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IS THERE A PRODUCTIVITY CRISIS IN PHARMACEUTICAL R&D?

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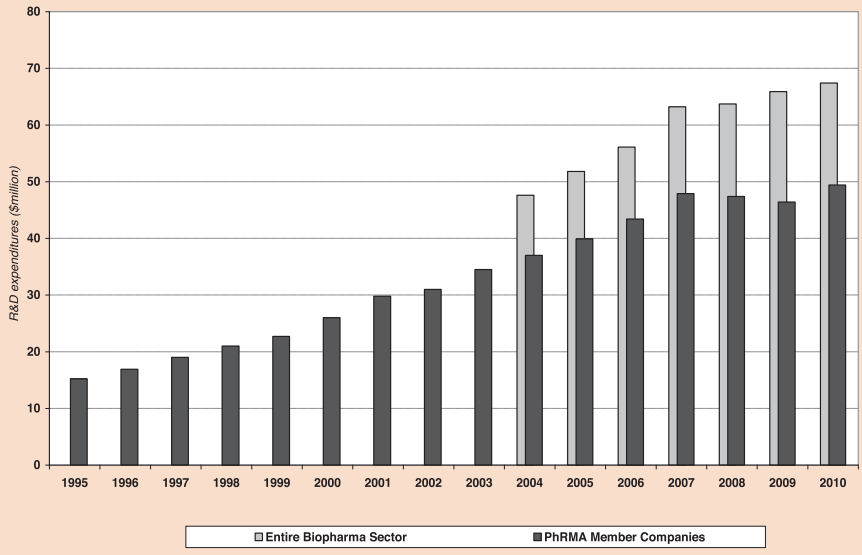
Introduction

This presentation is based largely on a paper I published in the June 2011 issue of *Nature Reviews Drug Discovery* with Fabio Pammolli and Laura Magazzini (Pammolli, Magazzini and Riccaboni, 2011). My discussion today will focus on two topics. The first is the R&D productivity slowdown in pharmaceuticals and the determinants of that slowdown. The second topic is the effect of location on R&D outcomes, related to the debate on whether R&D productivity in the US is higher or lower than in Europe.

The decline of R&D productivity

Productivity of R&D in pharmaceuticals has declined. This can be quantified as the ratio of outputs to R&D inputs. Outputs typically are the number of new chemical entities launched in the market, while inputs can be either total R&D expenditure or project-specific expenditure. We can see from Figure 1 that total R&D expenditure is increasing for PhRMA (Pharmaceutical Research and Manufacturers of America) member companies, as well as for the global biopharmaceutical sector. Figure 2 shows the increase in the total capitalised cost of developing a new drug.

Figure 1: Increasing R&D expenditures



Source: Author's own calculations based on PhRMA and Eurostat data.

Figure 2: Increasing cost of drug development

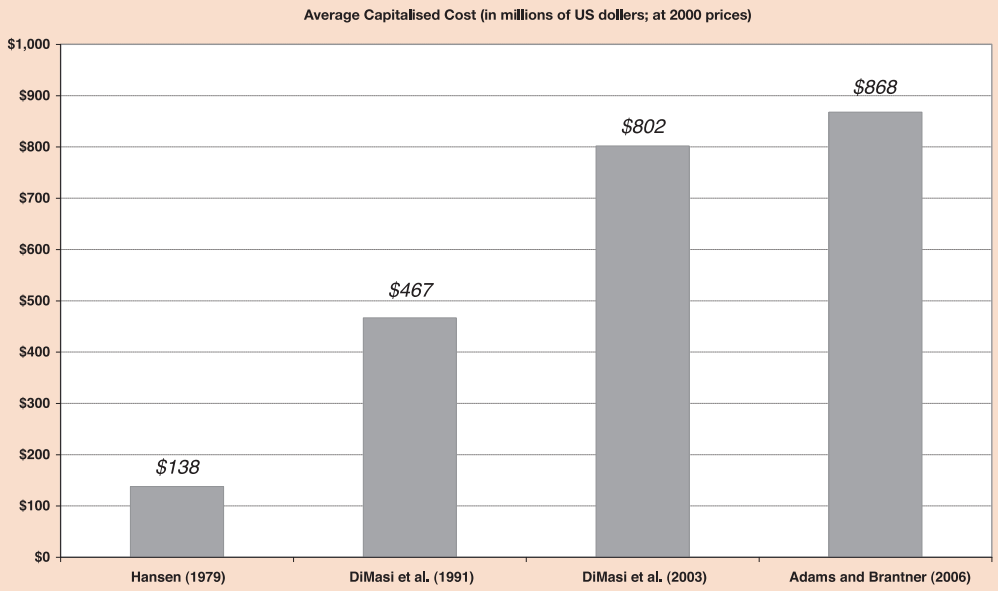
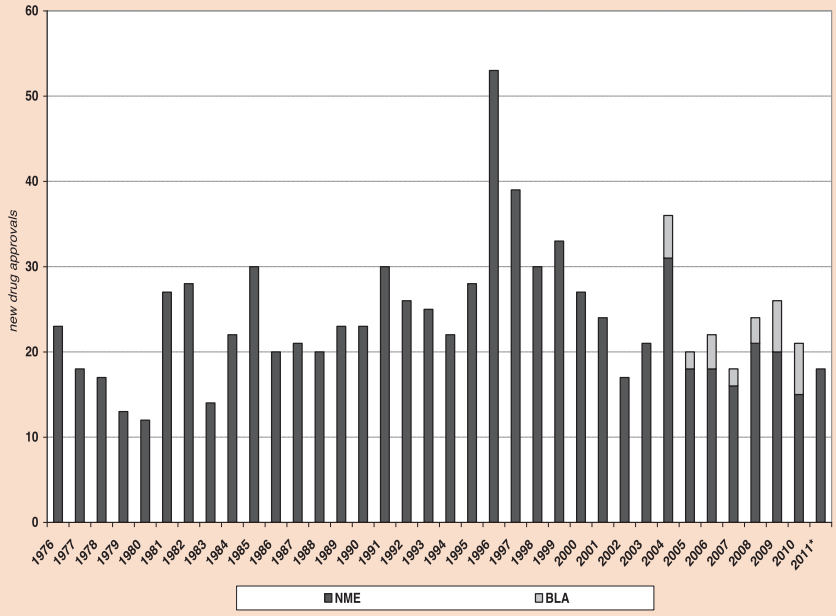


Figure 3 shows that on the outcomes side the number of new molecular chemical entities (NMEs) being launched is flat, at least since 2005. There was a decline from the mid-1990s to 2005 and since then about 20 new drugs have been launched every year (Pammolli, Magazzini and Riccaboni, 2011).

Figure 3: Rate of introduction of new molecular entities and Biologic License Applications[1]



Source: Author's own calculation based on FDA data.

[1] According to the FDA Glossary of Terms, "…a biologic license application (BLA) is a submission that contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology and the medical effects of the biologic product." If the information provided meets FDA requirements, the application is approved and a license is issued to the manufacturer allowing it to market the new product. (FDA, 2012)

The purpose of the 2011 paper was to provide an explanation for this observed decline in R&D productivity. To do this, we conducted an in-depth analysis of the database that we collected over ten years. The data come from multiple sources. To quantify the value of NMEs in the market, we used market data. On the R&D side, the data are for R&D projects and R&D collaborations. We monitored approximately 28,000 R&D projects from the beginning of the 1990s and know the outcomes of these projects -- whether and when they failed and in which field, i.e. the targets and biological mechanisms of the candidate drugs.

Let us focus on two statistics. The first is the average development time from patent to drug launch, which we found to have increased over time. In the EU-15 and the United States (US), the average time of development has increased from 9.7 years in the 1990s to 13.9 years beginning in 2000 (Pammolli, Magazzini and Riccaboni, 2011).

The second is the attrition rate. Figure 4 shows the attrition rates at the different stages of clinical and pre-clinical drug development.

The main point from Figure 4 is that the attrition rates are increasing across the board, but especially in Phase 2 and Phase 3 clinical trials. Not only are there more late stage failures than before, but compounds are also failing at a higher rate than before.

Combining the evidence thus far, we can argue that despite an increase in R&D effort, the number of new drug launches is flat both because the failure rate is increasing and because the lead time to market is longer.

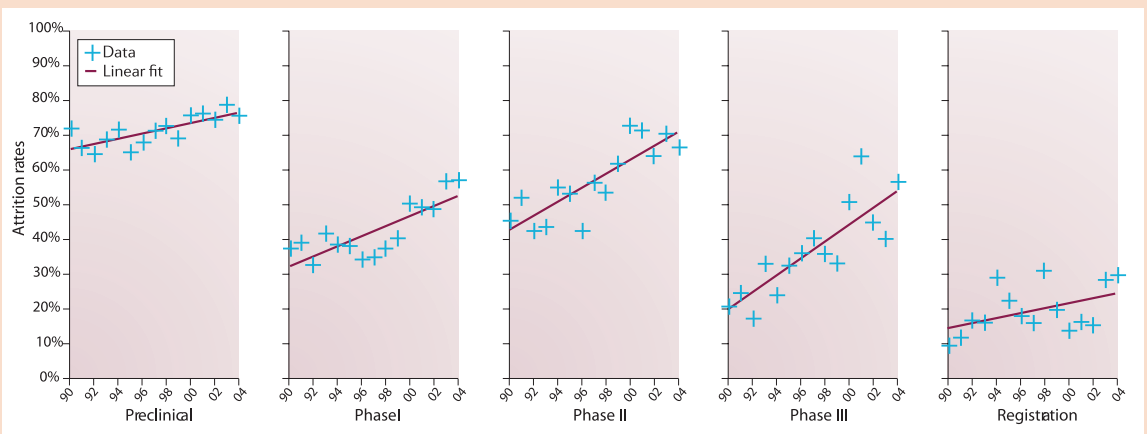
The determinants of the R&D productivity downturn

The previous analysis begs the following question: why is this happening? Briefly, it is a multifactorial problem. The first factor is the "fishing-out" effect – the "easy" problems have already been solved and we are left with the complicated, multifactorial diseases that entail a higher failure rate.

A second factor is the "gestation lag" that occurs when a radical change in technological capabilities, such as the molecular biology revolution, requires a corresponding shift in the way that new research is conducted. That change is good, of course, but it takes time to select which promising new targets and drugs likely will succeed. This is what we refer to as the "gestation lag". Similar breakthroughs occurred in the late 1970s, and even more in the 1990s, because of genomics and post-genomics which brought monoclonal antibodies onto the market. So success comes after a while, but one must be patient.

The third factor is that because the science is more complex, the degree of division of labour is increasing and multiple competencies are required to solve a problem. That implies that an organisational solution, like collaborative R&D, is required, involving teams of people who are competent in a certain business area.

Figure 4: Trends in attrition rates of drug development projects



Source: Pammolli, Magazzini and Riccaboni (2011)

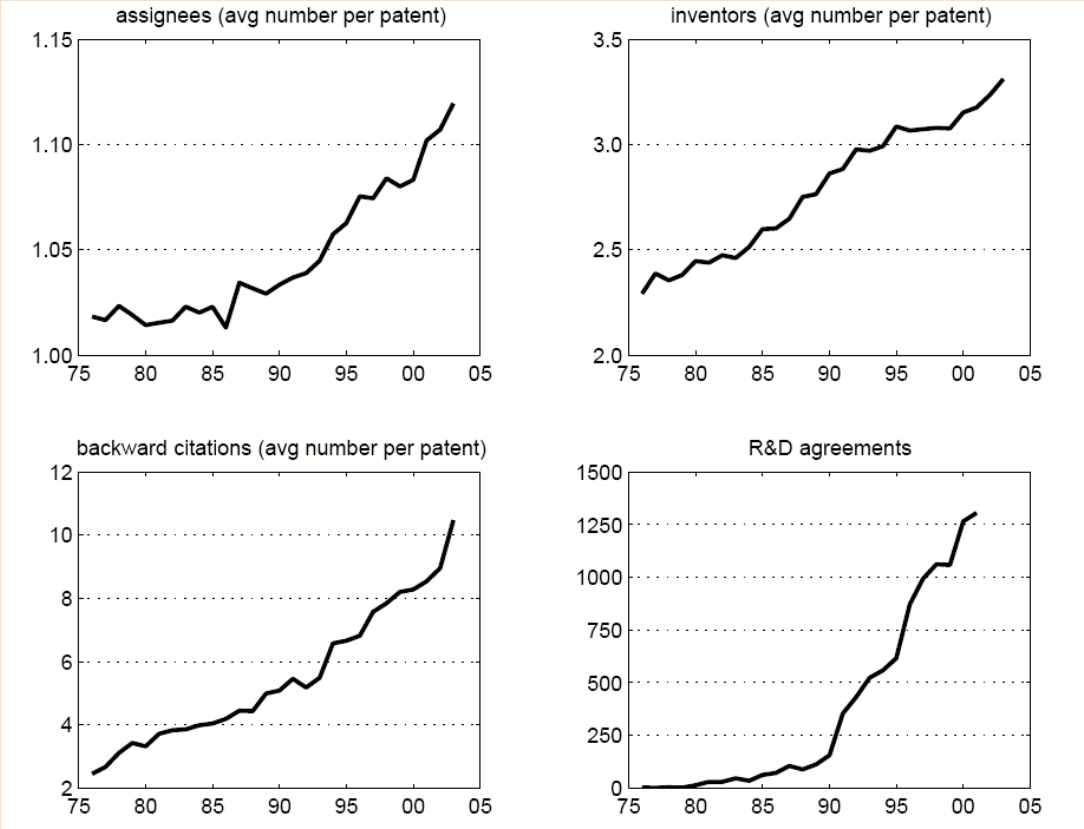
However, managing these collaborations and alliances is difficult -- properly managing R&D and incentives, as we know in economics, is important. The key issue is to ascertain how to design an approach that aligns the interests and goals of all participants. All of this taken together threatens a higher failure rate.

The fourth factor is the market side of the problem. As the technology improves and the science progresses, more companies will enter the field with new drugs thereby increasing competition for the launch and commercialisation of innovative drugs. Increased competition means that market mechanisms will help select out winners and losers – for example, exclusivity rules may mean that a project may be stopped when a competitive drug is already on the market because there is no room for another competing drug in the same field. We have data showing that the on-patent competition (i.e. between therapeutic alternatives) and off-patent (i.e. between the originator and its generic equivalents) competition is growing. Thus, a mixture of market-based effects and regulatory schemes are resulting in tougher competition on the marketing side. The regulatory burden is part of this picture; the lack of fully harmonised procedures across Europe, the US and Japan can also help explain the increase in failures.

The fifth factor, discussed in Jones (2009), is the "death of the Renaissance Man", a concept that is linked to the increasing division of labour. The Renaissance Man was someone like Leonardo da Vinci, who was proficient in many fields – mathematics, science, engineering, painting, and more. Today, however, just writing a paper may involve 60 people working together -- the Renaissance Man is gone.

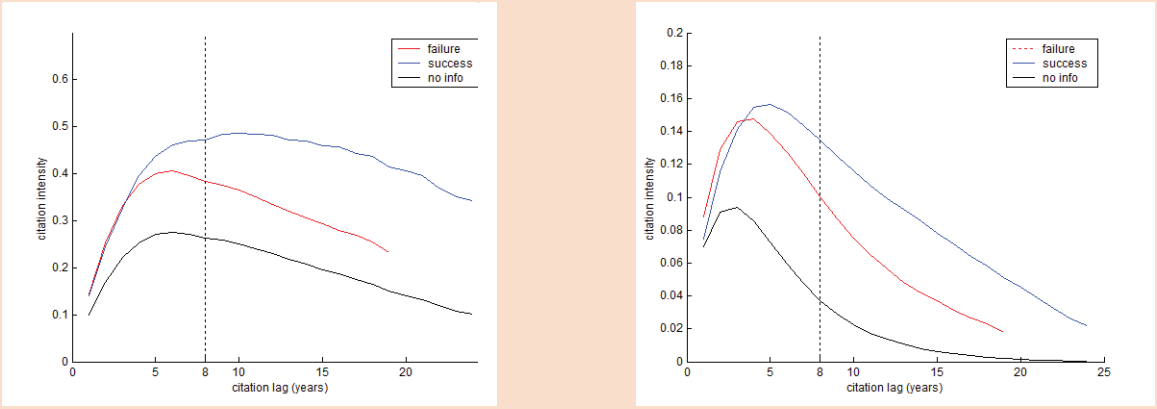
Possessing the knowledge needed to do something new in a certain field requires standing on the shoulders of giants. It takes more time than it used to take to accumulate the knowledge needed to provide the same contribution in a given technological or scientific field. Because it takes more time, productivity decreases and, again, a good organisational solution is needed.

Figure 5: The growing division of innovative labour in pharmaceutical R&D



Source: Magazzini, Pammolli and Riccaboni (2009)

Figure 6: Estimated citation lag distributions



Citations by others[1] Self-Citations[2]

Source: Magazzini, Pammolli and Riccaboni (2012)

[1] Patent citations by parties other than those listed on the patent
[2] Patent citations by those listed on the patent

The four plots below (Figure 5) give a sense of what I mean by the "death of the Renaissance Man" and the increasing burden of knowledge in biomedical R&D. In every plot, the trend is upward: the average number of assignees per patent, the number of inventors per patent, the number of backward citations and the number of R&D agreements all are increasing.

These five reasons summarise broadly what the literature says about the observed decrease in productivity; but we have one more potential explanation, which is similar to the fishing-out problem. Looking at the data, we observed a recombination or a shift in the composition of R&D portfolios of companies towards more complex and higher risk areas of research.

The shift in R&D portfolio composition

The data we used for the next part of the analysis focus on the value of a drug and the probability of success. Basically, we assume that failures do not have any value because not getting a drug on the market means no revenue. However, failures are very important from a learning point of view.

Figure 6 shows the citation lag of three groups of patents in pharmaceuticals: the blue line represents patents covering drugs that were successfully launched on the market, the red line represents patents for drugs that failed in clinical trials and the black line represents patents for compounds in on-going clinical trials or that never got to clinical trials.

If we use the number of patent citations as a proxy for information on innovation spillovers, what we observe is that failed drugs provide information for follow-on attempts to bring new drugs to the market. This is evident as the red line falls just below the blue line in both graphs. The cumulative knowledge from successes and failures is very important for learning how to develop an effective drug. We cannot consider failures in a field as wasted money or wasted effort, then, because successfully developing a new drug depends on learning from failures.

Table 1 shows, for each ATC1 disease area, statistics about the total number of projects we have in the data set, the average yearly sales for a branded drug (in US dollars) in the EU-15, the US and Japan and the percentage of total projects, which shows us the composition of the R&D portfolio by ATC1 area. We compared the R&D portfolio composition from 1990-1999 to 2000-2007 and determined the percentage change in the composition of this portfolio.

Table 1: Average success rate, sales and shares of R&D projects by ATC1 disease area

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

Source: Pammolli, Magazzini and Riccaboni (2011)

We found an 8% increase in cancer research projects and a 4.57% decrease in the cardiovascular area. Other therapeutic areas with increases are antineoplastic agents (6.88%), neurological (1.09%), and alimentary tract metabolism (1.56%). Importantly, all the rest are decreasing. This shows the shift and re-composition of project portfolios.

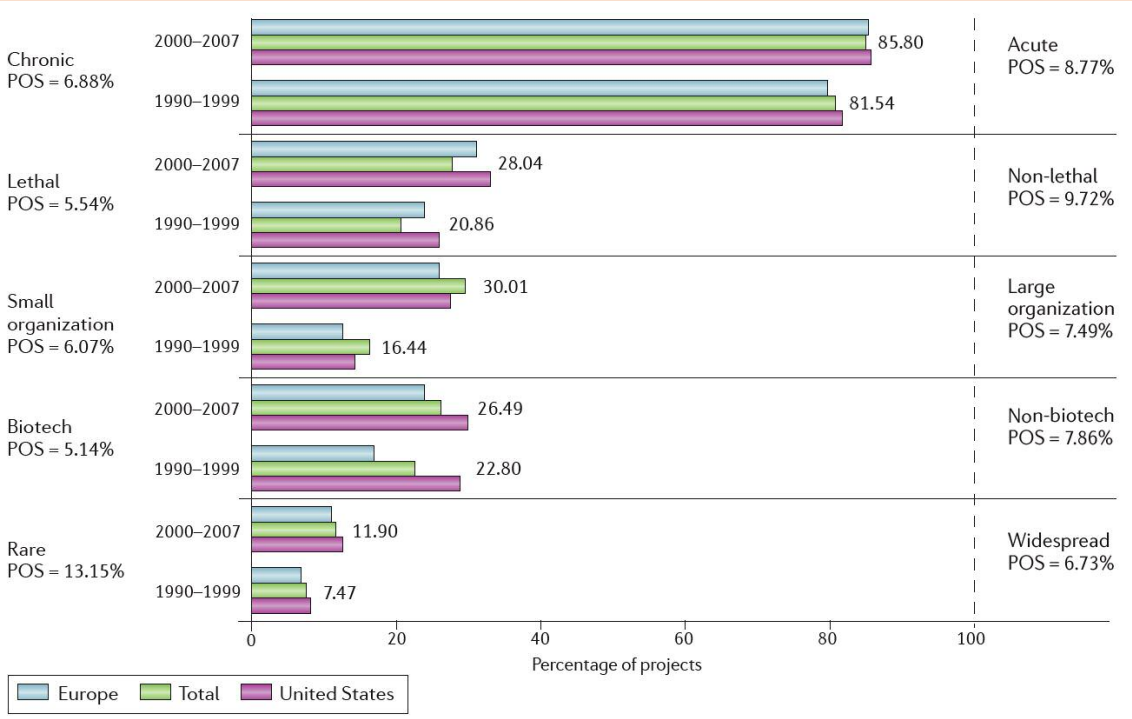
Crossing this data with the second and third columns in Table 1 (number of projects and average sales, respectively) shows that the average market value of a drug in the antineoplastic field is about twice as high as in the cardiovascular field and the average probability of success is far lower. This is the first bit of evidence showing that research portfolios are moving towards riskier and higher value areas of research.

Figure 7 provides more detail on the composition of research portfolios. It shows the distribution of R&D portfolios by disease target as well as the size and features of R&D. For example, in the first row we compare chronic versus acute diseases over two time periods, 1990-1999 and 2000-2007.

The percentage of projects dealing with chronic states grew from 81.54% to 85.80% of total projects. Again we have the average probability of success for R&D projects in the area of acute diseases (8.77%) and chronic diseases (6.88%). By doing more chronic than acute R&D, companies accept a lower probability of success.

Next we compared lethal and non-lethal conditions and observed the same trend. The number of projects for life-threatening diseases (cancers and some infectious diseases) has increased by 7.18%; however the probability of success is lower relative to non-lethal conditions. From the third row, we see that more projects are being sponsored by small organisations, defined as having less than 14 R&D projects, and the number of projects using biotechnology is increasing. But the probability of success is likely to be higher for a larger organisation than for a small one. Comparing the projects that use biotechnology to those that do not, we find the same pattern. The number of biotech projects has increased although their probability of success is lower.

Figure 7: Average success rate and distribution of R&D projects according to the characteristics of the disease targeted, size of organisation and research methodology



Source: Pammolli, Magazzini and Riccaboni (2011)

Rare diseases are an interesting counterpoint to the other examples. Thanks to fast-track mechanisms and other incentives, companies are increasing the number of projects they have in this area and the probability of success is increasing. However because they make up such a small portion of total R&D, overall the average probability of success still is decreasing.

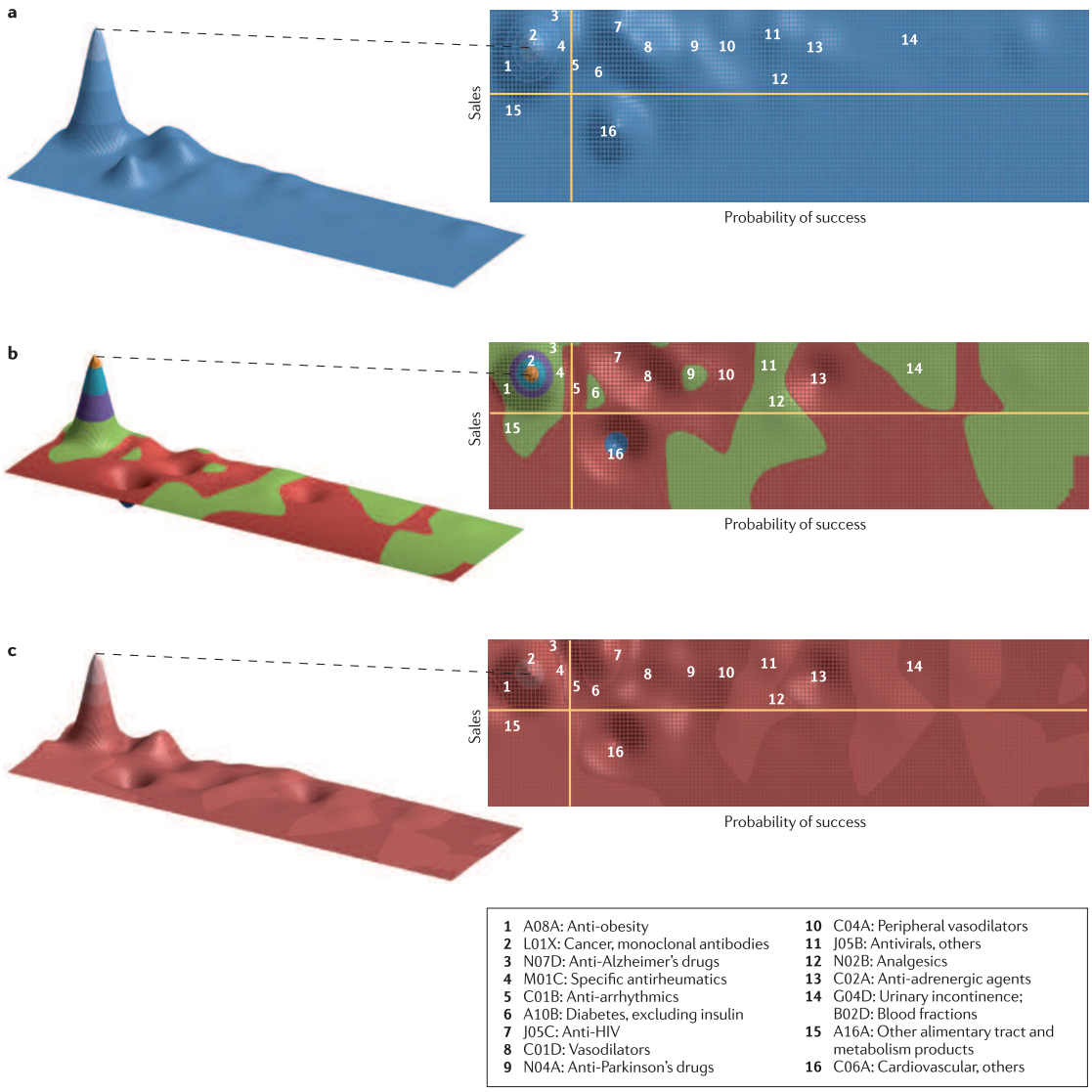
Figure 8(a-c) shows the results of a similar analysis at a finer level of distribution, the ATC3 level of aggregation.

Plot (a), at the top of the figure, has three dimensions: x, y and z. The x-axis shows the probability of success, which is the number of successful trials divided by the total number of trials in a certain field. Thus, the scale goes from zero to one. The y-axis shows the natural logarithm of sales or the average yearly sales of a branded drug in the ATC3 market. The z-axis shows the percentage distribution of R&D projects. The yellow lines indicate the median level and this divides the plot into four areas. The northwest quadrant is an area of low probability of success and high market value while the northeast quadrant is an area of high market value and high probability of success. Finally, the southwest and southeast quadrants are areas of low probability of success and low market value, and high probability of success and low market value, respectively.

Plot (a) shows the distribution of the number of projects across areas, based on the probability of success and sales. A peak, as in the northwest corner, indicates that most of the projects in the portfolio are in ATC3 areas with high market value and high risk. From the legend we see that these are anti-obesity drugs (1), cancer and monoclonal antibodies (2), anti-Alzheimer drugs (3), and anti-rheumatics (4). These are the ATC3 areas of research that are considered the most important, i.e. the therapeutic areas with the most projects.

Plot (b) has the same x- and y-axes, but now the z-axis shows something different: the percentage change in the composition of the portfolio between 1990-1999 and 2000-2007. The key message is that most of the projects are concentrated in this high risk, high payoff area and this area is growing. The troughs represent areas with fewer projects or less R&D effort -- cardiovascular (16), anti-HIV (7) and vasodilators (8), for example. Over time, we see a move towards more complex medical conditions.

Figure 8: The distribution of R&D projects by potential sales and probability of success



Source: Pammolli, Magazzini and Riccaboni (2011)

The final plot, (c), also has the same x- and y-axes, but the z-axis plots the difference between the composition of R&D projects started by European and US companies. Positive values (peaks) mean that the US companies are doing more R&D and negative values (troughs) are the areas of the research portfolio with more European projects. What this plot shows us is that the area that has more US projects is again the high risk and high payoff quadrant. The European companies are still in the areas that have less risk.

To sum up, projects in the R&D portfolio are becoming more high risk. If we compare across regions of the world, not only are US companies more risk-taking than European companies, but they also are moving towards the higher risk areas first.

If we compare companies based on the number of NMEs in the market, perhaps Europe is doing better than the US. But maybe that is because European companies are working on the easiest targets. Unless the analysis controls for that, the comparison is one of apples to oranges.

To help illustrate the importance of the re-composition of R&D portfolios, we use a simple equation (below) that shows the ratio of the expected number of NMEs in a given period[1]. What we want to know is: why is

[1] The expected number of NMEs is the probability of success multiplied by the number of projects (NP).

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

Source: Pammolli, Magazzini and Riccaboni (2011)

the yearly expected number of NMEs in period 2 (2000-2004) less than it was in period 1 (1990-1999) and, in particular, why is the ratio of the probabilities of success (POS) decreasing? To understand what is going on here, we have to consider two effects: the first is R&D effort (how many projects) and the second is the probability of success of trials.

Looking at the terms on the right hand side, POS2/POS(1,2) is the effect of R&D productivity on the change in the probability of success at the ATC level.

POS(1,2)/POS1 is the variation of R&D productivity that results from a change in the composition of the R&D effort. The term NP2/NP1 is the change in the total number of new projects.

If NME2/NME1 is less (higher) than 1, it implies that the number of expected NMEs in period 2 will be lower (higher) than in period 1. If we multiply the three terms together, the product is approximately 0.48, so the total effect is negative, i.e. every year the number of expected NMEs developed from projects that started between 2000 and 2004 is less than half the number of expected NMEs developed from projects started between 1990 and 1999. It is negative because of a dramatic change in the composition of the R&D portfolio. If the R&D portfolio had stayed the same, the ratio of probabilities of success would have remained constant as well. In reality, however, the ratio of probabilities of success is decreasing, indicating that the composition of portfolios has changed over time and that different companies around the world are heading in different directions with different strategies.

Europe versus the US: A look at comparative performance

The second part of this talk is focused on the R&D performance of European and US organisations. In our 2002 report for the European Commission (Allansdotti et al., 2002), we argued that the US is leading in pharmaceutical R&D. We looked at a set of statistics including number of patents, publications, drugs coming onto the market and the value of drugs on the market; the US was doing better than Europe across the board in the 1990s. A more recent paper suggested that this is no longer true and that the European companies are doing better than the US companies (Light, 2009). Further details help explain what is actually happening.

Figure 9 shows the share of the top drugs in the market by nationality of the firm. It is old data, but illustrates that the US share of the top 50 NMEs worldwide is growing. The US is dominating the innovation side of the market.

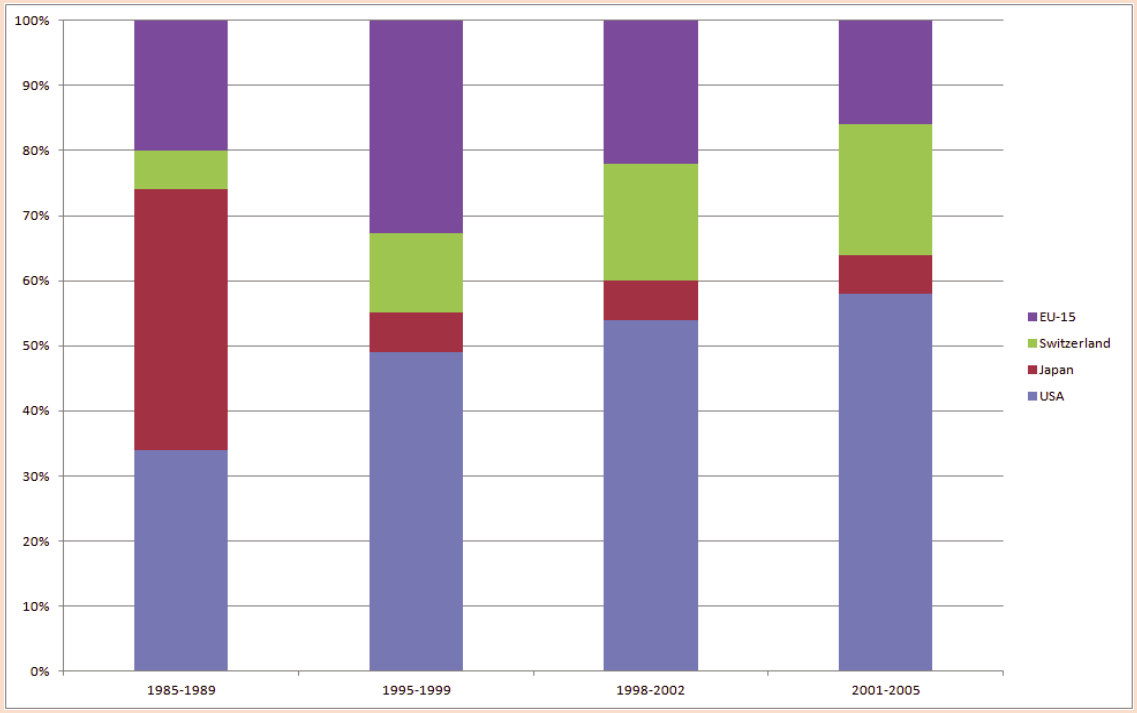
Figure 10 is similar but shows the share of sales of the top 50 NMEs; again we see that the market share of the US companies is larger.

This data can be misleading, however. Most of the literature that deals with the location and the productivity of R&D investments aggregates data based on the location of company headquarters (HQ). That is a reasonable way to calculate the Italian GDP, for example, and include the value added by Italian companies; such calculations should be based on the location of HQ. However, since the pharmaceutical industry has become truly global, this is no longer the most valid approach. Figure 11 shows the share of patents by location of the patent inventor at company level for the top ten pharmaceutical companies. The location of the company is HQ location.

If we look at Pfizer, a US-based company, most of the patents come from the US. For AstraZeneca, a UK-based company, the share of patents from the US is about 20% versus 80% in Europe. But right in the middle is GSK, with a 50-50 split between US and European patents. GSK is a UK-based company, which might suggest that all new GSK drugs are being invented in the UK, but that clearly is not the case because half of the R&D productivity of GSK comes from the US. The same applies to Roche; half of its patents come from Europe and half from the US.

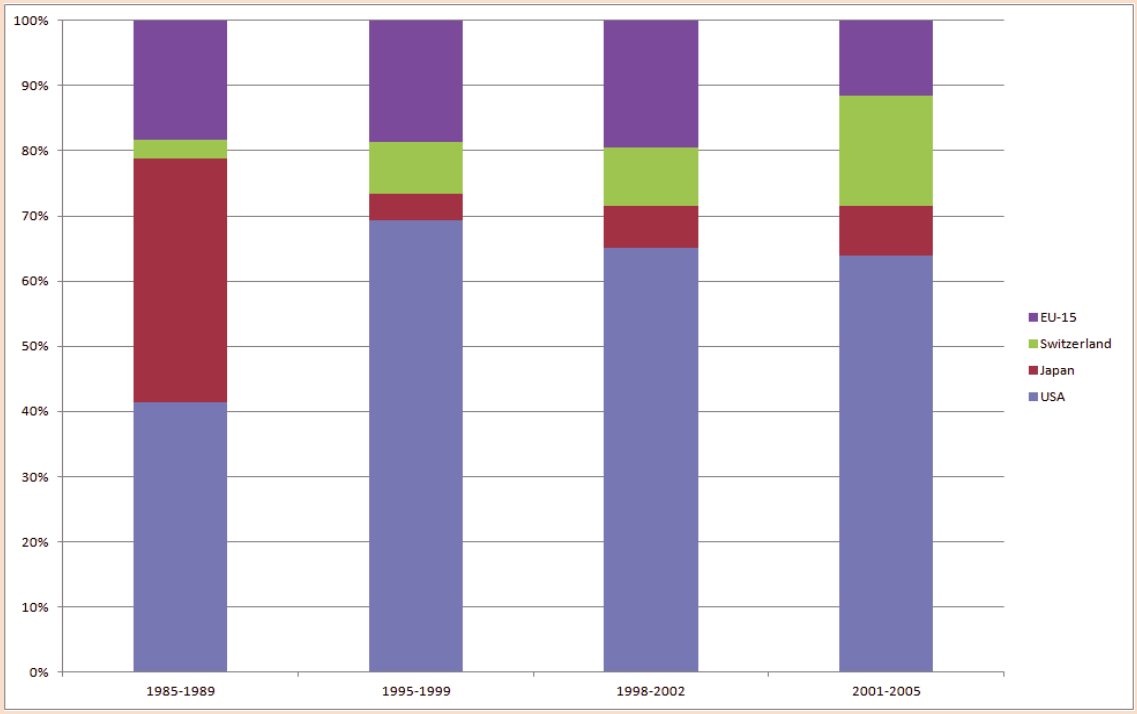
Table 2 shows the number of NMEs that have been launched for the top ten companies. The point here, again, is to show the R&D share of drugs that are launched by company.

Figure 9: Share of top 50 NMEs by firm nationality, % over number of compounds, 1985-2005



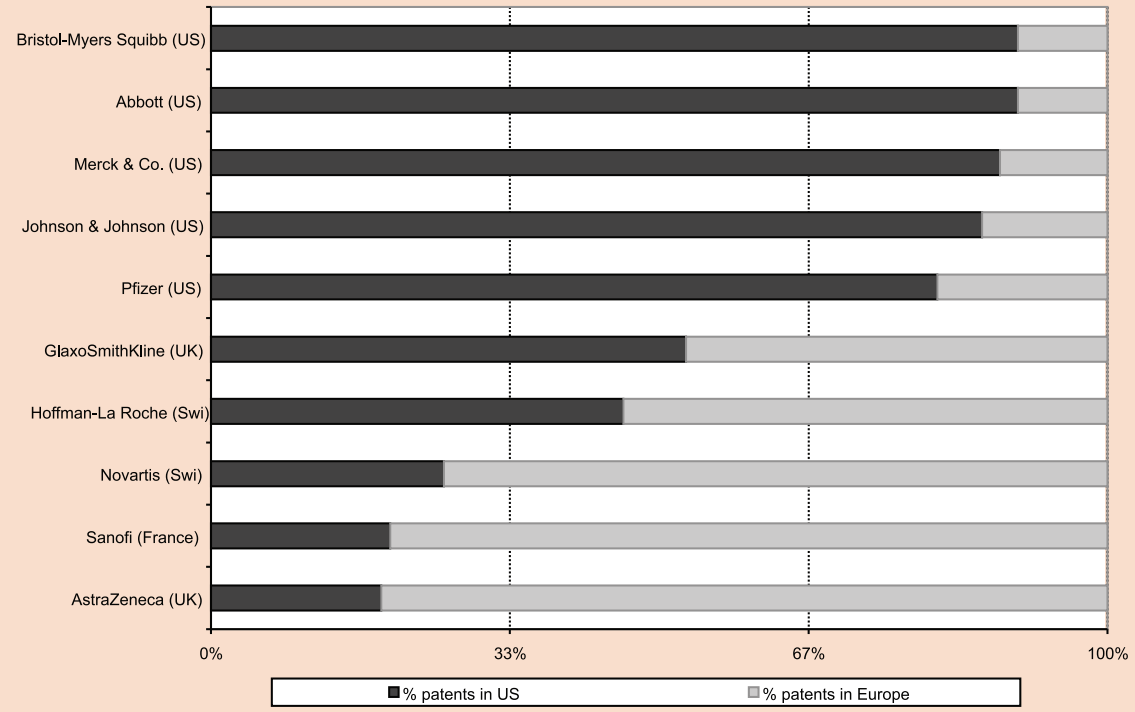
Source: Author's own calculations based on the University of Siena's Pharmaceutical Industry Database (PHID)

Figure 10: Share of top 50 NMEs by firm nationality, % over sales of compounds, 1985-2005



Source: Author's own calculations based on PHID data

Figure 11: Location of inventor of patents for top 10 pharmaceutical companies; location of headquarters in parentheses



Source: Author's own calculations based on PHID data

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

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 (France)	7 (Apidra, Abreva, Elitek, Ketek, Lantus, Uroxatral, Zemaira)	0.20	0.80
Novartis (Switzerland)	11 (Certican, Elidel, Enablex, Exjade, Galvus, Gleevec, Serbivo, Tasigna, Tekturna, Zelmac, Zometa)	0.26	0.74
Hoffman-La Roche (Swizerland)	10 (Actemra, Avastin, Bonviva, Fuzeon, Lucentis, Mircera, Pagasys, Tarceva, Tnkase, Xolair)	0.46	0.54
GlaxoSmithKline (United Kingdom)	7 (Abreva, Altabax, Arranon, Advodart, 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

Source: Pammolli, Magazzini and Riccaboni (2011)

Table 3: R&D productivity of top ten pharmaceutical companies by location of company headquarters

R&D productivity	No. of NMEs	Average per firm (per year)	Sales ($US millions)	Sales per NME	Standard Units (millions)	Standard Units 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	43,215	10

Source: Pammolli, Magazzini and Riccaboni (2011)

Table 3 presents the same data as above re-categorised according to location of company HQ, share of R&D by companies headquartered in Europe, and location of the inventors.

If we focus first on location of HQ, it seems as if European companies are doing well, since they launch more drugs than US companies (37 vs. 33 in Table 3). The average number of drug launches per year is higher, but the sales value is lower. Sales-per-NME also is lower and the number of standard units sold is below that of the US companies.

Next, we split the European group in two. The "Mostly European" category includes all of the top ten except GSK and Roche, which are 50-50 Europe-US and thus are categorised as "Global". Comparing productivity in this way, we find that the most productive European companies are the global ones -- GSK and Roche (1.21 NME per firm vs. 0.95).

Finally, we counted drugs based on the location of the inventors. GSK, for example, is 50-50, as noted above. GSK launched seven drugs so we assumed 3.5 were US-based and 3.5 European-based. We did a similar computation for all companies and allocated them to either Europe or the US and then compared them. Weighting productivity based on the location of R&D activities, we see that the US is still the main source of innovation.

Going back to the original research question, a potential explanation for why European-based companies now are doing better than US companies is that they are more globalised. They have more labs in the US, are more productive and thus are a main source of innovation. Especially for discussions about stimulating European innovation, however, this story may be misleading. Europe-based companies are doing well and the reason it is doing well is because companies are going where there are new research opportunities and talented people – outside Europe.

Table 4: R&D productivity by location of company 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

Source: Pammolli, Magazzini and Riccaboni (2011)

Table 5: 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

Source: Pammolli, Magazzini and Riccaboni (2011)

Tables 4 and 5 show the results of the analysis just discussed, but instead of using only the top ten companies we included more than 1800 R&D projects started by either European and US companies or public research organisations (PROs). Table 4 compares the productivity of European and US companies by the location of HQ, while Table 5 assigns the location of R&D based on where the inventor of the patented compound was located.

If we look at regression 1 in Table 4 and count the number of new drug launches, European companies appear to be doing better than US companies. But no significant difference exists after controlling for the kind of research European companies and US companies are doing and for the share of biotech companies and PROs. Recall that biotech projects have a lower probability of success and that is part of the explanation: US companies have more biotech projects, with a lower probability of success, in their portfolios.

In regression 2 in Tables 4 and 5, we looked at sales data and found that the market value of NMEs for European companies is far lower than the market value for US companies. A tentative explanation is that prices are higher in the US. However, even after controlling for a number of variables, including the difference in prices between the US and Europe, US originated drugs still had a higher market value. This difference in value likely reflects a difference in the quality of drugs being produced in the US compared to Europe. Interestingly, we found no difference between the market value of drugs produced by US companies and that of global companies that do most of their research in the US.

In regression 3 in Tables 4 and 5, we removed the price effect and looked only at the number of standard units sold. No statistically significant difference between US- and European-originated drugs was apparent.

Table 5 ran the same regression but included global companies. We found that the R&D productivity of global companies is higher compared to both European and US companies.

Summary and discussion

To summarise, we first showed that part of the decline of R&D productivity is due to the composition of the R&D effort; the R&D portfolio has shifted towards higher risk, higher payoff targets. We can argue that this is because of the "fishing-out" effect, i.e. the lower risk targets already have been developed, leaving only those that pose a higher risk. In the discussion section of our paper, however, we argue that two more possibilities must be considered (Pammolli, Magazzini and Riccaboni, 2011). The first is incentive schemes and the second is company strategies.

Let us consider how incentive schemes and company strategies can affect a company's portfolio. A company may decide to move its portfolio to riskier investments independently or because of the scientific complexity of the problems that now characterise R&D. Even though R&D is becoming more difficult, a company still has a choice whether to invest in a lower- or higher-risk area. This is a strategic decision, an investment decision. One company may choose to be more risk-taking than another. Similarly, a company's strategy can be influenced by public incentives. Just as an example, Europe offers no formal incentive for incremental innovation; higher prices are possible only for "breakthrough" drugs. This means that government has a role in pushing investment towards riskier areas, offering potentially more return for more risk.

Before concluding, let me quickly discuss the difference between "static" and "dynamic" decisions. Assume two projects with the same expected returns where Project A has a lower probability of success than Project B. Applying the net present value formula, the less risky project will be the best choice. Why? Because even though each has the same market potential, one is more likely to succeed than the other. It means that risk has a negative impact.

However, market competition also is affected by the degree of risk. For higher risk projects, success is less likely, but would mean no (or few) competitors in the market and implies more control over price. So the probability of success has a negative effect on net present value.

Dynamically, two effects are operating, not just one. If every company is moving towards more complex fields, the general rate of return or the interest rate will be the same for all companies. So, comparatively speaking, companies have more or less the same degree of risk since all are shifting and everyone has to pay the same interest rate to raise capital.

To conclude, even after applying some simple financial rules the situation is not so clear. It could be that strategic considerations are moving companies towards riskier areas. Or it could have to do with incentives that the regulatory frameworks in Europe and the US provide. Incentivising investments in particular medical conditions will cause companies to invest more in those fields. If there are no existing treatments in the market, any new drug will be a radical innovation. But if companies bring a follow-on drug to the market, even if it is a radical innovation, regulators in Europe will set its price at the level of existing competitors. The preference, then, will be for riskier R&D with the goal of being granted a higher price. Regulatory regimes, then, also play a role.

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