Tacit Demand and Innovation in the Global Pharmaceutical Industry

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Abstract *While localization of technology has been discussed at some length in the literature, localization of demand has been largely ignored. This study considers the global pharmaceutical market and examines the both demand and technology determinants of innovation. Our study examines every new drug launched into the global pharmaceutical industry during 1980 to 2001 by leading pharmaceutical firms to contrast anticipated demand and historical technology expertise as determinants of the realized pattern of innovations at the firm level. We find that demand is as important as technology in determining the pattern of innovation in this industry, and that innovation is a locally determined phenomenon. These findings contribute to research regarding determinants of innovations and provide a new explanation for clustering of innovation, distinct from local knowledge spillovers.*

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1. Introduction

Innovations tend to cluster geographically. A thriving literature has addressed this phenomenon, identifying a variety of mechanisms that account for it. Agglomeration economies enable increased productivity among local firms (Krugman, 1991; Romer, 1986). The supply of key inputs, such as knowledge or venture capital, is especially rich in certain locales (Florida and Kenney, 1988). Importantly, innovation-enabling knowledge is often tacit with limited or slow diffusion outside a specific geographic area (Audretsch and Feldman, 1996; Jaffe, et al., 1993, Feldman, 2000).

It is striking that these explanations are on the supply side for innovation, focused on the costs innovation. Yet, historically there has been a vigorous debate in economics as to whether innovation is indeed driven from the supply side, the "technology push" argument, or rather from inventor anticipation of consumer needs, the "demand pull" argument (Mowery and Rosenberg, 1979; Rosenberg, 1974). Our study draws from these historical arguments for the two-sided nature of technical change to identify demand-side mechanisms that account for the geographic clustering of innovation. In particular, information about anticipated demand can be as complex and tacit as knowledge inputs, with comparably limited diffusion outside the local region.

The historical debate over the supply-side and demand-side determinants of innovation raises a second debate as to why there is any localization at all. The theoretical mechanisms for clustering of innovation have tended to focus on entrepreneurial firms that are plausibly restricted in geographic scope to a specific region or firms that are active only in the focal region. Yet, in many industries, leading firms are very much multinational in scope, with operations scattered across a variety of geographic locales. Multinational firms ought to be able to transcend the enumerated localization mechanisms, and thereby innovate on a global scale. For example, localization effects due to tacit information operate because non-codified knowledge must be transmitted through relationships, not markets. Multinational firms provide within-firm relationships that are comparable to and arguably more intense and more formalized than those of ongoing local linkages. It is unclear why clustering is sustained in industries dominated by multinational firms (Patel, 1995; Patel and Pavitt, 1991).

This study addresses these twin debates on the origins of innovation: supply-side versus demand-side, and localized versus global. We integrate and build on existing literature regarding

technology push and demand pull innovation by examining a more nuanced affect of demand that incorporates the potential difficulty in anticipating or responding less familiar markets. We examine the pharmaceutical industry, one that is particularly "global" in that most large firms operate in multiple markets throughout the world. Evidence of localization in this industry will be especially striking.

The plan for our paper is as follows. The next section reviews the literature on the origins of innovation and the mechanisms for localized clustering of innovation, and presents hypotheses. The third section provides institutional context for arguments that demand is tacit information with limited diffusion. The fourth section discusses data and measures, notably the patent data we use to construct measures of technology push and the sales data we use to construct measures of demand pull. The fifth section describes the empirical methodology, and the sixth reports the estimates of the contributions of the local and non-local technology push and demand pull measures as determinants of the pattern of discovery for every new pharmaceutical molecule launched by large firms in leading countries between 1980 and 2001. We find strong and consistent evidence of innovation patterns that responds to local demand, but either ignore or avoid foreign market demand. In addition, we do not find any evidence of within-country or across-country technological spillovers. The seventh section provides conclusions.

2. Theory and Hypotheses: the Origins and Localization of Innovation

Existing theory relating to the drivers of innovation falls into two general categories: technology push and demand pull. Technology push theories of innovation focus on the supply of inputs for innovation and the institutions that govern them as the main determinant of the amount and types of innovation that occur. Demand pull theories of innovation focus on the potential revenues for innovation, based on consumer behavior and social institutions, and predict that the amount and composition of innovative activity is a response to expected pricing and diffusion of innovation. While early efforts to understand the pattern and directions of technological change focused on demand as a primary driver of innovation patterns and considered the state of technology and knowledge in a supporting role (Griliches 1957, Schmookler 1966), later work highlighted the importance of technology and knowledge as primary drivers of technological advance (Rosenberg 1974).

The central argument in this paper is that while both technology and demand are important drivers of innovation, existing work has failed to recognize the nuanced nature of the demand pull incentive. Specifically, the dimension of localization, which has been addressed at length with respect to technology drivers of innovation, has been ignored with respect to demand drivers. In the remainder of this section, we review the theory and major works that address various theories of innovation: technology push, demand pull, and localization. We contribute to this body of theory by considering the implications of geography for the demand pull theory of innovation and suggest the importance of "tacit" demand knowledge.

2.1 Technology push innovation

The "technology push" category of theories focuses on the relative technological opportunities and costs of innovation. The existing state of knowledge facilitates the very conception of new knowledge, as well as the relative ease of inventive activity across areas of technology (Rosenberg 1974). This linkage is consistent with the Romer (1990) growth model, in which the rate of technological process depends on the number of idea workers and the stock of ideas available to these workers. Central to theories of technology push is the argument that innovators are heterogeneous in their ownership of knowledge assets and that knowledge is not costlessly or readily transferable across inventors. Prior experience and knowledge assets at the firm level, as well as the knowledge base in the surrounding environment, greatly facilitate the creation of new knowledge (Jaffe, Trajtenberg, Henderson 1993, Almeida 1996, Teece 1982, 1995, Kogut and Zander 1992, Scott Morton 1999, Nerkar and Roberts 2004). Understanding existing fundamental principals and expertise from prior research decreases the difficulty of innovation in the same area and in technically related areas. An improved knowledge base improves the ability to productively focus search, to more efficiently search, and to speedily develop new innovations (Nelson 1982). Access to existing knowledge therefore lowers the cost of and increases the productivity of innovation efforts, and thereby guides and influences current innovation, and results in variance in the pattern of innovation results.

Recent research on innovation has been dominated by studies of the role of knowledge and science in guiding and enabling innovation, with a focus on knowledge transfer and knowledge spillovers (for example, see Nelson 1982, Jaffe 1986, Audertsch and Feldman 1996, Cohen and Levinthal 1990, Liebeskind et al. 1996). This literature suggests that differences in

innovation patterns across countries and across firms are established, augmented, and remain because of the past and current R&D investments and the supply-side policies of institutions in the country. Therefore, the pattern of prior innovation outcomes for a given firm or in a given country provides a reasonable proxy for the available technological base generated by the firm and the system of institutions within the country (Henderson and Cockburn 1996, Branstetter 2001). Consistent with substantial prior literature, we expect that differences in the prior knowledge stock will predict differences in the pattern of new innovations.

Hypothesis 1: Innovations in a particular technical area are more frequent when the firm has more historical experience with that particular technology.

2.2 Demand pull innovation

A second stream of research, beginning with seminal works by Griliches (1957) and Schmookler (1966), has demonstrated the relationship between the revenues from innovation and the pattern of innovations (also see Romer 1990 and Grossman and Helpman 1991). Rather than focusing on the existing knowledge base as the driver of innovation patterns, this "demand pull" theory of innovation highlights the importance of expectations about market demand and competition.

Schmookler (1966) specified and demonstrated empirically the importance of changes in the composition of demand as a driving factor in inventive activity. For example, in his analysis of the railroad industry, Schmookler uncovered a pattern of inventive activity that appeared to respond to increases in the purchase of railroad equipment. Based on this and similar evidence from other industries, he argued that the variation in and the composition of inventive activity is (at least partly) induced by variations in demand. Other early empirical work examining the relationship between demand and innovation patterns is reviewed and critiqued in Mowery and Rosenberg (1979). These authors comment that it is difficult to draw systematic conclusions from many of the early studies, due to differences in methodology, inconsistent measures of demand, and specifications lacking necessary controls, for example for technological changes.

More recent work in this vein includes Newell et al. (1999), Popp (2002), and Acemoglu (2002). In the pharmaceutical industry, Kremer (2002) argues that anticipated market size is an important determinant of the pattern of investment in drug research, resulting in under funding of research related to third-world diseases, due to the limited revenue from such markets. In a study

aimed at evaluating the effect of demand for drugs of different types on the supply of new drug innovations, Acemoglu and Linn (2004) examine the pattern of new drug innovations approved by the FDA. The authors estimate the relationship between exogenous changes in the pattern of demand across therapeutic areas (brought about by changes in the composition of the population over time and the variation in drugs demanded by different age groups) and the pattern of drug innovations across therapeutic areas. They provide evidence that the pattern of innovations across therapeutic categories is positively associated with the pattern of changing demand for drugs. This evidence suggests that pharmaceutical firms anticipate exogenous changes to demand and respond by reallocating investments in innovation to meet demand.

We are similarly interested in the relationship between the pattern of demand across therapeutic areas and the pattern of drug innovation. As in this earlier work, we expect that therapeutic areas with greater expected sales attract increased R&D efforts, and therefore will contain a greater number of innovations. Out test will be stronger, in the sense that we control for both the exogenous (common) technological opportunity in a therapeutic area and the firm specific accumulated technological expertise.

Hypothesis 2: Innovations in a particular technical area are more frequent where the anticipated demand for that particular technology is larger.

2.3 Localization

Our work differs from prior work first by considering both demand and technological drivers of innovations, and second by focusing attention on the localization of both of these factors. We define localization as the importance of national boundary. This is in contrast to globalization, or access to resources and knowledge irrespective of national location. While geographic proximity may play a role in localization (resources within a firm's home country may be geographically closer than resources outside of the country), we do not view distance per se as of primary importance. This perspective is consistent with the agglomeration literature, which considers differences across regions, and the National Innovation Systems literature, which highlights differences across countries.

Differences in relative patterns of innovation are attributable to national or regional institutional differences that shape the innovation system in various countries (Nelson 1993). At the country level, the National Innovation Systems literature focuses attention on the system of institutions that underlie the (relative) innovative ability of given countries. Particular

institutions and policies highlighted include public and private intellectual property policies, regulations, the nature of the university system, the historical development of the organization of R&D activities, and public funding policies, in addition to the accumulated technological expertise (Mowery 1984, Merges and Nelson 1990, Lundvall 1992, Nelson 1993, Nelson and Rosenberg 1994, Freeman 1995, Mowery and Oxley 1995, Mowery and Rosenberg 1998, Furman et al. 2002). The institutions that fund and perform R&D, generate and commercialize innovations, and control and influence the diffusion of new technologies are all part of the National Innovation System (Mowery and Oxley 1995, Freeman 1995). This includes organizations (such as firms, universities, public research organizations) as well as laws, regulations, and policies that perform and affect R&D in a country. The established and historical system in a given country creates the relevant environment in which innovation takes place, and thereby influences the level of innovativeness in of firms in the country as a whole.

Following the National Innovation Systems literature and Porter (1990), Furman et al. (2002) describe and model the "national innovative capacity" of a country, which they define as "country's potential – as both an economic and a political entity – to produce a stream of commercially relevant innovations." This capacity is modeled as a function of both past investments in technological expertise and the institutional and policy choices made by government and private sector actors, including the demand conditions, with a focus specifically on the linkages between the common innovation infrastructure in the country and the cluster-specific environment for innovation. They test this model on panel data across countries and time, with confirmatory results. However, the authors do not include measures of local or foreign demand conditions in the empirical analysis.

We submit that, beyond lack of attention or difficulty transferring knowledge, there is an underlying reason for the localness of response to demand conditions that is related to the National Innovation System focus on institutions. Importantly, the national institutional context in which the firm develops shapes key characteristics of the organization, including the organizational structure, routines, and activities. In their seminal work, Milgrom and Roberts (1990, 1995) model the firm as an activity system, or as a collection of discrete routines that are complementary to each other. Routines are complementary in the sense of Milgrom and Roberts if the benefit of one activity is increased as the scale of another activity increases. The firm is

thus seen as an integrated package of well-chosen internally consistent routines that "fit" with each other.

Routines by actors in the domestic context (consumers, suppliers, other firms, policy makers) are likely to be complementary to the internal routines developed by domestic firms. The activity set for domestic firms is indeed presumably structured from preexisting routines in the domestic context, such as HRM practices, science procedures, and marketing norms, and in response to environmental institutional practices, such as the nature of the policy making environment. Hence, domestic routines, because they are institutionally proximate, are highly likely to be complementary to and to "fit" with the domestic firms' activity set (Thomas 2004). Routines in foreign contexts (by consumers, suppliers, competitors, regulators, and so on) are more likely to be institutionally distant and not complementary. Indeed, foreign routines may even be dissonant with the existing activity system of domestic firms, in that adoption of isolated foreign routines reduces the benefits from the firm's current operations.

The initial papers by Milgrom and Roberts have stimulated a vigorous body of both theoretical and empirical work. Porter and Siggelkow (2001) have theoretically modeled the effects of different contexts on activity systems. Ichniowski and Shaw (1997, 1999) have provided empirical evidence that American manufacturing firms imitating their Japanese counterparts by adopting isolated human resource practices experienced no effect on their productivity. In contrast, American firms that adopted at once an internally coherent set of several of these HRM activities experienced large, positive effects on productivity. These Japanese HRM practices thus represent a documented complementary activity set.

We return to the technology and demand drivers of innovation and consider the implications of this complementarity between the routines of domestic firms and the home institutional environment for the local nature of each. First, this complementarily is one reason that firms are better able to tap into the local technological environment as a resource for development of new innovations. The firms have established linkages with the local infrastructure, including accumulated experience, human capital, and technological resources that allow them to more effectively access the local infrastructure for use in their innovative processes (Furman et al. 2002). In addition, existing literature posits geographically mediated knowledge flows as a potential explanation for regional clustering of innovation. Literature examining the drivers of geographic agglomeration and the benefits of proximity to either

specific resources or related firms has focused on three mechanisms for these benefits: access to specialized labor inputs, access to specialized suppliers of other inputs, and geographically mediated knowledge spillovers (Marshall 1920). In all cases, the agglomeration economies lead to increases in productivity due to geographic proximity to other firms.

Recent literature regarding geographic clustering of innovation activity has explored the existence, importance, and localized nature of knowledge spillovers (Feldman 2000, Audretch and Feldman, 1996; Jaffe et al., 1993; Zucker et al., 1998). Theoretical justifications for the benefits of proximity include the necessity of face-to-face interactions for the transfer of tacit knowledge, the benefits of local network connections, the ease of labor mobility within localities, and cultural similarity that promote knowledge exchange within regions. Due to the tacit nature of knowledge, proximity provides an advantage for knowledge transfer and allows firms to capture more knowledge spillovers, and therefore can lead to geographic clustering of industries, sustained firm advantage, and persistent differences across regions and countries (Furman et al. 2002). Research on localized industry "clusters" has demonstrated that industry-specific knowledge develops and largely is retained in geographically concentrated locations (Porter 1990). Consistent with the "technology push" theory of innovation, this literature predominantly views the knowledge inputs of innovation as the force driving location decisions and agglomeration benefits.

Empirical research on knowledge flows is consistent with the localization of knowledge spillovers among firms and from other research institutions, such as universities. For example, Jaffe (1986) demonstrates that firms' patents, profits, and Tobin's Q are increasing in the knowledge spillover pool available from other firms. Jaffe (1989) documents the knowledge spillover benefits that accrue to firms that are located near a university, providing additional evidence of proximity in determining the pattern of knowledge spillovers. Similarly, Jaffe, Trajtenberg, and Henderson (1993) and Jaffe and Trajtenberg (1996) show that patent citations, a common measure of knowledge flows, demonstrate geographically localized diffusion processes, with citations occurring more frequently and more quickly in geographically proximate follow-on innovation. The authors conclude that geographic proximity is associated with greater knowledge diffusion. These findings regarding the localization of knowledge flows have been cited as an important reason underlying the spatial clustering of innovation (Audretsch and Feldman, 1996). Consistent with this prior literature, we expect that the technology base that is

most geographically proximate to firms will have more influence on their pattern of innovations than more distant technological expertise.

Hypothesis 3: Local technological expertise has a greater (positive) impact on innovation than distant technological expertise.

In contrast, research in the "demand pull" stream of literature has typically (if implicitly) assumed that all inventors face the same market demand or can serve the entire market. Differences in innovation patterns across firms are either not considered or are explained by variations in the firm's knowledge base. This stream of literature has yet to recognize that knowledge about demand conditions may be differentially distributed across firms or countries, and knowledge flows about demand may be "sticky" and difficult to transfer across regions. We suggest that demand conditions are a critical part of the institutional environment that has been ignored in most studies of cross-national differences in innovation, which tend to focus on access to knowledge inputs. In fact, the market demand perceived by firms may differ in much the same way as the knowledge inputs available to firms differs.

Furman et al. (2002) do consider the "demand conditions" in a country as one determinant of what they call "national innovative capability," including the possibility that the demands of the customers in a firm's home country shape the incentives of the firm to innovate. We contend that this is particularly true when the nature of demand is complex and intertwined with the institutional environment of the country. When government policy, cultural norms, and history dependent relationships among institutional actors in the economy play a significant role in determining the pattern of demand, then demand is a critical component of the national innovation system. Firms with routines and systems that fit a given institutional environment will be at an advantage in terms of understanding and anticipating the pattern of demand. Section 3 details why the pharmaceutical industry is one in which demand conditions are intertwined with the institutional environment in a country, and therefore difficult to comprehend and anticipate for foreign firms.

Difficulty in understanding and relating to foreign markets is documented in the foreign direct investment literature. Existing work characterizes the motivation to invest abroad as two-fold: firms may seek to exploit a unique capability that they possess by expanding their reach, and/or firms may invest abroad in search of knowledge, technology, or capabilities which they

intend to acquire (Chung and Alcacer 2002, Cantwell 1989, Almeida 1996). This latter motivation recognizes the difficulty of knowledge or technology transfer across borders – effective transfer often requires the interaction and involvement that accompanies direct investment due to the tacit nature of such knowledge (Kogut and Zander 1992, Almeida and Phene 2004). Consistent with this, Feinberg and Gupta (2004) demonstrate that the location choice of R&D-related foreign direct investment is sensitive to the desire of a firm to tap into the spillovers available in a particular locality. By locating R&D activities in areas with a more substantial potential spillover pool, the firm is able to realize the additional benefits of its own R&D as a means to assimilate some of the available spillovers. This work is typical of such foreign direct investment research in the sense that it remains focused on accessing the research knowledge inputs to the innovation process.

The same challenge applies to developing an understanding of the demand characteristics of a foreign market. Foreign markets have characteristics that are difficult to observe from the outside, and knowledge about these characteristics is difficult to transfer. Knowledge of local market characteristics is therefore somewhat "sticky" or "tacit", giving those firms immersed in the market an advantage. This provides a locational advantage in addition to access to research knowledge – access to the tacit knowledge concerning the demand in the target market. The fundamental question here may be seen as a test of how globalized the pharmaceutical industry is, or, alternately, whether the home location of a firm affects the firm's pattern of innovations. In a truly global market, one would expect firms to respond to demand uniformly, regardless of where that demand originates. To the contrary, we expect that the pattern of innovations in a country remain driven primarily by the demand pattern in the home country or "proximate" markets, and respond less to the pattern of demand other markets.

Hypothesis 4: Local anticipated demand has a greater (positive) impact on innovation than foreign anticipated demand.

Following the foreign direct investment literature, we will also examine whether firm's involvement in foreign markets, including prior marketing of drugs and research activities, increase the impact of foreign demand patterns on the firm's innovation pattern.

Hypothesis 5: Firm involvement in foreign markets will increase the impact of foreign technological expertise and foreign demand on innovation.

3. Tacit Demand: Difference and Complexity in Country Demand for Drugs

We argue that the tacit nature of demand knowledge accounts for a significant portion of observed patterns of innovation at the country level for innovation of new pharmaceuticals. For our argument to be compelling, the pattern of demand for drugs must be significantly different across countries. For clustering to occur at the country level (rather than, say, the regional level), pharmaceutical demand must be plausibly similar among consumers within countries. Finally, country demand must also be sufficiently complex that it cannot be readily codified. In this section, we provide various examples of pharmaceutical demand across countries that illustrate these cross-country differences, within-country similarities, and systemic complexities.

One significant determinant of the nature of pharmaceutical demand is the country-level institutions that underpin drug consumption patterns. These institutions include safety regulations, price regulations, health insurance regimes, consumer information regimes (including marketing to doctors and direct advertising to patients), and political lobbying arrangements (including the absolute and relative power of drug firms, doctors and hospitals, insurance organizations, and patient groups). These institutions operate almost entirely at the country level, and thereby homogenize demand within countries. We illustrate the importance of these institutions with a brief discussion below of the changes in the institutions supporting demand for drugs in the United States over the last 15 years.

A second important determinant of the nature of pharmaceutical demand at the country level is social culture. Medicine, and the associated pharmaceutical industry, is deeply embedded in social culture (Payer, 1996). Medicine is physically invasive, and confronts norms and ideals for the body and physical being. Health, the outcome of medicine, is central to personal identity. And the great cost of medicine raises fundamental questions of status and social structure. We illustrate below the importance of social culture with brief discussions of three central dimensions: hierarchy versus egalitarianism, collectivism versus individualism, and risk tolerance. These aspects influence both the level of drug consumption over all and the pattern of consumption across therapeutic areas.

Our study uses actual country revenues for drugs in each therapeutic category for empirical tests, and does not seek to explain why these revenues achieve different levels across

different countries. Therefore, we do not deploy any measures of the institutions or culture that we discuss below that might underlie these recorded demands, except in a robustness check employing instruments. The concept of tacit demand across countries is novel for the literature, however, and we wish to illustrate why in at this industry observed demands are complex, different across countries, and similar within countries.

3.1 Economic Institutions for Drug Demand

Domestic markets for consumption of pharmaceuticals are underpinned by a variety of economic institutions. In every national market, safety regulation requires government approval before new drugs may be sold. Much of pharmaceutical consumption is covered by health insurance. Insurers decide the coverage and pricing for drugs. Their decisions determine the uptake and diffusion of drug products, and how drugs are combined with other inputs for medical care for treatment of patients. The routines for marketing and distribution of drugs are heavily regulated. All of these institutions are predominantly determined at the country level, with profound differences across countries and less difference within.

The economic institutions that underpin demand for pharmaceuticals also change significantly over time. The process for innovation of new drugs spans years, often up to a decade. Molecular compounds must be generated, their properties studied, pre-clinical tests must be conducted on animals to verify safety and effectiveness, clinical trials must be conducted on humans for further verification, final approval must be given by regulators, insurers must be convinced to cover and properly price the resulting innovations, and marketing must roll out a new product and change the behavior of doctors and patients. Drug innovators must therefore not only understand existing economic institutions, but must be able to accurately forecast the nature and performance of these institutions a decade or more in advance.

For example, during the 15 years from 1987 to 2002, the aggregate demand for pharmaceuticals in the USA increased enormously, usually at double-digit annual rates (see Figure 1). If we multiply together these annual rates, we find that aggregate demand for pharmaceuticals in the USA increased by a factor of seven during this period (Berndt, 2001; Danzon and Pauly, 2002). This large increase in demand was driven by two important institutional innovations. First, health insurance drastically expanded coverage to include pharmaceuticals. This expansion, for both government and private insurers, was accompanied

by significant organizational innovation. Formularies and other tactics of managed care arose to contain costs and optimize newly expensive care (Hillman, et al. 1999; Lyles and Palumbo, 1999; Danzon and Pauly, 2001). Generic copies of off-patent drugs were given significant competitive emphasis (Grabowski and Vernon, 1992). Off-patent drugs sometimes responded by switching to over-the-counter distribution without prescription. Each of these institutional innovations was complicated, and their interactions even more so.

Second, in 1997, the US Food and Drug Administration reinterpreted existing regulations to allow more extensive advertising of drugs directly to consumers. Drug firms responded by significantly increasing their consumer advertising in the USA, alongside established marketing to doctors (Calfee, et al, 2002; Ling, et al., 2002).

Drug innovators seeking to launch new drugs in the USA in the late 1990s had to forecast this complex and powerful mix of institutional change. It is important to recognize that these changes were not inevitable, and alternate paths could have easily emerged. For example, before 1993, the price increases accounted for over half of aggregate drug sales increases (again, see Figure 1). Between 1992 and 1994, the growth rate for United States drug sales slowed dramatically. After 1994, the great bulk of increases in drug sales were due to volume growth, not price increase.

These institutions underpinning United States demand for drugs represent a complex and dynamic system, grounded in politics and social culture. Knowledge about these institutions is arguably highly specific to the United States and constitutes tacit knowledge that is more difficult for foreign firms to comprehend.

3.2 Social Culture: Hierarchy versus Egalitarianism

In addition to economic institutions, social culture drives demand for pharmaceuticals. One of the most basic dimensions of social culture is power distance, or the tolerance of hierarchy among members of society. Hierarchical societies posit and expect privileges for individuals high in the social structure. In particular, decisions by individuals high in the social structure have great legitimacy and acceptance. One impact of hierarchical culture on pharmaceutical demand is tolerance of drug side effects (Griffin, 1986, 1987). Figure 2 plots the frequency of drug reaction reports (ADRs) in various European countries against a widely used measure of social expectations and tolerance for hierarchy. ADRs are spontaneous reports by

patients and doctors of potential side effects from drug consumption. Virtually none of these reports are corroborated by scientific tests, and many are probably false associations. ADRs provide a database that in the aggregate provides a useful tool for monitoring adverse reactions.

Note in Figure 2 that for countries with hierarchical social cultures such as Italy, drug side effects are readily tolerated, ignored, and not reported. Doctors who have high social status prescribe medicines, and Italian patients view any side effects as appropriate and normal. Drug firms have high social status, and Italian doctors are reluctant to challenge their products. In contrast, in egalitarian social cultures such as Sweden, drug side effects are extensively reported. Swedes regard drug firms, doctors, and patients as effective equal partners in health care and Swedes are quick to challenge unusual physical effects that might possibly be associated with drug consumption.

A second impact of hierarchical culture is the treatment of underprivileged populations, such geriatrics, AIDS patients, and the mentally ill. In hierarchical social cultures, the suffering of the underprivileged is simply the natural order of the world. In egalitarian cultures, all citizens expect to receive equal medical treatment regardless of social standing. Figure 3 plots the relative share of health care spending on the elderly in various countries. A level of "3.0" on the vertical axis indicates that a country spends three times as much per capita on the elderly (age 65 or older) as it does for the rest of the population. Note that the relative spending share is lower in more hierarchical countries and higher in more egalitarian ones.

Examples that combine these two effects of hierarchical social culture on pharmaceutical demand are not difficult to find. Atypical anti-psychotics are breakthrough treatments for schizophrenia that minimize adverse reactions to older drugs, such a weight gain (Berndt, et al., 2005; Frank, et al., 2004; Lehman, 1999). The adverse reactions produced by older treatments for schizophrenia are sufficiently severe that patients frequently cease to take their medicine and suffer relapse. Per-capita demand for atypical anti-psychotics in Britain and Sweden is twice that of Italy and six times that of Japan. Per-capita demand in the United States is nine times that of Italy and 25 times that of Japan. Egalitarian societies are far more likely to value and purchase new drugs that minimize adverse side effects, especially for underprivileged sub-populations.

3.3 Social Culture: Collectivism versus Individualism

Social cultures characterized as collectivist focus on shared experiences by society as a whole. In the realm of medicine, the collective experience is public health, or the mortality and morbidity of the population. In contrast to public health, private health considers the personal experience and values of individual consumers, including convenience of use, personal comfort, and attractive appearance. Examples of pharmaceutical innovation that promote private rather than public health are inhaleable insulin (versus insulin delivered by injection), combination drugs (versus separate pills for each drug), and once-a-day dosing (versus products that must be taken at several times during the day).

Again, it is not difficult to find examples of collectivist social culture on pharmaceutical demand. Cox inhibitors for treatment of arthritis eliminate the need to consume anti-ulcerant drugs along with aspirin. Per-capita sales of Cox inhibitors in the United States are 8 times those of countries of Western Europe. These products were not even introduced into Japan during the period examined by our study. Erectile dysfunction treatments improve male sexual performance. Per-capita sales of these drugs in Britain are twice those in Italy and Japan, while United States sales are 7 times those in Italy and Japan.

3.4 Social Culture: Risk Tolerance

New drugs are risky. Minor side effects from drugs are common, and even significant adverse reactions occasionally occur. While drug safety is heavily regulated, the physical and lifestyle diversity of patients exceeds that during highly structured clinical trials. Unexpected adverse effects are unavoidable.

New drugs also have important benefits. The willingness of regulators, insurers, doctors, and patients to suffer the unexpected risks of new drugs in order to receive the forecasted benefits varies greatly across countries. Social cultures characterized as risk avoidant will delay consumption of new drugs and rely on established, if less effective therapies. In contrast, social cultures with higher risk tolerance will display much more rapid uptake of new therapies and new drugs. Figure 4 plots a standard measure of social risk avoidance for the seven largest country drug markets against the percentage of drug sales in 2002 that were from drugs introduced after 1990. Clearly, there are significant variations across countries in the consumption of new drugs, and these variations are closely related to social culture.

Examples of the effects of risk avoidant social cultures on pharmaceutical demand are easy to find. Beta-blockers were an important innovation in cardiovascular care, launched by British firms in the 1970s. Over time, completely different classes of drugs were innovated to care for cardiovascular disease, and in risk tolerant countries, demand shifted away from beta-blockers to these newer therapies. In risk avoidant countries, demand for this older therapy remained strong. At the turn of the century, per capita sales of beta-blockers in France, Germany, and Japan are 2.5 times those of the United States and 5 times those of Britain, despite the initial innovation of these products in that latter market.

3.5 Demand as Tacit Knowledge

The information given above illustrates our argument that demand in the pharmaceutical industry is highly complex, is intertwined with and determined by the institutional environment, and constitutes tacit knowledge. Clearly, not all industries are like pharmaceuticals in this regard, since in some industries demand is simple, static, unidimensional, and easily codifiable. But in pharmaceuticals, demand is directly generated by the interactions of multiple economic institutions (safety regulation, insurance, the medical profession, marketing procedures). These institutions constitute a system that is highly complex. This system is also quite dynamic, with profound changes over time that are difficult for outsiders to understand, let alone predict. Underlying this system are deep and equally complex political and cultural norms and expectations.

This provides a substantial advantage to firms that develop within the institutional and cultural system of a particular country in terms of anticipating the demand patterns of that country. Note that this reasoning suggests a justification for localization of patterns of innovations that is distinct from access to knowledge spillovers and that has not been considered in the geography of innovation literature: preferential access to demand knowledge, which is an important determinant of investments in innovation.

4. Empirical Specification

Our analysis examines the pattern of innovations across the 125 therapeutic classes for all large pharmaceutical firms in each of seven countries. We combine the empirical approaches relied upon in the knowledge "production function" stream of literature (Griliches 1980, 1995, Hausman, Hall, Griliches 1985) and related knowledge spillover empirical work (Jaffe 1986,

1989) with those relied upon in empirical investigations of demand induced innovation (Acemoglu and Linn 2004, Popp 2002). In order to make the best use of the data available, we employ both aggregated cross section and annual, pooled cross section analysis. We describe the empirical methodology and specifications for each analysis in the following section, and then detail the data and measures used in the analysis.

Our analysis study examines the pattern of innovations across the 125 therapeutic classes for all large pharmaceutical firms during 1980 to 2000 in each of seven countries. In order to make the best use of the data available, we employ both cross section and time series analysis. We use a cross-sectional, cross-therapeutic-area analysis to estimate the relationship between the firm's pattern of innovation and both the pattern of technological expertise and the pattern of demand in each of the target markets. Second, we make use of the panel nature of our data to examine pooled cross sectional estimates.

Acemoglu and Linn (2004) develop a theoretical model and an empirical model of drug innovation as a function of market size. In that work, the authors estimate the relationship between the market size (in the United States) in a therapeutic area and the number of FDA-approved drug introductions in that area, control for differences (such as technological difficulty) across therapeutic areas. We start from and build upon their model with two added considerations. First for foremost, we will consider the market size and drug introductions in seven major global markets, and allow for the possibility that innovation does not respond equally to demand in each market. Second, because our analysis is at the firm level, we are able to more directly examine and control for the "technology push" explanation of innovation using technological expertise at the firm, country, and international levels.

4.1 Cross Section – Aggregate Drug Innovations:1980-2001

In order to make use of the full set of innovations, covering the 1980-2001 period, we first utilize the cross sectional variation (across countries, therapeutic classes, and firms) to estimate the relationship between demand, technological expertise, and the number of innovations generated by therapeutic area. We consider the determinants of the total number of new molecule innovations generated during the 1980-2001 period by each firm in each therapeutic area. Aggregating the number of innovations over the period has the benefit of avoiding the necessity of imposing an assumed timing lag structure. This is cross sectional data

is at the level of the firm-therapeutic class pair. Note that there are multiple observations for each firm – one for each therapeutic class.

The count nature of the dependent variable (number of innovations by a firm in a therapeutic class) calls for a Poisson model for the conditional number of new innovations generated by firm *f* in home country *h* in therapeutic class *k*. The base model is as follows:

$$E[N_{fk}] = \exp(Demand_{mk}'\beta_m + \alpha Expertise_{fk} + \gamma HomeTechExpertise_{hk} + \lambda ROWTechExpertise_{hk} + \sum_f \eta_f + \sum_k \theta_k)$$

Where N_{hk} is the total number of new molecule introductions by firm *f* in therapeutic class *k* during the 1980-2001 period. $Demand_{mk}$ is a vector of demand in the home market and the target markets (*m*) in therapeutic class *k*, equal to the per capita sales in 2001. $FirmTech.Expertise_{fk}$ is the firm's technological experience in the therapeutic area. Likewise, $HomeTech.Expertise_{hk}$ and $ROWTech.Expertise_{hk}$ are the technological experience of firms in home country *h* in therapeutic class *k*, and the sum of the technological experience of all *other* countries in therapeutic class *k*, respectively.

Due to over-dispersion present in several of the estimations, we rely on a negative binomial estimation for this model. In both the cross section and annual data estimations (described below), we adjust the standard errors for the non-independence across observations for the same firm, and report White (sandwich) standard errors adjusted for correlation within firms.[1]

Note that the equation to be estimated includes a full set of firm-level indicator variables (η_f), which control for the average number of innovations (per therapeutic class) by each firm[2]. If a particular firm, or the set of firms from a particular country, is more innovative in general, these variables will control for this difference. This controls for heterogeneity across firms and countries that is common across the therapeutic areas, including the average scale of demand in

[1] This adjustment to the standard errors does not alter the standard errors appreciably. We also tested for robustness to clustering instead by country, and found that there was no substantial difference in the results.

[2] As discussed in Acemoglu and Linn (2004) and Hausman, Hall, Griliches (1984), the nonlinearity of this equation makes it impossible to estimate true fixed effects. We have tested the specification with more complicated approaches that do yield consistent estimates, and have found very little difference between those results and the ones reported here with the linear indicator variables. Including country level, rather than firm level, indicator controls does not change the results substantially. Of course, each firm is associated with only one country, both sets of controls can not be included.

the home country. With the firm-level control variables, the estimates can be understood as within-firm, across therapeutic area relationships. Therefore, the coefficients on the market size reflect the relationship between sales revenue in a given market and therapeutic class and the number of innovations by a given firm in that therapeutic class, controlling for the overall innovative productivity of the firm and the average sales across therapeutic areas.

In some of the estimates, we include therapeutic class indicator variables (θ) for each of the 125 classes. These therapeutic class variables control for unobserved heterogeneity across the therapeutic areas, and thus control for the inherent differences in difficult in developing new innovations, "size" of the class, and the total world market for the class. Given the nature of the incidence of human diseases, it is possible that some therapeutic areas have greater levels of (per capita) demand in many areas of the world. If this is the case, it could appear that innovation is responding to local demand patterns when in fact innovators are actually focusing on therapeutic areas that are consistently in demand across the world. With the inclusion of these controls, we are estimating the relationship between the number of innovations generated by a firm in a given therapeutic class and the demand (or technological experience) of the home country in that class *relative to* the demand (or technological experience) in the rest of the world in that therapeutic class and *relative to* other therapeutic classes.

Controlling for the technological experience of the firm and other firms in the home country in a given therapeutic area, as well as the firm and therapeutic area effects, the coefficient β_m indicate the relationship between the pattern of demand across therapeutic areas in market m and the number of innovations generated by firms in home country h. As discussed below, we begin by considering separately the home or rest-of-world demand, then consider these together, and finally undertake a factor analysis to group demand patterns from the seven countries to three factors which are included in the estimation.

4.2 Annual Number of Drug Introductions

We also make use of the annual data to estimate the relationship between demand, technological expertise, and the number of innovations generated. The data include one observation for every firm-therapeutic class combination for each year. The panel here is of similar structure as the data described above – multiple observations for each firm, one for each of the 125 therapeutic area – with the added dimension of multiple observations for each firm-therapeutic area across

time. However, we must limit our analysis to the 1992-2001 period due to limited availability of the sales data. We again rely on a poisson specification to accommodate the count nature of the dependent variable. The base model is as follows:

$$E[N_{fkt}] = \exp(Demand'_{mkt-1}\beta_m + \alpha FirmTechExpertise_{fkt-1} + \gamma HomeTechExpertise_{hkt-1} + \lambda ROWTechExpertise_{hkt-1} + \sum_f \eta_f + \sum_k \theta_k + \sum_t \delta_t)$$

Where N_{fkt} is the number of new molecule introductions by firm *f* in therapeutic class *k* in year *t*. One benefit of the panel data is that it is possible to make use of a time lag in the sales data, thereby avoiding any concerns of endogeneity. $Demand_{mkt-1}$ is a vector of demand in the home market and the target markets (*m*) in therapeutic class *k* in year *t-1*. $FirmTech.Expertise_{fkt-1}$ is the total number of patented innovations by the firm allocated to the therapeutic class during the 10 year period ending in year *t-1*. Similarly, $HomeTech.Expertise_{hkt-1}$ and $ROWTech.Expertise_{hkt-1}$ are the technological experience of firms in home country *h* in therapeutic class *k*, and the sum of the technological experience of all *other* countries in therapeutic class *k*, respectively, for the 10 year period ending in year *t-1*. In addition to the firm level and therapeutic class level indicator variables, year indicator variables are now included as well to control for changes over time that are common across the firm-therapeutic area observations in the sample.

As above, the coefficients β_m indicate the relationship between the pattern of demand across therapeutic areas in market *m* and the number of innovations generated by firms in home country *h*. With the firm and therapeutic class level control variables, the relationships between demand (or technological expertise) and the number of innovations should be considered a comparison of relative levels across classes within the country and across countries within the class.

4.3 Empirical Concerns

One potential problem with empirical research seeking to estimate the relationship between market size and innovative activity is endogeneity – that market size might respond to the number of new inventions introduced to the market. Because we are particularly interested in the number of introductions as a function of *predicted* (and thus future) demand, we use end-of-period sales to predict the number of innovations during 1980 to 2001. There is a risk of endogeneity if the number of new drugs introduced in a therapeutic area by a given firm

increases the level of sales in that therapeutic area, and therefore determines end-of-period sales, rather than the direction of causation we assume. We view this outcome as rather unlikely because the demand volume for any therapeutic class is determined by the number of patients requiring therapy, the efficacy of drugs to provide that therapy, and the institutional environment for drug consumption. The number of innovations generated by one particular firm is unlikely to affect the total sales volume. In fact, within therapeutic area regressions using annual data predicting sales volume (either in total or in any given country) as a function of the number of new drugs (either annually or cumulatively) demonstrate a complete lack of significant predictive power of the number of innovations.

However, in order to evaluate the robustness of our results to this possibility, we take two approaches. First, in the cross section analysis, we instrument for the level of demand in a country-therapeutic class observation using the age of the therapeutic class and the interaction of the therapeutic class age with the country-specific risk aversion index (Holfstede 2005) as exogenous instruments in the first stage. Sales in a therapeutic class are expected to increase as the age of the class increases, due to greater awareness and acceptance of treating the ailments in that class. We expect that this increase will be smaller, however, for countries where there is less acceptance of new and uncertain things, as reflected in the risk avoidance index. The interaction of these two provides therapeutic class-country level variation. Second, when we make use of the annual data, we will use the one year lagged value of the sales variable. As the results demonstrate, our basic results are robust to both of these modifications.

5. Data and Measures

We test our hypotheses with data on every new drug launched in the world during 1980 to 2001. Below, we discuss the data and measures we use for innovations, firms, technology expertise, anticipated demand, and foreign direct investment.

5.1 Pharmaceutical Firms

We employed three rules to identify the "firm" that was responsible for a particular drug innovation. For each drug, we identify the corporate subunit filing the specific patent that provides the intellectual property rights for that drug. Our first rule is that we combined all subunits for each corporation into a single "firm" if these subunits were all located in the same

country and were collectively owned throughout the period of our study (1980 to 2001). For example, the subunits "Johnson and Johnson", "McNeil Laboratories", and "Ortho Pharmaceutical" were combined into the single "firm", Johnson and Johnson. The McNeil and Ortho subsidiaries of J&J are American, as is the parent corporation itself, and these subunits of J&J were established long before the period of our study. Our second rule is that we separate out subunits located in different countries from the parent corporate. For example, the subunit of Johnson and Johnson "Janssen Pharmaecutica" is tabulated for our study as the "firm", Janssen. This Belgian subunit, acquired by J&J in 1962, accounted for over half the new drugs of that global firm during 1980 to 2001. Our third rule is that we separate out subunits that merged into another firm late during out period of study. For example, we tabulate the current multinational firm GlaxoSmithKline as three British "firms" (Beecham, Glaxo, and Wellcome) and one American "firm" (SmithKline).

We restrict our empirical analysis to large firms (those that generate six or more innovations over the 1980-2001 period). This restriction provides a universe of 48 firms innovating 556 new molecules. These firms are based in seven nations: 4 in Britain (Beecham, Glaxo, Wellcome, Zeneca), 5 in France (Rhone Poulenc, Roussel, Sanofi, Servier, Sythelabo), 4 in Germany (Bayer, Boehringer Ingelheim, Boehringer Manheim, Hoechst, Schering AG), 13 in Japan (Daiichi, Dainippon, Eisai, Fujisawa, Kyowa Hakko, Mitsubishi, Ono, Otsuka, Sankyo, Shionogi, Sumitomo, Takeda, Tanabe, Yamanouchi), 4 in Switzerland (Alcon, Ciba-Geigy, Roche, Sandoz), 1 in Italy (Farmitalia), and 15 in the United States (Abbott, American Home Products, Bristol-Myers Squibb, Genentech, Janssen, Johnson & Johnson, Lilly, Marion Merrell Dow, Merck, Pfizer, Schering Plough, SmithKline, Syntex, Upjohn, Warner Lambert). We excluded from analysis large firms based in countries where we did not have access to data on domestic demand: AKZO of the Netherlands, Novo of Denmark, and Astra and Pharmacia of Sweden.

The nationality of the 48 firms in our sample is clear for 45 firms. For these firms, the corporate headquarters and core innovation activities are in the same country. We use the filer location for the US patent associated with each molecule to identify location of innovation activity. Virtually all the innovations of these 42 firms with unambiguous nationality are from the home country. The only noticeable exceptions are 9 innovations (out of 54) for British firms from their US laboratories, 9 innovations (out of 75) for the clearly Swiss firms that are from

their US subsidiaries, and 10 innovations (out of 191) for US firms in their British subsidiaries. For three large firms, nationality is ambiguous. Alcon is located in the US and files all of its patents from the US. Yet, since 1977, Alcon has been owned by the Swiss firm Nestle and operated as a subsidiary of that firm. Comparably, Janssen is located in Belgium with all its innovations covered by patents filed from Belgium, and has been since 1962 fully owned by the US firm Johnson and Johnson. And Roussel is located in France while owned by the German firm Hoechst. We regard the "nationality" of Alcon, Janssen, and Roussel as an empirical matter. For our base results, we exclude these firms. We provide a detailed consideration of these firms separately.

5.2 Pharmaceutical Innovations, 1980 to 2001

Our data begins with every pharmaceutical innovation launched in the world during 1980 to 2001. We consider a pharmaceutical innovation to be a patented new molecule. This definition is more stringent than used by some (Acemoglu and Lin, 2004) and excludes rebrandings (due to co-marketing by several firms), repackagings (e.g. pills, creams, sprays), reformulations (e.g. multiple to once-a-day dosings), and generic copies of branded drugs. We tabulate each of the 1085 new molecules launched worldwide during 1980 to 2001, and in so doing we generate the full universe of pharmaceutical innovations, not a sample. Our tabulations of new molecules are drawn primarily from records of IMS, Inc, supplemented to a minor extent for 1980 to 1982 by FDA (1985) and in recent years by the priority drug listings of the FDA (FDA website). IMS records miss a few minor innovations by southern European firms in the early years covered by our study. These records also fail to include certain recent innovations, specifically new drugs where patents cover biotechnology production rather than the original molecule (e.g. recombinant insulin).

For each new molecule, IMS collects the 4-digit demand class or therapeutic category. The vast majority of new molecules are sold in only a single demand class. A few molecules, however, have multiple therapeutic uses and are sold in separate demand classes. For example, finasteride, an innovation by the US firm Merck is sold as Proscar in demand class G4B2 Prostatic Disease Products (to treat enlarged prostates) and as Propecia in demand class D11A0 Other Dermatological Products (to treat pattern baldness). In our tabulations of innovations, we count new drugs sold in multiple demand classes as ½ an innovation in each class. For our

estimates, we aggregate the demand classes to the 3-digit level (G4B for Proscar and D11A for Propecia, to use the examples above).

5.3 Technological Expertise

Technology-based explanations of innovation regard new technology as an evolutionary outgrowth of the established technical base. Skilled labor, university science, venture capital, component suppliers, and the overarching institutions that facilitate trust and frequent interactions among these actors all drive innovation. Rather than directly measuring various components of the technical base and associated national innovation system, recent scholarship has used the historical innovations of regions and firms as a highly plausible proxy for the accumulated expertise that enables future innovation. In particular, the accumulated patent stock is prominently used to measure technical expertise or knowledge stock (Henderson and Cockburn 1994 & 1996, Kaplan, Murray, Henderson 2003, Nesta, Lionel and Saviotti 2005), and we follow this approach. We collected the USPTO patent number, filing date, and primary technology class (both 3-digit main and secondary) for every patent filed during between 1970 and 2000 assigned to any of the firms in our sample. We collect the same data for every patent during that period with an inventor origin in any of the countries in our sample,.

Our goal is to estimate the impact of this accumulated technological expertise on the pattern of innovations across therapeutic areas. But drug patents are for chemicals, and the USPTO technology classes describe chemical processes or at most chemical pathways in the human body. Pharmaceuticals are consumed, however, for therapeutic impact for specific medical problems, measured in our study by IMS 3-digit demand classes. We must therefore develop a mapping between the USPTO main and secondary technology classes and these IMS demand classes.[3]

We generate this technology-to-demand mapping by relying on the innovation data for our study—the new molecules innovated during 1980 to 2001. For these molecules, we have identified both the IMS demand class and the patent holder. For almost all of these innovations, the at least one of the patents providing intellectual property protection is a USPTO patent.

[3] To attempt to solve this same problem, Acemoglu & Linn (2004) relied upon a Thomas Derwent specialist to map patents to therapeutic categories. Empirical results indicating a surprising lack of a relationship between patents and the market size in a given therapeutic area led the authors to suggest this result may be due to the imperfect mapping procedure or lags between patents and introductions, among other possibilities. We pursued our matching strategy in an effort to generate a more representative mapping.

Some patents, however, are filed abroad or with the World Patent Organization, and we do not (yet) have consistent information on technology class for these non-US patents. Those drugs with USPTO patents provide a mapping between technology and demand classes.

This mapping is not one-to-one. The example of Merck's finasteride (mentioned above) demonstrates a single molecule (with a single primary technology class) that has multiple and profoundly different therapeutic effects (treating both enlarged prostates and male baldness). While there are very few drugs sold simultaneously in multiple demand classes, the several drugs associated with the greatest number of technology classes have multiple therapeutic effects. These patterns are usually regular. For example, in technology class 514, subclasses 200 to 207 [the class is drug, bio-affecting and body treating compositions, with subclasses 1-thia-5-aza-bicyclo (4.2.0) octane ring, containing different substituents for the various subclasses], all 20 drugs are cephalosporin antibiotics (in IMS demand class J1D). Likewise, in technology class 514/356 [subclass C=O in a C(=O)O group], all 6 drugs are calcium antagonists used to treat heart disease. The pattern is more complicated though still regular in technology class 514/254 [subclass polycyclo ring system having the plural nitrogen containing additional five-membered hetero ring as one of the cyclos], where 7 of the 11 drugs are fluoroquinolone anti-infectives while the remaining 4 are atypical anti-psychotics used to treat schizophrenia—chemicals work in unexpected ways in our bodies! At the opposite extreme is technology class 514/255 [subclass nitrogen or -C(=X)-, wherein X is chalcogen, bonded directly to the piperazine ring], where the 8 drugs are each in a quite different IMS demand class, even at the 1-digit level, ranging from an antihistamine, to an antidepressant, to a prostatic disease product, to a cytostatic used to treat cancer.

We compute our mapping by calculating the following share for each IMS therapeutic class *k*, and each USPTO technology class *j*:

$$\sigma_{k,j} = \frac{\text{\# Patent in tech class } j \text{ associated with Drugs in class } k}{\text{\# Drugs w/ patents in tech class } j}$$

We weight each patent originating from each firm (or country) for each year with the share appropriate to each technology class (*j*). Finally, we aggregate these weighted patents in each therapeutic class (*k*) for each firm (*f*):

$$\text{TechnologicalExpertise}_{f,k} = \Sigma_k (\sigma_{k,j} * \#\text{patents}_{j,f})$$

This provides the number of patents relevant to each therapeutic area, with the allocation of patents to therapeutic areas based on the patents for the drugs in our sample. Technological expertise at the country level is calculated analogously, summing allocated patents for each country-therapeutic class.

For the cross section analysis, we aggregate the technological expertise for the firm or country over the 1970-1989 period to capture the pre-existing knowledge stock.[4] For the analysis of annual data, we aggregate the technological expertise for the firm or the country during the prior 10 year period.

5.4 Market Demand

We examine every new drug launched (regardless of the country of origin) during 1980 to 2001. For each of these drugs, we collect sales data for markets of Britain, France, Germany, Italy, Japan, Switzerland, and the United States – the domestic markets of the seven highly innovative nations for pharmaceuticals. These data are available for each year of the 10-year period 1992 to 2001. We aggregate sales revenue in each year for all new drugs within each 3-digit IMS demand classes. Sales are measured in US dollars per capita for each of the seven countries. For the cross section analysis, we use sales in 2001 to proxy for anticipated demand. This is consistent with Acemoglu and Linn (2004), who find that the number of drug innovations was most sensitive to leading (i.e. future) demand. Summary statistics and correlations of the therapeutic area per capita demand across countries in 2001 are provided in Table 3. For the annual data analysis, we use sales in the prior year, in order to avoid endogeneity concerns.

5.5 Foreign Market Involvement

We develop two distinct measures of the level of firm's involvement in foreign markets based on two activities that a drug firm might carry out in foreign markets: marketing and research. With regard to marketing, it is important to recognize that the innovating firm quite often does not market the drug in foreign markets. The firm instead contracts with a local firm, presumably with better connections to the appropriate and necessary distribution channels, to market the drug. For each of the new molecule introductions in out data set, we collect detailed information on the

[4] We also executed our analyses using only patents filed during 1970 to 1979, and the resulting findings were essentially identical.

marketing company in every market in which the drug was introduced. Then, for each innovating firm in our sample, we calculate the total sales for which the company was the marketer occurred in each of the target markets. The share of sales in each market reflects the degree to which that firm is active in marketing in each target market. Based on these shares (s), we calculate the marketing-weighted foreign demand as follows, for firm f and foreign markets m:

$$MarketingWeightedDemand_f = \sum_m s_{mf} Demand_m$$

Similarly, we calculate the share of each firm's research that is performed in each of the target market countries. This is based on the inventor address provided in the patent data. For all patents assigned to each firm in our sample, we determine the country location of the inventor(s). From this, we calculate the percentage of patents developed in each of the target market countries. The share of patents developed in each country represents the relative research activity of the firm in each market. Based on these shares (*r*), we calculate the research-weighted foreign demand as follows, for firm *f* and foreign markets *m*:

$$\mathrm{Re}searchWeightedDemand_f = \sum_m r_{mf} Demand_m$$

5.6 Index of Risk Aversion

We use the country level index of uncertainty avoidance generated by Holfstede (2005), which capture the "society's tolerance for uncertainty and ambiguity…It indicates to what extent a culture programs its members to feel either uncomfortable or comfortable in unstructured situations." This index ranges from 0 to 100, with higher values representing greater tendencies toward uncertainly avoidance.

5.7 Therapeutic Class Age

We use the age of the therapeutic class, as well as this variable interacted with the risk aversion index, to instrument for sales in a therapeutic class and market. If a therapeutic class is older, it may have experienced more growth and acceptance, and therefore exhibit a higher level of sales. Note that the class age is not market specific – it is the number of years that have passed since the first drug introduction in the therapeutic class. The interaction of class age and risk avoidance captures the differential effect that class age will have on the market in a given country, based on that country's citizens' willingness to accept change and uncertainty associated with newer therapeutic areas. Sales are expected to be lower, all else equal, in a

younger therapeutic area in a country with greater risk avoidance than they will be in a country with lower risk avoidance.

6. Empirical Results

We begin with the cross section, estimating the relationship between sales in 2001 and the number of innovations generated by each firm in each therapeutic area during the 1980-2001 period. Results are reported in Table 4. The first column in Table 4 constrains the coefficient on demand to be constant across all demand from all seven markets, and therefore includes only the total sales for the therapeutic class[5]. This provides a base line against which we can test the more flexible specifications. Total market demand and the firm's own technological experience are both highly positive and significant. The second column in the table allows the coefficients on the firm's home market demand to be different from the sum of the foreign markets demand. The coefficient on home demand is significant and positive (as it is in all models), and the coefficient on foreign demand is negative and significant. Note that the coefficient on home demand is also significant and positive if foreign demand is not included in the estimate, indicating that the result is not due to the correlation of these two variables. This result indicates that the number of innovations in a given therapeutic area generated by a firm is significantly and positively associated with the level of (per capita) demand for drugs in that therapeutic area in the firm's home country. An LR test comparing these two models strongly rejects the constraint of equality of the coefficients on home and foreign demand. This provides evidence supporting the prediction that local and distant market demand patterns influence innovation investments differently. In particular, the coefficient on foreign market demand is negative, suggesting that firms in the domestic market may avoid therapeutic areas where there is strong foreign demand.

Column (3) includes the expertise of the rest of the country and rest of the world. The negative and significant coefficient of the rest of country experience is interesting. This is consistent with the negative "competition" effect found by Jaffe (1986) and Popp (2002). As both of those authors suggest, this coefficient is the net effect of any potential positive spillovers and the negative competition effect from local firms. The fact that this coefficient (and the coefficient on the rest of world technological expertise) is not positive suggests that the net

[5] Since total sales do not vary within therapeutic class, this constrained model can not be run with the therapeutic class indicator variables.

effects of within-country (and cross-country) technological spillovers are not positive. The coefficient on the rest-of-country technological experience variable becomes insignificant when the firm indicator variables are included (column 4), suggesting that it is the level of competitor accumulated knowledge (not the relative comparison across therapeutic areas) that drives this effect. In fact, once firm indicator variables are included, the coefficient on the rest of world expertise is negative. This is consistent with firms avoiding therapeutic areas that are dominated by firms located in other countries.

Equation 5 includes therapeutic class fixed effects, and therefore provides a comparison across countries controlling for unobserved differences across therapeutic areas. Because the home country and rest of world demand (and therapeutic experience) variables sum to a constant within therapeutic area, the rest of world variables must be dropped in this estimation. Results largely mirror equation (3), and the coefficient on home demand is in fact greater in magnitude. Equation 6 includes both firm and therapeutic area indicator variables. The coefficients in this estimate reflect the within-firm variation across therapeutic areas, controlling for the overall level of innovations in that therapeutic area. Results are quite similar to equation (4). For all estimates, the firm's own technological expertise is significant and positive, indicating (as expected) that innovations are more frequent in the technological areas in which a firm has more accumulated technological expertise.

In order to address the possibility of endogeneity of the sales revenue to the number of innovations, we instrument for home and foreign demand. The final column in Table 4 reports the second stage results when the level of home and rest of the world demand in 2001 are instrumented for using the therapeutic category age and the interaction of this age with the risk aversion index for the home country.[6] It is not possible to estimate the negative binomial model with instruments while also correcting the standard errors for the presence of the predicted variables, and so we use a linear approximation in OLS for this estimate. In both first stage regressions, the therapeutic category age variable is highly significant. The home country risk aversion and the interaction term are significant in the home country demand equation, as one would expect. The results for the second stage equation are quite consistent with the previous results.

[6] We are unable to make use of these instruments while also controlling for the therapeutic class because the age does not vary across the observations for the class. We would be left with only one viable instrument (the interaction term) that varies at the therapeutic class-country level. We need two instruments to perform this estimation.

These results together indicate that, comparing across countries and therapeutic areas, the number of innovations does in fact respond to local (home) demand and the firm's own technological expertise, and is unresponsive to the demand and knowledge in the rest of the world. Results of an analogous analysis of annual data, where the level of analysis is the firm - therapeutic class – year, are reported in Tables 5. We reproduce the estimates reported in columns 3-5 of Table 4 using the annual observations, with the home and foreign market demand measured by the one year lagged value of per capita sales. The results are completely consistent with those from the cross sectional analysis with regard to the demand influence on innovation. Neither the rest of country nor the rest of world technological expertise are significant predictors of the innovation pattern. The negative coefficients on foreign demand and rest of country technological expertise are significant only at the 10% level in the annual regressions.

In light of the substantial empirical research regarding knowledge spillovers, the lack of significance of positive rest-of-country and rest-of-world technological expertise may seem puzzling. It is important to keep in mind that within that body of research, the spillovers are primarily R&D spillovers – one firm's output (usually innovation) is positively related to other (local) firm's R&D investments. Our analysis is further downstream and evaluates actual drug innovations using introduced new molecules. We are using the stock of patents as a measure of accumulated knowledge expertise and a reflection of the pattern of that expertise across therapeutic areas. Knowledge outputs, such as patents, are generally reflective of the pattern of knowledge inputs, such as R&D investments. However, if R&D-generated knowledge does in fact spillover to a firm in our sample (either from within or outside of the home country), and that firm utilizes the acquired knowledge in their own innovation-generating R&D, that firm is also likely to patent their own research output. Therefore, such a knowledge "spillover" could be captured in the firm's own R&D. Since we are using the knowledge stock as predictor of the pattern of a firm's drug introductions, the use of an outcome variable like patents is not worrisome, and is in fact conservative with respect to finding a significant result on the demand variables. Because of this construction of the variable, our results can not rule out a situation where a firm engaged in research resulting in a patent makes use of other's knowledge as an input. In fact, it is not surprising that we find more evidence of the competition effect of local firms, given our downstream focus. These results *do* however rule out spillovers in the form of knowledge from the surrounding environment that increase the productivity of the relationship

between the firm's own R&D and new drug introductions. For example, the fact that a given country specializes (and hence has developed expertise in) antibiotics does not result in more antibiotic drug introductions for a firm in that country – it is the firm's own research expertise that matters.

Although the firms in our sample are large multi-national firms, there is heterogeneity in the degree to which these firms are involved in foreign markets. If firms that are involved in foreign markets are in fact acting as "global" innovators, while other firms are responding only to local demand conditions, the results above may fail to capture the global actors because the positive demand spillovers are not consistent across firms. In order to test the hypothesized benefit of firms' involvement in foreign markets, we supplemented the basic regression with the measures of Marketing- or Research- weighted demand (which replace the foreign market demand variable). These variables allow the coefficient on the foreign market demand variable to capture the potential relationship for those firms with involvement in foreign markets. A firm that does not engage in any marketing activity (or research activity) in foreign markets will have a value of zero for the variable.[7] Table 6 reports the results, which do not provide any substantial evidence that the innovation patterns of firms that are more involved in foreign markets, either through direct marketing or research activities, systematically respond to foreign demand patterns. Results using annual data are essentially the same, and are not reported in the interest of space.

Results thus far indicate that demand and technological drivers of innovations are both important, but also that both are dominantly local phenomenon. Foreign market demand and foreign country technological expertise does not predict the innovation patterns of multi-national pharmaceutical firms. This is a substantial and strong result is robust across multiple estimations and methods. All of the analyses this far, however, have constrained the coefficient on the various demand and technology variables to be constant across countries. It is certainly possible that these results are masking spillovers that are taking place, but that are not consistent across firms or countries. The results of the analysis of foreign market involvement demonstrate that the direct marketing and research activities of firms in foreign markets do not serve as consistent and

[7] The correlation between market-weighted foreign demand and foreign demand, and between research weighted demand and foreign demand are both negligible. The correlation between market-weighted and research-weighted demand is 0.93.

significant moderators that serve to generate such spillovers. To be as thorough as possible, we also searched for any evidence of positive spillovers at the country level.

First, we allowed the coefficient on foreign market demand, rest of country technological expertise, and rest of world technological expertise to vary by home country of the firm by interacting each variable with indicator variables for the home country of the firm. The interactions allow for the relationship with innovation activity to differ by home country location. The results (not reported in the interest of space, but available from the authors upon request) are very consistent with the results reported above. The coefficient on foreign market demand is negative and insignificant for every home country, whether we use the aggregated or annual data.[8] The coefficient on the rest of country technological expertise is insignificant, expect for Japan, where the firms appear to benefit from within-country spillovers (the coefficient is positive and significant). The coefficient on the rest-of-world technological expertise is negative and insignificant for every country. Therefore, there is no evidence that the results are driven by firms in just one country or that firms in any subset of countries experience more influence from foreign demand or technological expertise.

Second, we estimate the basic model separately for each home country and foreign market pair. Ideally, we could include variables for each market. However, there is substantial multi-collinearity across the vectors of demand (see Table 2). Therefore, we run a separate estimation for each home country-foreign market pair. The number of observations is the number of firm in the home country times the number of therapeutic classes (125). Rather than report the results of 36 regressions, we summarize the coefficients of interest (on home and other market demand) in Table 7.

For most countries, there is the familiar and clear result that the pattern of innovations responds to home country demand. Our results are clearly not driven by the relationships in only one or two countries. However, there are two possible cases of positive demand spillovers evident. The pattern of innovations generated by Swiss firms appears to respond positively to the demand patterns in Germany. Although the result is not as strong, the results do suggest that the patterns of innovations by firms in Britain respond positively to the pattern of demand in the US, since the home demand drops in significance and the coefficient on the US demand is positive.

[8] These results are based on the fully specified model, including therapeutic class effects. Excluding therapeutic class effects does not change the results.

However, there are many more cases of "strategic avoidance" where firms avoid therapeutic areas that are significant for other countries. Note also that the positive demand spillovers are not symmetric. Innovation patterns of firms in Germany do not respond positively to demand patterns in Switzerland, and those in the US do not respond positively to British demand. These results suggest that it is not simply cultural or geographic proximity that determines access to demand knowledge. It is likely related to specific multi-national activities of firms or the existence of adequate "national absorptive capacity," as suggested by Mowery and Oxley (1995). This is an area for future research.

In light of the substantial empirical research regarding knowledge spillovers, the lack of significance of rest-of-country and rest-of-world technological expertise may seem puzzling. It is important to keep in mind that within that body of research, the spillovers are primarily R&D spillovers – one firm's output (usually innovation) is positively related to other (local) firm's R&D investments. Here we are using the stock of patents as a measure of accumulated knowledge expertise and a reflection of the pattern of that expertise across therapeutic areas. Knowledge outputs, such as patents, are generally reflective of the pattern of knowledge inputs, such as R&D investments. However, if R&D-generated knowledge does in fact spillover to a firm in our sample (either from within or outside of the home country), and that firm utilizes the acquired knowledge in their own innovation-generating R&D, that firm is also likely to patent their own research output. Therefore, such a knowledge "spillover" could be captured in the firm's own R&D. Since we are using the knowledge stock as predictor of the pattern of a firm's drug introductions, the use patents to indicate the portfolio of R&D activity is not worrisome, and is in fact conservative with respect to finding a significant result on the demand variables. Because of the construction of this variable, our results can not rule out a situation where a firm engaged in research resulting in a patent makes use of other's knowledge as an input. These results *do* however rule out spillovers in the form of knowledge from the surrounding environment that increase the productivity of the relationship between the firm's own R&D and new drug introductions. For example, the fact that a given country specializes (and hence has developed expertise in) antibiotics does not result in more antibiotic drug introductions for a firm in that country – it is the firm's own research expertise that matters.

Collectively, these results consistently suggest that there are no global pharmaceutical firms, only national ones or (in a couple of isolated cases) bi-national ones. We confirm the

localization of research knowledge, and, more importantly, demonstrate the significant localization of demand knowledge. This implies that not only is the production of technology largely local, as demonstrated by Patel (1995) and Patel and Pavitt (1991), the innovations are largely shaped by and intended for the local market.

7. Discussion

This paper advances theory regarding why location matters for innovation. In particular, we emphasize the importance of access to tacit knowledge of location-specific demand characteristics. In addition to the availability of the firm's own technological knowledge, we demonstrate that the availability of knowledge regarding local demand patterns determines the pattern of innovations generated. Our findings suggest that the empirical magnitude of these effects is large and strategically important. From the perspective of innovation patterns, numerous therapeutic categories are dominated by regional clustering of firms. For example, Table 1 illustrates the degree of clustering for three categories of pharmaceutical innovation – in each case, per capita demand is much higher in the home/proximate markets of the innovators than in other markets. From the perspective of strategic importance, our initial results provide partial explanation for the remarkable rise of British drug firms and the corresponding eclipse of Swiss firms – we find British innovations to be predominantly demand-driven and (at least partially) focused on the enormous and rapidly growing US market for drugs, while Swiss firms focused on the more traditional and relatively stagnant German market.

This study highlights the importance of the "home country" of an innovative firm that is often ignored or forgotten in the National Innovation Systems literature. Just as the prevailing regulations, policies, and access to local technological knowledge generate benefits (or disadvantages) for the firms in a country, the pattern and characteristics of demand also shape the innovative trajectories of the firms in the country. Similarly, as technological knowledge is often difficult, costly, and slow to transfer across national boundaries, and thus limited in terms of diffusion to foreign innovators, knowledge regarding demand gleaned from experience in a home market is also not globally available. This is particularly true when the pattern of demand is a product of the complex and interdependent nature of social, political, and economic institutions, as it is in the pharmaceutical industry.

Table 1: Examples of New Molecule Innovation Clustering, New Drugs Launched 1980 to 2001

Fibrinolytics
(restrict fibrin, major component of blood clots)

anistreplase	UK	Beecham	
duteplase	Japan	Sumitomo	
monteplase	Japan	Eisai	
nasaruplase	Japan	Green Cross	
nateplase	Japan	Mitsui	
pamiteplase	Japan	Yamanouchi	
reteplase	German	Boehringer Mannheim	
silteplase	Japan	Daiichi	
tisokinase	Japan	Asahi Chemical	*7 of 9 are Japanese*

Beta-Blockers (cardiovasculars)

amosulalol	Japan	Yamanouchi	
arotinolol	Japan	Sumitomo	
bisoprolol	German	Merck KAAG	
bopindolol	Swiss	Sandoz	
bosentan	Swiss	Roche	
bucumolol	Japan	Sankyo	
carvedilol	German	Boehringer Mannheim	
celiprolol	France	Rhone Poulenc	
esmolol	Sweden	Astra	
mepindolol	Swiss	Sandoz	
nebivolol	Belgium	Janssen	
penbutolol	German	Hoechst	
tertatolol	France	Servier	*10 of 13 are continental European*

Anti-Migraine Triptans

almotriptan	Spain	Almirall	
eletriptan	US	Pfizer	
naratriptan	Britain	Glaxo	
rizatriptan	US	Merck	
sumatriptan	Britain	Glaxo	
zolmitriptan	UK	Glaxo	*5 of 6 are Anglo-American*

Table 2: Means and Correlations
For Country-Therapeutic Class Level Demand
(N=125)

	Mean	Correlation						
		Britain	France	Germany	Italy	Japan	Switzerland	USA
Britain	4.62	1						
France	5.13	0.82	1					
Germany	4.80	0.87	0.89	1				
Italy	5.02	0.83	0.90	0.91	1			
Japan	5.18	0.64	0.66	0.67	0.64	1		
Switzerland	5.20	0.86	0.88	0.90	0.87	0.60	1	
USA	5.77	0.87	0.82	0.86	0.78	0.60	0.87	1

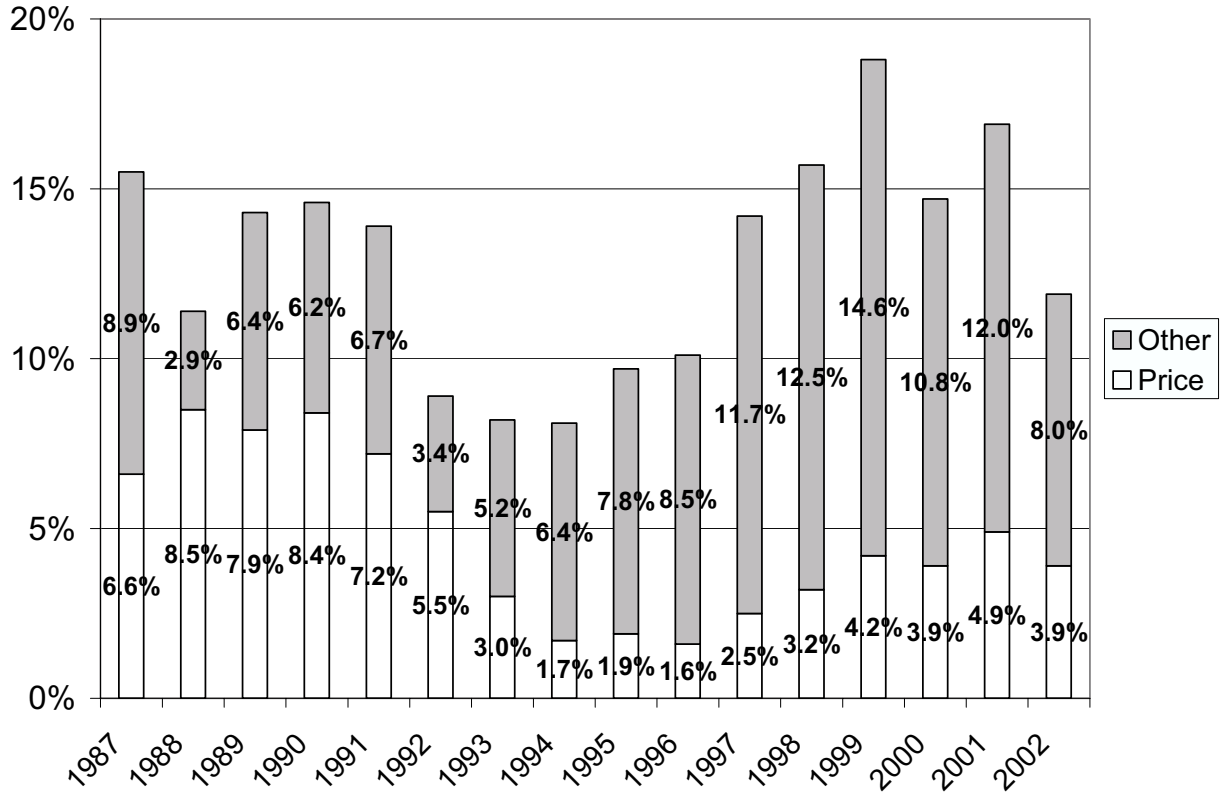
Country demand is log(1+Sales) in each of 125 ATC3 demand classes, where Sales gives per capita sales in 2001 in the given country expressed in US dollars for all drugs discovered during 1980 to 2001 in that demand class.

Table 3: Means and Correlations For Firm-Therapeutic Class Level Variables (N=5,625)

	Mean	# Intros	Home Demand	Foreign Demand	Firm Patents	ROWorld Patents	ROCountry Patents
# Innovations	0.10	1					
Home Demand	5.31	0.17	1				
Foreign Demand	7.36	0.13	0.76	1			
Firm Patents	0.70	0.34	0.36	0.36	1		
ROWorld Patents	4.71	0.14	0.49	0.52	0.48	1	
ROCountry Patents	2.86	0.11	0.48	0.41	0.40	0.73	1

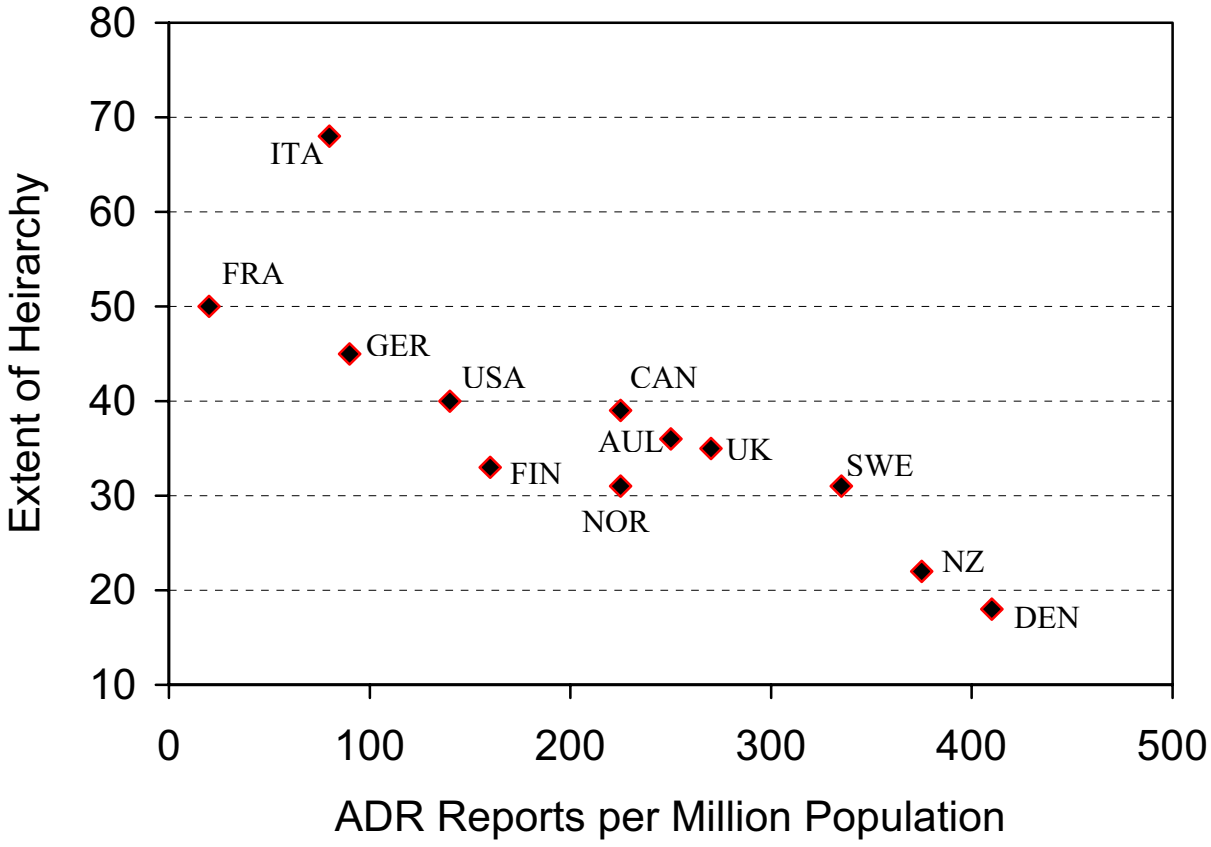
Innovations: number of new molecule innovations per therapeutic class.
Home Demand: ln(1+ Sales) in the therapeutic class where Sales is per capita sales in 2001 in firm's home country.
Foreign Demand: ln(1+ Sales) in the therapeutic class where Sales is per capita sales in 2001 in rest of world.
Firm Patents: ln(1+Patents) where Patents is count of patents by the firm during the 1970-1989 period allocated to the therapeutic class.
ROWorld Patents: ln(1+Patents) where Patents is the count of patents generated in other countries during the 1970-1989 period allocated to the therapeutic class.
ROCountry Patents: ln(1+Patents) where Patents is the count of patents generated in the firm's home country, excluding those by the focal firm, during the 1970-1989 period allocated to the therapeutic class.

Figure 1: Growth in Spending on Pharmaceuticals Due to Price versus Volume and Innovation (Other), 1987-2002



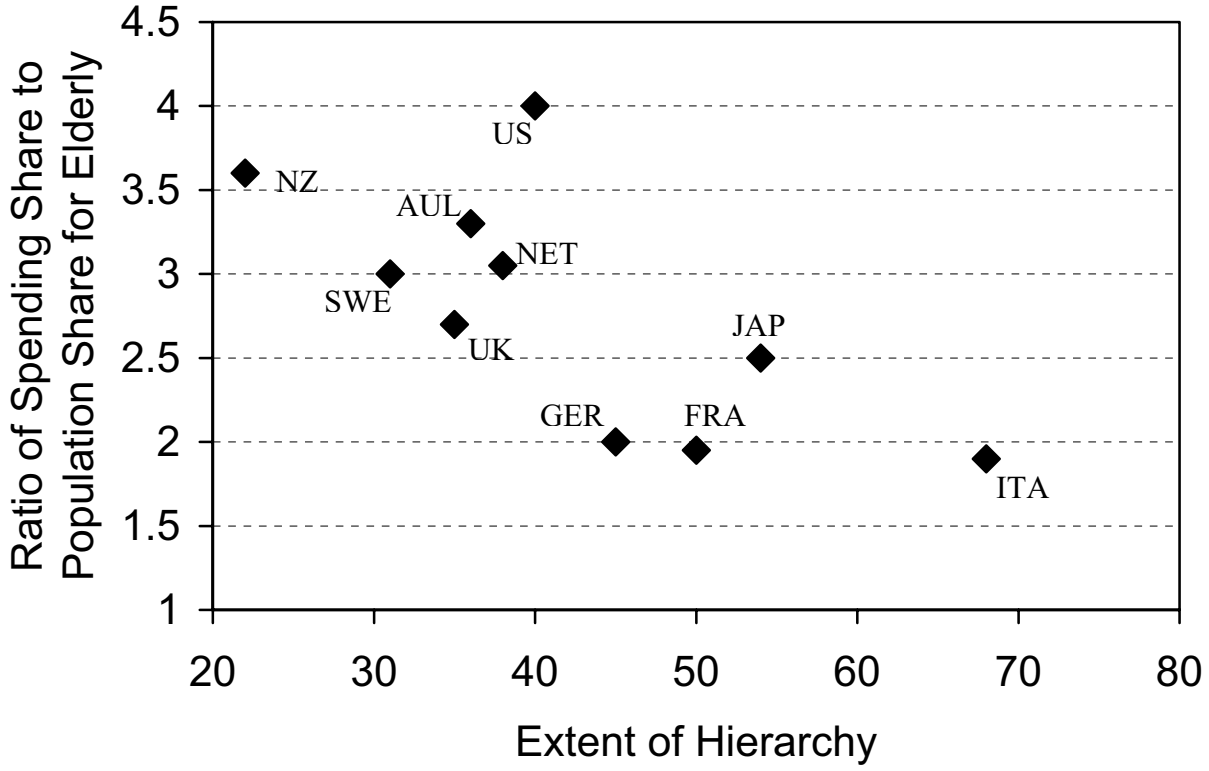
Source: Danzon and Pauly, 2002, p. 588.
Data from IMS Health, Retail and Provider Perspective (February 2003)

Figure 2: Data for 15 Countries on Rates of Reports for Adverse Drug Reactions and the Extent to which National Culture is Hierarchical



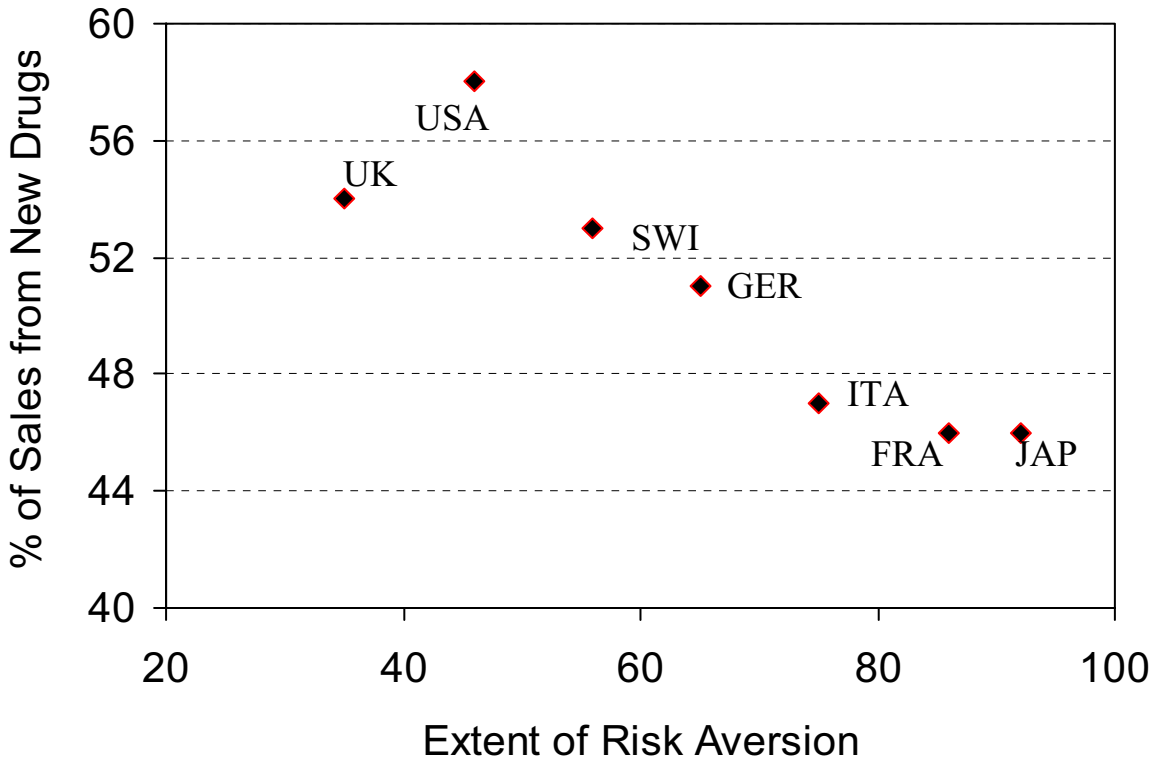
Sources: Extent of hierarchy is the power distance index of G. Hofstede and G.J. Hofstede (2005) Cultures and Organizations: Software of the Mind *2nd edition, New York: McGraw-Hill. Rate of adverse drug reaction reports is from J.P. Griffin (1986) "Survey of the Spontaneous Adverse Drug Reaction Reporting Schemes in 15 Countries"* British Journal of Clinical Pharmacology.

Figure 3: Data for 10 Countries on the Relative Share of Health Care Spending on the Elderly and the Extent to which National Culture is Hierarchical



Sources: Extent of hierarchy is the power distance index of G. Hofstede and G.J. Hofstede (2005) Cultures and Organizations: Software of the Mind *2nd edition, New York: McGraw-Hill. Data for the share of country health care expenditures on people 65 and the share of country population aged 65 or older are from Organization for Economic Cooperation and Development (2001)* OECD Health Data 2001: A Comparative Analysis of 30 Countries *Paris: OECD.*

Figure 4: Data for Seven Highly Innovative Countries on the Percentage of Domestic Sales in 2002 that Are from Drugs Launched in 1990 or Later and the Extent to which National Culture is Risk Averse



Sources: Extent of risk aversion is the uncertainty avoidance index of G. Hofstede and G.J. Hofstede (2005) Cultures and Organizations: Software of the Mind *2nd edition, New York: McGraw-Hill. The percentage of country sales in 2002 that are from drugs launched after 1990 is calculated from the data for this study.*

Table 4: Firm Innovations as a Function of Home and Foreign Demand and Technological Expertise: Aggregate Innovations 1980-2001
N=5,625

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Total Demand	0.10**						
	(0.03)						
Home Demand		0.21**	0.26**	0.29**	0.31**	0.36**	0.023**
		(0.03)	(0.04)	(0.04)	(0.05)	(0.05)	(0.007)
Foreign Demand		-0.11**	-0.13**	-0.15**			-0.014*
		(0.03)	(0.04)	(0.04)			(0.006)
Firm Tech. Experience	0.85**	0.83**	0.88**	1.08**	0.88**	1.20**	0.09**
	(0.06)	(0.18)	(0.06)	(0.05)	(0.05)	(0.06)	(0.006)
Rest of Country Tech. Experience			-0.15**	-0.01	-0.14**	0.06	-0.009
			(0.04)	(0.06)	(0.03)	(0.07)	(0.005)
Other Country Tech. Experience			0.03	-0.17**			-0.009*
			(0.06)	(0.07)			(0.004)
Incl FE				Firm	Ther. Class	Firm & Ther.Class	Firm

(1)-(6) Estimation is negative binomial, with dependent variable equal to the total number of innovations during the 1980-2001 period in each atc3-country observation.
(7) Second stage 2SLS, dependent variable is ln(1+#Innovations).
Robust standard errors (clustered by firm) in parentheses;
*significant at 5%; ** significant at 1%

Table 5: Firm Innovations as a Function of Home and Foreign Demand and Technological Expertise: Annual Innovations 1993-2001

	(1)	(2)	(3)	(4)
Home Demand	0.16** (0.04)	0.15** (0.05)	0.15** (0.05)	0.13** (0.05)
Foreign Demand	-0.08* (0.04)	-0.07 (0.04)		
Firm Tech. Experience	0.85** (0.08)	1.00** (0.10)	0.88** (0.08)	1.07** (0.12)
Rest of Country Tech. Experience	-0.09* (0.05)	-0.06 (0.09)	-0.08 (0.05)	0.001 (0.11)
Other Country Tech. Experience	0.07 (0.06)	-0.13 (0.07)		
Incl FE		Firm	Therapeutic Class	Firm & Therapeutic Class

Estimation is negative binomial, with dependent variable equal to the annual number of innovations in each atc3-country observation by each firm.
All equations include 8 year dummy variables.
Robust standard errors (clustered by firm) in parentheses;
*significant at 5%; ** significant at 1%

Table 6: Number of Innovations as a Function of Market Demand and Foreign Market Involvement

	(1)	(2)
Home Demand	0.18**	0.18**
	(0.02)	(0.02)
Marketing Weighted Foreign Demand	-0.00	
	(0.04)	
Research Weighted Foreign Demand		-0.00
		(0.04)
Firm Tech. Experience	1.07**	1.07**
	(0.05)	(0.05)
Rest of Country Tech. Experience	-0.02	-0.02
	(0.06)	(0.06)
Other Country Tech. Experience	-0.20	-0.20
	(0.06)	(0.06)
Incl FE	Firm	Firm

Estimation is negative binomial, with dependent variable equal to the total number of innovations during the 1980-2001 period in each atc3-country observation.
Robust standard errors (clustered by firm) in parentheses;
*significant at 5%; ** significant at 1%

Table 7: Firm Innovations as a Function of Demand: Coefficients from Dyadic Regressions
Coefficients on Demand from Negative Binomial Estimation:

E [#Innovation] =
$\exp(\beta_1 \text{HomeDemand} + \beta_2 \text{ForeignDemand} + \beta_3 \text{Firm Exp} + \beta_4 \text{RO Country Exp} + \beta_5 \text{RO World Exp} + \Sigma\eta_f)$

Country Dyad	# Observations	Home Demand (β_1)	Foreign Demand (β_2)
Home: US	1750		
UK		0.23**	-0.09^
France		0.14**	0.04
Germany		0.23**	-0.11
Japan		0.21**	-0.10^
Switzerland		0.23**	-0.10
Italy		0.14**	0.03
Home: UK	500		
US		0.14	0.07
France		0.30**	-0.12**
Germany		0.34**	-0.17^
Japan		0.27**	-0.11
Switzerland		0.18**	0.02
Italy		0.36**	-0.19*
Home: France	500		
UK		0.26*	-0.14
US		0.20^	-0.07
Germany		0.28**	-0.17*
Japan		0.20**	-0.12**
Switzerland		0.17**	-0.03
Italy		0.33**	-0.21*
Home: Germany	625		
UK		0.46**	-0.23**
France		0.41**	-0.19
US		0.37**	-0.13**
Japan		0.21**	0.04
Switzerland		0.39**	-0.15**
Italy		0.35*	-0.13
Home: Japan	1750		
UK		0.30**	-0.08^
France		0.32**	-0.12*
Germany		0.28**	-0.06
US		0.28**	-0.06
Switzerland		0.33**	-0.13*
Italy		0.30**	-0.09
Home: Switzerland	375		
UK		0.23**	-.11**
France		0.11	0.03
Germany		**0.09****	**0.06****
Japan		0.13**	0.02
US		0.31**	-0.17**
Italy		0.09*	0.06^

Significance based on robust SEs, clustered by firm.
**Significant at 1%, *Significant at 5%, ^Significant at 10%.

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