ORGANIZING FOR TECHNOLOGICAL INNOVATION IN THE U.S. PHARMACEUTICAL INDUSTRY

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ABSTRACT

The organization of R&D in geographic space has been identified as an important but neglected determinant of innovative performance. This study uses data on 21 U.S.-based pharmaceutical companies to investigate the potential impact of geographic organization on innovative output. Three dimensions of geographic organization are assessed: (1) centralization versus decentralization of laboratories in the United States; (2) localized spillovers among competing labs in the U.S.; and (3) globalization of laboratory networks. The findings point to the importance of international spillovers that pharmaceutical companies have harnessed through ownership of foreign laboratories. Thus, foreign labs appear beneficial for innovation, but no evidence is found of more localized spillovers among commercial labs. The analysis shows some benefits of centralization within the U.S., suggesting that an organization with one or two domestic laboratories may be optimal.

INTRODUCTION

The organization of R&D in geographic space has been identified as an important but neglected determinant of innovative performance (Cohen & Mowery, 1984;

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Hall, 1991). In this chapter we consider how the geographic organization of R&D laboratories may influence innovative output in the U.S. pharmaceutical industry. We consider three dimensions of geographic organization and their potential impact on innovation: (1) centralization versus decentralization of a company's laboratories in the U.S.; (2) localized spillovers with competitors' labs in the U.S.; and (3) globalization of laboratory networks. Our sample covers 21 U.S.-based companies that performed R&D to develop ethical drugs over a period of about three decades.

We test hypotheses on the impact of lab centralization and spillovers using two alternative measures of firms' innovative output: the annual number of "new chemical entities" (NCEs) approved by the U.S. Food and Drug Administration (FDA), and the annual number of U.S. patents granted. We link these output measures to detailed information on the geographic organization of R&D labs. Our findings suggest the importance of international spillovers that pharmaceutical firms have increasingly harnessed through growing networks of foreign laboratories. We do not, however, find evidence of agglomeration economies or spillovers related to geographic concentration of pharmaceutical laboratories within the U.S. Thus, foreign labs appear to be beneficial for innovation, but whether labs are located close to or far from similar facilities of rival firms appears to have little impact, at least within the United States. In addition, our patents analysis reveals some benefits of R&D centralization, suggesting that an organization with one or two domestic laboratories may be optimal.

The chapter is organized as follows. In the next section we discuss trends in the geographic organization of R&D laboratories devoted to drug discovery. The third sectiondescribes several trade-offs with respect to R&D centralization and location, which are formalized as a set of testable hypotheses. The fourth section presents our statistical model and the measures used in our analysis. Results are presented in the fifth section, followed by conclusions.

THE GEOGRAPHIC ORGANIZATION OF R&D IN THE U.S. PHARMACEUTICAL INDUSTRY

This study focuses on the U.S. ethical pharmaceutical industry, defined as all U.S. public firms with major ethical drug research programs leading to the invention of one or more NCEs between 1950 and 1989.[1] Several characteristics make this an attractive industry for assessing possible connections between geographic organization and research output. First, the industry is highly research intensive, and research is conducted in formal research laboratories, allowing for an accurate measurement of geographic organization. Second, organization in geographic

space is carefully planned. While impacted by historical factors (particularly mergers), geographic organization can hardly be attributed to chance. Pharmaceutical companies have been actively reorganizing and relocating their R&D labs in recent decades, despite the high costs of such activities. Third, the organization of R&D laboratories across geographic space varies greatly among firms in the pharmaceutical industry, allowing for an effective test of the hypotheses developed. Some companies conduct their R&D activities in one or very few labs while others, of equal size, have multiple laboratories. In addition, the distance between laboratories varies greatly. Some companies locate their R&D laboratories very close to each other, while others have them dispersed around the U.S. or the world. Fourth, the nature of competition in the ethical pharmaceutical industry generates multiple measures of innovative output, notably NCEs and patents. Moreover, the link between innovative output and financial performance in this industry has been demonstrated in prior studies (e.g. Geroski, 1994; Jaffe, 1986).

Table 1 lists the firms in our sample. The table also summarizes our data on the number of domestic and foreign ethical drug laboratories operated by each firm since 1960.[2] It reveals a strong trend toward decentralization and internationalization of pharmaceutical research. The average number of domestic laboratories per firm has been increasing, from 1.2 in 1960 to 1.8 by 1997. The number of foreign labs rose more steeply, from 0.2 labs per firm in 1960 to 1.9 in 1997. In other words, in 1960 the vast majority of U.S. firms operated only a single laboratory for ethical drug research, but by 1997 the median firm had two domestic labs and two foreign labs. Moreover, six firms in the sample were acquired by foreign drug companies, which contributed as well to the internationalization of laboratory networks in the global industry.

Figure 1 plots the growth in domestic and foreign labs operated by U.S. companies. It shows that the average number of foreign labs per firm has been rising steadily since the early 1960s, whereas about half of the increase in domestic labs per firm took place in the 1990s, as the result of mergers. Until the 1990s, the annual growth in foreign labs greatly exceeded the growth in domestic labs per firm.

Thus, most firms' research activities are no longer limited to a single large laboratory, as was the pattern decades ago. Furthermore, new scientific methods of drug discovery have encouraged firms to broaden their information sources. This is reflected in our data in instances where new laboratories were established, or where smaller pharmaceutical companies were acquired. U.S. pharmaceutical firms have also acquired many biotechnology start-ups whose labs are not shown in Table 1. There has also been a sharp increase in collaborations with university scientists, independent biotech firms, and start-up companies that apply genomics methods to drug discovery. These alliances and collaborations have become increasingly important but are not part of our laboratory count data. Some U.S.

Table 1. Number of Ethical Drug Laboratories by Company, 1960–1997.

	U.S. Ethical Labs					Foreign Ethical Labs				
	1960	1970	1980	1990	1997	1960	1970	1980	1990	1997
Abbott	1	1	1	1	1	0	0	0	0	0
AHP	2	2	2	3	5	1	2	2	2	1
A.H. Robins	1	1	1			0	0	0		
Am. Cyanamid	1	1	1	1		0	0	0	0	
Alcon	1	1				1	1			
AHS-Baxter	1	1	1	1	1	0	0	0	0	0
BM-Squibb				2	2				3	3
Bristol Myers	1	2	2			0	0	0		
Squibb	1	1	1			0	1	1		
Carter-Wallace	1	1	1	1	1	0	0	0	0	0
Johnson & Johnson	1	3	3	3	3	1	1	2	2	2
Lilly	1	1	1	1	1	0	1	1	2	3
Merck	2	2	2	2	2	0	2	3	5	6
Miles Labs	1	2	2			0	0	0		
Pfizer	1	1	1	1	2	0	1	2	2	2
Schering	1	2	2	1	1	0	0	0	1	1
Searle	1	1	1				0	1		
SmithKline	1	1	1	1	1	0	1	2	2	2
Sterling	1	1	1			0	0	1		
Syntex		1	1	1			0	3	4	
Upjohn	1	1	1	1		0	0	0	1	
Warner-Lambert	3	2	2	2	2	0	0	1	3	3
Mean	1.2	1.4	1.4	1.5	1.8	0.2	0.5	1.0	1.8	1.9
Median	1	1	1	1	2	0	0	1	2	2

pharmaceutical companies have maintained centralized laboratories while dramatically broadening their networks of outside scientific collaboration. To some extent, the international component of these networks is reflected by the growth of foreign labs, but otherwise our data fail to capture this increase in external collaborations.

Much of the U.S. pharmaceutical industry is concentrated along a regional axis centered in New Jersey and eastern Pennsylvania (c.f. Furman, this volume, Fig. 3). Our laboratory agglomeration measures bear out this regional focus. Table 2 ranks the companies in our sample in decreasing order of their average weighted distance from rivals. (Specifics of the distance measure are described in Section 4 below.) Firms near the top of Table 2 have located their domestic laboratories in New Jersey or Pennsylvania (or both). The two at the bottom of the list, Alcon and Syntex, operated single laboratories in Texas and California, respectively – locations

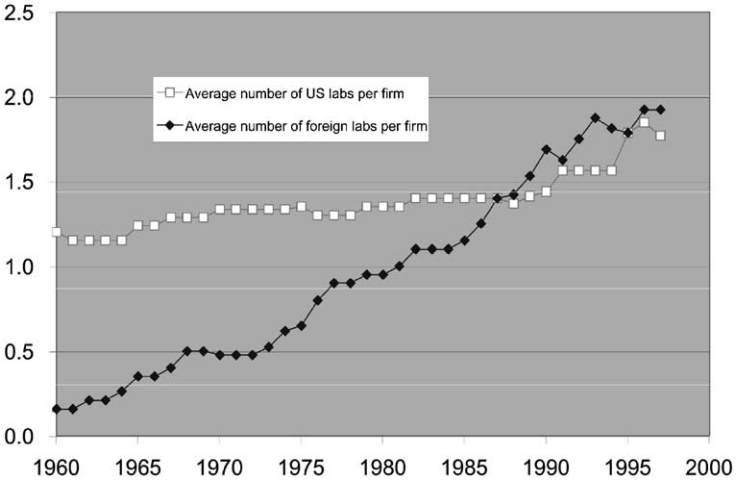

Fig. 1. Average Number of Ethical Labs per Firm.

Table 2. Companies Ranked by Average Distance from Rivals' Labs in 1986.

Firm Name	Number of U.S. Labs	Locations by State	Avg. Wtd. Distance (EDIST)	R&D ($)
Carter-Wallace Inc	1	NJ	7035.63	3.9
Johnson & Johnson	3	NJ, NJ, PA	6829.76	77.1
Squibb Corp	1	NJ	6716.40	16.9
Smithkline	1	PA	6308.61	33.7
American Home Products	3	NJ, PA, NY	6200.00	43.5
American Cyanamid	1	NY	6118.29	34.5
Schering-Plough	2	NJ	5971.15	23.5
Warner-Lambert	2	NJ, MI	5411.60	31.0
Merck	2	NJ, PA	4958.75	30.7
American Hospital Supply	1	IL	4643.87	NA
Bristol-Myers Company	2	NY, CT	4600.00	34.9
Miles Laboratories	2	CT, IN	4587.73	11.6
Sterling Drug	1	NY	4555.74	22.1
Pfizer	1	CT	4489.15	40.0
Abbot	1	IL	4379.75	35.8
Upjohn	1	MI	4356.13	20.7
Searle	1	IL	4321.53	NA
Robins (AH) Co	1	VA	3746.62	6.4
Eli Lilly	1	IN	3127.92	29.1
ALCON	1	TX	1463.78	NA
Syntex	1	CA	750.08	9.2

quite remote from those of other pharmaceutical companies. Thus, the degree of geographic co-location has varied considerably among the U.S. pharmaceutical firms.

As Table 1 indicates, the most prominent trend in geographic organization by U.S. pharmaceutical companies has been the growth of foreign laboratory networks. The companies in our sample operated a total of only three foreign labs for ethical drug research in 1960, rising to 25 labs by 1997. Unlike the growth in domestic labs, which has been largely due to merger and acquisition activity, growth in foreign labs has generally reflected management decisions to establish a research presence abroad. In many instances foreign labs began with clinical research and later expanded into drug discovery. Foreign labs extend a firm's information network and allow it to tap into localized knowledge, including that of university researchers. A foreign lab may make new drug discoveries directly or identify attractive opportunities for licensing.

Table 1 shows considerable variation across companies in the number of foreign labs devoted to ethical drug research. Merck, often regarded as the pioneer in scientific methods of drug discovery, emerged as the industry leader in degree of internationalization with six foreign labs by the late 1990s. In the 1960s and 1970s, differences in the number of foreign labs were largely explained by differences in firm size, but this has become less true over time.

Thus, there has been a clear trend by U.S. pharmaceutical companies toward globalization of R&D. U.S. pharmaceutical companies now operate nearly as many R&D facilities abroad as in the U.S. Foreign pharmaceutical firms have also internationalized their R&D activities. Indeed, the growth in the average count of U.S. domestic labs per firm, shown in Table 1, arises in part because foreign firms acquired smaller U.S. pharmaceutical companies that operated only a single U.S. lab. If we view these international acquisitions and the establishment of foreign research laboratories as the result of optimizing behavior, it suggests that firms have reaped benefits in drug discovery by globalizing their R&D network.

Nonetheless, this shift away from R&D centralization carries potential costs as well as benefits. In the next section we assess tradeoffs with respect to: (1) R&D centralization; (2) the more specific benefits and costs of international laboratory networks; and (3) the potential for geographic spillovers among labs.

TRADE-OFFS IN THE GEOGPRAHIC ORGANIZATION OF R&D

Geographic centralization is defined as the concentration of a firm's R&D laboratories in one or a few locations. Location decisions are purposive (e.g. Baum

& Haveman, 1997), and numerous potential economies and diseconomies of centralization have been identified in the literature (e.g. Audia, Sorenson & Hage, 2001). Table 3 summarizes these economies and diseconomies in the specific case of R&D. The net benefit of centralization, or the benefits of centralization less the costs associated with it, depends upon context. The optimal degree of R&D centralization is determined by balance among the forces described in the table. This optimum may vary by industry and even by firm. Ultimately, it is an empirical issue that we consider in our statistical analysis of the pharmaceutical industry.

Table 3 lists several factors that favor the geographic centralization of R&D. Perhaps most important, centralization helps to facilitate dense internal communication flows, which are often viewed as essential for innovation (Taggart, 1993).[3] Centralization also allows for the achievement of economies of scale in R&D operations (e.g. Pearce & Singh, 1992) as well as specialization, which may increase efficiency (Wollnik & Kubicek, 1981).[4] Other potential benefits of centralized R&D include a reduced likelihood of duplication of efforts (Taggart, 1993), and a "buffering" that isolates the company's most important know-how (Lawrence & Lorsch, 1967) and prevents potential leakages to competitors (Cordell, 1971; Dunning, 1994). Finally, centralization often enables better control by top management and avoidance of complexity and integration problems associated with geographically dispersed facilities (Adler, 1983; De Meyer, 1993; Gluck, 1985).

Various disadvantages of geographic centralization are also addressed in the literature: diseconomies of large size, insulation from external know-how and ideas, problems of coordination and know-how transfer, and potential loss of tax benefits. For example, excessive centralization or scale can hinder communication and interaction and create bureaucratic diseconomies (Williamson, 1991). Smaller laboratories can provide researchers with better access to internal information, which increases their involvement, commitment and understanding of organizational goals (Ouchi, 1982; Pierce & Delbecq, 1977; Thompson, 1967). Monitoring costs are also lower in small labs: the senior manager can evaluate researchers' performance directly and accurately, without the distortion that is created in large multi-level units (Ouchi, 1978; Stigler, 1962; Zenger, 1994). Centralization may also insulate researchers from competitors' know-how and from localized national or regional know-how pools that are distant from the company's central labs.

Pl. check reference "Pierce & Delbecq (1977)", which is missing in the reference list.

While some of the diseconomies of large size can be mitigated within a centralized structure through appropriate choice of organizational systems and incentives, other drawbacks of centralization, such as isolation from localized knowledge, are difficult if not impossible to mitigate, leading inevitably to

Table 3. Benefits and Costs of R&D Centralization.

Economies of Centralization		Diseconomies of Centralization	
Benefits	Argument Author(s)	Drawbacks	Argument Author(s)
Improved internal know-how exchanges	*See Section*	Reduced flow of external know-how into the firm	*See Section*
Economies of scale and minimum efficient scale		*Diseconomies of scale*	
Higher probability of having basic research on site	Taggart (1993)	Bureaucratic diseconomies	Williamson (1991)
Better library and other support services	Taggart (1993)	Need for more coordination	Ouchi (1982), Pierce and Delbecq (1977), Thompson (1967)
MES of labs and equipment	Taggart (1993)	Higher monitoring costs	Ouchi (1978), Stigler (1962), Zenger (1994)
Single site economies		*Single site diseconomies*	
Lower coordination and integration costs	Adler (1983), Gluck (1985), De Meyer (1993)	Less internal competition	Porter (1990)
Other		*Other*	
Lower likelihood of duplication of efforts	Taggart (1993)	Fewer direct contacts with customers	Von Hippel (1988)
"Buffering" of the internal core	Lawrence and Lorsch (1967)	"NIH" syndrome	Katz and Allen (1982)
Less know-how leakage	Cordell (1971), Dunning (1994)	Less direct contact with geographically distributed manufacturing operations	Clark, Fujimoto and Chew (1987), Clark and Fujimoto (1991)
Better control by top management/link to corporate HQ	Taggart (1993), Malecki (1980), Howells (1990, 1986)		
		International & government related	
		Loss of goodwill with local governments	Taggart (1993)
		Regionally based tax credits	Ziegler (1990)

pressures for a more dispersed laboratory network. Conceivably, the strong trend toward international laboratory networks in the pharmaceutical industry may reflect a growing desire to tap localized knowledge sources.

Considering that the net benefits of geographic centralization and spillovers could be either positive or negative, our hypotheses are set as duals. The hypotheses regarding geographic centralization are as follows:

Hypothesis 1a. Controlling for firm size, firms with more centralized research activities will be more technologically innovative than firms with less centralized research activities.

Hypothesis 1b. Controlling for firm size, firms with less centralized research activities will be more technologically innovative than firms with more centralized research activities.

Many of the tradeoffs identified in Table 2 are amplified when decentralization spans international boundaries. Greater physical distance and cultural differences make communication among laboratories more difficult (e.g. Strang, 2003). Managerial control and coordination also become harder, due to the same factors. Smaller companies may be unable to support foreign labs at an efficient scale. On the other hand, an international network of laboratories may offer considerable advantages with respect to the ability to tap into localized knowledge (e.g. Almeida, 1996), considering the barriers that prevent knowledge flows across geographic space (e.g. Jaffe, Henderson & Trajtenberg, 1993; Sorenson & Stuart, 2001). International barriers to information flows are likely to be much greater than those that exist regionally within a single country such as the U.S. In the pharmaceutical industry, foreign labs may help the firm access knowledge generated by university researchers and rival drug makers located abroad. If coordination and communication are managed well, such benefits of international labs may exceed the costs.

Pl. check the reference "Jaffe, Henderson & Trajtenberg (1993)", which is missing in the reference list.

Our data allow us to test for the influence of foreign laboratories separately from that of domestic labs. However, we lack information on the distance of foreign labs from universities and rival laboratories. We therefore test a single, joint hypothesis for foreign labs (capturing the combined effects of localized knowledge spillovers and decentralization):

Hypothesis 2a. Controlling for firm size, firms with more foreign research laboratories will be more technologically innovative than firms with fewer foreign labs.

Hypothesis 2b. Controlling for firm size, firms with more foreign research laboratories will be less technologically innovative than firms with fewer foreign labs.

Firms can also chose to locate their laboratories close to competitors labs in the hope of benefiting from knowledge spillovers that may occur. Alternatively, firms may be the unintended recipient of such spillovers if other firms follow its path and locate close to it. The importance of such spillovers has been well documented (e.g. Griliches, 1992), with these spillovers occurring in various ways, such as through direct informal contacts between researchers working for different companies (Von Hippel, 1988), or through the hiring of researchers from competitors. Evidence suggests that knowledge transfers are bound in space (e.g. Audretsch & Feldman, 1996; Edling & Liljeros, 2003; Jaffe, Henderson & Trajtenberg, 1993; Krugman, 1991; Marshall, 1879) and tacit knowledge transfers even more so (e.g. Zucker, Darby & Brewer, 1998). Tacit knowledge transfers can only occur through dense communication[5] (Feldman, 1994, p. 21; Hall, 1991, p. 165; Suzlanski, 1996, p. 32), which is facilitated by co-location.

However, it should be noted that while collocation may allow firms to capture the benefits of geographically localized spillovers, this same collocation may be detrimental in that it will allow competing firms to capture the firm's own knowledge. Firms are often engaged in technology races (e.g. Reingaum, 1989), and loss of knowledge to competitors may lead to losing such races. Although collocation and spillovers are likely to be beneficial to the economy as a whole, it is not clear overall whether collocating firms will benefit from it.

The following hypotheses address the potential impact of localized geographic spillovers on innovation. The first of these hypotheses reflects an environment with positive spillovers, whereas the second denotes the opposite case where isolation from competitors is beneficial for innovation:

Hypothesis 3a. Controlling for firm size, firms with research laboratories having more geographic contact with competitors' labs will be more technologically innovative than firms with research labs isolated from competitors' labs.

Hypothesis 3b. Controlling for firm size, firms with research laboratories having less geographic contact to competitors' labs will be more technologically innovative than firms with research labs isolated from competitors' labs.

EMPIRICAL MODEL AND MEASURES

In this study, our empirical approach is to regress measures of innovative output (NCE and patent counts) on explanatory variables relating to geographic

centralization and spillovers, controlling for R&D expenditures, time trends, and other factors. The basic models have the form:

$$\text{Count of Innovation} = f(\text{Geographic Centralization, Geographic Spillovers, R\&D Expenditures, Time, Other})$$

The data are annual at the firm level. Our measures of geographic centralization and potential spillovers include: (1) annual counts of U.S. and foreign laboratories for ethical drug discovery operated by each firm; (2) the average weighted distance between the firm's U.S. labs and those of other firms in the sample; and (3) the average distance between U.S. labs operated by the firm (for multi-lab firms). All regressions were estimated using the negative binomial model for count data available in the Stata statistical package.

Four types of data are combined in this study: data on new chemical entities, data on patents, financial data, and data on R&D laboratories. The following gives a summary of the data collected, and measures used in the analysis.[6]

Measures of Innovative Output

The *patenting data* were collected primarily from the NBER Patent Data File (Hall, Jaffe & Trajtenberg, 2001), supplemented by the Delphion patent database.[7] We took the annual count of patents, based on application year, that were assigned to each firm within the USPTO classes 424 and 514 (jointly corresponding to the NBER technical subclass 31, drugs).

The *New Chemical Entities data*, including information on inventor and licensee, were collected in two different ways for the periods 1983 to 1996 and 1977 to 1982. For the 1983–1996 time period, the *Pink Sheet*, a newsletter published by the Food and Drug Administration, was used to collect the information on NCE approvals. For each of these NCEs, the inventor was identified through companies' annual reports, the *Pink Sheet*, magazines and newspapers. For the 1977–1982 time period, the same information was extracted from De Haen (1990). The De Haen's directory lists all drugs brought into the market (whether generics or unique), the company that manufactures them, and the inventor(s)' name(s).

By comparing the identities and locations of the inventor and the licensee for each NCE, we obtained several innovation count measures. Each NCE for which the firm was listed as inventor was assigned to a count measure for "originated" drugs (155 NCEs total). NCEs for which the firm was listed as licensee, but not as inventor, were assigned to a count measure for "licensed" drugs. We also developed more detailed NCE counts by noting the international origin of the

inventor. This allowed us to break down the overall count of licensed NCEs into those licensed from other U.S. companies and those licensed from foreign firms and organizations. In addition, for the NCEs invented by the firm, we distinguished those that were developed in the firm's foreign research laboratories. Thus, the NCE count measures discriminate between invented and licensed NCEs as well between U.S. and foreign inventors. While licensed drugs are not part of the firm's research output, we investigate whether the location of the firm's labs may influence the rate and pattern of licensing.

NCE counts are a standard measure of innovation in the pharmaceutical industry. NCEs are important, since they represent the last hurdle in the innovation process. The FDA ensures that NCEs are effective in relieving or curing a particular disease. A very large proportion of firm revenues comes from NCEs, as they are guaranteed patent protection and exclusivity for a certain number of years and are thus free from competition. Hence, NCEs can be viewed as major innovations, and NCE counts have been used in many prior studies (e.g. Davis & Thomas, 1993; Graves & Langowitz, 1992, 1993; Jarrell, 1983; Jensen, 1987; Thomas, 1990).

To account for time lags between innovative activity and our measures of innovative output, we lagged all explanatory and control variables by two years in the patent and licensed NCE regressions, and by seven years in the originated NCE regressions. While a longer lag might be justified, particularly for the originated NCE regressions, it seems unlikely that a change in the lag structure would affect the results, given the strong persistence of most explanatory variables over time.

Explanatory Variables

The *financial data* on R&D and sales of ethical drugs were obtained from the Chicago *Compustat* Files from 1950 to 1996. Our control measure, "R&D," corresponds to the company's total annual expenditure on research and development as reported in the company financial statements.[8] Our control measure, SALES, was obtained by multiplying the company's reported annual sales by the proportion of sales in ethical drugs.[9]

The *R&D laboratories data* were collected from various sources. *The Industrial Research Laboratories of the United States* (various years) was the primary source of information on R&D laboratories. The information in this directory is compiled from a survey filled by the companies themselves. The data were validated using company annual reports and 10K statements, company histories when available, and newspapers and magazines articles. Information on foreign labs was obtained and validated using various foreign directories of R&D laboratories.

Our principal measures of geographic centralization are simple laboratory counts: the total number of U.S. labs (USLABS), and the total number of foreign labs (FORLABS), operated by the firm for ethical drug discovery in each year. As an additional measure of centralization, we obtained the average of the logged distance (in miles) between the companies U.S. labs. This measure, IDIST, is zero for single-lab firms and rises with distance between labs for multi-lab firms.

Our measure of geographic spillovers (EDIST) is the average weighted distance between the company's ethical drug laboratories and those of all other firms in the sample, i.e.

$$\text{EDIST}_i = \frac{?_{j=1,N}1}{N?_k}\frac{E_k}{D_{ijk}}$$

Pl. provide the missing matter denoted by '?'

where D_{ijk} is the distance from laboratory j of firm i to "external" laboratory k, E_k is the (approximate) employment of laboratory k, and N is the total number of U.S. labs operated by firm i. In other words, for each U.S. laboratory operated by a given firm, we first took the reciprocal of the distance between that lab and each lab operated by a rival company ($1/D_{ijk}$), weighting this value by the size (employment) of the rival lab (E_k). We then summed these weighted distances over all of the external labs to get a total weighted distance measure at the lab level. Finally, we took a simple average of the weighted distance values across all labs operated by the firm.[10] These are the values shown in Table 2.

RESULTS

In this section we present regression results for three sets of innovation measures: invented NCEs, licensed NCEs, and patents. All regressions were estimated using a negative binomial model for count data.

Invented NCEs

Table 4 presents the regression results for invented NCEs. The dependent variable in the first three regressions is the annual count of all NCEs invented by the firm, including those developed by the firm's foreign research laboratories. The dependent variable in the second set of regressions excludes the NCEs developed by foreign labs. We separated the NCE counts in this way to distinguish domestic versus global research output.

In both sets of regressions, the control variables are typically significant with the expected signs in the initial regressions where no other measures are included.

Table 4. Regression Results for Invented NCEs, 1970–1996 (Negative Binomial Model).

Dependent Variable	NCEs Originated by the Firm in All Labs			NCEs Originated by the Firm in U.S. Labs		
	4.1	4.2	4.3	4.4	4.5	4.6
Constant	119.841***	108.444***	101.856**	127.727***	108.456**	102.137**
Ethical drug sales	0.00035***	0.00012	0.00010	0.00043***	0.00021	0.0002
R&D	0.01797***	0.01226*	0.01828**	0.00730	0.00763	0.01321
Time trend	−0.06125***	−0.05558***	−0.0513**	−0.06517***	−0.05489**	−0.05095**
ONELAB		−0.03482	−1.32941		−0.75025	−1.71433*
USLABS		0.17433	−0.15932		−0.46867	−0.69625
FORLABS		0.24814**	0.19982*		0.1785	0.12761
IDIST			−0.19066*			−0.14427
EDIST			−0.00008			−0.00009
Log likelihood	−301.495	−297.996	−296.279	−277.163	−274.825	−273.731
Number of obs.	375	375	375	375	375	375
Number of NCEs	155	155	155	133	133	133

Note: Explanatory variables lagged seven years prior to date of NCE approval.

*Significant at the 0.10 level, two-tail test.

**Significant at the 0.05 level, two-tail test.

***Significant at the 0.01 level, two-tail test.

The control variables fall in significance, however, when the laboratory network measures are added, as these measures also capture aspects of firm size. The sole control variable that is uniformly significant across the regressions is the time trend, whose negative sign is consistent with the declining rate of NCE approvals documented in other studies.

One prominent finding in Table 4 is a positive, statistically significant connection between invented NCEs and the number of foreign labs operated by the firm. After adjusting for firm size, companies with a greater number of foreign labs had higher rates of NCE output. The positive FORLABS coefficient persists in the last set of regressions where NCEs originated by the foreign labs are excluded. This suggests that interaction with foreign labs may make U.S. laboratories more productive.[11]

The EDIST measure is uniformly insignificant in Table 4, and the sign of the coefficient is negative. Thus, we find no evidence that firms with labs proximate to rivals enjoyed higher research productivity. One possibility is that localized spillovers are generally unimportant in the pharmaceutical industry. Another is that such spillovers seldom arise between major pharmaceutical firms (who take strong precautions to prevent leakage of proprietary information to competitors), but they may be significant when company labs are located near smaller firms and universities, which are not included in our sample. The latter organizations may be less careful at guarding their innovations and more interested in sharing their knowledge with others, especially larger pharmaceutical companies who represent potential future sources of funding. Unfortunately, given the nature of our sample, the findings in Table 4 and elsewhere in this study provide no information on such spillovers.

The IDIST coefficients in Table 4 are negative, and weakly significant in regression 5.3. Thus, the regressions provide some evidence that among firms with multiple labs, greater distance between labs was detrimental to research productivity (H1a).

The ONELAB dummy is negative and significant in regression 4.6, where it serves largely as a control to avoid biased coefficient estimates for IDIST, which is set to zero for all firms with a single U.S. lab. In regressions 4.2 and 4.5, where IDIST is excluded, the coefficients of ONELAB and USLABS are insignificant, implying the lack of a relation between research productivity and the number of labs. One possibility is that the degree of lab centralization within the U.S. has no effect on research productivity; another is that the NCE regressions lack the statistical power to distinguish such an effect.

In general, the relatively small sample size and infrequency of NCE approvals limit the power of the NCE regressions to discriminate the more fine-grained effects of laboratory network structure. Given the long time lags assumed in our

NCE regressions and the fact that much of the growth in the U.S. lab counts occurred in the late 1980s and 1990s, relatively few observations in the in NCE regressions correspond to firms with more than two labs. Consequently, the NCE regressions have limited power to distinguish the net economies and diseconomies of lab centralization within the U.S. This problem is less severe for the patent regressions, reported below, given that patents have a much shorter gestation lag, and the annual patent counts are much higher than those for NCEs. (NCEs may, however, be a better measure of innovative output if the propensity to patent varies from firm to firm.)

Licensed NCEs

Table 5 presents the regression results for licensed NCEs. The dependent variable in the first three regressions is the total number of NCEs licensed by the firm. This is followed by regressions that deal separately with NCEs licensed from U.S. inventors versus NCEs licensed from abroad. Of the 111 total licensed NCEs in the sample, 21 were licensed from U.S. sources and 90 from foreign sources.

In the first set of regressions, for total NCEs, no explanatory variables (not even the control variables) reach conventional thresholds of statistical significance. Thus, the overall licensing of NCEs appears almost totally random in this sample. The rate of licensing is surprisingly unrelated to measures of firm size.

A limited pattern emerges, however, in the regressions that distinguish between U.S. and foreign sources of licensed NCEs. While the firm size measures (ethical drug sales and R&D) remain insignificant, a negative time trend appears for domestic licensing, and a positive trend for foreign licensing. Thus, over the period of the sample there was a significant shift in licensing, away from NCEs discovered in the U.S., and toward NCEs discovered abroad.

Given our finding (in Table 4) that the number of originated NCEs is positively related to the number of foreign labs, we sought to identify a similar possible effect of foreign labs on licensing. If foreign labs serve as "listening posts" to find attractive licensing candidates, we would expect a positive and significant relation between the number of foreign labs and foreign licensing. Table 5 shows negative (but insignificant) coefficients for FORLABS in the foreign licensing regressions, indicating a clear lack of support for this hypothesis. Thus, in general our findings show that the number of foreign labs was positively related to the number of NCEs invented by the firm, but not to the rate of foreign NCE licensing.

Table 5. Regression Results for Licensed NCEs, 1970–1996 (Negative Binomial Model).

Dependent Variable	Licensed NCEs (Total)			NCEs Licensed from U.S. Sources			NCEs Licensed from Foreign Sources		
	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9
Constant	−24.1355	−28.6566	−31.5035	576.1575***	573.4937***	597.8615***	−118.306**	−121.47**	−127.001***
Ethical drug sales	0.00003	0.00002	0.00004	0.000479**	0.000365	0.00037	−0.00003	0.0000	0.00001
R&D	0.008009	0.013018	0.0145*	0.015341	0.010625	0.001748	0.00669	0.01302	0.01499
Time trend	0.011369	0.014071	0.015404	−0.29262***	−0.29138***	−0.30554***	0.05873**	0.0608**	0.063625***
ONELAB		−0.49507	−0.12647		0.023454	2.320866		−0.53716	−0.26745
USLABS		−0.46301	−0.36453		0.156373	0.653409		−0.53837	−0.43607
FORLABS		−0.00312	−0.03146		0.233659	0.346444		−0.03551	−0.08378
IDIST			0.060907			0.342371			0.050448
EDIST			−0.00007			0.000199			−0.00011
Log likelihood	−230.053	−229.396	−228.935	−61.8823	−61.612	−60.896	−198.958	−198.137	−197.385
Number of obs.	344	344	344	344	344	344	344	344	344
Number of NCEs	121	121	121	90	90	90	21	21	21

Note: Explanatory variables lagged two years prior to date of NCE approval.

*Significant at the 0.10 level, two-tail test.

**Significant at the 0.05 level, two-tail test.

***Significant at the 0.01 level, two-tail test.

Table 6. Patent Regression Results, 1970–1996 (Negative Binomial Model).

Dependent Variable	Drug Patents (by Application Date)			
	6.1	6.2	6.3	6.4
Constant	−14.0291	−4.79808	−9.41174	−4.85982
Ethical drug sales	0.00031***	0.00031***	0.00029***	0.00031***
R&D	0.00911***	0.01436***	0.01583***	0.01494***
Time trend	0.00837	0.00468	0.00721	0.00475
ONELAB		−1.20302***	−1.48751***	−1.21358***
USLABS		−0.97792***	−0.99237***	−0.97543***
FORLABS		0.09268**	0.08207*	0.08303*
IDIST			−0.05406	
EDIST			−0.00003	−0.00002
Log likelihood	−1803.04	−1777.3	−1776.26	−1777.13
Number of obs.	433	433	433	433

Note: Explanatory variables lagged two years prior to patent application date.
Number of patents.
*Significant at the 0.10 level, two-tail test.
**Significant at the 0.05 level, two-tail test.
***Significant at the 0.01 level, two-tail test.

Patent Regressions

Table 6 gives regression estimates where the dependent variable is the count of drug patents issued to the firm in each year. These patent counts are much greater than the counts for NCEs, which are sparse. Hence, the coefficient estimates in Table 6 typically show higher levels of statistical significance than the corresponding NCE regressions in Table 4, even though the number of observations is about the same. Moreover, the (assumed) time lag is much shorter for patents than for invented NCEs (two years versus seven years), which makes available observations in the late 1980s and 1990s when firms operated relatively large numbers of domestic labs. This allows for stronger inferences in testing for the impact of lab centralization. The disadvantage of patents as a dependent variable is that patents are not a final measure of innovative output; patents vary in importance, and propensity to patent varies among firms.

Both of our control measures for firm size (ethical drug sales and R&D) are highly significant in these patent regressions. The time trend is not, implying a fairly steady rate of patenting over time (except for historical growth in proportion to rising sales and R&D).

The FORLABS coefficient is positive and significant in Table 6, indicating that patenting rose with the number of foreign labs, after controlling for firm size and other factors. This is consistent with the related finding in Table 4 of a positive relation between foreign labs and invented NCEs.

The other geographic organization measures, IDIST and EDIST, are insignificant in the patent regressions. Indeed, the degree of co-location with rival laboratories in the U.S. (EDIST) appears insignificant throughout the analysis in this study. Thus, the findings give no support to the hypothesis that localized spillovers and agglomeration economies among competing domestic labs serve to enhance innovative output (H3a).

The patent regressions do, however, provide evidence on the superiority of a relatively centralized laboratory organization within the U.S. The coefficients (roughly −1.2 for the ONELAB dummy, and −1.0 for USLABS) imply a maximum rate of patenting for firms operating one or two U.S. labs. (For example, a simple multiplication of the coefficients and variables gives −2.2 for a single lab firm, −2.0 for a firm with two labs, −3.0 for three labs, −4.0 for four labs, etc.) While the significance levels for these lab count measures appear high, the results must be interpreted with caution given that propensity to patent can vary, and only two companies in the sample operated with more than two domestic labs (AHP and Johnson & Johnson).

CONCLUSIONS

Our analysis of 21 U.S.-based pharmaceutical companies suggests that the geographic organization of a firm's R&D laboratories can have a significant effect on research productivity, at least in the pharmaceutical industry. Our main findings point to the importance of dispersing laboratories across countries to gain access to local scientific expertise. We also find some evidence that within the U.S., a relatively centralized laboratory structure may be beneficial. We find no evidence that location of research facilities in close proximity with rival labs helps to enhance productivity.

In terms of our specific hypotheses, we obtain mixed support for H1a/b, addressing the question of whether lab centralization is better than decentralization. Clearly, decentralization in the form is a foreign lab network appears beneficial. Within the U.S., however, decentralization seems less desirable: firms operating more than two domestic labs had significantly lower rates of patenting; and multi-lab firms introduced fewer NCEs when their labs were more dispersed geographically. These findings suggest benefits to

decentralization in the international domain but not regionally within a given country. Assuming that the main benefit of decentralization is to tap into localized knowledge, the findings suggest that the international barriers to information flows are much greater than those that operate regionally within a given country.

Consistent with this explanation, we obtain no support for hypotheses on the effects of laboratory co-location within the U.S. We find no evidence that co-location with rival labs has been beneficial (H2a) or detrimental (H2b) for innovation in the pharmaceutical industry. Our tests are limited, however, to average measures of geographic distance from the laboratories of all other major U.S. pharmaceutical companies. While no domestic spillover effects are evident in our results, such spillovers may be taking place only when explicit ties exist among firms (e.g. Almeida & Kogut, 1999; Zucker, Darby & Armstrong, 1998). Moreover, our results do not rule out the possibility of geographic spillovers with university labs, although some recent research was unable to find evidence of university spillovers in the Drugs & Chemicals industry (Anselin, Varga & Acs, 2000) unless they were based on specific ties between university and firms scientists (Zucker, Darby & Armstrong, 1998).

Our analysis of both NCEs and patents support H3a, that firms with more foreign laboratories are more technologically innovative than firms with fewer foreign labs. The statistical findings are also consistent with the strong trend in the industry toward more foreign labs and international consolidations. Presumably, managers believe that a network of international laboratories can be beneficial in the pharmaceutical industry, and they have taken major steps to create and expand those networks in recent years. Our findings suggest that firms pursue these networks to access localized scientific knowledge, which may be difficult to transfer, rather than to access information on licensing opportunities. Information on the latter may be relatively easy to disseminate, and parties on both sides of the transaction have incentives to do so.

Our study has many limitations, and additional research is needed to confirm and extend the results reported in this chapter. Our data sample of only 21 firms omits many important players in the broader drug industry, including biotech firms, universities, research institutes, and foreign pharmaceutical companies. Given the small sample size, some of the findings reported here may be strongly influenced by the performance of one or two firms. The dependent variables in the regression analyses are simple counts of NCEs and patents, which have not been weighted in terms of economic importance. Moreover, aggregation of these and other measures to the company level may conceal relationships that would be visible in a finer, laboratory-level study. Future research may be able to overcome some of these limitations.

NOTES

1. Extensive secondary data collection was required for this study as described in detail in Chacar (1998). The sample in Chacar (1998) includes 38 companies. The sample for the present study is smaller (21 companies), as firms without major research activity in ethical drugs and those operating primarily outside the drug industry are excluded. We also exclude biotechnology companies, given that their role in the pharmaceutical industry was comparatively minor over most of the historical period of the sample.

2. Many firms in the sample perform R&D and operate laboratories in a variety of medical areas. In this study we limit our attention to laboratories that were identified as performing research leading to the potential development of ethical drugs. Nine of the 21 firms in our sample disappear due to merger. Of these, six were ultimately acquired by foreign drug companies.

3. Dense communication is communication that requires a long interaction time between two parties, involving frequent contacts (Christie, Luce & Macy, 1952; Shaw, 1954, 1964). Several factors facilitate this type of communication. First, face-to-face meetings are required, at least periodically (Bordia, 1997; Browskowski, 1980; Daft & Macintosh, 1981). Second, interpersonal ties and networks are needed to provide channels through which the exchange takes place. Interpersonal networks are most dense closest to an individual's physical location and tend to be local or regional (Langlois, 1992; Malecki, 1987). Third, a shared culture and language allow a more accurate and efficient transmission of know-how (Bartlett & Ghoshal, 1989; Ouchi, 1980). Fourth, know-how is sometimes drawn from the organizational memory, which is often location-specific (Walsh & Ungson, 1991). Individuals in closer proximity to the memory will be more able to access the information residing in it (Marshall, 1879). These four factors, which facilitate dense communication, are most likely to be present when researchers are geographically co-located.

Pl. check the reference "Ouchi (1980)", which is missing in the reference list.

4. Geographically-bound economies of scale arise in several areas relating to R&D. First, the probability of having basic research on site increases with geographic centralization (Taggart, 1993). Second, the feasibility of having better library and other support services increases (Taggart, 1993). Third, the probability of reaching a minimum efficient scale in laboratories and technical equipment, or of having such equipment on site, increases.

5. Dense communication is communication that requires a long interaction time among two or more parties and that often involves repeated contact.

6. Chacar (1998) describes the data collection methodology in detail.

7. The Delphion patent database, available on-line from delphion.com, was used to obtain patent counts for those firms (principally, Searle and Squibb) that merged prior to the 1989 date used by the NBER researchers to link patents with their corporate assignees.

8. A close relationship between R&D expenditures and NCE output has been identified in numerous innovation studies (e.g. Graves & Langowitz, 1993; Jensen, 1987). Other researchers have found a strong positive relationship between R&D expenditures and patents (Hausman, Hall & Griliches, 1984). Based on previous research comparing various potential specifications, this study assumes constant returns to R&D (Bound et al., 1984; Hausman et al., 1984; Pakes & Griliches, 1984).

9. The percentage of sales in ethical drugs was obtained from annual reports and analysts' reports for the years 1984 and 1979. The 1979 percentages were used for all years of the sample available. Confidence in this procedure was given by anecdotal evidence showing slow variation in the relative importance of ethical activities in a firm over time.

An examination of the data at hand showed also little variation between the 1984 and the 1979 data. A *t*-test could not reject the hypothesis that the percentage of ethical drug sales was the same in 1979 and 1984.

10. We thank Olav Sorenson for assistance in geo-coding our data.

11. It is possible, however, that causality runs in the opposite direction: more successful pharmaceutical firms tend to establish more foreign labs, but these labs do not enhance innovation.

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