Tacit Demand and Innovation in the Global Pharmaceutical Industry

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Abstract *Our study examines innovations of new drugs in the global pharmaceutical industry. We contrast anticipated demand and historical technological expertise as determinants of the realized pattern of innovations at the country level. We further contrast local versus foreign determinants of innovation. We find that the pattern of demand is as important as technological expertise in determining the pattern of innovation in this industry. We also find that innovation is a locally determined phenomenon, with very little evidence of positive cross-country knowledge spillovers.*

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1. Introduction

What effect does location have on the nature of the innovations generated? 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 National Innovation Systems literature (Lundvall and Maskell, 2000; Mowery and Oxley, 1995; Freeman, 1995) has focused attention on the importance of the historical and ongoing development of national institutions and policies, especially the development of a research infrastructure including university scientists, to the innovativeness of a country's industrial sector. 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 most of these explanations are on the supply side for innovation, focused on inputs needed for inventions. 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 impact of geography on innovation. In particular, we argue that information about anticipated demand can be as complex and tacit as knowledge inputs, with comparably limited diffusion outside the local region.

This study addresses innovation in the pharmaceutical industry. The period for drug innovation is quite prolonged, with roughly a decade elapsing between the patenting of a new molecule and its initial sales to doctors and patients. The more downstream parts of this innovation process are highly globalized. Drug innovations have long been launched and sold in multiple countries (Kyle, 2006). In recent years, even clinical trials of new molecules have begun to migrate outside the initial country of discovery (Cockburn, 2006; Berndt, Cockburn, and Thiers, 2007). Our study examines the most upstream and strategic portion of pharmaceutical innovation – the selection of which products to innovate. Our finding that the pattern of innovations is highly localized is a surprising counterpart to evidence of downstream globalization, but is not inconsistent with them.

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 for innovation. The third section provides institutional context for arguments that demand is tacit information with limited diffusion across countries. 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 estimates 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 firms in leading countries between 1992 and 2001. We find strong and consistent evidence of innovation patterns that responds to *local* demand and technology, but either ignore or avoid *foreign* counterparts. The sixth 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 science inputs, as well as the institutions that support science and knowledge generation, 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 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 technical 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.

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 technical knowledge facilitates the very conception of new technology, as well as the relative ease of inventive activity across areas of technology (Rosenberg 1974). Central to theories of technology-push is the argument that innovators are heterogeneous in their ownership of technology assets and that technical knowledge is not costlessly or readily transferable across inventors. Prior experience and technical knowledge assets at the firm level, as well as the technological base in the surrounding environment, greatly facilitate the creation of new technical 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 technological base improves the ability to productively focus search, to more efficiently search, and to speedily develop new innovations (Nelson 1982). Access to existing technology 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.

This literature suggests that differences in innovation patterns across countries are established and remain because of past and current R&D investments and supply-side policies of economic institutions in the country. The pattern of prior technology outcomes in a given country provides a reasonable proxy for the available technological base generated by the system of institutions. Consistent with substantial prior literature, we expect that differences in the established technology base will predict differences in the pattern of new innovations.

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

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, or

demand, and the pattern of innovations (also see Romer 1990 and Grossman and Helpman 1991). Rather than focusing on the existing technology 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 the 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 or opportunity set changes.

More recent work in this vein includes Newell et al. (1999), Popp (2002), and Acemoglu (2002). 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 U.S. 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 suggests that pharmaceutical firms anticipate exogenous changes to demand and respond by reallocating innovation to meet demand.[1]

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 R&D efforts, and therefore will contain a greater number of innovations. Out test will be stronger, in the sense that we control for the

[1] The formal and empirical model in that study assume that the technological opportunities and expertise are constant across time for a given therapeutic area, and the authors do not examine the possible role of changing technological expertise in determining the pattern of innovations.

exogenous (common) technological opportunity in a therapeutic area as well as the country-specific 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 of Innovation

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 regional boundary. This is in contrast to globalization, or access to resources and knowledge irrespective of national affiliation. 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. Consistent with the National Innovation Systems literature, we regard differences across country level institutions as the major determinants of "proximity" and "distance."

Literature examining geographic agglomeration and the benefits of proximity to either specific resources or related firms has focused on the role of knowledge and knowledge diffusion (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 evidence on knowledge flows has demonstrated 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, 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. Note that all of these findings are on the supply side for innovation.

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). To the extent that inventors are exposed to similar knowledge, and that knowledge facilitates future innovation, then the pattern of such innovation should be more similar, or isomorphic, across inventors in a particular locale than across distant inventors. Consistent with this prior literature, we expect that the technology base that is most 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.

Furman et al. (2002) 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.[2] 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 are complementary to 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 of a country, and therefore difficult to comprehend and anticipate for foreign firms.

[2] Furman et al. (2002) don't explain why firms based in other countries would be unable to respond to this demand. In the empirical exercise, the authors do not consider patterns of demand.

The foreign direct investment literature recognizes the potential for difficulty in understanding foreign markets. 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. Similar to the difficulty in accessing technological knowledge, firms may have difficulty accessing, comprehending, and internalizing the market demand in geographically or institutionally different markets. As we detail in the next section, 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.

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

We argue that the tacit nature of knowledge about demand accounts for a significant portion of observed clustering and localization 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 and regions within countries. Finally, country demand must also be sufficiently complex that it cannot be readily codified and transferred to firms in other countries. 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 source of difference and complexity for pharmaceutical is the country-level institutions that underpin drug consumption. 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). A second source of difference and complexity for 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.

The prolonged time period of drug innovation makes understanding of anticipated demand particularly important, and thus understanding the economic institutions that underlie that demand. The process for innovation of new drugs spans many years – on average over 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. Understanding the underlying political and social culture of a country is central to such forecasts.

We note that our study uses actual country revenues for empirical tests, and does not seek to explain why these revenues achieve different levels in different countries. We do not deploy measures of institutions or culture that might underlie these recorded demands. It is our interpretation of our empirical results that motivates our brief discussion of institutions and culture. These interpretations are plausible so long as it is credible that these observed demands are complex, different across countries, and similar within countries. We therefore stress that we do not seek in this study to analyze the origins of the observed differences across countries in the demand for new drugs.

3.1 Economic Institutions for Drug Demand

Domestic markets for consumption of pharmaceuticals are underpinned by a variety of economic institutions. First, most pharmaceutical consumption is paid for 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. Second, drug prices are regulated by governments. In markets where government provides health insurance, drug prices are set through direct negotiations between governments and pharmaceutical firms. Even when drug prices are determined in private markets, regulations extensively impact prices (such as through of entry by off-patent generic products and parallel imports). Third, routines for marketing and distribution of drugs are heavily regulated. Fourth, new drugs must pass elaborate pre-marketing safety regulations. These regulations govern not only attributes of drugs that may be marketed, but also the clinical trials that document those attributes.

All these institutions are predominantly determined at the country level, with profound differences across countries and less difference within. Consider, for example, the extent to which patients are informed about possible drug treatments and influence the choice of treatment. In the United States, the Food and Drug Administration allows advertising of drugs directly to consumers. Drug firms engage in large-scale media advertising in the USA, alongside

traditional marketing to doctors (Calfee, et al, 2002; Ling, et al., 2002). American patients consequently have significant knowledge of possible drug treatments and exert considerable influence over doctor prescriptions of medicines. In contrast, in Japan patients have vastly less understanding of drug consumption options and less influence over their own care. The per-visit structure of national health insurance payments provides incentives for Japanese doctors to minimize time spent with patients, and any provision of information to patients. The vast majority of drugs are dispensed directly to patients by doctors themselves, without prescription or use of a retail pharmacy. Direct-to-consumer advertising of drugs is banned. As a consequence, Japanese patients often do not know exactly which products they are consuming or why.

The economic institutions that exist in a country are underpined by social culture, because these institutions are chosen in accordance with dominant public values. This underpinning gives consistency and complementarity across various economic institutions. For example, the political and social culture of the United States is far more individualistic and egalitarian than Japan. These cultural traits give greater value to patient choice and to a more equal role of patient and physician in health care in the United States. The different economic institutions in the United States embody these values, and in a complex, interactive manner reinforce the relative power of patients in determining drug consumption.

The institutions underpinning demand for drugs represent a complex and dynamic system. The social and political cultures than underwrite these institutions are even more complex and poorly codified constructs. Knowledge about pharmaceutical demand is arguably highly specific to individual countries and constitutes tacit information. Scientists who live in a particular country will understand this tactic information, while foreign scientists will not. We note that the pharmaceutical industry differs from most other industries both in the great importance of national economic institutions and regulations for consumption and in the great time period separating invention and the final realization of sales. Both these traits make it especially likely that demand will be tacit information in this industry.

3.2 Social Culture: Hierarchy versus Egalitarianism

Economic institutions are underpinned and shaped by social culture. Hence, much of the inter-country differences in demand are driven by cultural difference. 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 unexpected 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 USA 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 USA 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 US 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 systematically 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 USA and 5 times those of Britain, despite the initial innovation of these products in that latter market.

3.5 Demand as Tacit Information: Example of Anti-Migraine Products

Economic institutions and social cultures fundamentally interact. Different countries choose and configure their institutions based on their social culture, and the functioning of otherwise identical economic institutions varies across countries based culture. Institutions and culture form a complex, complementary, and dynamic system that cannot be codified, and must be directly experienced to be understood. Operation in a country therefore provides tacit information regarding demand that is not available to firms located elsewhere.

The anti-migraine products that are our first example of clustering in Table 1 offer a useful example of these interactions. The actual incidence of migraine headache is very similar across countries (Unger, 2006). Detailed epidemiological studies (usually based on doctor-analyzed patient-journals of all symptoms and activities over a set time period) report the frequency of migraine sufferers to be 8 percent in Japan, 12 percent in the United States and France, and 16 percent in Italy. But the level of medical treatment for migraine headache (hence demand) varies enormously across countries based on social culture, and health care institutions based on that culture. Pain is difficult to observe and almost entirely self-reported. Patients in individualistic cultures are far more likely to view their personal suffering as important and abnormal, and to seek treatment. Additionally, doctors and other health care institutions in individualistic countries are far more likely to positively respond to these patient complaints.

Most migraine sufferers are women (Martelletti, 2007). In hierarchical societies, women and health care institutions are far more likely to tolerate suffering from migraine headaches as somehow appropriate and deserved and refuse to allocate economic resources to treat them. Japan is a collectivist and hierarchical society (Hofstede and Hofstede, 2005).

Recent studies show that only 12 percent of the Japanese population with migraine headache is even aware of their condition (Sakai and Igarashi, 1997; Sakai, et al., 1999). Only 3 percent of migraine sufferers visit a physician regularly, while 70 percent have never consulted a doctor for their condition. Most migraine sufferers take some over-the-counter treatment, and many take no medicine at all. It is not surprising that demand for anti-migraine pharmaceuticals varies enormously across countries, even while the underlying incidence is very similar. Per capita demand for anti-migraine products in the United States is 10 times that of Italy and 20 times that of Japan.

We note that the great majority of pharmaceutical researchers in Japan will be themselves Japanese. Doctors needed for clinical trials likewise. Both are deeply embedded in the health care system of that country, a system comprised of values and institutions that are internally consistent and mutually reinforcing. The large demand of American women for anti-migraine products and the lucrative market there awaiting pharmaceutical firms that innovate these products is tacit information for these Japanese drug innovators. In contrast, the discovery process by American and British firms for their own anti-migraine products will be relatively more public and explicit information. The expected rivalry by these competitors provides a second, reinforcing reason for Japanese firms to avoid innovation in this market.

4. Empirical Specifications

Our predictions posit that innovation is driven by domestic historical technology expertise, domestic anticipated demand, rivalry from existing products, and various knowledge spillovers (of both technology and demand). We denote the number of innovations generated in country j in year t in therapeutic class k as N_{jkt}. The basic model predicting the number of innovations is:

$$E[N_{jkt}] = \exp(\alpha_1 * Demand_{jkt} + \alpha_2 * ROWDemand_{jkt} + \beta_1 * TechExpertise_{jkt} + \beta_2 * PublicTechExpertise_{jkt} + \beta_3 * ROWTechExpertise_{fkt} + \sum_j \eta_j + \sum_t \delta_t)$$

$Demand_{jkt}$ is the anticipated sales for all drugs in therapeutic class *k* in year *t* in the domestic market *j*, while $ROWDemand_{jkt}$ is the total demand in the rest of the world. $Tech.Expertise_{jkt}$ is the country's accumulated technological experience from corporate entities up to year *t* in the therapeutic area. $PublicTech.Expertise_{fkt}$ is the accumulated technological experience up to year *t* of non-corporate organizations (mostly universities, but also governments) in the home country j in therapeutic class k, while $\text{ROWTech.Expertise}_{jkt}$ is the accumulated technological experience of all other countries.

Note that the basic model includes a full set of country-level indicator variables (η_j), which control for the unobserved heterogeneity for each country. For example, the mix of diversified activities outside the ethical pharmaceutical innovations that we study (chemicals, OTC products, generic drugs, and non-drug medical products) varies widely across countries. The extent of entrepreneurship and entry of new firms also varies widely. These and other differences make some countries more innovative than others in general, even controlling for the extent of patenting. The country-level indicator variables control for these differences. The set of year indicator variables (δ_t) controls for any common shifts in the propensity to innovate over time.

There is also a strategic dimension to concentrations of knowledge. Firms may elect not to develop new drugs in therapeutic areas in which there is either substantial accumulated expertise in foreign countries ("strategic avoidance"), such that they would be at a disadvantage, or there are a substantial number of drugs already serving the market ("competition") (Branstetter 2001, Furman, et al. 2006, Kyle 2007). The inclusion of the rest-of-world technological experience controls for the first possibility. In some specifications, we also include a control for the number of drugs in the therapeutic area introduced in the prior 5 years, either in total ($PriorDrugs_{kt}$) or separately for market j ($PriorDrugs_{jkt}$) and elsewhere in the global marketplace ($ROWPriorDrugs_{jkt}$).

We estimate this equation using poisson quasi-maximum likelihood (PQML) estimation, with conditional fixed effects for the therapeutic classes (*k*) to control for heterogeneity across therapeutic areas. Given the nature of the incidence of human diseases, it is possible that some therapeutic areas have greater levels of demand in many areas of the world. The fixed effects control for the relative "size" of the therapeutic area, as well as the (time invariant) opportunities for and ease of innovation in the area. Additionally, Kyle (2007) has demonstrated that inclusion

of therapeutic category fixed effects is necessary to correctly estimate the impact of existing rivals. Some categories will have unobserved lower costs of entry, hence higher numbers of both innovations and existing rivals. PQML conditional fixed effects model is preferable to negative binomial fixed effects model because it is consistent under a weaker set of assumptions, allows a flexible function form, is robust to arbitrary heteroskedasticity, and allows us to easily accommodate and adjust for correlation across the observations within a therapeutic class (Wooldridge 1999, Simcoe et al. 2007).

The model is identified by the considerable variance in demand across therapeutic categories, across countries, and over time. With the inclusion of the country level indicator variables and the therapeutic class fixed effects, the coefficient on home country demand, α_1, can be interpreted as the effect of a larger market size in a given class in the home country, relative to the market size in other countries in that class, on the number of innovations in that therapeutic class.

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. Although exploratory analyses do not suggest that such reverse causation is present, we treat $Demand_{jkt}$ as potentially endogenous, and take two approaches to account for this. First, we will compare our estimates with those using one-year lagged demand. Second, we will instrument demand using lagged demand and the interaction of the global age of the therapeutic category *k* in year *t* with the country-specific risk aversion index (Holfstede 2005). 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 over time will be greater for countries where there is less acceptance of new and uncertain things, as reflected in the risk avoidance index.

5. Measures and Data

In this section, we discuss in sequence the data and measures we use for innovations, technology expertise, and anticipated demand,

5.1 Pharmaceutical Innovations

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 989 new molecules launched 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). The 989 new molecules we study are distributed over 165 3-digit demand classes.

For each new molecule, we also identify the patent filer. Our data source for patents for most all our molecules was the Merck Index (2003), supplemented in a few cases by the FDA Orange Book (online) and internet searches using generic and trade names for new drugs. We identify the country of innovation as the country of the inventor listed on the patent.[3] Our data thus record the following allocation of pharmaceutical innovation across countries:

• USA	277.5	• Italy	75
• Japan	257	• Sweden	22.5
• France	75.5	• Netherlands	13
• Germany	82.5	• Spain	14
• Switzerland	56	• Denmark	11
• Britain	63	• Belgium	17

[3] This is the country of the residence address of the actual inventor, not the firm to which the patent is assigned.

with eight other countries recording innovations in the single digits. We restrict our empirical analysis to the seven most highly innovative countries listed above. This provides a set of 886 innovations across 160 technology classes for the 1980-2001 period.

5.2 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 (Henderson and Cockburn 1994 & 1996, Kaplan, Murray, Henderson 2003, Nesta, Lionel and Saviotti 2005), and we follow this approach.[4] We collected the USPTO patent number, filing date, and primary technology class (both 3-digit main and secondary) for every patent filed during 1970 to 2000 with an inventor origin in each 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.[5]

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,

[4] Conceptually, one would also want to control for the exogenous and common technological opportunity in a given technological area. We do so by comparing the pattern of innovations across countries within the same therapeutic areas.

[5] 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. We pursued our matching strategy in an effort to generate a more useful mapping.

the at least one of the patents providing intellectual property protection is a USPTO patent. Some patents, however, are filed abroad or with the World Patent Organization, and we do not 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). Few drugs are sold simultaneously in multiple demand classes, but several technology classes are associated with multiple demand classes. 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 *i*, and each USPTO technology class *j*:

$$\sigma_{i,j} = \frac{\text{\# Patent in tech class } j \text{ associated with Drugs in class } i}{\text{\# Drugs in tech class } j}$$

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

$$\text{Demand Class Expertise}_{k,i} = \Sigma_j \, (\sigma_{i,j} * \#\text{patents}_{j,k})$$

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. To capture the accumulated expertise of countries, we use the patent portfolio of the country over the previous 10 year period. Means and correlations for the technology expertise measure at the country level are reported in Table 2.

5.3 Market Demand

We assume that innovating firms forecast future demand based on past demand at the therapeutic category level for their domestic market. For each new drug launched during 1980 to 2001, we collect sales data for markets of Britain, France, Germany, Italy, Japan, Switzerland, and the USA – 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 up sales revenue in that year for each new drug across the 160 3-digit IMS demand classes. Sales are measured in US dollars for each of the seven countries.

6. Empirical Findings

Unfortunately, because our sales data are limited to the 1992-2001 period, we can only examine innovations during these years. This restriction results limits our analysis to a set of 369 innovations across 116 therapeutic classes.

The first set of results (presented in Table 3) controls for the technological expertise of the home country, rest-of-world technology, and the home and rest-of-world demand. The first column reports results without the therapeutic class fixed effects, for comparison. In all estimates, the technological expertise of the home country is significant and positive, indicating (as expected) that innovations are more frequent in the technological areas in which a country has more accumulated technological expertise. However, it is the corporate accumulated expertise, not that of public institutions, that directly drives innovation. This is consistent with public institutions generating research that is generally upstream, requiring more development (and the expertise of firms) before being reflected in innovations. Interestingly, the rest-of-world technological expertise is negative when therapeutic class controls are not included (column 1) and not significant when they are included. This suggests that accumulated expertise in other

countries may deter innovation, or at a minimum that positive cross country technological spillovers are not significant.

The home country demand is significant and positive in all estimations, as predicted. This indicates that the number of innovations in a given therapeutic area generated in a country is significantly and positively associated with the level of demand for drugs in that therapeutic area in the home country. Greater foreign market demand, on the other hand, is associated with fewer innovations, suggesting some degree of strategic avoidance.[6]

We examine this further by including controls for the number of prior drug introductions in the therapeutic class. Column 3 includes the aggregate number of prior introductions, which has a significant and negative effect on the number of current innovations, consistent with the expected competition effect. Note that one we control for the competition from existing drugs, the negative effect of foreign demand disappears, suggesting that this competition and strategic avoidance are responsible for the noted negative relationship. Column 4 breaks out the number of prior introductions generated by the home country and rest of the world. While both coefficients are significant and negative, the negative effect of rest of the world introductions is significant larger than that of home country prior introductions. This is consistent with firms in one country avoiding areas of strength for other countries. Finally, Column 5 considers separately the effect of recent (in the last five years) and older (great than give years) introductions. There is no significant difference in the effect of these two variables.

Table 4 provides robustness checks to account for the possible endogenous nature of demand. In column 1, we replace the home and foreign market contemporaneous sales with the sales lagged one year – so that *prior period* sales are predicting *current period* innovations. This specification forces the exclusion of innovations introduced in 1992, because we lack sales data for 1991. Even with this limitation, the results are similar to those with contemporaneous sales (the relevant comparison is Table 3, column 3 with Table 4 column 1). The decrease in magnitude of the home demand variable is not surprising – lagged demand is less reflective of anticipated future demand than is the current demand.

[6] We were concerned that the negative coefficient on foreign demand might reflect high correlation between foreign and home country demand. In order to investigate this, we re-ran the regression including foreign demand and excluding home demand. The coefficient on foreign demand was negative and significant, suggesting that this result is not due to correlation.

We also experimented with instrumenting for home market and foreign market demand with the lagged relevant demand and the interaction of the global age of the therapeutic class and the risk aversion index in the home country. We use a linear approximation of the Poisson model and implement OLS two stage least squares (2SLS) to estimate the two first stage equations and the second stage equation. For comparison, we provide the linear approximation of our base specification in Table 4, column 2. This specification is comparable to that reported in Table 3, column 3. The use of these instruments requires excluding observations for which we do not have lagged sales data and those in the first year for the therapeutic class (age is zero). In Table 4 column 3 we drop the observations that will be excluded from the 2SLS estimation to check that the results are not sensitive to this change in sample and provide a basis for comparison with the 2SLS results. Finally, column 4 provides the results of the second stage of the 2SLS estimation.[7] Comparing results in columns 3 and 4 suggests that the positive and significant coefficient on home demand is robust to explicitly controlling for endogeneity. Foreign demand remains insignificant. These results together indicate that, comparing across countries and therapeutic areas, the number of innovations does in fact respond to local demand and technological expertise, and is unresponsive to the demand and knowledge in the rest of the world.

Finally, we set out to examine differences in the determinants of the innovation patterns across various countries. In order to do so, we estimated our base specification separately for each pair of countries. In other words, for each home market, we considered the influence of each of the six foreign markets separately. This required 42 regressions, each of which still controlled for technological expertise, prior drug innovations, and year effects. In 25 of the regressions, home and foreign demand were *jointly* significant at the 5% level or better. These observations are represented graphically in Figure 4, which plots the coefficient on home demand and the selected foreign market demand for each of the regressions. In 10 cases, coefficients on *both* measures of demand were statistically significant at the 5% level or better. These cases are represented by round dots in Figure 4.

First, note that the coefficient on home demand was positive in all cases. As in the pooled regressions reported above, home country demand continues to be a significant driver of the innovation pattern in a country. Second, note that the great majority of points (and in fact all

[7] We did not report the two first stage regressions in the interest of space. As expected, the lagged demand instrument was positive and significant and the interaction of risk aversion and class age was positive and significant in the home demand equation.

points for which both coefficients were independently significant) fall below the x-axis. This indicates that innovations are less frequent in therapeutic class in which foreign demand is greater – consistent with strategic avoidance of the other country's area of strength. There are some interesting exceptions: Germany responds positively to Japanese demand, and is the only country to do so. Britain appears to respond positively to both Swiss and US demand. It is also important to note, however, that these relationships are not symmetric. Japan does not respond positively to German demand, and the US appears to avoid areas in with Britain has greater demand.

Collectively, these results consistently imply that innovation in the pharmaceutical sector is largely local, not global, in nature. 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. The few examples of the innovation pattern in a country responding positively to the demand pattern in a foreign country are Britain's innovation pattern and the demand pattern of the United States and Switzerland, and Germany's innovation pattern and the demand pattern in Japan. Importantly, this transfer of demand knowledge is not symmetric. This suggests 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.

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 local 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.

This study highlights an aspect 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.

Our results also suggest an important strategic aspect of demand induced innovation. First, it is clear that there is a strong competitive effect from existing drugs on the market that leads to fewer new innovations. This effect is particularly strong for drugs innovated in other countries, suggesting an avoidance of therapeutic areas in which other countries have an established position. Consistent with this strategic avoidance, innovation in a given country appears in many cases to avoid areas in which other countries exhibit relatively greater demand. This is in stark contrast to a global market place in which companies are generating innovations to service global demand.

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*

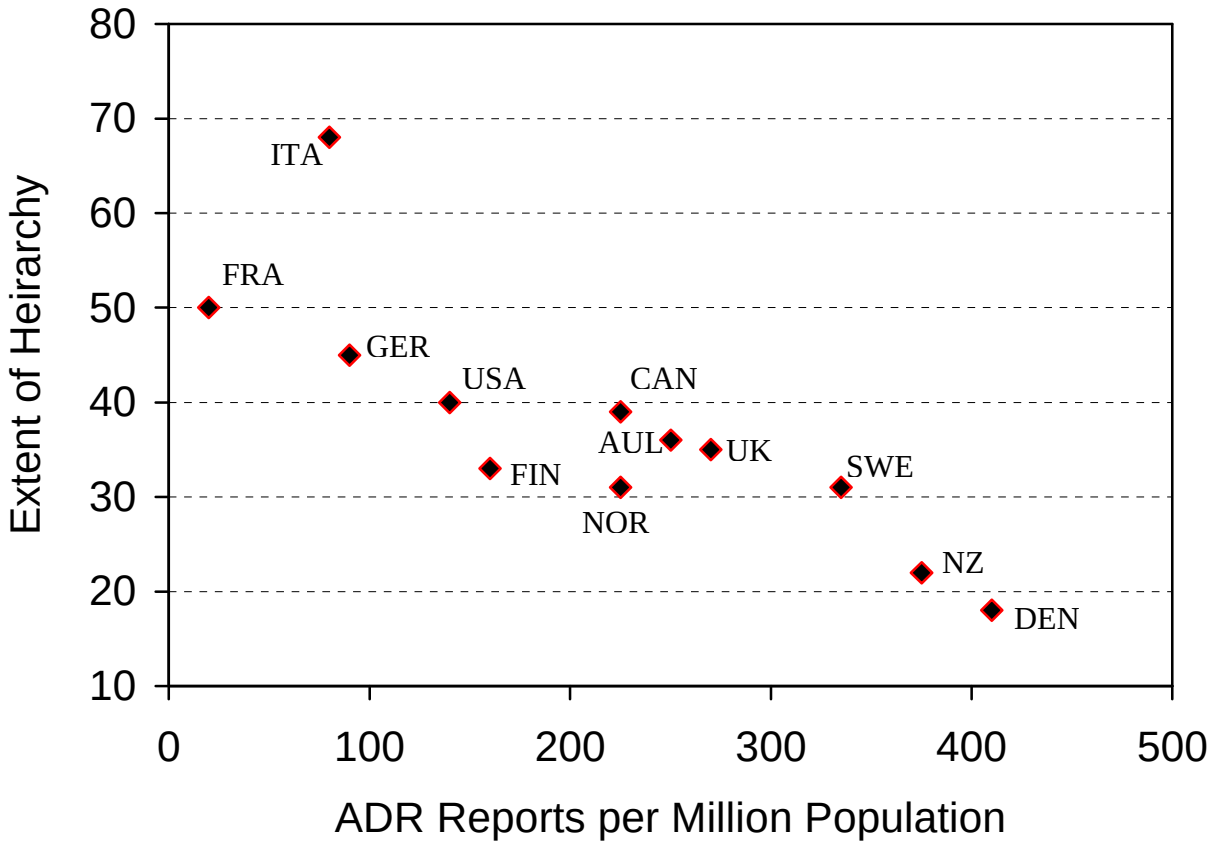
Beta-Blockers (cardiovasculars)

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

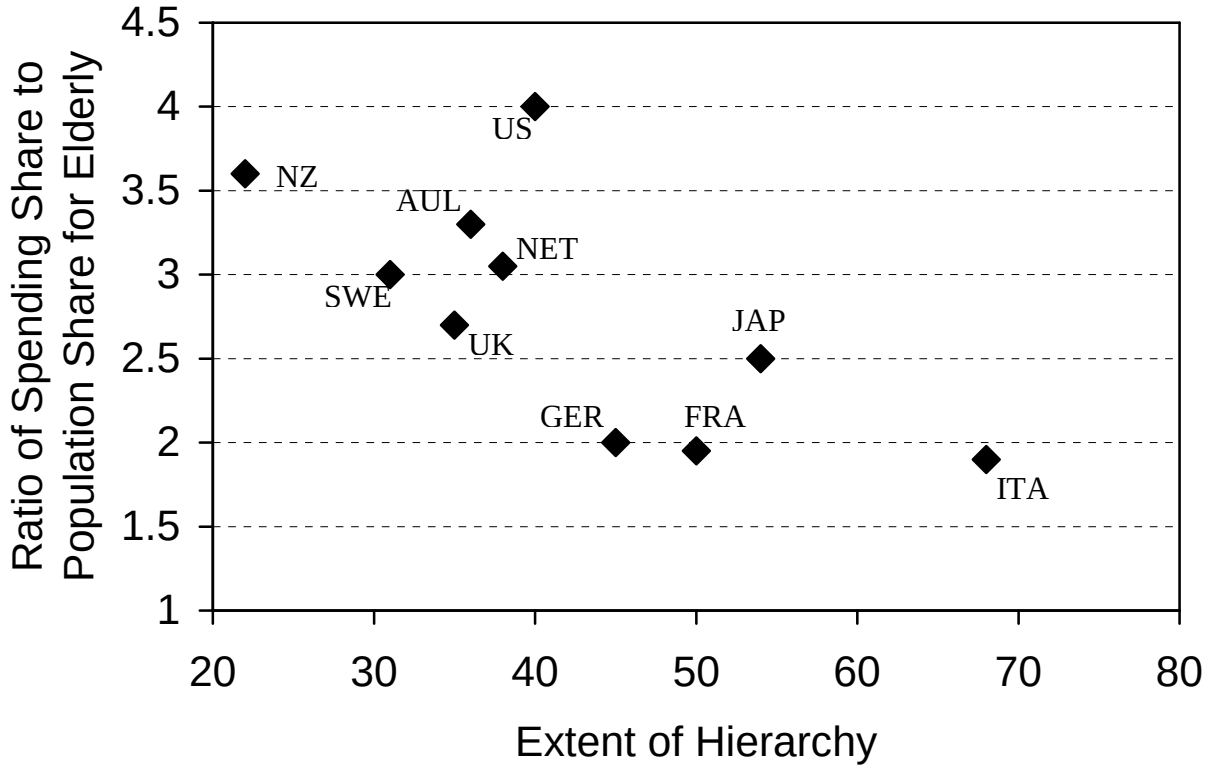
almotriptan	Spain	Almirall	
eletriptan	US	Pfizer	
naratriptan	Britain	Glaxo	
rizatriptan	US	Merck	
sumatriptan	Britain	Glaxo	
zolmitriptan	UK	Glaxo	*5 of 6 are Anglo-American*

Figure 1: Data for 15 Countries on Rates of Reports for Adverse Drug Reactions and the Extent to which National Culture is Hierarchical



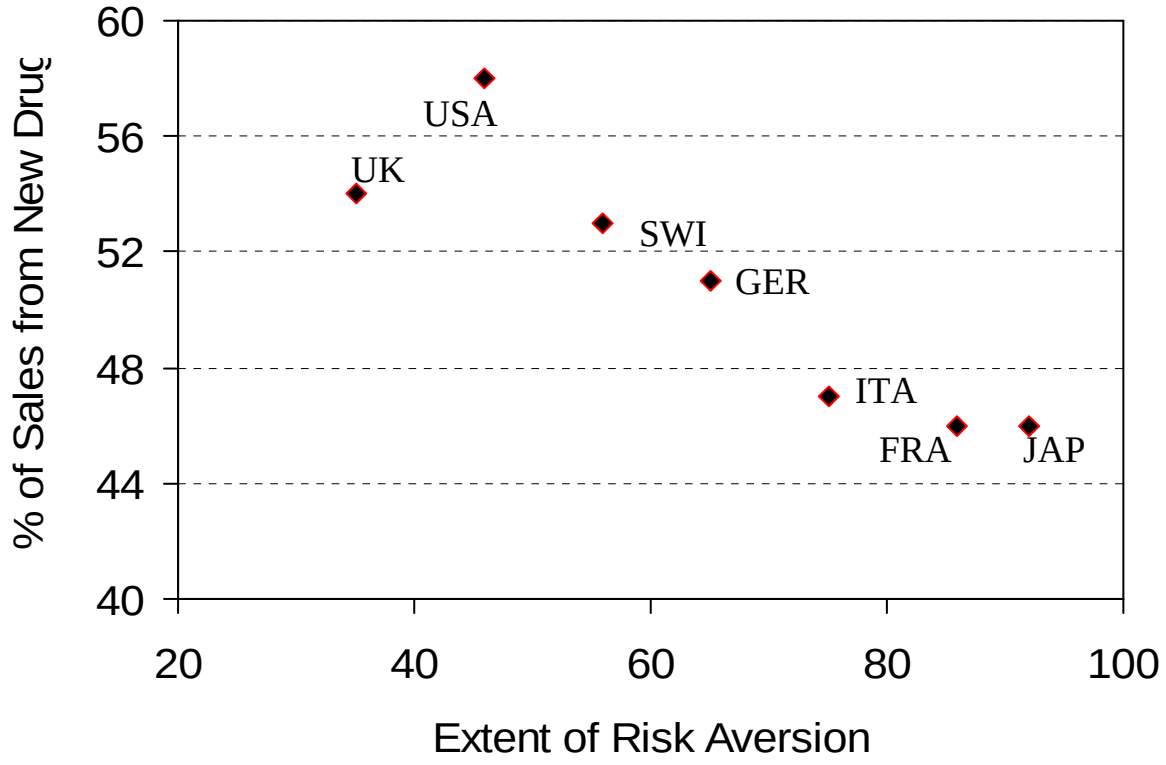
Sources: Extent of hierarchy is the power distance index of G. Hofstede and G.J. Hofstede (2005) Cultures and Organizations: Software of the Mind *2nd edition, New York: McGraw-Hill. Rate of adverse drug reaction reports is from J.P. Griffin (1986) "Survey of the Spontaneous Adverse Drug Reaction Reporting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

Figure 2: 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 3: 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 2: Country-Year-Therapeutic Class Technological Expertise Summary Statistics
N=1160

	France	Germany	Italy	Japan	Switzerland	Britain	US
France	1						
Germany	0.53	1					
Italy	0.48	0.66	1				
Japan	0.41	0.56	0.49	1			
Switzerland	0.42	0.81	0.57	0.54	1		
Britain	0.56	0.79	0.62	0.55	0.72	1	
US	0.51	0.60	0.50	0.53	0.63	0.72	1

Table 3: Number of Innovations as a Function of Home and Foreign Demand, Technological Expertise, Competition

	(1)	(2)	(3)	(4)	(5)
ln(Home Demand)	0.19** (0.02)	0.19** (0.04)	0.27** (0.05)	0.21** (0.04)	0.23** (0.05)
ln(Foreign Demand)	-0.11** (0.03)	-0.15** (0.03)	0.03 (0.05)	-0.00 (0.04)	-0.06 (0.04)
Home Tech Expertise (Corporate)	0.38** (0.06)	0.51** (0.14)	0.55** (0.15)	0.45** (0.15)	0.57** (0.15)
Home Tech Expertise (Public)	0.02 (0.06)	0.15 0.14)	0.18 (0.14)	0.17 (0.14)	0.18 (0.14)
ROW Tech Expertise	-0.05* (0.02)	-0.04 (0.04)	-0.05 (0.04)	-0.06 (0.04)	-0.05 (0.04)
ln(#Prior Drugs)			-3.27** (0.48)		
ln(#Prior Drugs_Home Market)				-0.85** (0.18)	
ln(#Prior Drugs_ROW)				-2.47** (0.29)	
ln(#Prior Drugs_Recent)					-1.21** (0.21)
ln(#Prior Drugs_Old)					-1.53** (0.47)
Year Indicators	Yes	Yes	Yes	Yes	Yes
Country Indicators	Yes	Yes	Yes	Yes	Yes
Therap. Class FE	No	Yes	Yes	Yes	Yes
# observations	8120	8120	8120	8120	8120

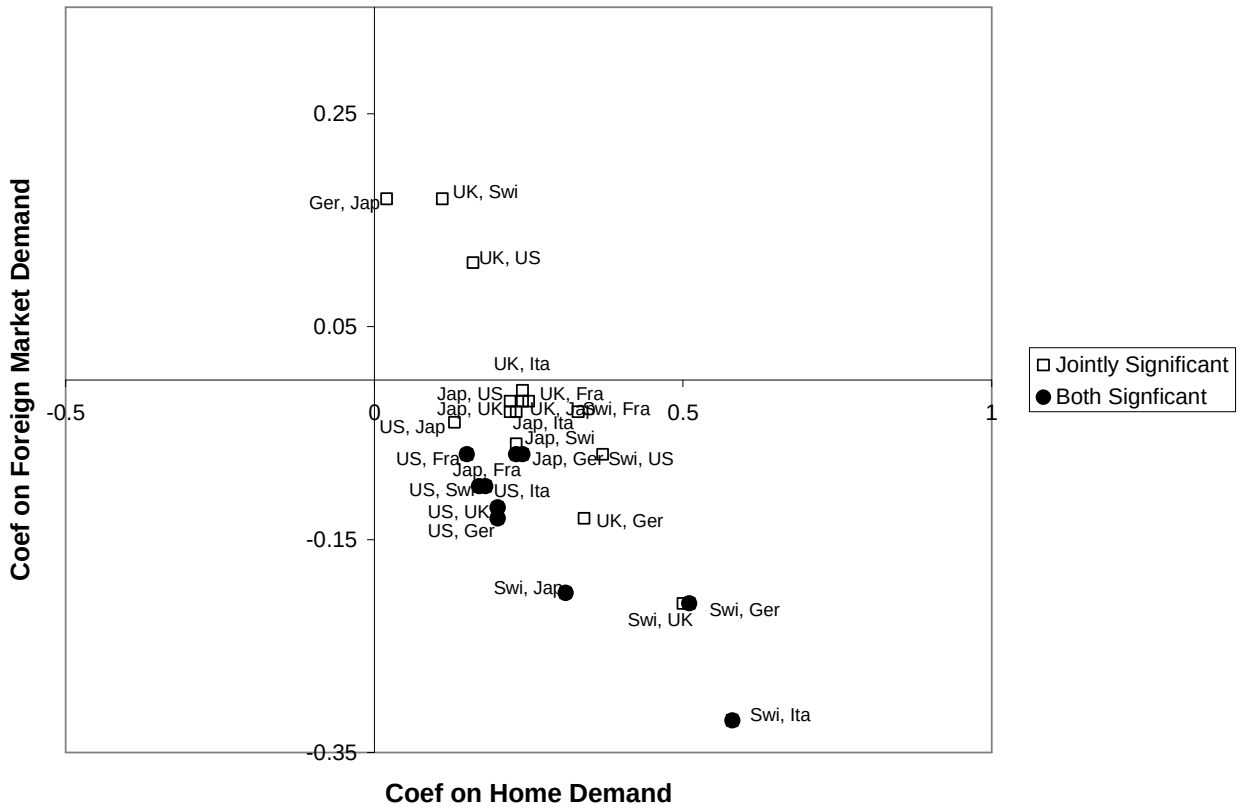
Estimation method if Poisson Quasi-Maximum Likelihood with conditional Fixed Effects at the therapeutic class level.
Robust standard errors, adjusted for correlation within therapeutic class, reported in parentheses.
Dependent variable is the number of innovations in the country-year-therapeutic class observation.
*significant at 5%, ** significant at 1%

Table 4: Number of Innovations as a Function of Home and Foreign Demand, Technological Expertise, Competition – Robustness Checks

	(1)	(2)	(3)	(4)
ln(Lagged Home Demand)	0.14** (0.03)			
ln(Lagged Foreign Demand)	0.04 (0.07)			
ln(Home Demand)		0.006** (0.001)	0.005** (0.001)	0.004** (0.001)
ln(Foreign Demand)		0.001 (0.001)	-0.006** (0.002)	0.002 (0.003)
Home Tech Expertise (Corporate)	0.63** (0.16)	0.013** (0.003)	0.012** (0.004)	0.014** (0.004)
Home Tech Expertise (Public)	0.11 (0.15)	0.019** (0.006)	0.020** (0.007)	0.020** (0.007)
ROW Tech Expertise	-0.06 (0.04)	-0.002* (0.001)	-0.003* (0.001)	-0.003* (0.001)
ln(#Prior Drugs)	-3.01** (0.49)	-0.090** (0.010)	-0.100** (0.012)	-0.112** (0.013)
Year Indicators	Yes	Yes	Yes	Yes
Country Indicators	Yes	Yes	Yes	Yes
Therap. Class FE	Yes	Yes	Yes	Yes
# observations	6930	8120	6622	6622

Dependent variable is the number of innovations in the country-year-therapeutic class observation.
* significant at 5%, ** significant at 1%
(1) Estimation method if Poisson Quasi-Maximum Likelihood with conditional Fixed Effects at the therapeutic class level. Robust standard errors, adjusted for correlation within therapeutic class, reported in parentheses.
(2) Linear approximation using OLS. Dependent variable is the natural log of 1+# innovations. Robust Standard Errors clustered by therapeutic class.
(3) Linear approximation using OLS. Dependent variable is the natural log of 1+# innovations. Excludes observation for therapeutic classes in first year (age=0) and with not prior year sales data. Robust Standard Errors clustered by therapeutic class.
(4) Second stage of linear two stage least squares. Dependent variable in second stage is the natural log of 1+# innovations. Instrumenting for home and foreign demand with lagged values of each and the age of the therapeutic class interacted with home country risk aversion index. Excludes observation for therapeutic classes in first year (age=0) and with not prior year sales data. Robust Standard Errors clustered by therapeutic class.

Figure 4: Innovations as a function of demand: Country dyad results
Graph of coefficients on own country and select foreign market demand



Coeffiecients graphed are result of Poisson estimation of the number of innovations in a therapeutic area in the home country as a function of home demand, one specific foreign market demand, technological expertise in home and rest of world, number of prior drugs in class, and year indicator variables.
Note: Points are labeled as home country, foreign market pairs.

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