Global Drug Discovery: Europe is Ahead

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A re-analysis of data from 1982–2003 contradicts the claim that U.S. drug firms overtook European firms in pharmaceutical innovation.

Abstract: It is widely believed that the U.S. has eclipsed Europe in pharmaceutical research productivity, and some leading analysts claim that while fewer drugs are being discovered, most are therapeutically important. Yet a comprehensive data set of all new chemical entities (NCEs) approved between 1982 and 2003 shows that the U.S. never overtook Europe in research productivity, and that Europe in fact is pulling ahead of the United States. Other large studies of quality show that most new drugs add few if any clinical benefits for patients to previously discovered good drugs. The policy implications for Congress, employers and insurers of current discussions about increasing value and revitalizing the industry are discussed.
Global Drug Discovery: Europe is Ahead

For more than a decade, industry and official reports have concluded that the United States has overtaken Europe in the discovery of new drugs, commonly defined as new chemical entities (NCEs). "Europe risks to be relegated into the fringe of the industry," concluded a seminal report that has shaped European policy.¹ "The United States has become the dominant player," the European trade association reported in 2008, as research investments grew 5.2 times in the U.S. from 1990 to 2007 compared to 3.3 times in Europe.² Reinforcing this view, Henry Grabowski and Richard Wang (G&W) examined all NCEs discovered between 1982-1992 and 1993-2003 and concluded that U.S. firms overtook their European counterparts in discovering NCEs.³ They also concluded that although the number of NCEs declined, the quality of NCEs is high and has increased. In other words, most new NCEs are better than existing drugs and come from the United States.

This paper offers a different perspective based on a reanalysis of G&W’s key findings and large studies of clinical quality over many years. It thus poses important challenges to widely held American beliefs about U.S. dominance in pharmaceutical research productivity and about the superior quality of new drugs. The findings suggest that Congress and large purchasers are motivating companies to develop and market drugs that add little value, rather than rewarding true added value. This is not good for the long-term vitality of the industry, nor for those paying too much for too little.

Research Productivity: The Basic Picture
Let us start with the findings of G&W based on their comprehensive data set from IMS of all 919 NCEs approved between 1982 and 2003.⁴ They used various criteria to identify which were "global" NCEs (introduced into four or more of the G7 countries), first-in-class (FIC), biotech, and orphan NCEs. NCEs were assigned to the country in which the headquarters were located of the company that first launched them. This resulted in an exhibit showing how many of each type were discovered in Europe, the U.S., or Japan for 1982-1992 and 1993-2003. The present reanalysis accepts their data and definitions in order to examine percentages and ratios of innovation.⁵

If one simply calculates the percent of NCEs credited to the U.S., Europe, and Japan, one sees in the second half of Exhibit 1 that the share of all NCEs rose
dramatically in the U.S., from 25.3% in the first period to 35.9% in the second, while it declined in Europe from 48.4% to 43.3%, and in Japan from 26.3% to 20.8%. The U.S. gained in global, first-in-class, biotech, and orphan NCEs as well. One can see, however, that European research productivity hardly declined, and Europe continued to dominate in discovering all NCEs as well as the highly profitable Global NCEs.

Exhibit 1 here

Clearly, the United States did not overtake Europe in discovering new NCEs, and European researchers lost less ground than either Europeans or Americans believe. Despite the appeal of launching first in the big, highly profitable U.S. market, where companies face the fewest delays to market and can charge the highest prices, overall NCE research productivity in Europe using Grabowski and Wang’s criteria and data was greater, even in the recent period.

Research Productivity on a Level Playing Field
Research productivity and total funding are often confounded as in the typical claim that “the US has established itself firmly as the key innovator in pharmaceuticals since 2000." To what degree is this a self-fulfilling prophecy due to the industry pouring more money into American R&D, and to what degree are American labs and teams becoming more innovative, dollar for dollar?

A simple but important measure of research productivity would compare the proportion of industry R&D funding for the U.S., Europe, and Japan to the proportion of new NCEs. The European Federation of Pharmaceutical Industries and Associations has culled investment figures for 1990 and 2000 reported by member companies to the US, Japanese, and European trade associations and corrected for exchange rates. Since no annual figures are given, these can approximate funding distributions for the first and second decades analyzed by Grabowski and Wang, and thus they can be used to roughly calculate the relationship between research productivity and funding.

As shown in the top half of Exhibit 1, pharmaceutical companies increased their R&D investments in the United States from about a third in 1990 to half in 2000. R&D investment in Europe dropped twelve percentage points during the decade, and investment in Japan declined around two percentage points.
Absolute numbers increased everywhere because companies reported a rapid increase in total R&D investments, from €15.9 billion in 1990 to €48.3 billion in 2000.

Overall research productivity can be measured by the proportion of NCEs to the proportion of R&D investment for the U.S., Europe, and Japan. For example, if U.S. research teams received 33 percent of the budget, they should discover about 33 percent of all NCEs, a ratio of 1.0. By dividing the percent of All NCEs in Exhibit 1 by the percent invested, one can see that the U.S. discovered far fewer NCEs than its proportional share of funding, 0.76 (25.3/33.3) in the first period and 0.75 in the second. Europe’s ratio of all NCEs to investment went from 0.99 in the first period to 1.17 (43.3/36.9) in the second. Japan’s proportionate ratio of all NCEs was the highest, 1.49 in the first period and 1.36 in the second.

The big news in terms of innovation and international policy is the low and flat productivity of the U.S. and Japan’s high productivity. Of course these ratios are constantly changing and there is a lagged effect; but G&W’s conclusions about American dominance are not supported by their own data.

How did the U.S., Europe, and Japan perform for global and FIC NCEs? Exhibit 2 shows that in global NCEs, European research productivity was about the same as the U.S. in the first period but increased by 30 percent in the second period of 1993-2003 to 1.48, while U.S. research productivity declined to 0.83. In FIC drugs, European relative innovativeness moved from well behind the U.S. in the first period (0.90 vs 1.39) to well ahead in the second (1.22 vs 1.04). These are the most commercially and therapeutically important types of NCEs.

Exhibits 2 & 3 here

Exhibit 3 shows that in biotech products, European researchers became much more innovative in the second period but did not catch up with their American counterparts, even though their productivity declined. In orphan drugs, proportional European research productivity gains and American decline resulted in Europe moving from well behind the U.S. (0.92 vs 1.50) to about even in the second period (1.15 vs 1.20). Overall, these results do not support the claim that “U.S. firms overtook their European counterparts in innovative performance of first-in-class, biotech, and orphan products.”
Evidence of European research productivity would be stronger if one corrected for G&W ruling out first-in-class NCEs launched in Europe or Japan but not yet available in the United States, while they ruled them in if launched in the U.S. but not in Europe or Japan. They do not disclose how many there were. Likewise, the authors excluded orphan products not yet available in the United States, but included orphan drugs available in the U.S. but not in Europe or Japan. A third source of possible bias favoring U.S. productivity comes from assigning NCEs to the country in which the launching company is headquartered. This tends to favor the United States because more companies have located there through mergers, acquisitions, and strategic business decisions since 1982. Twelve of the largest twenty companies are headquartered in the U.S.

To summarize, this reanalysis provides strong, general evidence that U.S. firms have not overtaken their European counterparts in pharmaceutical innovation. European research productivity has actually increased in proportion to funds received and would prove still stronger if new first-in-class and orphan drugs launched in Europe but not the U.S. had been included. Given the new institutes in European countries that bring together applied scientists from industry and academe to translate discoveries into drugs, such TI Pharma in The Netherlands,¹² Karolinska Institute Innovations in Stockholm,¹³ and the broader European Innovative Medicines Initiative,¹⁴ returns on R&D investment in Europe may increase further during the next decade of 2004-2014.

**No Good Evidence of Better Quality**

The claim that most new drugs are of high quality or “important” for patients is puzzling, because G&W never really define what they mean by “quality,” and extensive correspondence with Grabowski produced no clear answer. From the perspective of patients, physicians, and health plans, “quality” means new drugs are clinically more effective or have fewer side effects than existing treatments; but the authors do not use data or studies of therapeutic outcomes. Instead, for example, they claim that global NCEs launched in four or more G7 countries are an “indicator of a drug’s commercial and therapeutic importance.” This confounds two quite different attributes.

Nexium and Lipitor, for example, are among the world’s top-selling drugs, but Nexium is widely regarded as a textbook case of a me-too drug, and Lipitor has little proven clinical advantage over other statins.¹⁵ Most new cancer
drugs generate large revenues at high prices but have not proven to be clinically superior to existing ones.\textsuperscript{16} Only 7 percent of new biotechs were proven clinically superior to comparator drugs in randomized trials.\textsuperscript{17} In short, commercial success is often distinct from therapeutic importance.

The best evidence of clinical quality comes from systematic efforts to assess therapeutic advantage and adverse effects compared to existing drugs. A detailed analysis of therapeutic quality in new drugs over the past 20 years has found that 14 percent of all NCE drugs are either therapeutic breakthroughs or substantially superior to existing medications.\textsuperscript{18} Likewise, a comprehensive review of all new drugs approved between 1989 and 2000 in the U.S. concluded that 14.8 percent were NCEs that provided significant clinical improvement, and the Canadian review board concluded that 10.7 percent of NCEs between 2000-2004 did so.\textsuperscript{19} During an earlier period, an often-cited industry assessment of all global NCEs in the 1970s and 80s found that only about 11 percent of all new “international” drugs brought substantial new benefits to patients, a ratio of 1 in 9.\textsuperscript{20} These figures are lower than the proportion of drug-candidates given a priority rating by the FDA, because this rating is based on several criteria of promising benefits that do not always prove out.

Thus different organizations, using somewhat different criteria and procedures, have found that over the past 40 years about 11-15 percent of NCEs are therapeutically “important,” as Grabowski and Wang put it, and 85-89 percent are not, a contrast with their using non-therapeutic criteria to conclude 88.8 percent of all new NCEs are therapeutically important.

\textbf{Policy Reflections}

This study shows how data purporting to document how “U.S. firms overtook their European counterparts in innovative performance” actually documents the greater and increasing research productivity of Europe. On the European side, a series of reports commissioned by the department of commerce (DG Enterprise) of the European Commission between 1993 and 2003 pronounced the U.S. had eclipsed Europe in research productivity, yet contained little solid evidence that it had.\textsuperscript{21}

Congressional leaders and others concerned about high prices of new patented drugs will be heartened by this analysis, because lower European prices seem to be no deterrent to strong research productivity.\textsuperscript{22} A previous
analysis using industry-based data showed that pharmaceutical companies recover all costs and make a good profit at European prices. Europeans are not “free riders” on American patients, another myth promoted by the industry that assumes countries are separate R&D/market silos that should each pay for themselves.

The real innovation crisis for patients and society is not the recent decline in new molecules but the small percent over many years of new molecules that provide clinical advantages to patients over existing medications. This longer pattern stems from defining “effective” as better than placebo and using soft surrogate end points, or substitute criteria, instead of hard clinical end points. As a result, the vast majority of new drugs that constitute 80 percent of American pharmaceutical cost offer few therapeutic advantages and greater risks than good drugs discovered in prior years. High prices for these new drugs enable companies to spend about 2.5 times more on marketing than R&D to persuade physicians to prescribe them and patients to want them. Thus current incentives reward better marketing more than better value.

If we want new drugs to be clinically superior to existing ones, we need to reward companies for developing them and not for developing placebo-superior drugs. Arjun Jayadev and Joseph Stiglitz propose a key strategy: pay in terms of clinical value added, as some large purchasers already do and as Consumer Reports Best Buy Drugs does by comparing value with price. Jayadev and Stiglitz also recommend having clinical trials independently run and paid by a public body like NIH so they can be designed to measure comparative advantages and risks over existing treatments. Publicly funded trials would also reduce cost and risk for pharmaceutical companies and increase competition from smaller firms by lowering the high cost barrier that company-funded trials pose. These are some ways in which incentives can be restructured to foster greater competition for clinically superior drugs and lower overall expenditure.
Exhibit 1

<table>
<thead>
<tr>
<th></th>
<th>USA</th>
<th></th>
<th>Europe</th>
<th></th>
<th>Japan</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>% R&amp;D Invested</td>
<td>33.3%</td>
<td>47.8%</td>
<td>49.1%</td>
<td>36.9%</td>
<td>17.6%</td>
<td>15.3%</td>
</tr>
<tr>
<td>(€ bn euros)</td>
<td>(5.3)</td>
<td>(23.1)</td>
<td>(7.8)</td>
<td>(17.8)</td>
<td>(2.8)</td>
<td>(7.4)</td>
</tr>
<tr>
<td>% NCEs Discovered</td>
<td>82-92</td>
<td>93-03</td>
<td>82-92</td>
<td>93-03</td>
<td>82-92</td>
<td>93-03</td>
</tr>
<tr>
<td>% All</td>
<td>25.3</td>
<td>35.9</td>
<td>48.4</td>
<td>43.3</td>
<td>26.3</td>
<td>20.8</td>
</tr>
<tr>
<td>% Global</td>
<td>37.3</td>
<td>39.5</td>
<td>55.9</td>
<td>54.6</td>
<td>6.6</td>
<td>5.8</td>
</tr>
<tr>
<td>% FIC</td>
<td>46.2</td>
<td>50.0</td>
<td>44.2</td>
<td>45.0</td>
<td>9.6</td>
<td>4.5</td>
</tr>
<tr>
<td>% Biotech</td>
<td>45.0</td>
<td>53.6</td>
<td>30.0</td>
<td>33.3</td>
<td>25.0</td>
<td>13.0</td>
</tr>
<tr>
<td>% Orphan</td>
<td>50.0</td>
<td>57.4</td>
<td>45.0</td>
<td>42.6</td>
<td>5.0</td>
<td>0.0</td>
</tr>
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</table>

Sources: R&D investment figures from EFPIA, Note 7. Company-reported figures converted to euros. NCE figures calculated from Grabowski & Wang, Exhibit 4, minus "rest of world."
Exhibit 2
Return on R&D Investment

Proportional Ratio of Global and First-in-Class New Drugs to R&D Industry Funding
(1.00 = innovation proportionate to investment in Exhibit 1)

<table>
<thead>
<tr>
<th></th>
<th>Global 82-92</th>
<th>Global 93-03</th>
<th>Global Productivity Change</th>
<th>FIC 82-92</th>
<th>FIC 93-03</th>
<th>FIC Productivity Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>1.12</td>
<td>0.83</td>
<td>-26%</td>
<td>1.39</td>
<td>1.04</td>
<td>-25%</td>
</tr>
<tr>
<td>Europe</td>
<td>1.14</td>
<td>1.48</td>
<td>+30%</td>
<td>0.90</td>
<td>1.22</td>
<td>+36%</td>
</tr>
<tr>
<td>Japan</td>
<td>0.38</td>
<td>0.38</td>
<td>-00%</td>
<td>0.55</td>
<td>0.30</td>
<td>-40%</td>
</tr>
</tbody>
</table>
Exhibit 3  
Return on R&D Investment

Proportional Ratio of New Biotech and Orphan Drugs to R&D Industry Funding  
(1.0 = innovation proportionate to investment in Exhibit 1)

<table>
<thead>
<tr>
<th></th>
<th>Biotech 82-92</th>
<th>Biotech 93-03</th>
<th>Biotech Productivity Change</th>
<th>Orphan 82-92</th>
<th>Orphan 93-03</th>
<th>Orphan Productivity Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>1.35</td>
<td>1.12</td>
<td>-17%</td>
<td>1.50</td>
<td>1.20</td>
<td>-20%</td>
</tr>
<tr>
<td>Europe</td>
<td>0.61</td>
<td>0.90</td>
<td>+48%</td>
<td>.92</td>
<td>1.15</td>
<td>+25%</td>
</tr>
<tr>
<td>Japan</td>
<td>1.42</td>
<td>0.84</td>
<td>-41%</td>
<td>0.28</td>
<td>0.00</td>
<td>-100%</td>
</tr>
</tbody>
</table>

NOTES


4 IMS Health is the global leader in market intelligence and information on pharmaceuticals. See www.imshealth.com/.

5 Limitations of this analysis lie mainly in the original data. For example, assigning NCEs by where the launching company’s headquarters was located is commonly used.
but clearly less accurate than investigating where the real discovery and development took place. The FIC designation is the object of methodological debates discussed in the original article, but this reanalysis uses the count provided. Further limitations about R&D investments also reside in the figures given. They cannot be verified and may include costs not reasonably considered R&D for new drugs. They may have been assembled by different trade associations in different ways. As in the original article, such limitations are accepted in order to focus on major trends using data presented by the industry.

6 Grabowski and Wang identify 659 global, FIC, biotech and orphan NCEs out of their total 919 NCEs for both periods.


9 EFPIA, op. cit., pg 4. I initially contacted PhRMA in Washington to ask for the best information on changes in industry R&D investments. The Senior Manager of Policy, Gretta Thorn, sent me the EFPIA report as the best source. Extensive and ultimately unresolvable debates could be held about the consistency and quality of R&D funding reported by different companies to their trade association.

10 More fine-grained analyses will run into the problem of small numbers for FIC, biotech, and orphan drugs.

11 Grabowski and Wang, op. cit. p. 452.


13 One of Europe’s leading research institutes, Karolinska Innovations aims to develop commercial uses more fully before transferring technology through a licensing agreement to obtain more profitable terms. See http://www.karolinskainnovations.ki.se/. Accessed 11 April 2009.


U.S. Senate, Committee on Finance, "Baucus Condemns Senate Failure on Medicare Drug Price Negotiation." (Washington DC: U.S. Senate, Committee on Finance).


