

# The Global Location of Biopharmaceutical Knowledge Activity: New Findings, New Questions\*

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## Abstract

Location possibilities for biopharmaceutical firms are expanding, driven by factors such as falling natural and political barriers to trade and communication, extension and strengthening of patent protection through institutions including the World Trade Organization, and growing supplies of skilled labor and related infrastructure in large, relatively low-cost countries. This paper examines the causes and consequences of this global expansion of knowledge discovery by biopharmaceutical firms. We first discuss the empirical evidence on the extent and nature of this process. We then examine whether this global spread of biopharmaceutical R&D supports or hurts host-country knowledge activity. We conclude that foreign knowledge discovery by biopharmaceutical companies tends to complement, not substitute for, home-country activities.

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## *I. Introduction*

Location possibilities for biopharmaceutical firms are expanding, driven by factors such as falling natural and political barriers to trade and communication, extension and strengthening of patent protection through institutions including the World Trade Organization, and growing supplies of skilled labor and related infrastructure in large, relatively low-cost countries. Issues of activity location are increasingly central to the performance not just of biopharmaceutical companies, but also of their suppliers, customers, and host countries as well. Anecdotal evidence suggests that the outsourcing of economic activity seen in manufacturing, information technology, and business services is now taking place in the biopharmaceuticals sector.

This reallocation of work across countries and institutions may generate significant economic benefits to the US and other economies. For example, drug development is increasingly expensive, and together with publicly funded biomedical R&D is consuming a larger and larger fraction of total R&D effort. Any restructuring of the biopharmaceutical sector that lowers the cost of drug development (or increases R&D productivity) can be expected to flow through into improved performance of firms, lower drug prices, and faster introduction of new products that improve human health. But this globalization of biopharmaceutical activity is not seen as an unambiguous good. Indeed, there is rising concern that global engagement by biopharmaceutical companies harms local workers and the overall economy—much as there has been concern about the home-country impacts of foreign expansion of other industries such as manufacturing and information technology. The following quote from *The New York Times* demonstrates how increasing attention is also being paid to the biopharmaceutical industries:

### *Medical Companies Join Offshoring Trend, Too*

“The exporting of jobs is now spreading to a crown jewel of corporate America: the medical and drug industries...It could be a worrisome sign. The life sciences industry, with its largely white-collar work force and its heavy reliance on scientific innovation, was long thought to be less vulnerable to the outsourcing trend. The industry, moreover, is viewed as

an economic growth engine and the source of new jobs, particularly as growth slows in other sectors like information technology.”

- Andrew Pollack, *The New York Times*, February 24, 2005

What is currently known about the causes, extent, and consequences of globalization in the biopharmaceutical industry—especially its various components of knowledge discovery? This paper offers some new answers to these questions. Previous studies of the location of pharmaceutical R&D have found an important role for agglomeration externalities, proximity to publicly funded science, and related effects in drug discovery. A growing literature has also examined the international scope of product launches for drugs. But relatively little is known about the geography of other knowledge-related economic activities in the biopharmaceutical industry: clinical trials, manufacturing sites, and marketing and sales efforts.

Again, there is rising anecdotal evidence that these activities are increasingly spread across borders, outside the industry’s historical geographic base. But there is little evidence on the causes, magnitude, and impact of this spread. It is also clear that company location decisions are shaped by a broad range of government-policy choices such as reimbursement policies and price controls; basic and scientific education; tax provisions; R&D support; patent policies; safety-review processes; manufacturing-siting regulations; and environmental concerns.

In this paper we discuss recent findings about the globalization of knowledge discovery in the biopharmaceutical industry. Section II discusses the empirical evidence on the extent and nature of this process. Section III then discusses whether this global spread of biopharmaceutical R&D supports or hurts host-country knowledge activity. Section IV concludes.

## *II. Globalization of Biopharmaceutical Research and Development*

The pharmaceutical industry has historically been dominated by multinational companies that engage in significant business activity in many countries and whose products are distributed and

marketed worldwide. While many companies have operated labs and other research facilities in multiple countries, R&D activity has been largely concentrated in the U.S., Europe, and Japan. The transformation of the global economy in recent decades, and in particular the rapid industrialization and changing business environment of many countries suggests that new opportunities have emerged for these companies to conduct R&D in locations with lower costs or opportunities to tap into new sources of human capital. At the same time, new competitors are springing up in these new locations. Companies in countries such as India have grown beyond their roots in manufacturing for their domestic market to become global suppliers of generic drugs, and have become increasingly interested in developing their own new branded products.

The extent to which the global allocation of R&D is changing in response to these forces, and its impact on the U.S. domestic industry, is not easy to assess. For 2008, members of the U.S. trade association for R&D-based biopharmaceutical companies (PhRMA) reported spending almost \$12BN on R&D outside the U.S., and almost 3-fold increase since 2000. But it is easy to misinterpret these figures.

### US PhRMA Members R&D Spending Abroad

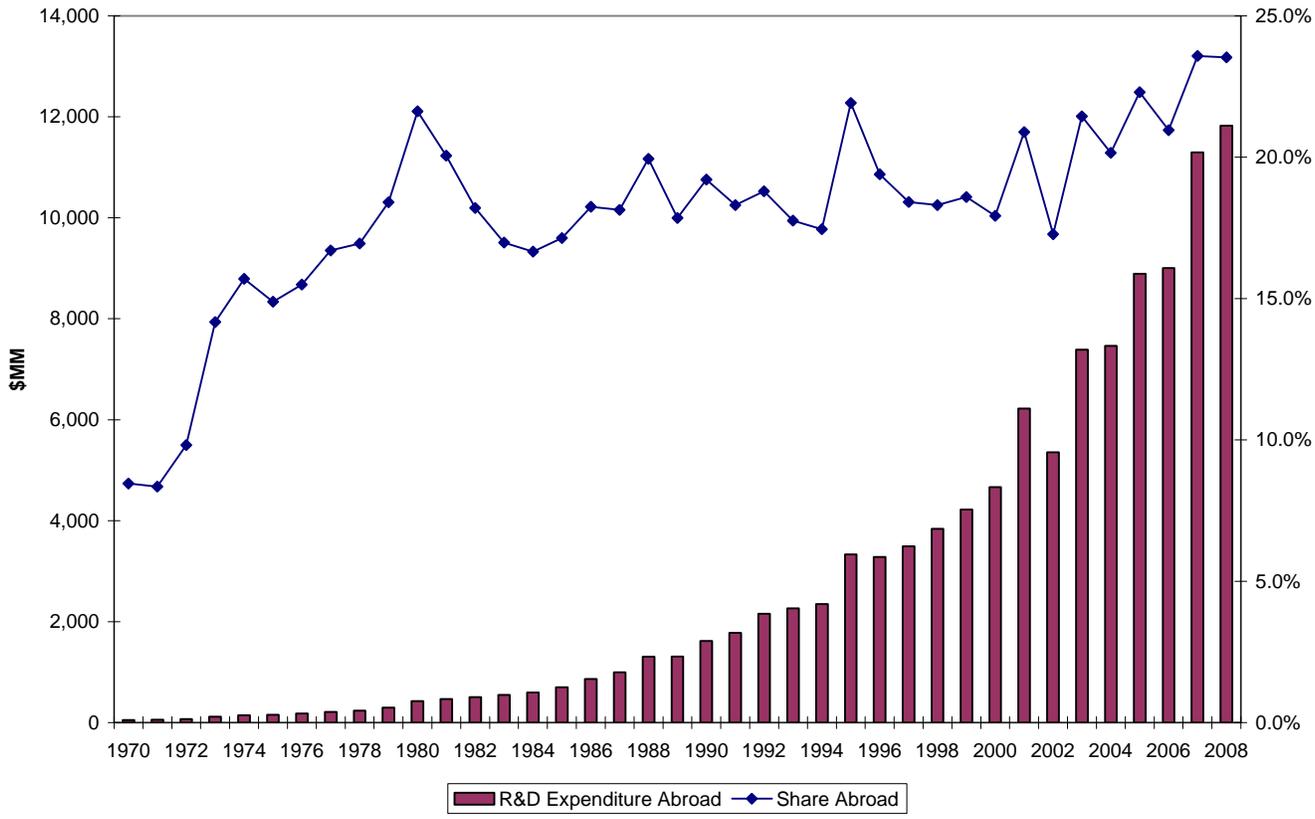


Figure 1 provides some historical perspective: what is particularly noteworthy is that R&D expenditure abroad has been roughly constant 20% share of total R&D since the early 1980s: the growth in “offshore” R&D spending has largely just kept pace with growth in domestic spending. Apparent increases in the “abroad” share since 2000 do, however, suggest some significant geographic reallocation.

Is this a real phenomenon, as opposed to an artifact of particular data sources, and how large is its economic impact? Unfortunately, comprehensive, internationally comparable data on R&D spending or employment of R&D workers in the biopharmaceutical sector collected by government agencies is not available for many countries, or is difficult to interpret, and while individual companies and national or regional trade associations occasionally report R&D expenditures broken out on a geographical basis, these data are not always transparently collected or easy to compare across different sources. Other indicators of R&D activity such as patent filings or operation of clinical trial sites, which are collected consistently across countries and can therefore provide a useful window. We summarize below the evidence from these sources on changing geographical allocation of R&D. Interestingly, there is little evidence of large shifts—to date—in the global allocation of biopharmaceutical R&D away from its traditional locations. Rather, various indicators point to a small but increasing share of R&D taking place in “new” locations, with the volume of activity growing rapidly from a very small base.

Table 1 shows the geographic allocation of private sector R&D spending based on data compiled by the OECD from national statistical agencies. As shown in the table, the U.S. share of total private sector pharmaceutical R&D measured by the OECD fell from 41.5% to 36.5% between 1995 and 2004. But this largely reflects relative gains by European and other developed

countries rather than a shift to emerging markets: the EU-15 countries' share of the OECD total rose from 36.3% to 39.0% over the same period. (Notice also that these shifts were preceded by a period when the U.S. gained share against the European countries.) While the share of "New Europe" and other emerging middle-income economies such as Mexico and Turkey grew dramatically between 1995 and 2004, this was from a very small base, and accounted for less than 2% of total pharmaceutical R&D expenditure in the OECD database.

**Table 1. Business Expenditure on Pharmaceutical R&D by Country**

	1990	1995	2000	2004
Total Business Expenditure on R&D at PPP (current \$MM), of which:	16,853	24,587	33,781	46,216
USA	37.3%	41.5%	38.3%	36.5%
EU-15	39.8%	36.3%	40.4%	39.0%
UK	12.1%	11.8%	13.3%	11.1%
France	6.4%	8.5%	7.8%	7.6%
Germany	8.1%	5.0%	6.7%	7.5%
Italy	5.5%	2.5%	1.9%	1.5%
Sweden	2.1%	2.7%	3.7%	3.6%
Japan	16.2%	14.9%	14.3%	14.8%
Other developed countries <sup>a</sup>	6.7%	6.3%	5.8%	8.0%
"New Europe" <sup>b</sup>	.	0.8%	0.9%	1.2%
Other emerging economies <sup>c</sup>	.	0.1%	0.4%	0.6%

Notes. Sources: OECD Main Science and Technology Indicators Vol. 2006 release 02, and UK Pharmaceutical Industry Competitiveness Task Force: Competitiveness and Performance Indicators 2005.

<sup>a</sup> Australia, Canada, Iceland, Korea, Norway, Singapore, Switzerland.

<sup>b</sup> Czech Republic, Hungary, Poland, Slovenia.

<sup>c</sup> Taiwan, Mexico, Turkey.

In 2004, data for Australia, France, Greece, Japan, Mexico, Sweden and Turkey are inferred from 2003 values and the AAGR of BERD over the past 5 years in that country. In 2003 data for Austria, Denmark, Greece, and Iceland are inferred from adjacent year values and the 5 year AAGR of BERD in that country. The same applies to Austria in 1990 and 1995, and Belgium in 1990. Data for Switzerland may not be consistent over time.

Other indicators of research effort present a very similar story. Table 2 shows the volume of U.S. patent applications for biopharmaceuticals (international patent class A61K) broken down by the country of the patent assignee. Patent applications can be useful indicator of "discovery"

or pre-clinical research activity, though unfortunately due to lags in the patent examination process and in the publishing of pending applications make it difficult to observe activity in the most recent years.

Application date	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	Total
Africa	0.01	0.05	0.05	0.04	0.04	0.03	0.02	0.03	.	.	0.03
Asia	9.93	9.88	9.82	10.74	11.51	11.60	10.03	8.47	8.27	6.93	10.27
China	0.10	0.12	0.10	0.20	0.40	0.50	0.42	0.32	0.31	0.36	0.27
India	0.36	0.38	0.50	0.75	0.95	1.23	1.34	0.94	0.85	0.72	0.79
Caribbean	0.15	0.18	0.38	0.68	0.47	0.34	0.46	1.08	0.22	0.63	0.43
EU-15	23.67	22.94	24.07	23.39	24.09	22.83	20.51	19.02	18.06	17.64	22.63
Eastern Europe	0.40	0.38	0.17	0.39	0.44	0.26	0.41	0.48	0.22	0.45	0.35
Latin America	0.04	0.05	0.15	0.17	0.14	0.17	0.18	0.22	0.09	0.36	0.14
Middle East	1.05	0.93	1.06	1.38	1.15	0.93	0.99	1.21	1.30	1.35	1.10
Other OECD	5.54	6.09	6.83	6.71	7.17	7.68	6.72	6.37	5.50	6.57	6.65
US	59.20	59.50	57.48	56.51	54.99	56.15	60.67	63.13	66.34	66.07	58.39
Total (number of patent applications)	6755	6531	7853	8421	8558	7629	5431	3718	2237	1111	58244

Note that these are applications at the U.S. Patent Office. While the U.S. is the largest and most attractive national market, and therefore patent protection is likely to be sought there for most significant inventions regardless of national origin, these data may underweight activity outside the U.S. Table 3 presents similar data on PCT filings at WIPO, a transnational agency that accepts “placeholder” applications for patents that may be later sought in a very wide range of countries. Here applications are broken down by the priority date of the invention, and the country where they originated.

Application date	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Africa	0.09	0.12	0.12	0.06	0.15	0.14	0.10	0.12	0.17	0.09	0.07
Asia	7.89	7.43	11.41	15.11	11.34	13.04	13.72	15.76	15.82	14.88	14.64
China	0.25	0.21	2.87	5.51	0.80	1.05	1.25	1.44	1.48	1.84	1.97
India	0.02	0.11	0.49	0.39	0.61	1.10	1.52	1.84	2.00	1.93	1.59
Caribbean	0.16	0.19	0.22	0.33	0.26	0.52	0.48	0.31	0.36	0.45	0.41
EU-15	28.03	28.89	27.99	28.26	30.99	29.04	26.69	26.97	28.70	28.20	27.34
Eastern Europe	0.44	0.40	0.58	0.61	0.56	0.78	0.84	1.04	1.03	1.15	1.41
Latin America	0.12	0.07	0.18	0.19	0.26	0.37	0.40	0.38	0.34	0.47	0.64
Middle East	1.40	1.19	1.24	1.10	1.58	1.48	1.84	1.55	1.90	1.80	1.81
Other OECD	7.58	7.72	8.19	7.94	9.60	9.47	9.01	10.02	11.36	11.35	13.00
US	54.30	54.01	50.07	46.39	45.25	45.15	46.93	43.85	40.33	41.62	40.67
Total applications	6429	7488	9010	10904	10615	10579	11314	13615	15073	14953	11092

Table 4 presents a third cut of the patent data, here the table entries are the share of each region in “inventorships” i.e. the number of distinct instances of an individual appearing as a listed inventor on a U.S. patent.

Application date	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	Total
Africa	0.05	0.05	0.07	0.05	0.03	0.02	0.02	0.07	0.02	0.02	0.04
Asia	13.25	12.53	12.25	12.89	13.11	13.74	11.83	10.60	9.02	9.20	12.45
China	0.12	0.22	0.21	0.24	0.49	0.64	0.57	0.38	0.43	0.54	0.37
India	0.55	0.60	0.63	1.18	1.13	1.60	2.17	1.70	0.82	1.28	1.15
Caribbean	0.07	0.07	0.11	0.14	0.05	0.13	0.02	0.06	0.01	0.04	0.08
EU-15	25.88	25.98	26.87	25.52	27.37	25.14	23.21	21.56	22.37	21.99	25.28
Eastern Europe	0.92	1.22	0.98	0.80	0.93	0.74	0.77	0.91	0.63	1.12	0.90
Latin America	0.15	0.13	0.25	0.38	0.27	0.19	0.37	0.21	0.17	0.54	0.25
Middle East	0.80	0.89	0.93	1.11	1.08	0.74	0.74	0.99	1.25	1.01	0.93
Other OECD	6.12	6.43	6.74	6.20	6.46	7.24	7.07	7.35	6.28	7.41	6.66
US	52.75	52.71	51.82	52.92	50.70	52.06	55.96	58.25	60.24	58.67	53.41
Total Inventors	22177	21287	25814	28583	29906	27438	20524	14098	8580	4466	100.00

All three tables are very much alike, and illustrate the global dominance of the U.S. in drug discovery activity: US-based assignees and inventors are responsible for about half of global patenting, with the EU-15 countries making up a further 25-30% of the total in any given year. Only in the PCT applications (Table 3) is there any suggestion that the U.S. is losing ground: here the share of the U.S. has fallen quite substantially since the late 1990s, largely accounted for by the growth of PCT filings originating in Asia. (Note that China and India are small components of total activity: the Asia category is dominated by Japan with about 10% of global biopharmaceutical patents.) PCT filings present a wider picture of global patenting activity, but we should be cautious in interpreting these data: not all applications will mature into issued patents that meet standards of patentability in the U.S. or Europe, and some of these inventions

may be products or technologies that have limited relevance for the U.S. based industry which is focused on creating new products that meet stringent standards for safety and efficacy.

Table 5 presents some evidence on the challenging allocation of research at a different point in the drug development process: clinical trials. As documented by Berndt et al. (2009), clinical trials are the largest single component of pharmaceutical R&D, and are increasingly global in nature, with a single trial enrolling patients in as many as several hundred distinct sites spread across multiple countries. As the industry has moved towards a standard practice of publishing trial protocols in open registries, the number of and location of these sites has become visible, providing another useful window into the location of research activity.

Table 5 breaks down trial sites by region and the start date of each trial for more than 11,000 industry-sponsored clinical trials of drugs and biologics.

Time Period/Region	2003	2004	2005	2006	2007	2008	Total	ARAGR 2003-08
North America	61.2	60.4	57.0	51.9	50.2	50.7	54.2	-3.7%
Western Europe	22.5	24.3	24.2	22.9	23.1	22.9	23.3	0.3
Oceania (incl. Japan)	3.1	3.1	3.2	4.4	4.8	4.3	4.0	6.7
<i>Total Traditional</i>	<i>86.8</i>	<i>87.7</i>	<i>84.3</i>	<i>79.2</i>	<i>78.2</i>	<i>77.9</i>	<i>81.4</i>	<i>-2.1</i>
Africa/Middle East	1.5	1.6	1.6	1.9	1.8	1.6	1.7	1.6
Asia (excl. Japan)	2.1	2.0	3.4	4.2	5.0	5.0	3.9	16.8
Eastern Europe	6.2	6.1	7.3	10.0	10.5	10.6	8.9	10.7
Latin America	3.4	2.5	3.3	4.7	4.6	4.8	4.1	7.1
<i>Total Emerging</i>	<i>13.2</i>	<i>12.3</i>	<i>15.7</i>	<i>20.8</i>	<i>21.8</i>	<i>22.1</i>	<i>18.6</i>	<i>10.2</i>
<i>Global Total Sites</i>	<i>25313</i>	<i>30973</i>	<i>33546</i>	<i>54018</i>	<i>49005</i>	<i>44003</i>	<i>236858</i>	

As with indicators of pre-clinical R&D activity, the U.S. dominates global activity in clinical trials, accounting for more than half of all sites.<sup>1</sup> The “traditional” regions (U.S., Europe, and Japan) together account for of 80% of global clinical research, by this measure. Note however that the share of the emerging regions has grown substantially. Over the five years 2003-2005 the traditional regions share in activity fell at about 2% per year, while the emerging regions share in activity grew at about 10% per year. Much of the expansion in activity outside the traditional locations is in Eastern European countries and Asia.

What explains these observations? Research in management and economics has identified a number of factors that may affect R&D location decisions. In many respects, R&D may be easier than some business activities to move across different locations. However location decisions reflect complex tradeoffs. On the one hand, R&D is increasingly less tightly bound to other functions of the firm. Pharmaceutical companies have always been able to operate R&D facilities largely independently from other functions: though a typical large pharmaceutical firm operates as an integrated economic entity, it normally conducts R&D in multiple locations around the world. The nature of the product development process, along with historically strong intellectual property rights, and relatively straightforward licensing practices has allowed pharmaceutical companies to “decouple” manufacturing and marketing from R&D. This has been the case for many decades, but increased vertical disintegration in R&D activities since the mid-1980s has further relaxed organizational constraints on the location of research activity, permitting extensive geographic reorganization of R&D across countries and regions, as well as vertical reorganization within firms. In the US, for example, “upstream” firms specializing in new technologies for drug discovery are now often located in different locations (such as Boston

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<sup>1</sup> There may be some “home bias” in this data source (clinicaltrials.gov) which is maintained in English by the National Library of Medicine. Data submissions reflect both FDA requirements, and a policy instituted by editors of the world’s leading medical journals, but likely under-represent trials which the sponsor does not intend to publish in an international journal, or does intend to use as part of an FDA submission.

and the San Francisco Bay area) than those historically used by the “big pharma” firms concentrated in Philadelphia, New Jersey, Connecticut, and the mid-west.

Yet other considerations suggest that firms are not free to relocate. Economies of scale and scope in performing R&D, the presence of internal knowledge spillovers, and costs of coordinating activity across dispersed units suggest that, all else equal, firms should limit geographic dispersion of R&D. Furthermore while some locations may be more intrinsically economically attractive because of lower costs, access to government subsidies, or favorable tax treatment of R&D, these factors may be dominated by the benefits conveyed by proximity to centers of academic excellence and other forms of non-commercial research. Co-location with academic science or a “cluster” of producers of complementary technologies also appears to raise research productivity, see Furman et al. (2006.) Note also that these economic factors tending to concentrate R&D are offset by political considerations. In some countries, pharmaceutical companies face strong political pressure to maintain domestic R&D. Some countries, such as the UK, have explicitly linked the stringency of price regulation to local R&D spending levels, in other cases, such as Canada, local R&D spending reflects a political bargain to avoid compulsory licensing.

Historically, the US has been perceived by the industry as a very attractive location for pharmaceutical R&D because of its very limited use of price regulation and government purchasing, and strong patent rights. In contrast, in the late 1990s, EU governments became very concerned that overly aggressive price controls and hard bargaining by state purchasers were driving away investment in pharmaceutical R&D and adversely affecting the competitiveness of EU-based companies, though there is little evidence (see Table 1 above) of any major shift in R&D spending away from Europe. Episodes such as Canada’s experience with compulsory licensing of pharmaceuticals in the 1970s and 80s, or more recent examples

such as the periodic heated disputes between OECD-based companies and governments of developing countries over pricing of anti-retroviral drugs suggest that R&D location decisions can be quite sensitive to government policies directed at lowering the cost of acquiring pharmaceuticals. Notwithstanding its long tradition of excellence in medical and pharmaceutical research, and substantial historical investments by multinational drug companies, Canada experienced a steep decline in domestic R&D activity in pharmaceuticals when it introduced its compulsory licensing regime. Only when full patent rights were restored, and a relatively loose drug price regulation scheme was instituted did commercial R&D spending return to previous levels. Countries such as Australia, which have relatively stringent drug price controls, continue to face major challenges in attracting significant R&D investment by multinational drug companies, in spite of strong academic research capabilities, an attractive business environment, and substantial public support of commercial biomedical research.

Beyond these “price” drivers, several other factors have been identified as influencing R&D location decisions. These often work through indirect, or unpriced, effects such as knowledge spillovers that are conveyed by “open” publications, geographic proximity, or communication through informal professional networks rather through economic transactions. For example, drug discovery labs sites tend to specialize in therapeutic areas or scientific disciplines and since proximity to publicly funded science appears to be an important determinant of research productivity, these often reflect local academic centers of excellence in particular fields. Furman et al. (2006) show that patenting by pharmaceutical companies is positively correlated with the volume of academic publications by “local” public sector scientists. The very substantial levels of publicly funded biomedical research in the US, the UK, and some other countries has therefore played an important role in sustaining similarly high levels of commercial investment in drug discovery in these countries.

More generally, like other knowledge-intensive activities, discovery research appears to display substantial agglomeration externalities. Drug discovery activity tends to “cluster” in a small number of locations around the world: many major discovery labs are located in the New York/New Jersey/Connecticut SMSA, Boston, the San Francisco Bay area, the suburbs of Philadelphia, Research Triangle in North Carolina, the Rhine Valley, the suburbs of London, Stockholm, and Tokyo/Kansei. These are conspicuously not low cost locations, so this clustering suggests substantial offsetting economic benefits derived from being co-located with other firms. Beyond the role of localized knowledge spillovers, benefits from co-location with other pharmaceutical firms include access to skilled labor and “infrastructure” in the form of specialized services and suppliers, and efficient interaction with collaboration partners.

A final factor that may affect R&D location decisions is the strength of intellectual property protection. Though there is no obvious connection between the degree of patent protection in the local product market and the productivity of R&D conducted in any given country, the nature of a country’s IP regime appears to affect multinationals’ willingness to conduct R&D activities there. This may be because weak patent protection for products often correlates with weak legal protection of other forms of IP such as trade secrets and associated contractual agreements with employees and suppliers, and limited avenues to enforce these rights. Both patent and non-patent protection of intellectual property play an important role in maintaining exclusive access to, and control over, proprietary knowledge, and in countries with weak IP companies may have well-founded concerns about “leakage” of valuable information to local competitors. Zhao (2006) argues that weak IP regimes need not deter R&D investment by multinationals: absent strong IP rights, companies can nonetheless develop alternative mechanisms for realizing returns on innovation and intellectual property. These mechanisms include rapid “internalization” of knowledge through efficient internal organizational processes and control of complementary

assets, and may make it possible to profitably exploit low prices of R&D inputs and underutilized domestic innovation capabilities. However, this argument is most appealing for technologies that have a substantial tacit component, are strongly complementary to other protected assets held by the firm, and have rapid development cycles. This is not the case for pharmaceutical R&D, where results from R&D are often easy to “externalize” and imitate, and product lifecycles are measured in decades.

Not surprisingly, therefore, R&D activity in pharmaceuticals has historically been concentrated in countries with strong and enforceable IP and has only just begun to grow in countries that have recently adopted OECD-style patent systems under the provisions of the TRIPS agreement. Compliance with TRIPS requires all WTO members to (ultimately) adopt key features of the patent systems of wealthy industrialized countries, such as a 20 year term, non-discrimination across fields of technology and nationality of applicants, and effective enforcement procedures. Strong patent protection for pharmaceuticals is controversial in many of these countries (see discussion of India in Cockburn, 2008) and the degree to which domestic political pressures will limit the enforceability of patents, or push the limits of the TRIPS agreement by, for example, instituting compulsory licensing of drugs remains to be seen. Patent rights obtained by multinationals in countries such as India give these companies the ability to exclude generics, and set prices above marginal cost. But patents also provide protection for domestic firms conducting R&D, and political choices to weaken or limit patent protection on the products of multinationals may have serious consequences for nascent research sectors in these economies.

An ongoing NBER project is investigating a number of additional aspects of the economics of location of biopharmaceuticals. We now briefly describe some key findings.

Thursby and Thursby (2008) provide direct survey evidence on managers' motivations to globalize R&D activity. Asked to rate the importance of a variety of factors influencing location choice, R&D managers in this sample rated IP Protection, access to qualified research personnel, and opportunities to collaborate with local universities much more highly than cost advantages or absence of regulatory restrictions.

Arora, et al (2008) focus on the development of the Indian pharmaceutical industry, and in particular the impact of the dramatic shift in India's patent policy following the TRIPS agreement. Analysis of the market valuation of Indian pharmaceutical companies as the TRIPS reforms began to "bite" show a very strong effect of patent reform. Domestic firms which had developed internal research capabilities, and who had external collaborative linkages to other (multinational) research-intensive firms saw a very substantial increase in stock market valuation, while those with limited accumulated R&D investment or an inward focused business model paid a penalty. Host country policies thus play an important role in shaping the global R&D decisions of companies.

Fabrizio and Thomas (2008) examine the importance of "local" knowledge, specifically knowledge about the structure of demand, as a driver of R&D decisions. They find that the number of new drugs introduced in a country is strongly affected by the producer's degree of knowledge/experience in the local market, as opposed to more general knowledge from experience in foreign market, above and beyond the effect of its local technological expertise.

Argyres, Breugmann, and Furman (2008) focus on the impact of cross-border mergers and acquisitions on R&D choices. Mergers are important mechanisms for accessing the "knowledge capital" or R&D capabilities of competitors or partners. Contrary to earlier work which appeared to show that merger activity results in a scaling back of R&D, in this paper M&A

activity is found to result in higher levels of collaboration and an increase in innovative output in some of the labs of acquired firms.

This new research both supports some existing ideas, and points to the complexity of the phenomenon. One clear common theme emerging from these studies is that the global allocation of R&D expenditure, though quite “sticky”, may also be sensitive over the long run to aspects of the policy environment (IP rules, competition policy, price regulation, etc.). Importantly, the “big bucks” continue to be spent by multinational companies, which respond to changes in the overall international policy environment, rather than just domestic considerations.

### *III. Host-Country Evidence on the Globalization of Knowledge Creation: Are Good Jobs at Good Wages Being Exported?*

As Section II of this paper has documented, biopharmaceutical companies are increasingly spreading around the world their various knowledge-discovery efforts. An increasingly pressing question this raises is the home-country impact of this global engagement. Recall the quote from Section I, and the question it poses of whether biopharmaceutical companies are exporting abroad their key knowledge-creation and related activities. Critics contend that multinational companies—in biopharmaceuticals and many other industries as well—have abandoned the United States and other host countries, and that policy needs to rebalance their domestic and international operations. Such charges have been leveled for many years, with the accusations of the 2004 U.S. presidential campaign of “Benedict Arnold” CEOs exporting jobs persisting to today where the deep recession has boosted fears about good jobs at good wages.

This section addresses the empirical evidence on how expansion abroad by multinational companies affects their home-country activities. First, it will review the international-trade literature on globalization and innovation. Next, it will first examine this question from the

broad perspective of the theory and empirical evidence of multinational companies in all industries. Finally it will then turn to what (limited) evidence exists for answering this question specifically for biopharmaceutical companies.

*A. Theoretical Perspective on Globalization and Innovation*

The benchmark Heckscher-Ohlin trade theory has guided much of the research in international trade for decades. But this benchmark is lacking in two important respects: the assumed exogeneity both of national factor endowments and of production technologies.

There is now a substantial theoretical framework in international trade on the channels by which globalization shapes the incentives of a country's firms to innovate. Central to this work has been formalizing the choice of forward-looking, profit-maximizing firms to invest in R&D—versus the Heckscher-Ohlin assumption of exogenous technological progress. Attention has been paid to the fact that outputs of innovation efforts, i.e., new technologies, are typically non-rival and at least partially non-excludable, and can be either specific or general in terms of their applicability. These features all inform the innovation efforts chosen by firms, such that observed R&D spending is an equilibrium outcome. At the same time, much of this work has embedded the innovation choice into Heckscher-Ohlin general-equilibrium foundations, such that the new focus on the dynamics of factor accumulation and discovery efforts can augment traditional emphases such as the pattern of specialization and returns to factors of production.

Much of the seminal work on innovation and globalization was done by Grossman and Helpman (1991). The main implication of their and related work is twofold: (1) there are multiple dimensions of global engagement for a country and its firms, and (2) different channels of global engagement can have different impacts on incentives for innovation efforts—contrary to much of the popular discussion that presumes many, if not all, channels reduce the incentives for R&D in advanced countries like the United States.

One important dimension of globalization and innovation is the greater ability to exchange information across borders—through market transactions of customers and suppliers and the related process of industrial learning, and also through non-market channels as well. The recent explosion of connectivity thanks to the Internet and related technologies is a vivid example of this. In theory, international information exchange can boost innovation efforts in all countries by reducing their cost of research: R&D scientists can be more productive because of their access to larger stocks of existing ideas. The extent of this boost for each country, however, depends crucially both on the degree to which pools of knowledge are global rather than national and on the country's research history. For a country like the United States that has a long history and institutions of R&D activity, with less-than-global pools of knowledge—e.g., if there are large benefits of geographic proximity of researchers—comparative advantage in innovation will be more likely to continue. For countries without such institutions and history, hysteresis may impede greater innovation.

A second link from greater global engagement to greater innovation effort can be the pressure of international competition through freer trade and/or FDI. Trade and FDI tend to make product markets more competitive, which in turn can force researchers to increase effort—in particular, to avoid duplicating innovations created abroad and thus facing smaller returns on those innovations. Integration of product markets can thus spur innovation efforts to seek those larger and hopefully higher-return market opportunities.

Consistent with many of the current business-policy concerns, however, through other channels the incentives of a country's firms to innovate can be dampened by greater global engagement. One such channel is national factor markets. All dimensions of globalization—trade, FDI, immigration, etc.—can alter a country's returns to its factors of production. This, in turn, can alter the costs of innovation effort. If globalization raises the returns to a country's

skilled workers, then its innovating firms face higher costs (more-expensive knowledge workers). This possibility resonates with many U.S. anecdotes today, where against the backdrop of rising returns to skills in the U.S. labor market since the late 1970s many companies are today arguing that (quality-adjusted) costs of R&D are substantially lower in newly integrating countries like China and India. In turn, these relative costs of R&D activity are ultimately determined in part by national relative supplies of these skilled workers—again, a point that resonates with discussion of international differences in tertiary graduation rates. Thus, comparative advantage in innovation can evolve dynamically, with no guarantee against country switches.

Another dimension of globalization and innovation with ambiguous impacts on a country's innovation activity is the spread of global production networks, especially those within multinational firms. If multinationals are important vehicles by which ideas transfer across borders, then the expansion of international production mediated by multinationals can entail the expansion of innovation capacity as well. In theory, firms in the FDI-host country (which may in fact be affiliates of the multinationals headquartered in the FDI-sending country) may start innovating more—in particular, imitative activity—and may thereby reduce returns to innovation elsewhere. This logic clearly resonates with many real-world examples cited in the introduction.

But the net effect on multinationals' innovation activity in the home country—and whether more innovation abroad necessarily substitutes for innovation at home—could run in the other direction. In particular, surviving multinational parents at home may now enjoy higher returns on innovation thanks to facing less competition and thus lower costs in home labor markets for knowledge workers. This possibility accords with the “knowledge capital” framework of multinational firms (see Markusen, 2002, for an overview), which assumes high-productivity knowledge assets are generated in parents and then transferred to host-country affiliates.

More recent research on innovation, productivity, and global engagement has added firm heterogeneity into general-equilibrium perspectives. This new line of inquiry has been motivated by the emerging empirical evidence that in many countries firms exhibit a large degree of heterogeneity in TFP and related performance, and also that globally engaged companies tend to be more productive. For example, Eaton and Kortum (1999, 2002) have addressed how innovation incentives are shaped by global engagement, but with the added richness of distributions of firm outcomes within sectors.

Related to this, a set of recent papers has built general-equilibrium models where heterogeneity in productivity is due to exogenous draws. Firms with better draws can cover the costs of entering export markets or, if especially good, the even higher costs of becoming a multinational by establishing a foreign affiliate.<sup>2</sup> In these models, trade liberalization (e.g., lowering ad valorem tariff rates) alters the within-industry productivity mix. Despite different causal forces at play in different models, a common prediction is that liberalization forces the least productive firms to close while expanding the market shares of more-productive firms; on net, industry average productivity rises.

That said, these papers do not explicitly model the innovation decisions of firms, which are presumably in the background of TFP outcomes. Yet predictions of how policy liberalizations can alter the within-firm distribution of productivity suggest related predictions for the related within-firm distributions of innovation effort.

### *B. The Global Engagement of Multinationals Generally Complements Their Home Activities<sup>3</sup>*

Much of the public-policy discussion surrounding multinationals presumes that expansion and engagement abroad necessarily substitutes for home activity—in particular, for employment and capital investment. Some have argued that as multinational affiliates expand operations

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<sup>2</sup> Recent models tracing heterogeneous productivity to global engagement include Bernard, Eaton, Jensen, and Kortum (2003); Melitz (2003); and Helpman, Melitz, and Yeaple (2004).

<sup>3</sup> This section draws extensively from Slaughter (2009), with slight edits.

abroad, they simultaneously reduce activities in parent operations back home. Is this substitution idea accurate? The short answer is no. There are three crucial features of company operations that the substitution idea alone misses: *complementarity, scale, and scope*. Consider the effect of each on employment, from the perspective of a U.S.-based multinational company.

- For some given level of firm-wide output, when firms employ many kinds of workers and many non-labor factors of production as well then affiliate and parent labor can often be *complements*, rather than substitutes, in which more hiring abroad means more hiring in the United States as well.
- As discussed in the previous section, affiliates generally expand to access foreign customers and/or to save costs. Both these motives allow multinationals to expand their *scale* of output—both abroad and also in U.S. parents, which can often mean more hiring in the United States as well.
- Affiliate expansion is likely not only to boost firm scale but also to refine the mix of firm activities across parents and affiliates. U.S. parent employment can rise as they expand their *scope* into higher value-added tasks such as R&D, finance, and general management.

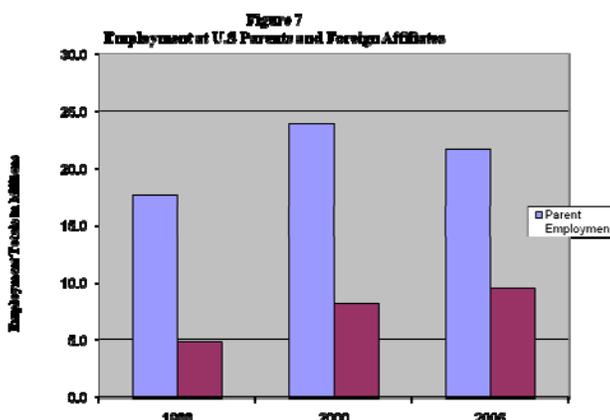
The total impact of affiliate expansion on U.S. parent activity is clearly more complex than the overly simplistic story of straight substitution. The net impact depends on the predominance of substitution versus complementarity, on scale effects, and on scope changes.

For many businesses there is no inherent substitution possibility between foreign expansion and U.S. operations, but rather an inherent complementarity. This is particularly true for many services: e.g., the distribution activities of wholesale and retail trade must be performed in close proximity to final customers, and affiliate expansion here tends to boost many parent activities like logistical management and technology support. This complementarity often arises in

manufacturing as well: e.g., in cross-border networks, in which different stages of production are located in different countries with output levels moving in tandem in all locations.

But the ultimate proof lies in the empirical evidence. Both aggregate and company-level statistics show that foreign-affiliate expansion tends to complement U.S. parent employment, investment, and sales as well.

Start with the aggregate evidence. Using data from the U.S. Bureau of Economic Analysis, Figure 2 reports total employment in U.S. parents and majority-owned foreign affiliates in three years of the past generation: 1988, 2000, and 2006 (the most recent year of available data).



From 1988 through 2006, affiliate employment rose by 4.7 million workers, from 4.8 million in 1988 to 9.5 million. Over that same period parent employment in the U.S. rose by nearly as much: 4.0 million, from 17.7 million to 21.7 million. *This broad pattern of rising employment globally suggests that employment at U.S. parents and foreign affiliates tend to be complements.*

A similar picture of complementarity is given by capital expenditures. From 1988 through 2006, affiliate capital spending rose by \$106.6 billion, from \$46.6 billion to \$153.2 billion. Over that same period parent capital spending in the U.S. rose by two and a half times that amount: \$265.4 billion, from \$177.2 billion to \$442.6 billion. *This broad pattern of rising capital investment globally suggests that investment at U.S. parents and foreign affiliates also tend to complement each other.*

The broad evidence of the above figure is not to say that every single expansion abroad by U.S. multinationals leads to expanded home activity. It is also not to say that every single year, affiliate and parent activity moves in tandem. The employment statistics of Figure 2 show this quite clearly. 1988 to 2000 was a period in which the total affiliate employment increase of 3.3 million (from 4.8 million to 8.1 million) was nearly doubled by U.S. parents as their total payrolls rose by 6.2 million (from 17.7 million to 23.9 million).

2000 to 2006 was a different period, however. As overall affiliate employment rose by 1.3 million, overall parent employment fell by 2.2 million. What accounts for the fact that from 2000-2006, aggregate U.S. parent employment has fallen while aggregate foreign-affiliate employment has continued to rise? Disaggregating by industry reveals a pattern not of affiliates hollowing out parents, but rather of different business cycles and overall business environments facing U.S. parents and affiliates.

First, 67.5% of the 2000-2006 employment increase in foreign affiliates was accounted for by just three industries—retail trade (+340,900), business administration and support services (+288,600), and food and accommodation services (+265,500)—that are the very sort of businesses discussed earlier in this chapter where reaching foreign customers necessarily happens through affiliates, not exporting, and where foreign expansion tends to complement parent activity, not substitute for it. Indeed, over this time period U.S. employment was rising for parents operating in both retail and food/accommodations, and was down only slightly for parents operating in business administration and support services.

In the U.S. parents, several major industries experienced moderate employment declines post-2000. Manufacturing parents experienced a very large fall: by over 1.6 million workers, or 76.0% of the all-parents decline 2.2 million. But contrary to the common assertion that falling U.S. manufacturing employment is being caused by U.S. parents exporting these jobs to their

foreign affiliates, it is notable that during this same period foreign-affiliate employment in manufacturing moved very little: rising by 128,300, or just 2.9%.

Instead of jobs being exported, widespread U.S.-parent employment declines since 2000 were likely driven by two major forces. One was the U.S. recession in 2001, which continued to pressure the U.S. labor market until mid-2003 and which was not experienced by much of the rest of the world. Indeed, overall U.S. manufacturing employment during this time fell by slightly over 3 million. The other major force was the strong productivity performance of U.S. parents. Productivity gains can reduce short-term employment when sales growth is not strong enough to keep pace with the innovations. Indeed, since 2003 when the economic recovery was well underway, total U.S. parent employment has risen slightly: from a trough of 21.1 million to the 21.7 million reported in Figure 2.

Over the full generation described in Figure 2, to the extent that there was faster foreign-affiliate growth than U.S.-parent growth much was driven by faster growth abroad in overall output and incomes—and thus in customers to be served. From 1990 through 2008, growth in U.S. gross domestic product averaged 2.7%—in contrast to 1990-2007 averages of 3.4% for the overall world, 4.6% for emerging and developing countries as a whole, 6.3% in India, and a remarkable 9.9% in China.<sup>4</sup>

These growth-rate differentials carry significant implications for the evolving size of national markets and thus prospective customers. At an annual rate of growth of 2.8%, the U.S. market doubles in size every 25 years. The comparable doubling periods for India and China are just 11.4 and 7.3 years, respectively. And despite the recession in many parts of the world today, these growth-rate differentials are widely forecast to persist into the future. If past becomes prologue, then in the time it takes the U.S. market to double from its current size the Chinese

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<sup>4</sup> These average rates of growth of gross domestic product were calculated from annual rates of GDP growth reported in International Monetary Fund (2008), Tables A1-A4.

market will expand more than tenfold. The bottom line here is that to achieve strong revenue growth, U.S. multinationals must expand their access to foreign customers.

What about company-level evidence on parent and affiliate activities? Some of the most compelling evidence of complementarity between U.S. parents and foreign affiliates comes from analysis of the raw company-level data collected in legally mandated surveys of the Bureau of Economic Analysis that underlie Figure 2. These raw data permit analysis of changes in affiliate and parent activity within each company, rather than aggregating these changes across all companies.

In recent years, a small number of studies using these company-level data have been conducted. Desai, Foley, and Hines (2009), in particular, carefully analyzed a panel data set of all U.S. multinationals in manufacturing from 1982 to 2004.<sup>5</sup> They estimated that a 10% increase in foreign-affiliate capital investment causes an average response of a 2.6% increase in that affiliate's U.S. parent capital investment. They similarly found that a 10% increase in foreign-affiliate employee compensation causes an average response of a 3.7% increase in that affiliate's U.S. parent employee compensation. Growth in affiliates tends to bring growth in parents as well. Each additional dollar in an affiliate's employee compensation generates an average increase in its parent employee compensation of about \$1.11. And each additional dollar in an affiliate's capital investment cause an average increase in its parent's capital investment of about \$0.67. Accordingly, more affiliate activity tends to cause more, not less, parent activity.

The authors of this study concluded, "These results do not support the popular notion that expansions abroad reduce a [multinational] firm's domestic activity, instead suggesting the opposite." The perspective of a fixed amount of activity being reallocated between parents and

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<sup>5</sup> BEA company-level data are not publicly available and so research on these data can be performed only by scholars granted special clearance by the BEA.

affiliates is not accurate. Rather, the correct perspective is one of parallel changes over time in both affiliates and parents—driven by considerations of complementarity, scale, and scope.

A second piece of company-level evidence on parent-affiliate complementarity is differences between parent and affiliate industry classifications. Worldwide in 2006 there were 23,853 majority-owned foreign affiliates of 2,278 U.S. multinationals. Each can be classified in an industry one of two different ways: based on the primary activity of the affiliate itself or the primary activity of its U.S. parent. The top row of Figure 3 counts affiliates classified by industry of *parent* for three broad groups. The bottom row repeats this using industry of *affiliate*.

Figure 3  
Complementarity Between Affiliates and Parents

	Manufacturing	Wholesale Trade	Other Sectors
# of Affiliates when Classified by Industry of Parent	15,683	1,355	6,815
# of Affiliates when Classified by Industry of Affiliate	8,319	4,265	11,269

There is a dramatic difference in the industrial composition of affiliates between these two classifications. When classified by their parents' primary activity, the majority of affiliates is in manufacturing. But when classified by their own primary activity, the majority of affiliates is outside manufacturing. This substantial swing—7,364 affiliates, or 30.9% of the total—is driven by differences in the activities of parents and affiliates drive. Although the majority of parents—and thus their affiliates when classified by parents' industry—operate mainly in manufacturing,

the majority of affiliates operate in services.<sup>6</sup> This is strong evidence that parents and affiliates perform complementary activities.

One clear example of this complementarity highlighted in Figure 3 is wholesale trade. In 2006 there were just 1,355 affiliates—just 5.7% of the total—owned by parents whose main line of business was wholesaling. But looking at the affiliates themselves, 4,265—17.9% of the total—were wholesalers. This difference accounts for 39.5% of the difference in manufacturing counts, and it indicates that an important dimension of global engagement for many manufacturing parents is to establish foreign affiliates that distribute manufactures into host-country markets. Cross-border links like these revealed by Figure 3 are not about substitution, but rather about rich patterns of dynamic complementarity and breadth of scope.

*C. Evidence that Foreign Knowledge Discovery by Biopharmaceutical Companies Complements Their Home Activities*

The evidence of the previous sub-section does not speak specifically to biopharmaceutical companies and their knowledge-discovery efforts, but rather to companies in all industries across all activities taken together. But the balance of evidence on complementarity between affiliate and parent activity within multinational companies suggests that a good starting assumption is that as biopharmaceutical companies globalize knowledge discovery, this will tend to support—not substitute for—their home-country knowledge discovery as well.

Some more-direct evidence on this can be gleaned from publicly available BEA data on U.S. multinational companies. First is the fact that worldwide R&D expenditures of U.S. multinational companies have long been highly concentrated in America in their U.S. parents, not abroad in their foreign affiliates. In 1982 U.S. parents accounted for 93.6% of the global R&D of U.S. multinational companies. In 2006 U.S. parents still performed 86.8% of worldwide

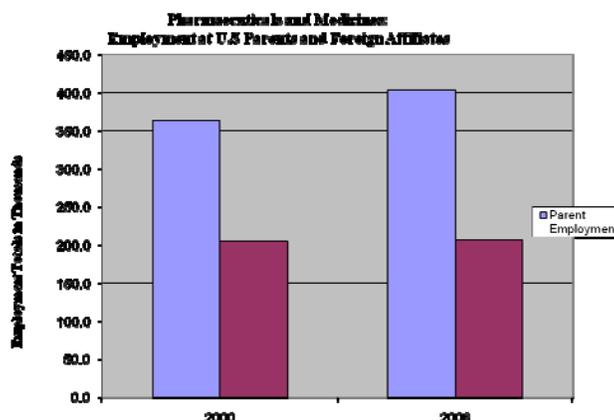
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<sup>6</sup> Of the 2,278 parent firms in 2006, 1,132 were primarily in manufacturing. BEA classifies the main line of activity for each parent and affiliate based in terms of the industry composition of sales.

R&D by U.S. multinationals: \$187.8 billion versus just \$28.5 billion, or \$6.59 in parent knowledge discovery for every \$1 by affiliates. Over 24 years the affiliate share had grown by only about seven percentage points, and during that time parent R&D expenditures were still increasing substantially.

What about biopharmaceutical companies in particular? With the BEA's 1999 conversion to the North American Industry Classification System, its closest grouping to this area is called, "pharmaceuticals and medicines." In 2006, 43 U.S. multinational companies were operating with this as their primary line of business. What was the global footprint of these companies that year in terms of parent-affiliate relative sizes, and have these relative sizes changed over time?

Figure 4 reports 2000 and 2006 total employment in U.S. parents and majority-owned foreign affiliates whose main line of business was pharmaceuticals and medicines.



From 2000 through 2006, affiliate employment rose by 2,400 workers, or 1.2%: from 205,100 to 206,500. Over that same period parent employment in the U.S. rose by 39,800, or 10.9%: from 363,600 to 403,400. This broad pattern of rising employment globally suggests that employment at U.S. parents and foreign affiliates in biopharmaceuticals tend to be complements. Indeed, the larger U.S. employment increases in recent years—in both level and percentage terms—have meant that global employment in these companies is becoming more concentrated in the United States, not less: rising from 64.0% to 66.1%.

A similar picture of complementarity is given by other activity measures the BEA reports at this level of industry disaggregation. From 2000 through 2006, affiliate value added rose by \$11.9 billion, from \$25.7 billion to \$37.6 billion. Over that same period parent value added in the U.S. rose by \$30.5 billion, from \$63.2 billion to \$93.7 billion. Indeed, the parent increase was larger in percentage terms, such that as with employment global value added in these companies was also becoming more concentrated in the United States—rising from 71.1% to 71.4%. This broad pattern of rising output globally also suggests that activity at U.S. parents and foreign affiliates generally complement each other.

Unfortunately, only in 2004 did the BEA begin reporting affiliate R&D expenditures for detailed industry groupings. In 2006, foreign affiliates in pharmaceuticals and medicines performed \$5.2 billion in R&D. This contrasted with \$36.2 billion in R&D performed by U.S. parents in pharmaceuticals and medicines. This was up 75.6% from the 2000 parent tally of \$20.6 billion, a percentage increase that exceeded the 2000-2006 percentage increase in employment and output by these parents. Thus, in 2006 U.S. parents accounted for 87.5% of the worldwide R&D conducted in pharmaceuticals and medicines by these companies—slightly above the 86.8% worldwide R&D share cited earlier across all industries.<sup>7</sup>

One additional piece of evidence that expansion abroad by biopharmaceutical companies tends to complement their home-country activities comes from industry classification. Again, in 2006 there were 43 U.S. parents classified in the primary activity of pharmaceuticals and medicines. When classified by their parents' primary activity, there were 1,256 majority-owned affiliates in this same industry. But when classified by their own primary activity, there were just 425 affiliates classified in pharmaceuticals and medicines. This small degree of overlap

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<sup>7</sup> The BEA data discussed here differ in several ways from the PhRMA data in Figure 1. One important difference is that the PhRMA data report non-U.S. R&D spending that is outside of the foreign affiliates of U.S. multinationals. This scope difference helps explain the slightly higher U.S. shares of R&D in the BEA data than the PhRMA data.

indicates that most foreign affiliates of U.S. biopharmaceutical parents are engaged in different activities such as wholesale distribution.

Our conclusion from the various pieces of evidence in this sub-section is that foreign knowledge discovery by biopharmaceutical companies tends to complement, not substitute for, their home-country activities.

#### *IV. Conclusions and Directions for Future Research*

Location possibilities for biopharmaceutical firms are expanding, driven by factors such as falling natural and political barriers to trade and communication, extension and strengthening of patent protection through institutions including the World Trade Organization, and growing supplies of skilled labor and related infrastructure in large, relatively low-cost countries. This paper has examined the causes and consequences of this global expansion of knowledge discovery by biopharmaceutical firms.

We first discussed the empirical evidence on the extent and nature of this process. We then examined whether this global spread of biopharmaceutical R&D supports or hurts host-country knowledge activity. Our conclusion was that foreign knowledge discovery by biopharmaceutical companies tends to complement, not substitute for, their home-country activities.

There are several lines of inquiry left unexamined in our paper and its focus on business-strategy and economic considerations. One in particular is the ethical and philosophic issues raised by the globalization of pharmaceutical companies. Glickman, et al (2009) discuss these ethical issues, many of which do not arise in other industries such as information technology and transportation products, and argue (p. 820) that “it is essential to create a robust framework to ensure the integrity of research, wherever it takes place.” We share this sentiment, and encourage future work in this important area along both economic and non-economic lines.

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