Did the U.S. eclipse European pharmaceutical research productivity?

An analysis of major reports as searchlights in the fog

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“It is hard to escape the conclusion that the United States, rather than Europe, is now the main base for pharmaceutical research and development and for therapeutic innovation.”

European Commission 1994

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1- Introduction

“Europe has reached a major turning point concerning the future of the Pharmaceutical sector in Europe. This sector, which was once the bastion of European innovation and the pharmacy of the world, is increasingly under threat. In 1992, six out of the top ten medicines were developed in Europe; by 2002, this had fallen to only two. Europe, the Commission and Member States, must decide whether we want to continue to be a leading player in pharmaceutical innovation or whether we simply step aside and let others overtake this job.”

- Gunther Verheugen - Vice-President of the European Commission responsible for Enterprise and Industry. Annual Meeting of European Federation of Pharmaceutical Industry and Association (EFPIA), Brussels, 1 June 2005

In recent years, there has been much discussion about the dearth of innovation in the pharmaceutical industry. 1,2 Around the globe, regulators and international organizations such as WHO have expressed concerns about the declining output of the pipeline of the pharmaceutical industry. 3,4 These concerns focus both on the decline of the total number of New Chemical Entities (NCEs) released into the major markets, and on the many real public health needs of the population are not addressed by new medicines 5.

Within the European Union, these concerns have been complemented by fears about the deterioration in the relative competitiveness of the European pharmaceutical industry. Since the early 1990s, leaders of the European Union and nation states have expressed alarm at reports commissioned by DG Enterprise or issued by the industry, showing the loss of European dominance in pharmaceutical research and innovation compared to the United States. 6,7 The opening quote of this paper from the European

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Commission in 1994 reflects the depth of concern, which keeps being repeated, as reflected in the second quote above reaching a “turning point” in which the European pharmaceutical sector is “under threat”, 11 years later in 2005. In response, a number of initiatives to bolster European research capacity and innovativeness have been undertaken. These actions have been fuelled by several key reports that provided the framework and the evidence based for steps that were taken.  

The term competiveness is very broad, and encompasses a variety of terms. In this paper, we focus on the quantitative data that underpin assessments about the European loss of research productivity and innovativeness in some of the key reports. We also look at the data presented on several measures industry-sector performance, such as sales, employment, labor productivity, and R&D investment. For each of these we address three questions. First, what measures were used in some of the leading European reports on competitiveness in the pharmaceutical sector, and how relevant were these measures? Second, might a re-assessment using data that came available since the publication of the report show that the evidence used was misleading or more mixed than the singular policy conclusions? Third, what kind of variables should be collected for future reports that focus on the issue of the relative productivity of pharmaceutical research in the US and EU to provide a meaningful groundwork for assessing the current state of affairs and identifying future actions?

The paper is organized into six sections: (1) this introduction, (2) selection of reports and methods, (3) an overview of the pharmaceutical sector in the EU and the debate about competitiveness, (4) the innovative output of the industry in the form of New Chemical Entities (NCEs), (5) the use of Evidence relating to the structure of the industry, and (6) a conclusion with recommendations for putting future European reports on more solid ground.

2- Selection of reports
We have selected four reports that have played an important role in the
European discussion about the relative productivity of European and US researchers and which made use of quantitative data to support their arguments. This selection is not meant to be exhaustive, but provides an overview of the debate, and how the different arguments are presented and corroborated with evidence and data.

The four reports discussed in this review are:

- ‘On the outlines of an industrial policy for the pharmaceutical sector in the European Community – communication from the Commission to the Council and the European Parliament’, by the European Commission (1994)\(^{12}\). (Referred to in this paper as the ‘EC-94 communication’);
- ‘Global competitiveness in pharmaceuticals a European perspective’, by Alfonso Gambardella, Luigi Orsenigo and Fabio Pammolli (2000)\(^{13}\). (Referred to in this paper as the ‘Pammolli Report’);
- ‘High Level Group on innovation and provision of medicines in the European Union’, by High Level Group on Innovation and Provision of Medicines\(^{14}\). Referred to in this paper as the ‘G10 Report’;
- ‘A Stronger European-based Pharmaceutical Industry for the Benefit of the Patient – A Call for Action. Communication from the Commission to the Council, the European Parliament, the Economic and Social Committee and the Committee of the Regions’, by the European Commission in 2003\(^ {15}\). (Referred to in this paper as the ‘EC call for action’)

We carried out a textual analysis of the reports and corresponded with the authors on questions of data, measurement, calculations and conclusions. We also searched for related data sets and conducted interviews with experts on the pharmaceutical sector. We carried out our own independent analysis of research productivity.

\(^{12}\) Commission of the European Communities. On the outlines of an industrial policy for the pharmaceutical sector in the European Community; communication from the Commission to the Council and the European Parliament. COM (93) 718 (March 1994). Referred to as ‘EC94’.


\(^{15}\) Commission of the European Communities. A stronger European-based pharmaceutical industry for the benefit of the patient, a call for action : communication from the Commission to the Council, the European Parliament, the Economic and Social Committee and the Committee of the Regions. COM (2003) 383 final (July 2003).
3- Overview of the competitiveness debate in the European pharmaceutical sector

The EU as a stage for the debate about relative competitiveness
Within the EU\textsuperscript{16}, most of the reports discussed in this paper originate from, or are commissioned by, the European Commission. The European Commission is one of the five main organs of the European Union (besides the European Parliament, the Council of the European Union, the Court of Justice of the European Communities and the European Court of Auditors). The role of the European Commission mainly focuses on running the day-to-day affairs of the EU, upholding the treaty, proposing new legislation, and implementing decisions. The civil servants that work for the Commission are part of a number of Directorates-General.

The discussion about pharmaceutical products in the EU has mostly focused on industrial policy and the impact of a healthy and profitable pharmaceutical industry on the economy of the member states. These states, however, are in most cases the principal payers as well so that the economic impact of industrial growth must be weighed against the resulting expenses of new medicines. The so-called subsidiarity principle\textsuperscript{17} has to be respected. Within the Treaty establishing the European Community this is laid down in Article 152 that stipulates that Community activities “shall fully respect the responsibilities of the Member States for the organisation and delivery of health services and medical care.”

Juxtaposed to the national cost of industry growth through increasing drug expenditures, however, are four gains: (1) the increased therapeutic benefits and quality of life for patients, (2) the savings in other medical costs, (3) the growth of high-tech employment, and (4) exports. The latter two are relatively easy to quantify, and ample data is available on this. For example, the relevance of the pharmaceutical sector for EU exports is undisputed. In 2007 the total value of EU-25 pharmaceutical exports was 54.7 billion euros\textsuperscript{18}, making it one of the major exporters of the EU. However, how large therapeutic benefits and cost savings throughout the system are, and what

\textsuperscript{16} In this paper, when we will use the term European Union to refer to the so-called ‘EU-15’, the countries that were members of the European Union before the EU enlargement of 1 May 2004 (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Spain, Sweden and the United Kingdom).

\textsuperscript{17} As described in the (never implemented) European Constitution (Article 9): “Under the principle of subsidiarity, in areas which do not fall within its exclusive competence the Union shall act only if and insofar as the objectives of the intended action cannot be sufficiently achieved by the Member States, either at central level or at regional and local level, but can rather, by reason of the scale or effects of the proposed action, be better achieved at Union level.”

newly introduced drugs have contributed to this, is hard to quantify. As is exemplified by the debate about the gains in benefits and savings from new medicines over and above the repertoire of effective medicines discovered in years past.\textsuperscript{19,20,21,22}

Therefore, the debate about pharmaceuticals in the EU is heavily influenced by two characteristics of pharmaceuticals. On the one hand, pharmaceuticals are the product of capital and knowledge-intensive, globally oriented companies which provide jobs for thousands of people and adds significant value to the European economy. While on the other hand, pharmaceuticals are a major cost in health systems, while adding (usually) unmeasured therapeutic value at the population level.

\textit{EU vs. US competitiveness, a debate with a long history}

As the two main blocks in the pharmaceutical market, comparisons between the EU and US have a long tradition in the discussion about the comparative innovativeness of their respective pharmaceutical companies has a long tradition. Since the 1970s, the main issue in the discussion about international competitiveness has been the US losing it’s edge, due to long review times in comparison to the rest of the world, a trend that mainly occurred during the 1960s and 1970s, because the more stringent requirements to demonstrate efficacy and safety, that resulted from Congressional hearings in 1959-61, led to a series of industry-supported studies that built the case for declining innovation in the US due to the new regulations that were introduced.\textsuperscript{23,24,25,26,27,28,29,30,31}

Calls for action by the industry and its allies culminated in the Hatch-Waxman Act of 1984 and the extension of patent protection.\textsuperscript{32}

During the early 1990s, the debate about the lack of innovativeness shifted to
Europe. One of the earliest reports about the innovativeness of pharmaceuticals at the European level was a Commission White paper from 1993 entitled ‘Growth, Competitiveness, Employment’\textsuperscript{33}, which states that “the greatest weakness of Europe’s research base…. is its comparatively limited capacity to convert scientific breakthroughs and technological achievements into industrial and commercial successes.” However, it also stated that “in most major fields and disciplines, Europe is up to the highest standards in the world in terms, for example, of the number of publications by researchers and of references thereto….. The European chemical and pharmaceutical industries are in the forefront on world markets.”

A turning point occurred when DG Enterprise, as the EC body responsible for industrial growth, sponsored a white paper that focused on the outlines of an industrial policy for the pharmaceutical sector in the European Community. Published six months later, it makes the first major reference to the declining competitiveness: “there are signs that the community industry is yielding in comparison with its main competitors.”\textsuperscript{34} And “…the first signs of structural difficulty have appeared recently.”\textsuperscript{35}

During the 1990s, the perception that the European industries were faltering in the light of global competition gained momentum. In 2000 the landmark Pammolli report, funded by and prepared for DG Enterprise, stated in its introduction that “it is now a diffused perception that the European pharmaceutical industry is losing ground vis-à-vis the United States.”\textsuperscript{36} Near the end of this report, the authors are more damning: “Europe risks to be relegated into the fringe of the industry, surviving and even thriving through imitation, generics, marketing, but giving up a large share of the value added and becoming dependent on the USA for the develop of new products.”\textsuperscript{37}

To substantiate these claims, major sections of the Pammolli Report use synthetic measures of high-level data about production as evidence that research and innovativeness are declining, such as sales data and R&D expenditures. For example, The authors emphasize that “the European Pharmaceutical industry is more labour intensive than the US or the Japanese industries.” The authors also state that “in the European pharmaceutical industry there is less pronounced specialization in R&D activities…”\textsuperscript{38}
Subsequently, reports have continued to stress the same message of lower levels innovation, risks of job losses and bleak perspectives for patients in the EU member states when it comes to access for innovation. In this report we reassess the quantitative evidence presented in these reports.

4- The innovative output of the industry – New Chemical Entities

Innovation is the lifeblood of the pharmaceutical industry and the core issue in these seminal reports leading to a large effort to bolster innovativeness in Europe. Therefore, in many reports the number of new chemical entities (NCEs) plays a key role in the analysis. In this section we will examine how the output of the industry in the various reports is measured, how the evidence from past reports looks in the context of more recent information, and what kind of measures of industry output would be best suited for future analyses. Our main assumption here is that one is interested in measuring how ‘innovative’ or important new drugs produced by companies are.

4.1 Total number of new NCEs

Use in reports

A direct measure of industry research output is simply counting the number of newly market drugs for each region (e.g., Europe or the USA). In the discussion about relative productivity, this has been a part of the debate from early on. In our selection of reports, the EC ’94 report is the only report that uses the total number of NCEs as a way to make a comparison between the EU and the US in terms of industry output. The Pammolli report, discussed elsewhere in this section, is based on sales data. Other reports do not use data on industry outputs in the form of new drugs.

The EC’94 report uses industry output measures as one the main foundations for the argument about the shift of pharmaceutical R&D from Europe to the US: “twenty years ago [i.e. 1974], half of all new medicines were developed in the Community. Today this share has fallen to about one-third. Over the same period, the USA has continued to discover about a quarter of all new active substances, whilst Japan has increased its share from 10% to 22%.”39 The authors conclude, “It is hard to escape the conclusion that the United States, rather than Europe, is now the main base for pharmaceutical research and development and for therapeutic innovation.”40

39 EC ’94. P. 6
This observation was based on data depicted in Figure 1. They do not comport with these conclusions. A more accurate summary of these data would be: “In the last decade, European innovation as defined by NCEs attributed to where the headquarters of the final sponsor is located has declined significantly, while Japanese innovation has risen sharply and the U.S. has held steady.”

Figure 4.1 – Relative share in NCEs 1961 -1990
(Source: EC ‘94 report)

Updating a fuzzy picture
How has the picture changed since this influential report based on Figure 1? We requested the self-reported number of NCEs from the European Federation of Pharmaceutical Industries and Associations (EFPIA). For the assigning NCEs to regions we relied on the assignment made by EFPIA, based on the location of the company headquarters. “Europe” here includes Switzerland. Figure 2 picks up with the last period in Figure 1 and carries forward to 2005.

Notice the short-term fluctuations, for example a plunge for the U.S. of 25 percent from 1988 to 1989 and a sharp rise of 18 points from 1995 to 1997.

41 The self-reported industry data used were published in a German journal (Pharmazeutische Industrie) which is also the official bulletin of the pharmaceutical industry trade associations for Germany, Austria and Switzerland.
European innovation had a spectacular rise of 30 points from 1994 to 1996. Such plunges and spikes raise questions about the quality of the data because they are likely only with small numbers (like the number of gold medals won in the Olympics by a small country), changes in how data are reported or measured, or changes in calculations – not changes in reality. Thus policy and industry leaders need to be wary of such patterns and not overinterpret short-term changes. To conclude in 1996 that “Spectacular gains in European pharmaceutical innovation,” would be as imprudent as concluding in 2002, “European innovation plunging as U.S. eclipses it.” Three years later, the “plunge” had been fully recovered. The only long-term trend that appears credible is a decline in Japan in the mid-90s that has changed little since. The conclusion that the US is the main base for pharmaceutical innovation is not shown by the data.

Figure 4.2 – Relative share of NCEs 1986 – 2005, annual data points
(Source: EFPIA)

Methodological challenges
A general problem with these kinds of analyses is the fact that it is almost impossible to assign a certain molecule to a particular geographical region. For example, many companies may be headquartered in one country, but conduct significant amounts of their research outside of the country where their headquarters are located (for example, GSK has significant research facilities in the US while its headquarters are located in the UK). Another possibility is that the company is the result of a merger between two entities from different sides of the Atlantic (for example, the Belgian company Janssen Pharmaceutica, which has an extensive R&D department, is part of the US based Johnson & Johnson group).

More importantly, counting up NCEs is not an accurate way to measure the innovativeness of the industry. What society, patients, and doctors mean by innovation is better clinical outcomes than comparable therapies already on the market, but such measures are not required for market authorization. Therefore, the simple fact of being a newly marketed NCE is not a guarantee
for providing a significant therapeutic advantage. For example, it may only mean another molecule that acts through a therapeutic pathway that is already targeted by other drugs with no real therapeutic advantages, such as several recently marketed follow-on statins. Or a compound whose chemical structure is only slightly different from existing compounds (e.g. esomeprazol compared to omeprazol).

4.2 Sales data as measure of innovation

Use in report
The number of new NCEs was not the only output measure used to discuss the output of the European industry. Some reports assume (erroneously) that innovation is reflected in sales. Two of the four reports in our assessment use sales data as a measure of innovativeness (the EC ’94 report and the Pammolli report).

An approach that is sometimes used measures innovative quality in terms of ‘global NCEs’. For example, in a paper by Wang and Grabowski, a global NCE is defined as a drug that is marketed in more than half of the G7 countries. The EC ’94 report measures the innovativeness of drugs using this ‘global NCE’ concept; ‘major global drugs’ are defined as drugs that are present in 6 of the 7 major markets in the world. According to the report Europe was lagging in this market in comparison to the US: “Today [1993] the United States holds 43% of these major global drugs, Europe 31% and Japan 11.” What policy and industry leaders need to ask here is precisely what does “holds” mean and how is it measured?

The Pammolli report had a large impact on the discussion within the EU and significantly influenced the G10 report written by the G10 High Level Group on Innovation and Access, which was established in March 2001 to consider ways to strengthen the competitiveness of the European pharmaceutical industry. The group included top EU decision-makers, European commissioners, ministers, industry CEOs and patient representatives. The report measured innovativeness, however, using IMS global sales data and concluded, “US companies have gained a clear and growing leadership in terms of relevance, as measured by sales and geographical diffusion of New Chemical Entities (NCEs) launched on the marketplace”. What, readers should ask themselves, does “terms of relevance” mean? The data used represented the 15 NCEs with the largest global sales, not research productivity, by origin of corporation (i.e. based on the location of the company headquarters). These data are reproduced in Table 4.1.

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Table 4.1 – World Top 15 Drugs, by origin of main producer corporation
(based on the location of its headquarters). 44

<table>
<thead>
<tr>
<th></th>
<th>Total Sales, $ million, 1989</th>
<th>%</th>
<th>Total Sales, $ million, 1999</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>1,697</td>
<td>47.94</td>
<td>11,227</td>
<td>82.06</td>
</tr>
<tr>
<td>Japan</td>
<td>1,173</td>
<td>33.14</td>
<td>460</td>
<td>3.36</td>
</tr>
<tr>
<td>Switzerland</td>
<td>0</td>
<td>0</td>
<td>835</td>
<td>6.10</td>
</tr>
<tr>
<td>EU-15</td>
<td>670</td>
<td>18.93</td>
<td>557</td>
<td>4.07</td>
</tr>
<tr>
<td>TOTAL</td>
<td>3,540</td>
<td>100</td>
<td>13,682</td>
<td>100</td>
</tr>
</tbody>
</table>

Re-assessment of the data
Sales data for top selling drugs play an important role in many of the storylines on innovation presented in the reports, but a key flaw of Table 4.1 is that it cites only two single years, and patterns can fluctuate widely when patents expire. For example, in 1989, companies with world headquarters in Switzerland apparently had none of the top best-selling drugs worldwide, while companies with headquarters in Japan accounted for 33 percent of global sales for the top 15 drugs. In 1999 (but perhaps not in 1998 or 2000), those Japanese companies had only 3.36 percent of sales, while Swiss companies went from 0 to 6.10 percent. Even the share of top-15 sales by American-based companies, a larger and thus more stable sample, might drop or rise substantially from one year to the next. Also, during the 1990s, European revenues from export sales to the US have risen much faster than American revenues from export sales to Europe, a pattern not reflected in the table. 45

We decided to look at the top selling drugs in 2004 and 2007 and their country of origin. When we extracted data on the 15 top-selling drugs from self reported industry data published in Drug Discovery Today (2004) and the trade publication Med Ad News for (2007) and analysed them in the same manner as Pammolli, we found a very different picture (Table 4.2). Instead of a totally dominant US industry, with European companies being relegated to the fringes of the market, European-based companies account for a significant and fluctuating percent of sales, while the market share of American-based companies dropped from 65 percent to 45 percent. Switzerland and Japan happen to more than double their market share. But no trends, however, should be inferred from data like this. Fluctuations occur from the inherent volatility of which drugs are among the top 15 in global sales, due to patent expiration and new product introduction. For example, due to patent life it is unlikely that a drug will dominate the sales charts for a period of more than 8 years or so.

44 Pammolli. P. 34.
<table>
<thead>
<tr>
<th>Origin</th>
<th>Total Sales, $ million, 2004</th>
<th>%</th>
<th>Total Sales, $ million, 2007</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>42,150</td>
<td>65.17</td>
<td>42,657</td>
<td>49.93</td>
</tr>
<tr>
<td>Japan</td>
<td>1,550</td>
<td>2.40</td>
<td>4,333</td>
<td>5.07</td>
</tr>
<tr>
<td>Switzerland</td>
<td>3,100</td>
<td>4.79</td>
<td>9,056</td>
<td>10.60</td>
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<tr>
<td>EU-15</td>
<td>17,880</td>
<td>27.64</td>
<td>29,391</td>
<td>34.40</td>
</tr>
<tr>
<td>TOTAL</td>
<td>64,680</td>
<td>100.00</td>
<td>85,436</td>
<td>100.00</td>
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</table>

Table 4.2 – World Top 15 Drugs in 2004\(^46\) and 2007\(^47\), by origin of main producer corporation.

**Methodological Challenges**

Although sales data as a measure for the innovativeness may be easily available from data suppliers such as IMS or the trade associations, it is a poor indicator of innovativeness. Sales are heavily affected by factors that do not measure innovativeness, such as the impact of marketing activities, the type of use (acute v. chronic), and the prevalence of the disease. Furthermore, some blockbusters rely on the large prevalence of the target disease to achieve high sales, not on the relative innovativeness of a new drug. By contrast, some therapeutic breakthroughs will never attain high sales because of the low prevalence of the therapeutic indication. Therefore, using solely sales data is a poor method for comparing the output of different companies or different countries.

There is also the problem of “US” versus “European” companies when so many have operations in both places. These types of analyses are complicated further by the trend of joint development and marketing of products by European and US firms. For example, in the analysis we present in Table 2 we ‘split’ the sales for Plavix®/Isocover® between the EU and the US since it was jointly developed by the European firm Sanofi-Aventis and the US firm Bristol-Myers Squibb. Another example is Pantozol®, a drug developed by the German firma Altana, which during our study year (2007) sold its pharmaceutical activities to NycoMed, a pharmaceutical firm based in Switzerland, but owned by Swedish and Swiss private equity firms. We decided to assign the sales to the EU for 2007. Also, Risperdal® was developed by Jansen-Cilag, a European member of the Johnson & Johnson group. We assigned Risperdal® sales to the EU, but what other researchers would do in this case is not clear. In these and other reports surveyed, Tables rarely state how jointly developed products are assessed. Moreover, any


assignment of compounds to a certain geographic region is fraught with ambiguities and subject to multiple interpretations. In sum, sales should be dropped as a measure either of scientific or therapeutic innovativeness.

One cannot base sound decisions and inferences on just a few data points. As our analysis of sales data shows, using only a few data points for an analysis can tell the wrong story, this was both the case for the number of NCEs as for sales. The pharmaceutical marketplace is very volatile: new drugs come and go, patents expire and companies merge. Making sweeping statements about industry trends therefore always requires longitudinal datasets with sufficient data points.

4.3 Research Productivity
To illustrate the complexities encountered when studying industry output, we want to discuss a recent analysis led by Henry Grabowski, who has done many distinguished studies used by the American pharmaceutical industry. Grabowski analyzed all NCEs approved in 1982-92 and 1993-2003. Compared to the measures used in the key policy reports on research productivity in Europe analyzed in the rest of this report, approved NCEs is a good, direct measure of research outcome. Grabowski and Richard Wang concluded that the US overtook Europe in discovering global, first-in-class (FIC), biotech, and orphan NCEs ⁴⁸. However, if one simply divides to calculate the percent of NCEs attributed to the US and Europe (the EU-15 plus Switzerland), Europe is well ahead in the first decade and stays ahead of the US in the second, as shown in Table 4.3. The same is true for global NCEs, the most profitable ones. The US outperforms Europe in F-I-C, biotech, and orphan NCEs in the first decade and pulls farther ahead in the second.

<table>
<thead>
<tr>
<th></th>
<th>All NCEs</th>
<th>Global NCEs</th>
<th>First-in Class NCEs</th>
<th>Biotech NCEs</th>
<th>Orphan NCEs</th>
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<tr>
<td>82-92-93-03</td>
<td>82-92</td>
<td>93-03</td>
<td>82-92-93-03</td>
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<td>EU15 &amp; Switz.</td>
<td>48.4%</td>
<td>43.3%</td>
<td>55.9%</td>
<td>54.6%</td>
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<td>42.6%</td>
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<td>USA</td>
<td>25.3%</td>
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<td>Japan</td>
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Table 4.3 - Percent of New Chemical Entities Discovered by the USA, Europe, and Japan, 1982-2003 (based on Grabowski & Wang, 2006 )

During this time, however, European companies shifted much more of their R&D budgets to the US; so the greater production of NCEs in the US may have been an artifact of greater investment. According to EFPIA, from 1990 to 2000 (midpoints in the two periods), companies reduced their R&D investments in Europe from 49.1 to 36.9 percent, while they increased their share to the US from 33.3 to 47.8 percent.\(^4^9\)

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<tbody>
<tr>
<td>% R&amp;D Invested (€ bn euros)</td>
<td>33.3% (5.3)</td>
<td>47.8% (23.1)</td>
<td>49.1% (7.8)</td>
<td>36.9% (17.8)</td>
<td>17.6% (2.8)</td>
<td>15.3% (7.4)</td>
</tr>
<tr>
<td>% All NCEs</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 NCEs</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 NCEs</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 NCEs</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 NCEs</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>
</tbody>
</table>

Table 4.4 Pharmaceutical Industry R&D Investment and Research Productivity in the U.S., Europe, and Japan 1990, 2000

Sources: R&D investment figures from EFPIA, Note 7. Company-reported figures converted to euros. NCE figures from Exhibit 1. Europe as defined by Grabowski & Wang in original.

If we then ask how productive European teams were compared to US teams in proportion of the funding they received, and very different picture emerges. For global NCEs, European researchers rose from 1.14 NCEs in proportion to their share of funding in the first decade to 1.48 in the second, a sharp increase. American researchers, by contrast, fell from 1.12 NCEs in proportion to their share of funding to 0.83 in the second period, a sharp decrease (Table 4.5).

Table 4.5 - Return on R&D Investment. Proportional Ratio of Global and First-in-Class (FIC) New Drugs to R&D Industry Funding

(1.00 = innovation proportionate to investment).

<table>
<thead>
<tr>
<th></th>
<th>Global Productivity Change</th>
<th>FIC Productivity Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>82-92</td>
<td>93-03</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>1.12</td>
<td>0.83</td>
</tr>
<tr>
<td>Europe</td>
<td>1.14</td>
<td>1.48</td>
</tr>
<tr>
<td>Japan</td>
<td>0.38</td>
<td>0.38</td>
</tr>
</tbody>
</table>

For first-in-class NCEs, European researchers rose from 0.90 NCEs in proportion to their share of funding in the first decade to 1.22 in the second, a substantial increase. American researchers, by contrast, fell from 1.39 NCEs in proportion to their share of funding to 1.04 in the second period. In biotech NCEs, European researchers rose from 0.61 NCEs in proportion to their share of funding in the first decade to 0.90 in the second, a substantial increase. American researchers, by contrast, fell from 1.35 NCEs in proportion to their share of funding to 1.12 in the second period. For orphan NCEs, European researchers rose from 0.90 NCEs in proportion to their share of funding in the first decade to 1.15 in the second, while American researchers fell from 1.50 NCEs in proportion to their share of funding to 1.20 in the second period.

(Table 4.5)
Table 4.6 - Return on R&D Investment. Proportional Ratio of New Biotech and Orphan Drugs to R&D Industry Funding

(1.00 = innovation proportionate to investment)

<table>
<thead>
<tr>
<th></th>
<th>1.35</th>
<th>1.12</th>
<th>-17%</th>
<th>1.50</th>
<th>1.20</th>
<th>-20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>0.61</td>
<td>0.90</td>
<td>+48%</td>
<td>0.92</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>

Although this data set has shortcomings, it is a much more direct measure of research productivity than sales, number of employees, research funding, or confounded measures like the total productivity factor. Because the information used in the study by Grabowski & Wang is commercially protected, we do not know how NCEs were counted, and once again, they are assigned to the country in which the headquarters of the company at time of approval was located. Nevertheless, they indicate that during the period when reports commissioned by DG Enterprise rang the alarm that price controls and lower sales were undermining research productivity in Europe, productivity actually increased in developing top-selling drugs, first in class, biotech, and orphan drugs.

4.4 True innovation? Better patient outcomes

In the reports include in this paper the output was mainly measured in terms of sales or number of NCEs and remarks about the innovativeness of compounds were based on that. However, the only approach that recognizes the patient’s and society’s point of view measures innovativeness in clinical terms. Other reports and publications show that it is very well possible to gain insight in the added value of new drugs in a meaningful way. One of the ways in which the added clinical value of a drug can be operationalised is by assigning every new compound a rating or score. This score can be a composite measure based on several criteria such as the structural, pharmacological, pharmaceutical, pharmacokinetic and clinical aspects of a drug in relation to other drugs that are already on the market.\(^{50}\) This method of determining the innovativeness requires the weighing of diverse characteristics of a drug to produce an individual score for each drug; this can

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\(^{50}\) Aronson J. Something new every day – defining innovation and innovativeness in drug therapy. J Ambul Care Manag 2008;31:65-68.
result in quite complicated assessment techniques. Examples of organizations that routinely assess new drugs through this method are Prescrire in France, the Canadian Therapeutics initiative and to a significant degree the National Institute for Clinical Excellence in the UK. Table 4.6, adopted from Prescrire International summarizes the most therapeutically innovative or significant new medicines over a 15-year period. Real breakthroughs (‘Bravo’) make up only a small fraction of all new medicines marketed. Over this 15-year period, only two drugs, antidigitalin antibodies and the orphan drug nitisinone, were considered a breakthrough, and 42 a “real advance.” These represent 1.3 percent of all new products or indications assessed by Prescrire. If one adds in new medicines that offer an advantage for patients, based on clinical hard end points, the percent rises to 5.0. But which of the clinically innovative drugs were discovered and developed where? No one appears to have researched this critical question for European innovation policy. It should be done.

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bravo (a real breakthrough)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>A real advance</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>16</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Offers an advantage</td>
<td>15</td>
<td>8</td>
<td>12</td>
<td>15</td>
<td>8</td>
<td>12</td>
<td>17</td>
<td>17</td>
<td>9</td>
<td>11</td>
<td>9</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Possibly helpful</td>
<td>44</td>
<td>15</td>
<td>27</td>
<td>15</td>
<td>25</td>
<td>38</td>
<td>23</td>
<td>20</td>
<td>24</td>
<td>17</td>
<td>18</td>
<td>23</td>
<td>12</td>
<td>20</td>
<td>31</td>
</tr>
<tr>
<td>Nothing new (including generics)</td>
<td>69</td>
<td>61</td>
<td>65</td>
<td>52</td>
<td>85</td>
<td>(67)</td>
<td>125</td>
<td>(81)</td>
<td>193</td>
<td>(150)</td>
<td>165</td>
<td>(134)</td>
<td>219</td>
<td>(166)</td>
<td>157</td>
</tr>
<tr>
<td>Not acceptable</td>
<td>8</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>9</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Judgement reserved</td>
<td>7</td>
<td>4</td>
<td>10</td>
<td>5</td>
<td>16</td>
<td>6</td>
<td>4</td>
<td>9</td>
<td>5</td>
<td>7</td>
<td>0</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>144</td>
<td>91</td>
<td>121</td>
<td>91</td>
<td>154</td>
<td>184</td>
<td>243</td>
<td>215</td>
<td>263</td>
<td>203</td>
<td>233</td>
<td>178</td>
<td>225</td>
<td>239</td>
<td>53</td>
</tr>
</tbody>
</table>

Table 4.7 – Prescrire scores for clinical advantages minus adverse effects for all new products over the past 15 years

For lack of space, this table summarises only the results for the last 15 years. This table includes new products and indications presented to both prescribers and pharmacists by drug companies, in the community or hospital setting, and also, since 2005, range extensions (new dose strengths, new forms of existing drugs and over-the-counter products and self-medication scored by Prescrire. (Source: Prescrire International)
4.5 Assessment and recommendations

Only two of the reports in this study provide any information on output measures of the industry (the ‘94 EC report and the Pammolli report). The former uses a simple NCE count, the latter an analysis based on sales data.

It is remarkable to discover that among the major reports on which European pharmaceutical innovation policy has been developed, none provides a detailed analyses of comparative innovativeness in terms of structural, pharmacological, pharmaceutical, pharmacokinetic and clinical criteria. What payers, patients, and doctors expect are new medicines that improve patient outcomes, whether in death or disease averted, diseases cured, pain reduced, or functions increased. Increasingly, payers are demanding increased value if they are going to pay more for new medicines.

To its credit, the G10 call for “the development by the Commission of a comprehensive set of indicators covering: the performance of the pharmaceutical industry in relation to indicators of industrial competitiveness.” It does not provide any information, however, about the relative therapeutic benefits of compounds marketed in the EU and the US compared to drugs that are already available. In the 2004 Call for Action, which was a response to the G10 report, the first set of indicators was published. As one can see from the indicators in Annex 1 of this report, none of them includes any information on the output of the industry or the innovative quality of new medicines. Three measure funds for R&D – venture capital, government funds, and industry expenditures. None measure innovativeness.

Likewise, although the concept may sound tempting, ‘global NCE’ diverts attention from medicines that really make people healthier to medicines that are heavily promoted. For example, Nexium is a “global NCE” that represents no significant clinical innovativeness, but mostly marketing creativity. A focus on “global NCEs” and blockbuster drugs poses a basic question of European policy and strategy: large profits and sales can result from the innovative and aggressive marketing of new products with marginal therapeutic advantages in the short run, but will this focus serve the pharmaceutical industry in the long run?

If clearly superior new medicines for patients, like Gleevec, are the drivers of sales and profits for this technologically based industry, then a focus on sales, profits, and indirect measures may be short-sighted. Focusing on sales or the total number of drugs marketed does not serve either the individual or society well, because it rewards marketing innovativeness to sell new medicines that offer limited clinical advantage, rather than rewarding the development of clinically superior new medicines. It is also unclear – and has been for years – how drugs that come out of the pipeline of European and US

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companies differ. Therefore, it is hard to make any meaningful comparisons of the innovativeness of the drugs that are discovered and developed by US and European researchers.

Another issue is the assignment of a drug to a certain geographic region. This is something that will always be very problematic, but there is a need for clearer or more meaningful definitions for this. Assigning a drug to a certain region according to the location of the company headquarters is obviously indirect and may be misleading. Especially in a world where initial drug development is more and more conducted by small companies and drug development is often a partnership between global corporations from different continents.

Finally, this section began with a good example of a biased conclusion not based on the evidence and even contradicted by the limited data presented. Policy and industry leaders put their countries and companies at risk if they read only summaries and conclusions without seeing if they are supported by the data. Overinterpreting short-term trends is a related, serious danger. Yet it is found right up through the recent report *Creating an Innovative Europe* which makes much of 1-year changes.

To conclude, if the European pharmaceutical industry wishes to increase its innovativeness in terms of safer, clinically superior drugs that offer better value for money, then it needs to measure its new products by these metrics and analyze how it can improve its performance.

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Key points

- Do not use basic NCE counts as a basis for measuring industry output.
- Assign molecules to the countries in which they were discovered and developed. Assigning a molecule to a continent according to where the market authorization holder has its headquarters is not a valid method.
- Incorporate real measures for clinical advantages when measuring the output of the industry.
- Try to base assessments on longitudinal data and as many data points as possible. Beware of lumping data together (e.g. 5 year groups). The volatility of the pharmaceutical marketplace is high.

5- Evidence relating to the structure of the industry

The reports commissioned by D G Enterprise to show that Europe has lost ground to the US in pharmaceutical innovativeness depend heavily on evidence that is secondary to research productivity or innovation. We assess three of them: R&D investments, employment, and labor productivity.

5.1 R&D investment

One of the original concerns voiced was that the ability of the industry to finance the development of new and innovative medicines was weakening in the EU. The background for the worries on this topic was the statement that the costs for developing a new medicine were increasing and that “an investment can be financed only if the company is able to generate the necessary cash flow during the period of patent protection. [Therefore,] it is essential to launch the medicinal product on the markets of large industrial countries as quickly as possible. The survival of large pharmaceutical companies depends on the profitability of a small number of products (sometimes on that of just one successful product), and also on the regular renewal of portfolios of patents on new medicinal products.”

According to most reports included in this paper one important argument

55 EC ’94. p. 4
that is used to describe a worrying trend in the EU industry compared to their US counterparts lies in the differences in R&D expenditures. For example, the EC ’94 report states that: “...on average, European companies generally obtain results vastly inferior to those of American companies: for many years, budgets allocated to R&D investments by EC companies have accounted for only half of the [R&D] budgets available to American companies.”

Here again the problem of assigning a nationality to a company is at issue. In the Pammmoli report the same argument for differences between the EU and the US are found: “The amount spent on R&D increased in all the three regions. The US ranks first in terms of both R&D spending and ratio of R&D to production...” Based on this the authors conclude the US was “consolidating their supremacy during the Nineties.” The 2003 Call for Action also uses R&D spending to make sweeping statements about the innovativeness of the European pharmaceutical industry. The call for action states that one of the key problems of the European industry is “a weak growth in R&D spend: the USA has led the way in developing new technology suppliers and innovation specialists; and R&D spending in the USA grew at twice the rate of the EU during the 1990s. [Although it is] noted that the effectiveness of this expenditure remains below that of Germany, the UK, the Netherlands and Spain.”

The R&D expenditure by industries is used as one of the proposed indicators for benchmarking the EU industry. In this same report, Industry Pharmaceutical Research and Development, expenditures are suggested as one of the nine main indicators to benchmark the EU and US pharmaceutical industries.

A re-examination of R&D data
Because R&D expenditures apparently play such a significant role in assessing the industry, we want to perform a brief re-examination of the data at this moment. The time series of R&D investment, based on self-reported figures by industry trade associations, for the period 1986-2006 is shown in Figure 5.1. The data shows a strong divergence between 1996 and 2006 between how much of the industry’s expenditures are placed in the EU, the US, and Japan.

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56 EC ’94. p. 5
57 Pammmoli. P. 15.
58 Pammmoli. P. 15.
Figure 5.1 – R&D spending for EU, USA and Japan 1986-2006

The main question is what causes this diverging trend? Why are R&D expenditures in the US apparently growing so much faster the EU? Could this be because, when making the decision to allocate research investments, companies have decided to reallocate their R&D expenditures from the European region to the US? To explore this in more detail, we collected data from PhRMA, the US trade association, on where US companies invest their R&D money, shown in Figure 5.2. The data on billions spent abroad is not quite comparable to the billions spent in the US. The former includes expenditures by U.S.-owned PhRMA member companies and the U.S. divisions of foreign-owned PhRMA member companies but not the foreign divisions of foreign owned PhRMA member companies. The billions spent in the US, however, includes R&D expenditures within the United States by all PhRMA member companies.
Figure 5.2 – R&D expenditures domestic and abroad for PhRMA member companies. 59

Under the hypothesis that US companies decided to shift their money away from overseas R&D and focus on R&D facilities in the US, the share of R&D expenditures abroad by US firms should fall over time. However, data from the US trade association (Figure 5.2), shows that the percentage of R&D expenditures of US firms continue to value the research productivity of overseas teams. More than three quarters of those funds go to Europe (Table 5.1). We sought comparable data for other years, as well as for European firms, but could not find it.

<table>
<thead>
<tr>
<th>Region</th>
<th>R&amp;D investment (million USD)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total worldwide R&amp;D</td>
<td>43439.1</td>
<td>100.0</td>
</tr>
<tr>
<td>Within US (domestic)</td>
<td>34467.8</td>
<td>79.3</td>
</tr>
<tr>
<td>Outside of US</td>
<td>8971.3</td>
<td>20.7</td>
</tr>
<tr>
<td><strong>Breakdown outside of US</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>25</td>
<td>0.3</td>
</tr>
<tr>
<td>Americas (excl. US)</td>
<td>672</td>
<td>7.5</td>
</tr>
<tr>
<td>Asia-Pacific</td>
<td>1039.2</td>
<td>11.6</td>
</tr>
<tr>
<td>Australia and New Zealand</td>
<td>135</td>
<td>1.5</td>
</tr>
<tr>
<td>Europe</td>
<td>6963.5</td>
<td>77.6</td>
</tr>
<tr>
<td>Middle East</td>
<td>38.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Unknown</td>
<td>97.4</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Table 5.1 – Breakdown of destinations for R&D expenditures of US firms for 2006 (Source: PhRMA).

This suggests that the increase in US R&D expenditures is unlikely to be caused by changing allocation policies for R&D, but may be caused by the faster growth of US firms *per se*, especially from higher prices and the success of US blockbusters. Of course, it is still possible that European firms have decided to move their R&D expenditures from Europe to the US, but we did not find the data to study this. However, it is unlikely that the trends for European companies are very different.

**Methodological challenges**

The R&D expenditures presented here are based on self-reported data by the industry. Furthermore, the data are collected in two separate surveys, and based on our experience it is hard to determine how data were collected exactly. We requested the exact question that was posed to the companies, but did not receive a response. Therefore, it remains unclear what data exactly is part of investments in the US and investment in the EU, especially since the data were collected by both EU and US trade associations separately. Therefore, bias inherent in collecting the data using two instruments in two very different environments makes comparisons ambiguous and unreliable.

Since the late 1970s, there may have been efforts by US companies to make the cost of R&D as large as possible. Several accounts have identified expenses counted as R&D that most people would not include, such as upgrading the company-wide computer system or legal expenses involved with patents. Emanuel and Barton estimated that 40 percent of US R&D expenses do not
have to do with discovering and developing new drugs.\textsuperscript{60} The National Science Foundation surveys found that 18\% of pharmaceutical R&D was devoted to basic research to discover new medicines.\textsuperscript{61} These may explain why US firms appear to be investing 50 percent more in R&D than European companies. Or the denominator for Europe may include all the non-research companies so that the percent in R&D is artificially pulled down.

Future assessments should not use macro R&D expenditures as a key measure. Therefore, including such an indicator in a proposed set of benchmarks, as was done by the EC Call for Action, is not useful. It may be more relevant to measure research productivity in terms of outputs, like NCEs or patents, relative to research funds.

\subsection*{5.2 Employment}

Employment has also been used in the discussion about the health of the EU industry. Moreover, industry employment was suggested as one of the Benchmarks in the Call for Action as a measure for how the EU industry is doing. A good illustration of possible problems are with using these kinds of measures is found in the 1994 EC commission report. It stated that

"Despite the recession, the pharmaceutical industry has been expanding its workforce between 1981 and 1992, by an average of 2.4\% per year. Since the beginning of 1993, however, this trend has gone into reverse. For the first time in 20 years the total employment in the pharmaceutical industry did not increase in 1993 but rather decreased by 1.4 \%. Furthermore, even more important reductions of the workforce have already been announced and will take place through the coming years. Thus, within three years (1993-1995), nearly 27,000 jobs could be lost in the pharmaceutical industry. A substantial part of the lay-off stems from the closing of research or manufacturing sites, or delocalizations.\textsuperscript{62}\)

Furthermore, due to disinvestments, about 5,000 – 10,000 new jobs would not be created. The projections stemming from this document are shown in Figure 5.3. That these total employment figures are perceived as important indicators for the health of the pharmaceutical industry as a whole is shown by the EC Call for Action which included ‘total pharmaceutical industry employment’ as Indicator 9 for benchmarking the industry (Appendix 1).

\textsuperscript{60} Barton, JH, Emanuel, E “The patent-based pharmaceutical development process: rationale, problems, and potential reforms” JAMA 2005; 294:2075-82
\textsuperscript{62} EC ‘94 . p. 6
Actual historical trend and methodological considerations
Were the predictions of the EC ‘94 report in line with reality? A retrospective analysis based on data provided by EFPIA shows the actual historical trend for the years after the publication of the EC ‘94 report in Figure 5.4. The main problem with this influential policy analysis resulted again from taking a short-term fluctuation of one year (1993), projecting further declines for the next two years, and then declaring a crisis. As Figure 5.4 shows, there was no perceptible decline – only a dip – and jobs slowly grew thereafter. The dire conclusion was based on extrapolating from a slight, short-term decline in a biased way to fit a foregone conclusion, as indicated by using “should” and “would.” They evoke a sense of an impending strong decline not justified by the data then or since. In fact, the number of jobs increased”, and Figure 5.4 shows they increased in research even during this very period that D G Enterprise, writing for the EC, emphasized they were shrinking.

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Figure 5.3 – Employment in the pharmaceutical industry. Projection for 1993 – 1995 based on EFPIA data ⁶³

⁶³ EC ‘94. p. 28.
The dire prediction of 1994 included the closing of “research and manufacturing” sites in the EU, which is a piece of evidence that can be seen in various publications, such as data published by the industry itself. The statement reads as if the industry was shutting down, when clearly it was not. How the 5,000-10,000 jobs that might be lost was calculated is unclear and is made to sound dramatic. It also confounds two very different kinds of sites and jobs, making it more rhetorical than factual. Whether the closing of research sites constitutes ‘moving’ sites to other locations, or consolidations to single sites within the EU, or true shrinkage cannot be determined because no data are given. Site closings could actually be a positive sign of consolidation, since the fragmentation of the European pharmaceutical industry is often cited as a negative feature of the European industry.

The total number of employees is an indirect and oblique measure of research productivity, analogous to using sales as a measure. Total employees may rise because people are hired in marketing, not research. More employees might reflect greater inefficiency rather than growth, and not more innovation. More pertinent is the number of employees in R&D functions. Figure 5.5 shows the number of employees in R&D jobs in the EU, the US and Japan for the years 1993, 1997, 2003 and 2005 (years for which data was available to make a comparison between the EU and the US).

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65 EC ‘94. p. 8
Figure 5.5 does not show that the US has eclipsed Europe. On the contrary, it shows that the US is behind but catching up in terms of R&D personnel, despite a huge shift in R&D funding. There is no gap between the US and the EU, with the US in the lead, as is suggested by the R&D expenditures.

When both of these data sources (R&D expenditures & R&D employees) are taken into consideration it shows that using either one of these figures for making sweeping statements about the pharmaceutical industry in the EU and the US should be avoided.

5.3 Labor productivity
The Pammolli report provides an extensive analysis of the relationship between labor costs and the total value added. This analysis showed that “the share of labour cost in Europe is higher than in the US and Japan, and this is stable across the two periods [1986-1991 & 1992-1997 – PS/DL]. This suggests that the European industry is more labour-intensive than the US or Japanese ones.” This difference could not be explained by higher labor cost charges, the authors concluded, though labor costs in Europe are higher. The researchers attributed the difference to “the presence in Europe of a relatively larger share of fringe companies that are specialised in low value added activities, like manufacturing and commercialisation of products licensed from other companies, or simply of low value added medical or medical-like substances.”

The authors continue with a more detailed analysis of the factors that drive

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66 Data obtained from EFPIA (data available on request).
67 Pammolli report. p. 4.
68 Pammolli report. p. 22
the growth of the drug industry. They constructed a model in which the contribution of measurable inputs (such as labor and capital) on sales growth was determined. They conclude that growth in Japan and the US was to a large extent accounted for by measure non-labour inputs such as capital and R&D investment, but in the EU growth was mostly explained by the residual ‘total factor productivity.’ This important sounding variable is a residual of equations taking into account labour and non-labour factors. It appears, as best we can tell, to lump together all factors besides capital and labor, including R&D along with technological, organizational and regulatory factors. The authors concluded that “not only is the European industry more labour intensive, but it responds less substantially to growth in non-labour inputs like research or capital. The industry in Europe responds mainly to “exogenous” factors unrelated to the growth in these inputs”.

The analysis raises more questions than it answers. How can Europe be discovering more NCEs (though a declining proportion) if it is populated by a large share of companies peripheral to R&D? What are we to make of the fact that the residual category, ‘total factor productivity,’ includes ‘technological factors’ not unlike research factors and other kinds of non-labour inputs that are not part of ‘non-labour inputs’? If there are clear differences between the EU and the US, they are hard to discern. Yet clarion conclusions are drawn: European companies are said to somehow not respond as well to inputs like research and capital, though this is inferred without actual evidence.

Re-analysis of the data
A re-analysis for the data in the 2000 report was done by the authors themselves in a book published in 2008. This time they developed a more complicated and different picture regarding the value-added of labor and non-labor inputs that centered around differences between states. Paradoxically, given what the authors concluded in 2000, they report that the relative value of non-labour inputs in the US is lower this time. What happened is the interim is unclear. Furthermore, within the EU a distinction should be made between what they authors call EU ‘tigers’ with high productivity growth (e.g. Belgium, France, UK, Ireland and Sweden) and EU ‘tortoises’ (e.g. Austria, Germany, Finland, Italy and The Netherlands). Are these reasonable characterizations, and does “productivity” confound research productivity with manufacturing productivity? Is Sweden, for example, a ‘tiger’ because of its research while Ireland is a ‘tiger’ because of its boom in manufacturing? Is it reasonable to characterize The Netherlands as a ‘tortoise’?

The authors also carried out a new analysis on their residual catch basin, total

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69 Pammolli report. p. 23.
70 We have corresponded with the authors about such questions but have received no answer.
factor productivity. This analysis again showed that total factor productivity was the main driver for output growth in the EU and, although overall productivity growth was lower, it played a more prominent role than in the US. Furthermore, it should be noted that while in the 2000 ‘Pammolli Report’ Ireland played a unique role as the only EU country where TFP was not the main driver for growth, this was no longer the case in the 2008 analysis.

5.4 Discussion and conclusions

This section shows that using indirect and confounded measures provides no useful picture of research productivity. For example, what does R&D employment really tell us? Is a lot of researchers working at a company necessarily a good thing? Or would we be more interested in how and to what extent the work of researchers leads to new products and patents? The same holds for R&D expenditures and measures such as Total Factor Productivity. Again, such measures can only be interpreted in the light of key industry outputs such as new and innovative drugs.

A further significant problem with the data presented in this section is the question whether data collected in Europe and in the US really measure the same thing. For example, our enquiries asking how R&D expenditure was defined in the European and in the US industry survey were not answered, and the way figures are gather probably varies from one company to another and even from one executive team to the next. Such variations may significantly influence results if questions are phrased in a different way or if accounting procedures vary by company, by country, or by region.

It is a worrying development that such high level indicators are lent credence by their being including in leading reports that suggest them as indicators for benchmarking the pharmaceutical industry. We hope that the discussion above shows that we should look for other and more meaningful measures. It is true that high level data is easily available, since it is often collected by trade associations, but this does not indicate relevance.

The 2003 Call for Action correctly identifies ‘research productivity’ (Indicator 7) as one of its key indicators, but then only measures R&D expenditures (see Appendix 1). As shown in the reanalysis of the Grabowski and Wang article, the two are not the same, though related. We believe that industry and academia should come together to define research productivity and then measure it directly. Any message that is provided by the data may be confounded by factors that are not necessarily the hallmark of an innovative company. Therefore, any benchmarks should be carefully selected.

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72 Innovation and industrial leadership, p 43-50.
To summarize, our reassessment of key reports and statements, most sponsored by DG Enterprise, find unclear evidence to support the strong conclusions about the EU losing out to the US in pharmaceutical research productivity. At times, the evidence provided directly contradicts the conclusions drawn. At other times, projected “facts” are made to support foregone and inaccurate conclusions. The members of the European Parliament and officers of the European Commission, as well as leaders of the pharmaceutical industry, need clear measures of research performance in order to make good policy.

Key points
- Given the significant fluctuations in the pharmaceutical industry, one should be wary of extrapolation drawn from short-term changes.
- Avoid using very broad or high level data to make sweeping statements.
- Benchmarks should measure inputs and outcomes as directly as possible.
- When wanting to benchmark the pharmaceutical industry, use indicators that are unambiguous and really link to what is expected of a healthy industry.
6 – Conclusions

In this report we have devoted considerable attention to the first key report for DG Enterprise in 1994 and its policy conclusion that the pharmaceutical industry in Europe was in serious decline. We have shown that based on a widely used outcome measure for research productivity, NCEs, that from 1982 to at least 2003, the European researchers were highly productive and became more so in recent years, not less.

Many analyses on which the sweeping assumptions about the research productivity of European pharmaceutical industry are based suffer from using measures of other factors and synthetic indices of large, undifferentiated data sets so that policy leaders cannot know what is really happening on the ground. In this report we saw that this happened at different levels: assigning molecules to certain countries is ambiguous, sales data do not provide a clear picture, and NCE counts do not show which drugs truly add clinical value. Furthermore, analyses such as the ones that focus on labor productivity do not seem to provide a coherent picture. Moreover, all these measures are subject to strong between-year variability, which makes basing policies on short term trends unwarranted.

Therefore, clear and unambiguous benchmarks are needed that measure inputs and outputs of European pharmaceutical R&D as clearly as possible. These indicators should be unambiguous and really link to what is expected of a healthy industry. The G10 has made a start towards clear measures through its process of developing benchmarks. However, the indicators mentioned in the 2004 Call for Action (Appendix 1) as the outcome of this process do not provide indicators of the level and quality of research innovation that are needed for policy assessments.

Although the reports that we have discussed here have been published several years ago, the critical issues highlighted remain. For example, the 2006 report by the Independent Expert Group on R&D and Innovation, Creating an Innovative Europe, is much more focused on the conditions for innovation than the previous reports. Yet it presents no data or detailed empirical analysis, and in several places it signals a trend based on a 1-2 year changes. It also uses selected years and measures that fluctuate significantly from year to year, such as how many of the top ten best-selling drugs came from Europe in 2002.

These critical comments do not mean that Europe does not have reason to work hard at make its institutions, laws, and programs more conducive to innovation, translation research, and integrated consortia like T I Pharma. The European environment is historically and culturally much more complex to operate in.

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Institutional and cultural obstacles need to be reduced or removed. As they are, clear measures of research productivity and innovativeness will help document the strong record that EU researchers have established and we have documented in this report.
Appendix 1 – Benchmarks for competitiveness based on G10 report
(Source: 2004 Call for action).

<table>
<thead>
<tr>
<th>Benchmark</th>
<th>Description</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Venture capital invested</td>
<td>Venture capital</td>
<td>Millions of euros invested</td>
</tr>
<tr>
<td>2. Government funds for Health R&amp;D</td>
<td>Government spending reserved for health R&amp;D</td>
<td>% of GDP and euros</td>
</tr>
<tr>
<td>3. Uptake of new medicines</td>
<td>Market share for new molecular entities launched in the last 5 years.</td>
<td>% by value of national pharmaceuticals markets accounted for by NMEs launched in last 5 years</td>
</tr>
<tr>
<td>4. Market share of generics</td>
<td>Measures development of price-competitive markets</td>
<td>% (by value) of national pharmaceuticals market accounted for by generics</td>
</tr>
<tr>
<td>5. OTC market</td>
<td>Measures dynamics of transfers into non prescription medicines</td>
<td>Non-prescription medicine sales as a % of the total pharmaceuticals market.</td>
</tr>
<tr>
<td>6a. Time from approval to launch</td>
<td>This measure captures the time lag between application for launch in any market to launch in specific markets for NMEs launched in the period</td>
<td>Times elapsed from first world application to application in market, to regulatory approval and to market launch</td>
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<tr>
<td>6b. Time for pricing reimbursement decision</td>
<td>Elapsed time for pricing and reimbursement decisions for European countries</td>
<td>Days between application for decision and reimbursement decision</td>
</tr>
<tr>
<td>7. Industry expenditure on, and productivity of pharmaceutical R&amp;D</td>
<td>Real expenditure on industrial pharmaceutical research and development</td>
<td>Millions of euros</td>
</tr>
<tr>
<td>8. Trade balance</td>
<td>Measure for the international trade in pharmaceuticals</td>
<td>Trade in millions of euros</td>
</tr>
<tr>
<td>9. Pharmaceutical industry employment</td>
<td>Measure for the development of the labor market</td>
<td>Number of employees (overall)</td>
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