is it really $802 million? *Health Affairs* **25**, 420–428 (2006).
23. DiMasi, J. & Faden, L. Factors associated with multiple FDA review cycles and approval phase times. *Drug Inform. J.* **43**, 201–225 (2009).
24. Keyhani, S., Diener-West, M. & Powe, N. Are development times for pharmaceuticals increasing or decreasing? *Health Affairs* **25**, 461–468 (2006).
25. Ma, P. & Zemmel, R. Value of novelty? *Nature Rev. Drug Discov.* **1**, 571–572 (2002).
26. Yin, W. Market incentives and pharmaceutical innovation. *J. Health Econ.* **27**, 1060–1077 (2008).
27. Cotê, T., Kelkar, A., Xu, K., Braun, M. M. & Phillips M. I. Orphan products: an emerging trend in drug approvals. *Nature Rev. Drug Discov.* **9**, 84 (2010).
28. Trusheim, M. R., Berndt, E. R. & Douglas, F. L. Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. *Nature Rev. Drug Discov.* **6**, 287–293 (2007).
29. DiMasi, J. & Grabowski H. G. Economics of new oncology drug development. *J. Clin. Oncol.* **25**, 209–216 (2007).
30. Acemoglu, D. & Lin, J. Market size in innovation: theory and evidence from the pharmaceutical industry. *Q. J. Econ.* **119**, 1049–1090 (2003).
31. Kneller, R. The importance of new companies for drug discovery: origins of a decade of new drugs. *Nature Rev. Drug Discov.* **9**, 867–882 (2010).
32. Grabowski, H. G. & Wang, Y. R. The quantity and quality of worldwide new drug introductions, 1982–2003. *Health Affairs* **25**, 452–460 (2006).
33. Friedman Y. Location of pharmaceutical innovation: 2000–2009. *Nature Rev. Drug Discov.* **9**, 835–836 (2010).
34. Light, D. Global drug discovery: Europe is ahead. *Health Affairs* **28**, W969–W977 (2009).
35. Cohen, W., Nelson, R. & Walsh, J. Protecting their intellectual assets: appropriability conditions and why U.S. manufacturing firms patent (or not). NBER Working Paper No. 7552 (National Bureau of Economic Research, 2000).
36. Henderson, R. & Cockburn, I. Scale, scope, and spillovers: the determinants of research productivity in drug discovery. *Rand. J. Econ.* **27**, 32–59 (1996).
37. Arora, A., Gambardella, A., Pammolli, F. & Riccaboni, M. in *Innovation and Competitiveness in the European Chemical Industry* (eds Cesaroni, F., Gambardella, A. & Garcia-Fontes, W.) 175–202 (Springer, 2004).
38. Arora, A., Gambardella, A., Magazzini, L. & Pammolli, F. A breath of fresh air? Firm type, scale, scope and selection effects in drug development. *Manage. Science* **55**, 1638–1653 (2009).
39. Danzon, P. M. & Chao, L. W. Cross-national price differences for pharmaceuticals: how large, and why? *J. Health Econ.* **19**, 159–196 (2000).
40. Drews, J. Drug discovery: a historical perspective. *Science* **287**, 1960–1964 (2000).
41. Hopkins, A. L. & Groom C. R. The druggable genome. *Nature Rev. Drug Discov.* **1**, 727–730 (2002).
42. Drews, J. Strategic trends in the drug industry. *Drug Discov. Today* **8**, 411–420 (2003).
43. Overington, J. P., Al-Lazikani, B. & Hopkins, A. L. How may drug targets are there? *Nature Rev. Drug Discov.* **5**, 993–996 (2006).
44. Pammolli, F. & Riccaboni, M. Market structure and drug innovation. *Health Affairs* **23**, 24–43 (2004).
45. Gambardella, A., Orsenigo, L. & Pammolli, F. *Global Competitiveness in Pharmaceuticals: a European Perspective* (Directorate General Enterprise of the European Commission, 2001).

Acknowledgements
This work was supported by a grant from selected members of the Ad Hoc Working Group on the Economics of the Pharmaceutical Industry (AstraZeneca Pharmaceuticals LP, Novartis, Pfizer, and the National Pharmaceutical Council). Discussions with members of funding companies and with B. Munos and W. Looney are gratefully acknowledged. We also benefited from comments and suggestions from anonymous referees.

Competing interests statement
This research was funded, in part, by grants from AstraZeneca Pharmaceuticals, Novartis Pharmaceuticals, Pfizer and the National Pharmaceutical Council. The authors are solely responsible for the design, conduct and analysis of the study, and the conclusions that are drawn.

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