# Are licensing markets local? An analysis of the geography of vertical licensing agreements in bio-pharmaceuticals

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Abstract. As the value chain of the pharmaceutical industry dis-aggregates, upstream discovery is increasingly carried out by small research-specialized firms while downstream development, testing and marketing is conducted by global pharmaceutical firms. Licensing plays an important role in this emerging division of labor. We theorize that, similar to markets for upstream inputs such as scientific knowledge, proximity may also matter for licensing, which we conceptualize as downstream end markets for small biotechnology firms. We examine whether co-location affects the likelihood of vertical licensing transactions between biotechnology firms and global pharmaceutical firms. Discussions with industry executives indicate that large firms search globally for in-licensing opportunities and that licensing transactions should not be sensitive to the geographic locations of the transacting parties. However, an analysis of compounds developed by small biotechnology firms licensed to global pharmaceutical firms suggests that licensing transactions are more likely to occur between firms located in the same geographic area. Our results point to the possibility that licensing markets are sensitive to the proximity of the partners, and that despite global search processes by multinationals in the pharmaceutical industry, licensing markets are localized.

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## 1. Introduction

The pharmaceutical industry is undergoing a significant change in the organization of its value chain. The industry has historically consisted of large, vertically integrated companies that relied on in-house research to discover new compounds that could be developed, tested and distributed through a firm's marketing network. Increasingly, large pharmaceutical firms are outsourcing upstream discovery to small research-intensive firms that will never grow the point where they can undertake the significant capital investments required to develop and market a new compound. According to industry data, of the 324 biopharmaceutical drugs in development in 2004, 72% were developed by small, specialized biotechnology firms and 16% by large pharmaceutical firms; however, pharmaceutical firms accounted for 45% of 108 already-approved biotechnology drugs, suggesting that a large proportion of biopharmaceutical drugs are discovered by small biotechnology firms and developed and/or subsequently marketed by large pharmaceutical firms.[1]

As a result of these changes, the industry is characterized by an unusual degree of fragmentation in upstream discovery and concentration in downstream development, testing and marketing. Licensing between small and large firms plays a large role in this emerging division of innovative labor. Between 1996 and 2005, the number of out-licensing deals in biotechnology increased from about 380 to 700, with the value of those deals increasing from $10 billion to about $55 billion[2].

These shifts in value chain have implications for the geographic distribution of value-adding activities, which is the focus of this paper. While research-intensive firms are often clustered near critical inputs, particularly scientific labor markets, markets for new drugs are national or global in scope. Pharmaceutical firms operate multinational networks of subsidiaries that can develop and market drugs on a global scale. If the dis-aggregation of the industry results in an increasing shift of the research function to small firms that are geographically dispersed, it is important that licensing markets can operate to link those firms to the handful of global pharmaceutical firm possessing downstream capabilities in

[1] Figures from authors' analysis of data published by Phrma, Medicines in Development: Biotechnology. 2004 Survey.
[2] Figures for the US only. "Avoiding premature licensing" Nature, December 2006, p. 986.

development and marketing. To accomplish this, licensing markets must bridge not only organizational boundaries but significant geographic boundaries as well.

We analyse the extent and geography of licensing between small biotechnology firms and the world's largest pharmaceutical multinationals. If licensing markets operate as arms-length transactions, then markets for technology should not be sensitive to the locations of buyers and sellers. However, it is not hard to imagine that markets for discoveries developed by small firms are fraught with difficulties, and that these would be exacerbated by both geographic and cultural distance. If this is the case, geographic distance could impose significant frictions on the operation of licensing markets such that local actors have significant informational advantages in identifying, evaluating and selecting drugs for further development.

We focus on this issue, analyzing whether geographic proximity matters for licensing between biotechnology firms and global pharmaceutical firms. The question has both public policy and managerial implications. The shift of early-stage discovery to small, specialized firms means that the locations of research can now expand beyond the geographic footprint of large firms to countries and regions that have historically been outside the industry. Indeed, municipalities around the world have invested significant efforts to develop bioclusters in order to gain an entry ticket into the industry and capitalize on local scientific expertise. These clusters are typically situated near universities and research centers, and as a result biotechnology firms are often founded in different locations from pharmaceutical firms, whose geographic locations reflect the industry's roots in the chemical and dye industry. For instance, major pharmaceutical firms in the United States and Switzerland are headquartered in New Jersey and Basel, respectively, whereas important biotech clusters are located in California, Boston, and Zurich, where there has not been a significant presence of large pharmaceutical firms. Dis-aggregation of the industry can thus lower entry barriers for regions and countries that historically have not participated in the industry.

At the same time, if the broadening geographic scope of the industry continues, pharmaceutical firms will need to develop capabilities to search for, identify, and assess potential license opportunities

outside the traditional geographic footprint of their subsidiary networks. If distance creates frictions in licensing markets, the spread of locations that can support specialized biotechnology firms will be limited. In that case, some locations may become isolates, limited to transactions between local parties. Locations that directly connect specialized research firms to global pharmaceutical firms will emerge as important geographic nodes in the industry.

We interviewed several industry executives about the processes by which they search for and identify new licensing opportunities. With growing pressures to outsource discovery, large pharmaceutical firms are increasingly investing in routinized processes to "shop the globe" for new licensing opportunities. Our interviews suggest significant investment in global scanning and screening capabilities. Informal contacts and scientific connections are also important means by which firms find new licensing opportunities. Our discussions suggest that licensing markets do not operate at the local level but are global in nature and often flow through the "invisible colleges" of research scientists.

We also investigate these issues utilizing data on licensing of new drug compounds. We analyze the geographic footprints of both the developers and licensees of drug compounds and estimate whether, conditional on a compound being licensed, co-location is an important predictor of the choice of licensing partner. We find that co-located are more likely to be licensing partners, even after controlling for a number of firm- and drug-specific characteristics. Our finding indicates that co-location matters to licensing transactions, despite the global search processes of large firms.

## 2. Vertical licensing agreements: background literature

It is well-established that innovation in bio-pharmaceuticals takes place within networks of heterogeneous organizations, and that these networks frequently are structured into vertical collaborative alliances. Major categories of organizations include universities, biotechnology firms, and integrated pharmaceutical companies. These organizations have broadly different but complementary capabilities to innovate. Specialized biotechnology firms, which are often university-spin offs, can be seen as playing a linking role, in-licensing early stage discoveries from universities and translating them into marketable technologies that can be out-licensed for further development and commercialization by large

pharmaceutical firms (Gittelman, 2006; Stuart et al, 2007).

A number of studies have shown the importance of vertical collaborative alliances in linking biotechnology firms and pharmaceutical firms. Pisano (1991) points out that because biotechnology-based compounds often have a number of potential downstream applications, a market for R&D is an efficient means for specialized biotechnology firms and large firms to share R&D risks. Reviewing secondary data from the late 1980s, he finds that many specialized biotechnology firms are forward integrated into manufacturing, but not into distribution and marketing, which are often handled by larger partners. Most biotechnology-based drugs were developed by entrepreneurial biotechnology firms, but pharmaceutical firms were also diversifying their R&D into biotechnology-based methods. He argues the tacitness of R&D explains vertical integration between R&D and specialized manufacturing, but that hazards are lower for exchanges between R&D and distribution. These latter transactions are therefore likely to occur through licensing and other collaborative arrangements between small and large firms with complementary R&D and distribution capabilities, respectively.

Arora and Gambardella (1990) assert that the strategic intention of most agreements between small biotechnology firms and pharmaceutical firms is to develop and commercialize discoveries made by the smaller firm. They find that alliances between large pharmaceutical firms, universities and biotechnology firms are complementary strategies, supportive of a division of innovative labor among these organizations. They also find that pharmaceutical firms with higher in-house technological assets in biotechnology are more likely to ally with biotechnology firms, indicating that in-house knowledge can help assess and evaluate external partnerships.

In a subsequent paper, Arora, Fosfuri and Gambardella (2001) develop a framework to show that markets for technology serve several important functions in technology-intensive industries. They encourage the creation of small firms specializing in research, and reduce internal technological assets as a source of distinctive competitive advantage for vertically-integrated firms. A strong patent system and well-functioning licensing markets enable better standalone valuations of knowledge assets, lowering informational frictions in trade in technology. Well-functioning markets for technology thus make

possible increased specialization and a dis-intermediation of the value chain, reducing the need for firms to invest in in-house complementary assets, both upstream or downstream. Small firms pursuing different research paths generate increased variety and broaden the scope of discoveries from which pharmaceutical firms may select for further development. Their framework suggests that well-functioning markets for technology leads to an increasing organizational division of innovative labor and a corresponding rise in innovative output in the industry.

Gittelman (2006) and Stuart, Ozdemir, and Ding (2007) conceptualize specialized biotechnology firms as critical technology brokers between universities and large pharmaceutical firms. Gittelman (2006) measures knowledge flows across universities, biotechnology firms, and large pharmaceutical firms by tracking scientists who patented at more than one of those organizations. She finds that patents are more highly cited when they include scientists that patented for both universities and biotechnology firms but finds no effect on citations to patents that include scientists that patented for universities and large pharmaceutical firms. Stuart et al (2007) analyse the relationship between biotech firm's licensing with these two sets of partners. They find that biotechnology firms with extensive upstream links to universities are more likely to out-license to pharmaceutical firms, but that the relationship attenuates with the age of the biotechnology firm, indicating that as firms mature they perform more development in-house.

None of these studies consider the effect of co-location on the likelihood of vertical licensing agreements. And yet geographic proximity has been shown to play a critical role in facilitating upstream linkages in the industry. In an influential paper, Zucker, Darby and Brewer (1998) find that biotech firms locate nearby "star" scientists working at universities; Audretsch and Stephan (1996) find that scientists engaged in direct knowledge transfer are more likely to be co-located with biotechnology firms than those with arms-length relationships. Gittelman (2007) finds that teams that combine researchers at biotechnology firms and universities are more likely to patent their research when they are located in close proximity than when they are geographically dispersed. Stuart and Sorenson (2003) find that venture capital relationships are localized in biotechnology. Furman et al (2006) find that proximity to

public research increases the productivity of private research of pharmaceutical firms, although they find the reverse for spillovers from private sources. Thus, localization is important in facilitating access to critical inputs, particularly research scientists, and firms have clustered nearby pools of scientific labor and scientific research institutions.

However, there has been little research on whether downstream product markets of small research- based firms are subject to similar pressures for localization. We conceptualize out-licensing as important end-markets for specialized research firms, and as important input markets for large pharmaceutical firms. We explore whether these markets are sensitive to the proximity of the partners. Our question is motivated by the broader proposition that licensing markets may be similar to markets for scientific knowledge in benefiting from geographic proximity.

This may be true for a number of different reasons. First, geographic co-location can assist in identifying and evaluating promising technologies for in-licensing. The search process is likely to involve significant costs and time, as it requires scanning the discoveries of hundreds if not thousands of small firms that are frequently private and are geographically dispersed. Even if pharmaceutical companies are able to scan globally for licenses, local subsidiaries may be positioned to learn first about promising technological opportunities in their region.

Second, co-location can help evaluate the desirability of allying with a specific partner. Our industry informants stress that apart from technological uncertainty, firms face significant risks in allying with unknown partners, and that reputation effects are very important for both small and large firms in selecting partners. Recent research (Guedj and Scharfstein, 2005, Arora et al, 2007) shows that small biotechnology firms are more likely to continue to promote unsuccessful drugs than large pharmaceutical firms, which are more selective in the drugs they choose to develop. This suggests that moral hazard problems are likely to be especially high for licenses from small firms. Co-location can lower these risks, insofar as reputational knowledge is likely to be richer for co-located partners, and flow through a variety of actors, including other partners, finance providers and employees (Powell and Owen Smith, 2006).

Finally, co-location assists in knowledge transfer. Licensing agreements often do not require a one-off transfer of technology but represent a significant commitment of resources and time to an ongoing collaborative venture. In a recent example, Novartis entered a 10-year agreement worth over $1 billion with a German biotechnology firm to develop a range of new drugs, with payments contingent on successful milestone completion of clinical trials and marketing approvals.[3] New drugs developed by biotechnology firms are frequently based on a discovery path that lies outside the traditional synthetic chemistry expertise of large pharmaceutical firms, increasing the need for ongoing knowledge transfer in developing a drug. The more early-stage the deal, the more likely joint research and coordination will be required, and the more likely knowledge transfer will be facilitated by proximity between partners. However, even co-marketing agreements can impose significant coordination requirements. When Imclone and its European licensee could not agree on payment terms for modifications to European clinical trials, the partner refused to implement those modifications, causing Imclone to lose valuable data for its American trials. If co-location facilitates cooperation and enables parties to develop shared and common understandings of a compound's development and marketing trajectory, it should benefit all stages of technology licensing, not only early-stage licenses.

We test the hypothesis that licenses will be more likely to occur between co-located partners than between geographically dispersed partners, controlling for a variety of firm- and drug-specific characteristics. Our data consists of licenses on drug compounds, and therefore do not include numerous patent cross-licenses that would not fall into the category of vertical linkages that we are interested in. We further restrict our tests to licenses between small biotechnology companies and global pharmaceutical firms, as these are the most likely to capture these vertical linkages in which early-stage compounds discovered by a small firm are out-licensed to a large firm for further testing and development.

[3] "Novartis, MorphoSys expand antibody R&D agreement; payments may exceed 1 bln usd", Forbes, Dec 2, 2007.

## 3. Interviews with licensing executives

In order to understand the processes by which firms search for potential licensing partners, whether as buyers or sellers, we interviewed a number of managers involved in licensing at their firms. Managers we spoke to worked at two global pharmaceutical firms, two small biotechnology companies, and one mid-sized pharmaceutical firm (in a few cases we interviewed more than one manager at the same firm). Discussions focused on the following topics: factors influencing the decision to out-license a compound; the process by which firms search for licensing partners; the risks of licensing versus internal development and how those risks are managed. Because of the relatively small number of managers we spoke with, the information we gathered is not necessarily representative of practices in the industry at large.

Overall, our interviews suggest that large pharmaceutical firms are increasing formalizing and systemizing the in-licensing process; are investing significant resources in search for in-licensing opportunities; and seek to scan globally for such opportunities. At the same time, scientific networks play an important role in opportunity identification. Prior research (Gambardella, 1995; Cockburn and Henderson, 1998; Gittelman, 2007) examines how participation in scientific communities improves firm's in-house research productivity. Our interviews suggest that, as emphasized by Hicks (1995), these connections are also valuable in generating new business leads for external partnering. Despite increasing formalization of the process, informal connections to scientific communities and in-house research expertise in a field were stressed as critical in the ability to scan and spot licensing opportunities.

The major stages of in-licensing include search and screening; in-depth analysis and final screening; and deal negotiation. The process is initiated by scientific experts in their field who work for the firm (at one large firm we interviewed, these individuals, called "finders", are specialized in searching for licenses, whereas at another they are senior directors of research units). These individuals combine expertise in their scientific specialty with knowledge of the firms' drug development strategy in that field. Potential licensing opportunities are identified by experts in a variety of ways, including informal contacts and participation at industry and scientific meetings. Indeed, one informant told us that knowledge of the

landscape of scientific opportunities and the location of the "frontier" was not a major challenge, given the effectiveness and speed of the system of scientific communication (publications, conferences, etc.). Codified, publicly available information does not appear to play a major role in lead identification: vendor-supplied databases of drug compounds are used primarily for information on stage of development rather than to identify opportunities, although one large company developed an internal database to track leads around the world, investing significant amounts in proprietary in-house information-gathering and monitoring.

The managers we spoke with stressed that companies search globally and are not sensitive to the location of a drug's originator. One executive told us: "We are border blind as to where an asset comes from. There could be great scientists anywhere." In addition to informal participation in sc ientific communities, formal company events play a role in global search. One firm sponsors private meetings in different bioregions around the world. Some 80-100 local firms are invited to present their work in short informational sessions. From those, about 10-15 are selected for further in-depth evaluation and analysis, from which perhaps one or two may eventually lead to a licensed compound.

In addition to the efforts of large firms to search globally, small firms also actively seek out partners outside their home country. One executive mentioned that the business model of partnering globally had diffused rapidly and that firms in developing countries such as India had become quite sophisticated: "All it takes is one business development person sitting in New York." She stressed that co-location was not a critical factor in choosing licensing partners on either the buy or the sell side.

Another executive discussed the importance of informal contacts in the licensing community itself in the licensing process. While these contacts were not used to scan for initial leads, the network was cited as important in updating information about compounds and, in particular, gaining a foot in the door to firms with promising licensing opportunities.

At two of the large firms interviewed, multi-functional teams were central in the evaluation process once leads were identified. Teams consist of individuals with scientific, business, and legal expertise, and an exhaustive analysis is conducted on multiple aspects of each of these factors. One

executive spoke about investing as much as possible in learning about a compound and a company before signing a deal to minimize the chance of failure.

Our interviews suggest that licenses between large and small firms would not be sensitive to co-location. First, companies scan globally and our informants claimed that they were agnostic to the location of a firm developing a compound, and were not inclined to favor nearby firms over those located in other regions or countries. Second, ongoing collaboration post-licensing did not emerge as an important variable in the decision to in-license. The degree to which firms collaborated post-license appeared varied by licensee strategy as well as the type of license. One executive spoke of needing to work with the small firm only if their scientists possessed specialized and unique knowledge of a compound, while another spoke of wanting to remove the small firm altogether from development since this was generally outside their area of expertise. Instead, she highlighted due diligence and exhaustive review done prior to a deal so that the need for post-deal collaboration would be minimal.

The role played by in-house experts suggests, however, that co-location might matter, at least for the scanning process. Subsidiaries frequently specialize in research fields or disease categories. If a firm's scientists in those subsidiaries are more aware of business prospects in their immediate region then they may be inclined to recommend opportunities that are co-located with their own subsidiary. In that case, co-location between licensing partners could reflect a local bias not so much in knowledge transfer post-license as in the ability of scientists to scan the scientific opportunity landscape prior to a license.

Indeed, recent geographic shifts by pharmaceutical firms suggests that co-location does matter to opportunity scanning. In 2006, Novartis moved its vaccine and diagnostics headquarters to Cambridge, Mass., and many other drug companies have recently opened research facilities in Boston (Heuser, 2006). Pfizer has built a major lead screening facility to support the firm's internal research; the facility was located in the Cambridge/Boston area "to identify and develop collaborations with academic, medical and biotechnology partners" (Pfizer, 2006). These recent moves suggest that pharmaceutical firms are re-orienting their subsidiaries to gain better access to licensing opportunities in prominent biotechnology clusters.

## 4. Data description

Our data are drawn from Pharmaprojects, an industry database that tracks the progress of new drug compounds. The company records, collects and tracks data on all new compounds, starting from an early (pre-clinical research) stage of development. A new compound is included if it meets the criteria of being a potentially viable drug candidate, and the company tracks drugs as they progress through the development process, updating the clinical status as it changes over time. Importantly, compounds whose development is ceased for whatever reason are not removed from the data, so our analysis includes drugs that failed or were withdrawn along with those that are launched or in active development.[4] We match each compound to its earliest recorded entry in the data to identify the date of compound discovery. In total, there are 36,646 compounds in the dataset, spanning new compound introductions from the late 1980s through 2006.

The data provide information on the therapeutic and pharmacological properties of drugs, as well as the technique used to discover the compound. We utilize these codes to categorize drugs into two main technological categories. A compound is coded as a *Biotechnology drug* if it falls into one of a number of categories that are distinctive to biotechnology methods of drug discovery. All other compounds are categorized as *Non-Biotechnology drug*. The majority of these were developed using traditional synthetic chemistry methods[5].

Where possible, we adjust names of originators to reflect the earliest firm listed, and account for name changes due to mergers. We then group firms into four broad categories:

[4] The Pharmaprojects data has an advantage over other data sources, eg, patent applications, in that Pharmaprojects screens out compounds that are not considered to be viable drug candidates and thus present a more realistic picture of actual product pipelines. Sources of the data are company contacts, websites, press releases, presentations, journal references, and published scientific reports.

[5] Biotechnology origin of materials include the following categories: biological proteins (including sub-categories antibodies and recombinant proteins); Virus particles; Nucleic acids (including sub-categories viral vectors and non-viral vectors); recombinant peptides; cellular therapy; bacterial cells.

**Global Pharmaceutical Firms** – We identify 25 of the largest pharmaceutical firms, ranked by the number of drugs in the dataset and the number of in-licenses[6].

**Biotechnology firm** – A firm is coded as belonging to this category if its research focus is listed as "biotechnology" in Pharmaprojects and/or if over 30% of its drugs fall into one of the biotechnology categories as defined above.

**Small and Medium sized firms** – All firms not falling into one of the two categories above.

**Universities and Tech transfer** - Academic and other non-profit institutions and technology transfer organizations.

Table 1 shows the number and average drugs compounds of each of the four broad category of organizations listed above, showing firms that developed at least one compound (firms that were only licensees are not shown in the table). In these tables we use the average number of drugs as a rough proxy for firm size, since comparable sales and employment data are difficult to collect for thousands of small (frequently private) firms located in multiple countries.

[6] The firms are, in descending order of compounds developed: Sanofi-Aventis, Pfizer, Novartis, GlaxoSmithKline, Hoffmann-La Roche, Bayer, Wyeth, Johnson & Johnson, Abbott, Bristol-Myers Squibb, AstraZeneca, Merck & Co, Astellas, Daiichi Sankyo, Eli Lilly, Schering-Plough, Boehringer Ingelheim, UCB, Merck KGaA, Dainippon Sumitomo Pharma, Takeda, Mitsubishi Pharma, Teva, Solvay, Gruenenthal.

Table 1: Types of firms developing compounds, all years, by type of compound and firm type

| | | Number of compounds, Total (*Average/firm*) | | |
|---|---|---|---|---|
| | **Number of Firms** | **Non-Biotech compounds** | **Biotech compounds** | **All compounds** |
| Biotechnology firms | 678 | 2,783<br>*4* | 2,910<br>*4.3* | 5,693<br>*8.3* |
| Global Pharma firms | 25 | 11,841<br>*474* | 1,045<br>*41.8* | 12,886<br>*515.4* |
| Small/Mid-sized firms | 1,758 | 14,950<br>*9* | 1,876<br>*1.1* | 16,826<br>*9.6* |
| University/Tech Transfer | 30 | 758<br>*25* | 275<br>*9.2* | 1,033<br>*34.4* |
| Total | 2,491 | 30,332 | 6,106 | 36,438 |

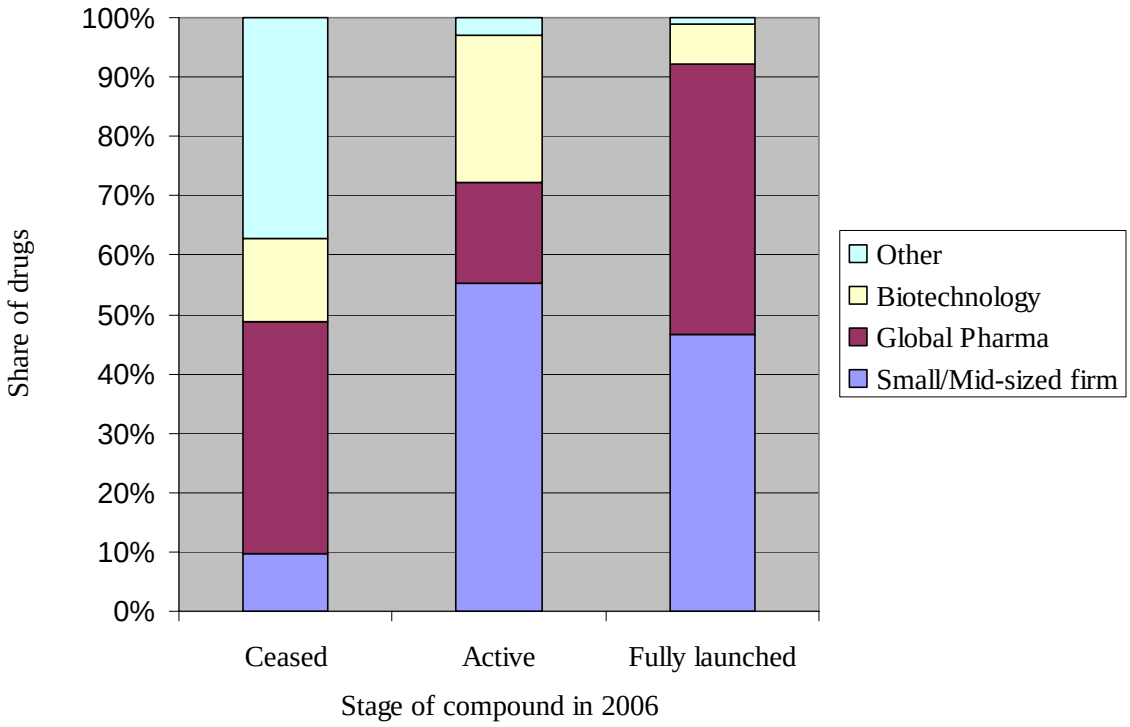
| | | Shares of compounds by type of firm | | |
|---|---|---|---|---|
| | **Number of Firms** | **Non-Biotech compounds** | **Biotech compounds** | **All compounds** |
| **Biotechnology firms** | 27% | 9% | 48% | 16% |
| **Global Pharma firms** | 1% | 39% | 17% | 35% |
| **Small/Mid-sized firm** | 71% | 49% | 31% | 46% |
| **University/Tech Transfer** | 1% | 2% | 5% | 3% |
| **Total** | 100% | 100% | 100% | 100% |
| | | | | |
| | | **Firms' shares of type of compounds** | | |
| | **Number of Firms** | **Non-Biotech compounds** | **Biotech compounds** | **All compounds** |
| **Biotechnology** | 678 | 49% | 51% | 100% |
| **GlobalPharma** | 25 | 92% | 8% | 100% |
| **Small/Mid-sized firm** | 1,758 | 89% | 11% | 100% |
| **University/Tech Transfer** | 30 | 73% | 27% | 100% |
| **Total** | 2,491 | 83% | 17% | 100% |

The table reveals two main patterns. First, the industry is dominated by small firms, both in terms of number of firms as well as share of new compounds. There are 1756 small and mid-sized pharmaceutical firms and 678 biotechnology firms, which account for 46% and 15% of new compounds, respectively. The top 25 firms account for about one third of new drug compounds. Academic institutions make up a very small proportion (3%). Thus despite increasing concentration in the industry and sharp size disparities between the largest and median-sized firms, close to two-thirds of drugs are discovered by

small and mid-sized firms (including biotechnology firms). This pattern underscores the importance of trade in technology between small and large firms to facilitate the commercialization of discoveries.

One concern in interpreting these data is that the largest companies may not be inclined to publicize information about drugs in their development pipelines for competitive and intellectual property reasons. Smaller firms may be more eager to publicize their drugs in the pipeline, in order to attract investors and potential partners. The information in Pharmaprojects may thus be biased towards smaller firms in terms of number of compounds reported. However, this is unlikely to be the case for launched drugs since information on those drugs is publicly available and large firms do not have incentives to withhold information on launched drugs. The bias is also less likely for ceased drugs that were already launched. We therefore examine shares of the different firm types by stage of development. Figure 1 shows that the share of large firm's launched and ceased drugs is much higher than their share of active compounds (45% and 39%, against 17% respectively). These figures do give some support for the idea that the share of global pharmaceutical firms' in total compounds in development could be understated in these data. Since our analysis focuses on licenses of drugs developed by biotechnology firms – which have greater incentives to report data on active compounds – this potential bias in the data should not affect our statistical results.

Figure 1. Share of firms by stage of compound




The second pattern we observe from Table 1 is that firm size and technological specialization do not map cleanly onto one another. Biotechnology firms and small and mid-sized firms are similar in terms of size (with 8.4 and 9.6 average drugs/firm, respectively) but they differ in terms of their relative technological focus. About one-half (51%) of new compounds discovered by biotechnology firms are in the biotechnology categories. As a result, biotechnology firms account for the highest share (48%) of biotechnology compounds, much higher than their share of non-biotechnology drugs (9%). In contrast, only 11% of compounds discovered by mid-sized pharmaceutical firms are biotechnology compounds, slightly more than the share of global pharmaceutical firms (8%). These numbers give a broad indication that small and mid-sized pharmaceutical firms, which include well-established mid-sizecd firms such as Shire and Forrest Labs, resemble larger firms in terms of technological focus on traditional chemical-based methods of discovery. The distinction between "biotechnology firms" and "small and medium-sized pharmaceutical firms" is thus mostly meaningful in terms of relative technological focus, whereas

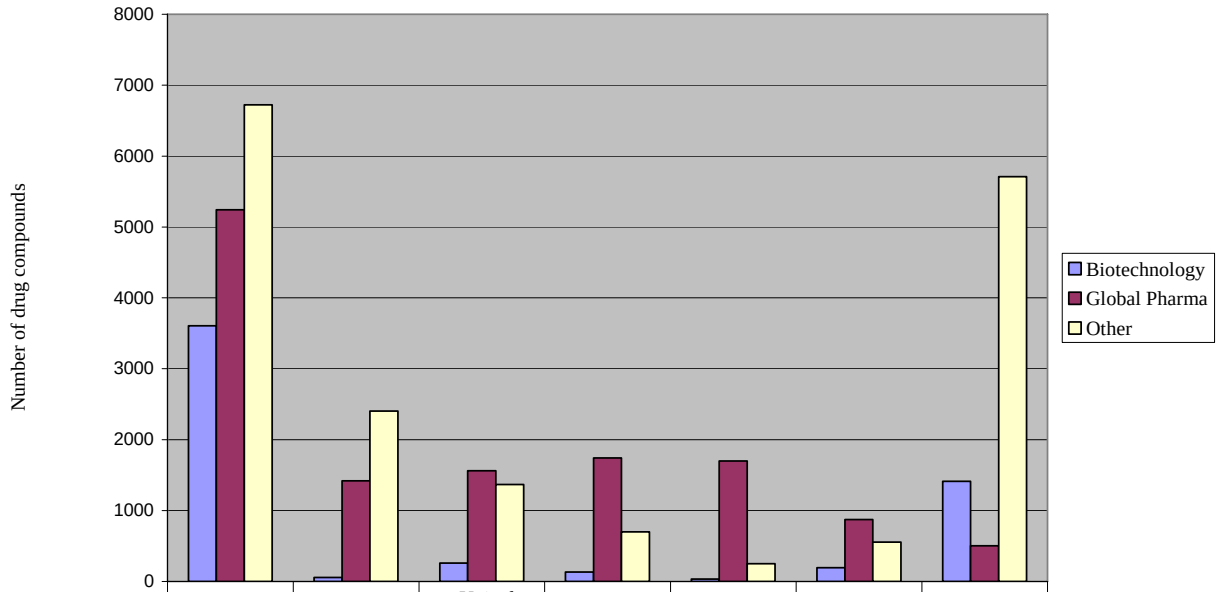
the distinction between "small and medium-sized pharmaceutical firms" and "global pharmaceutical firms" is mostly meaningful in terms of firm size. In our models, we focus on licensing between biotechnology firms and global pharmaceutical firms as capturing transactions across groups of firms that differ *both* in terms of firm size and technological focus. These transactions are most likely to capture licensing arrangements that bring together complementary capabilities in biotechnology drug discovery and downstream development, testing and marketing.

*Geography of firms, drug compounds and licenses*

We collect data on the geographic footprints of the firms in our dataset. We utilize the Directory of Corporate Affiliations and for firms not listed in the DCA – mostly smaller firms - we use information given in Pharmaprojects. We record the location of a firm's headquarters and its subsidiaries in a given year. We identify 14,144 locations associated with 2,654 firms that are either drug originators or licensees. For all firms, we are able to identify the country, state and city of the headquarter location. For the total set of facilities, including subsidiaries, we can identify locations for 80% of facilities at the country, state and city level (11,253 locations). For the remaining 2891 facilities, 36 can be identified at the country and state level, and 2,891 at only the country level.

The majority of drugs are developed and licensed by firms headquartered in the United States, Japan, and a handful of European countries: the UK, France, Switzerland, and Germany. Figures 2 and 3 show the number of drugs and firms by the headquarters location of the firms developing those drugs. They also show the breakdown by the three main categories of firms described above[7]. About 70% of firms are headquartered in those six countries, out of which about half are in the United States (figure 3), and these firms account for about 80% of all new drug compounds (figure 2). Note that these figures only show headquarters locations and some unknown share of drugs by global pharmaceutical firms have been developed in a country different from the headquarters of the firm. Biotechnology firms are highly concentrated in the United States, which accounts for 53% and 63% of firms and new drugs, respectively. Since biotechnology firms are more likely to be single-site firms, those shares track more closely the geographic origin of those drugs.

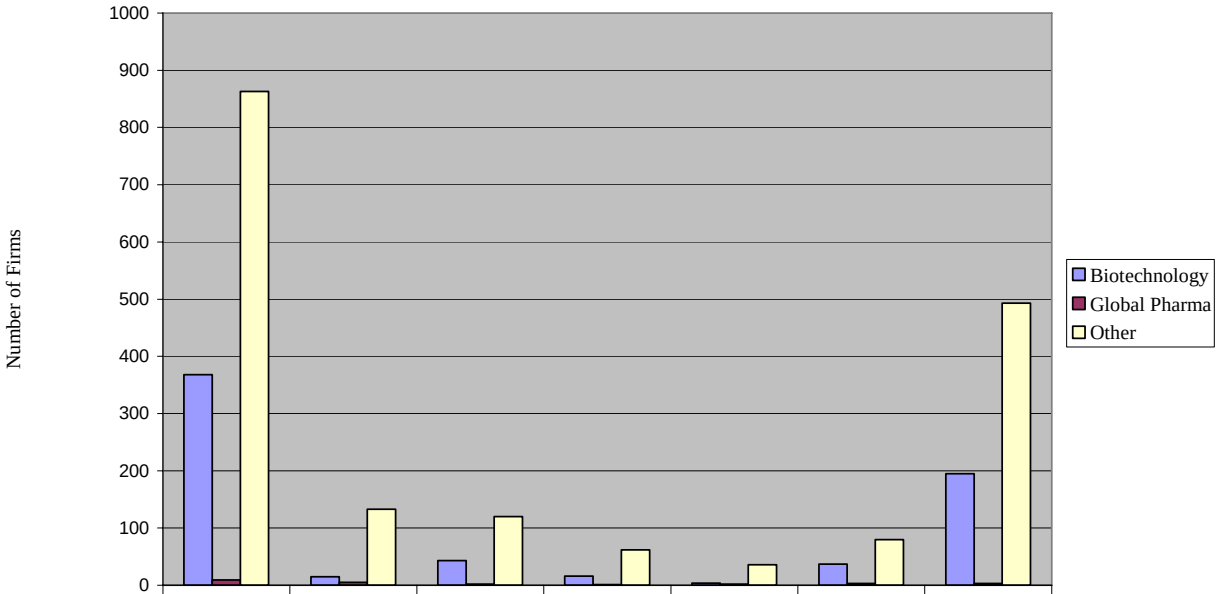
Figure 2. Number of drugs by HQ country and type of originating firm




| | US | Japan | United Kingdom | France | Switzerland | Germany | Rest of World |
|---|---|---|---|---|---|---|---|
| Biotechnology | 3604 | 57 | 259 | 134 | 33 | 194 | 1413 |
| Global Pharma | 5242 | 1418 | 1562 | 1741 | 1699 | 873 | 504 |
| Other | 6724 | 2403 | 1365 | 699 | 251 | 554 | 5710 |

[7] Note that the "other" category includes mostly mid-sized firms, but also shows data for universities and unidentified firms.

Figure 3. Locations of Firms Developing New Drug Compounds, by Firm Type



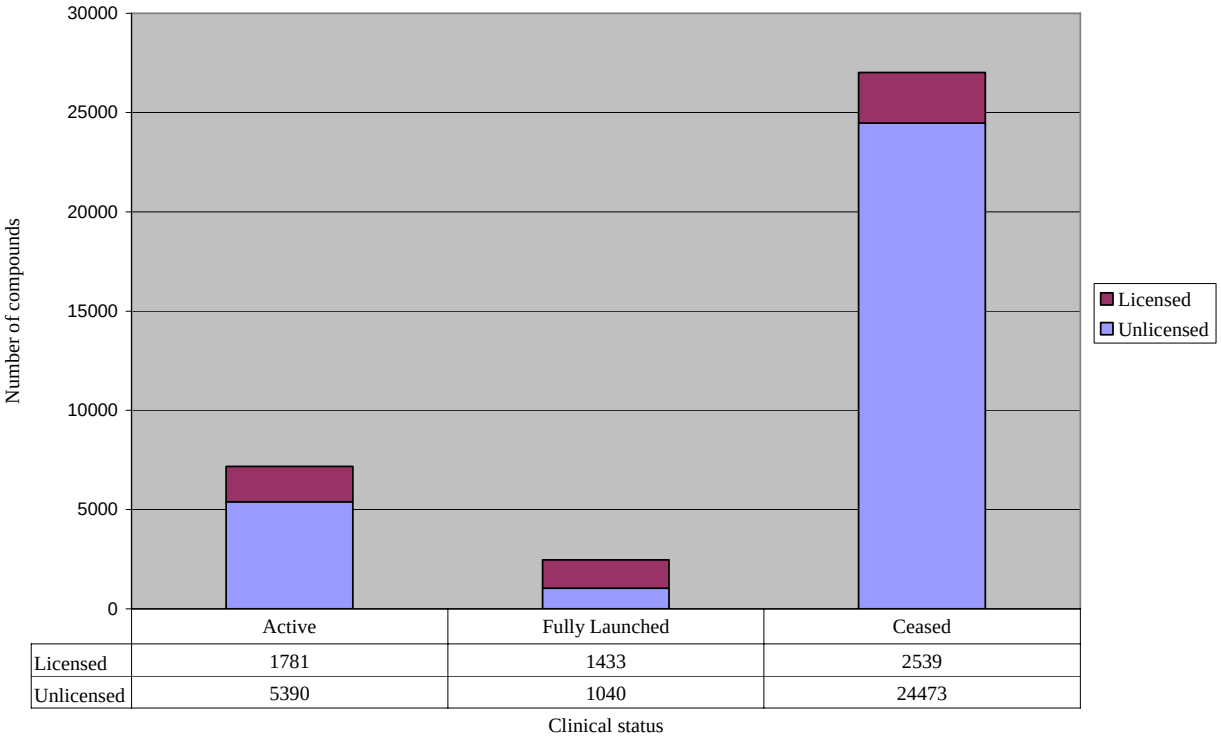

| | US | Japan | United Kingdom | France | Switzerland | Germany | Rest of World |
|---|---|---|---|---|---|---|---|
| Biotechnology | 368 | 15 | 43 | 16 | 4 | 37 | 195 |
| Global Pharma | 9 | 5 | 2 | 1 | 2 | 3 | 3 |
| Other | 863 | 133 | 120 | 62 | 36 | 80 | 493 |

Figure 4 shows all drugs by their clinical and licensing status in 2006[8]. About three-fourths (74%) of compounds in the database are ceased, meaning development was discontinued and/or they are no longer being marketed. The remaining compounds are either Active, meaning they are still in development (20%) or Fully Launched (7%). Only one-third of all compounds are ever licensed. The highest rate of licensing (58%) is for fully launched drugs, followed by active drugs (25%) and ceased (9%). This is intuitive, suggesting that more successful drugs are more likely to be licensed as a means of increasing the geographic and product market scope of a drug. On average, licensed drugs have 2.1 licenses, with higher averages for launched drugs (3.1 licenses). Thus, successful drugs may be marketed

[8] Because of the way the data are structured, we can only observe clinical status in the last year for which we have data (2006).

to a number of partners, further suggesting the importance of licensing markets in disseminating drugs to new markets.

Fig. 4 Licensing and Clinical Status

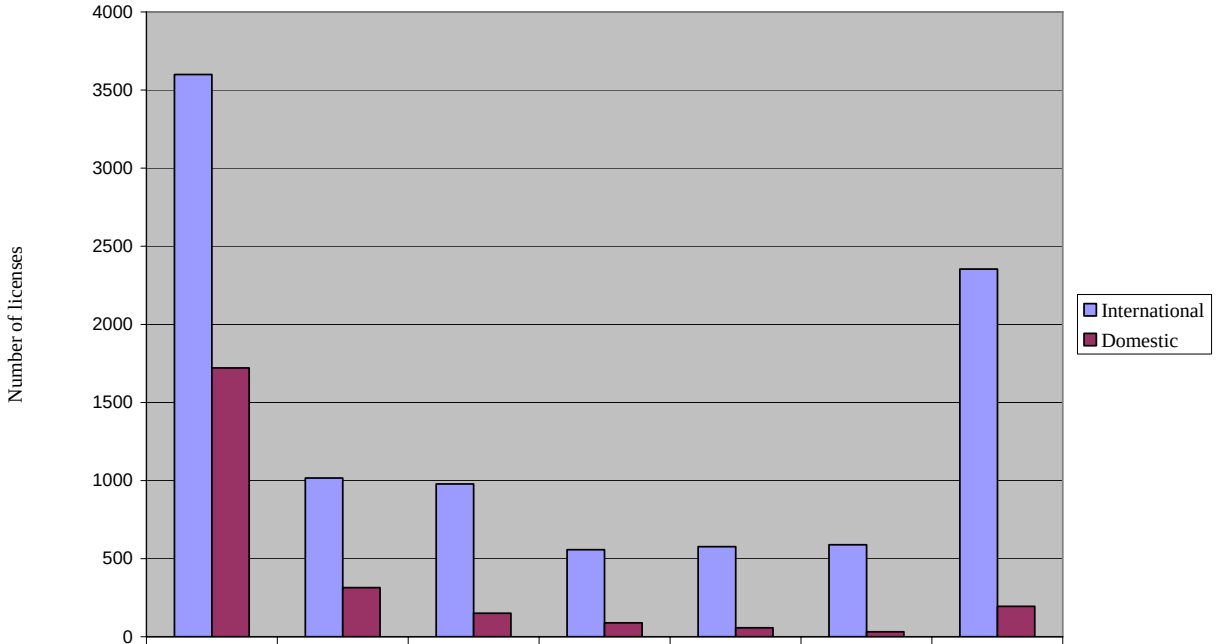



| | Active | Fully Launched | Ceased |
|---|---|---|---|
| Licensed | 1781 | 1433 | 2539 |
| Unlicensed | 5390 | 1040 | 24473 |

Clinical status

Figure 5 shows that a strikingly high proportion of licenses are international: overall, 80% of licenses involve firms whose headquarters are in different countries. The data indicate that licensing is an important mechanism for cross-border flows of technology in pharmaceuticals. Among the top licensing countries, the US has the lowest rate of international licensing (67%) which likely reflects the relatively large size of its domestic market.

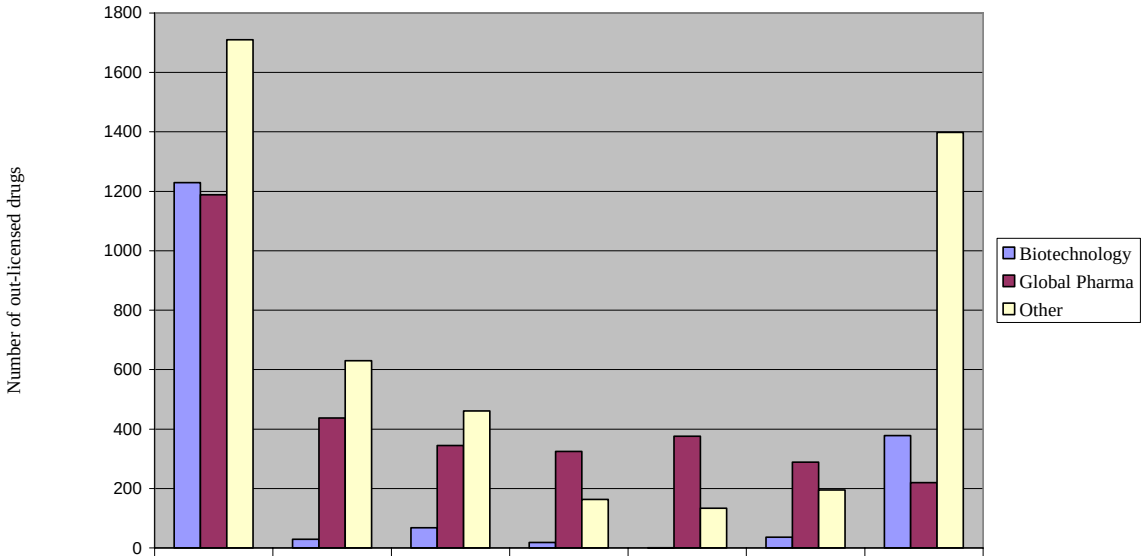
Figure 5. Domestic vs. International Licenses, by HQ country of Licensor Firm




| | USA | Japan | UK | Germany | France | Switzerland | Rest of World |
|---|---|---|---|---|---|---|---|
| International | 3599 | 1016 | 978 | 557 | 577 | 590 | 2354 |
| Domestic | 1721 | 315 | 151 | 89 | 57 | 32 | 194 |

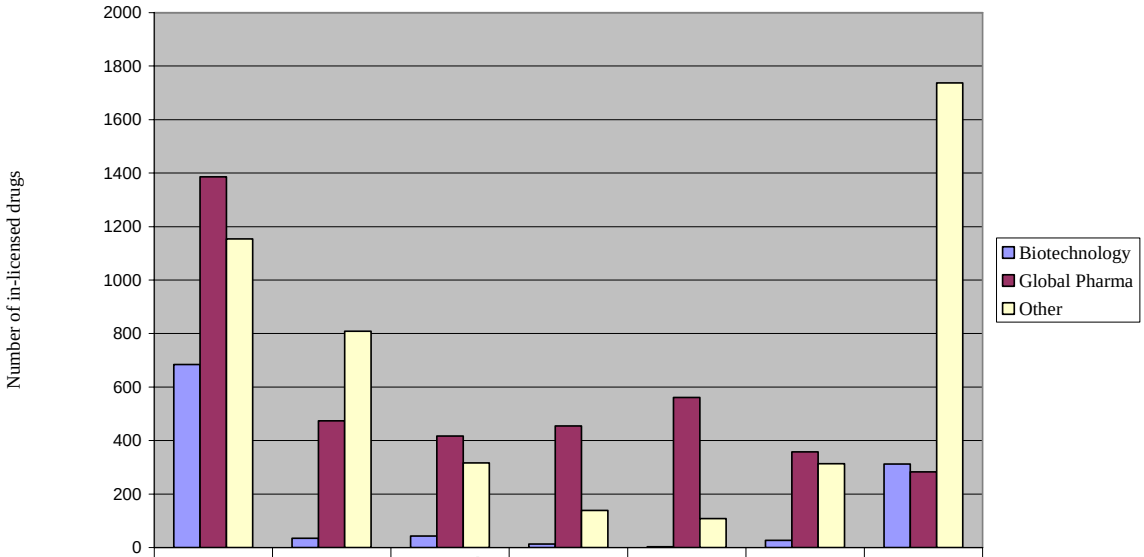
Figures 6 and 7 show the origin and destination countries of licensed drugs. Note that these figures count multiple licenses of a single compound as separate licensing transactions. Again, the top 6 countries dominate. The figures indicate that the US is a net exporter of licenses, accounting for 43% of out-licenses and 33% of in-licenses. US biotechnology firms are an important source of licensed compounds, out-licensing slightly more compounds than US-based global pharmaceutical firms. They account for 13% of all out-licensed drugs and only 7% of in-licensed drugs. This pattern is only apparent in the US; in other countries biotechnology firms out-license to a much lesser extent than other firms. This gives an indication that US biotechnology firms may be relatively more specialized in research, and hence more likely to engage in vertical licensing transactions, than biotechnology firm in other countries.

Fig. 6 Licensed drugs by HQ Country and Type of Licensor Firm




| | US | Japan | United Kingdom | France | Switzerland | Germany | Rest of World |
|---|---|---|---|---|---|---|---|
| Biotechnology | 1229 | 29 | 68 | 19 | 1 | 36 | 378 |
| Global Pharma | 1188 | 437 | 345 | 325 | 376 | 289 | 220 |
| Other | 1710 | 630 | 461 | 163 | 134 | 195 | 1398 |

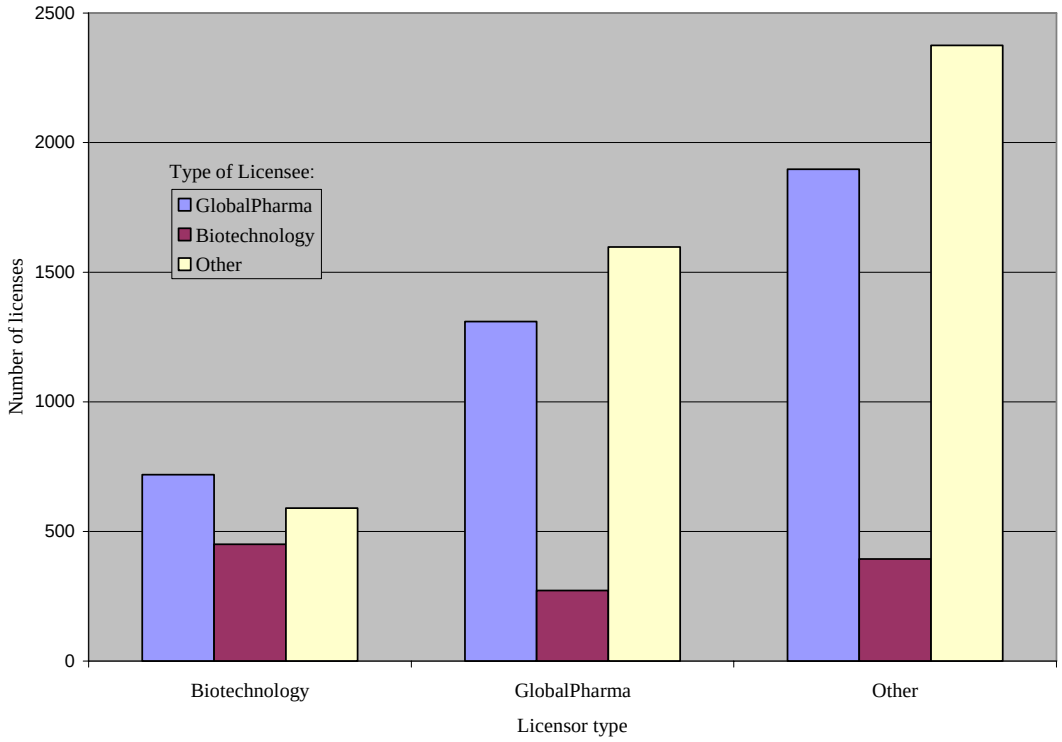
Fig. 7 Licensed drugs by HQ country and type of licensee firm




| | US | Japan | United Kingdom | France | Switzerland | Germany | Rest of World |
|---|---|---|---|---|---|---|---|
| Biotechnology | 685 | 35 | 43 | 13 | 3 | 27 | 312 |
| Global Pharma | 1386 | 474 | 417 | 455 | 561 | 358 | 283 |
| Other | 1154 | 809 | 317 | 139 | 109 | 314 | 1737 |

Figure 8 shows licensing flows among the different categories of firms we identify. In terms of volume, the majority of licensing transactions is between and within global pharmaceutical firms and firms in the small and mid-sized firm category. Overall biotechnology firms are relatively small in terms of their in-licensing from those groups of firm, in-licensing less than 10% of licensed compounds from both groups. About 41% of compounds out-licensed by biotechnology firms are licensed to global pharmaceutical firms, followed by "other" (33%) and other biotechnology firms (25%). We focus on the first group as likely to capture transactions involving development and commercialization of new compounds. Overall, these comprise 720 licenses or 7% of all licenses in our data.

Fig 8. Licensed drugs by type of licensor and licensee




## 5. Econometric models of co-location

We estimate the likelihood that a drug developed by a biotechnology firm will be licensed to a global pharmaceutical firm, and whether co-location increases that likelihood. We include all drugs

developed by biotechnology firms as the set of potentially licensed drugs, with the 25 large pharmaceutical firms as potential licensees of those drugs. We focus on licenses between these groups of firms as most likely to capture the vertical transactions that we theorize will benefit from co-location.

Most drugs are never licensed, and if we don't control for the initial licensing decision we may bias our estimate of co-location by including drugs which were never at risk of being licensed in the first place. The initial licensing decision is based on a number of firm-, drug- and market-specific factors, many of which we cannot observe in our data: the biotechnology firm's financial resources, existing product portfolio, strategy, and development capabilities; the stage of a compound in the pipeline; its clinical prospects, uniqueness, market demand, and the competitive landscape of a drug's product class. In order to estimate the co-location variable correctly, therefore, we employ a Heckman selection correction in which we first estimate a logit model of whether a drug was ever licensed, controlling for a variety of drug-, firm-, and technology-specific characteristics. The licensing model generates a statistic, rho, that indicates whether the Heckman correction improves the model specification. In all our models rho is highly significant ($p<0.001$) so we report results of the Heckman models.

To examine the effect of co-location between parties, we estimate conditional logit models of whether a drug developed by a biotechnology firm is ever licensed to any of the 25 global pharmaceutical firms, conditional on being licensed. For each drug, we create a series of 25 dyads, corresponding to each of the global pharmaceutical firms. If a drug is licensed to one of those firms, the dyad for that firm is coded as 1. All of the 25 dyads are coded as 0 if the drug was licensed to a firm outside the 26 included in our choice set or never licensed. We include as a regressor a dummy variable that indicates whether the licensing partners were co-located (this is coded as 0 if the originator developed the drug). A significant effect on the co-location dummy variable indicates that co-location significantly increases the chances that a given partner will be selected among the potential buyers we identify (conditional on being licensed).

We measure co-location as occurring if, at the time of the license, the partners shared *any* location. That is, our co-location variable takes a value of 1 if *any* subsidiary of the global

pharmaceutical firm is in the same location as *any* location of the biotechnology firm at the time of the license. Note that we cannot observe the actual location in which a licensing transaction takes place. Most biotechnology firms are single-site companies, so we feel safe in assuming that the drug was developed at that site. However we do not know which subsidiary in the pharmaceutical firms' network was responsible for the license and/or development of the compound. Moreover, the deal itself could have originated in a third location that we cannot observe. Given these data limitations, our co-location measure simply indicates whether there was any overlap in the geographic footprints of the licensing partners at the time of the license.

We construct three different measures of co-location. The first measures co-location at the city level, the second at the state level, the third at the country level. We can only measure co-location at the state level for the United States, so for the state proximity measure we code partners as co-located in a state if both are within the US, or they are in the same country, if both are outside the US. In our results, co-location at the state level does not change results from the city-level models. Since the latter are a more stringent test of a co-location effect, we report city-level results, and note that state-level measures yield very similar results.

In the licensing models, we include a number of variables that control for unobservable differences across partners and drugs. The stage of a drug's clinical development influences the probability of licensing; we include dummy variables LAUNCHED and CEASED indicating the most advanced stage a drug has progressed to by 2006, with the omitted category ACTIVE. We include a variable YEARS, a measure of the age of a compound, which ranges from 0 (if the drug entered the database in 2006, the last year for which we have data) to 11, if it entered the data in 1995 or before[9]. We include fixed effects for each of 59 therapy codes that indicate major disease categories and (in some cases) drug classes, eg, "Anti-depressant", "Anti-psoriasis", "Anti-cancer, interferon". These fixed effects control for both competitive and demand conditions in a given class of drugs. We also include

[9] We only have entry year data for drugs entering in or after 1995.

fixed effects for each of the 25 global pharmaceutical firms. In both the logit and conditional logit regressions we estimate robust standard errors for each of the originating biotechnolpogy firms.

We estimate two sets of models: the first including all biotechnology firms, the second only those within the United States. The vertical dis-aggregation of the value chain that we describe is likely to be most extensive in the United States, where a number of institutional factors make research specialization a viable strategy for small biotechnology firms – strong patent protection for genetic discoveries; a financial and fiscal environment that is supportive of entrepreneurial firms lacking tangible product revenues; and a well-developed services sector and labor market to facilitate licensing negotiations and transactions. The institutional apparatus supporting research-specialized firms may be weaker outside the US, and biotechnology firms may be more likely to choose a strategy of downstream integration into development as compared to those located in the US. Hence, estimating the US separately provides a stronger test of our theoretical propositions than for all firms worldwide.

**Empirical Results**

Model 1A includes all biotechnology firms worldwide, and model 1B only biotechnology firms located in the United States. The first column of each (labeled "Licensed") shows results of the logit regression of whether a drug is licensed. In both cases there is a positive and significant coefficient on YEARS, indicating that older drugs are more likely to be licensed. In Model 1 CEASED and LAUNCHED are both significant and negative, indicating that relative to active drugs these categories are less likely to be licensed. It is somewhat unexpected that LAUNCHED should be negative, if we expect that drugs with better clinical prospects are more likely to be licensed. On the other hand, firms could choose to keep those drugs in-house and seek to out-license those they judge as more likely to fail, and to the extent that their judgements correlate with actual success we may expect the observed result. In Model 1B, CEASED is not significantly different from ACTIVE, and LAUNCHED is positive and significant. This is more in line with the expectation that more successful and marketed drugs will be out-licensed. The difference in signs on LAUNCHED across the models might indicate that, as discussed above, non-US biotechnology firms are more likely to forward integrate into development than US

biotechnology firms.

The second columns of models 1A and 1B are the conditional logit models of co-location. The variable CITY_CO-LOCATE shows whether the licensor and licensee shared at least one city location at the time of license. In both models, it is positive and significant, indicating that conditional on being licensed, and controlling for age, technology class, and development status, a compound is more likely to be licensed to a partner that shares a location with the developing firm.

We further explore this result with additional tests. It may be that some regions are more likely, for historical or other reasons, to include both biotechnology and large pharmaceutical firms, and these unobserved regional characteristics are driving the co-location effect. In Japan and France, for instance, Tokyo and Paris are important locations for both global firms and biotechnology firms, whereas in the US the leading locations are different for these two groups of firms. In that case, we may observe a spurious co-location effect between partners that is being driven by variations in the demography of locations. If that is the case, the co-location effect should disappear if we include a variable that controls for whether the biotechnology firm shares a location with *any* of the top 25 global pharmaceutical firms.

In Models 2A and 2B we add a variable to our selection model, CO-LOCATE_ANYPHARMA that is coded 1 if the biotechnology firm shares a location (measured at the city level) with at least one of the top 25 pharmaceutical firms. It is positive and significant in Model 2A but not in Model 2B. This could reflect different organizational demographics within and outside the United States, as discussed above, since in the United States important biotechnology centers are less likely to include large firm headquarters than outside the US. After we include this variable in our selection model, the co-location variable remains significant in both the full sample and in the US-only regressions. The result provides support for our earlier finding that city co-location increases the probability of licensing, even after controlling for the presence of potential partners located in that city.

Lastly, we restrict our sample to drugs that were eventually marketed, whether by the original developer and/or a licensee (Models 3A and 3B). This drops the number of observations by eliminating drugs that were never marketed. This is an even stronger test than the Heckman selection model and our

controls for drug status, by limiting the sample to drugs that, ex-post, were more successful and, presumably, "at risk" of being licensed. The selection model results remain the same (CEASED is no longer significant, since ceased drugs that were never launched are dropped from the regression). The co-location variable remains the same, and is robust to this further restriction of the sample.

## 6. **Discussion and conclusions**

Our statistical findings support the idea that, conditional on being licensed, firms are more likely to license to partners located in close proximity. Prior research has shown that input markets for small, research-intensive firms – primarily financial and human capital resources - are sensitive to proximity. Our findings show that output markets in the form of technology licenses may be similarly sensitive to co-location.

Our finding needs to be interpreted with caution. First, we cannot observe the actual site of the licensing transaction, only whether there was any overlap between the geographic footprints at the time of license. Since biotechnology firms tend to be single-site organizations we are fairly confident that the location of the firm identifies the compounds' location of discovery, but we do not know if the co-located subsidiary of the pharmaceutical firm conducted the licensing deal. Second, we may not have fully controlled for the underlying demographics of regions. If some regions are specialized in specific scientific specialties, then co-location may reflect the underlying terrain of scientific opportunity rather than a bias towards local markets. Insofar as our technology fixed effects and other controls do not capture this, we may be observing the geographic specialization of research which would also lead to localization of technology markets, though not for the reasons we theorize.

With these caveats in mind, we note that our finding on co-location is unexpected, for a number of reasons. The global reach of multinational firms, their efforts to search globally for licensing opportunities, and well-established channels of generating business leads can substitute for co-location as a means of gathering information about the landscape of licensing opportunities. Extensive review and due diligence prior to licensing can overcome the need for co-location in gathering information about a compound's scientific prospects and a firm's record of trustworthiness in licensing deals. Our informants

did not stress collaboration as important in developing a compound, indeed they often sought to discourage such collaboration, such that the need for proximity should not matter to post-deal success. In sum, there are many mechanisms actively pursued by firms to overcome the significant informational and moral hazard problems that are present in technology licensing markets that should overcome any barriers presented by geographic distance.

And yet recent research has shown that proximity has an effect even for markets where distance should not matter to the ability to access and evaluate information. Hortaçsu, Martinez-Jerez and Douglas (2007) find that distance continues to be an important deterrent to trade between geographically separated buyers and seller even when the transaction occurs over the Internet. Malloy (2007) finds that equity analysts are able to predict stock prices more accurately when they are closer to the firms they analyse, and that the effect is strongest for small firms. These studies suggest that co-located parties possess an information advantage, and that the advantage is particularly important when evaluating information emanating from small firms, consistent with our finding.

There are several interpretations for our finding. One is that local subsidiaries of global pharmaceutical firms serve as "listening posts" that funnel information about local licensing opportunities to the firm at large. In that case, co-location increases the probability that a firm becomes aware of a potentially attractive technology for licensing. This may occur both because a local presences gives rich information about local business opportunities, and because firms may locate research subsidiaries in regions that are particularly rich in specific opportunities in that field. In either case, it suggests that participation in scientific communities does not serve as a fully effective means of conveying information about licensing opportunities, and that a local presence is needed to accurately scan these markets and evaluate firms and compounds. This strikes us as a plausible interpretation of our finding, especially since many small firms may not have the resources or scientific visibility to be noticed in the crowded landscape of scientific research. The finding may also reflect unmeasured heterogeneity in the capabilities of global pharmaceutical firms to search globally for licensing opportunities.

A second interpretation of the finding is that partners need to collaborate on compound development post licensing, and co-location can significantly eases that process. While there is ample research to document the role of proximity in technology creation, the licensing directors we spoke to stressed that post-license collaboration was not a common, nor even desirable, element of in-licensing compounds from small firms. Further information about the relationship between proximity and the stage of licensing would be helpful in knowing if this aspect is driving our results.

Overall, our results have implications for the evolving organizational and geographic configuration of the value chain in biopharmaceuticals. Whereas research is increasingly performed by small firms, often located in "bio-clusters", downstream value-adding activities are carried out by large firms with the scale and scope to carry out expensive drug development, testing, and marketing, often on a global scale. Technology markets, as stressed by Arora and colleages (1998, 2001), perform a vital role in linking these two groups of firms together and moving upstream discoveries to a market. If licensing transactions are conducted globally, without regard for the location of buyers and sellers, then bio-regions could remain geographically distant from pharmaceutical firms with few consequences for the movement of their discoveries to a market for further testing development. However, if co-location matters – as our results indicate – then regions that directly connect sellers with buyers will emerge as important nodes in the industry. In this case, attracting pharmaceutical firms to a location where biotechnology firms are active may be an important element for successful development of a bio-cluster, and small firms that remain isolated both from the industry and scientific research communities may find themselves at a disadvantage in commercializing their discoveries through licensing. Our findings thus have implications for policy-makers as well as managers of small, research-based firms seeking to commercialize their research through partnerships with large pharmaceutical firms.

Table 2. Effect of firm co-location (city level) on probability of license

Models include all compounds developed by biotechnology firms. Models labeled A include compounds of biotech firms in all countries. Models labeled B include compounds of US biotech firms only. First column of each model is logit of whether a compound is ever licensed, and includes fixed effects for the therapy code of the compound and each of the 25 global pharma firms. Second column of each model is conditional logit of whether a compound was licensed to any of the 25 global pharmaceutical firms. Model 2 includes a co-location variable in the licensing regression. Model 3 excludes all compounds that were never marketed. All models are estimated with standard errors clustered for a compound's originating biotechnology firm.

| | 1A. All biotech firms | | 1B. US biotech firms | | 2A. All biotech firms | | 2B. US biotech firms | | 3A. All biotech firms | | 3B. US biotech firms | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Licensed | Co-location | Licensed | Co-location | Licensed | Co-location | Licensed | Co-location | Licensed | Co-location | Licensed | Co-location |
| City_Co-locate | | 0.17 | | 0.24 | | 0.17 | | 0.24 | | 0.20 | | 0.28 |
| | | (5.51)** | | (3.91)** | | (5.30)** | | (3.90)** | | (6.41)** | | (4.38)** |
| Years | 0.18 | | 0.18 | | 0.18 | | 0.18 | | 0.18 | | 0.18 | |
| | (123.26)** | | (77.56)** | | (120.86)** | | (77.23)** | | (24.68)** | | (15.53)** | |
| Co-Locate_AnyPharma | | | | | 0.13 | | 0.01 | | | | | |
| | | | | | (14.96)** | | -0.68 | | | | | |
| Ceased | -0.02 | | 0.00 | | -0.03 | | 0.00 | | -0.02 | | 0.00 | |
| | (2.41)* | | -0.23 | | (3.70)** | | -0.23 | | -0.51 | | -0.05 | |
| Fully Launched | -0.34 | | 0.42 | | -0.33 | | 0.42 | | -0.34 | | 0.42 | |
| | (15.56)** | | (7.90)** | | (14.69)** | | (7.89)** | | (3.12)** | | -1.55 | |
| Constant | -1.23 | -1.77 | -1.13 | -1.74 | -1.31 | -1.77 | -1.13 | -1.74 | -1.23 | -2.07 | -1.13 | -2.04 |
| | (40.93)** | (38.84)** | (23.24)** | (28.10)** | (42.45)** | (38.85)** | (22.91)** | (28.09)** | (10.24)** | (119.82)** | (5.78)** | (85.15)** |
| Observations | 154850 | 154850 | 61750 | 61750 | 152975 | 152975 | 61750 | 61750 | 43298 | 43223 | 18118 | 18118 |
| Chi-Square | | 30.34 | | 15.25 | | 28.09 | | 15.19 | | 41.07 | | 19.16 |
| Ch-Square compared | | 59.07 | | 32.47 | | 59.36 | | 32.50 | | 1.76 | | 3.01 |
| P-value | | 0.00 | | 0.00 | | 0.00 | | 0.00 | | 0.19 | | 0.08 |
| Significance | | 0.00 | | 0.00 | | 0.00 | | 0.00 | | 0.00 | | 0.00 |
| Rho | | -0.24 | | -0.27 | | -0.25 | | -0.27 | | -0.08 | | -0.18 |

Robust z statistics in parentheses* significant at 5%; ** significant at 1%

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