INCENTIVES FOR RESEARCH, DEVELOPMENT, AND INNOVATION IN PHARMACEUTICALS

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CHAPTER 5

The Contribution of the United States, Europe and Japan in Discovering New Drugs: 1982-2003

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Introduction

In an article published in *Health Affairs* in 2006, Grabowski and Wang (G&W) examined trends in the introduction of new chemical entities (NCEs) worldwide from 1982 to 2003¹. Although there is a well documented decline over time in total worldwide introductions, we found various quality indicators such as the number of global, first-in-class, biotech and orphan drugs exhibited more positive trends. U.S. headquartered firms also assumed a strong leadership position in terms of being the initial introducers of the most novel compounds including first-in-class, biotech and orphan drugs.

In this paper, I provide a complementary analysis to our earlier paper by focusing on the drug discovery stage across each of these regions. Multinational firms perform research and develop new drugs in several locations. Firms also enter partnering and licensing agreements involving new drug candidates, so the nationality of a firm introducing a product is often different from the one where the drug was invented and initially developed. There is also a well-defined and studied “market for innovation” in pharmaceuticals². This is especially true in the biotech industry which has been the source of many novel products over the past two decades.

I utilize information contained in patent data to establish the region of discovery for all the first-in-class, biotech, global and orphan compounds in the G&W sample. These data show that R&D labs located in the U.S. have discovered more products in these categories than R&D labs based in Europe or Japan. U.S. leadership also has increased over time. These findings are consistent with other studies using different samples and indicators of drug discovery by countries and geographical regions.

In the next section, I summarize prior literature and discuss the rationale for utilizing first-in-class, biotech, global and orphan drugs as measures of drug quality. In the following sections, I present the empirical findings on the location of pharmaceutical discoveries in the United States, Europe and Japan for each of these drug quality measures. A subsequent section also considers several issues surrounding an analysis of R&D

productivity by region by Light that utilizes our data on new drug introductions³. The final section offers some observations on the policy implications of the analyses on international competitiveness undertaken here and in related studies.

Drug quality measures in the prior literature

In examining international data on innovative performance, various scholars and research organizations historically examined different output and input measures, such as new drug introductions, patent counts, and research and development expenditures⁴. While these provide nice aggregate quantitative measures, they do not capture the quality of introductions over time or how quality indexed introductions compare across countries.

A quality-oriented index that began receiving attention by scholars in the 1980s was the concept of consensus or global new chemical entities (NCEs)⁵. Global NCEs are defined as new drugs introduced into a majority of the world's leading drug markets. Several scholars noted that a large percentage of drug introductions historically were introduced into one or a few closely related countries. Global NCEs capture important therapeutic advances from a medical perspective as well as drugs that address significant market opportunities. In this regard, Grabowski (1989) found that although there were over 50 annual NCEs introduced internationally from the 1970s through 1983, only 24 percent of these were introduced into a majority of the world's largest markets.

In my study with Richard Wang, we considered global introductions as one index of drug quality, but developed some alternative measures that reflect other specific quality attributes. We gave particular attention to drug novelty or first-in-class drugs. In addition, we examined trends in and sources of biotech drugs and orphan compounds given that these entities often provide therapeutic advances for illnesses and disabilities with substantial unmet medical needs.

Sample Scope and Definitions in Grabowski and Wang's Analysis

The current analysis builds on Grabowski and Wang's sample and methodology to examine the country of discovery. In this section, a brief summary of the underlying data source is provided. Using the new Product Focus database (IMS Health Incorporated, Fairfield, Conn.), Grabowski and Wang identified all NCEs first introduced worldwide between 1982 and 2003. The database reports all drug launches in 68 countries. IMS Health defines NCEs based on the first international launch of a new active substance, including both new chemical entities and new biological products (specifically recombinant proteins and recombinant vaccines).

The definition of globe introductions in the Grabowski and Wang study considers dissemination in the G7 countries (Canada, France, Germany, Italy, Japan, the United Kingdom and the United States). We defined global NCEs as those introduced in a majority (at least four) of the G7 countries. These countries are the world's seven largest pharmaceutical markets.

We also identified the first NCE in a therapeutic class (first-in-class drugs). Therapeutic class is defined as the unique combination of the five-digit Uniform System of Classification (USC) and the four-level Anatomical Therapeutic Classification (ATC) system. We used the National Disease and Therapeutic Index in the United States for September 2003 to August 2004 (IMS Health) to obtain the USC and ATC classifications.

In addition, we focused on two further categories of NCEs of policy interest, i.e. biotech products and orphan products. We utilized the IMS database to identify the category of biological drugs. We defined an orphan product as an NCE launched in the United States within six months after FDA approval of its earliest orphan indication. This definition excludes NCEs that gained orphan indications after launch. The defined orphan products excluded those not yet available in the United States.

We then defined the corporation that first launched an NCE in the database and assigned its headquarters country as the nationality of the NCE. If more than one firm first launched an NCE, each firm received an equal share of that NCE for nationality assignment purposes. The IMS data base allows one to track the nationality of the company at the time of first global introduction, and therefore avoids issues raised by subsequent mergers that would change the corporation's identity.

A total of 919 NCEs were introduced from 1982 through 2003. Of these NCEs, 42 percent were global NCEs, 13 percent were first-in-class NCEs, 10 percent were biotech products, and 8 percent were orphan products. First-in-class NCEs, biotech products, and orphan products were more likely to be global products – 76 percent, 56 percent, and 61 percent, respectively.

Key Findings of the Grabowski and Wang Study

Two important results emerged from the Grabowski and Wang analysis. First, the observed trends suggest that the relative quality of NCEs has increased over time. In particular, the strong downward trend observed in total new chemical entities by many researchers is moderated when one looks at more selective measures of drug quality – namely trends in global drugs, first-in-class drugs, biotech and orphan products. This is shown in Figure 5-1, reproduced from the Grabowski and Wang study. In particular, all of these product categories have grown relative to total introductions over time. Furthermore, first-in-class, biotech, and orphan drugs have exhibited significant positive growth over time.

A second important finding relates to the source of quality-adjusted outputs across countries. Table 5-1 shows the nationality of NCEs from the Grabowski and Wang study based on the headquarters location of the company making the initial global introduction. European companies introduced the most NCEs in both periods as well as the most global NCEs. U.S. firms introduced the most first-in-class, biotech NCEs and orphan NCEs. U.S. leadership in these three categories was more pronounced in the 1993 to 2003 period, accounting for 48 percent of first-in-class drugs, 52 percent of biotech drugs, and 55 percent of orphan drugs.

Source: Grabowski and Wang, *Health Affairs* (2006)

— All NCEs - - - First-in-class NCEs
 Global NCEs - . - Orphan NCEs
 - - - - - Biotech NCEs

Year	All NCEs	Global NCEs	First-in-class	Biotech	Orphan
1982	36	10	5	0	1
1983	34	17	4	0	1
1984	34	9	4	0	2
1985	59	17	5	2	2
1986	47	19	5	1	1
1987	57	15	5	0	1
1988	51	17	6	2	3
1989	39	18	4	2	1
1990	37	19	5	1	2
1991	45	21	5	7	2
1992	43	17	5	4	4
1993	38	18	2	1	4
1994	42	15	3	5	4
1995	41	20	6	6	3
1996	44	29	6	7	5
1997	50	27	5	3	4
1998	45	25	10	14	6
1999	41	21	6	7	5
2000	39	11	5	4	6
2001	33	20	6	13	5
2002	35	--	7	4	4
2003	29	--	6	7	3

Figure 5-1. Annual Introduction on new chemical Entities (NCEs), by category, 1982-2003.

of novel drug categories. A more detailed list of these new classes and early entrants for the U.S. market is provided by DiMasi and colleagues⁹.

The 1982-1992 sub-sample period saw the introduction of several new classes that addressed disease areas with few or inadequate treatments (e.g. the nucleoside reverse transcriptase inhibitors to treat HIV infections, the quinolones and the extended spectrum macrolides to treat bacterial infections, and various new classes such as taxanes to treat cancers). In addition, new classes were introduced that improved treatment effectiveness and patient tolerability for widespread medical problems such as depression, cholesterol reduction, migraine, and GERD (e.g. the SSRIs, statins, triptans and proton pump inhibitors).

Notable therapeutic advances in the 1993 to 2003 period included the introduction of protease inhibitors that were used in combination with nucleoside and non-nucleoside reverse transcriptase inhibitors for HIV infection. These antiretroviral combination protocols revolutionized the treatment of AIDS¹⁰. In addition, several new classes of cancer treatments were introduced that included the topoisomerase-I inhibitors for colorectal cancer, the tyrosine kinase inhibitors to treat leukemia, and the epidermal growth factor receptor kinase inhibitors for various types of cancer. Other new classes of drugs introduced during this period included the selective estrogen receptive modulators to treat osteoporosis, the angiotension-receptor blockers for hypertension, the glycoprotein IIb/III antagonists to treat acute myocardial infarction and unstable angina, and the carbonic anhydrase inhibitors to treat glaucoma.

In constructing the category of first-in-class drug introductions, G&W used a unique combination of the ATC and USC classification codes. This permitted a more representative grouping of new classes than utilizing either source individually. One limitation was the fact that both classification codes were only available for drugs approved and marketed in the United States. Given the size and significance of the U.S. market, there are strong economic incentives to introduce important new classes of drugs in the United States. However, some new classes of drugs introduced first in Europe or Japan may not have been available in the United States by 2003, especially if they were launched toward the end of our sample period. To check for the possibility of such omissions, I have examined additional information sources for the sample of drugs that are available in the United Kingdom or Japan since 1982, but were not available in the United States before 2003¹¹. I also considered whether any drugs that qualify as first-in-class drugs under our criteria were available worldwide before 2003 and subsequently introduced into the United States from 2003 through October 2009. These supplementary searches yielded one additional first-in-class drug that was assigned to Europe based on the nationality of the firm discovering and introducing this product¹².

Biologics

The biotech industry is a relatively new source of medical innovation. The first wave of biotech products focused on recombinant forms of natural substances. The initial approvals were for synthetic human insulin in 1982 and human growth hormone in 1985. This was followed by a number of advances in the first decade of biotech products. Other notable biologicals during this first decade included erythropoietin, used extensively

for dialysis patients and as supportive care for cancer and AIDS patients, filgrastim for neutropenia, and interferon alpha indicated for hepatitis C and leukemia.

The growing contribution of the biological sector is particularly evident in the 1993-2003 period. A newer class of biotech products focused on monoclonal antibodies and other types of proteins. These products were targeted to many life threatening diseases and illnesses with high unmet need. For example, the TNF inhibitors introduced in the late 1990s have approved indications for rheumatoid arthritis, psoriasis and Crohn's disease. Several of the new monoclonal antibody introductions in the oncology area have played a significant role in improving survival. These new products included the introduction of rituximab in 1997, trastuzumab in 1998, and bevacizumab in early 2004¹³. As discussed further below, these first-in-class and new biological products were disproportionately discovered in the United States, but often developed in collaboration with both U.S. and foreign headquartered companies.

Orphan Compounds

The number of orphan products also dramatically increased in the wake of the 1984 Orphan Drug Act in the United States. This law provided tax credits and market exclusivity incentives for products targeting rare diseases. Japan passed orphan drug legislation in 1993 and the European Union in 1999. Some of the notable orphan drug introductions since 1982 include therapies for multiple sclerosis, Gaucher's disease, and rare forms of cancer. Most of the new orphan drugs introduced in the United States are rated as important therapeutic advances by the FDA, and several qualify for the accelerated approval and fast track programs¹⁴.

To address whether these are orphan products currently available in Europe and Japan but not in the United States, I examined all orphan products for the European Union and Japan, based on lists of approved orphan drugs for these countries. For these compounds, I first identified whether the product was a new molecular entity and also that the first-approved use was an orphan indication as in our earlier study for U.S. approvals. This yielded two additional orphan products assigned to Japanese firms and one additional orphan product assigned to an EU firm¹⁵.

Global or Consensus Drugs

As discussed, global drug introductions drugs launched in a majority of the world's largest markets have been utilized by a number of past researchers as an indicator of a drug's commercial and therapeutic importance. This measure also can reflect marketing capacity and multinational structure of the originating organization compared to more selective measures such as first-in-class drugs. One limiting feature of our prior definition of global NCEs is that European countries make up four of the seven G7 countries that we used as the benchmark countries in our prior analysis. This gives European countries the greatest weight in the consensus measures. In particular, in our prior study, a drug could be considered global by diffusing only through the four largest markets of Europe. Although the United States and Japan constitute the two largest pharmaceutical

markets, they receive only two “votes” while the much smaller European country markets receive four votes out of seven in measuring global introductions. When focusing on Europe as a single entity and drawing comparisons with the United States and Japan as in the current analysis, a more selective measure of global introductions is warranted.

In the analysis which follows, I define a global drug as one that must be marketed in six of the seven largest markets. This means that even for those drugs introduced in the four European countries, it must still be introduced in at least two of the other three G7 countries (United States, Japan and Canada) to be considered a global drug. Under this definition, there are 256 global drugs, or roughly 30% of the full sample of 919 worldwide introductions over the 1982 to 2003 sample period. This compares to 385 NCEs or roughly 40% of total introductions that diffuse through four or more of the G7 countries¹⁶. The more selective measure utilized here focuses on drugs representing consensus introductions that are approved in nearly all of the leading pharmaceutical country markets. This should also make the global measures in this analysis a more targeted index from the standpoint of a “must have” addition to the physicians’ therapeutic arsenal in treating patients.

Total Sample of First-in-Class, Biotech, Global and Orphan Drugs

The combined sample of first-in-class, biotech and global introductions, has 380 introductions originating in the United States, Europe or Japan that qualify for one or more of these categories¹⁷. This is the sample of introductions for which I analyze the geographical area of discovery in the current analysis. This sample is also utilized to compare nationality based on the NCE inventor’s region to those based on the introducing firm’s headquarter location.

NCE inventor region versus firm headquarters region

Methodology and Data

To gain further insights on where a particular NCE was invented, I have assembled patent data on the sample of all first-in-class, biotech, global and orphan drug introductions. This data allows determining the inventors and affiliated organizations for each introduction, and correspondingly, the location of the R&D laboratory that originated the drug introduction. This measure is an interesting indicator of innovative performance in its own right, and also allows constructing alternative measures of R&D productivity to compare with those based on the nationality of firms making the first global introduction of an NCE.

As our first data source on patents, I utilize patent information from the United States and the United Kingdom. Both countries allow companies to restore part of the patent time lost in clinical development and regulatory review. The firm can only extend one patent, and this generally will be the core invention that offers the most protection (i.e. the composition of matter in the case of a new chemical entity). Where no patent information is available on a global introduction from these U.S. and UK patent files, I utilize the core patent listed in IMS R&D Focus, as well as information on the originator or

innovation listed in the Pharma Projects, to determine who discovered the drug and the country of origin. I am able to determine inventors and country of origin for all but a small percentage of the total observations in the combined first-in-class, biotech, global and orphan drug samples. For a few cases where this information was missing, I utilize information available on the internet to establish the region of origin. These were generally attributed to foreign rather than U.S. companies¹⁸.

The above approach allows me to identify for each drug introduction in the combined sample: (i) the country or region of discovery using patent data, and (ii) the location of the headquarters of the firm making the first global introduction using IMS New Product Focus database. When there are different companies involved in discovery and introduction, the country of discovery is assigned based on the location of the R&D lab that invented the compound. On the other hand, the headquarters location of the company making the first introduction generally provides information on where the compound's development was supported and carried forward to the point of worldwide introduction. Even when the same company is the discoverer and introducer, these two measures may be different when an R&D subsidiary located in a foreign location is the discoverer of a new compound. However, the "parent company" would still normally play a role in supporting the compound's development. In the current analysis, the region of discovery is the main focus of interest and the firm headquarters region provides a useful point of comparison.

Results

Figure 5-2 provides a summary of our findings regarding the 380 drug introductions that qualify either as first-in-class, biotech, global or orphan drug products for the full 1982 to 2003 period. Figure 5-2 shows that, based on NCE inventor region, the United States is the source of 52% of these worldwide introductions, Europe is the originator of 38%, and Japan accounts for 9%. When the classification is based on the firm headquarters region, the U.S. headquartered firms introduced 46% of these introductions compared to 45% for European firms and 9% for Japanese firms.

Figure 5-2. Combined first-in-class, biotech, global and orphan NCE shares by region.

Table 5-2 provides disaggregated information for each category and subperiod. The percentage shares of the United States based on region of invention are larger than those based on firm headquarters' region for all four categories of novel introductions. For example, if one considers the United States, European and Japanese shares in discovering first-in-class drugs, the United States accounts for just over 50% of these introductions in the 1982-1992 period, increasing to 58.3% in the 1993-2003 period. This compares to invention shares by Europe in the mid 30% over these two periods and shares for Japan that are in the 5-10% range. Clearly, the United States has been the country of origin for these novel first-in-class new therapies, and the United States' prominence has been growing over time.

An even more dramatic picture emerges for biotech products in Table 5-2. In particular, for the 1993-2003 introductions, the United States was the country of origin in three quarters of the introductions. This compares to originating shares of 15.9% for Europe and 8.7% for Japan during this period. My analysis for this category is confirmed in a recent OECD study that examined the country where original development occurred for 138 approved biotherapies introduced between January 1989 and January 2000. The OECD data indicates that U.S. located labs accounted for the initial development of 73.5% of biotherapies, compared to 18.1% for Europe and 8.4% for Japan¹⁹. These values are very similar to the ones we obtained using patent information to determine geographical region of discovery for the period 1993-2003 in Table 5-2.

In terms of the third category of drug introductions in Table 5-2, orphan compounds, a similar pattern is also observed. When orphan drug introductions are classified by geographical region of origin, the United States accounted for over 60% of the orphan drugs in the 1993-2003 period compared to Europe's 33.3% and Japan's 39%. Most of the orphan drugs are concentrated in this period. This strong U.S. leadership

Table 5-2. Shares in First-in-Class, Biotech, Global and Orphan NCEs by Region 1982-1992 and 1993-2003

Type of NCE	NCE Inventor Region (%)			Firm Headquarters Region (%)		
	U.S.	EU	Japan	U.S.	EU	Japan
First-in-Class						
1982-1992	50.9	37.7	11.3	46.2	44.2	9.6
1993-2003	56.7	38.3	5.0	49.2	45.9	4.9
Biotech Drugs						
1982-1992	66.7	16.7	16.7	45.0	30.0	25.0
1993-2003	75.4	15.9	8.7	53.6	33.3	13.0
Orphan Drugs						
1982-1992	55.0	40.0	5.0	50.0	45.0	5.0
1993-2003	62.9	33.3	3.9	54.0	42.0	4.0
Global Drugs						
1982-1992	43.5	49.6	7.0	43.5	51.8	4.6
1993-2003	48.2	41.9	9.9	36.9	57.3	5.8

Source: Author's own analysis.

is reflective of U.S. policy initiatives in this area. It was not only the first country to pass legislation on orphan drugs, but has more generous tax credits and other incentives²⁰.

In the case of global drugs, Europe was the source of discovery for more of these drugs in the 1982-1992 period than the United States (49.6% to 43.5%). However, this pattern reversed in the 1993-2003 period in which the United States discovered more global drugs than Europe (48.2% to 41.9%). Interestingly, firms headquartered in Europe were the first introducers of the most global products in both periods. In the 1993-2003 period, for example, European headquartered firms introduced 57.3% of all global drugs even though only 41.9% were discovered in Europe. By contrast, the United States headquartered firms introduced 36.9% of these global drugs, but the U.S. geographical area accounted for 48.9% of discoveries in this period.

As noted, the shares based on the headquarters location of the introducing company are best interpreted as indicators of development support in those cases when discovery and development takes place in different organizations or locations. Viewed in this way, U.S. firms also emerge as leading developers and introducers of novel new products, but the differences are not nearly as great as those based on the geographical region of discovery. The difference between U.S. and European firms in developing first-in-class drugs is only a few percentage points, whereas European firms lead in developing global drugs (but not in the area of discovery as discussed above). The U.S. headquartered firm leadership is most pronounced as first introducers of biotech and orphan drugs.

These patterns are consistent with several trends described in the industry trade literature. In particular, many European firms focused increased R&D in the United States, both in their own labs and in partnership with U.S. development stage firms. This is reflected in the differences between output measures based on location of discovery versus headquarters of first introducer. For example, for the 17.5 global drugs first introduced by Hoffman LaRoche, only 6 were discovered in Europe whereas 9.5 originated in the United States and 2 originated in Japan. Some of these U.S. discovered drugs originated in its U.S. partner, Genentech, while others were discovered in their U.S. laboratories in New Jersey and California²¹. As another example, Glaxo-Wellcome became the industry leader in new product introductions indicated for AIDS based on research programs in anti-viral drugs located in the United States²². However, all these introductions would be assigned to Europe in classifications based on the location of their European headquarters.

Our results on the importance of the United States as the country of origin for new pharmaceuticals and biotherapies are also confirmed for a much broader class of inventions. Gambardella and colleagues examined the location of inventions for all European patents filed between 1978 and 1997. For the most recent decade covered in their work, 1988-1997, the United States originated a larger share of European patents in both pharmaceuticals and biotherapies than those that originated in all the European countries, and U.S. shares were growing over time. The same report provides an analysis of licensing agreements in R&D, which shows the United States as the primary source of licensing agreements in Europe with shares exceeding those of Europe and Japan from the three regions of U.S., Europe, and Japan²³.

R&D Productivity by region

In a follow-on article to G&W's study in *Health Affairs* in 2009, Donald Light utilized our data on international drug introductions to offer a different perspective on innovative performance across national industries²⁴. In particular, he focuses on R&D productivity by European, U.S., and Japanese firms. He claims that in terms of new drugs introductions per R&D dollar invested, the European industry is ahead of its U.S. counterparts. However, his analysis is subject to a number of conceptual, as well as empirical, issues.

Conceptual and Measurement Problems

Light's R&D productivity measure for the United States, Europe and Japan confounds two different concepts of nationality. His numerator is based on a company's nationality: the number of new drugs accounted for by companies headquartered in a particular country or region. His denominator is area-specific: the R&D performed in a particular country or region by all the domestic and foreign companies operating in that geographical area. If European headquartered companies obtain a higher percentage of introductions from discoveries that originated in the U.S. compared to what U.S. headquartered companies obtain from Europe, Light's method would result in underestimation of R&D productivity in the United States, relative to Europe. Our findings from patent data indicate this is the case.

If one considers the number of drugs discovered or developed in a region divided by appropriately lagged R&D inputs, one would obtain a more consistent means of R&D productivity than Light's measure, which mixes different national concepts. At best, however, R&D productivity measures by nationality can be suggestive and not determinative because there are no data series available that precisely match the values in the numerator with the denominator. All measures are necessarily qualified by the fact that some of the relevant R&D expenditure will not be included in existing industry data (e.g. R&D funded by private equity sources). Furthermore, R&D development often spans multiple countries and it is not possible with existing data to parse out the amounts expended in each country over the R&D life cycle for particular introductions. Given these qualifications, it is still instructive to consider how robust Light's results are to alternative, more plausible formulations of R&D productivity.

R&D Funding Patterns by Region

A second problem associated with Light's R&D productivity analysis is that he uses an inappropriate lag structure for R&D expenditures. In particular, Light divides the 1982-1992 introductions for each national region by R&D expenditures undertaken in the year 1990. Correspondingly, he divides 1993 to 2003 period introductions by R&D expenditures undertaken in 2000.

A central finding of numerous R&D studies is that a lengthy R&D process in pharmaceuticals generally spans a decade or more. In particular, DiMasi et al. observe a

twelve-year period from synthesis to approval for the average new drug approval in the United States²⁵. Moreover, more than half of the out-of-pocket R&D expenditures (including failures) undertaken to discover and develop a new drug are made by year six of this process. Given these facts, the R&D period for 1982 to 1992 introductions would typically cover 1971-1991 with a median year of 1981. Similarly, the R&D process for 1993 to 2003 introductions spans the 1982 to 2002 period with a median year of 1992.

Using R&D expenditures at the end of each period is not only inappropriate given the lengthy R&D process in pharmaceuticals, but it also introduces further problems associated with exchange rate fluctuations. In particular, U.S. exchange rates against the euro were uncharacteristically high in 2000. In Light's analysis, the exchange rate was 1.27 dollars to a Euro in 1990, compared to 0.92 dollars to a euro in 2000²⁶. Exchange rate differences between 1990 and 2000 account for approximately one-half of the increased share of R&D expenditures for the United States during the periods in Light's calculations. Therefore, U.S. productivity values are correspondingly lowered in Light's analysis of the 1993-2003 period as a result of these exchange rate fluctuations.

Using information from the R&D cost studies to construct an appropriate lag structure, I employ a three-year period on regional R&D shares centered around 1981 for the 1982-1992 introductions, and centered around 1992 for the 1993-2003 set of introductions²⁷. Selecting these years for the lag between R&D and NCEs also effectively moderates the exchange rate fluctuations that beset Light's analysis. In particular, the exchange rates for these two periods are roughly comparable and more characteristic of the overall period encompassed by the complete R&D series²⁸.

Figure 5-3 shows the percentage breakdown of R&D expenditures for the United States, Europe and Japan for the relevant periods. Europe accounted for the highest R&D shares in both of the periods. Its share is 50.9% in the 1980-1982 period, and 44.8% in the 1991-1993 period²⁹. Correspondingly, the United States experienced a modest increase in its R&D shares over the two periods (33.1% to 35.7%) as did Japan (16.1% to 19.5%). In contrast, Light's analysis has the United States' share increasing from 33.3%

Figure 5-3. R&D Shares in 1980-1982 and 1991-1993. *Source: Author's own analysis.*

in 1990 to 47.8% in 2000. However, as noted, in using these years to calculate R&D shares for his productivity analysis, he fails to account properly for the long lags between R&D inputs and outputs, and R&D shares are also heavily influenced by the very strong U.S. dollar in 2000.

Proportionality Ratios

One can express a region's R&D productivity measure as a proportionality ratio. In particular, under this approach the shares in the output measures for the United States, Europe and Japan are divided by the corresponding R&D shares for each sub-period. A proportionality ratio above one implies a region's output share exceeds its R&D share, a relative measure of that region's innovative performance.

Figure 5-4 shows the proportionality ratios for the 1993-2003 period. These are obtained by dividing the share of discoveries for the different introduction categories accounted for by the United States, Europe and Japan (from Table 5-2) by the lagged R&D funding shares (from Figure 5-4). As this figure shows, the United States had proportionality ratios in excess of 1.0 in each category (ranging from 1.35 to 2.11), whereas Europe had ratios below one (0.36 to 0.94), and Japan had the worst performance for these novel drug categories (ranging from 0.20 to 0.51). This pattern is generally repeated across all these four classes for the 1982-1992 period. These are shown in Table 5-3.

Figure 5-4. Proportionality Ratios Based on NCE Inventor Region 1993-2003.

Indeed, the proportionality ratios for the United States based on region of discovery increased between the first and second period for all four categories of drug introductions, and are always substantially greater than 1.0 in value, whereas those for Europe and Japan are much smaller in value.

Table 5-3 also indicates that even if one uses an output measure based on headquarters location of the region first introducing a new product, the United States has proportionality ratios above 1.0. By contrast, Europe's ratios are generally smaller and below 1.0 in value. The only exception is for global drugs, where Europe's ratio increased sharply in 1993-2003 in accord with the trend toward greater licensing activity from—and R&D investment in—the United States, as discussed earlier.

The proportionality ratios based on company headquarters location give a different view of nationality. They are more selective indications of drug development support and ownership than drug discovery. In any case, they contradict Light's findings. He concludes that Europe's productivity exceeded that of the U.S. in first-in-class and global drugs in 1992-2003, and that they were catching up to the United States in biotech and orphan compounds. This conclusion, however, was based on an implausible lag structure between R&D and introductions. When a more appropriate lag structure is utilized to compute these measures, the finding that Europe has greater and increasing research productivity in these innovative new drug categories is not supported by the data³⁰.

As previously noted, all R&D productivity analyses must be qualified by the fact that currently available data does not permit establishing exact matches between outputs in the numerator and the appropriate R&D expenditures in the denominator for particular geographic regions. Nevertheless, after making reasonable corrections to Light's productivity analysis, I conclude that his findings are not robust. They do not support his

Table 5-3. Proportionality Ratios Based on NCE Inventor Region and Firm Headquarters Region 1982-1992 and 1993-2003

Type of NCE	NCE Inventor Region (%)			Firm Headquarters Region (%)		
	U.S.	EU	Japan	U.S.	EU	Japan
First-in-Class						
1982-1992	1.54	0.74	0.71	1.40	0.87	0.60
1993-2003	1.59	0.86	0.26	1.38	1.02	0.25
Biotech Drugs						
1982-1992	2.02	0.33	1.03	1.36	0.59	1.55
1993-2003	2.11	0.36	0.45	1.50	0.74	0.67
Orphan Drugs						
1982-1992	1.66	0.79	0.31	1.51	0.88	0.31
1993-2003	1.76	0.74	0.20	1.51	0.94	0.21
Global Drugs						
1982-1992	1.31	0.97	0.43	1.31	1.02	0.29
1993-2003	1.35	0.94	0.51	1.03	1.28	0.30

Source: Author's own analysis.

conclusion that Europe has experienced greater productivity with respect to the quality-oriented NCEs categories.

Conclusions and policy considerations

One of the key new findings of the current analysis is that when new drugs groups, such as first-in-class, biotech, global, and orphan drug products, are collected by country of discovery using data on patented inventions, the United States is the world leader in discovering these innovative compounds. There is net outflow of inventive activity from U.S. R&D laboratories to the rest of the world. This finding is consistent with other recent international comparative analyses sponsored by the OECD and the European Union³¹.

The leadership of the United States in the innovative process, which has grown over time, is reflective of both supply and demand side developments. Since the early 1980s, U.S. industrial policy has fostered many new discovery-oriented firms in the life sciences through public support of basic biomedical research, favorable university technology transfer processes, and highly supportive private and public equity markets. While U.S. institutions promoting these life science entities have been more developed than abroad, other countries are closing the gap, as has been noted in earlier papers³².

On the demand side, the shift toward more innovative introductions in the United States has been fostered by the growth of managed care plans and pharmacy benefit management firms. These plans utilize various instruments—including tiered formularies with differential co-payments, prior authorization, and step therapy—to manage drug benefits. Innovative products with few close substitutes can earn premium prices, but drugs with close substitutes or generic alternatives are subject to strong price competition. Prices in foreign countries are subject to competitive pressure through reference pricing and other approaches, but innovative products generally obtain lower prices than in the United States. Often, new products receive little more than much older products with similar indications but fewer therapeutic benefits³³.

Many studies point out that price controls in particular countries have encouraged imitative type introductions because they under-reward innovation relative to imitation. In addition, countries will often offer more favorable pricing decisions to companies that invest domestically in terms of facilities and R&D. Favoritism or protection of the domestic industry nurtures a more imitative industry. Historically, Japan, France, and Italy have provided prominent examples³⁴. Some firms eventually look beyond the domestic market and produce innovative products that take advantage of global opportunities, but many retain an imitative focus because of price regulation and protectionism. This helps to explain how patterns of poor performance across national industries can persist over time and erode only slowly, even in a globally-oriented industry like pharmaceuticals.

Some observers such as Donald Light imply that price controls in the U.S. market, as practiced widely throughout Europe, would not affect the availability of useful new drug introductions produced globally. His R&D productivity measures are flawed empirically and conceptually, and do not provide support for this position. More importantly, numerous studies indicate that if one lowers the rewards for innovation significantly in

the world's largest market, R&D expenditures will be affected³⁵. This will be true not only for U.S. firms but for foreign firms that plan to market their drugs here. The R&D process is long, costly, and uncertain, and a cut in R&D expenditures will affect both the quality and quantity of new drug introductions on a global basis. Start-up firms and development R&D companies with early stage risky R&D projects are likely to be most adversely affected by such price controls. These firms have been disproportionately located in the United States. Light's advocacy of greater use of comparative effectiveness and cost-benefit analyses is a worthy goal, but there is more to be gained from implementation in a market-based system, insulated from political considerations and bureaucratic implementation.

Public policy toward biopharmaceutical innovation has many interacting parts, including support of basic research and technology transfers, intellectual property protection provisions, regulation of product safety and efficacy, and pricing reimbursement of approved medicines³⁶. No country has a claim to optimal policies in all these dimensions, and these policies are subject to considerable legislative and regulatory changes over time. The U.S. ban on federally supported stem cell research is an example of how policy actions can adversely affect a region's innovative performance and location of new drug discoveries³⁷. Nevertheless, our analysis on where novel new drug discoveries have originated since the early 1980s indicates that, on balance, the United States has maintained the most positive environment to stimulate biopharmaceutical innovation.

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 12. This product was telithromycin (Ketek), a member of the ketolide class which was first introduced worldwide in October 2001 and subsequently in the United States in April 2004.
 13. Bevacizumab (Avastin) was first approved in February 2004 just after the December 2003 sample period of our analysis. For a description of the lengthy development process of bevacizumab, which was first isolated in 1989 by scientists at Genentech, see H. Grabowski, "Follow-on biologics: data exclusivity and the balance between innovation and competition", *Nature Reviews Drug Discovery*, vol. 7 no. 6 (June, 2008), pp. 479-488.
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 17. In addition, there were five introductions originating outside of the United States, Europe or Japan in at least one of these four categories that are not included, as I am focusing on the three regions that dominate pharmaceutical R&D innovation.
 18. After utilizing all the available information from the patent data registries and IMS and Pharma Projects databases on country of discovery, we obtained information on the innovator for six introductions from other internet sources. In these cases where inventors were located in more than one geographical region, we selected the region where the majority of the inventors were located.
 19. OECD Biotechnology Statistics 2009 (<http://www.oecd.org/dataoecd/4/23/42833898.pdf>), p. 85. This analysis utilized Pharma Projects database of drugs to determine the geographical location of initial development.
 20. For discussion of the differences in orphan drug laws for the United States, Japan and Europe, see H. Kettler, "Narrowing the Gap between Provision and Need for Medicines in Developing Countries" (London: Office of Health Economics, 2000) 40-43.
 21. Examples of biotech products discovered by the U.S. partner, Genentech, and introduced worldwide by Roche include rituximab and trastuzumab. Products emerging from its U.S. R&D laboratories in Nutley, NJ and Palo Alto, CA included valganciclovir and mycophenolate mofetil.
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- at Wayne State University, but proved ineffective in this use. Based on the discovery of AZT as an AIDS treatment, scientists in the anti-viral group at Burroughs Wellcome were awarded a method of U.S. patent in 1985 by the U.S. Patent Office. Judy Forman, "3 Share Nobel Prize for Medicine", *Boston Globe*, Tuesday, October 18, 2008, p. 1; H. Grabowski, "Are the Economics of Pharmaceutical R&D Changing? Productivity, Patents and Political Pressures", *PharmacoEconomics* 22, suppl. 2 (2004); 15-24.
23. A. Gambardella, L. Orsenigo and F. Pammoli. "Global Competitiveness in Pharmaceuticals: A European Perspective", (Luxembourg: Officer for Official Publication of the European Communities, 2001) pg. 31, 51. For 1988-1997, the United States was the country of discovery for 44.9% of European pharmaceutical patents and 46.8% of the biotech patents versus 39.8% and 34.2% respectively emanating from European countries (Table 16, p. 38).
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 27. Data series on annual R&D expenditures assembled by the EFPIA, the European Federation of Pharmaceutical Industries and Associations beginning in 1980 are available in PAREXEL'S Bio/Pharmaceutical R&D Statistical Sourcebook 2007/2008, p. 283. Information on R&D expenditures in the United States is available from PhRMA Annual Survey 2007 (Washington, DC: Pharmaceutical Research and Manufacturers of America: 2007). It is also available in PAREXELS Sourcebook on page 4. Information on R&D expenditures in Japan is available from the Japan Pharmaceutical Manufacturers' Association (JPMA) Data Books, various annual editions.
 28. Annual exchange rates for U.S. dollar to Euro in 1980-1982 ranged from 0.98 to 1.39 with a three-year average of 1.16. This compares to a range in annual exchange of 1.17 to 1.30 in 1991-1993 with a three-year average of 1.23.
 29. To check on our approach, we also construct a variable lag model structure for 1993-2003 introductions using all of the R&D expenditure data by origin from the 1982-2002 years. This approach combines the appropriate weights derived from the DiMasi cost study for this 11-year span of introductions, together with the annual exchange rates for the 1982 to 2002 period. The R&D shares are not materially affected for 1993-2003 introductions whether one employs the three-year average around 1992, or alternatively uses a variable lag structure spanning the full 1981 to 2002 period. In particular, for 1993 to 2003 introductions, the weighted variable lag model yields shares of 44.4% for Europe, 37.3% for the United States, and 18.3% for Japan.
 30. I have also analyzed proportionality ratios on all 919 introductions based on the headquarters country's count of introductions in the numerator. These data indicate that U.S., European and Japanese headquartered firms had shares of all drug introductions roughly proportional to the total R&D investment performed by all firms in their home regions during the 1993-2003 period. I have not undertaken an analysis based on the region of discovery for all 919 worldwide introductions using the patent databases. This would be an ambitious undertaking, given that many of these drugs were introduced in only one or two countries and patent databases are likely to be incomplete, especially when considering worldwide introductions from earlier periods. However, there is reason to expect that when regions are analyzed by NCE inventor location, the pattern observed in Exhibit 1 for the combined innovative drug categories would hold for larger samples. This notion is supported by the findings discussed earlier from a large universe of European patent data and licensing agreements.
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