Entrepreneurship and Desperate Poverty:
Biopharmaceutical Innovation in China, India, and Brazil

Peter G. Klein*
Division of Applied Social Sciences, McQuinn Center for Entrepreneurial Leadership, and Truman School of Public Affairs
University of Missouri
135 Mumford Hall
Columbia, MO 65211 USA
pklein@missouri.edu

Anita M. McGahan
Rotman School of Management and Munk School of Global Affairs,
University of Toronto
Institute for Strategy and Competitiveness Harvard University
105 St. George Street
Toronto, ON M5S 3E6 Canada
amcgahan@rotman.utoronto.ca

Rahim Rezaie
Munk School of Global Affairs, University of Toronto
Asia Pacific Foundation of Canada, Vancouver BC
1 Devonshire Place
Toronto, Ontario, M5S 3K7 Canada
rahim.rezaie@utoronto.ca

* Corresponding author. Phone: +1 573 882 7008; fax +1 573 882 3958

We are grateful to Guest Editor Garry Bruton, two anonymous reviewers, Jordan Cohen, and seminar participants at the 3rd Annual Darden Entrepreneurship and Innovation Research Conference and at the London Business School Ghoshal Conference for comments, discussions, and suggestions. We are indebted to Peter A. Singer and the Sandra Rotman Centre (www.srcglobal.org) for sharing their emerging markets database. McGahan thanks Canada's Social Sciences and Humanities Research Council (SSHRC) for financial support.

Entrepreneurship and Desperate Poverty:
Biopharmaceutical Innovation in China, India, and Brazil

Abstract: Poverty is intricately linked to pervasive underlying health problems, including infectious diseases that are rare in wealthy countries. Prior research has documented that leading biopharmaceutical firms have not invested comprehensively in diseases that mainly affect patients in developing countries. Theory suggests that indigenous firms may have a greater incentive to invest in diseases that primarily affect poor patients than large biopharmaceutical multinationals. Yet little empirical evidence exists of significant biopharmaceutical innovation in emerging markets. In this paper, we provide evidence from three countries where poverty is prevalent -- Brazil, China, and India -- that a growing number of indigenous biopharmaceutical companies are investing in innovation on diseases that primarily affect the poor. The results suggest a subtle set of interrelationships as co-located firms benefit from spillovers across research projects. We identify complementarities for performance in the clustering of disease-targeted projects but substitution effects for performance in the clustering of firms. These results indicate that indigenous biopharmaceutical firms are most productive when they co-specialize to maximize knowledge spillovers and minimize competition for funding and knowledge workers.

Keywords: entrepreneurship, biopharmaceuticals, poverty, innovation, neglected diseases

1. Introduction

In countries where desperate poverty is prevalent, economic development is constrained in many ways, but no constraint is more important than ill health. The poor simply cannot work as productively as the rich. When health improves even modestly, the poor regularly seek better work (Farmer, 2004). For the desperately poor, health is wealth and wealth is health (Hum, Jha, McGahan, and Cheng, 2011; Jamison *et al*., 2006). A major constraint on economic development is the absence of effective healthcare, and particularly shortages of life-saving medicines and of clinical infrastructure for delivering such medicines (Jamison *et al*., 2006).

Over the last twenty years, a number of policies have been implemented with the objective of remediating this situation. In particular, the World Trade Organization was formed in 1994 with a constituent requirement for membership as adoption of TRIPS (Trade-Related aspects of Intellectual Property Rights). This policy included the extension of patent protection in developing and, eventually, least-developed countries partly as an incentive for new drug development on the so-called "neglected diseases," which are defined by the World Health Organization as diseases from which more than 90% of deaths occur in developing countries. Subsequent research shows that leading biopharmaceutical firms in resource-rich countries have tended not to distribute drugs in emerging markets (Delgado, Kyle, and McGahan, 2011) or to invest in drug development for neglected diseases (Kyle and McGahan, 2011; Lanjouw and Cockburn, 2001). The gap between the rich and poor in health persists (Hum, Jha, McGahan, and Cheng, 2011).

For a range of reasons that we discuss below, multinational biopharmaceutical companies do not have as strong an incentive as indigenous biopharmaceutical organizations to invest in diseases that primarily afflict the poor in emerging economies. This difference in incentive arises from the potential for greater marginal returns to innovation for indigenous companies than for multinationals as well as from legal, institutional and political considerations that may lead local governments to induce local innovation. Yet despite these incentives, sparse evidence exists that indigenous biopharmaceutical companies are conducting research on diseases that primarily afflict the poor. Just a few previous studies using qualitative research methodologies (Frew *et al*,

2007; Rezaie *et al*, 2008; Frew *et al* 2008; Rezaie and Singer, 2010) observe that indigenous biopharmaceutical enterprises studied in emerging markets appeared to be expanding in general and to have a predilection for addressing locally relevant neglected diseases. One purpose of this paper is to test theories regarding the differential incentives for indigenous biopharmaceutical innovation by reporting the results of a quantitative empirical investigation on the nature of biopharmaceutical projects in these settings.

A second purpose is to identify the mechanisms associated with the emergence of research on diseases of the poor among indigenous biopharmaceutical companies. These mechanisms are important both as evidence of theoretical relationships on the establishment of new industries in a general sense as well as of policy relevance. How do entrepreneurs in emerging markets overcome the liability of newness to create biopharmaceutical organizations that are viable, even if less profitable as those targeting diseases prevalent in developed markets? Moreover, given that health-technology innovations in industrialized economies often neglect needs exclusive to poor-market segments in the developing world, and that resulting solutions typically diffuse slowly into these markets, how have domestic entrepreneurs in these settings performed in terms of technological advancement and innovation - particularly regarding products and services targeted at the most impoverished populations?

Research on settings of poverty has demonstrated that constraints on development tend to shift over time (Banerjee and Duflo, 2011) and that conventional approaches to aid have not been sufficiently effective (Easterly, 2006; Moyo, 2011). As a result, one important new emphasis in current aid policy is on the development of knowledge-based capabilities in settings of poverty (United Nations, 2011) such as are embedded in biopharmaceutical innovation. While policy has historically focused on technology transfer through foreign direct investment, alliances, and other cross-border partnerships to boost developing-country entrepreneurship (Lado and Vozikis, 1996), indigenous innovation and entrepreneurship are receiving increasing attention as means of improving the health and wealth of the poor directly and for cultivating knowledge capabilities in resource-limited settings (Daar and Singer, 2011). Poor countries typically have radically under-

developed knowledge-intensive industries such as software, business services, and pharmaceuticals—if they have any activity in these areas at all. Knowledge industries are important as direct sources of economic activity and because of their role in a country's innovative capacity (Furman, Stern, and Porter, 2001). Building knowledge capacity is particularly challenging because the forces of comparative advantage tend to lock poor countries in industries such as mining, agriculture, and retail (Porter, 2003).

This paper examines domestic biopharmaceutical entrepreneurship in China, India, and Brazil, three emerging economies that have achieved considerable success in biopharmaceutical development and production despite constraints such as shortages of skilled labor, high capital costs, and the absence of robust product markets. These three countries are important in their own right as the largest developing nations in the world by population and gross domestic product (United Nations, 2011). They are also important to studies of destitute poverty as more than half of the world's population living on less than $2 per day is located in these countries. The world's population of the destitute poor is concentrated in China, India, and Brazil.

This paper draws on two related bases of evidence. First, we exploit insights gained from field interviews with executives in indigenous biopharmaceutical firms, as well as other institutional informants drawn from government, industry, academic and venture capital organizations in China, India and Brazil. We supplement the interview data with a quantitative analysis of projects (defined as products either marketed or in development that have resulted from material in-house discovery) by 70 indigenous enterprises. While some of the firms studied are established generics firms that have ventured into innovation, most are small- and medium-sized entrepreneurial firms. The database is compiled from the Sandra Rotman Centre's[1] dataset of marketed and pipeline products, the IMS Health dataset (2010), and other sources.

The findings of our analysis show that, first, indigenous biopharmaceutical firms in China, India and Brazil invest significantly in locally relevant diseases of the poor as well as in diseases

[1] The Sandra Rotman Centre (www.srcglobal.org; formerly the McLaughlin-Rotman Centre for Global Health) is based at the University of Toronto and the University Health Network.

that are globally important. All else equal, larger firms, firms located in a cluster of same-industry projects, publicly traded firms, and firms with fewer products already on the market are more likely than other firms to have projects in clinical trials or elsewhere in the drug-development pipeline. We find similar results for firms' investments in neglected diseases: larger firms and firms able to take advantage of local-market knowledge spillovers are more likely than other firms to have neglected-disease projects in clinical trials, and to have more of such projects.

Our investigation into the mechanisms associated with investment suggests that neglected-disease research tends to be associated with larger clusters of projects but smaller clusters of firms. This result is an important general finding for theory and policy regarding the emergence of knowledge-based industries as it indicates both that knowledge spillovers are important and that strong competition among local firms (e.g., for skilled labor and government funding) may make it more difficult for these firms to target neglected diseases. Firms with products already on the market, while having fewer innovative projects overall, are more likely to have projects targeting neglected diseases. We interpret this result as evidence that firm diversification across biopharmaceutical disease categories is initially important for diversification but that subsequent specialization by disease are is an important to facilitate knowledge spillovers across projects by disease.

2. Theory

Three sets of factors explain in theory why indigenous biopharmaceutical organizations may have stronger incentives to invest in neglected diseases than multinationals.

2.1 Marginal returns to innovation on neglected diseases for indigenous firms

The marginal returns to investments in innovation on neglected diseases may be greater for indigenous biopharmaceutical companies than for MNCs for a range of reasons that reflect the requirements for investment in research prior to the development of drugs that can be marketed and eventually administered to patients.

2.1.1 The structure of biopharmaceutical investment

The development of innovative blockbuster drugs in countries that have implemented patent protection generally occurs over a period of about 10 years and proceeds through phases of discovery, pre-clinical development, and three phases of clinical trials. While the costs of drug discovery are difficult to assess, estimates indicate the total from discovery through phase III clinical trials at over $400 million out-of-pocket (2000 dollars) on average when accounting for compounds abandoned during development (DiMasi, Hansen *et al.*, 2003). These costs rise dramatically when opportunity costs are taken into account. Generic products also require time-consuming investment, but on a much reduced financial scale (Grabowski, 2002). The variable costs of production are much smaller than the fixed costs of development, so private pharmaceutical firms and their investors can justify such substantial R&D investments only with the prospect of large sales volumes or very high profit-margins. The profitability of drug development is thus significantly influenced by characteristics of the target markets such as size, incomes, and legal protection (Kyle and McGahan, 2011). Evidence shows that target-market size has a modest, positive effect on the development of new drugs, and patents are believed to be particularly important in pharmaceuticals (Cohen *et al.*, 2000). At the same time strengthening intellectual property protection does not appear to have a significant impact on increasing R&D expenditures

overall, especially for neglected diseases (Sakakibara and Branstetter, 2001; Qian, 2007; Kyle and McGahan, 2011).

The institutional environment for biopharmaceutical activity in emerging economies differs from developed countries in several important ways. First and fundamentally, the lower incomes of emerging markets are tied to a lower ability to pay among patients, insurers, and governments. Thus, the reduced ability to pay of purchasers in emerging markets is important because biopharmaceutical innovators must allocate scarce resources based on projections of the future returns to investment. Lower ability to pay among prospective purchasers, all else equal, is tied to lower prospective returns. At the same time, the markets in our study—China, India, and Brazil—are among the world's most populous countries, each with a rapidly growing middle-class, and the potential for vast sales volumes. These factors should in theory support development of technologies that address locally relevant diseases.

Therefore, the overall incentive system in biopharmaceuticals is heavily influenced by disease prevalence in different geographies. In general, many diseases affect both developed and developing countries, a category we call "global diseases." These conditions typically offer greater incentives for biopharmaceutical companies since they hold significant potential for monetary returns. With neglected diseases, in contrast, the potential financial returns are smaller because the market is limited to poor countries. The demand for drugs is likely to be highly elastic in low-income countries, leading to smaller markups and lower prices, making it particularly difficult for manufacturers to recoup their initial investments. With drugs targeting global diseases, revenues from developed markets, where higher prices can be charged, may be expected to cover these costs, such that distribution in poor countries is feasible as long as revenues there can cover the marginal costs of production and distribution. If the target market consists entirely of low-income consumers, however, the prospects for profitability are dim and compounded by underdeveloped healthcare and pharmaceutical distribution systems.

Within neglected disease categories, incentives for vaccines and diagnostics are further reduced for global biopharmaceutical multinational companies (MNCs). At the same time, these

products can often be the most cost-effective health solutions in settings with underdeveloped health systems. This reduced incentive for instance caused many industrialized world vaccine manufacturers to abandon developing world markets, a function later filled by developing world entities such as those in Brazil and India (Milstien, Gaul *et al.*, 2007). Diagnostic tests, particularly those suitable for small laboratories and rural settings have also not proven attractive for significant investment by global firms. Previous studies have provided some evidence that local entrepreneurial firms in emerging markets have often addressed these market gaps profitably, although leveraging existing technologies (Frew, Rezaie, *et al.*, 2007; Rezaie, Frew, *et al.*, 2008). Kyle and McGahan (2011) find no indication that the adoption of the TRIPS agreement by many developing nations has stimulated further research into neglected diseases by pharmaceutical MNCs —contrary to arguments that suggested this would be a result. A key question is whether incentives for emerging market firms are sufficiently different so as to allow them to invest in new innovations for neglected diseases in a comprehensive fashion.

2.1.2 Marginal returns to innovation by innovator location

As a result of the structure of innovation, a series of factors may make the net returns to investment in innovation on neglected diseases greater for indigenous firms than for MNCs. First, indigenous firms may have benefit from lower costs and risks of innovation due to *complementarities in distribution* ex post (Immelt, 2009). In particular, local firms may have preferential access to hospital formularies and greater credibility and access to local insurers than companies located remotely (Chittoor and Ray, 2007). Local biopharmaceutical innovators may better understand local protocols for the administration of medicines and may be better able to support physicians in the prescription of drugs for the poor (Chittoor and Ray, 2007; Chittoor *et al*, 2008). Each of these factors could reduce the cost and risk in the launch phases of marketing drugs.

Second, indigenous firms may benefit from access to a *low-cost scientific labor force.* In countries such as China and India, the wages paid to scientists are lower than in the countries that

host established multinational biopharmaceutical companies for a range of reasons, including an abundance of supply and macroeconomic differences that suppress the general level of wages (Brown and Hagel, 2005). Reduced wages have a direct impact on the costs of biopharmaceutical investment across the entirety of the research and development process. Local firms are better able to access the local labor force than foreign firms, which lack the on-the-ground capability to incorporate these workers into their global operations (Immelt, 2009). Furthermore, indigenous organizations may not suffer the consequences of *intra-firm price discrimination on scientist salaries* as compared to established multinational firms, which manage research teams operating in different geographies on varying international wage standards (Radjou, Prabhu and Ahuja, 2012). The consequences of internal conflicts between research teams engaged in risky, innovative inquiry include unobservable slack and self-dealing in the execution of research duties.

Third, *less local competition* may reduce the costs and risks to innovative investment by indigenous entrepreneurs as compared to established multinationals for a range of reasons including reduced knowledge spillovers, lower risk of idea preemption, greater market power over scientist salaries, and larger projected ex post price-cost markups on marketed products (Prahalad, 2004).

Fourth, indigenous firms may benefit from greater *alignment of interests with public-health authorities and a consequent internalization of externalities* to reduce the risk and raise the prospective revenues associated with investment in research on neglected diseases (Grace, 2004). These include a reduced risk of compulsory licensing under WHO exceptions for essential medicines and a greater exposure to forward commitments for purchase (Kyle and McGahan, forthcoming); . In some countries, local governments and public agencies may also subsidize local investments in research on neglected diseases and have mechanisms for preferential procurement of indigenously developed technologies.

Fifth, indigenous firms may have *superior knowledge about local demand* for therapies, including information about the nature and extent of affliction (Grace, 2004; Radjou, Prabhu and Ahuja, 2012; Kumar and Puranam, 2011). Local companies may have superior access to lan-

guage-based insights about challenges in the administration of therapies and better access to information arising through clinical trials (Radjou,Prabhu and Ahuja, 2012; Immelt, 2009).

Finally, indigenous companies may benefit from *the prospect of comparative advantage relative to established multinationals by focusing on new therapeutic categories.* Established multinationals, faced with a choice between investing a marginal research dollar in an established category vs. an emerging neglected-disease category, may confront a greater comparative advantage relative to indigenous firms in the established category for the reasons listed above, while indigenous firms may face an advantage in the emerging neglected-disease category (George, McGahan and Prabhu 2012). Thus, the forces of comparative advantage may compound the economic incentives listed previously.

2.2 Legal and institutional factors favoring indigenous firms

Kyle and McGahan (forthcoming) suggests that the implementation of patent protection through TRIPS encouraged the development of indigenous biopharmaceutical companies in countries such as China, India and Brazil, but that these companies tended to invest in the same complement of global diseases as their multinational counterparts. Further research (Delgado, Kyle, and McGahan 2011) indicates that the time required for patent protection to stimulate such indigenous activity is greater in the biopharmaceutical sector than in other patent-sensitive sectors such as information, telecommunications and computing, largely because of the absence in developing countries of complementary institutions required for successful distribution of biopharmaceuticals. These institutions include, for example, clinics, cold-chain pharmacy distribution, medical schools, licensing bureaus, insurers, pharmacological scientists, licensed pharmacists, and medical laboratories. Delgado, Kyle and McGahan (2011) specifically identified a six-year lag after the implementation of TRIPS in adjusted trade flows of biopharmaceuticals but an immediate response to TRIPS in adjusted trade flows of information, computing and telecommunications products. They posit that, during this six-year period, the complementary institutions required for successful indigenous entrepreneurship on global diseases for export may have

emerged. Under this hypothesis, the most important complementary institutions for export are those that improve the returns to innovation globally rather than only locally: pharmacological scientists, human-trial protocols, etc. After the establishment of local innovation infrastructure, the institutions required for the administration of medical protocols may have begun to develop.

In China, India, and Brazil, where TRIPS was implemented between six and ten years ago (Ginarte and Park, 2008; Kyle and McGahan, forthcoming), indigenous entrepreneurs may now have a greater incentive than established multinational corporations to invest in neglected diseases as a result of local initiatives to continue the development of complementary institutions that specifically enable the administration of medicines to the destitute poor, and particularly of medicines for neglected diseases.

Indigenous biopharmaceutical innovators may benefit from these local institutions to a greater extent than established biopharmaceutical multinationals for a number of reasons (Kumar and Puranam, 2011). First, co-investments by indigenous entrepreneurs and other indigenous organizations, including government actors, may *enhance access* (Immelt, 2009: Radjou, Prabhu and Ahuja 2012). In other words, local barriers to entry into neglected-disease therapeutic categories may be greater for non-local biopharmaceutical companies than for indigenous firms.

Second, indigenous firms may have *lower opportunity costs* as government agents and other local actors seek to promote local capacity both for promoting public health and for encouraging an internationally competitive knowledge sector (Porter 2003; George McGahan and Prabhu, 2012).

Finally, indigenous firms may have *superior influence* as compared to multinational companies on the nature and direction of investment in complementary institutions, and thus may encourage institutional developments that enhance their competitive advantages over established multinational companies (for example, anecdotal evidence suggests that indigenous entrepreneurs in India encouraged the adoption of export laws that would factor the distribution of drugs for neglected diseases internationally that were manufactured in India, Chittoor and Ray, 2007; Chittoor *et al*., 2008; Kumar and Puranam, 2011).

2.3 Political factors favoring indigenous firms

A related set of explanations arise from political factors. In countries such as China, India, and Brazil, the consequences of ill health under rapid urbanization, migration, resource shortages and economic volatility create the potential for political unrest and instability (Grace 2004; Rodrik 1997). Investments in improving indigenous biopharmaceutical capacity for innovating on and manufacturing drugs for neglected diseases may have a direct and unambiguous mitigating effect on this potential (Kohler, 2007; Kremer 2001). In Brazil, for example, investments in programs for improving the health of impoverished HIV-positive patients were motivated by concern for the political instability that could arise from the epidemic; similarly, in South Africa, local capacity for manufacturing HIV treatments was specifically encouraged by public policy during the 2000's (Cohen 2006). Political leaders may seek to encourage the development of drugs for neglected diseases by indigenous firms over established multinational corporations as a matter of *national security*.

2.4 Mechanisms of spillover and competition

Research on agglomeration economies has long pointed to a tension that arises from the co-location of innovators in a particular cluster, city, or geographic region (Porter, 1999, 2003; Furman, Kyle, Cockburn, and Henderson, 2006). Co-location on the one hand may enhance the competitive advantages of the group of co-located firms by improving collective access to critical resources, labor, markets, and complementary services. Geographic concentration and the attendant knowledge spillovers are believed to be particularly important for pharmaceutical research (Furman *et al*., 2005; Henderson and Cockburn, 1996). On the other hand, co-location may damage the competitive advantage of any particular co-located organization by exposing it to excessive competition. The literature on agglomeration economies describes contingencies under which each countervailing effect dominates. When innovation tends to lead to specialized investments that are subject to strong appropriability regimes and that are difficult to imitate (Cockburn and Griliches, 1991), then co-location may confer important benefits (Porter, 1999).

But when particular resources—including human resources—are scarce and the markets to obtain such resources are competitive (Gambardella and McGahan, 2010; Arora, Fosfuri, and Gambardella, 2001), then co-location may enhance competition and suppress risk-taking, such as is required to generate innovative output. The generality versus specialization of the technology investments made by companies depends endogenously on the level of local competition (Gambardella and McGahan, 2010).

This theoretical lens suggests a tradeoff in the organization of indigenous entrepreneurship on neglected diseases. The co-location of innovating organizations may incite racing behavior across projects within particular therapeutic categories and thus improve innovative outcomes (Jaffe, 2006). Similarly, co-location may enhance knowledge spillovers across projects within particular categories (Argyres and Mayer, 2006).

Alternatively, the co-location of firms may reduce projected returns to innovation through the anticipation of competition both in the development and marketing phases of the product life cycle. As a result, the co-location of firms innovating in a particular therapeutic category may reduce the incentive for innovative investment (Cockburn and Griliches, 1991).

In our empirical analysis, we explore the evidence for each of these mechanisms.

3. The Biopharmaceutical Industry Context

Henderson *et al.,* (1999) trace the origins of the modern pharmaceutical industry to the synthetic dye industry in Germany and Switzerland and the discovery of medicinal effects of some dyestuffs. The large-scale production of penicillin during World War II followed by "a golden age for the pharmaceutical industry" spanning 1950–90 saw commercialization of many new chemistry-based medicines (Henderson, Orsenigo, and Pisano (1999: 272). The 1976 inception of Genentech in San Francisco (now part of Basel-based Roche) spawned the modern biotechnology sector, which is increasingly becoming integrated with the more traditional pharmaceutical sector. A handful of countries including the U.S., U.K., Switzerland, Germany, and France continue to host the largest innovative biopharmaceutical companies. However there is a grow-

ing dispersion of innovation activities in biopharmaceuticals with a particularly expanding role for emerging markets.

3.1 Biopharmaceutical Sectors of China, India, and Brazil

In emerging markets the biopharmaceutical industry is being reshaped by a variety of factors including: institutional reforms, the growing presence of major pharmaceutical MNCs, and enhanced governmental commitment to science, technology and innovation. Although the institutional environments in China, India, and Brazil differ significantly, these countries share some important attributes and have witnessed the development of certain institutional elements along similar lines. The most salient among these is the implementation of intellectual-property laws and mechanisms for enforcement. China, India, and Brazil all adopted the TRIPS agreement as part of their commitments under WTO membership. Brazil became TRIPS compliant in 2001, while China and India followed in 2005 (Ginarte and Park, 1997). Adoption of the TRIPS agreement by these countries represents a discontinuity for indigenous industries that creates a greater impetus for value generation through innovation. How firms and industries manage through this discontinuity may not only shape their global competitiveness, but also their ability to address healthcare needs of the poor. The growing presence of biopharmaceutical MNCs has also created new opportunities for indigenous health enterprises in some emerging markets to participate in the global health-technology value chain.

Biopharmaceutical firms in the countries studied have also benefitted from increased public and private investment in incubators and Science Parks. China's Zhangjiang hi-tech park (Shanghai), Brazil's Biominas Foundation (Belo Horizonte), and India's ICICI Knowledge Park (Hyderabad) are examples of prominent institutions that provide an array of business incubator services to technology-based enterprises. Incubators are known to play an important role in linking entrepreneurs to other financing sources (Aernoudt, 2004; Finer and Holberton, 2002) and in the context of developing countries "focus on creating market institutions more intensively than on cultivating business capabilities" (Dutt, *et al.*, 2011).

The following paragraphs provide a brief overview of each country with respect to industry structure and institutional context.

3.1.1 China

China's pharmaceutical industry is a complex milieu of enterprises involved in Traditional Chinese Medicine (TCM), conventional chemistry-based pharmaceuticals, and the more modern biotechnological applications. TCM accounts for approximately 40% of all health care delivered in China (Hesketh and Zhu, 1997), and pharmaceuticals in particular compose about 50% of all healthcare expenditures in the country (Sun, Santoro, *et al.,* 2008), with an annual growth rate of 15–20% in recent years (Campbell and Chui, 2010). The pharmaceutical industry, estimated at 4000–5000 manufacturers, spends on average about two percent of sales revenues on R&D, compared to 14–18% for leading global companies (Sun, Santoro, *et al.,* 2008). China has built considerable manufacturing capability in recombinant products and a growing number of biotech startups are focused on innovative R&D. These developments are considerably stimulated by enhanced governmental commitment to innovation and industrial development. The country's overall R&D expenditure reached 1.7% of GDP in 2007 (China Statistical Yearbook, 2010) and the country's 12th Five-Year Development Plan (2011–15) continues to prioritize biotechnology and drug development as key areas for investment.

3.1.2 India

The Indian pharmaceutical industry has been shaped by a host of factors aimed at import substitution (Kale and Little, 2007), reducing the pre-1970s dominance of the local market by foreign firms (Chittoor, 2008) and supporting Indian companies' desire to become global competitors. A number of key policies dating back to the early 1970s have led to the dominance of domestic firms in the Indian market and helped to make India one of the leading producers and exporters of chemistry-based medicines and pharmaceutical ingredients to the rest of the world (Chaturvedi, 2007; Chittoor, 2008; Kale and Little, 2007). However, while beneficial in some respects, India's institutional context, prior to enforcement of the TRIPS agreement, did not pro-

vide an environment conducive to research and development for novel health products, and contributed to the underdevelopment of the country's pharmaceutical regulatory capabilities (Kale and Little, 2007). The Indian government was among the first in developing countries to identify modern biotechnology as an important area for advancement in 1982 (Chaturvedi, 2007) and has since expanded its investments into this sector considerably (Natesh and Bhan, 2009). Chittoor *et al*. (2008) argue that India's economic liberalization, beginning in early 1990s, has facilitated the reorganization of firms with the ultimate aim of internationalization.

3.1.3 Brazil

The Brazilian pharmaceutical sector also benefited from a permissive intellectual property regime, which allowed domestic firms to copy innovations made elsewhere. This resulted in the emergence of an almost exclusively generic-based industry with very limited innovative product development. Recent institutional changes aim to enhance innovation indigenous capability including the enactment of a new Intellectual Property Law in 2007 in accordance with obligations under the TRIPS agreement, subsequent pharmaceutical regulatory adjustments, and the introduction of the Generics Law (2002), the Innovation Law (2005), and "The Good Law" (2006). Modeled on the US Bayh-Dole Act of 1980, the latter two statutes aim at fostering innovation, in part by sharing of IP and other resources between the public and private sectors, and also through direct subsidies for innovative activities within private companies. In 2007, Brazil had 181 life science companies nationwide, 71 of which were classified as biotechnology companies, with a minority of these (17%) involved in health (Pereira, 2007). A characteristic feature of the Brazilian context is the considerable involvement of State institutions in research and manufacturing of vaccines and medicines (Rezaie, Frew *et al.*, 2008). At the same time the state is increasingly active in stimulating industrial R&D and has offered financial, and other incentives to advance these objectives.

3.1.3 Summary

While there are interesting and important differences among the three sample countries, they share important characteristics. China, India, and Brazil are the three most populous, fastest growing, and economically significant countries of the developing world, each housing millions of people that are inflicted by consequences of poverty. More important, the biopharmaceutical sectors of these three countries share similar recent histories and other important similarities—limited access to capital, skilled labor, and other resources; relatively weak IP protection; and complex public-private interactions—that justify treating them together.

4. Data and methods

We use both quantitative and qualitative approaches to analyze indigenous biopharmaceutical entrepreneurship in China, India, and Brazil, and particularly on innovative investments on neglected diseases.

Our qualitative insights result from 99 field interviews with executives in indigenous biopharmaceutical firms in China, India, and Brazil and an additional 25 institutional informants in these countries conducted between 2006 and 2009. The latter group includes representatives of governmental organizations involved in the promotion of health technology development, industry associations, venture capital firms, and academic organizations. Approximately two-thirds of these interviews formed the basis for a series of previously published country case studies (Frew, Rezaie, *et al.*, 2007; Frew, Sammut, *et al.*, 2008; Rezaie, Frew, *et al.*, 2008), while the remainder were conducted as part of follow-on analysis. The interviews were semi-structured and conducted face-to-face between 2006 and 2009, lasted approximately 60-90 minutes and, with few exceptions, were conducted through site visits to firms and institutions concerned. Firm-based interviews covered several themes including: a) the nature and extent of innovative activities/projects, b) entrepreneurial challenges related to innovation, c) local and national policy supports for innovation within enterprises, and d) degree of focus on local versus global needs. Interviews with institutional informants explored: a) the contextual background with respect to na-

tional science, technology and innovation policies, b) the degree to which the latter support/hinder entrepreneurial engagement in innovation activities, and c) private capital availability for innovative biopharmaceutical projects and companies. The institutional informants, as well as other publications and policy documents were also utilized to triangulate data from private-sector interviewees. Insights gained through qualitative interviews allow us to contextualize quantitative findings, described below, and also to better cope with the complexities inherent in having to deal with many variables of interest given limitations on data.

For the purposes of this paper we have constructed a new quantitative database, which features a comprehensive compilation of pipeline projects within a total of 70 indigenous enterprises in China, India and Brazil. The sample includes only indigenous enterprises with one or more innovative projects—vaccines, diagnostics or therapeutics—in their pipeline, along with those that have already succeeded in bringing innovative technologies to market. We selected these firms to (a) study the extent and nature of innovation within emerging market biopharmaceutical enterprises, (b) explore the potential of these firms to address neglected diseases through innovation, and (c) identify firm characteristics that may correlate between their involvement in innovation in the one hand and the degree of focus on neglected diseases on the other. We have the classification used by Kyle and McGahan (2011) to decide which diseases fall within the 'neglected disease' category. We exclude indigenous enterprises in China, India, and Brazil that are not, to our knowledge, developing innovative health technologies, even if they are marketing products developed by other firms that address neglected diseases. Moreover, we focus on innovations in vaccines and therapeutics, with less coverage of the diagnostics sector.

We construct the quantitative dataset from three sources. The first source is the Sandra Rotman Centre's (SRC) database of marketed and pipeline products for domestic health enterprises in select developing countries. This database is a by-product of extensive data collection efforts by researchers at the SRC over the past six years. We complement and substantially update the SRC database with information from the IMS Health Database (2010) as well as web-based sources such as company websites, newswires, and other publications. Our final dataset contains

758 projects within 70 indigenous companies in China, India, and Brazil. To our knowledge this is the most comprehensive dataset covering innovation pipelines of indigenous enterprises in the stated countries.

Variables included in our final database of firms are company and country names, city location, size as indicated by the number of employees, ownership status, inception year, total number of products on the market, as well as individual products under development with their respective disease indication(s) and latest developmental phase. The majority of firms have private ownership, followed by those listed in stock market and two firms that are state-owned. We use the firm as a unit of analysis throughout and refer to each marketed or pipeline product as a project.

Figure 1 lists all disease indications for which five or more products were included in the sample, broken down by country. It shows that approximately one third of the top 26 indications listed are relevant to neglected diseases, including three of the top five most commonly targeted diseases, cancer, hepatitis, diabetes, HIV/AIDS, and tuberculosis. Fourteen of the 26 most common diseases targeted also fall into the infectious disease category, illnesses which have a much greater burden under conditions of desperate poverty. In India, the most common disease indication targeted by indigenous firms studied is diabetes, which is known to have a significant, disproportionate, and growing prevalence in India (Ramachandran *et al*., 2001; Wild *et al*., 2004). Similarly, the innovative Chinese firms have a considerable focus on both hepatitis-related conditions and cancer—especially liver and head and neck cancers—all of which have high incidences in the country (Liang *et al*., 2009; Perez *et al*., 2006; He *et al*., 2005; Jia *et al*., 2006). These results clearly suggest that indigenous firms are focusing on diseases that are highly relevant to local populations. However, those diseases that have a high local prevalence with the potential to reach a considerable global market as well—such as diabetes in India and hepatic cancers in China—receive the most attention from domestic firms.

[Figure 1 about here]

5. Analysis and results

5.1. Summary statistics

5.1.1. Projects

Table 1 describes the 758 projects in the sample, in total and by country. More than half the sample projects are in India, which has the most developed pharmaceutical industry of the three countries. China has the most firms in the sample, 31, compared to 29 in India and 10 in Brazil, but these firms have the fewest projects (median of 3 projects per firm, compared to 7 and 11 for Brazil and India, respectively). India has the highest number of innovative projects and the highest percentage of projects in clinical trials, which likely reflects India's earlier foray into the biopharmaceutical industry, and Indian firms' larger size—approximately 70% have over 250 employees—which provides them with the necessary financial and human resources to undertake such trials. China has the highest percentage of projects targeting neglected diseases, a fact that is likely skewed by the country's considerable focus on hepatitis.

[Table 1 about here]

Of the full sample, 31% of all projects target neglected diseases, of which 17% are in the clinical trials. Therefore, as a group, indigenous enterprises in China, India, and Brazil have a considerable focus on neglected diseases. In contrast, in studying global pharmaceutical MNCs Kyle and McGahan (forthcoming) find that "the introduction of patents in developing countries has not been followed by greater R&D investment in the diseases that are most prevalent there."

Looking across development phases, India has the highest proportion of projects in preclinical testing and in clinical trials, consistent with the maturity of the industry and its ability to finance these innovations through internal revenue generation, in many cases boosted by product and service exports. The Chinese and Brazilian biopharmaceutical industries have thus far been much more inward-looking with minimal exports of finished products to the rest of the world, especially to the more lucrative developed economies. Moreover, India has a considerably great-

er focus in the vaccine sector, which on the whole is less resource-intensive than medicaments allowing for more projects to be undertaken. Indian innovations in this area have also involved combination and second generation vaccines and therefore have been largely incremental in nature. Public-sector vaccine manufacturers in Brazil such as the Butantan Institute (São Paulo) have largely crowded out private sector activity in this sphere. While China manufactures a considerable number of vaccines, it has traditionally not been as active as India in vaccine development—although the Chinese government it is now paying considerable attention to this sector.

5.1.2. Firms

Using data in the project-level database we construct several additional firm-level variables, such as the percentage of the firm's projects in the pipeline (discovery, pre-clinical, and clinical-trials phases), the percentage of the firm's projects in clinical trials, and two clustering variables, the number of projects across all firms in the focal firm's city, and the number of firms in the focal firm's city. The firm-level dataset is described in Table 2.

[Table 2 about here]

The median firm has 260 employees, is 12.5 years old, and has 7 projects, one in clinical trials and one targeting a neglected disease. There is considerable variation across countries. Indian firms are the largest and oldest (medians of 500 employees and 18 years old); Brazilian firms are the smallest (median 260 employees), and Chinese the youngest (median 11 years old). There is substantial clustering of innovative firms by city, particularly in China and India. The median Indian firm is in a city with 7 firms and 73 projects; for China these numbers are 8 and 56, respectively, and 2 and 25 for Brazil.

Table 3 shows pairwise correlations among the firm-level variables. As expected, the different outcome measures are positively (and statistically significantly) correlated. Firm size and age are generally positively correlated with outcomes (larger and older firms have more projects), as are the clustering variables.

[Table 3 about here]

5.2. Regression analysis

We next run a series of regressions on the firm-level data to see what factors affect the firm's commitment to innovation—the number and percentage of its projects that are in the pipeline, and in clinical trials specifically—and the firm's emphasis on research and development in neglected diseases.

Table 4 reports the results of four regressions of innovation on firm characteristics (robust standard errors, clustered by country, are given in parentheses). Models 1 and 2 use count data; in Model 1 the dependent variable is the number of projects in the pipeline, meaning discovery, pre-clinical, and clinical-trials phases, and in Model 2, the dependent variable is the number of projects in clinical trials only. The dependent variables are overdispersed, so we use the negative binomial specification. (Many firms have no projects in trials, so we use the zero-inflated negative binomial specification, with the full set of independent variables used to predict the zero observations.) In Models 3 and 4 the dependent variables are expressed as percentages, the percent of the firm's projects in the pipeline and the percent in clinical trials, respectively, and we run them using OLS. Independent variables include country dummies; indicators for firm size (1–19 employees, 20–49 employees, 50–99 employees, and 100–249 employees, with 250+ employees the excluded category)[2]; the log of firm age; two clustering variables, the number of nearby projects (projects in the focal firm's city) and the number of nearby firms (firms in the focal firm's city), along with their squared terms to check for nonlinear relationships; indicators for publicly traded and state-owned firms (privately held firms being the excluded category); and the number of products the firm has already on the market (expressed in logs).

[Table 4 about here]

[2] We use indicators, rather than a continuous measure, because for some observations we have only a size range, rather than the exact number of employees.

A few patterns emerge from Table 4. The coefficient on the Brazil indicator is positive and significant in Model 1 and negative and significant in Models 2 and 4, suggesting that Brazilian firms, on average, have more projects than India in the pipeline but fewer in clinical trials. Chinese firms also have more projects, on average, in the pipeline than their Indian counterparts. Smaller firms are generally less innovative: the coefficients of the size dummies (with the largest category, 250+ employees, excluded) are mostly negative, and five are negative and statistically significant. Firm age, surprisingly, is not statistically significant in any specification.

The clustering variables hint at some effects that will be made clearer below. In Model 1 the coefficient on nearby projects is positive and significant, while the second-order term is negative and significant. In other words, all else equal, the agglomeration of projects facilitates innovation, but with diminishing returns. The effect of nearby firms is similar, with a positive effect and negative second-order effect in Model 2, suggesting that the positive externalities apply to firms as well as projects; however, we find the opposite result when looking specifically at projects targeting neglected diseases, as discussed below. In general, the presence of positive spillovers is consistent with previous observations that limitations on specialized skills and funding for innovation are major impediments for indigenous firms in the countries studied, and that government funding has been a key stimulant to enterprise-led innovation, especially in China and Brazil (Frew, Rezaie, *et al.,* 2007; Frew, Sammut, *et al.,* 2008; Rezaie, Frew, *et al.,* 2008).[3]

Table 4 also reveals that publicly traded firms are more innovative, even controlling for firm size and age. This stands in contrast to the usual developed-country argument that listed firms, facing the pressure to meet short-term earnings forecasts, tend to neglect long-term, uncertain projects (Hitt and Hoskisson, 1994; Hitt, Hoskisson, and Kim, 1997; Klein, 2011). It also contradicts anecdotal evidence suggesting that investors in the emerging market exchanges undervalue biopharmaceutical companies conducting R&D—in part because they are not sufficiently in-

[3] Variance inflation factor tests indicate multicollinearity among the two clustering variables (and their squared values), but not for the other independent variables. The multicollinearity is not surprising given the way the clustering variables are constructed and the small sample size (70 firms). Fortunately, omitting the clustering variables has a very small effect on the coefficient estimates and significance levels for the remaining independent variables.

formed of the potential value in these activities. In at least one case, an Indian company spun-off its R&D department into a separate venture precisely because of this perception. However, research on diversification in emerging markets, where external capital markets are weak, suggests that diversified conglomerates and business groups may have advantages in allocating funds to R&D (Khanna and Palepu, 1997, 2000). We also find, consistent with our expectations, that state-owned firms are substantially less innovative than private firms.

Moreover, firms appear to be more innovative when they have fewer products already on the market—the coefficient on existing projects is negative in three of the four models (statistically significant in Models 3 and 4). This echoes Christensen's (1997) argument that established firms face particular barriers to disruptive innovation (the "innovator's dilemma"). In the case of indigenous biopharmaceutical companies, substantial resources may be dedicated to producing and marketing existing drugs developed outside the home country and, given capital-market constraints, firms are limited in their ability to attract outside financing to invest in drug development. Other possible barriers to innovation by established generics firms include institutional changes (such as more stringent manufacturing requirements in China and Brazil), interest in export markets by existing manufactures (again necessitating improvement in manufacturing, and particularly salient in India), and governmental efforts to encourage use of generics medicines. In Brazil, for instance, these changes have been critical in helping indigenous manufactures to dominate the generics market segment.

We turn next to the determinants of R&D on neglected diseases. Table 5 reports the results of three regressions of neglected-disease emphasis on the same explanatory variables used above. Model 1 is a logit regression with dependent variable equal to one if the firm has any projects targeting neglected diseases. Models 2 and 3 are negative binomial regressions with the dependent variables as the number of projects targeting neglected diseases (Model 2) and the number of projects in clinical trials targeting neglected diseases. Robust standard errors are given in parentheses (in the negative binomial regressions, the standard errors are clustered by country).

[Table 5 about here]

The coefficients on Brazil and China are positive and significant in Model 1, indicating that Brazilian and Chinese firms are more likely than Indian firms to have projects targeting neglected diseases. However, coefficient on Brazil is negative and significant in Model 3, suggesting that Brazilian neglected-disease projects are more likely to be at the early stages and not yet in clinical trials. The coefficient on China is negative and significant in Model 2, so while Chinese firms are more likely than Indian firms to have any neglected-disease projects at all, they do not have very many. As suggested previously, this difference is related to the considerable number of Chinese projects targeted against hepatitis, which in its communicable forms is considered a neglected disease. The coefficients on most of the size dummies are negative, some statistically significant, indicating that smaller firms are less likely to emphasize neglected diseases, other things equal. Firm age is positive and statistically significant in two models; older firms have more projects and more clinical-stage projects targeting neglected diseases than younger firms. This former observation is consistent with the expectation that older firms, which are generally larger also, are better able to absorb costs, and risks, of clinical trials. Qualitative interviews reveal that most firms, particularly small ones, aim to sell/license their innovative technologies prior to entering clinical trials or at the initial stages of human experimentation. Enhanced focused on neglected diseases by older firms suggests that they may have identified these areas as business opportunities, again consistent with broad themes emerging from our interviews with company executives.

No clear pattern emerges from the ownership and governance variables; publicly held firms have fewer projects targeting neglected diseases (although they are more innovative overall as stated above), while the few state-owned firms in our sample have more, though fewer in clinical trials targeting neglected diseases.

The innovator's dilemma does not extend to research and development on neglected diseases; the more products a firm has on the market, the more likely it will target neglected diseases. This

suggests that neglected disease research is, in Christensen's (1997) terminology, a sustaining rather than disruptive innovation, or simply that firms with more success bringing projects to market have a revenue stream in place that allows them to target neglected diseases. This may also be related to directed funding from national governments that attempt to incentivize R&D for neglected diseases.

Perhaps the most interesting finding relates to clustering. As in Table 4, the coefficients on projects in the focal firm's market are positive (statistically significant in two of the three models), while the coefficients on firms in the focal firm's market are negative (statistically significant in all three models). In other words, there are positive project-level spillovers from clustering (with diminishing returns), but negative firm-level spillovers (with diminishing returns). This suggests interactions between clustering and competitive effects—knowledge spillovers are important for research and development on neglected diseases, but these spillovers are best exploited when there is not too much competition among local firms (e.g., competition for specialized labor and limited funding).

5.3 Limitations

Our approach relies on much finer-grained, project-level data than has been included in previous research on biopharmaceutical innovation, yielding unique insights about investments in innovation and neglected diseases. However, our approach features important limitations. First, while we have a nearly comprehensive population of innovative firms in our three sample countries, limitations on publically available information and the fact that web-based inquiries were made in English means that we may have missed some products and companies that fit the selection criteria. Time lags associated with data collection and the disclosure of information by companies may also mean that some of the information, particularly those related to development stage, may not be up to date in all cases.

Second, judgments about the degree of scientific novelty are subject to limitations on publicly available information related to specific products. For the purposes of this paper we have re-

lied on product descriptions by the firms themselves as well as our own judgment to select project candidates that we believe represent significant technological advancements and require considerable technical and financial resources to commercialize. Third, we lack information about projects that failed or were otherwise abandoned during development, nor do we include information on firms that had no projects in the pipeline at all as of April 2010—i.e., firms that could have innovated, but did not.

Fourth, we treat firm and cluster characteristics as exogenous, while they can also be modeled as choice variables. In principle, firms choose size, location, ownership structure, and the like to maximize expected future profitability, so we cannot treat these as exogenous determinants of behavior. Moreover, we lack firm-level information on the expected returns to innovation, and are unable to say to what extent innovation, or a particular disease focus, is efficient for the individual firm.

Fifth, our data are cross-sectional, so we do not have information about changes in firm characteristics and behavior over time, or the effect of firm behavior on economic growth. Prior research suggests that innovation and entrepreneurship are extremely important for national growth, but that different kinds firms make different contributions—high-growth firms have the greatest impact on growth, for example (Wong, Ho, and Autio, 2005). In future research we hope to track the behavior of these sample firms over time, not only to compute growth rates but to look at other changes in characteristics that might help us identify exogenous determinants of behavior and performance. We also plan to explore more closely the internal incentive structures used by these firms, particularly factors that allow them to have a greater focus on neglected diseases, and examine international knowledge flows that enable health technology entrepreneurship in the emerging markets.

Finally, as public research institutions and universities, not included in our study, engage independently in some of the same drug and vaccine innovations as our sample firms, our results should not be taken to describe the overall innovative capability of the nations concerned. Notwithstanding the stated limitations, we believe the data presented and analyzed here provide a

comprehensive view of the overall innovative effort by indigenous enterprises in the emerging markets studied as well as their focus on addressing neglected diseases.

5.4. Contextual implications

Historically, a challenge for China, India and Brazil has been abundant labor and demand for medicines but relatively few globally competitive specialized capabilities. Human resource deficiencies, inadequate capital stocks targeted at technological advancement and innovative activities, disaggregated product markets, and reduced private incentives for innovation are among key institutional factors that contributed to this phenomenon. In the context of the biopharmaceutical sectors our analysis suggests that knowledge-based capabilities have begun to emerge. Indigenous firms are building innovation capabilities and in doing so have a considerable focus on local health challenges, including those affecting the most impoverished populations. As such, the results here have implications for national and international strategies aimed at addressing neglected diseases. Firm-specific characteristics and clustering have a considerable influence on these dynamics. While clustering has positive spillover effects and enhances innovation at the project level, limitations on local resources may constrain competition at the firm level. On the whole, larger firms have a greater propensity to address neglected diseases. Lastly, different incentive structures between emerging market firms and their global competitors appears to be allowing the former to invest in neglected diseases, where the latter have largely failed.

6. Discussion and conclusions

Our findings reveal substantial investments in innovation, including research on neglected diseases, among indigenous biopharmaceutical entrepreneurs in Brazil, China, and India. These investments are not philanthropy; as one entrepreneur told us, “what you call a neglected disease, I call a business opportunity.” Indigenous entrepreneurs appear to be taking advantage of their higher marginal returns to investment and their local knowledge of the legal, institutional, and political context. They are also thinking big; another entrepreneur noted that “discovering and

developing new drugs will change the paradigm as India brings affordable drugs not just for India but for the global market."

By analyzing our dataset of detailed, project-level data on indigenous biopharmaceutical innovation we can offer several insights for theory, empirics and policy. In particular, we find theoretical support for mechanisms that emphasize the benefits of knowledge spillovers through local agglomeration as well as for mechanisms that emphasize the blunted returns associated with local inter-firm competition. Firms tend to engage in more innovative projects on neglected diseases when they are located in areas in which other such projects are under way. Firms tend to engage in fewer innovative projects on neglected diseases when they are located in areas where many other firms also engage in innovation on neglected diseases. These results together suggest that firms may first engage in a portfolio of projects, perhaps to amortize the risks of failure, but then benefit from the knowledge spillovers that arise from specialization. Further research is needed to understand the implications for the inception of new industries as the results point to the potential importance of firm specialization by project area once the research capabilities of firms are revealed.

The analysis also contributes to our understanding of the empirics of new-drug development for neglected diseases. This study is among the first to develop evidence of indigenous entrepreneurship in biopharmaceuticals on neglected diseases – an area of drug discovery that is only rarely pursued by established multinational biopharmaceutical companies (Kyle and McGahan, forthcoming; Lanjouw and Cockburn, 2001). The results suggest that developing-country entrepreneurship can be a significant contributor to advancing global health challenges. Despite resource constraints and weaknesses in the institutional environment biopharmaceutical firms in China, India, and Brazil have substantial investments in drug development, including for neglected diseases. Firm size, governance, and agglomeration affect both overall investment and commitment to neglected diseases, in complex ways. These results suggest that future research should focus on specific mechanisms by which size, governance, and clustering affect firm behaviour and its effects.

Our results also carry implications for theory. Recent calls for policies that enable knowledge-based clusters in emerging economies emphasize the importance of innovation within corporations for national competitiveness (Porter, 2003). The results indicate that this policy prescription may not only carry benefits for the comparative advantages of emerging economies in global biopharmaceuticals, but that local knowledge clusters may also benefit indigenous health as companies seek competitive advantages by specializing in neglected-disease categories. In other words, innovation in biopharmaceuticals may improve national competitiveness and generate benefits in new drugs for poor people.

References

Aernoudt, R. (2004) “Incubators: Tool for entrepreneurship?” Small Business Economics, 23: 127–135.

Brown, J.S. and J.M Hegel III (2005), “Innovation blowback: Disruptive management practices from Asia,” McKinsey Quarterly 1, pp. 34-45.

Campbell, D. and M. Chui (2010). “Pharmerging Shake-up: New Imperatives in a Re-defined World.” IMS Health.

Chaturvedi, S. (2007). "Exploring Interlinkages between National and Sectoral Innovation Systems for Rapid Technological Catch-up: Case of Indian Biopharmaceutical Industry." Technology Analysis & Strategic Management 19(5): 643.

Chittoor, R., Ray S. (2007), “Internationalization paths of Indian pharmaceutical firms: A strategic group analysis,” Journal of International Management 13(3): 388-355.

Chittoor, R., Ray S., Aulakh P. S., Sarkar M. B. (2008). "Strategic responses to institutional changes: 'Indigenous growth' model of the Indian pharmaceutical industry." Journal of International Management 14, pp. 252-269.

Christensen, C. M. (1997). The Innovator's Dilemma. Cambridge, MA: Harvard Business School Press.

Cohen, J.C. (2006), “Expanding Drug Access in Brazil: Lessons for Latin America and Canada,” Canadian Journal of Public Health 97(6): I15-18.

Daar, A. S., Singer, P. A. (2011) “The grandest challenge; bringing life-saving medicines from lab to the village” Doubleday Canada. Toronto

Delgado, M., Kyle, M., McGahan, A.M. (2011) “The influence of intellectual property protection on the geography of trade in knowledge-intensive goods” Working Paper.

DiMasi, J., R. Hansen, *et al*. (2003). "The price of innovation: new estimates of drug development costs." Journal of health economics 22(2): 151-185.

Dutt, N., Hawn, O., Vidal, E., Chatterji, A., McGahan, A. M., Mitchell, W. (2011) “The co-development of markets and firms: business incubators in emerging economies”. Working Paper, Duke University and University of Toronto.

Easterly, W. (2006). The White Man's Burden: Why the West's Efforts to Aid the Rest Have Done So Much Ill and So Little Good. Penguin Press.

Finer, B., and P. Holberton (2002). Incubators: There and back. Journal of Business Strategy 23(3): 23-25.

Frew, S. E., R. Rezaie, *et al*. (2007). "India's health biotech sector at a crossroads." Nature Biotechnology 25(4): 403-417.

Frew, S. E., S. M. Sammut, *et al*. (2008). "Chinese health biotech and the billion-patient market: Chinese government support and 'sea turtles' are spurring the sector, but investors lack exits." Nature Biotechnology 26(1): 37-54.

Furman, J. L., M. K. Kyle, I. Cockburn, and R. B. Henderson (2005). Public & Private Spillovers, Location and the Productivity of Pharmaceutical Research. Annals of Economics and Statistics 79/80: 165-188.

Furman, J, L, S. Stern, and M. E. Porter (2002), “The Determinants of national innovative capacity,” Research Policy 31(6): 899-933.

George, G., McGahan, A.M. and Prabhu, J. (2012), “Innovation for Inclusive Growth: Towards a Theoretical Framework and a Research Agenda,” Journal of Management Studies, forthcoming.

Ginarte, J. and W. Park (1997), "Determinants of patent rights: a cross-national study," Re-search Policy 26(3): 283-301.

Grabowski, H. (2002), “Patents, Innovation and Access to New Pharmaceuticals,” Journal of International Economic Law 5(4): 849-860.

Grace,C. (2004). “The Effect of Changing Intellectual Property on Pharmaceutical Industry Prospects in India and China: Considerations for Access to Medicines,” DFID Health Systems Resource Centre working paper.

Hafner, T., Popp, D. (2011) “China and India as Suppliers of Affordable Medicines to Developing Countries.” NBER Working Paper No. 17249

He, J., Gu, D., Wu, X., Reynolds, K., Duan, X., Yao, C., Wang, J., Chen, C. S., Chen, J., Wildman, R. P., Klag, M. J., Whelton, P. K. (2005) “Major causes of death among men and women in China.” New England Journal of Medicine. 353(11): 1124-1134.

Henderson, R. L., and I Cockburn (1996). "Scale, scope, and spillovers: The determinants of research productivity in drug discovery.” RAND Journal of Economics 27(1): 32-59.

Henderson, R., L. Orsenigo, *et al*. (1999). "The pharmaceutical industry and the revolution in molecular biology: Interactions among scientific, institutional and organizational change." In Sources of industrial leadership: studies of seven industries: 267-311.

Hesketh, T. and W. Zhu (1997). "Health in China: Traditional Chinese medicine: one country, two systems." British Medical Journal 315 (7100).

Hitt, M. A., Hoskisson, R.E. (1994). Downscoping: How to tame the diversified firm. New York: Oxford University Press.

Hitt. M. A., Hoskisson, R. E., Kim, H. (1997). "International Diversification: Effects on Innovation and Firm Performance in Product-Diversified Firms." Academy of Management Journal 40(4): 767-798.

Hum, R., Jha, P., McGahan, A.M. (2011). Global divergence in critical income for adult and childhood survival between 1970 and 2007: an interpretation of the Preston curve. Working Paper, University of Toronto

Immelt, Jeffrey R., (2009), "How GE is Disrupting Itself," Harvard Business Review (October)

Jamison, D.T., Breman J. G., Measham, A.R., Alleyne, G., Claeson, M., Evans, D. B., Jha, P., Mills, A., Musgrove, P. (2006) "Disease Control Priorities in Developing Countries." 2nd Edn. Oxford University Press. New York

Jia, W., Huang, Q.H., Liao, J., Ye, W., Shugart, Y.Y., Liu, Q., Chen, L.Z., Li, Y. H., Lin, X., Wen, F.L. (2006) "Trends in incidence and mortality of nasopharyngeal carcinoma over a 20-25 year period (1978/1983-2002) in Sihui and Cangwu counties in southern China." BMC Cancer. 6(1): 178

Kale, D. and S. Little (2007). "From Imitation to Innovation: The Evolution of R&D Capabilities and Learning Processes in the Indian Pharmaceutical Industry." Technology Analysis & Strategic Management 19(5): 589.

Khanna, T. and K. G. Palepu (1997). "Why Focused Strategies May Be Wrong for Emerging Markets." Harvard Business Review 75(4): 41-51.

Khanna, T. and K. G. Palepu (2000). "The Future of Business Groups in Emerging Markets: Long-Run Evidence from Chile." Academy of Management Journal 43(3): 268-285.

Klein, P. G. (2011). "Corporate Diversification and Innovation: Managerial Myopia or Inefficient Internal Capital Markets?" Working Paper, McQuinn Center for Entrepreneurial Leadership, University of Missouri.

Kohler, J.C. (2007), "Reflections On Pills and Poverty," Canadian Pharmacists Journal 140(6) (November-December): 378-382.

Kremer, M. (2002), "Pharmaceuticals and the Developing World," Journal of Economic Perspectives 16(4): 67-90.

Kumar, N. and Puranam, P. (2011), India Inside: The Emerging Innovation Challenge to the West (Harvard Business School Press)

Kyle, M.K, and McGahan, A.M. (2011) "Investments in Pharmaceuticals Before and After TRIPS". Accepted by *The Review of Economics and Statistics Journal* (Expected Publication 2012)

Lado, A. A., and G. S. Vozikis (1996). "Transfer of technology to promote entrepreneurship in developing countries: an integration and proposed framework." Entrepreneurship: Theory and Practice 21(2): 55-73

Lanjouw, J. O. and I. M. Cockburn (2001). "New Pills for Poor People? Empirical Evidence after GATT." World Development 29(2): 265-289.

Liang, X., Bi, S., Yang, W., Want, L., Cui, G., Cui, F., Zhang, Y., Liu, J., Gong, X., Chen, Y. (2009) "Epidemiological Serosurvey of hepatitis B in China--declining HBV prevalence due to hepatitis B vaccination." Vaccine. Nov 5;27(47): 6550-7

Milstien, J. B., P. Gaul, *et al*. (2007). "Access to vaccine technologies in developing countries: Brazil and India." Vaccine 25(44): 7610-7619.

Moyo, D. (2011). How the West Was Lost: Fifty Years of Economic Folly—And the Stark Choices that Lie Ahead. New York: Farrar, Straus and Giroux.

Natesh, S. and M. K. Bhan (2009). "Biotechnology sector in India: strengths, limitations, remedies and outlook." Current science 97(2): 157.

Pereira, F. B. (2007). "A Biominas Study of the Brazilian Biotechnology Companies."

Perz, J., Armstrong, G.L., Farrington, LA, Hutin, Y.J.F., Bell, B.P. J. (2006) "The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide." Hepatology 45(4): 529-538

Porter, Michael E (2003), "The Economic Performance of Regions," Regional Studies 37(6-7) (August/October): 549-578.

Prahalad, CK (2004). The Fortune at the Bottom of the Pyramid: Eradicating Poverty Through Profits (Wharton School Publishing).

Qian, Y. (2007), "Do National Patent Laws Stimulate Domestic Innovation in a Global Patenting Environment? A Cross-Country Analysis of Pharmaceutical Patent Protection, 1978-2002," Review of Economics and Statistics 89: 3

Radjou, N., Prabhu, J., and Ahuja, S. (2012). Jugaad Innovation: Think Frugal, Be Flexible, Generate Breakthrough Growth (Jossey-Bass)

Ramachandran, A., Snehalatha, C., Kapur, A., Vijay, V., Das, A.K., Rao, P.V., Yajnik, C.S., Prasanna Kumar, K.M., Nair, J.D. Diabetologia. (2001) "High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey" 44(9): 1094-1101

Rezaie, R., S. E. Frew, *et al*. (2008). "Brazilian health biotech--fostering crosstalk between public and private sectors." Nature Biotechnology 26(6): 627-644.

Rezaie, R., P. A. Singer (2010). "Global Health or Global Wealth?" Nature Biotechnology 28(9): 907-9.

Rodrik, R. (1997). "Democracy and Economic Performance," Harvard University working paper.

Statistical-Yearbook (2010), China Statistical Yearbook 2010. Beijing, Government of the People's Republic of China.

Sun, Q., M. Santoro, *et al*. (2008). "Pharmaceutical policy in China." Health Affairs 27(4): 1042.

Wild, S., Roglic, G., Green, A., Sicree, R., King, H. (2004) “Global prevalence of diabetes: estimates for the year 2000 and projections for 2030.” Diabetes care. 27(10): 2569

Wong, P., Y. Ho, and E. Autio (2005). "Entrepreneurship, Innovation and Economic Growth: Evidence from GEM data." Small Business Economics, Springer 24(3): 335-350.

Table 1: Summary statistics by project

	All	Brazil	China	India
Total projects	758	102	240	416
Number of firms	70	10	31	29
Projects per firm (mean)	10.8	10.2	7.8	14.3
Projects per firm (median)	7	7	4	11
Percent of projects in clinical trials	17%	11%	14%	20%
Percent of projects targeting neglected diseases	31%	31%	38%	28%
Percent of projects in clinical trials targeting neglected diseases	17%	13%	25%	15%
Projects by development phase:				
Early Discovery	169	35	59	75
Pre-clinical (Animal Studies)	129	14	31	84
Phase I clinical trials	50	6	8	36
Phase II clinical trials	57	1	17	30
Phase III clinical trials	28	4	9	15
On market	332	42	114	176

Table 2: Summary statistics by firm

		All	Brazil	China	India
Total projects	mean	10.8	10.2	7.8	14.3
	median	7	7	4	11
Innovative projects	mean	6.1	6.0	4.1	8.3
	median	5	5	3	6
Projects in clinical trials	mean	1.8	1.1	1.1	2.8
	median	1	1	1	2
Projects targeting neglected diseases	mean	3.5	3.2	3.0	4.0
	median	1	1	0.5	1
Projects in clinical trials targeting	mean	0.26	—	0.26	0.34
neglected diseases	median	0	0	0	0
Firm size (employees)	mean	954	606	346	1,613
	median	280	65	200	500
Firm age (years)	mean	18.5	22.6	13.0	23.0
	median	12.5	17	11	18
Projects in firm's city	mean	62.8	20.3	59.3	81.2
	median	56	25	56	73
Firms in firm's city	mean	5.7	2.4	6.9	5.4
	median	5	2	8	7
Projects already on the market	mean	4.7	7.7	3.7	6.1
	median	0	1.5	0	0

Table 3: Correlation matrix for firm-level variables

	Total projects	Innovative projects	Projects in clinical trials	Projects targeting neglected diseases	Projects in clinical trials targeting neglected diseases	Firm size	Firm age	Projects in firm's city	Firms in firm's city	Projects already on the market
Total projects	1									
Innovative projects	0.6134***	1								
Projects in clinical trials	0.3084***	0.7353***	1							
Projects targeting neglected diseases	0.7539***	0.1903	−0.0459	1						
Projects in clinical trials targeting neglected diseases	0.3095***	0.2153*	0.2398**	0.3892***	1					
Firm size	0.0539	0.3266**	0.4473***	−0.121	0.0102	1				
Firm age	0.301**	0.306**	0.2727**	0.1381	0.1659	0.3843***	1			
Projects in firm's city	0.0862	0.0083	−0.0784	0.1428	0.0648	−0.1947	−0.2416*	1		
Firms in firm's city	0.3593***	0.3139***	0.1576	0.2594**	0.2991**	-0.0622	−0.0114	0.7823***	1	
Projects already on the market	0.8641***	0.1326	−0.0805	0.8232***	0.2519**	-0.1356	0.1813	0.1001	0.2489**	1

* p < 0.10
** p < 0.05
*** p < 0.01

Table 4: Determinants of innovation

	Model 1	Model 2	Model 3	Model 4
Dependent variable	Number of innovative projects (negative binomial)		Percentage of innovative projects (OLS)	
	All projects in pipeline	Projects in clinical trials	All projects in pipeline	Projects in clinical trials
Brazil	0.485***	−0.326***	0.149	−0.096*
	(0.293)	(0.099)	(0.068)	(0.028)
China	0.198**	−0.219	−0.030	−0.057
	(0.312)	(0.230)	(0.036)	(0.030)
1–19 employees	0.266***	−0.147	−0.104	−0.120***
	(0.327)	(0.107)	(0.044)	(0.010)
20–49 employees	−0.060	1.030***	0.030	−0.287**
	(0.350)	(0.210)	(0.039)	(0.029)
50–99 employees	−0.408	−1.020	−0.168	−0.247***
	(0.566)	(0.120)	(0.153)	(0.002)
100–249 employees	−0.648***	−0.966***	−0.218	−0.103
	(0.244)	(0.170)	(0.109)	(0.093)
Log (firm age)	0.220	0.219*	0.026	−0.039
	(0.183)	(0.111)	(0.034)	(0.035)
Nearby projects	0.022***	0.001	−0.003	−0.004
	(0.012)	(0.001)	(0.002)	(0.002)
Nearby projects (squared)	−0.001***	−0.000	0.000	−0.000
	(0.000)	(0.000)	(0.000)	(0.000)
Nearby firms	0.049	0.451***	0.060	0.023
	(0.099)	(0.030)	(0.026)	(0.038)
Nearby firms (squared)	−0.012	−0.038***	−0.003	−0.001
	(0.008)	(0.001)	(0.002)	(0.002)
Publicly held	0.440***	0.707***	0.081	−0.048
	(0.087)	(0.096)	(0.069)	(0.029)
State-owned	−0.961	−15.326***	−0.061	−0.006
	(0.995)	(1.157)	(0.084)	(0.022)
Log (products on market)	0.054	−0.024	−0.243***	−0.098**
	(0.160)	(0.023)	(0.011)	(0.022)
Constant	0.292***	−0.716**	0.795**	0.658**
	(0.022)	(0.357)	(0.108)	(0.148)
Log pseudo-likelihood	−174.6	−94.1		
R^2			0.79	0.38

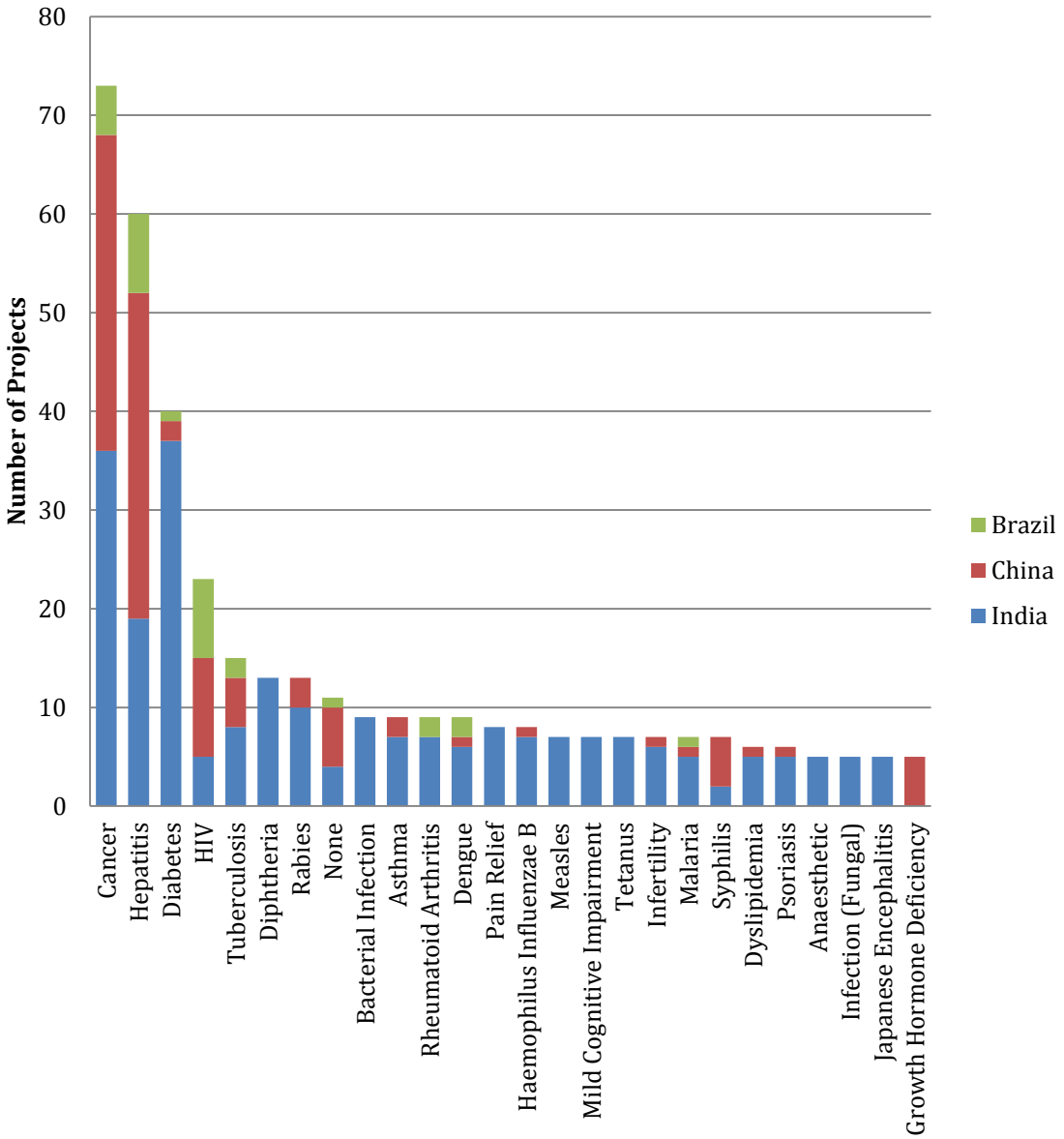
N = 66. Robust standard errors, clustered by country, in parentheses. The negative binomial is zero-inflated in Model 2.
* p < 0.10
** p < 0.05
*** p < 0.01

Table 5: Investment in neglected diseases

	Model 1	Model 2	Model 3
Dependent variable	Firm has any projects targeting neglected diseases (logit)	Number of projects targeting neglected diseases (negative binomial)	Number of projects in clinical trials targeting neglected diseases (negative binomial)
Brazil	2.385***	−0.137	−15.816***
	(0.790)	(0.370)	(1.226)
China	1.530**	−0.742***	1.234
	(0.647)	(0.173)	(0.904)
1–19 employees	——	−17.345***	−1.506***
		(1.402)	(0.061)
20–49 employees	0.795**	0.377	−18.183***
	(.390)	(0.477)	(0.979)
50–99 employees	0.268	0.926**	0.408*
	(0.789)	(0.423)	(0.227)
100–249 employees	0.004	−0.009	−17.663***
	(1.727)	(0.972)	(1.069)
Log (firm age)	0.317	0.181**	0.200**
	(0.479)	(0.087)	(0.074)
Nearby projects	0.171***	0.010	0.072***
	(0.013)	(0.012)	(0.009)
Nearby projects (squared)	−0.001***	0.000	−0.000
	(1.000)	(0.000)	(0.000)
Nearby firms	−1.892***	−0.823**	−1.637***
	(0.510)	(0.325)	(0.546)
Nearby firms (squared)	0.073*	0.058***	0.077**
	(0.040)	(0.020)	(0.040)
Publicly held	1.926	−0.020	−0.991***
	(0.595)	(0.379)	(0.181)
State-owned	——	1.036***	−19.142***
		(0.209)	(1.232)
Log (products on market)	0.529***	0.826***	−0.150
	(0.054)	(0.098)	(0.149)
Constant	−0.737	0.271	−0.917
	(1.730)	(0.635)	(1.941)
Pseudo-R^2	0.30		
Log pseudo-likelihood		−109.6	−26.0
N	63	65	62

Robust standard errors, clustered by country, in parentheses.
* p < 0.10
** p < 0.05
*** p < 0.01

Fig 1. Major* Disease Indications Targeted by Innovative Firms in Brazil, China and India



* Only diseases for which five or more projects were targeted in all three countries are included here.