Health Technology Innovation by Indigenous Enterprises in China, India and Brazil

by

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Abstract

This thesis explores health technology innovation within indigenous enterprises in China, India, and Brazil. The main discussions are presented in five papers/manuscripts. The first is a case study of Brazil's health biotechnology sector. It concludes that systemic tensions between the country's public and private sectors may be detracting from its overall innovative success.

The second paper gauges vaccine and medicinal innovation within enterprises in the stated countries by analyzing new technologies in their pipelines or on the market. It concludes that that a growing number of health enterprises in these countries are tackling more technologically challenging and costly innovations.

The third paper explores how national institutions and industry globalization interact to shape commitments to new drug and vaccine innovations by enterprises in the three countries. It concludes that; a) the introduction of pharmaceutical product patent regimes has had a modest impact on entrepreneurial attempts to develop new technologies, b) key challenges that diminish patent incentives tend to be institutional in nature and, c) the increasingly globalized nature of health product innovation limits what countries can achieve independently.

The fourth paper analyzes key issues and trends in health biotechnology firms' transition to innovation in China, India, Brazil, and South Africa. It concludes that this transition often entails greater integration into the global system.

The fifth paper ponders the implications for global health of the emerging market firms' transition to innovation. It concludes that these enterprises have the potential to simultaneously address global health needs while exploiting global markets, provided support mechanisms are put in place to enable product development for the poorest market segments.

This research suggests that to succeed in biopharmaceutical innovation, nations need to adjust scientifically, sectorally and globally all at the same time. Also, that national governments and the global health community need to enhance engagement of emerging market enterprises in related efforts.

Dedication

To Bahareh with love.

Acknowledgments

I am grateful and indebted to Peter Singer who supported me throughout this endeavor. Despite his always-hectic schedule he was very accessible, helpful, insightful and enthusiastic. Peter's passion for global health, determination to make a positive impact and openness to new ideas continues to be a true inspiration for me.

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The late Sara Al-Bader conducted a country analysis of South Africa's health biotech sector as part of her PhD thesis on Africa. Her work forms the basis for the inclusion of this country in one of the manuscripts. Sadly, Sara and her husband Mike Smoughton who came to Canada from

England for Sara's studies both died in a car accident a few months prior to finishing her thesis. It was a true loss of a friend and comrade.

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Chapter 1
Introductory Chapter

1 Introduction

This thesis is concerned with health technology innovation by indigenous, private-sector enterprises in the emerging markets of China, India and Brazil. In particular, it explores the nature and extent of innovative activities within the entrepreneurial sector and examines key contributors and impediments to innovation in vaccines, diagnostics and therapeutics for human use. It investigates how entrepreneurial strategy, industry dynamics, and the institutional context work together to shape the development of country-specific entrepreneurial capacity to innovate in health technology.

China, India and Brazil are among the most populous and fastest-growing economies in the world, with an eye to join its rank of leading innovating nations. This desire is motivated by the countries' development goals, the prevailing economic thought that technology is a key driver of productivity and sustained economic growth, and the knowledge that innovation underpins technological change. In recent decades considerable changes have taken place in the overall institutional environment of all these countries, aimed at the creation of environments more conducive to entrepreneurship and technological advancement. Biotechnology ranks high as a priority area for national policies across the three emerging markets studied, with emphasis on a variety of applications including in health, agriculture and industry. This thesis is focused on health technology innovation in China, India, and Brazil – including both modern biotechnologies as well as pharmaceuticals.

1.1 Purpose Statement

The purpose of this study was to explore health technology innovation within the domestic private sectors in China, India and Brazil. The study sought to examine key institutional, entrepreneurial and industrial factors that shape innovative capabilities of health technology enterprises in these countries. Furthermore, it set out to ponder implications for global health of attempts to transition into innovation by emerging market companies.

1.2 Overall Research Question

The overall research question addressed is; *What are the roles of indigenous enterprises and institutional policies in health technology innovation in China, India and Brazil, and how can the innovation environment be improved?* To address this question, I aimed at exploring the following aspects:

1. Current innovative capabilities and entrepreneurial innovation strategies of indigenous health biotech firms in the countries concerned

2. The various factors, including barriers and incentives that impact on the ability and/or willingness of domestic entrepreneurs to undertake innovative activities related to the development of new health technologies

3. The role of government policy on innovation within domestic enterprises and how the innovation environment can be improved

4. Potential implications of study findings for addressing global health issues related to the development and commercialization of health technologies targeted primarily at diseases of poverty

1.3 Overall Study Approach

This study uses a qualitative case study approach, where each of the three countries constitute a country case, and are in turn informed by a set of company cases nested within them, as well as interview data from other institutional informants and information from secondary sources. Methodological aspects are covered in Chapter 3.

The theoretical focus of this thesis lies at the intersection of institutional context, entrepreneurship and health technology innovation in China, India and Brazil. More specifically, it explores how institutional factors and industry characteristics work together to shape the development of country-specific entrepreneurial capabilities to develop and commercialize health products.

The analytic framework informing this study is the Systems of Innovation (SI) approach, in particular the national [1-3], and sectoral [4, 5] systems of innovation approaches. A basic premise underlying this approach is that innovation is a byproduct of an interactive process involving various actors, institutions and organizations. I study the innovation process primarily from the vantage point of the firm, which is broadly recognized to play a central role within innovation systems. From this perspective, I delve deeper into the various factors that influence innovation within domestic companies in the countries concerned.

1.4 Key Terminologies

For the purposes of this study, the terms "health technology", "health biotech", "health biotechnology", and "biopharmaceutical" are used interchangeably and are intended to be inclusive of: a) chemistry-based pharmaceuticals, b) health products based on the more modern recombinant DNA technologies, genetic therapies and stem cells, and c) use of national endowments such as traditional medicines as a source of innovation for new and more efficacious health products. My analysis is inclusive of firms involved in development of vaccines, diagnostics, and therapeutics regardless of the precise technology that underlies their work, but excludes multinationals and generics firms that do not undertake innovative activities. The scope of diagnostic technologies covered does not include imaging technologies or medical devices. Therefore, reference to "health products" is intended to be limited to vaccines, diagnostics and therapeutics and "health innovation" refers to health technologies and products and not health systems innovations for instance.

The inclusive nature of this study is justified since; (1) it is increasingly difficult to separate out companies based on the conventional, and arguable outdated, terminology of *biotechnology* and *pharmaceuticals* - especially since a growing number of firms undertake both activities simultaneously, (2) notwithstanding technical differences, the underlying mechanisms and processes of innovation are largely overlapping for both bio-based and chemistry-based technologies, (3) from the perspective of health product innovation, and global health in particular, the eventual market is primarily concerned with the availability of safe and efficacious products and generally not with the precise molecular composition of an end product.

The terms “domestic”, “indigenous” or “home-grown” are used interchangeably throughout this work and refer to the group of firms that are based in one of the three countries studied and whose majority ownership shares are held by nationals of that country. It must be stated however that due to the complexities often associated with the ownership structure of some Chinese firms in particular, it is not always possible to establish this fact a priori with high certainty. Indeed, a few firms that for all intents and purposes consider themselves to be Chinese and only have operations in this country may, strictly speaking, have majority ownership by ‘foreigners’, who are almost always Chinese expats. In addition, some firms are based out of tax havens such as the Cayman Islands. I have generally considered the latter groups of firms to be indigenous enterprises in China.

1.5 Study Rationale

Yin (1992) found that all research efforts, whether qualitative or quantitative, share the four common goals; using others’ expertise for understanding an issue or phenomenon, collecting all pertinent data, testing competing explanations, and assessing the applicability of their findings in other contexts [6]. These capture the essence of what I have tried to achieve in this multidisciplinary work. The basic premise underlying this research is that promoting indigenous capacity to innovate in developing nations is an effective way to improving health and social well-being in these societies in a more sustainable and appropriate fashion. Of course, implicit is the idea that studying technological innovation and the factors that impact it, can ultimately promote development of the indigenous capabilities to innovate. Previous studies have found that biotechnologies [7, 8] and nanotechnologies [9] hold significant potential for such impacts in the developing world, and harnessing them for these purposes can enhance global health equity [10].

Through this work I have attempted to understand and describe the existing capabilities to innovate in health biotech, and to enquire about key barriers and incentives that health biotech entrepreneurs face in China, India and Brazil and contributing factors to these. Such insights can contribute to enhancing indigenous innovation in these, and other developing nations, by identifying business and policy strategies with the potential to accelerate domestic technological development in health. Another important motivation has been to help expose the burgeoning innovative capabilities in the countries concerned to the broader community of enterprises, investors and global health promoters. Greater exposure can help enhance linkages between entrepreneurs in the global South with other interested parties globally and has the potential to advance global health over the longer term.

1.6 Organization of the Thesis

This dissertation is divided into nine chapters. It is a manuscript-based format, indicating that each of the five chapters (4-8) are either published articles or intended to be published in peer-reviewed journals in the near future. This means that each of these chapters is structured as a stand-alone piece. While this often makes for more concise and focused discussion of topics within given chapters, the manuscript-based format does create a certain degree of discontinuity in flow. Certain themes may also be covered in more than one manuscript due to their salience to the relevant discussions. Lastly, it means that some of the methodological aspects and literature background relevant to each of the chapters concerned is covered within those chapters themselves. I have attempted not to replicate these insights within earlier chapters including the literature review chapter (Chapter 2) and the chapter on research design and methodology (Chapter 3).

Chapter 2 - This chapter is a literature review. It places this research in the context of existing literature and expands on some of the key topics discussed throughout.

Chapter 3 - This chapter covers the research design and methodologies used. As stated above, methodological specificities to given chapters are presented in those respective chapters.

Chapter 4 – This chapter is a reproduction of an article published in the *Nature Biotechnology* journal in June 2008, entitled: "*Brazilian health biotech – Fostering cross-talk between public and private sectors*" [11]. It is based on case studies of 19 Brazilian health biotech firms and 4 large public institutes involved in development and manufacturing of health products. It covers firm-specific data with respect to existing products and those in development, identifies key barriers to innovation in Brazil and makes policy recommendations to accelerate health biotech development in the country.

Chapter 5 – This is a manuscript submitted for publication in the *Nature Biotechnology* journal, and gauges novel vaccine and medicinal innovations by domestic enterprises in China, India and Brazil. It covers new chemical and biotechnological entities in development within company pipelines and discusses the composition of these based on the types of innovation, targeted indications, and stages of development.

Chapter 6 - This chapter is a manuscript intended for submission to a peer-reviewed Journal. It uses the insights from Chapter 5 related to new product innovations and suggests that the innovative performance of the entrepreneurial sectors in these countries has been modest, relative to what one may expect given the size and growth rates of domestic pharmaceutical industries in China, India and Brazil. It then relates this lackluster response to the adoption of pharmaceutical product patent regimes to the prevalent institutional environments in each country and the role of extra-national factors in shaping industry evolution in the emerging markets concerned.

Chapter 7 – This chapter is a manuscript intended for submission to an appropriate target journal. It is a comparative case study analysis and looks into key issues and trends in health biotechnology firms' transition to innovation in China, India, Brazil and South Africa. The core research questions addressed in this paper are: how do health biotechnologies develop in emerging economies? What entrepreneurial strategies and enterprise structures have been commonly used to facilitate transition into innovative sectors? What are the key barriers deterring health product innovation and what role does the government play in assisting enterprises to overcome these challenges? It also highlights important similarities and differences across China, India, Brazil, and South Africa.

The data for this chapter draws on analysis of interview data collected in China and India by another colleague, as well as subsequent interview data – from firms and institutional informants - that I personally collected. Indeed I also participated in the primary analysis of interview data from India and writing a manuscript, which led to the publication of an article in the *Nature Biotechnology* journal in April 2007 [12], and I was a co-author on a similar article focused on China [13]. The South African component was the contribution of the late Sara Al-Bader, who conducted an analysis of that country's health biotech companies, initially published in the *Nature Biotechnology* journal in May 2009 [14].

Chapter 8 – This chapter, entitled "Global Health or Global Wealth" is a reproduction of an article published in the *Nature Biotechnology* journal in September 2010 [15]. The article argues that firms in the emerging markets collectively represent a considerable, growing, and largely untapped resource for global health. It raises the question of whether challenges associated with the transition from generics-based to innovation-based industries may compel many firms in these markets to largely abandon the health needs of the global poor, in favor of more lucrative markets at home and abroad. It suggests that targeted interventions by domestic governments, and the broader global health community can help reduce the risks of such an event, and goes on to review and propose a number of measures to this effect.

Chapter 9 – This chapter presents some overall conclusions together with limitations of this work as well as possible future directions for continued analysis.

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Chapter 2
Literature Review

2 Introduction

This chapter is organized as follows. It begins by highlighting the importance of innovation in the context of economic growth and reviews some of the theoretical aspects related to innovation processes. The interactions between innovation systems, the state, and globalization are explored from the perspective of what they may mean for technology policy. The chapter goes on to present an overview of the biopharmaceutical industry evolution in industrialized-world settings and the emerging markets under study. In this regard, it also explores various factors that are believed to facilitate health technology innovation. Lastly, it presents an overview of factors related to advancing health technology innovations specifically targeted at poor markets and reviews some of the strategies utilized for this purpose thus far.

Overall, it is suggested that the available literature: a) does not provide adequate understanding of the extent and nature of health technology innovation by indigenous private sectors in China, India and Brazil, b) has little to say about key factors that influence innovation in the emerging markets, particularly with respect to health technologies, c) does not provide sufficient guidance on which analytical or theoretical framework(s) is best suited to explain biopharmaceutical innovation, particularly in the context of emerging markets and other developing countries, d) has a bias towards a *national* innovation systems approach, even when this use may not be warranted, and e) has not paid adequate attention to the role and potential of domestic health technology enterprises in the emerging markets to address global health needs.

It should be noted however, that due to the format of this thesis, some of the background literature is included in the individual manuscripts themselves and I have tried to minimize repetition by not including those in this chapter.

2.1 Innovation and Why it Matters

The prevailing economic thought is that technological change is a key contributor to enhanced productivity, itself a major driver of economic growth. Until a few decades ago reducing nominal national wages or devaluation of a county's currency were thought of as the most effective approaches to enhance national competitiveness [1]. However, it is increasingly accepted that to be competitive, firms and countries need to be innovative in both organizational and technological terms. Dosi states that: *"…innovation concerns the search for, and the discovery, experimentation, development, imitation, and adoption of new products, new production processes and new organizational set-ups"* [2]. Others have simply defined innovation as the production, diffusion and use of new, and economically useful knowledge [3]. Dosi suggests that modern innovations share a few key characteristics including: a fundamental element of uncertainty, increasing reliance on science and technology, and increasing complexity favoring formal organizations over individual inventors [2].

While it is believed that technological change underpins economic growth, changes in economic conditions do not sufficiently explain patterns of technological change. The direction of technological change is often determined by the state-of-the-art technologies in use, and "it is the nature of technologies themselves that determines the range within which products and processes can adjust to changing economic conditions" [2]. Therefore, the level of previous technological achievements (by firms, organizations and countries) to a considerable extent determines the probability of subsequent achievements. These insights raise the fundamental question that if technological change is cumulative by nature, then knowledge regarding the present state of technologies in a given context – a country for example – is crucial to gauging its future technological trajectory. In this respect, available literature has paid little attention to the present innovative capabilities within the indigenous companies in the emerging markets, including China, India and Brazil and factors that shape it.

Another relevant question is whether the predominant tools and theoretical approaches used to explain technological innovations are applicable in the context of 'catch-up' sectors of emerging economies. After all, much of what we know about innovation and technological change is based on experiences in the industrialized world. Also, of considerable ambiguity is whether industry globalization has changed the rules of the game sufficiently as to diminish the utility of lessons learned from experiences elsewhere and at times prior. The background to these topics is discussed throughout this chapter, but suffice it to say that their relevance to policymaking in the context of developing countries remains understudied.

Traditionally, developing countries have been viewed as technology users [4], with their ability to absorb technologies from abroad as key to their development [5]. However, in the context of a knowledge-based economy, "the role of the South as a 'technology user' is becoming increasingly problematic and raises the specter of a cumulative and path-dependent growth in inequalities between North and South in the future, particularly in science-based industries such as (bio)pharmaceuticals" [6]. In order to avert such an outcome, some developing countries have undertaken institutional reforms aimed at increasing their capacity for technological advancement, encouraging entrepreneurship and ultimately innovation. Among the leaders in this group of countries are China, India and Brazil, each of which has identified a number of priority areas for technological advancement. For the past two decades, biotechnology has consistently been singled out as a high priority area for development in all three countries, although with differential emphasis on various aspects within this field – that includes health, agriculture, and industrial applications.

2.2 The Innovation Systems Framework

The Systems of Innovation (SI) approach has been developed by a number of authors including Freeman [7, 8], Lundvall [9, 10] and Nelson [11, 12]. **Chapter 6** (Section 6.3) provides an overview of innovation systems theory and the importance of institutional dimensions with a focus on intellectual property (IP) and national policies. Discussions below are meant to provide a fuller background regarding the SI perspective, its application in the context of developing countries, and its implications for this research.

Lundvall defines a system of innovation to be "constituted by elements and relationships which interact in the production, diffusion, and use of new and economically useful knowledge…(and) a national system encompasses elements and relationships, either located within or rooted inside the borders of a nation state" [13] (p.2). Edquist has defined system of innovation to include: "all important economic, social, political, organizational, institutional, and other factors that influence the development, diffusion, and use of innovations" [14]. A system, on the other hand, "is made up of components, relationships, and attributes" [15]. The SI view rests on the basic notion that innovation is the outcome of an interactive social process, in an economic context where knowledge is the most important resource and learning the most important process [9](p.1). The SI is made up of various actors (individuals and organizations), institutions (policies, rules, norms, and so on) as well as the interaction between these elements. These elements "either reinforce each other in promoting processes of learning and innovation or, conversely, combine into constellations blocking such processes" [13](p.2). The SI approach recognizes that innovation is a complex and non-linear phenomenon with "*the understanding that firms do not innovate in isolation*" [14], and that in doing so they are impacted by external dynamics such as institutional factors [7]. However, the complexity of innovation processes, and in particular its systemic dimension, is not well understood [14], but is believed to flow from interactive relationships including user-producer, and competitive interactions [9](p.4 and 116-127).

The SI approach has also garnered significant debate ranging in topic areas from the geographic "boundedness" of the approach, to discussions on what precisely constitutes a "system". The notion that innovation can be viewed as a territorial phenomenon has contributed to the development of national systems of innovation (NSI) and 'regional' systems of innovation (RSI). Other approaches, such as the sectoral innovation systems (SIS) and technological systems framework have lesser emphasis on geography and more on technologies, product classes and innovating firms. These are discussed in more detail below. However, according to Edquist [3] all these systems share the following characteristics:

1. They place innovation and other learning processes at the centre of focus.
2. They adopt a holistic and interdisciplinary perspective.
3. They use a historical perspective and consider innovation processes to be evolutionary.
4. They stress differences between systems, and that the notion of optimality is irrelevant.
5. They emphasize interdependence between actors - in the sense of 'players'.
6. They include product and process innovations, as well as their development and diffusion.
7. They emphasize the central role of institutions - in the sense of 'rules of the game'.
8. They are associated with conceptual diffuseness.
9. They are conceptual frameworks, rather than formal theories.

2.2.1 National Systems of Innovation (NSI)

Most attempts thus far to identify the level at which innovation systems operate have tended to place the boundaries of the system at geographic borders of individual nations and within national jurisdictions. Lundvall states that: "…*a national system encompasses elements and relationship, either located within or rooted inside the borders of a nation state"* [9](p.2). The NSI approach therefore emphasizes the role of the state and various actors within a particular country. Major components of an NSI include organizations (firms, universities, public research institutes), institutions (various laws, regulations, cultural norms), and governments. The main focus of NSI is on non-firm organizations, which provide a contextual background within which innovation can take place. In agreement with the nation-centric view of innovation, Björn Johnson states that: "…if innovation reflects learning and if learning is interactive, it follows that innovation is rooted in the institutional set-up of the economy… and if learning emanates from routine activities in economic production, innovation must be rooted in the prevailing economic structure" [16]. Therefore, he concludes, innovation is rooted in economic history, which necessarily highlights the concept of 'nation' within the SI framework. The notion that the nation state is the most appropriate level at which to place the boundaries of innovation systems has garnered some objections too. For example, Nelson and Rosenberg, state:

> "*On the one hand, the (NSI) concept may be too broad. The system of institutions supporting technical innovation in one field say pharmaceuticals, may have very little overlap with the system of institutions supporting innovations in another field, say aircraft. On the other hand, in many fields of technology, including both pharmaceuticals and aircraft, a number of institutions are or act transnational*" [17].

Despite the predominant use, thus far, of the SI approach for descriptive purposes, Lundvall clearly views the this framework through a prescriptive lens, and considers it to be "in direct competition with standard economics when it comes to give advice to policy makers on issues related to the dynamic performance of the economy" [18]. The NSI approach is said to build on previous economic theories, which mainly focused on resource allocation and the efficiency with which resources, including the labor-force, are utilized [9](p.26). In contrast to the latter approaches, Lundvall suggests that: "the most relevant performance indicators of national systems of innovation … reflect the efficiency and effectiveness in producing, diffusing and exploiting economically useful knowledge” [9](p.1). He does not consider technical progress as a goal in itself and suggests that economic growth should be the main objective of innovation policy. Furthermore, economic growth indicators such as national income or consumption per capita individually may have little to do with how innovation takes place, he believes, although these maybe useful in comparing across national systems.

The perception of innovation as being highly context-specific leads some to observe that transplanting a “high performance element from one system to another” puts in doubt the performance of the element in the new system [18]. For example, Gjerding highlights that the Japanese management system as being a by-product of the Japanese culture and hence not likely to be easily transplantable in other national contexts [9](p.95-115).

Notwithstanding its stated prescriptive limitations, the NSI approach has gained significant following amongst policymakers from the OECD to the EU [14] and even some developing countries. South Africa’s is an example of a developing country that made this use explicit when in 1996 it conceptually based its science and technology policy on the NSI approach. However, Lundvall views the wide diffusion of the NSI approach in policy circles as a “mixed blessing”; since, he believes, it has in some cases led to the distortion of the idea from what it’s original proponents intended [18]. He states that this distortions “gives rise to the so called ‘innovation paradoxes’ which leaves significant elements of innovation based economic performance unexplained. He argues that in terms of analysis, such paradoxes are reflected in studies of innovation policy that focus on science-based innovation and on the formal technological infrastructure. In terms of policy, they are reflected in a bias in favor of science-based innovation and in highly problematic attempts to subordinate all academic scientific work to the logic of the market” [18]. With respect to the latter point, he cites the example of Denmark, where in some cases knowledge resulting in patents is preferred over knowledge that does not translating to patents. Factors contributing to this presumed distortion “reflect remnants of the linear model and narrow definitions of the innovation system and are reinforced by Triple Helix and Mode II production of knowledge models and, not least, by standard economics approaches to innovation” [18]. Lundvall goes on to charge that authors from the U.S. focus on innovation systems in the *narrow sense*, where they view national innovation systems as an extension of ‘national science systems’ or ‘national technology policies’. Similarly, in Europe, the ‘*narrow* *view of innovation systems*' is thought to have led to "focus on an innovation mode based in scientific progress" [18]. "The focus should be much more on people and competence and upon how the relationship and interactions between people promote learning", he asserts. "This is especially important in the current era of the globalizing learning economy where the key to success for individuals, firms, regions and national systems is rapid learning while disembodied codified knowledge flows more freely across borders" [18].

The divergence of perceptions regarding NSI, and what Cook refers to as the "massive complexity" [19] associated with the NSI approach have contributed to the propagation of other territorially embedded, but more geographically limited, approaches; most prominently that of regional systems of innovation (RSI).

2.2.2 Regional Systems of Innovation (RSI)

Proponents of the regional innovation systems conception typically extend the idea of innovation systems to sub-national regions, although there is no apparent consensus on what constitutes a region as such. Phil Cooke prefers to use the RSI approach by which "…to observe the ways in which different sectors or even clusters interact with the regional governance and innovation support infrastructures as well as the national and global levels" [19]. He goes on to say: "this will open up understanding of what kinds of interactions are primarily occurring with a regularity that would warrant the designation 'systemic' at which level, or indeed multilevels" [19]. Asheim and Isaksen reason that if learning is important for innovation, and learning itself is a social process, then it follows that geographic proximity - which presumably facilitates interactive processes - would be important for innovation [20]. The implication is that the closer the actors or stakeholders are to each other, geographically speaking, the greater the learning, and the higher the expected innovative success. The RSI approach has been criticized however by a number of authors. Lundvall states: "...I see the direct application of the core element of the innovation system – interactive learning – to the regional level as problematic. Much of the relevant interaction takes place at the national/international rather than at the regional level and other 'systemic' mechanisms may be more important when it comes to explain the formation and evolution of regional clusters" [18]. Echoing similar concerns Bathelt suggests that empirical studies on clusters, which have been used to support arguments favoring the RSI approach, have been biased in favor of exceptionally successful innovation clusters and regions [21]. He elaborates that: a) highly autonomous regions as described by Asheim and Isaksen (1997) are indeed hard to find, b) decisive institutional conditions are regulated at the level of nation states, not regions and c) regions can benefit economically by tapping into parts of value chains, which extend widely across regional borders. Other innovation systems approaches have de-emphasized geography altogether, instead focusing on other aspects that are believed to have significant impacts on technological innovation.

2.2.3 Sectoral Innovation Systems (SIS)

The sectoral innovation systems (SIS or alternatively SSI) has been defined as: "a set of activities that are unified by some linked product groups for a given or emerging demand and which share some common knowledge" [22]. Breschi and Malerba state that the SIS is: "that system (group) of firms active in developing and making a sector's products and in generating and utilizing a sector's technologies; such a system of firms is related in two different ways: through processes of interaction and cooperation in artifact-technology development and through processes of competition and selection in innovative and market activities" [23]. The SIS framework focuses on three main dimensions, including: a) knowledge and technological domain, b) Actors (organizations or individuals) and networks, and c) Institutions [22]. Breschi and Malerba [23] suggest that the SIS has three main characteristics involving: a) firms as central actors within the innovation system, b) the importance of 'selection environment' vis-à-vis competitive relationships among firms, and c) the notion that the boundaries of the system are determined by technological features. With respect to the latter, they assert that: "…the forces that account for the dynamics of SIS and shape their spatial boundaries should be found in some specific features of technologies. Such features define broad prescriptions and trade-offs and ultimately shape and broadly determine the nature and intensity of competition and selection processes, the geographical distribution of innovative activities, and the relevant boundaries of the innovative process" [23]. Carlsson also relates systemic boundaries to the nature of technologies in saying that: "the patterns and direction of innovative activity are strongly technology-related, and it is quite clear that the boundaries and contents of coherent innovation systems are to a large extent shaped by the technologies on which they are based" [24](p. 2). Malerba relates the specific features of technologies to the concept of Technological Regime (TR) [22]. According to Malerba and Orsenigo [25-27], a TR constitutes four fundamental factors including: a) opportunity conditions (likelihood of innovating for a given amount of investment in research), b) appropriability conditions: (possibility of protecting innovations from imitation and reaping profits), c) cumulativeness of technological knowledge: (degree of serial correlation among innovative activities at the technological-, firm-, sectoral-, local levels), and d) the nature of the relevant knowledge-base. With respect to the nature of the underlying knowledge, factors such as specificity, tacitness, complexity, independence, and the means of knowledge transmission are viewed to play an important role in a technological regime. Dosi observes that: "one empirically observes a significant inter-sectoral variety in the rates of technological progress, modes of search, (and) forms of knowledge on which innovation draws" [2]. He relates this differential rate of technological change across sectors and time to: a) opportunities presented by each technological paradigm, b) the degree of appropriability of innovation, which differs between industries and technologies, and c) the pattern or structure of demand facing firms [2].

Breschi and Malerba elaborate that SIS and TR may co-evolve, in that not only the SIS is influenced by technology-specific factors, the way innovative activities are undertaken can impact on the technological regime [23]. Also, more than one selection process may exist within a given sector, and "in such circumstances, the competitive dynamics may differ remarkably across groups of firms, leading to the co-existence of different SIS…(and) different industries may have different competitive, interactive and organizational boundaries which are not necessarily national" [23]. They further point out that firms in some industries may compete at the global level but have a local organization, while in other industries firms may operate at a regional level but rely on foreign firms for supply of equipment and other things. In short, "both country specific and technology specific factors affect in essential ways the sectoral as well as the spatial organization of innovative activities within given industries" [23].

Although technological regime crucially affects the structure of innovative activities, it does not negate the important role of institutions and other organizations. Breschi and Malerba suggest that the relationship between TR and SIS has three dimensions including: 1) Schumpeterian dynamics of innovators, 2) Geographic distribution of innovators, and 3) knowledge spatial boundaries of firms' innovative process, which is concerned with the geographic location of scientific and technological knowledge accessed by innovators. Schumpeterian dynamics "relates to the number, size, and concentration of innovators, their change over time, and the degree of turbulence" [23]. Technological regimes and Schumpeterian patterns of innovation are both not viewed as being static but can change over time [28].

One might conclude then that the dynamic nature of knowledge- and technology-base associated with biopharmaceutical innovation has a considerable impact on shaping industry structure and where/how related activities take place. A relevant feature of biopharmaceutical innovation is that it relies on a compilation of a diverse set of activities, expertise and technologies often sourced from different locals, often in countries. For example, the discovery stages of a therapeutic may rely on a variety of screening methods and bioinformatics, its synthesis on recombinant DNA capabilities or chemical synthesis techniques, its preclinical and clinical testing on relevant expertise in different regions/countries for access to facilities and patients, and regulatory approval dependent of awareness of pertinent regulations in targeted jurisdictions. With the exception of large biopharmaceutical firms, few companies have the ensemble of these capabilities. Indeed, even large firms are increasingly outsourcing much of these activities to specialized firms. Therefore, related innovations provide an opportunity for the often-distinct expertise and actors to pool their knowledge, and other resources, to develop a given product.

2.2.4 Technological Systems

A technological system is the defined as "the socioeconomic networks generating, transferring and utilizing technologies", and concerns itself with the flow of technology and knowledge rather than goods [24] (p.1-2). First proposed by Carlsson and Stankiewicz [29], technological systems focus on generic technologies, which have applications in many industries and are constantly in flux [15]. In general Carlsson suggests that technological systems make four key assumptions including: 1) The systems as a whole constitutes the unit of analysis, 2) the innovation system is dynamic and demands that feedbacks be accounted for, 3) that global technological opportunities are limitless (i.e. "the main focus is on how well the system can identify, absorb, and exploit global technological opportunities", and 4) actors within the system operate under bounded rationality resulting from limited capabilities and information.

2.2.5 Innovation Systems, the State and globalization

It is known that different countries vary with respect to their overall orientation towards the industry [30]. While some nations have a tendency to leave industry competition and relations with the public sector to the market, others have traditionally adopted a more interventionist approach. The general orientation of the state towards industry has undergone significant change in China, India and Brazil in recent decades. Particularly in China's case, we have witnessed an evolution from outright prohibition of private enterprise to a situation where, in some cases, government funds are flowing into private enterprises with the aim of advancing innovation. India and Brazil's responses have been less dramatic, but all three countries have adopted a more open posture towards industry.

The general, the extent and nature of state intervention in the economy is a live discourse in the literature. Viewed from an innovation systems perspective, it is clear that the state is almost always involved in the innovation process, if only by virtue of its effect on the institutional environment and/or support for basic research. Therefore, the relevant question is not whether the state should be involved in the innovation system, as it almost *always* is, but rather what sort of involvement maximizes innovative potential. Wong suggests that an appropriate mix of interventions is most desirable in the context of the post-industrial, developmental states, for which technology adoption is increasingly less of an option, replaced by the need for greater technological innovation [31].

However, in the particular case of developing countries, the extent to which the nation states can effect change in light of increasing globalization of economic activities, particularly in high-tech industries, is unclear. In examining the internationalization of innovation systems, Carlsson finds that relatively few innovation systems studies have focused on globalization of innovation systems, in part, owing to the fact that most SI studies have focused on *national* innovation systems [32]. This is in spite of broad recognition that not all institutions are national. At the same time, he finds that there is a much larger body of work related to the internationalization of corporate R&D activities. Among the latter group, Carlsson (2006) cites the work of Pavitt *et al* [33-36] concluding that most firms with internationally-dispersed operations, even large ones, tend to conduct activities that provide them with competitive advantage in their home countries – with the implication that national innovation systems, and by extension national institutions, continue to play a key role in innovation. Carlsson concludes that: “there is ample support for the claim by Pavitt that the innovative activities of firms are significantly influenced by their home country’s national system of innovation. But there is also evidence that national innovation systems themselves are becoming internationalized, even if the institutions that support them remain country-specific” [32]. He continues: “The role of tacit knowledge and the spatial limits on knowledge spillovers have caused firms to locate R&D facilities where new knowledge is being created. As their absorptive capacity increases and they learn to transfer knowledge within their organizations and in the networks and alliances in which they participate … firms become vehicles for internationalization of innovation systems” [32]. Recognizing the role of companies in globalization of innovation, Mytelka also observes that: “Without a firm grasp on the changing nature of competition in globalized industries, it is no longer possible to assess the dynamics of local innovation systems or develop appropriate policies to stimulate and support them … In building the system-wide capabilities required to access information and use new knowledge most effectively for innovation … managing the interface between the global and the local will be critical.” [37]. She argues that the *national* innovation systems approach makes a number of critical assumptions that often do not hold, particularly in the context of developing countries. These include the assumption that: a) “enterprises are more attuned to conditions and actors in the domestic market”, which in turn shapes how they respond to situations, and b) that other necessary actors/elements for innovation are generally present nationally [37]. “A static bias that does not do justice to the dynamics of industrial, technological and institutional change at the global level within which national and local systems of innovation are embedded is also common to most applications of the system of innovation concept” [37].

There are examples of how select countries have managed the global/local interface to their benefit by taking advantage of opportunities presented by globalization. Fransman states that Japan’s Ministry of International Trade and Industry: “has responded to the globalization of science and technology by retaining its objectives of strengthening both the competitiveness of Japanese companies and Japanese competencies in basic research and science; by internationalizing its national co-operative R&D programs by allowing and encouraging the participation of foreign companies; and by taking the initiative in establishing fully internationalized co-operative research programs whose objectives and modus operandi are negotiated with the other participating countries”[38]. Chang found that Taiwan and South Korea adopted effective strategies to catch up in the semiconductors area in 1990s by tapping into innovation systems in Japan and the U.S. [39]. Brazil's aircraft manufacturing sector is an example of a sector that relies heavily on foreign technology [40].

A number of authors have suggested that the system of innovation approach – and NSI in particular – may need to be adapted for use in developing countries, with some attempts taking place in this regard [3]. Notwithstanding these observations, the SI approach, as a concept, has been used to analyze and compare innovation systems across countries and sectors in both developed and developing nations [41-44].

In the area of biotechnology, the role of government policy is recognized to be of crucial importance. In the case of biotechnology Wong (2005) states that: "… cultivating biotechnology and promoting bio-industry require a state that at once facilitates collaboration while promoting competition among a range of actors. Biotechnology innovation and bio-industry commercialization also require a state that can effectively regulate knowledge creation and its application. In conceptualizing the post-industrial developmental state, then, we should be less concerned about quantitative questions of "how much" state intervention, but rather focus on the more nuanced problem of identifying the right mix of public policies aimed at facilitating technology innovation and knowledge-based industrial development" [31]. Casper's (2000) study of the German biotech sector highlights that government role is not limited to developing countries. He recommends a "*resource orchestration*" approach, through which "Government policies can develop financial subsidies, alternative technology transfer mechanisms, and other resources to create customized institutional frameworks to support particular sectors" [45]. He suggests that technology policies, particularly those aimed at firm-creation, should be sector-specific and exact their influence by providing resources and incentives to encourage participation in the given sector. In his view: "sector-specific support structures can essentially circumvent the 'normal' institutional incentives and constraints within the economy", but these incentives and constraints need to be systematically identified [45].

The interventionist perspective is in contrast to the view that treats innovation with such complexity, and the state of present knowledge in this regard so lacking, that it explicitly rules out any attempt at designing or even replicating innovation systems [14]. While such assertions seem more plausible in the context of whole economies, it is not clear whether the implied prescriptive paralysis ought to extend to industrial sectors for instance, and in particular in the context of developing countries. Such a stance would largely reduce the utility of the SI approach to its descriptive power. It has been suggested that to be of prescriptive utility in the context of developing economies, the SI framework needs to be modified to allow for "system design" [1].

Through this work I begin to ask the question of whether technology and innovation policies in China, India, and Brazil have sufficiently taken into account sector-specific dynamics as related to the biopharmaceutical sector. I essentially argue that an adaptation of the SI framework may not be necessary and that looking at innovation processes from a sectoral innovation systems perspective, as already developed by Malerba and others, may be sufficient to inform innovation policy in the emerging markets.

2.3 Global Pharmaceutical Industry Evolution

Henderson *et al* [46], 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. They credit the large-scale production of penicillin during World War II – a major research and production initiative of the U.S. government – as a major turning point for the pharmaceutical industry that eventually resulted in commercialization of many new drugs. Henderson *et al* state that:

> "The commercialization of penicillin marked a watershed in the industry's development …The period from 1950 to 1990 was a golden age for the pharmaceutical industry, as the industry in general, and particularly the major U.S. players – Merck, Eli Lilly, Bristol-Myers, and Pfizer – grew rapidly and profitably. R&D spending literally exploded and with this came a steady flow of new drugs" [46].

The above-mentioned companies, as well as a handful of others, remain dominant players in the pharmaceutical industry to date, notwithstanding competitive threats posed by the emergent health biotechnology sector in recent decades. The biotechnology industry spawned by the inception of Genentech (San Francisco, now part of Roche based in Basel, Switzerland) in1976, has come to be characterized by many small- and medium-sized enterprises (SMEs) and a relatively few large firms – including Genentech, Amgen (Thousand Oaks, CA), Genzyme (Cambridge, MA) and Biogen Idec (Weston, MA). To date, a handful of countries including: the U.S., the United Kingdom, Switzerland, Germany, and France continue to host the largest innovating pharmaceutical and biotechnology companies – although a considerable number of smaller firms exist in a number of other countries. In general, differential institutional environments have been credited for this concentration of health technology innovation in a relatively few countries [46].

Over time, pharmaceutical and biotechnology sectors have grown closer together. The slow response of pharmaceutical companies as a whole to what has been called the "revolution in molecular biology", resulted in distinct developmental trajectories for the two sectors in the 1980's and 1990's [46]. However, today these sectors are becoming increasingly integrated. Biotechnological applications are increasingly just another tool in the repertoire of the old pharmaceutical companies. There is also a significant level of collaboration between biotech and pharmaceutical companies and mergers and acquisitions have further blurred the line between the traditional pharmaceutical and biotech sectors. For all intents and purposes, what seems to be emerging is an integrated sector, particularly within the segment of companies that are focused on the discovery and development of novel health technologies. A similar trend can be seen in the emerging markets studied as well.

2.4 Industry Evolution in the Emerging Markets

2.4.1 Industry Dynamics in 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 [47]. It is estimated that the country has approximately 5,000 pharmaceutical manufacturers, who on average spend about two percent of sales revenues on R&D, compared to 14-18 percent for leading global companies [48].

Sun *et al* estimate that pharmaceuticals account for approximately 50% of all healthcare expenditures in the country, providing a ripe area for reform as part of the country's broader healthcare reform agenda now underway [48]. High drug prices have served to subsidize other hospital services ever since government cutbacks to public hospitals began in the 1980s [48], and in some cases have shown to distort physician prescribing practices [49]. Government price control mechanisms and new regulatory requirements for medicinal manufacturing in recent years have been part of efforts to provide affordable and quality medicines to the Chinese population. “Pharmaceutical policy in China acutely illustrates the dilemma of promoting both static and dynamic efficiency, or balancing cost control with incentives for innovation, that plagues health policymakers everywhere”, conclude Sun *et al* [48]. Overall, dating back to the early 1990s, which saw the institution of pharmaceutical patents, the country’s pharmaceutical industry has grown substantially. This growth has coincided with a 15-20% annual expansion of the domestic pharmaceutical market in recent years, which is forecast to make China the third largest pharmaceutical market globally in 2011 [50]. This growth has included expansion of the market for recombinant products, stimulating many firms to build capabilities in this area as well.

2.4.2 India’s Pharmaceutical Industry and Emergence of Biotech

Prior to 1970s, the Indian pharmaceutical market was relatively small in value terms and was dominated by foreign firms [51]. In an attempt to advance self-reliance in pharmaceuticals and help foster its domestic industry, the Indian government introduced two landmark pieces of legislation in 1970 related to the control of drug prices and instituting a more lenient pharmaceutical patent regime [51, 52]. These and other initiatives helped to strengthen the domestic pharmaceutical industry to the point where it is now ranked 4th globally in terms of production volume and 13th in terms of monetary value [51].

The Indian pharmaceutical industry, post independence in the mid 20th century, has been shaped by a host of government policies and initiatives, with the primary aim of import substitution via what Kale and Little call a process of ‘*indigenization*’; aimed at internalizing drug production and related capabilities [53]. These authors report that the most important policies dating back to the early 1970s included those related to: a) control of drug prices, b) adoption of a new and weaker patent regime in 1972, c) institution of a new industry licensing scheme in 1978 with the goal of enhancing capabilities within the domestic sector, d) putting in place foreign exchange control mechanisms, which in-effect reduced foreign holdings of multinational firms (MNCs) to under 40%. Together, these mechanisms led to the dominance of domestic firms in the Indian market. Kale and Little suggest that the overall contours of the Indian pharmaceutical industry followed three distinct phases, moving from ‘duplicative imitation’ to ‘creative imitation’ to ‘collaborative R&D’. The first two phases in particular are characterized by increasing capabilities of the sector in reverse engineering of drugs marketed outside India and a considerable buildup of manufacturing capacity in the country.

India was also among the first developing countries, when it identified biotechnology as an important area for advancement 1982 [52]. Upon this recognition, it constituted an organization that eventually became the Department of Biotechnology (DBT) in 1986 [52]. This organization has since spearheaded the development of biotechnology in the country and has enjoyed a growing government commitment in terms of financing for its activities [54]. In 2003, it was estimated that there were approximately 140 health biotech firms in India [55]. The country’s market for biotech-based products was valued at just over $1billion dollars in 2005 [52], and approximately $2.5 billion in 2007-8 [54]. The overall market for pharmaceutical products was estimated at approximately $US 20 billion dollars in 2008 (see Table 7.1).

The overall approach of Indian biotech/pharma firms over the past decade can be described as an ambitious attempt at building capabilities to serve the global pharmaceutical markets. Larger Indian firms such as Ranbaxy (Gurgaon, now part of Japan’s Daiichi Sankyo), Wockhardt (Mumbai) and Dr. Reddy’s Laboratories (Hyderabad) already sell dozens of medicinal products in the US, Europe and other parts of the industrialized and developing world. Today the country is estimated to have the largest number of FDA-compliant manufacturing laboratories for medicines outside of the US itself. Chittoor *et al* argue that India’s economic liberalization, beginning in early 1990s, has facilitated the reorganization of firms with the ultimate aim of internationalization [51]. While this logic is partially based on the idea that economic and political liberalization makes it easier to garner foreign investment, most Indian firms have done so through a process of “indigenous growth” over the past decade or so, with little foreign investments [51]. Indeed, as demonstrated in later chapters, this self-financing model has also been a key driver of Indian firms’ foray into the innovative landscape in recent years.

In sum, it is generally agreed that while beneficial in some respects, India’s institutional context has historically not provided an environment conducive to research and development for novel health products, and also contributed to the underdevelopment of the country's pharmaceutical regulatory capabilities [53].

2.4.3 Biopharmaceutical Sector in Brazil

Similar to the Indian industry, the Brazilian pharmaceutical sector benefited from a permissive intellectual property regime, which allowed domestic firms to copy innovations made elsewhere. Likewise, it also resulted in the emergence of an almost exclusively generic-based industry with limited or no innovative product development. After the adoption of the TRIPS agreement in 1996 and subsequent regulatory adjustments the Brazilian industry underwent a period of consolidation. However, the country's introduction of the Generics Law, enacted in 2002, gave a new lease on life to domestic firms and resulted in the domestic industry now controlling approximately three quarters of the generics market, which is itself estimated at approximately 10% of the $ 10 billion pharmaceutical market in Brazil (see Table 7.1). However, the Brazilian pharmaceutical market as a whole remains dominated by foreign firms and branded products.

In 2007, Brazil's Biominas Foundation (Belo Horizonte) identified 181 life science companies nationwide, 71 of which were classified as biotechnology companies [56]. The majority of biotech companies were reported to be small enterprises and less than 10 years old, with about 17% of them involved in the human health area. Prior to my research, almost nothing was known about innovation within indigenous health enterprises in Brazil, with respect to the extent and nature of their involvement in this endeavor and the key factors that contribute to it.

Additionally, a characteristic feature of the Brazilian context is that the state, via its public-sector institutions, undertakes many activities that are generally the purview of the private sector in most major economies. While some studies have focused on the health biotech sector more broadly [57], it was not clear how the public-sector involvement in health product development and manufacturing impacts on the private industry. This work explores the resultant dynamics across these sectors, and examines potential consequences for innovation within private companies (see **Chapter 4**).

Lastly, while previous studies have covered biotech business models in general [58-61] and with regards to biotechnology in developed nations – for example, the US[62, 63] , Italy [64], France

[65], Germany [45] and the Netherlands [66] – little comparable analysis concerning emerging markets has been conducted [67], particularly as concerned with business models of innovative firms. This work begins to examine business models to the extent that these models facilitate innovation.

2.5 Key Factors Promoting Biopharmaceutical Innovation in Industrialized Countries

Based on analysis of pharmaceutical industries in the industrialized world, Henderson *et al* , observe that: "from its inception, the evolution of the pharmaceutical industry has been tightly linked to the structure of national institutions…(that) played a critical role in generating isolating mechanisms" [46]. The authors go on to state that: "*In the post-war era, the institutional arrangements surrounding the public support of basic research, intellectual property protection, procedures for testing and approval, and pricing and reimbursement policies have all strongly influenced the process of innovation directly and the economic returns…for undertaking such innovations*" [46]. For Pisano the combination of knowledge creation and spillover, capital markets, and a market for know-how create a powerful system for innovation in high-tech sectors – although he has explored their limitations with respect to biotechnology [63](p.132). What is less clear is the extent to which these, or other factors unique to emerging markets, shape health technology innovation in these contexts. Key factors believed to facilitate innovation elsewhere are reviewed below.

2.5.1 Knowledge Creation and Transfer

Nearly all industrialized nations, and many developing countries, invest substantially in research and development, with a considerable emphasis on life sciences [68]. The emerging economies of China, India and Brazil have been increasing their R&D commitment in recent years, resulting in enhanced scientific publications and patenting records [69-71]. However, the papers just cited also reveal that the level of R&D expenditure by the enterprise sector in these countries varies substantially. It is also generally true that the public sectors in the countries studied, and many others, have historically seen their role as knowledge creators – with the implicit assumption that commercializable knowledge would eventually reach firms that can develop them further. However, recognizing that the technology transfer process – including what is often termed knowledge/technological spillover – is not automatic, there has been a growing emphasis on more active/intentional technology transfer mechanisms from universities and research institutes to industry [68]. Indeed, some consider tech-transfer to be the central activity of innovation systems, regardless of whether it happens intentionally or not [15].

While technology transfer from universities and research institutes to companies has been a major stimulator of bioscience development in key parts of the industrialized world, in-house R&D within companies is also considered an important factor for innovation. Audretsch has shown that overall R&D expenditure is associated with knowledge production and innovation within industries [72], although this trend holds strongest at the aggregate industry level and less so at the level of individual enterprises and specific lines of business [73]. Audretsch suggests that this discrepancy may be explained, in part, because knowledge resulting from R&D investments spills over to third parties [74]. Furthermore, "The model of the knowledge production function becomes even less compelling in view of the recent wave of studies revealing that small enterprises serve as the engine of innovative activity in certain industries" [74], such as biotechnology. He suggests that new knowledge for small firms appears to originate from an attempt on the part of individual scientists (and others) to appropriate value from their knowledge. Consistent with this view Zucker *et al*, have shown that U.S. universities and their faculty play a prominent role in initiating new biotechnology firms [75], in part because they are typically at the leading edge of science and there is an information asymmetry between university professors and existing firms, making it difficult for existing firms to know about new technologies and their true potential [63]. Furthermore, Audretsch and Stephan explore the role of the career trajectories and the incentive system as facilitators of knowledge spillover. These authors suggest that why and how spillovers occur depends on "the incentives confronting scientists to appropriate the expected value of their knowledge considered in the context of their path-dependent career trajectories" [74]. They conclude that; *"*spillover of knowledge from the source creating it, such as a university, research institute or industrial corporation, to a new – startup firm facilitates the appropriation of knowledge for the individual scientist(s) but not necessarily the organization creating that new knowledge in the first place*"* [74].

The research presented in this thesis adds to the literature by exploring the nature and extent of commitment to innovation by firms in the emerging markets – as indicated by their R&D expenditures and activities. It also reveals new insights into the nature of interactions between innovative companies and domestic universities and research institutes, and highlights challenges that entrepreneurs face in this respect.

2.5.2 Intellectual Property Protection

Chapter 6 explores the relationship between intellectual property (IP) protection and innovation, particularly as related to pharmaceuticals (Section 6.3.3). It also reviews key country-specific peculiarities in pharmaceutical patenting regimes for each country (Section 6.2.1). For the purposes here, suffice it to say that IP protection is generally recognized as an important factor for pharmaceutical innovation globally. Furthermore, newly instituted pharmaceutical patent regimes in China, India and Brazil – as part of their commitment under the TRIPS agreement – continue to evolve as these countries attempt to balance various interests and improve enforcement mechanisms. This research contributes to the present understanding regarding IP protection and biopharmaceutical innovation by suggesting that the realization of incentives associated with strong IP protection is highly contingent upon other institutional factors.

2.5.3 Capital Markets

In the industrialized economies public and private equity and alliances with other firms represent key sources of financing for innovative biopharmaceutical companies. Public equity offers companies the option to list in a stock exchange and raise capital from a variety of investors. However, it is usually an option more suited to mature companies. Private equity investments, particularly in the form of venture capital (VC), serves as a major source of financing for biopharmaceutical firms in developed countries, particularly the U.S. VC firms not only provide capital to existing and new firms to develop new technologies and explore new markets, but also offer management and strategic support to startups. Research shows that VCs play a very important role in the innovative process [76, 77]. Alliances among firms are another way that smaller biopharmaceutical firms have traditionally financed their innovative activities. Through these transactions, larger firms often provide smaller ones with upfront and/or milestone payments in return for marketing rights or royalties if/when products reach the market.

A contribution of this research has been to explore how health enterprises finance their innovative activities in China, India, and Brazil, and to identify key underlying reasons, and challenges in this regard.

2.5.4 Market for IP

The long gestation period and considerable costs associated with biotech innovations has stimulated the trade of biotech know-how and IP among entrepreneurs and with pharmaceutical companies. Pisano (2006) suggests that this market came about because, a) biotech firms lacked all the capabilities required to discover, develop and market drugs, so they relied on these capabilities within the established pharmaceutical companies, b) due to informational and institutional barriers, pharmaceutical companies were at a disadvantage in technology licensing directly from universities, so they used biotech firms as "middlemen in a R&D supply chain", and c) it was a reaction to the problem of *information asymmetry* that was of particular concern in the public markets. Pisano suggests that public markets were never designed to deal with R&D entities that were to have no products or revenues for years to come. Therefore, they relied on alliances between biotech firms and major players such as large pharmaceutical companies as a measure of the *potential* of given biotech firms. If a small biotech company signed a deal with a big pharmaceutical firm, typically it would be perceived to be of a higher value from investors' perspective. My research attempted to addresses this question by inquiring whether companies in China, India and Brazil planned to develop technologies fully or to license/sell their IP prior to commercialization. Furthermore, I inquired about who the most likely buyers/licensors of those technologies might be.

Notwithstanding the above observations, the very factors that are believed to have facilitated some innovations, in the U.S. and other parts of the developed world, may at the same time have a diminishing effect on firm-specific learning. Pisano (2006) suggests that a few factors serve to restrain industrial learning including: a) the short time-span of venture capital (VC) investments, which means that they are interested in a liquidity event in a few years hence not necessarily interested in firm learning, b) new firms need to succeed on their first attempt(s) to hit a commercial success, otherwise they fail and will not have the opportunity to accumulate experience over a long period of time, and c) the market for IP and know-how (through alliances between firms) tend to be very short-lived, meaning that typically alliances last a few years and if milestones are not met these relationships often terminate, adversely impacting firm learning. Pisano further points out that often all these mechanisms are at work simultaneously and negate firm and industry learning. To the extent that the emerging biopharmaceutical sectors in China, India and Brazil rely on similar approaches for innovation they may be impacted in similar ways. It can be stated however, that notwithstanding the potentially adverse consequences for learning, VC involvement and firm alliances as models of financing for innovation are highly desired, and are increasingly being adopted in the emerging markets studied.

In the context of developing countries, after studying pharmaceutical development in India, Cuba, Iran, Egypt, Taiwan and Nigeria, Mytelka [6] concluded that four types of policies supported innovation processes. These included policies that: a) strengthened the knowledge base, b) stimulated capacity building, c) created space for companies to emerge, and d) provided incentives for innovation.

2.6 Health Technology Innovation for the Poor

It is widely recognized that the prevalent pharmaceutical innovation model, with the dominance of pharmaceutical MNCs, has not adequately addressed health technology needs of poor market segments in the developing world. The result has been a failure to address a set of diseases that have come to be known as neglected diseases. The basic presumption by business has often been that these diseases, as well as some small-market diseases in the developed world, do not provide sufficient monetary market potential to justify pharmaceutical company expenses to address them.

A number of arguments and approaches have emerged in recent years to compensate for this market failure. Previous efforts to advance global health have included the formation of a variety of public-private-partnerships (PPPs) [78], advance market commitments (AMCs) [79, 80], priority review vouchers [81], patent pools to share intellectual property [82], and formation of funds to finance related activities such as the Global Fund to fight malaria, tuberculosis and HIV (www.theglobalfund.org). Most of the above efforts are fairly recent undertakings, but arguably they will not be sufficient to address existing and emerging needs of poor markets in a sustainable fashion.

Another line of argument put forth most prominently by the late C.K. Prahalad has suggested that large global companies can address poor markets in a profitable fashion [83]. Indeed one of the core arguments used to rationalize TRIPS adoption by developing countries was that it would create a larger pool of patients suffering from concerned diseases, making it more likely that pharmaceutical companies would address their needs. Kyle and McGahan find that contrary to these arguments, TRIPS adoption has not stimulated greater investments by large pharmaceutical MNCs in diseases of poverty [84].

An area that has thus far been largely, though not entirely [85], neglected in the literature and to which this work makes contributions to, is the potential role that indigenous companies in the emerging markets can play with respect to innovation in health technology targeted at the poor, and factors that may help to realize this potential.

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Chapter 3
Research Approach

3 Research Design and Methodology

3.1 Research Design

This is a *qualitative, multiple-case* (or multicase) study of health technology innovation by indigenous companies in China, India, and Brazil. As such, "*health technology innovation within emerging market enterprises*" is the central phenomenon under investigation, and constitutes what Robert E. Stake calls the *quintain*, which he likens to the elephant in the proverbial blind men describing an elephant [1](p1-16). Stake says:

> "*Multicase research starts with the quintain. To understand it better, we study some of its single cases – its sites or manifestations. But it is the quintain we seek to understand. We study what is similar and different about a case in order to understand the quintain better*" [1](p.6).

I find the concept of quintain, as conceived by Stake, a useful notion that captures well the approach I have adopted for this work. As such, each of the country cases (China, India and Brazil) contributes to understanding how health technology innovation takes place in the context of emerging markets, and developing countries more broadly.

Below, I elaborate further on the key components of the chosen research design and provide a brief rationale for their selection.

3.1.1 Research Paradigm

Cresswell [2] identifies three types of research designs including: quantitative, qualitative and mixed-methods. Quantitative study design generally aims at testing a hypothesis or theory and allows the researcher to control certain variables. The intent is often to establish cause and effect between two or more variables or to draw conclusions about associations among them. It uses a *deductive* mode of inquiry with the strengths to generalize and replicate findings [2] (p. 3-21). Qualitative research on the other hand, is "a means for exploring and understanding the meaning individuals or groups ascribe to a social or human problem" [2] (pg.4). It uses an *inductive* data analysis approach to build general themes from specificities of contextual data, and is generally considered to be more subjective as it involves researchers interpreting the data. Mixed methods designs combine qualitative and quantitative forms to overcome limitations associated with either design individually. Mixed methods requires that researcher(s) themselves collect both the quantitative and qualitative data, either concurrently or in a sequential fashion, and to use both data sets for interpretation [2] (p. 3-21).

I have adopted a qualitative research approach for a number of reasons. I sought to understand how innovation takes place within contexts that cannot be controlled, and on a topic that has not been well studied in the settings concerned – both of which favor a qualitative design [2] (p. 3-21). Also, qualitative research can help us understand a phenomenon of interest in its complexity, to identify areas that need to be influenced, and to see the consequences of policy intervention in real life [3](p.10) all of which are important aspects of my inquiry into health technology innovation in the countries concerned and the impact of institutions in this regard. Qualitative research uses inductive thinking, aimed at understanding a larger phenomenon (in this case health technology innovation at a national level) by studying smaller components (i.e. specific firms and institutions) [4] (p. 93-100). Therefore, the qualitative research paradigm as an analytic framework allowed me to address the core objectives of the proposed research.

Cresswell suggests that the researcher's generalized orientation, or what he calls philosophical worldview, shapes the approach he/she takes towards conducting a research project. He states that there are four generalized philosophies including: postpositivist, social constructivist, advocacy and participatory, pragmatism [2](p. 5-11). My research is most closely aligned with the social constructivist view since I have: a) relied "as much as possible on the participants' views of the situation being studied", b) used open-ended questions to gather relevant insights and allow participants to express their views, c) not started with a theory, but rather worked inductively to interpret how study participants view issues related to health technology development, and d) tried to develop an appreciation for the broader context and settings of participants by conducting interviews primarily in the premises of the interviewees and gathering the information personally [2](p. 5-11).

3.1.2 Case Study Approach & Unit of Analysis

Within the context of a qualitative approach, I have chosen the case study approach as the main research strategy for this enquiry. The case study approach has been used to describe a specific entity, phenomenon or event, to test theory or even to generate theories [5]. Robert K. Yin defines a case as "an empirical inquiry that investigates a contemporary phenomenon in depth and within its real-life context, especially when the boundaries between phenomenon and context are not clearly evident" [6] (pg.18). Yin goes on to state that: "case study inquiry copes with the technically distinctive situation in which there will be many more variables of interest than data points …(and it) relies on multiple sources of evidence, with data needing to converge in a triangulating fashion" [6] (pg.18). Furthermore, case study research is more appropriate for answering "how" and "why" questions as opposed to "what" and "how many" questions, which tend to be exploratory in nature and are best addressed using other research strategies [7](p.1-18). Case studies are generally divided into two main categories including: *intrinsic* and *instrumental* case studies [8]. In intrinsic case studies, research is conducted on a given case with the sole purpose to understand the case itself. In instrumental case studies however, particular case(s) are studied mainly to understand an issue or phenomenon, not necessarily the case itself. In other words, in instrumental studies "the purpose of the case study is to go beyond the case", in contrast with *intrinsic* case studies, in which the case itself is of main interest [1] (p. 8). While, the first objective of multiple-case studies is to understand individual cases, the ultimate objective is to understand the quintain, or the main issue or phenomenon under study. Indeed, it has been suggested that the researcher faces a case-quintain dilemma, where s/he "*is pulled toward attending more to both the pieces and the whole…The pursuit of science seems to place the highest value on the generalizable, and the pursuit of professional work seems to value the particular most, but they both need both. For the multicase researcher this is a dilemma*." [1](P.7). Indeed, this has been an ongoing dilemma for me as well. On the one hand, I have tried to understand each case as well as possible, while including a significant number of cases (both country and company cases) to increase confidence in findings. On the other hand, I have been drawn into more literature-based and theoretical information, analysis of broader industry dynamics and globalization effects, as well as country-specific peculiarities, all of which have the potential to impact on technological innovation in the contexts under study.

An instrumental, multiple case-study approach was found most appropriate in the context of this work. This is because it: a) aims to study a contemporary phenomenon in its real life context involving innovating firms, b) addresses key research questions that involve "how" and "why" questions, c) involves a number of country and company cases, and d) entails the use of multiple data sources to inform the study. In multiple-case study designs each case can teach us about itself as well as other cases, and helps to move from the specifics of each case to more general observations [9]. I was therefore not only able to understand innovation in given countries by examining nested country cases, but also to examine certain themes collectively and comparatively across the three countries concerned.

Furthermore, this research has both exploratory and explanatory components. The exploratory aspect has allowed me to gain a general understanding of each country's innovative health biotechnology sector by focusing on individual company cases. For instance, a key question in this regard was to determine specific innovative products/technologies within companies and to analyze related trends in this regard (see **Chapter 5**). Another important exploratory dimension has been to identify specific institutional factors that either support or hinder innovation within enterprises. The explanatory aspect involved a deeper analysis of factors that influence observations made in the exploratory phase. For instance, **Chapter 6** essentially answers the question 'why has the entrepreneurial response in terms of undertaking innovative activities not been stronger than we presently observe, years after adoption of the TRIPS agreement'.

Notwithstanding the above observations, the individual firm constitutes the main unit of analysis for this study. This is, in part, because firm-specific data constitute the main source of data; it is where I initiated my inquiry and analysis, and it has often been the vantage point from which I have viewed the various factors that impact on innovation. In this context, I have viewed each country case as an aggregation of data obtained from firms within that country as well as institutional insights gained from interviews and other sources. Choice of the firm as the primary unit of analysis is also in recognition of the central role, which these organizations play within broader innovation systems. Bengt-Åke Lundvall, a key proponent of the Innovation Systems framework, suggests that analysis of firms in developing nations constitute a viable first step in adapting the SI approach for use in the developing world [10]. By studying firms he suggests one can get an idea for the boundaries of the innovation system, which can ultimately advance understanding of its constituent elements and deficiencies.

3.2 Research Methodology

Below, I review the overall methodological approaches that I have utilized for this work, but I digress momentarily to say that I have throughout tried to be cognizant of the assertion by Stake that: "good research is not about good methods as much as it is about good thinking" [11](p. 19). "Perhaps the simplest rule for method in qualitative casework is this: place your best intellect into the thick of what is going on" he states years later [8]. I have found that to engage in the epistemological immersion necessary for sufficient understanding requires that one is: a) not bound by strict methodologies - as important as these are, b) sufficiently familiar with the basic features of the phenomenon under study to appreciate important nuances, and c) not encumbered by ideological baggage that can unnecessarily limit exploration or understanding.

3.2.1 Study Settings

This study is focused on the three emerging economies of China, India, and Brazil. These countries are three of the world's largest, most populous, and fast-growing economies, with rapidly expanding biopharmaceutical markets. Selection of the stated countries as country cases is relevant to the exploration of the quintain, which is health technology innovation in emerging markets. By studying them I have aimed to develop an appreciation for national, regional and political influences on health technology innovation. While different in important ways, the three countries have undertaken significant initiatives in recent decades to build capacity in health biotechnology innovation. Therefore, this study was an opportunity to, in part, explore what achievements made thus far and identify policies and strategies that have influenced outcomes. As such, focusing on these countries provided an opportunity for closer examination of the interplay between the domestic institutional context, industry structure at both local and global level, and firm behavior and how this interaction impacts on the capabilities of firms, and by extension of countries with respect to innovation.

3.2.2 Data Collection

In general, data collected for this study was intended to inform analysis at two levels; individual company cases and country cases. Data for company cases was collected from interviews with senior executives, other firm-specific documents, websites and pertinent publicly available information, and direct observation of firm facilities/activities. The latter was possible in approximately two-thirds of the cases as certain firms did not provide access to their laboratory facilities or interviews were conducted off-site – often at company headquarters. Data related to analysis at the country-level (i.e. country cases) include; a) the aggregate of firm-specific data related to the group of firms studied in each country, b) interviews with institutional informants involved in or informed about health technology sectors in each country, as well as relevant publications, policy documents, and governmental agency websites.

Overall, I have personally conducted interviews with 87 participants from 45 companies and 29 other individuals/organizations as elaborated in **Table 3.1 and Table 3.2**, below. Primary data was collected through site visits and semi-structured, face-to-face (except 5 conducted over the phone) and interviews. Interviews generally lasted about 90 minutes, were digitally recorded (with a few exceptions), and most often took place at the premises of the interviewee. Where interviewees wished not to be recorded written notes were taken.

Research questions specific to the study can be found at the interview guide provided in **Appendix A.** These questions were used as a guide and were adapted according to the situation or the informant being interviewed, while addressing as many of the key areas of interest as possible. Questions for institutional informants essentially inquired about: a) their personal and/or organization's role/mandate, how their activities relate to health technology innovation, what factors they considered to be the main barriers and incentives for innovation in their country, and what policies they would recommend to advance innovation within domestic health enterprises.

Primary data collection was conducted in two phases as follows.

> **Phase I:** This was a country case study of health biotech sector in Brazil, as published in the in the *Nature Biotechnology* journal and reproduced in **Chapter 4**. Related interviews were conducted between the fall of 2006 and the spring of 2007.

Phase II: Company and institutional informant interviews in China and India (Listed in **Tables 3.1 and 3.2**) were conducted from April-September, 2009. In addition, 5 telephone interviews were conducted with Brazilian companies and informants in late 2009 and the spring of 2010. The latter were to update my insights on Brazil and note any changes that may have been made within key innovative companies over the past few years prior.

Over the past few years I have maintained contact with a number of study participants as a way to keep abreast of changes taking place and have tried to monitor others company's activities indirectly to note important changes during the study period.

In addition to primary data that I collected myself in all three countries, I have benefited from involvement in a two previous studies related to India and China, for which primary data was collected by a colleague. I was a co-author on these studies, which have been published in the *Nature Biotechnology* journal [12, 13]. These studies reported on 21 Indian and 22 Chinese health biotech enterprises. I have reproduced these publications as appendices (**Appendices C and D)** in this dissertation as they are pertinent to some of the discussions presented in this thesis, provide some relevant background for this work, and have contributed to my overall understanding of the biopharmaceutical sectors in the countries concerned.

Subsequent to the publication of the above cited papers on China and India, I personally went back to conduct more interviews in these countries (referred to as Phase II above) in order to: 1) develop a first-hand and deeper understanding of these countries and address new research questions, 2) interview additional firms that were developing novel technologies, but had not been included in the initial studies, 3) interview select institutional informants in these countries to better understand the contextual dynamics of biopharmaceutical innovation, and 4) note the evolution of innovative activities within some of the firms we had studied for the original studies in China and India [12, 13]. Overall, 9 Chinese and 8 Indian companies that I personally interviewed had been included in the two previous studies.

Therefore, data for this research originated from multiple data sources and relied on several data collection techniques, as suggested by Cresswell [2] and Yin (2003) [7]. Primary interview data were collected during three trips to Brazil, two to China and one to India.

I re-iterate that different manuscripts included in later chapters have sometimes relied on different subsets of the overall dataset mentioned above, or may have used a somewhat different dataset (**Chapter 5**). Where applicable, these have been highlighted within these respective chapters themselves.

Table 3.1 List of Companies in China, India and Brazil that I Interviewed for This Research.

Country	**China (16)**	**India (10)**	**Brazil (19)**
Companies Interviewed	Beijing Haiyan Pharmaceutical (Beijing) Beijing Wantai Biological Pharmacy Enterprise (Beijing) CapitalBio Corporation (Beijing) FusoGen Pharmaceuticals (Tianjin) Hutchison MediPharma (Shanghai) HD Biosciences (Shanghai) Kanghong Pharmaceutical Group (Chengdu) Shanghai Ambrosia Pharmaceutical (Shanghai) Shanghai Genomics (Shanghai) Shanghai Sunway Biotech (Shanghai) Shenzhen Chipscreen Biosciences (Shenzhen) Shenzhen Tiandakang Gene Engineering (Shenzhen) SiBiono GeneTech (Shenzhen) Simcere Pharmaceutical Group (Nanjing) Sinovac Biotech (Beijing) Zensun Sci. &Tech. Co., Ltd. (Shanghai)	Avestha Gengraine Technologies (Bangalore) Advinus Therapeutics (Bangalore) BigTec Laboratories (Bangalore) Jubilant BioSys (Noida) Lupin Pharma (Pune) Piramal Life Sciences (Mumbai) Panacea Biotec (Delhi) Suven Life Sciences (Hyderabad) Transgene Biotek (Hyderabad) Wockhardt (Mumbai)	Aché Laboratories (São Paulo) BioCancer (Belo Horizonte) Biolab Sanus Farmacêutica (São Paulo) BioGene (Recife) BIOMM Technology (Belo Horizonte) COINFAR (São Paulo) Cryopraxis Criobiologia (Rio de Janeiro) Eurofarma Laboratórios (São Paulo) FK Biotecnologia (Porto Alegre) Hebron Farmacêutica (Recife) Intrials Clinical Research (São Paulo) Katal Biotecnológica (Belo Horizonte) Labtest Diagnóstica (Lagoa Santa) Nortec Química (Rio De Janeiro) Pele Nova Biotecnologia (São Paulo) Recepta Biopharma (São Paulo) Scylla Bioinformatics (Campinas)

			Silvestre Laboratories (Rio de Janeiro) União Química (São Paulo)

Table 3.2 Institutions and Organizations whose Representatives Participated in this Research as Key Informants

Country	**China**	**India**	**Brazil**
Participating Institutions	The TORCH Program Beijing Municipal Bureau of Industrial Development Beijing Pharma and Biotech Centre Shanghai Science and Technology Commission Centre for BioPharmacy and Agriculture (Part of Shanghai S&T Commission) State Food and Drug Administration China Medical Biotech Associations Shanghai Bio-Industry Association BioVida Venture Morningside Technologies Venture Shanghai Pudong S&T Investment Co., Ltd. (Government Funding body) Zhangjian High-tech Park (Shanghai) Shanghai Pharm Valley Corp.	Department of Biotechnology (3 Informants) National Pharmaceutical Pricing Authority Association of Biotechnology-led Enterprises (ABLE) Confederation of Indian Industry (CII) Dr. R.A. Mashelkar (Former head of CSIR, now at National Chemical Laboratory) Dr. Ganguly (National Institute of Immunology, Formerly head of ICMR) Dr. Sachin Chaturvedi (Researcher at Research and Information Systems for Developing Countries, Delhi)	Biominas Foundation The Butantan Institute (2 Informants) Biomanguinhos* (2 Informants) Farmanguinhos* Centre for Development of Technologies in Health (CDTS)*

* These are three institutes within the Oswaldo Cruz Foundation (Fiocruz) that are involved in development and manufacturing of health products.

3.2.2.1 Selection of Cases

It is well recognized that proper case selection is imperative for understanding the phenomenon under study [1, 14-16]. For Stake, in the context of multiple case study research, the chosen cases need to be similar in some ways, be relevant to the quintain, provide sufficient diversity across cases, and present "good opportunities to learn about complexity and contexts" [1] (p.1-23).

To achieve the above objectives, purposive sampling was used to select not only the countries to study, but also specific companies within them. The rationale for selecting specific countries was provided above, under section 3.3.2. These country cases were informed by a group of company cases, which a) were based within the particular country concerned, b) whose majority shareholders were citizens of the given country, and c) whose activities were related to the discovery and development of vaccines, diagnostics and therapeutics. Company case selection was made with these key criteria but the chosen firms were otherwise diverse with respect to geography, core technological focus area(s), other activities and capabilities not directly related to innovation, ownership structures, history, age, local context and so on. The approach taken to select the final cases was essentially based on the approach proposed by Yin, which involves screening "candidate" cases and choosing the best cases among them [7].

To illustrate more specifically, my approach for the Brazil study (**Chapter 4**) was to first make a database of all companies that I could find, which met conditions a, and b (this resulted in a list of over 100 enterprises). I then looked for and recorded any information that indicated whether a given firm undertook innovative activities. The latter was complemented by consultation with individuals knowledgeable regarding domestic health enterprises. These efforts helped me to identify an initial half-dozen companies, which were then instrumental in identifying more firms along with other local informants that I met as I travelled through Brazil. It is important to note that prior to my study, no government or industry association that I contacted even had a comprehensive list of domestic companies and the various informants I consulted often had knowledge of a relatively small number of firms. Fortunately, identifying appropriate firms in India and China was somewhat easier due to the availability of more public information and our previous work and contacts in these countries. However, the general approach for firm selection in China and India was the same as that of Brazil, although making a comprehensive list – as I did in Brazil – at the outset was not a viable strategy due to the large number of domestic firms in these countries. These are intended to highlight the challenges that one often faces when conducting research in developing countries, especially in an under-studied field, and the flexibilities required to adapt to such conditions. In this respect I disagree with Yin, who states that: “The goal of the screening procedure is to be sure that you identify the final cases properly prior to formal data collection” [6](p.91). Data collection from initial cases was indeed the best and most reliable source of identifying subsequent cases, an approach often referred to as the snowballing technique.

3.2.2.2 Selection of Other Key Informants

Key institutional informants were chosen to provide a broad perspective of the institutional landscape in each country. Informants are comprised of individuals who had significant expertise with respect to the institutional environment related to the advancement of innovation in general and health technology in particular. As such, these informants were a diverse group including policy makers, academics with expertise on the subject matter, industry-association representatives, representative of key governmental funding institutions, and venture capitalists. A list of participating individuals/organization can be found in Table 3.2, above.

It is noteworthy that firm representatives were also asked questions related to their institutional environment as relevant to them. Therefore, inclusion of non-firm informants was merely to complement insights from company representatives, triangulate the insights gained and better understand the institutional backdrop in each country.

Firms and individual/organizational participants were identified through extensive search of publicly available information as well as consultation with individuals familiar with the sector in the countries concerned. In addition, interviewees were asked to identify other individuals, companies or organizations that would be suitable candidates for this research. Once identified, interviewees were invited to participate in the research through an invitation letter, and where necessary through follow-up phone calls.

3.2.3 Data Analysis

Interview recordings were transcribed, coded, and analyzed using qualitative research methodology. Thematic network analysis as described by Aattridge-Stirling [17] was utilized as a tool to organize and analyze interview data. “Thematic analyses seek to unearth the themes salient in a text at different levels, and thematic networks aim to facilitate the structuring and depiction of these themes” [17]. Once various themes were identified from coded text and refined, a thematic network was constructed to arrange themes in a manner that linked them in logical networks. In thematic analysis, themes generally operate at three levels: *basic* themes, *organizing* themes and *global* themes, which have parallels in other coding approaches, such as in grounded theory as discussed by Strauss and Corbin [9]. Basic themes are the lowest-order themes emerging from textual data. Organizing themes are middle-order and serve to organize basic themes into clusters of related issues. Global themes are "super-ordinate themes that encompass the principal metaphors in the data as a whole" [17]. These themes are then depicted as a network, a mind-map of sorts, to help decipher meaning and insights. For example, a simplified map of entrepreneurial barriers to health product innovation in a given country could be constructed to place "barriers" as a global theme, "financial" as an organizing themes, and aspects related to the state of "venture capital industry" and "macroeconomic context" as basic themes. Refinement, description and exploration of the established thematic networks and the relationships between the various parts of the network and themes were helpful in describing the context and deducing novel insights.

3.2.4 Data Validation

To enhance data validity and reliability, I have utilized a number of approaches. Most of these efforts can be captured under the umbrella of data triangulation, which is essentially "a process of repetitious data gathering and critical review of what is being said" [1](p. 34). My approach has been to:

a) Complement interview findings with descriptive and quantitative indicators identified from key documents and relevant publications to maximize the comprehensiveness of data and enhance reliability

b) Use within-case triangulation by ensuring for instance that assertions made during interviews are in line with knowledge gained through observation of company facilities or other information at hand. Where I noticed important discrepancies I attempted to resolve them by seeking clarification.

c) Use cross-case triangulation by testing new or unusual assertions with other research participants. In many occasions I added additional questions to my basic interview guide to enquire about such aspects. Often these led to new and significant insights, while on other occasions they pointed to relevance of the issue for a subset of cases or the individual case.

d) Study as many cases as reasonably possible. I have done this not only through selecting a significant number of company cases in each country to study firsthand, but have also reviewed and analyzed pertinent interview data collected by colleagues.

e) Fact-check selected information with study participants. This was, in large part, to ensure data submitted for publication were accurate and up to date.

f) Lastly, to submit resulting manuscripts (presented as chapters in this dissertations) for publication in peer-reviewed journals. The anonymous peer-review process has been an important test of the insights deciphered and presented, and has often served to improve them considerably.

3.3 Research Ethics

Ethics approval was obtained from the University of Toronto Research Ethics Board for all phases of this research. Written, free and informed consent was obtained from almost all participants before interviews proceeded and after the details of the study and the nature of their participation had been explained. In a few cases, interviewees verbally consented to participate but did not feel comfortable signing a consent form. All digital files and transcripts are kept on secure, password-protected computers and only accessible to the research team. All back-up files are stored in a locked cabinet at the McLaughlin-Rotman Centre for Global Health. All interviewees were informed that the information provided may be used in publications and public presentations and consented to this through the signed consent form. However, I also made it a practice to inform interviewees verbally that if we were to attribute specific quotations to them in publications, we will seek their prior consent. A copy of the consent form used for this study is provided in **Appendix B.**

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Chapter 4
Health Biotechnology in Brazil

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4 Brazilian health biotech-fostering crosstalk between public and private sectors

4.1 Introduction

Brazil boasts world-class biomedical science, but tension between the public and private sectors hinders progress in health biotech innovation.

The Brazilian health biotech sector has made considerable progress in recent years toward becoming truly innovative. This sector comprises private enterprises as well as government-controlled institutes and is involved in the development and/or provision of health products for human consumption. To address the sizeable demand for health products for Brazil's 190 million people, many of whom live in poverty [1], the country has taken several concrete steps, legislative and otherwise, to build upon its innovative capacity in health. In recent years, increasing emphasis has been placed on the role of the private sector as a means of complementing public-sector efforts in accelerating health product innovation and provision.

In previous studies, we explored the health innovation systems of seven developing nations, including Brazil [2]. The Brazil case study highlighted the considerable scientific strength within Brazilian universities and institutes as well as some of the challenges hindering biotech innovation [3]. In the present study—similar to previous work characterizing the private health biotech sectors in India [4] and China [5]—we use qualitative research methodology (see supplementary methods at the end of this document) to conduct case studies of 19 domestically owned Brazilian health biotech firms (**Table 4.1**) and four public institutes. Purposive sampling was used to select a diverse group of firms and government-affiliated institutes covering a wide range of activities related to the development and production of health products. The firms and institutions undertaking innovative activities or following innovative business models were of particular interest. The Butantan Institute (São Paulo) and the three other public institutes, which are all part of the Oswaldo Cruz Foundation (Fiocruz; Rio de Janeiro), were included because they play a major role in the development and provision of health products for the Brazilian population, increasingly collaborate with the private sector and undertake many activities that are characteristic of private enterprises in most other countries. They thus enrich analysis *vis-à-vis* the private sector and help develop a more complete understanding of domestic capabilities to address local health needs and develop novel products. A total of 23 individuals from 19 private firms and 6 key interviewees representing the four public institutes participated in the study.

Our primary objective was to develop a broad understanding of the overall state of the domestic health biotech sector in Brazil and identify current challenges and opportunities facing this industry. As the majority of interviewees were drawn from the private sector, the views highlighted here may more closely reflect their perspectives and reality. Although divergent views may exist regarding some of the material presented here, this paper is primarily concerned with exploring factors that have an impact on the private sector. Inclusion of both public and private entities in the study has allowed us to make observations regarding the overall impact and effectiveness of the seemingly dual-purpose policy of the Brazilian government to develop a robust private sector alongside its chain of public sector health product developers and manufacturers. We also make a series of recommendations, targeted at both the Brazilian government and the country's domestic health biotech industry to help address some of the remaining challenges. To our knowledge, this study is the most comprehensive and systematic analysis of the barriers and opportunities facing the Brazilian domestic health biotech entrepreneurial sector to date.

4.2 Economy and legislative context

Over the past decade, Brazil has laid a strong foundation for overall economic growth as well as health biotech development. The trends of decreasing the public debt to gross domestic product (GDP) ratio since 2003, historically low inflation and overall macroeconomic stability are expected to facilitate the country's continued growth [6]. The market for health products in general has also witnessed significant growth over recent years, with generic medicines leading the way.

For many years, the lack of a patent regime for pharmaceutical products in Brazil contributed to the emergence of a domestic industry characterized by a strong focus on off-patent and copycat medicines. In 1996, however, the adoption of the World Trade Organization's (WTO; Geneva) Trade Related Aspects of Intellectual Property Rights (TRIPS) agreement, which was followed by the reintroduction of medicinal patents a year later, forced many of these generic companies out of business. Nevertheless, Brazil's domestic health biotech sector today remains dominated by a few domestic generics manufacturers, including Aché Laboratories (São Paulo), Eurofarma (São Paulo) and EMS-Sigma (Hortolândia). Even these large generics firms are, however, increasingly cognizant of the importance of innovation as a strategy for future survival and growth.

Despite the continued overall market dominance of the generics sector, a recent report by the Biominas Foundation (Belo Horizonte) (http://www.biominas.org.br/) depicts a young and growing domestic biotech sector that is mostly populated by small- to medium-sized enterprises (SMEs). Although most Brazilian biotech SMEs focus on agricultural applications, some small firms are also focusing on innovative health biotech. The overall contribution of such companies, however, is relatively meager compared with the needs of the country's vast population for sustainable and affordable health products. Therefore, in an attempt to foster growth of more homegrown innovation, Brazil is trying to strike a better balance between its public and private sectors. Having focused mostly on the public sector over the past decades, it is now paying increasing attention to the role of its domestic private sector in health.

Several legislative changes in recent years have helped to create significant momentum for the development of the health biotech sector and continue to reshape this industry. The implementation of a new patent law in 1997, in compliance with the WTO's TRIPS agreement, has necessitated a transition to business models that position companies as innovators, developers or, at the very least, licensors of proprietary products. In particular, the national government has recently introduced two pieces of legislation to accelerate technological innovation: the Innovation Law and "the law of the good," implemented in 2005 and 2006, respectively. These statutes have provisions for sharing of intellectual property and other resources between public and private entities and allow direct support of R&D activities in private enterprises [7]. The latter approach builds on an initiative by the São Paulo state funding agency (FAPESP), which, through its Technological Innovation in Small Businesses (PIPE) program, has already spent >$29 million between 1997 and 2005 on over 400 projects [8]. The objectives of these initiatives are to promote technological innovation in all areas, especially through collaborative projects between the public and private stakeholders. They also act as incentives to boost overall business R&D expenditure, which in the year 2004 was estimated to comprise only 40% of the total national expenditure for this purpose [9]. Government R&D expenditures in Brazil represent 58% of the total national expenditure, which was estimated at 0.91% of GDP in 2004 [9]. Comparatively, in the Organization for Economic Cooperation and Development (OECD; Paris) countries, businesses finance, on average, >62% of national R&D expenditures, which in 2005 was equivalent to 2.25% of GDP [9]. It is not clear what the present R&D contribution of the domestic health biotech sector in Brazil is as a portion of total national expenditure.

4.3 Products and services

A range of private companies in Brazil, together with prominent public research institutes, play a role in providing health products for the population. Indeed, most of the companies in this study are increasingly focusing on innovative diagnostics or drug products that are affordable and easy to use. With the exception of service companies, who often engage foreign clients, few companies report exporting products outside of Brazil to any significant degree.

Brazilian health biotech SMEs interviewed in this study regard local health needs, and more broadly neglected diseases, as viable market entry points. In general, many tend to view innovation as intrinsically linked with issues of access to health products. For example, Fernando Kreutz, president of FK Biotecnologia (Porto Alegre) puts it this way: "What you call neglected diseases, I call a business opportunity." William Marandola, project manager at the Consortium of Pharmaceutical Industries (COINFAR; São Paulo) also suggests that the increasing attention to neglected diseases by prominent nonprofits, such as the Bill and Melinda Gates Foundation (Seattle), presents Brazilian SMEs with an ideal opportunity to build up their international linkages. According to Leonides Rezende of Katal Biotechnológica (Belo Horizonte), adapting existing technologies in Brazil to local conditions and markets can be a viable business strategy for small firms. "In Brazil, and also in other developing countries, we have to redefine the term modernity," he says. "What's modern here in Brazil? For instance, although ELISA [enzyme-linked immunosorbent assay] technology is about 25 years old, in Brazil the development of simple ELISA kits is a modern approach to diagnostics." There is no reason to develop a product that already exists, he adds, "unless you have a social need for that product and the price is very high...so you develop this technology to give your people access."

Apart from the types of activities mentioned above, several other Brazilian health biotech firms are providing contract services—either to local entities or to multinationals. In the following paragraphs, we describe the main types of products and services under development in the Brazilian health biotech sector: vaccines, diagnostics and reagents, therapeutics and services.

4.3.1 Vaccines

Currently, two government-owned vaccine manufacturers, namely the Butantan Institute tied to the Secretary of Health of the State of São Paulo and the Immunobiologicals Technology Institute (Rio de Janeiro) better known as Biomanguinhos, which is part of the Oswaldo Cruz Foundation, are the primary suppliers to the Brazilian Program for National Immunization (PNI). The veterinary and private human vaccine markets are primarily the domains of multinational firms and we do not discuss them here. Production of vaccines by the Butantan Institute and Biomanguinhos is determined by the forecasts of the PNI, and the prices at which they are procured must be comparable to those set by the Pan American Health Organization (PAHO; Washington, DC) or United Nations Children Fund (UNICEF; New York).

Between the years 2003 and 2006, the Butantan Institute produced 588.6 million doses of different vaccines using technology developed in-house and filled 73 million doses of inactivated trivalent influenza vaccine, using hemagglutinin surface glycoprotein antigens from different viral strains acquired from outside. The institute manufactures ~80% of the domestic human vaccine antigens in Brazil and has recently built a production facility for influenza vaccine in an effort to reduce the country's dependence on imports. Its product portfolio includes several vaccines (modified diphtheria-pertussis-tetanus (DPT) vaccine, recombinant hepatitis B virus surface antigen (HBsAg) vaccine, inactivated rabies vaccine and others) as well as several types of hyperimmune sera and antitoxins. During the same period, Biomanguinhos produced 127.1 million doses of yellow fever and Bacille Calmette Guérin (BCG) vaccines using its own technology and filled 375.2 million doses of vaccine together with Ataulfo Paiva (Belo Horizonte), the active ingredient for which was purchased from other firms. Products offered by Biomanguinhos include vaccines (yellow-fever, *Haemophilus influenzae* type b (Hib), meningitis and others) and diagnostic kits (including immunodiagnostics for HIV, Chagas disease, leishmaniasis, dengue and hepatitis B). The supply of affordable vaccines to the PNI by the two organizations mentioned contributes to vaccination coverage of nearly 100% of the population for most routine vaccines [10].

Innovative activities within these public institutes have had a major impact on local and global health needs. Biomanguinhos' live attenuated yellow fever virus vaccine (17D) not only benefits its own population, but is also supplied to UNICEF and PAHO for use in many other countries. It continues to invest in projects, both within and outside Fiocruz, to enhance its capabilities and product portfolio. Elsewhere, the Butantan Institute's research activities have led to in-house development of several vaccines and other immunologicals, and improvements in others. For example, by removing a lacto-polysaccharide (LPS) from the pathogen *Bordetella pertussis*, institute investigators have been able to lower reactogenicity associated with the cellular pertussis vaccine, while maintaining efficacy. Isaias Raw, the director of the Butantan Institute, points out that this simple innovation allows the safe use of a whole-cell DPT vaccine at a cost of only ~12–15¢ per dose (for the DPT vaccine) compared with its acellular vaccine counterpart, which 30 years after development still costs the PAHO revolving fund ~$8 per dose. In addition, the removed LPS shows promise as a very effective adjuvant and is being tested for use with several vaccines. The Butantan Institute now has excess production capacity for the production of DPT vaccine and plans to use it to provide low-cost DPT vaccine to other developing countries.

The Butantan Institute's pentavalent rotavirus vaccine, developed in collaboration with the US National Institutes of Health (NIH) and financial support from the Bill and Melinda Gates Foundation, is expected to be marketed in the near future. Butantan director Raw speculates that this vaccine could be marketed at ~$1–2 per dose, much lower than the existing price of ~$7. Butantan has also developed a combined BCG–recombinant HBsAg neonatal vaccine to protect newborns against tuberculosis (TB) and the occasional mother-to-child transmission of hepatitis B. This vaccine also reduces the high costs of the alternative approach, which would involve testing all pregnant women for hepatitis B virus and administering the recombinant HBsAg vaccine to neonates whose mothers test positive, at a significantly increased cost. Other products in development at Butantan include the following: a rabies-leishmaniasis vaccine (for the vaccination of dogs) being developed in collaboration with the University of Washington (Seattle), a dengue tetravalent vaccine with technology from the NIH, a hookworm vaccine in collaboration with George Washington University (Washington, DC) and the Sabin Vaccine Institute (Washington, DC), a vaccine against the human papilloma virus in collaboration with the University of Colorado (Boulder), as well as several other combination vaccines. In addition, the Butantan Institute is developing a DPT-HBsAg-Hib combination vaccine exclusively for the export market.

Two Brazilian health biotech companies are also actively developing vaccine products. FK Biotecnologia has taken a whole-cell autologous vaccine for prostate cancer into human trials, obtaining promising results in phase 1/2 testing. In addition, BIOCANCER (Belo Horizonte) is developing an autologous dendritic cell vaccine against metastatic melanoma, an intralymphonodal vaccine based on multi-peptides associated with granulocyte macrophage colony stimulating factor (GM-CSF) in individuals with melanoma, and a vaccine based on dendritic cells pulsed with specific peptides in hormone-resistant patients with prostate carcinoma.

4.3.2 Reagents and diagnostics

FK Biotecnologia produces a host of monoclonal antibodies for various diagnostic tests and Katal Biotecnológica and Labtest Diagnóstica (Lagoa Santa) both provide diagnostic kits suited for small laboratories and rural settings in Brazil, a market typically neglected by large companies. In this spirit, Katal is developing a TB test, using PCR technology, that it plans to market for ~\$25 each; Katal's Leonides Rezende estimates that comparable products currently on the market cost ~\$150 per test. With a prevalence of ~140,000 cases of TB in 2005 (http://www.who.int/), the impact of such a product is expected to be substantial for Brazil's public health system. The company's innovative 'visual' prostate specific antigen (PSA) test is currently supplied to the public health system and used for prostate cancer screening (~25 million Brazilian men over the age of 45 are potentially at risk). Katal, in collaboration with the Federal University of São Paulo, has also developed a test for Chagas disease, which can be read by ELISA readers. ELISA readers are much more commonly found in Brazil than luminometers, a specialized device, which the original test relies upon.

4.3.3 Therapeutics

Many of the private companies in our study have developed, or are developing, innovative therapeutics (**Table 4.1**). Examples of innovative products commercialized include Aché Laboratories' topical anti-inflammatory Acheflan (a natural product extracted from the plant *Cordia curassavica*) and Pele Nova Biotecnologia's (São Paulo) BIOCURE (a natural latex membrane derived from the plant *Havea brasiliensis* containing vascular endothelial growth factor (VEGF)) for the treatment of skin lesions, such as diabetic ulcers, pressure sores and surgical wounds. Pele Nova is also testing the VEGF protein for several other applications. Silvestre Laboratories (Rio de Janeiro; Box 1) is marketing several drugs that have resulted from significant in-house R&D, including Dermacerium (a formulation of cerium nitrate and silver sulfadiazine), which is used for the treatment of burns and other skin lesions, and a sodium artesunate anti-malarial rectal capsule for pediatric use (**Table 4.1**). Other notable products in the pipelines include the following: several monoclonal antibodies for oncology by Recepta Biopharma (São Paulo); a recombinant protein for treatment of melanoma as well as an anti-hypertensive and an analgesic peptide (both isolated from snake venom) by COINFAR; and fetal, neonatal and adult stem cell therapies for cardiac disease, type I diabetes and neonatal hypoxia under development at the cell bank firm Cryopraxis Criobiologia (Rio de Janeiro).

4.3.4 Contract services

The Brazilian contract service companies included in this study focused on a variety of areas including clinical research, protein manufacturing and bioinformatics. In the area of clinical research, Intrials (São Paulo) claims to be the largest full-service domestic clinical research organization in Brazil. The company offers a range of services, including selection and qualification of study centers, regulatory affairs services, monitoring of clinical trials, data management and cold/secure storage for clinical trial materials. The firm conducts clinical investigations from phase 2 to phase 4 in various therapeutic areas, with the majority of its clients being foreign firms (8 of the top 20 multinational pharmaceutical companies are among their clients).

Another company involved in clinical research is BIOCANCER, a site-management organization that offers a number of services, primarily focused in the area of oncology. A unique aspect of this company is that it is concurrently developing two innovative and proprietary cancer vaccines (**Table 4.1**). The company's services include recruitment of patients and investigators, protocol and database design, statistical analysis report preparation and others.

Publicly listed BIOMM Technologies (Belo Horizonte) is a spin-off of Biobrás (São Paulo), which was the fourth largest recombinant insulin manufacturer in the world before it was acquired by Novo Nordisk (Bagsvaerd, Denmark) in 2002. BIOMM assists in process development and is dedicated to the transfer of fermentation and purification technologies for the production of recombinant proteins. The company has a proprietary bacterial expression system, which can be used for the production of a variety of proteins.

Lastly, Scylla Bioinformatics (Campinas) provides bioinformatics solutions to various clients. Although the company's clients have primarily been those in the agricultural sector, its capabilities are also applicable to health biotech firms. With the exception of Scylla Bioinformatics, the other service companies studied mostly provide services to foreign clients.

4.4 Partnerships for innovation

Because Brazilian health biotech firms lack the necessary R&D capabilities required for the development of complex innovative products, effective partnerships with Brazilian universities and public institutes are central to the innovation strategy of most companies (**Table 4.2**). The underlying objectives for most collaborative efforts with universities are to access services, such as target identification and validation, or to conduct other preliminary studies on lead molecules. As indicated in -**Table 4.3** and **Table 4.4**, domestic collaborations are more common than partnerships between Brazilian firms and foreign entities.

4.4.1 Local collaborations

Although a significant number of interactions exist between the domestic health biotech firms and public universities and institutes, partnerships between the domestic firms themselves, particularly for product co-development is uncommon (**Table 4.3**). The primary objective for most existing collaborations is access to services for health product development. R&D-intensive companies (for example, COINFAR, Recepta Biopharma and FK Biotecnologia) tend to be most heavily involved in collaborations with universities and public institutes.

Inter-firm co-development interactions remain limited, and when they are present, they often involve joint ventures, in an attempt to share development costs and minimize risks associated with innovative activities. For example, COINFAR (Box 2) was formed, and is mainly financed, by the joint investments of three generics firms, namely Biolab Sanus Farmacêutica (São Paulo), União Química Farmacêutica Nacional (São Paulo) and Aché. A different approach to collaboration taken by Recepta Biopharma involves a joint partnership between a private entity, PRD Biotec (Sao Pãulo), and the Ludwig Institute for Cancer Research (São Paulo), an international nonprofit organization. Recepta Biopharma is partially owned by the Ludwig Institute and works to further develop a set of anti-cancer monoclonal antibodies originally developed at the Ludwig Institute. Headed by José Fernando Perez, the former scientific director of the State of São Paulo Funding Agency (FAPESP), Recepta Biopharma has so far been awarded two government grants of ~$8.5 million (16 million reais in total) with an additional $2 million in co-funding coming from private investors. Similar to many other domestic firms, Recepta Biopharma's business model relies on product development through strategic partnerships with research institutes (for example, Ludwig and Butantan Institutes), universities and various hospitals.

Our interviewees attribute the lack of significant collaborations between local firms to cultural and perceptional factors. Some interviewees indicated that there is a perception among many Brazilian scientists and entrepreneurs that "everything that's good is outside Brazil." Others suggest that because the innovative biotech sector is fairly young, most domestic firms do not possess wide-ranging technological capabilities to offer other firms. Our impression is that the degree of awareness among Brazilian entrepreneurs themselves, regarding each other's capabilities, may contribute to the low level of domestic inter-firm collaborations.

4.4.2 International collaborations

Brazilian entrepreneurial partnerships with foreign entities are often limited to marketing or service provision relationships, with relatively few co-development efforts (**Table 4.4**). For example Aché works with the University of Geneva (Switzerland) and the University of Barcelona (Spain) for chemical studies on plant extracts. Stem cell banking firm Cryopraxis is partnering with the Texas Heart Institute (Houston) in cell-therapy clinical trials and with Saneron CCEL Therapeutics (Tampa, FL, USA) for studies using umbilical cord blood for treatment of amyotrophic lateral sclerosis, stroke, neonatal hypoxia and pulmonary dysplasia. Eurofarma (Box 3) was the only company in our sample to have a joint venture with a foreign firm. It has formed a joint venture with Edol Laboratory (Linda-a-Velha, Portugal) for export of medicines to other countries.

4.5 Financial environment and business models

The general perception among Brazilian entrepreneurs is that although financial resources from public sources have improved significantly in recent years, securing private equity financing remains a significant challenge. Private funding in particular, in the form of domestic or offshore professionally managed capital or equity relationships with offshore companies, remains inadequate. For at least half of the firms in this study, government agencies and development banks are major funding sources (**Table 4.2**).

Although the Financing Agency for Studies and Projects (FINEP; Rio de Janeiro) remains the primary source of grants for most companies, the Brazilian Development Bank (BNDES; Rio de Janeiro) is the major source of low-interest capital. In September 2006, FINEP had two calls for proposals totaling $209 million to support areas of strategic interests [7]. This included, for the first time, ~$70 million targeted at drug development within private companies [7]. As a result of this tender, four health biotech companies were funded, including Eurofarma and Recepta Biopharma. FAPESP is also considered a major funder specific to the state of São Paulo.

Although appreciative of government attempts to support company R&D, some firms criticize how funds are allocated. First, they are concerned about certain conditions associated with financial support from various governmental sources. For instance, funds allocated through FINEP cannot be spent to fund work conducted outside of Brazil, even when desired capabilities are not available in the country. An associated problem, as articulated by Marcio Falci, the innovation director at Biolab, is that companies must obtain permission from FINEP should they consider licensing a technology, the development of which has been partly funded by this agency. The potential risk of not approving such a transaction in the future is sufficient for some companies to forgo the financial assistance from FINEP.

Second, they are concerned about the operation of certain funding institutions. For instance, some interviewees suggested that a systemic bias exists within FINEP, which favors projects that lead to publications rather than products. This bias is attributed, in large part, to the lack of practical experience on the part of evaluators within funding agencies. One interviewee expressed a common sentiment by saying that project evaluators "are being educated and this can take years. I don't think we can afford that." The FAPESP approach, which uses a peer-review system to assess which projects to fund and is considered much less bureaucratic, is preferred to that of FINEP, its federal counterpart.

The dearth of private capital targeted to health biotech forces many companies to rely heavily on government funding or generate revenues from early on. Factors that contribute to the scarcity of private capital include the following: the lack of adequate knowledge about the health biotech sector among most Brazilian investors; the risk-averse nature of most Brazilian venture capital (VC) investors; potential legal complications for angel investors who in some cases can be held liable for actions of firms they invest in; the strong performance of the Brazilian financial markets in recent years and the relatively high interest rates (~12%). Together, these conditions discourage investments in high-risk ventures that require protracted development times, a characteristic feature of health biotech enterprises.

Despite the stated challenges, four companies in our study (FK Biotecnologia, Pele Nova Biotecnologia, Scylla Bioinformatics and BIOCANCER) have been able to raise funding from Brazilian VC investors, and all but one also received financial support from angel investors. It is important to note, however, that in the past three to four years, there have been few VC investments in health biotech SMEs, and to our knowledge, very few such investments have been divested. This is, in part, because of the lack of viable exit strategies available to VC and angel investors, such as a demand for initial public offerings in the biotech sector or an established history of company acquisitions by domestic or foreign companies. The only company in our study that is listed on the Brazilian stock exchange (BOVESPA) is BIOMM Technology because it is a spin-off from its predecessor, Biobrás. A few companies are considering public offerings in the coming years. FK Biotec is strongly considering listing on the BOVESPA-MAIS (São Paulo), a new addition to the main stock exchange targeted more to investors with a longer investment horizon. There are also indications that some large Brazilian pharmaceutical firms are considering going public in the near future. We have not seen any indications on the part of larger Brazilian pharmaceutical companies that they are interested in investing in or acquiring biotech SMEs. It is not yet clear whether this is a function of the products not meeting the market focus of prospective acquirers or whether the larger corporations prefer to invest only in fully developed products.

Several SMEs in this study started in technology incubators, science parks or universities. For example, Katal Biotechnológica started at the Biominas Foundation, which is a private institution focused on providing a host of services that facilitate the formation and growth of new biotech companies. FK Biotec initiated its activities at CIENTEC, a science and technology incubator in the city of Porto Alegre. Bio-Rio Foundation (Rio de Janeiro) is a major science park located within the grounds of the Federal University of Rio de Janeiro, and is the site of Silvestre Laboratories and Cryopraxis among other firms. Direct spin-offs from universities include Biogene (from the University of Pernambuco, Recife), Scylla Bioinformatics (from the University of Campinas, Campinas) and Biomm Technology, whose parent company, Biobrás, was itself a spin-off from the University of Brasilia (Brasilia).

These smaller health biotech firms have either started with initial private equity financing or grown organically by adopting a 'hybrid' business model from the outset. In this context, a hybrid business model refers to the internal funding of development projects from cash flows resulting from offering one or more products or revenue-generating services. Several other companies were launched as a result of private financing from VC firms and/or angel investors, as mentioned previously. With the exception of COINFAR and Recepta Biopharma, which are companies purely focused on developing therapeutics, all other SMEs included in the study already had at least one product or service on the market from early in their life cycle. Even those with some early VC investments, such as FK Biotecnologia and Scylla Bioinformatics, had to generate revenues shortly after inception. As FK Biotechnologia's Fernando Kreutz states, in Brazil, "you not only have to worry about development, but you have to worry about making money. You have to survive from the money you make." Indeed, one interviewee cites the perceived expectation of Brazilian VC firms for early revenues as a main reason that they chose not to seek this type of support from the outset. The rationale for this position was that such expectations may not be in the long-term interests of the enterprise, and are not feasible for small, innovative companies.

Business models for larger pharmaceutical firms tend to vary, but in general they involve production and marketing of generic pharmaceuticals, which in 2006 comprised over 10% of the pharmaceutical market in Brazil [11]. Many firms in Brazil import foreign products and simply re-package and market them as their own. Some within the sector still suggest that one of a few viable business opportunities remaining for Brazilian firms is the marketing of products for foreign companies that do not have their own distribution capabilities in Brazil. Most firms interviewed, however, consider innovation to be the only viable approach for long-term growth and survival. Stimulated by Brazil's adoption of the TRIPS agreement in 1996 and increased regulation of medicinal products in the country, several of the major Brazilian generics manufacturers are now expanding their focus to include R&D on novel therapeutics. Certain companies, most prominently Aché and Eurofarma, have already expanded their R&D activities to develop proprietary products.

The transition from an industry based purely on generics to one capable of producing innovative products is manifesting itself as a staged and cautious approach. For instance, Eurofarma's strategy emphasizes technology in-licensing over the short term in conjunction with in-house R&D for incremental and radical innovations. The company's interest in expanding its focus in oncology is said to be the primary reason for its foray into recombinant technology, a capability that the company is presently seeking to develop. Similarly, Aché is building on its in-house R&D team to facilitate the development of its pipeline of lead natural products from plants. Currently, the R&D departments within most medium to large companies are fairly small and are often composed of a team of professionals who coordinate R&D activities within universities, public institutes and hospitals. This trend is also true for some of the smaller firms, such as COINFAR, Recepta Biopharma, Pele Nova (Box 4) and Cryopraxis, all of whom coordinate much of their research activities at various public institutions. Most firms plan a phased-in approach where they internalize R&D capabilities over the longer term. Factors contributing to this guarded foray into the innovation landscape include the lack of previous experience in developing complex innovative products, as well a number of remaining challenges that add to the risks of innovative R&D in the country.

4.6 Barriers to development

As the Brazilian health biotech sector becomes more innovative, deficiencies in R&D infrastructure and inadequate institutional performance are starting to surface. This section reviews some of the changes that have occurred since our last study on Brazilian health innovation system, published in 2004 (ref. 3), and also highlights a new set of barriers. In our previous study, we identified four major challenges for development: macroeconomic conditions, missing linkages among private enterprises and with universities, issues related to the lack of dedicated health biotech policies and an inefficient patenting system. Although economic growth has persisted and inflation continues to decline, high interest rates pose a significant challenge to health biotech firms with respect to raising financing. The result is that debt capital for expansion is too expensive and private equity sources have higher hurdles for returns. Industry collaboration is still deficient and better coordination and communication of needs across the industry may itself be an effective way to help address some of the ongoing challenges. With respect to governmental policies, there have been significant changes in recent years, with the most prominent being the enactment of the Innovation Law in 2005.

4.6.1 A patent regime in need of speed and reform

The Brazilian patenting system for health biotech products is perceived by the interviewees in our study to be woefully inadequate and bureaucratic. The Brazilian patent office (INPI; Rio de Janeiro) can take over seven years to process patent applications for drug candidates. Brazilian law prohibits patenting of some important biotechnologies, such as recombinant versions of proteins found in nature. Some interviewees expressed concern over the Brazilian National Health Surveillance Agency's (ANVISA; Rio de Janeiro) "prior consent" right over pharmaceutical patents. ANVISA is the national regulatory agency that approves health products, among other activities. Under the present system, once a pharmaceutical invention has been deemed patentable by INPI, it must then be approved by ANVISA before a patent can be granted. ANVISA uses several criteria to evaluate patent applications, including considerations for public health implications, such as those related to eventual public access issues [12].

More recently, the Brazilian Health Ministry has publicly opposed a patent application by Gilead Sciences (Foster City, CA, USA) for the AIDS drug tenofovir disoproxil fumarate on the grounds that it would compromise the country's public health program [13]. Notwithstanding the stated challenges, Brazilian firms are increasingly cognizant of patenting, although the trend is not as prominent as might be expected over 10 years after the country's adoption of the TRIPS agreement. Just over half of the firms studied reported having one or more patents, with several of them having several applications pending approval both in Brazil and abroad (**Table 4.5**). Only a handful of firms studied currently possess patents outside Brazil, perhaps contributing to the limited history of co-development partnerships with foreign firms. These observations are consistent with previous reports showing that overall health biotech patenting, as judged by Brazilian patenting activity in the United States, remains fairly tenuous[3]. There is a general consensus among the study participants that the patenting process for medicinal products needs to be accelerated, streamlined, merit-based and free from subjective and speculative criteria. The present situation has substantially increased uncertainty with respect to whether and when patent protection will be obtained for novel technologies. This increased risk adversely affects private investments in new health technologies and impedes collaborative product-development arrangements, which often hinge on the sharing of intellectual property rights among partners.

4.6.2 Regulatory issues

Despite improvements in recent years, lack of practical experience on the part of many health product regulators, delays in the ethics approval process for clinical trials as well as issues related to biosafety and biodiversity remain major obstacles to health product commercialization in Brazil. The main regulatory issue highlighted by interviewees, both from the public and private sectors, relates to the lack of practical experience on the part of regulators. Although interviewees acknowledge that ANVISA regulators are often highly educated and accomplished professionals, they cite a lack of necessary product development and manufacturing experience as a significant challenge. One interviewee captured this sentiment by stating that ANVISA "hired a young group with PhDs and so many highly educated people, but they lacked experience in the field or experience in production .... I think they will be ready in ten more years and we will suffer [in the meantime]." Recognizing that ANVISA has made some important strides forward in recent years, the broad consensus is that the agency needs to improve the efficiency of its decision-making process.

Another problem that negates the strength of the country in clinical research are the significant delays in research ethics approval encountered by many foreign-sponsored clinical research protocols. Brazil is an attractive location for conducting clinical investigations because of its considerable pool of trained professionals, the ease and speed of patient recruitment (due to a large pool of pharmaceutically naive patients in many therapeutic areas) and high compliance rates. Delays in the ethics approval process, estimated at six months on average, are thought to be a significant stumbling block preventing the country from reaching its potential in clinical research. Claudio Ortega, vice president of Intrials and Carlos Guimarães, CEO of BIOCANCER, independently estimate that if this timeline were shortened to approximately two months, the number of clinical trials coming to Brazil would increase by at least twofold. The delay is said to especially discourage clinical trials with short recruitment periods from coming to Brazil. The involvement of multiple bodies, such as local Research Ethics Boards, the National Research Ethics Board (CONEP) and ANVISA are contributing factors to these delays, with the last two perceived as primarily responsible. CONEP for example, is staffed by volunteers who often have other full-time employment responsibilities elsewhere and thus cannot be fully committed to reviewing research protocols.

Brazil's biosafety and biopiracy regulations are also thought to pose significant stumbling blocks to the development of the domestic health biotech industry. The Biosafety Law of 1995 (Law 8.974) and its revised version of 2005 (Law 11.105) created the National Technical Biosafety Commission (CTNBio; Rio de Janeiro) [14]. This commission is responsible for approving the use of genetically modified organisms and their derivatives. Although national concerns over biosafety typically relate to genetically modified agricultural products, the approval of which often garners much attention from the national media and nongovernmental/governmental agencies, the spill-over effect seems to be a strict application of biosafety rules to the health area as well. For example, obtaining approval for the use of a genetically modified bacterium for the purpose of production of proteins for diagnostic test kits can often be a lengthy and time-consuming process. Brazilian concerns over biopiracy, stimulated by several past transgressions in which foreign entities took what is considered undue advantage of Brazil biodiversity [15], have helped set the stage for the creation of the Council for Management of Genetic Patrimony (cGEN; Rio de Janeiro) in 2003. The cGEN's responsibilities are to set regulations, authorize access to Brazil's genetic resources and ensure that indigenous knowledge is compensated for when used for commercial purposes. In practice, it is often very difficult for entrepreneurs to identify which community(ies) ought to be compensated, or to determine the extent of compensation at early stages of R&D. In 2003, in response to objections from Brazilian researchers, cGEN approved new rules easing restrictions for research on biodiversity, but as long as it was not intended for commercial purposes [16]. Despite these rule changes, many in the Brazilian research community remain concerned, especially following the recent prosecution of a prominent primatologist, Marc van Roosmalen, on charges related to his work in the Amazon [15].

4.6.3 Poor university–industry interactions

For innovative SMEs one of the biggest challenges is affordable access to required services. The country possesses few good laboratory practice–certified preclinical facilities, with existing facilities largely limited to studies in rodents, and no contract manufacturing organizations for protein synthesis. There is an apparent disconnect between the regulatory demands and the capabilities and infrastructure available in the country. William Marandola of COINFAR, says that innovative companies "often need to go abroad for most of their preclinical testing and biotech manufacturing needs, which diminishes the capacity of investing in more projects." He goes on: "One way to solve this is to partner with local universities to strengthen existing infrastructure...but doing so depletes money from [the] existing R&D portfolio." In this respect, COINFAR is investing $350,000 (675,000 reais) in a new facility in the University of Minas Gerais (Belo Horizonte) for early-stage development assays, which they need for future projects. The rigid rules for government funds, which increasingly complement innovative research, that stipulate grants cannot be spent outside Brazil, regardless of the availability of required services within the country, serve only to exacerbate the situation. Another major obstacle is that in many cases, the services hired from abroad are taxed at very high rates and R&D expenditures outside Brazil cannot take advantage of incentives offered for similar activities conducted within its borders. The overall impact of the stated challenges appears to be a reluctant, but nonetheless heavy, reliance on services within universities, which introduces its own set of challenges.

Collaboration with universities and research institutes is a central aspect of the innovation strategy of almost all the Brazilian firms interviewed. Lack of considerable in-house R&D capability for new product development and recent governmental incentives both serve to encourage university–industry research collaborations (**Table 4.3**). Even so, several factors make it difficult for these collaborations to be effective. One problem is that historically there has been a relatively low level of collaboration between the public and private sectors in the health area. Cultural differences and divergent goals and aspirations between academic and private researchers, which stem, in part, from different incentive systems, are the main reasons cited for some of the challenges in setting up university-industry partnerships. It has been suggested that a generalized aversion to entrepreneurs among Brazilian researchers, and the public in general, acts as a cultural barrier for the biotech sector [17]. There are also suggestions that many universities still remain uneasy with respect to interacting with the private sector. A manifestation of the related challenges for private enterprises is the difficulty of conducting R&D projects within universities that meet time and budgetary constraints.

There are, however, a few public universities and organizations that are said to be much easier to work with, in part because they have personnel who are dedicated to innovation and technology transfer activities. The State University of Campinas or UNICAMP (Campinas) is identified as exemplary in this regard. Governmental initiatives, such as the Partnerships for Technological Innovation program of the São Paulo State, have encouraged collaborative activities for technological innovation by investing in many joint projects [8]. Overall, although it is likely that university-industry collaborations have increased in absolute numbers, many may still lack overall effectiveness under present circumstances. This assertion is warranted, given that a number of private-sector interviewees currently involved in collaborative projects with the public sector (or involved in the past) are only marginally optimistic regarding the satisfactory conclusions of such collaborative projects. This guarded optimism relates to the reasons stated previously, as well as the recognition that universities, often through no fault of their own, are not presently structured to undertake many of the activities that are of interest to the private industry. To ensure domestic success in health technology innovation, Brazil's resources need to pull in the same direction and of crucial importance in this regard is a fuller appreciation of the significant entrepreneurial challenges and complexities associated with drug development.

4.6.4 Human resources

Brazil's formalized attention to improve its human resources in science and technology dates back to the National Program for Post-Graduate Studies in the late 1960s [18]. The resulting efforts from the 1970s to the 1980s led to the expansion of programs and fellowships for graduate students [19], helping to increase both the quantity and quality of research output for the country [18]. Brazil has also seen a positive trend for health biotech publications in recent years [7]. However, ~95% of the country's publications originated from the public sector [19]. Although these activities have raised the level of expertise in biotech in general, several factors contribute to severely limit the presence of highly trained personnel in the private industry.

It has been previously suggested that the problem with respect to human resources in biotech is not one of supply, but of the lack of demand by private firms [17]. This is consistent with the finding that by 2005, Brazil was already graduating ~9,000 new PhDs each year [8]. Although the shortage in demand by the private sector for highly trained personnel has largely been a function of this sector's almost exclusive focus on generics and copycat products, a few other factors also contribute to dampen this demand. There are indications of a disconnect between the expertise generated by existing training programs and the industrial needs of the health biotech sector as a whole. Lack of sufficiently specialized and targeted training programs, and what is often referred to as the 'academic model' of university preparation, are two of the factors that appear to limit the supply of appropriately trained personnel. Many of the study interviewees were highly critical of university training programs, suggesting that they mainly prepare students to become university professors, rather than train them for opportunities in different areas, including careers in the private industry.

An additional challenge for private industry, especially SMEs, is its inability to match or exceed the incentive system in place for careers in the public sector. When available, skilled personnel often present themselves in the form of tenured university professors, unwilling to leave the job security and other extensive benefits, which often cannot be matched by private-sector employers. Strict Brazilian labor laws also contribute to making the hiring of highly trained personnel an expensive undertaking for the private sector due to the high cost of employee benefits and the many conditions associated with hiring personnel [20]. The relatively few companies that can afford to offer competitive salaries are often inclined to recruit internationally because of the limited pool of highly experienced personnel in drug development, which is in part due to the relatively recent shift of focus to this area in Brazil. Taken together, these and other factors contribute to the finding that ~70% of Brazilian scientists work in the public sector (http://www.mct.gov.br), with relatively few employed by the health biotech sector (as represented by the companies interviewed for this study). A recent government program to subsidize researcher salaries within private companies is an attempt to increase the mobility of expertise across public and private organizations. However, at the same time we find that R&D commitment for private companies is not very significant at this stage (**Table 4.2**). To be successful, government initiatives need to be complemented by significantly greater investments in innovative R&D activities by the private firms themselves. If such innovative programs materialize, Brazilian health biotech firms can become a more receptive environment for academic researchers.

4.7 Concluding remarks

Despite the challenges listed above, Brazil possesses some of the most important and basic elements for a strong and innovative health biotech sector. The country's strong scientific capability, especially in health sciences, provides the basic building block for an innovative sector. Indeed, the fact that several SMEs have already succeeded in making innovative products in the face of numerous challenges is a testament to the country's strength in health sciences. Many of the health biotech sector's innovations address the health needs of the local population, a market that remains the primary focus of Brazilian entrepreneurs. An increasing number of firms are becoming involved in innovative activities, using creative approaches and business models that help them to survive and prosper despite challenges, financial and otherwise. Various laws related to technological advancement, such as the Innovation Law enacted in 2005, are fostering more intensive and meaningful collaborations between public universities and research institutes and private companies. The nation's economic improvement, growing financial markets, stable currency and low inflation rate also provide an atmosphere conducive to sustained growth of the health biotech sector. For Brazil to capitalize on these building blocks for health innovation, it now needs to pay close attention to organizational management and performance. Although financial and legal/regulatory issues need further fine tuning, the efficiency, effectiveness and transparency of government institutions involved in health product development, regulation and oversight remains a key factor in determining the speed and scope of Brazilian success in health product innovation. We present a few recommendations for Brazilian policymakers and industrial actors in Box 5 (below), which, if implemented effectively, we believe will help to accelerate health biotech innovation in the country.

Brazil's traditional view of expenditure in health as an expense, rather than as an investment, in sharp contrast to other areas, such as agriculture, has contributed to creating a primarily inward-looking industry. Following with this approach, the country has often looked for the lowest-cost and short-term solutions to addressing local health needs, to the possible neglect of greater overall gains, including economical, which may be offered by alternative mechanisms. In the view of some observers, Brazil's strategy of negotiating discounted prices, exemplified by the issuance of a compulsory license for Merck's (Whitehouse Station, NJ, USA) antiretroviral efavirenz (Sustiva) [21] against HIV/AIDS, may be a prime example in this respect. Some interviewees expressed concern that the overall economic costs of the present approach may be much higher in the long run than the savings achieved through current measures. Although Brazil's HIV/AIDS program, which provides free medicines to all infected individuals, is credited for stabilizing infection rates and reducing hospitalization and mortality [22,23], questions have been raised with respect to the sustainability of this program given the rising prevalence of infected individuals as well as the costs of newer, often patented, AIDS drugs [24]. There is no doubt that these are challenging issues that Brazilian policy makers do not take lightly. However, they also speak to the importance of domestic capability in health innovation, particularly for populous countries like Brazil with more limited resources. Uncertainty surrounding intellectual property protection negates this objective by increasing risks and reducing incentives for domestic innovation.

Whether for cost reduction or other reasons, the Brazilian government has had a strong focus on the role of the public sector over much of the past few decades, including for the development and production of some health products. Additionally, because the public sector has been a major source of medicines procurement for many private companies, its policies have likely had a disproportionate effect with respect to creating a primarily inward-looking industry. To the extent that past government policies supported the local industry, it appears to have been with the primary objective of import substitution, with little attention to the export of health products. It is not surprising then that few of the firms in our study reported exporting products to any significant degree (**Table 4.2**), contributing to the country's $2.1 billion negative balance of trade in pharmaceuticals in 2005 (ref. 25). Loss of export revenues also limits the ability of companies to make significant investments in R&D, which is often required for development of health products.

The Brazilian constitutional declaration of 1988, that health is the right of every citizen and the obligation of the state, has had a profound impact on the way in which many Brazilians view public health. Although challenging to fully implement, this pronouncement nevertheless seems to provide a prism through which the Brazilian policymakers view healthcare. There are also indications that it may validate the perception in the country, at least in some circles, that all health-related issues ultimately belong in the public sphere. If true, it would follow that the public sector can and is obliged to develop and deliver all health products and services to the population. The reality, however, speaks otherwise. Following this logic, the central question becomes, if the realistic and pragmatic solution to addressing health needs of the population while reaping economic benefits is the involvement of both the public and private sectors, then what should the involvement of each be? Stated differently, where does the role of the public sector end and that of the private sector begin? This question appears to be at the heart of the Brazilian dilemma with respect to developing a robust private sector, while addressing its local health needs in a sustainable and affordable fashion. If the country can manage to strike an effective balance between its public and private sectors, it may not only maximize both health and economic benefits to its own people, but also provide an intriguing model for other developing nations. As a first step, Brazil can benefit by ensuring that the activities of its government-affiliated health product developers and manufacturers complement rather than oppose those of the domestic private sector.

Attempts thus far to balance the country's public and private sector involvement in health product provision have created uncertainty for Brazilian entrepreneurs and contributed to a palpable tension between the two sectors. Several public initiatives contribute to this lingering uncertainty. First, the Brazilian federal and state governments develop, produce and deliver some health products themselves, a role often played by the private sector in other countries. For instance, the public sector manufactures a set of essential medicines at a network of 18 public laboratories, which are primarily distributed free of charge through the Ministry of Health. Those institutes with significant R&D capabilities, such as Farmanguinhos (Rio de Janeiro), sometimes serve a dual purpose for the public health program. They not only develop and manufacture needed drugs, but also, in some cases, serve as instruments to realize lower drug prices from other providers. Therefore, the true value of some of these organizations to the Brazilian public health program appears to extend beyond the presumed cost savings achieved through direct manufacturing. In this respect, they occasionally attempt to distort the market toward lower prices, through direct competition or the threat of competition in the near future. The overall working policy of the Brazilian government, whether by design or default, appears to be that if a public institution can provide a particular health product, then the government would procure the given product from only the public source, circumventing the otherwise open tendering process. This approach raises several issues for the private industry. There does not appear to be any obvious boundaries to the type of products that public institutions can choose to produce, which increases uncertainty for the private sector with respect to investing in human health products. Public-sector manufacturing may also take away some opportunities for Brazilian companies to generate revenues that would allow them to then invest in further development, akin to the strategy used effectively by many Indian companies [4]. In a related theme, many of our interviewees call on the Brazilian government to use a portion of its procurement budget to purchase products from innovative SMEs. This is thought to be an essential step in accelerating domestic innovation, particularly in the context where small innovative firms must rely on early revenues for further growth and development, and where the public sector is the only effective mechanism for reaching the mass market. Although some interviewees felt that legal mechanisms for such initiatives are already in place, many regret the government's reluctance to take advantage of available opportunities to the detriment of small innovative firms.

The second strategy to provide affordable health products to the country's poor is through government control over drug prices, as stipulated by Law 10.742 (2003). This law includes provisions for setting drug prices based on a host of factors, including the cost of inputs and marketing, prices of comparable products on the market and treatment cost per patient using a given product. The objection on the part of some of the interviewees in this study is that the price increases allowed annually are often less than the inflation rate. Although this has not been a significant issue in recent years primarily because of a reduction in the costs of imports, realized by a rising Brazilian currency, it adds to the uncertainty going forward. This is a common government policy in many nations, however, and in those places, price compression necessarily reduces the ability of companies to fund new product development themselves.

Lack of a true and broad-based appreciation for the challenges associated with drug development and the global nature of this undertaking are at the center of many difficulties facing the Brazilian industry. As such, it is essential that steps be taken to increase awareness in this regard, particularly among policymakers, regulators and academics. A notable observation is the high regard for the scientific capability of Brazilian academics within the private sector. Increased awareness of challenges faced by private industry among the academic sector will help to reciprocate this feeling and improve public–private interactions. To advance the innovative ability of the country, it is essential that a culture of innovation be fostered both within universities and the private industry. Imperative to such a culture is a mutual understanding between the public and private sectors of the challenges and nuances associated with the development of human health products in a heavily regulated area. It is broadly recognized that biotech innovation is a global phenomenon and Brazilian policies, such as those related to project funding, need to reflect this reality. Therefore, what is needed is a holistic approach in devising a biotech policy that considers various options and objectives and makes necessary adjustments in a sector-specific manner. For instance, increased harmonization of Brazilian regulations with export markets can, over the long run, make it easier and more cost-effective for Brazilian companies to obtain approvals not only in Brazil but also abroad, in terms of facilitating product exports. At the same time, a sector-specific industrial policy, in recognition of the increasingly global nature of the health biotech business, may help to better identify and focus on niche areas—within the health product development value chain—where Brazil can be most competitive.

Perhaps as a manifestation of a less than holistic approach to biotech development, some of the rules and institutions put in place with the purpose of protecting public interests act as significant roadblocks to research and commercialization. Rules regarding biosafety and access to biodiversity need to be updated in light of existing evidence not only within Brazil but also internationally. The country would also be well advised to pay closer attention to the composition of its decision-making bodies, ensuring their independence, transparency and operation in an evidence-based mode to the extent possible. The issue of 'prior consent' requirement by ANVISA for drug patents is likely to become more significant as Brazilian companies increase their efforts to develop more complex innovative products for both domestic and international markets. As such endeavors are likely to be much more costly, the resulting innovations may be deemed not patentable due to access issues related to projected costs into the future. Should such scenarios come to pass, it will likely inflict immeasurable damage to the health biotech sector and drastically reduce private investments in health product innovation.

Despite some limitations in trained human resources, the Brazilian biotech sector has yet to feel an acute shortage of human resources in most areas. Thus far, this is, in large part, due to the relatively small demand for highly trained research personnel by the private life science industry. This limited demand is especially true for larger Brazilian pharmaceutical firms, which have an R&D commitment (in terms of targeted expenditures and dedicated personnel) that remains relatively tenuous. Given that the domestic pharmaceutical sector in Brazil is now attempting a metamorphosis from an almost exclusively generics-based model to an innovative one, the demand for a highly trained workforce is likely to increase significantly over the coming years. Even in areas where the country possesses strong capabilities, such as in clinical research, the depth of the trained human resource pool is not perceived to be very extensive, a factor that is likely to restrain a significant expansion of the industry, at least in the short term. Current trends in the rising number of university graduates may help to compensate to a degree; however, training needs to be tailored more to the industrial needs of the country.

Although Brazilian law now allows academics to work in private industry for a period of time, there is yet little indication that this newly found opportunity is being taken advantage of to any significant extent. Both industry and universities need to devise new approaches to make this a possibility for a greater number of academic scientists. Individual companies can facilitate this process by accelerating their efforts to provide a more suitable environment for R&D within companies to help attract such talent.

Lastly, Brazilian entrepreneurs and private companies themselves have a major role to play in ensuring that necessary changes take place to help foster an innovative sector. Currently, the domestic private sector health biotech enterprises appear fragmented, lacking a unified voice and an effective and coordinated strategy to address mutual challenges. Brazilian entrepreneurs recognize the valuable role that organizations, such as the Biominas Foundation, the Brazilian Biotechnology Industry Association (ABRABI; Belo Horizonte), the BioRio Foundation (Rio de Janeiro) and various other industry organizations play in trying to bring together various stakeholders within the biotech industry and increase the overall awareness within the sector. Such efforts need to be supported and expanded to ensure knowledge flow and coordination among industry actors. Brazil can also benefit from publicizing its capabilities at major international conferences to signal the global markets that it is 'open for business' in biotech. Moreover, existing firms, particularly the larger and more profitable pharmaceutical companies, need to display more ambition and courage in their foray into innovative activities. Although some companies have already expanded efforts to enhance their R&D capabilities, more need to do so if the sector is to live up to its own prognosis that innovation is the most viable option for future growth.

Now that a strong scientific foundation has been laid, a sustained focus on effective policies and their implementation, together with enhanced organizational competence and the facilitation of interactions among various stakeholders, can help Brazil replicate in health biotech its considerable technological success in other areas, such as aviation and deep-sea drilling. Only by doing so will the Brazilian public begin to truly reap the health and economic benefits of a thriving life sciences sector.

4.8 Case Study Boxes

4.8.1 Case study: Silverstre Laboratories (Box 1)

Silvestre Laboratories is a private company, with revenues of ~$10 million for 2007, that was initiated in 1984 by Eduardo Cruz. Cruz started the company to identify the active ingredient in a burn treatment donated by a group from Texas to treat burn patients at a hospital in Rio de Janeiro. After the active pharmaceutical ingredient was characterized as silver sulfadiazine, a broad spectrum anti-microbial, Silvestre Laboratories devised a new method for the synthesis of this compound and in 1991 launched a topical cream for the treatment of burns called Dermazine (silver sulfadiazine). The company then reinvested revenues from the success of this first product into further research and a few years later launched Dermacerium, a formulation of cerium nitrate and silver sulfadiazine, which was found to prevent 50% of deaths among severe burn victims. Dermacerium can also be used for the treatment of other skin lesions, such as leg ulcers, diabetic foot and surgical ulcers. The company's innovative activities have also led to the commercialization of several other products, with other candidates at various developmental stages (**Table 4.1**). Dermacerium and Extragraft XG 13 (a bovine collagen-hydroxyapatite composite scaffold for bone regeneration) are currently being registered in the United States, Malaysia, the United Arab Emirates, Korea, China and South Africa. In recognition of these activities, the company received the Brazilian Innovation Award in 2007.

The company's research and interest in other areas, including stem cell research and recombinant protein synthesis, has led to the creation of two spin-off companies, namely Cryopraxis and Chron-Epigen, respectively (both in Rio de Janeiro). Cryopraxis is currently the largest stem cell and cord blood bank in Brazil, with over 10,000 banked samples. According to Silvia Azevedo, vice president of Cryopraxis, the company uses revenues from its cord blood banking activities to sponsor a series of preclinical and clinical trials using standardized mononuclear stem cell formulations. These studies are focused primarily on cardiac lesions, type-1 diabetes and neonatal hypoxia. The research activities are conducted under the company's subsidiary in the United States, CellPraxis USA Inc. (Jupiter, FL).

4.8.2 Case Study: COINFAR (Box 2)

COINFAR, or Consórcio da Indústria Farmacêutica, is a joint venture that was launched in 2001 as a result of collaboration between three Brazilian pharmaceutical companies: Biosintética (now part of Aché), Biolab and União Química. The company's business model is to focus on the discovery and development of drugs until clinical phase 1 or phase 2 and then license them out for further development. COINFAR has a team of six scientists, who coordinate the company's R&D activities carried out by ~20 investigators in various Brazilian universities and institutes.

Together with the technology-transfer initiative of the Centre for Applied Toxicology (CAT) at the Butantan Institute, COINFAR is helping to develop two new drugs, which are currently undergoing preclinical studies: an endogenous vasopeptidase inhibitor (EVASIN), a type of anti-hypertensive derived from *Bothrops jararaca* venom, and an analgesic for chronic, neuropathic pain, also originating from snake venom. Other projects include investigations into toxin-based drugs for such indications as blood clotting, pain perception and immune suppression, all of which are at the pre-clinical stage. Another lead compound is a recombinant protein from tick saliva, which has shown to be active against melanoma. The company already has over 8 granted patents and has 36 patent applications pending approval, the majority of which are in the United States, Europe, Japan, India and China.

Since its inception, COINFAR has had significant investments from both public and private sources. From 2002 to 2006, the company received $6 million from its shareholders; between 2005 and 2006, it received $2 million in government funding for joint projects with universities. Plans are in the works to invest a further $1.6 million on prospecting activities for new molecules in the coming year; the company has numerous partnerships with various universities and is expanding its efforts to forge further collaborations both in Brazil and abroad, including plans to start an affiliate company in the United States in 2008.

4.8.3 Case study: Eurofarma Laboratorios (Box 3)

Eurofarma Laboratórios is a private company founded in 1972 that has grown to become the third largest pharmaceutical retailer in Brazil. The company manufactures and commercializes over 220 generic pharmaceutical product formulations, which are distributed through its five business divisions: hospital, oncology, veterinary, generics and medical prescription. It also possesses a factory producing glass vials for its own use and sale to third parties. In 2007, Eurofarma commenced production of pilot batches of the recombinant protein filgrastim (a recombinant granulocyte-colony stimulating factor; G-CSF), a biogeneric drug for treatment of cancer, which was licensed from DevaTal. The Brazilian company hopes filgrastim will be its first biotech drug, which it expects to market by 2009. Eurofarma's foray into protein manufacturing is part of a strategy to bolster its position within the oncology segment.

Eurofarma is also involved in product co-development and clinical research with some of its international partners, such as development of a novel monoclonal antibody against epidermal growth factor receptor for the treatment of solid tumors. In 2002, the company launched its international trademark Themaxis in Mexico, which together with Laboratórios EDOL (Linda-a-Velha, Portugal), have formed Edol-Themaxis to export medication to countries that include Costa Rica, Colombia, Mexico and Venezuela. It also has a joint venture called Incrementha PD&I (São Paulo) with Biolab, which is dedicated to incremental innovation of new products and technologies that typically involve new fixed combinations and/or formulations. The company is also undertaking activities related to development of several novel products in partnership with universities. These include studies to identify new drugs from the country's rich biodiversity resources; all are financed, in part, through research grants from FINEP, a government funding agency.

Since 2001, Eurofarma has been involved in the analytical aspects of bioequivalence studies and in 2006, invested $3 million to initiate the ANVISA-certified Magabi Clinical Research and Pharmaceuticals, which conducts about 15 such studies per year. The company has a workforce of 2,300 people with revenues reaching $444 million in 2006, and invests ~6% of its turnover profits into new products, technologies and markets. It has recently built a state-of-the-art manufacturing facility according to the FDA standards to allow good manufacturing practice production of drugs, especially those targeted to export markets. Technology in-licensing is a central component of Eurofarma's growth strategy in the short term, which it hopes will allow the company to access proprietary products and build on its technological capability.

4.8.4 Case Study: PeleNova Biotecnologia (Box 4)

Pele Nova Biotecnologia is a private company launched in 2003, originating from the work of two researchers at the University of São Paulo: Fatima Mrue and Joaquim Coutinho Netto, a surgeon and a biochemist, respectively. While working on a technique to surgically repair esophageal lesions in dogs, the investigators discovered that one of the implanted latex materials they had used helped to regenerate esophageal tissue and restore normal function. Recognizing the potential in the discovery, they filed for a patent for the product now referred to as BIOCURE. Applications have also been submitted in more than 60 countries with patents granted for parts of Europe.

Ozires Silva, one of the founders of Embaer (São José dos Campos), the Brazilian aircraft manufacturer, was instrumental in mobilizing the necessary investment for the company. Silva, now chairman of the Board at Pele Nova, helped raise ~$4 million in seed capital from REIF Venture Capital firm, an angel investor and three private equity firms (Burity Group, DeltaCare and SilverStar) to help launch the company.

BIOCURE was approved by ANVISA in 2004 and is being used for wound healing applications, including diabetic ulcers, vascular insufficiency ulcers, pressure sores, vasculogenic ulcers, surgical and traumatic wounds. The product is also under investigation for use in second- and third-degree burns, treatment of urinary incontinence in women and tympanoplasty surgery. The active ingredient in the material, derived from Brazilian rubber trees or *Hevea brasiliensis*, has been identified to be a VEGF, which helps to promote angiogenesis. This protein is being tested for various indications, including cosmetic applications.

After four years of operation, Pele Nova's revenues are forecasted to reach $1.8 million for 2007, an increase of 80% over the previous year. Currently, the company commits 35% of its annual budget for R&D.

4.8.5 Recommendations for biotech development in Brazil (Box 5)

- Improve the performance and transparency of government institutions involved in health product development, regulation, ethics review and intellectual property assessment and approval; re-evaluate the two-tiered approach to medicinal patent issuance.
- Promote and support the filing of patents outside Brazil and develop policies that encourage the partnering of Brazilian companies with offshore collaborators based on the formation of international intellectual property assets.
- Administer biosafety and biodiversity laws in ways that encourage use of Brazilian resources for product discovery and creation while still preserving the knowledge rights of the indigenous population.
- Identify crucial gaps in health product development infrastructure and stimulate the creation of facilities to provide required services.
- Modify or remove policies that levy taxes or otherwise penalize companies that must outsource portions of their development programs to offshore vendors.

- Help build a culture of innovation by stimulating dialog among regulators, policymakers, academics and the private sector to raise awareness and seek resolution of issues that hamper health product development.
- Clarify the domain within which the public sector will operate so as to allow the private sector to target their investments more effectively.
- R&D commitment should be substantially increased in private firms to ensure they are viable employment destinations for academic researchers; firms should also build stronger linkages with each other to strengthen industry associations, identify challenges and implement appropriate solutions.
- Identify human resource requirements in specific disciplines and technical specialties and create and/or adapt training programs to meet the identified needs.
- Stimulate the creation and expansion of academic and executive programs in entrepreneurial training specifically for the biotech sector.
- Use public procurement mechanisms to support innovative startup firms.

4.9 Tables

Table 4.1 Brazilian health biotech firms interviewed and their product portfolios and pipelines

Company or organization	Products on the market	Products in development	Domestic/international quality certification
Innovative SMEs			
Aché Laboratórios Farmacêuticos	240 formulations for various therapeutic areas, including cardiology, the respiratory system, digestive system, central nervous system, obstetrics and gynecology, musculoskeletal system, dermatology and others. Main products include: Acheflan (an extract of the plant *Cordia verbenacea*used as topical anti-inflammatory), Tandrilax (muscle relaxant made of paracetamol, carisoprodol, diclofenac sodium and caffeine), Sinergen (an antihypertensive formulation of amlodipine besylate and enalapril maleate).	Six products, including drug candidates for treatment of hypertension, anxiety, diarrhea and fungal infections.	ANVISA-BPF (GMP), ISO 14001, OHSAS 18001, BS8800 certification and US Occupational Health and Safety Act standards. GMP-compliant plant opened in 2007.
Biogene	ELISA test for visceral leishmaniasis in animal hosts to prevent transmission to humans.	ELISA-based tests for diagnosis of leishmaniasis in dogs (allowing infected and vaccinated animals to be distinguished) and toxoplasmosis, a serodiagnostic test for brucellosis, which uses a recombinant antigen. Co-development of a test for human visceral leishmaniasis with FK Biotech.	National Technical Biosafety Commission (CTNBio) monitors research and production.
Biolab Sanus Farmacêutica	Approximately 60 products for various indications, including Aradois (potassic losartan, for hypertension), Pressat (amlodipine besilate, for hypertension), Quinoflox (ciprofloxacine, antimicrobial) and Lovell (levonorgestrel and ethynilestradiol, a vaginal contraceptive).	Nanoparticle-based products for dermatologic and cosmetic usage and mucus-adhesive products for vaginal treatment.	GMP according to ANVISA.
COINFAR	No products on the market yet.	Antihypertensive protein (from*Bothrops jararaca* snake venom), a peptide-based analgesic (isolated from snake venom and acts through κ and	N/A

Company or organization	Products on the market	Products in development	Domestic/international quality certification
		some δ opioid receptors), an anticancer recombinant protein derived from tick saliva showing activity against melanoma.	
Eurofarma Laboratórios	Approximately 260 drug formulations for various indications, including: oncology, antifungals, bronchodilators, antidepressants, benzodiazepines, antihypertensives, anticonvulsives, antihistamines, analgesics, a veterinary line of drugs and a line of drugs targeted to hospitals.	Products for treatment of meningitis, *Helicobacter pylori* infections, hypertension, nosocomial infections and an analgesic. A project is also underway to develop a neutropenia treatment.	REBLAS (Brazilian Network of Analytical Health Laboratories) and ANVISA GMP certified, implementing ISO 9001 version 2000 and ISO 14001 version 2000. New facilities meet FDA standards.
FK Biotecnologia	Over 70 different hybridoma lines producing different monoclonal antibodies for diagnostics tests and other applications. Immunodiagnostic kits for flow cytometry (for HIV follow up), point-of-care testing platform (for dengue, leishmaniasis, leptospirosis, Chagas disease, hepatitis B, HIV I/II and pregnancy).	Whole-cell autologous anticancer vaccine in clinical trials for prostate cancer (phase 1/2 completed) and myeloma, ovarian, breast, pancreatic and renal cancers (phase 1). Automated ELISA-based diagnostic tests (for PSA, HIV I/II strains and others).	ANVISA certified.
Hebron Farmacêutica Pesquisa, Desenvolvimento e Inovação Tecnológica (Recife)	Approximately 135 pharmaceutical products in 13 medical specialties, including pediatrics, internal medicine, gynecology and cardiology. Main products developed with universities include Giamebil (extract from the plant *Mentha crispa* with antigiardia and amoebicide properties) and Prostokos (mesoprostol formulations, used as a labor stimulant).	A few plant-derived natural products in development but details not disclosed.	Not indicated.
KATAL Biotecnológica	Forty-three products, including ELISA tests for: glycohemoglobin, PSA (with a visual readout for prostate cancer), toxoplasmosis, hormones (for example, human choriogonadotropin (hCG), luteinizing hormone, prolactin, triiodothyrionine, thyroxine and estradiol), ferritin and IgE.	PCR-based test for *Mycobacterium tuberculosis*, ELISA test kits for Chagas disease, TB-drug sensitivity, rubella IgG/IgM, herpes simplex viruses 1/2 and cytomegalovirus.	Not indicated.

Company or organization	Products on the market	Products in development	Domestic/international quality certification
Labtest Diagnóstica	A line of clinical chemistry reagents and automatic analyzers, immunoassay-based rapid tests (for hCG, HIV, dengue, others), urinalysis strip test (for example, for glucose or leukocytes) and ELISA-based kits (for herpes simplex virus 2, cytomegalovirus, rubella, toxoplasmosis).	Liquid stable enzymatic assay for chloride, potassium and sodium. Liquid stable control and calibrators for clinical chemistry, and test kits for hemoglobin A1C for use in small laboratories.	ISO 9001 version 2000. Follows international GMP guidelines. ANVIAS GMP-certified for manufacturing *in vitro*devices.
Nortec Química	Forty-nine active pharmaceutical ingredients (APIs) for >70 medicines, including: antivirals, antiretrovirals, benzodiazepines, cardiovascular drugs and others.	APIs for new antiretrovirals and central nervous system drugs.	New production plant approved by ANVISA and compliant with US FDA guidelines.
Pele Nova Biotecnologia	BIOCURE (a natural latex biomembrane extracted from the plant *Havea brasiliensis*) used for treatment of skin lesions (diabetic ulcers, vascular insufficiency ulcers, pressure sores, wounds, others).	Testing the Biomembrane product for timpanoplasty surgery, treatment of second- and third-degree burns, and treatment of urinary incontinence in women. Active ingredient in the membrane product (a VEFG protein) is being developed for cosmetic applications.	Manufacturing according to ANVISA GMP.
Recepta Biopharma	No product on the market yet.	Four monoclonal antibodies at different stages of development for cancer treatment.	Not applicable (no in-house R&D or production facilities).
Silvestre Laboratories	Products include Dermazine (silver sulfadiazine) used as a broad spectrum antibiotic with wound healing activity, Dermacerium (formulation of cerium nitrate and silver sulfadiazine) for burns, diabetic foot, leg ulcers, surgical wound, and Extra Graft XG-13 (bovine collagen-hydroxyapatite composite scaffold for bone tissue regeneration).	Artezine (sodium arthensunate antimalarial rectal cap), Reage (an antiwrinkle cosmetic), HS (herpetic lesion treatment), and a Dermacerium-based leprosy lesion treatment.	ANVISA GMP certified.
União Química Farmacêutica Nacional (São	Over 200 different drug formulations in various categories (for example, antibiotics, corticoids, neuroleptics, anticonvulsives and antidepressants), including \>20 over-the-counter products, 27 generic medicines, 17 ophthalmic	Mucus adhesive and nanoparticle-based ophthalmic products. More details not available.	ANVISA GMP certification.

Company or organization	Products on the market	Products in development	Domestic/international quality certification
Paulo)	products, 75 hospital-use products and 48 products for animal health.		
Service companies			
BIOCANCER	Design, conduct and manage phase 1 through phase 4 clinical trials, including clinical trial planning, site and investigator identification, patient recruitment, medical writing, protocol design and review, data management activities, site monitoring, and conduct of cGCP, cGLP and cGMP audit and compliance activities.	Three products in clinical development: an autologous dendritic cell vaccine against metastatic melanoma, an intralymphonodal vaccine based on multi-peptides associated to GM-CSF in patients with melanoma, and a vaccine based on dendritic cells pulsed with specific peptides in hormone-resistant patients with prostate carcinoma (all were in phase 1 studies in mid-2007).	Not indicated.
BIOMM	Technology transfer and setup of fermentation and purification facilities for protein manufacturing. The company possesses a proprietary bacterial protein expression system.	The company aims to become a contract-manufacturing organization for recombinant proteins and is in the process of setting up a pilot manufacturing facility.	Not applicable.
Cryopraxis Criobiologia (Rio de Janeiro)	Brazil's largest private umbilical cord blood and stem cell bank (with ~10,000 samples stored already). R&D focus on providing cell therapies in the future.	Clinical trials for development of cell therapy procedures for heart malfunction, type I diabetes and neonatal hypoxia. Preclinical tests on cellular differentiation.	ANVISA- cGMP, cGTP and GCP, ISO 9001: 2000, FDA registration.
Intrials Latin America Clinical Research (São Paulo)	A full range of services related to clinical research, including clinical trial design and monitoring, regulatory affairs and data management. Participated in ~130 clinical studies thus far, including pivotal investigational new drug (IND) trials for submission to the US Food and Drug Administration (FDA).	Not applicable.	Adheres to ICH-GCP guidelines; phone audit by FDA in May 2007.
Scylla Bioinformatics	Writes software to assist companies analyze genomic data for a variety of applications. Most of the company's clients have been agricultural firms thus far.	Applications are tailored to client needs.	Not applicable

Company or organization	Products on the market	Products in development	Domestic/international quality certification

cGCP, current good clinical practices, cGLP, current good laboratory practices, cGMP, current good manufacturing practices. FDA, US Food and Drug Administration; ISO, International Organization for Standardization; OHSAS, Occupation Health and Safety Assessment Series.

Table 4.2 Financial background for companies interviewed

Company name	Year founded	Public or private	Approximate revenues (millions Brazilian reais (R$) or US dollars ($))	Grants or low-interest loans from governmental sources (millions Brazilian reais (R$) or US dollars ($))	Sources of private investment/amounts (millions Brazilian reais (R$) or US dollars ($))	Revenues from exports (millions Brazilian reais (R$) or US dollars ($))	Approximate R&D expenditure annually or as stated[b](millions Brazilian reais (R$) or US dollars ($))	Total number of employees (involved in R&D where available)
Aché Laboratórios Farmacêuticos	1966	Private	R$1.77 ($951)	N/A	N/A	R$1.1 ($0.54) in 2006	R$11.9 ($6.4)	2,800
BIOCANCER	2004	Private	N/A	~R$1.5 ($0.8) in 2005 and 2006	Investors include FIR Capital, Biominas Foundation, Jardim Botânico Partners' Novarum Fund (all based in Belo Horizonte)/amounts not disclosed	Many foreign clientele	N/A	15
Biogene	1995	Private	R$0.17 ($0.094)	R$0.09 ($0.05) each year from FINEP and FACEPE	N/A	Just started exporting	R$0.098 ($0.053)	4 (4)
Biolab Sanus Farmacêutica	1996	Private [c]	R$335 ($180)	R$3.7 ($2) from FINEP; R$0.93 ($0.5) from CNPq and R$37 ($20) from BNDES at 6% per year interest (R&D funds shared with União Química)	Castro-Marques Group/R$56 ($30) in past 3 years	N/A	R$20.8 ($11.2); approximately half targeted for radical innovation	1,542 (35)

Company name	Year founded	Public or private	Approximate revenues (millions Brazilian reais (R$) or US dollars ($))	Grants or low-interest loans from governmental sources (millions Brazilian reais (R$) or US dollars ($))	Sources of private investment/amounts (millions Brazilian reais (R$) or US dollars ($))	Revenues from exports (millions Brazilian reais (R$) or US dollars ($))	Approximate R&D expenditure annually or as stated[b] (millions Brazilian reais (R$) or US dollars ($))	Total number of employees (involved in R&D where available)
BIOMM	2002	Publicly listed (On BOVESPA)	R$5.6 ($3)	N/A	N/A	100% foreign clientele base	N/A	15 (8)
COINFAR	2001	Private	No revenues yet	R$3.8 ($2) from FINEP (2005–2007)	Founding shareholders R$11 ($6) from 2002 to 2006	N/A	R$3 ($1.6) expected for 2008 to 2009	6 internal with 20 researchers contracted in Brazilian universities
Cryopraxis Criobiologia	2001	Private[d]	R$22.3 ($12) in 2007	None	None	N/A	N/A	100 (10)
Eurofarma Laboratórios	1972	Private	R$826 ($444)	FINEP funded projects with Brazilian universities (amounts not disclosed)	N/A	N/A	R$37 ($20)	2,300 (20)
FK Biotecnologia	1999	Private	R$0.37 ($0.2) in 2006; R$1.86 ($1) up to July 2007	FINEP loan of R$0.14 ($0.075) in 2001. FINEP grants totaled R$ 3.7 ($2) from 2005 to 2007. R$0.07 ($0.04) in 2004	Angel investors provided R$0.034 ($0.02) in 1999. First-round VC by RSTec venture fund[e] R$1.16 ($0.62) in 2000	Small amounts	R$1.86 ($1)	25 (18)
Hebron Farmacêutica	1990	Private	R$56 ($30)	N/A	N/A	N/A	N/A	550
Intrials Latin America Clinical	1999	Private	N/A	N/A	3 angel investors	Most foreign clientele	N/A	30

Company name	Year founded	Public or private	Approximate revenues (millions Brazilian reais (R$) or US dollars ($))	Grants or low-interest loans from governmental sources (millions Brazilian reais (R$) or US dollars ($))	Sources of private investment/amounts (millions Brazilian reais (R$) or US dollars ($))	Revenues from exports (millions Brazilian reais (R$) or US dollars ($))	Approximate R&D expenditure annually or as stated[b] (millions Brazilian reais (R$) or US dollars ($))	Total number of employees (involved in R&D where available)
Research								
Katal Biotecnológica	1994	Private	R$4.6 ($2.5) in 2005	N/A	Investment by Interteck Internacional Imp. e Exp. (São Paulo) [f] amount not disclosed	N/A	N/A	35 (2)
Labtest Diagnóstica	1971	Private	R$31.6 ($17) in 2006 estimated at R$35 ($19) in 2007	Low-interest loans from Bank of Development, Minas Gerais R$2.8 ($1.5) and BNDES R$2.4 ($1.3)	Undisclosed private sources provided R$0.9 ($0.49)	R$0.84 ($0.45)	R$1.15 ($0.62)	110 (27)
Nortec Química	1985	Private (partly owned by government)	R$37 ($20) in 2006	R$6 ($3.2) from FINEP	N/A	10% of sales revenues	N/A	180 (6)
Pele Nova Biotecnologia	2003	Private	R$1.86 ($1) in 2006; estimated at R$3.3 ($1.8) in 2007	None	REIF Fund (managed by DGF Investments in São Paulo) and two angel investors/over R$7.4 ($4)	N/A	~35% of revenues and investments	15 (4)
Recepta Biopharma	2006	Private	No revenues yet	R$16 ($8.6) from FINEP	Angel investors provided R$3.7 ($2)	N/A	R$6.1 ($3.3)	4 (43 in partner institutions)
Scylla	2002	Private	N/A	R$0.15 ($0.08)	Votorantim	N/A	N/A	8

Company name	Year founded	Public or private	Approximate revenues (millions Brazilian reais (R$) or US dollars ($))	Grants or low-interest loans from governmental sources (millions Brazilian reais (R$) or US dollars ($))	Sources of private investment/amounts (millions Brazilian reais (R$) or US dollars ($))	Revenues from exports (millions Brazilian reais (R$) or US dollars ($))	Approximate R&D expenditure annually or as stated[b] (millions Brazilian reais (R$) or US dollars ($))	Total number of employees (involved in R&D where available)
Bioinformatics				from each of FINEP and FAPESP, with some funds from CNPq	Venture (São Paulo) provided R$0.5 ($0.27)			
Silvestre Laboratories	1984	Private [d]	~R$18.6 ($10)	None	None	N/A	R$3.7 ($2)	65 (10)
União Química Farmacêutica Nacional	1936	Private	R$279 ($150) in 2006	See Biolab information above	See Biolab information above	N/A	R$3.7 ($2) year (for incremental innovation) and R$10 ($5.4) per year for radical innovation	1,800 (some R&D shared with Biolab)

[a]Some figures were provided to us in US dollars, others in Brazilian reais (R$). For consistency, data are presented in both currencies using an exchange rate of $1 being equal to R1.86 Brazilian reais (the approximate exchange rate on September 25, 2007). Where figures have been converted from US funds, the actual amounts in terms of Brazilian currency may differ slightly from the amount stated here depending on the actual exchange rate at the time when they were realized. All financial figures are close approximates and do not represent exact figures.

[b]R&D expenditure is not limited to activities related to novel product development; four digit numbers in parentheses.

[c]Biolab and União Química Farmacêutica Nacional are both owned by Castro Marques Group.

[e]RSTec Venture Fund is a joint creation of Inter-American Development Bank, Brazilian Development Bank (BNDES) and other individuals and programs.

[f]Since the interview, Katal Biotecnológica has been taken over by Interteck International Imp. e Exp. (São Paulo), a former shareholder, and its founder Leonides Rezende has started a new firm focused on molecular diagnostics. N/A, data not available or not disclosed; FINEP, Financiadora de Estudos e Projetos–Brazilian National Studies and Project Funding Agency; FACEP, Fundação de Amparo à Ciência e Tecnologia do Estado de Pernambuco–State of Pernambuco Science and Technology Funding Agency; CNPq, Conselho Nacional de Desenvolvimento Científico e Tecnológico–National Counsel of Scientific and Technological Development; BNDES, Banco Nacional de Desenvolvimento Econômico e Social–Brazilian Development Bank; RHAE, Recursos Humanos Em Áreas Estratégicas–Human Resources in Strategic Areas; FAPESP, Fundação de Amparo à Pesquisa do Estado de São Paulo–The São Paulo State Funding Agency.

Table 4.3Alliances/collaborations between companies interviewed and domestic organizations

Company	Brazilian alliances (past and/or present) and their objectives (where stated)
Aché Laboratórios Farmacêuticos	Joint venture with União Química and Biolab to form COINFAR. Partnerships with the UNICAMP for synthetic compound for type 2 diabetes, with University of Santa Catarina for pharmacological and toxicological studies and with the University of São Paulo for studies in a variety of areas.
BIOCANCER	Partnerships with various hospitals, the Ecoar Image Centre and the Federal University of Minas Gerais (all based in Belo Horizonte) for conducting clinical research.
Biogene	Partnership with FK Biotecnologia for developing human visceral leishmaniasis diagnostic kit. Partnership with Federal University of Campina Grande (Campina Grande) for new brucellosis and toxoplasmosis diagnostic tests. Collaborative and co-development efforts with the Federal University of Pernambuco (Recife).
Biolab Sanus Farmacêutica	Involved in two joint ventures; one with Aché and União Química called COINFAR, which focuses on radical innovations, and the other with Eurofarma and União Química called Incrementha (São Paulo), which is focused on incremental and process innovations. Collaborations with Institute of Energy and Nuclear Research (São Paulo) for Bandgel bandage that enhances treatment of burns and wounds; Federal University of the State of São Paulo and Paulista School of Medicine (São Paulo) for lead compounds in phase 1 and 2; University of São Paulo Faculty of Pharmaceutics and Biochemistry at the University of São Paulo for bioequivalence and bioavailability tests of new pharmaceutical formulations; Centre of Research and Support in Human Reproduction (Salvador) for co-development of Lovelle (desogestrel combined with ethinyl estradiol), a hormonal vaginal contraceptive pill.
BIOMM	Collaborations with University of Brasilia and University of São Paulo for development of bacterial and mammalian expression systems.
COINFAR	Collaboration with Centre for Applied Toxicology at Butantan Institute (São Paulo) for production of EVASINS (endogenous vasopeptidase inhibitors), venom-based hypertension drug and other toxin-based drugs for blood clotting, cardiovascular system, pain perception and immune suppression in preclinical trials. Investment in an early-stage drug development facility with University of Minas Gerais for cardiovascular disease and cancer. Collaborations with the University of Santa Catarina (Florianópolis), University of São Paulo, University of Brasilia, University of Campinas for efficacy and safety testing of various molecules.
Cryopraxis Criobiologia	Collaborations with Federal University of Rio de Janeiro and several hospitals for clinical trials using standardized mononuclear stem cell formulations and Universidade Federal Fluminense (Niterói) for experimental research on cellular differentiation in animal models.

Company	Brazilian alliances (past and/or present) and their objectives (where stated)
Eurofarma Laboratórios	Partner in Incrementha, a joint venture with Biolab and União Química dedicated to development of new products and technologies using nanoparticles and solubilization of insoluble molecules. Collaborations with Inova Biotecnologia Saude Animal (Juatuba); the State University of São Paulo (UNESP) for development of a topical antifungicide and antibiotic, with UNIVALI (Universidade do Vale do Itajaí, Itajaí) in Santa Caterina for an oral analgesic, with Federal University of São Paulo (USP), UNICAMP (State University of Campinas). Working with some Brazilian universities to develop new herbal medicines using Brazilian biodiversity.
FK Biotecnologia	Distributing products through LIFEMED. Collaborations with a large Brazilian firm (not disclosed) and Nanocore (Campinas) for new product development; with Federal University of Rio Grande do Sul (Porto Alegre) for development of biotech products; with the Center for Tumoral Immunology, Immunotherapy and Immunodiagnostics (Porto Alegre), Hopital de Clínicas de Porto Alegre for a clinical trial of a prostate cancer vaccine, the Oswaldo Cruz Foundation (Rio de Janeiro) to develop public health assays, including tests for dengue, leishmaniasis, leptosporosis, HIV and toxoplasmosis.
Hebron Farmacêutica Pesquisa, Desenvolvimento e Inovação Tecnológica	Collaboration with the Antibiotics Institute from UFPE (Federal University of Pernambuco) for development of two of its drugs (Florax, a suspension of *Saccharomyces cerevisiae*; and Giamebil, a hydroalcoholic extract from the *Mentha crispa*plant); with Oncology Department of São Paulo School of Medicine and São Paulo Federal University for development of Imunoglucan; with Pharmacy Laboratory at UFPE for development of Kronel; and with UNICAMP to develop Prostokos (mesoprostol) as a labor inducer.
Katal Biotecnológica	Partnerships with the Federal University of Minas Gerais (UFMG, Belo Horizonte) and University of São Paulo (USP, São Paulo) for development of tests for Chagas disease, rubella, herpes simplex viruses 1 and 2, cytomegalovirus; with UFMG for development of technology for macromolecular stabilization (for example, glycoproteins); with Federal University of Porto Alegre (FEPPS) to develop a less expensive TB test kit for public health; and with the University of São Paulo for oxidized low-density lipoprotein, a sensitive marker of cardiac disease
Intrials Latin America Clinical Research	Offering a joint post-graduate course on clinical research with the Santa Casa School of Medicine (São Paulo) and the Brazilian Association of Contract Research Organizations (ABRACRO; São Paulo) the Brazilian Association of clinical research organizations.
Nortec Química	Collaborations with Cristalia (São Paulo) to develop APIs; ongoing partnership with Farmanguinhos (part of Fiocruz based in Rio de Janeiro) to develop new molecules including antiretrovirals and those for neglected diseases, as well as transfer of technology for production of statins; with Federal University of Rio de Janeiro for consulting services related to chemical synthesis.
Pele Nova Biotecnologia	Collaborations with University of São Paulo for pre-clinical animal models for proof of concept and assessment of therapeutic activity of the company's Biomembrane product and with the University of Campinas to test

Company	Brazilian alliances (past and/or present) and their objectives (where stated)
	dermatological applications of active protein for cutaneous permeation evaluation.
Recepta Biopharma	Funding a laboratory at the Butantan Institute to develop high yielding cell lines for monoclonal antibodies; collaborations with University of São Paulo School of Medicine for immunohistochemical assays; with Sírio Libânes Hospital (São Paulo), Clinical Hospital of University of São Paulo, the Brazilian Institute for Cancer Control (São Paulo), Baleia Hospital (Belo Horizonte), Clinical Hospital of the Federal University of Minas Gerais and the National Cancer Institute (Rio de Janeiro) for conducting clinical research on the company's monoclonal antibodies. Ludwig Institute is both a shareholder and a development partner.
Silvestre Labs	Deal with Farmasa (São Paulo) to promote and distribute Dermazine, Dermacerium and GinoDermazine (1% silver sulfadiazine). Collaboration with Federal University of Rio de Janeiro, University of São Paulo, Federal University of São Paulo, UNICAMP for the development and exchange of projects.
União Química Farmacêutica Nacional	Joint venture with Aché and Biolab to form COINFAR. Collaboration with Universidade Federal do Rio Grande do Sul (Porto Alegre) for development of nanoparticles and UNIFESP for generics bioequivalence studies.

Table 4.4 Collaborations / partnerships between firms interviewed and foreign entities

Company	Alliances and their objectives
Aché Laboratórios Farmacêuticos	Partnerships: with Zeller (Romanshorn, Switzerland) for development of three phytomedicines; with Laboratorios Silanes (Mexico City) to market medicines in different countries; with University of Geneva (Switzerland) and University of Barcelona (Spain) for studies on plant extracts of clinical interest. Deal to distribute cosmetic products for Beiersdorf AG (Hamburg, Germany). Joint venture in planning stage with a foreign firm to construct a factory for the production of biotech-based medicines.
Biogene	Partnership with Fort Doge Animal Health (Kansas City, KS, USA) to develop a diagnostic test for leishmaniasis that can distinguish between leishmania-infected and vaccinated dogs, facilitating vaccination of dogs to prevent human transmission.
Biolab Sanus Farmacêutica	Collaboration with companies in Canada, Italy, Spain and Germany (details undisclosed). Co-marketing deal with AstraZeneca for Crestor (rosuvastatin).
BIOMM	Licensing agreement for tech-transfer and setup of a recombinant human insulin manufacturing facility with a company from Saudi Arabia. Collaborations with University of Halle (Germany) for protein purification and folding; with the University of Miami (Miami) to develop biomaterials and cell encapsulation technologies; with the University of Oulu (Finland) and the Shemyakin Research Institute (Moscow) for other activities; with equipment suppliers for equipment dimensioning and specification, process and equipment scale-up simulations.
COINFAR	Collaboration with US universities to advance safety and efficacy testing of lead molecules.
Cryopraxis Criobiologia	Collaborations with Interchem (Paramus, NJ, USA); with Saneron CCEL Therapeutics for development of clinical trials using umbilical cord blood; with the Texas Heart Institute (Houston) for the development of cell therapy procedures.
Eurofarma Laboratórios	Collaboration with Laboratorio Pablo Cassara (Buenos Aires) and Jurox (Rutherford, Australia). Joint venture with Edol Laboratory (Linda-a-Velha, Portugal) called Themaxis; In-licensing products from Almirall (Barcelona, Spain), Faes Farma (Madrid), Astellas Pharma (Tokyo), Bioderma (Lyon Cedex, France), CIMAB (Havana, Cuba) and DevaTal (Hamilton, NJ, USA) for technology transfer of recombinant Filgrastim and a number of other products. Co-development of a novel monoclonal antibody against EGFR for solid tumors with an international partner.

Company	Alliances and their objectives
FK Biotecnologia	Partners in France for nanotechnology, in Canada for new immunotherapy diagnostics and in Korea for cell therapy. Deal to market in Brazil various products for Applichem (Darmstadt, Germany) and PARTEC (Munster, Germany).
Labtest Diagnóstica	Agreement with Tokyo Boeki (Tokyo) for supplying automatic analyzers. Collaboration with BioKit (Barcelona, Spain) to launch turbidimetric assays and ELISA products.
Nortec Química	Collaborations with Profarmaco (Milan) in joint-venture to manufacture active pharmaceutical ingredients (API); with Rhodia (Paris) to market and provide technical services for API. Deal with Albemarle (Richmond, VA, USA) to distribute an API in Brazil. Collaboration with World Health Organization (Geneva) resulting in export of anthelmintic diethylcarbamazine (anti-filariasis drug) and with the Clinton Foundation (Little Rock, AR, USA) to manufacture the HIV drug dideoxyinosine.
Silvestre Labs	Collaborations with Interchem (Paramus, NJ, USA) to help launch its Dermacerium and ExtraGraft products in the US; with the University of South Florida (Tampa, FL, USA) and Gamete Center at University of Michigan (Ann Arbor, MI, USA).

Table 4.5 Intellectual property (IP) portfolios / marketing rights for the companies interviewed

Company	Patent filed or issued
Aché Laboratórios Farmacêuticos	Thirty international patent applications, including 15 in Brazil. Acheflan (a topical anti-inflammatory) is patented in Brazil and application also submitted through patent cooperation treaty (PCT) in several countries. Shared IP with UNICAMP for a synthetic compound for diabetes.
Biogene	Ten new proteins patents (for diagnosis and vaccination against visceral leishmaniasis). Shares patent with Federal University of Pernambuco in Recife (for new diagnostic tests for leishmaniasis in animals).
Biolab Sanus Farmacêutica	Joint patent with COINFAR for Evasin (an endogenous vasopeptidase inhibitor) filed in Brazil. Others filed through Incrementha for solubilization methods of drugs.
BIOMM	Patents on expression and production of recombinant proteins granted in US, Europe, Russia, Israel, India and pending elsewhere. IP rights on technology platform to produce recombinant proteins in US, Europe and Asia.
COINFAR	Eight patents granted (until 2004) and 36 patent applications filed around the world, mainly US, EU, Japan, India, China.
Cryopraxis Criobiologia	One patent application in Brazil for an umbilical cord blood collection and shipping system.
FK Biotecnologia	One patent application through PCT and Brazilian patent office for cancer vaccine procedure.
Katal Biotecnológica	Two patent applications, including a joint patent application with a university for toxoplasmosis testing during pregnancy.
Nortec Química	Three patents filed in Brazil for production processes
Pele Nova Biotecnologia	One patent in Europe (through European Patent Office) in 2006 and applications filed in over 60 countries for BIOCURE (a rubber material used to treat skin lesions). Applications filed for uses of a VEGF protein with angiogenesis properties for various applications.
Recepta Biopharma	Worldwide licenses for patents related to four monoclonal antibodies held by the Ludwig Institute with worldwide

Company	Patent filed or issued
	rights.
Silvestre Labs	Shares US patent application with an American scientist for the development of filler agents, anti-wrinkle substance, wound healing dressings, cell manipulation technologies.

4.10 Supplemental Information

Purposive sampling was used to identify a representative group of home-grown Brazilian biotechnology and pharmaceutical companies involved in development and provision of health products relevant to prevention or treatment of human diseases. Areas of specialization include: development of biologicals, pharmaceuticals, diagnostics, stem cell therapies, and related technologies and services, targeted to address domestic health needs. We used a case study design where the case was defined as the individual firm. Methodology included consulting local and global experts familiar with the Brazilian biotechnology sector, literature resources, and industry reports and websites, to assist with the selection of cases. For the purpose of this paper, the term biotechnology is used broadly to include the more traditional pharmaceutical companies also, which were included in this study to: a) provide a more comprehensive understanding of the capabilities of the country in providing health products and the challenges facing it, b) these companies are often involved in more classic biotechnological activities also or tend to be among first entrants into this business, c) they are better positioned to conduct innovative activities related to development of health products.

In addition to private companies included in this study, we interviewed representatives of 4 public institutes in order to better understand the Brazilian context, with respect to domestic health product development and commercialization. These organizations play a key role in development and production of many health products in the country and in many cases work with the private sector to facilitate development and production of health products. They include three institutes within the Oswaldo Cruz Foundation in Rio de Janeiro (including: Farmanguinhos, Biomanguinhos and the Centre for Development of Technologies in Health) as well as the Butantan Institute (Sao Paulo). Overall, 24 private companies were approached for an interview: 1 declined outright, 1 withdrew from the study a few months after the interview, and 2 others were not able to participate due to time constraints. Herein we describe the comparative case study analysis of 19 private-sector Brazilian health biotechnology firms, which fully participated in the study (listed in **Table 4.1**). The vaccine manufacturers, the Butantan

Institute and Biomanguinhos, are also covered extensively due to their prominent role in providing vaccines for the Brazilian population.

Semi-structured and open-ended interviews were conducted on-site with representatives of all firms and institutes listed, between August 2006 and March 2007, were recorded by audiotape, transcribed, coded and analyzed using qualitative research methodology. The five major themes explored during the interviews included: core competencies, product/service portfolios and pipelines; capabilities along the product development value chain; alliances and partnerships; barriers and incentives for development; and financial issues. In addition to the primary interviews, data was also collected from literature sources, and relevant documents and company websites. Study participants were asked to fact-check the data presented in the tables and boxes prior to publication, to ensure the information is up-to-date and accurate. This study was approved by the research ethics board of the University of Toronto.

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Chapter 5
New Vaccine and Medicinal Innovations

5 Globalization of Health Innovation

5.1 Introduction

After decades of copying existing health products developed elsewhere, a growing number of indigenous enterprises in China, India, and Brazil have begun to develop innovative products of their own. This change has been sparked by these countries' adoption of pharmaceutical product patent regimes—as part of their commitments under the World Trade Organization's Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement—and enhanced governmental support for innovation.

During the past four years we have published a series of articles in this journal discussing health biotech sectors in China, India, Brazil, and South Africa [1-4]. Each of those studies focused on approximately two-dozen indigenous enterprises involved in the development and provision of vaccines, therapeutics, and diagnostic tests. The cited publications covered products and services, partnerships, intellectual property portfolios, business models, financial environments, entrepreneurial barriers to innovation and recommendations for advancing health biotech development in each country. We have also discussed the potential role of emerging market enterprises for global health [5-7].

This paper builds upon and updates our previous work and focuses more deeply on new vaccines and therapeutics in the innovation pipelines of indigenous enterprises in China, India, and Brazil. We examined: a) pharmaceutical innovations based on small-molecule drug development involving *new chemical entities* (NCEs), b) biotech-based innovations based on large molecules, nucleic acids, and whole cells (collectively referred to as *biotechnological entities* or BEs), and c) innovations involving traditional medicines, herbal compounds and other biodiversity resources, which are collectively referred to here as *plant-based medicines*. The third group can involve finished products or the generation of NCEs or BEs as therapeutic leads.

The key criteria for including specific firms in our analysis were that: 1) companies had to be indigenous enterprises and not off-shoots of multinationals or foreign companies, and 2) they needed to have one or more new vaccine or therapeutic leads in their pipeline and/or have already succeeded in developing and marketing such products. Company selection was informed by our previous studies, through an extensive search of publicly available online sources and publications, and consultations with key informants familiar with biotech and pharmaceutical sectors in each country. Approximately two-thirds of companies included for this analysis have been interviewed as part of our previous studies, while one-third update that earlier data set. Data derive from interviews with firm representatives (in the two thirds of companies studied previously), company websites, and other publicly available online sources. Information regarding specific product leads, their chemical/molecular nature, targeted indication(s), and the latest known developmental phase were tabulated and analyzed.

Overall, we identified 176 innovative products within 43 indigenous firms in China, India, and Brazil. Data on specific firms, their innovative products and respective development phases are presented in **Table 5.1, Table 5.2, Table 5.3**, and **Figure 5.1** and **Figure 5.2**. Of all the products studied, Indian firms had 87 (49% of total), Chinese firms had 63 (36%) and Brazilian firms had 26 (15%). We describe below the types of innovation, therapeutic and vaccine applications, stages of development, and targeted indications with respect to innovative products or product leads. To our knowledge, this is the first empirical study to detail innovative health products in the pipeline of companies in these emerging economies in a comprehensive fashion.

5.2 Types of Innovation

Overall, pharmaceutical and biotech-based innovations are roughly equally represented in our sample (composing 45% and 44% of products respectively), but with considerable variation in their distribution across countries (see **Figure 5.1**). While China has a greater focus on biotech innovations (57% of its products), India's main focus is on pharmaceutical innovations (56% of its products). Approximately a third of Indian and Brazilian products involve biotech innovations. Brazil's greater focus on plant-based medicines (20% of cases) distinguishes it from China (at 13%) and India (at 7%).

5.2.1 Therapeutics

Seventy-nine percent of all product leads identified across the three countries target therapeutic applications. This portion is composed of all pharmaceutical, 53% of biotech, and all plant-based product leads identified. Examples of pharmaceutical NCEs in development include a drug candidate for HIV/AIDS by China's Fusogen (Tianjin), and two therapeutic leads for diabetes by India's Dr. Reddy's Laboratories (Hyderabad) and Glenmark (Mumbai). Over half (56%) of biotech-based leads in China are targeted at therapeutic applications compared to 34% in India—relating to China's unique focus on genetic and stem cell therapies and India's greater focus on vaccines for communicable diseases. Anti-cancer gene therapy products marketed a few years ago by Shanghai Sunway (Shanghai) and Shenzhen SiBiono (Shenzhen) are among nine such products within four Chinese companies. A number of Chinese companies, including Beike Biotechnology (Shenzhen) and SinoCells Biotech (Beijing), are engaged in development and marketing of stem cell therapies [8]. Other BEs in development include peptide-based therapeutic candidates and monoclonal antibodies. Overall, we identified 8 peptide-based therapeutic leads and 12 drug candidates based on monoclonal antibodies. Biocon's (Bangalore) oral insulin and Zenson's (Shanghai) recombinant peptide against heart failure are in phase III clinical development. The most advanced monoclonal antibody candidates include one against glioma and non-small cell lung cancer (NSCLC) being developed by Biocon (Phase III), and another against ovarian cancer by Brazil's Recepta Biopharma (phase II, São Paulo).

5.2.2 Vaccines

Of the 40 projects (23% of total) involving vaccine development, India accounts for 21 (53%), followed by China at 17 (42%) and Brazil at 2 (5%). Almost all vaccine leads in China and India target infectious diseases. Examples of innovations in this category include marketed H1N1 vaccines by China's SinoVac (Beijing) and India's Zydus Cadila (Ahmedabad) and Bharat Biotech International (Hyderabad), a novel hepatitis E vaccine awaiting regulatory approval by China's Xiamen Innovax Biotech (Xiamen), and two malaria vaccines in development by Bharat Biotech and Ranbaxy (Gurgaon). Brazil's FK Biotec (Porto Alegre) has two therapeutic Vaccines in development against prostate cancer (in phase III) and myeloma (phase I), and China's Zenson is developing a therapeutic vaccine for a variety of cancers (phase I).

5.3 Stages of development

The majority of innovative products are at an early developmental stage (see **Figure 5.3**). Thus far only 14 products (8%) have reached the domestic market, and Chinese firms account for 8 (57%) of these. Another 22 (13%) product leads are in phase III clinical trials or awaiting regulatory approval from their respective national regulatory agencies, with India accounting for 11 (50%) of these, followed by China and Brazil at 8 (36%) and 3 (14%), respectively. Balaglitazone, a lead drug candidate for type II diabetes—discovered by India's Dr. Reddy's laboratories, and being co-developed with Denmark's Rheoscience (Roedovre)—has the potential to become the first major FDA-approved innovative drug developed by an emerging market company. Other products in phase III clinical trials include: a lead candidate for diabetes by Glenmark, an oral insulin formulation by Biocon, a recombinant peptide for heart failure and dilated cardiomyopathy by Zenson, and Aché Laboratories' (São Paulo) phytotherapeutic against metabolic syndrome.

5.4 Indications

Approximately 20 (11%) of all product leads in the three countries target diseases that primarily affect the developing world; with the vast majority being vaccines against infectious diseases. Examples of such products involve cholera vaccines (by India's Shantha Biotechnics and China's Shanghai United Cell Biotechnology), malaria vaccines (by India's Bharat Biotech and Ranbaxy), and rabies vaccine (by China's SinoVac). The majority (89%) of innovative products within the pipeline of emerging market firms target global diseases that have markets in both developed and developing nations. The leading indications targeted by the Chinese and Brazilian firms studied involve various forms of cancer, accounting for approximately one-third of innovative products in each country. By contrast, the most commonly targeted indication for Indian companies is diabetes and closely related indications (accounting for 25%), followed by cancer (14%). Liver disease prevention and treatment constitutes the second most commonly targeted indication among the Chinese firms studied—accounting for approximately 16% of their projects. Furthermore, among the innovative leads in China that target cancer there is a considerable emphasis on head and neck cancers. These findings coincide with studies showing that liver diseases and head and neck cancers are of particular relevance to China [9-13], and diabetes is a major and growing condition afflicting the Indian population [14, 15].

5.5 Concluding Remarks

The results presented here suggest that the near monopoly on innovation in vaccines and medicines by firms in the industrialized world is near an end. “India is poised to become the medicine maker to the world,” Dr. Swati Piramal, Vice Chairperson of Piramal Life Sciences (Mumbai) told us in an interview. “‘In-China for global’ is our business model”, said Dr. Samantha Du, CEO of the Shanghai-based Hutchison Medipharma, when we visited her company. The confidence exuded by Drs. Piramal and Du is increasingly common among health entrepreneurs across the emerging markets studied in our experience interviewing dozens of such individuals over the past five years.

We will not have identified every innovative product or every innovating company in these three countries, so the view is necessarily incomplete. However, it is clear that a growing number of health enterprises in these emerging economies are moving up the value chain by taking on the more challenging and costly innovations required to create new medicines and vaccines. At the same time, most innovative products we identified are still in early stages of development. So the full force of the innovative capacity of these countries will be seen in the future. Dr. Piramal told us that: “discovering and developing new drugs will change the paradigm as India brings affordable drugs not just for India but for the global market”. Time will tell if this prediction is correct.

5.6 Figures

Figure 5-1 Total number of companies, new chemical entities (NCEs), new biotech entities (BEs) and plant-based leads in the pipelines of indigenous companies in China, India and Brazil; 2009/2010

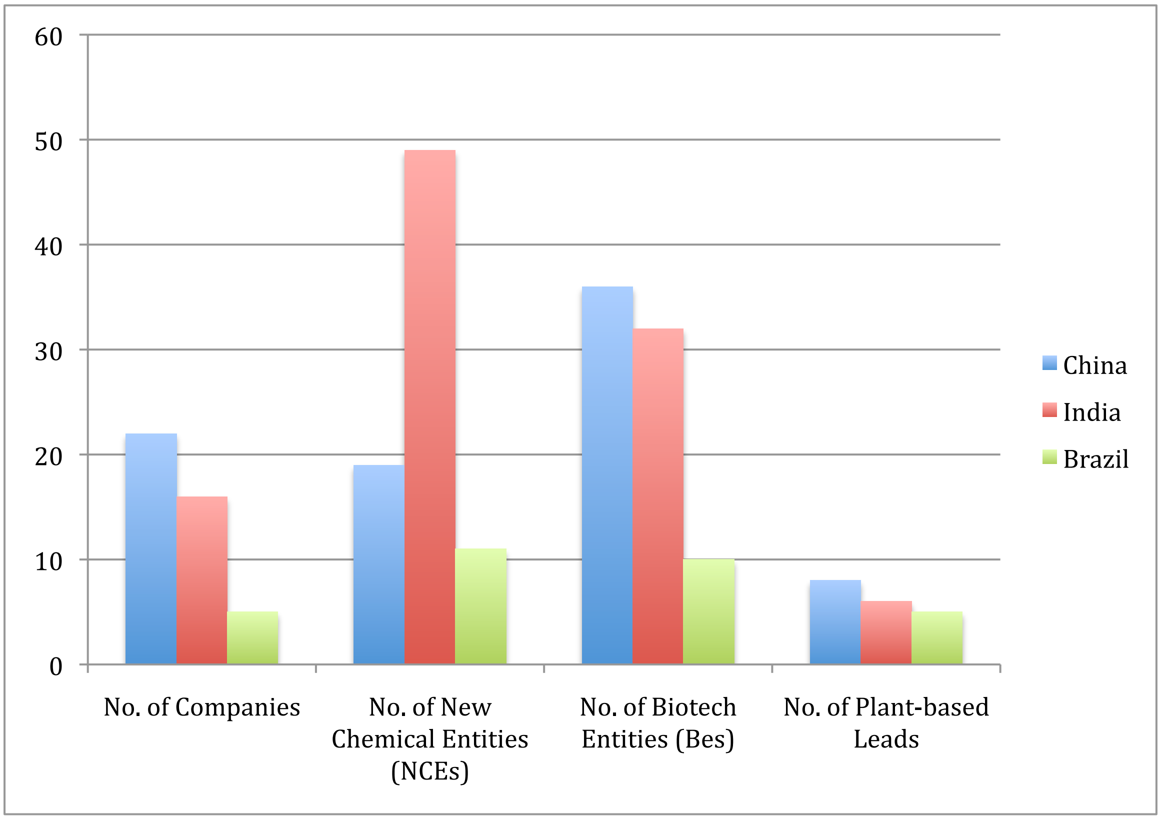
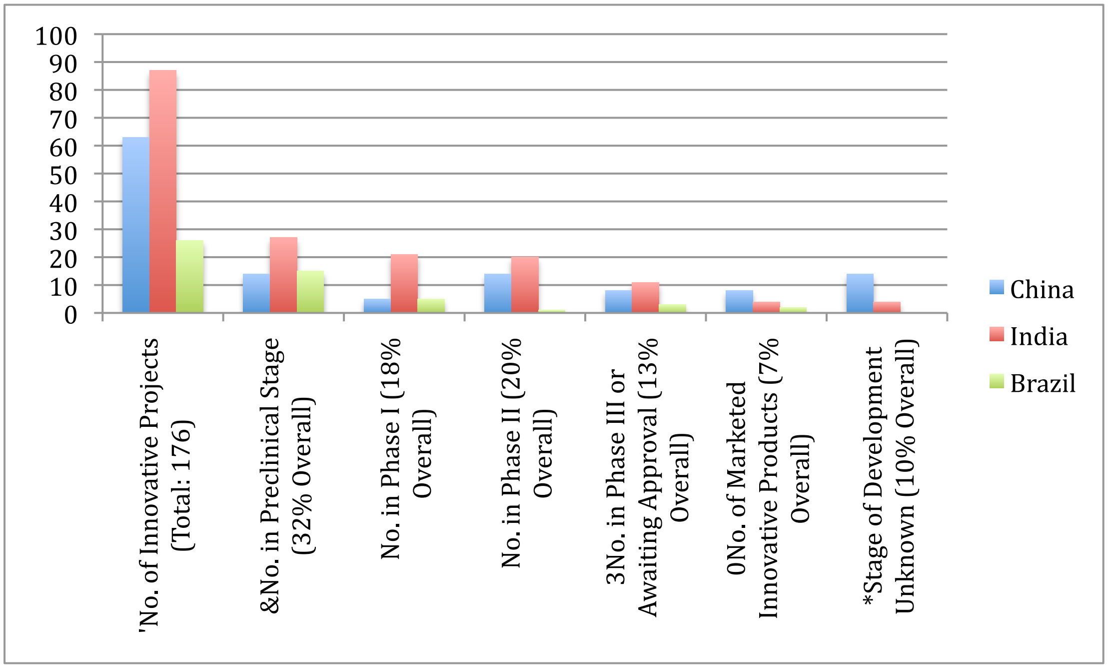


Figure 5-2 Total number of innovative therapeutic or vaccine candidates within indigenous companies in China, India and Brazil and their stage of development; 2009/2010



5.7 Tables

Table 5.1 Chinese companies with innovative vaccines or medicines in development or on the market, and breakdown of these products with respect to the nature of the product, targeted indication(s) and development phase

Company Name	Innovative Pipeline Leads or marketed Products	Targeted Indication(s)	Development Phase	Nature of the product*
Fusogen (Tianjin)	Sifuvirtide (HIV Fusion Inhibitor)	HIV/AIDS	Phase II	NCE
Hutchison MediPharma (Shanghai)	HMPL004	Ulcerative Colitis and Crohn's Disease	Phase II Completed	Plant-based Medicine
	HMPL011 (A Cytokine Modulator)	Rheumatoid Arthritis and Multiple Sclerosis	Phase II	NCE
	HMPL-813 (EGFR Kinase Inhibitor)	Cancer	Preclinical	NCE
	PMPL012 & PMPL013	Cancer	Preclinical	NCE
Sinovac Biotech (Beijing)	Hepatits A Vaccine (Inactivated)	Hepatitis	On the Market	BE
	Hepatitis A & B Combination Vaccine	Hepatitis	On the Market	BE

	Haemophilus Influenza Type b (HiB) Vaccine	Haemophilus Influenza	N/A	BE
	H5N1 Influenza Vaccine	Influenza	On the Market	BE
	Attenuated mumps vaccine	Mumps Disease	Under Review at SFDA	BE
	H1N1 Influenza Vaccine	Pandemic Influenza	On the Market	BE
	SARS Vaccine	Severe Acute Respiratory Syndrome	Phase II	BE
	Enterovirus 71 (EV71) Vaccine	Hand, Foot and Mouth Disease	N/A	BE
	Animal Rabies Vaccine	Rabies	N/A	BE
	Meningitis Vaccine	Meningitis	N/A	BE
Shanghai Ambrosia Pharmaceuticals Co. Ltd. (Shanghai)	2 Natural Anti-inflammatory Compounds (From TCM) APL 001 & APL 002	For leucopenia and also in combination with IFNs to treat hepatitis and other viral infections	N/A	Plant-based Medicine
	APL 003	Rheumatoid arthritis, asthma and other autoimmune diseases	N/A	Plant-based Medicine

	APC001 and APC002	Cancer	N/A	Plant-based Medicine
	2 Synthetic Compounds (APC 004 & APC 005)	Anti-cancer	Preclinical	NCE
	APV-001	Anti-viral	N/A	Plant-based Medicine
	APD-001 to APD-003	Diabetes	N/A	Plant-based Medicine
Shanghai Genomics (Shanghai)	F351 - A Non-steroid Anti-inflammatory	Pulmonary Fibrosis	Preclinical	NCE
		Liver Fibrosis	Phase II	NCE
Shanghai Sunway (shanghai)	Oncorin (Modified Oncolytic Adenovirus H101)	Nasopharyngeal squamous cell carcinoma	On the Market	BE
	Modified Oncolytic Adenovirus H103	Cancer	Phase II	BE
	Modified Oncolytic Adenovirus H102	Cancer	Preclinical	BE
Shenzhen Chipscreen (Shenzhen)	Chidamide Class I histone deacetylase (HDAC) Inhibitor (HBI-8000)	NSCLC, Breast Cancer, Prostate Cancer, DLBCL, CTCL, PTCL-U)	Phase II	NCE
	Chiglitazar - PPAR Pan Agonist	Type 2 Diabetes	Phase II	NCE

	Modified Oncolytic Adenovirus H101	Cancer	Preclinical	BE
	3 other NCEs	Cancer	Preclinical	NCE
Shenzhen SiBiono (Shenzhen)	Gendicine - Recombinant Human p53 Adenovirus	Nasopharengeal Carcinoma	On the Market	BE
	New Gendicine Formulations (fortified with additional genes)	Various cancer types	Various stages of development	BE
Tiandakang Gene Engineering (Shenzhen)	Novel Drug Candidate	Liver Cancer	Phase II	NCE
Kanghong Pharmaceuticals (Chengdu)	KH902- A Recombinant Fusion Protein	Age-related Macular Degeneration	Phase II	BE
Zensun Sci & Tech Co. (Shanghai)	NEUCARDINTM (rhNRG-1 is a genetically engineered recombinant peptide fragment of neuregulin-1 (β2a isoform))	Intermediate to advanced heart failure and dilated cardiomyopathy	Phase III	BE
	Therapeutic Vaccine (rhErbB3-f is a recombinant human ErbB3 receptor fragment)	ErbB2-overexpressing breast, ovarian, colon, lung and prostate cancers	Phase I	BE
	Monoclonal Antibody	Small Cell Lung Cancer (SCLC)	Preclinical	BE
Xiamen Innovax Biotech	Hepatitis E Vaccine	Hepatitis	Under Review	BE

Co.,Ltd. (Xiamen)	Hepatitis E Vaccine	Hepatitis	at SFDA	BE
	HPV Vaccine	Cervical Cancer	Phase I	BE
Shenzhen Beike Biotechnology (Shenzhen)	Umbilical Cord Mesenchymal Stem Cells	Being tested for Duchenne Muscular Dystrophy, Spinocerebellar Ataxia and Multiple Sclerosis	Phase II	BE
	4 Other types of Stem Cells	Variety of Indications including: systemic lupus erythematosus; Optic nerve hypoplasia; Diabetic foot; Spinal cord injury; Cerebral palsy	Phase I/II	BE
SinoCells Biotech (Beijing)	Autologus Mesynchimal Stem Cells	Corneal Disease	N/A	BE
Shanghai United Cell Biotechnology Co. Ltd. (Shanghai)	Recombinant human parathyroid hormone rhPTH (1-34)	Osteoporosis	Under review at SFDA	BE
	Recombinant B-subunit/Whole Cell Cholera Vaccine	Cholera and Enterotoxigenic *E. Coli*	Under Review at SFDA	BE
Vector Gene Technology Co. Ltd. (Beijing)	Gene Therapy Product	Lower Limb Ischemia	Phase I	BE
	Gene Therapy Product	Hemophilia B	Preclinical	BE

			Completed	
	Gene Therapy Product	Lung Cancer	Preclinical Completed	BE
Beijing Weigu Biopharmaceutical Co. Ltd. (Beijing)	EV71 Vaccine (Inactivated)	Hand, foot, and mouth disease (HFMD)	Under Review at SFDA	BE
Yuxi Walvax Biotech Co. Ltd.	Polyvalent Pneumococcal Vaccine	Pneumococcal Disease	Under Review at SFDA	BE
Beijing Minhai Biotechnology Co. Ltd. (Beijing)	Polyvalent Pneumococcal Vaccine	Pneumococcal Disease	Under Review at SFDA	BE
Gloria Pharmaceuticals Co. Ltd. (Harbin)	SX004 (a multi-target tyrosine kinase inhibitor)	Leukemia	Preclinical Completed	NCE
Jiangsu Chia-tai Tianqing Pharmaceutical Co. Ltd (Lianyungan)	Magnesium Isoglycyrrhizinate	Chronic viral hepatitis	On the Market	NCE
	Adefovir Dipivoxil	Hepatitis B Infection Treatment	On the Market	NCE
Shenzhen Kangzhe Pharmaceutical Co. Ltd. (Shenzhen)	Tyroserleutide (mitomycin, Fluorouracil Combination)	Hepatocellular Carcinoma	Phase II	NCE

* Abbreviations: NCE = New Chemical Entity, BE = Biotechnological Entity.

Table 5.2 Indian companies with innovative vaccines or medicines in development or on the market, and breakdown of these products with respect to the nature of the product, targeted indication(s) and development phase

Company Name	Innovative Pipeline Leads or marketed Products	Targeted Indication(s)	Development Phase	Nature of the product*
Biocon (Bangalore)	IN-105 (Oral Insulin)	Diabetes	Phase III	BE
	T1h - Anti-CD6 (Humanised Monoclonal Antibody)	Inflammation in Rheumatoid Arthritis and Psoriasis	Phase II	BE
	BIOMAb EGFR	Glioma and NSCLC	Phase III	BE
	BVX-20 (Monoclonal Antibody)	Non-Hodgkin's Lymphoma	Preclinical	BE
	2 Other Mabs	Cancer	Preclinical	BE
Panacea Biotec (New Delhi)	Small Molecule	Anti-infective	Preclinical	NCE
	Small molecule	Diabetes	Preclincal	NCE
	Small Peptide	Rheumatoid Arthritis	Preclinical	BE
	H1N1 Flu Vaccine	Swine Flu	Phase III	BE

	Dengue Vaccine	Dengue Fever	Phase 1	BE
	Japanese Encephalitis Vaccine	Japanese Encephalitis	N/A	BE
	Bivalent Oral Polio Vaccine	Polio	On the Market	BE
Shantha Biotechnics (Hyderabad)	Recombinant Hepatitis B Vaccine	Hepatitis	On the market	BE
	Oral Cholera Vaccine	Cholera	Phase I	BE
	Typhoid Vaccine	Typhoid Fever	Phase I	BE
	Pneumococcal Vaccine	pneumococcal infections	Preclinical	BE
	Rotavirus Vaccine	Infectious Diarrhoea	Phase II	BE
Bharat Biotech (Hyderabad)	Malaria Vaccine	Malaria	Phase I	BE
	Typhoiv Vaccine	Typhoid Fever	Phase III	BE
	H1N1 Flu Vaccine (Cell based)	Swine Flu	On the Market	BE
	Rotavirus Vaccine	Infectious Diarrhoea	Phase II	BE

Serum Institute of India (Pune)	Meningitis A, Y, C, W-135 Quadrivalent Vaccine	Meningitis	N/A	BE
	Bladder Cancer Vaccine	Cancer	N/A	BE
	Rotavirus Vaccine	Infectious Diarrhoea	Phase II	BE
	H1N1 Flu Vaccine	Swine Flu	Phase III	BE
	Pneumococcal Polysaccharide & Conjugate Vaccine	Pneumonia	Preclinical	BE
	Aerosol-based Measles Vaccine	Measles	Phase II	BE
Piramal Life Sciences (Mumbai)	P276-CDKs (individually and in combination with Gemcitabine and Radiation)	Head and Neck, Mantle Cell Lymphoma and Pancreatic Cancers	Phase II	NCE
	P1446-CDKs	Oncology	Phase I	NCE
	P2745	Oncology	Preclinical	NCE
	NPB00105-Bcr-Abl	Chronic Myeloid Leukemia	Phase II	Plant-based Medicine
	NPS31807-TNFα	Rheumatoid Arthritis and Psoriasis	Phase II Completed	Plant-based Medicine

	P1736 (Non-PPARɣ)	Type II Diabetes	Phase II	NCE
	NPH30907	Dermatophytosis	Phase II Completed	Plant-based Medicine
	PP9706642	Herpes Simplex Virus-Type 2	Preclinical	Plant-based Medicine
	PM181104	MRSA/VRE	Preclinical	NCE
	PM181108	Anti-Infective (MRSA and Vancomycin-resistant enterococcus)	Preclinical	NCE
	P3914 - NSAID	Nonsteroidal anti-inflammatory Diseases	Preclincal	NCE
	DGAT1	Obesity/Metabolic Disorders	Preclinical	NCE
	PL225B-Merck	Oncology	Preclincal	NCE
	P1201-Lilly, P2202-Lilly	Diabetes and Metabolic Disorders	Phase I	NCE
Wockhardt (Mumbai)	WCK771 - Antibiotic	Antibiotic against staphylococcal infections	Phase II	NCE
	WCK1152 - Antibiotic	Respiratory tract infections	Phase I	NCE
	DRL 17822 (CETP Inhibitor)	Dyslipidemia and Atherosclerosis	Phase I	NCE

Dr. Reddy's Laboratories (Hyderabad)	DRL 17822 (CETP Inhibitor)	Dyslipidemia and Atherosclerosis	Phase I	NCE
	Balaglitazone	Diabetes	Phase III	NCE
	DRL 2546	COPD	Phase I	NCE
	DRL 21994 and DRL 21995	Dyslipidemia	Preclinical	NCE
Suven Life Sciences (Hyderabad)	SUVN-502	Alzheimers, Schitzophrenia	phase II	NCE
	4 leads (5-HT6 Antagonists)	Neurodegenerative Diseases	Preclinical	NCE
	SUVN-504 (5-HT6 Antagonist)	Obesity/Metabolic Disorders	Preclinical	NCE
	SUVN-911 (nAChR Alpha-4 Beta-2 Antagonist)	Major Depressive Disorder	Preclinical	NCE
Gelnmark Pharmaceuticals (Mumbai)	Melogliptin	Diabetes	Phase III	NCE
	GRC 4039 (PDE IV Inhibitor)	Rheumatoid Arthritis, Multiple Sclerosis	Phase I Completed	NCE
	GRC 8200 (DPP IV inhibitor)	Type II Diabetes	Phase II Completed	NCE
	GRC 10693 (CB-2 Receptor Agonist)	Neuropathic Pain, Osteoarthritis and other Inflammatory Pain	Phase I Completed	NCE
	GRC 15300 (TRPV3 Antagonist)	Osteoarthritic and Neruopathic pain	Phase I	NCE

	Crofelemer (CFTR Inhibitor)	HIV Associated Diarrhoea, Adult Acute Infectious Diarroea	Phase III	NCE
	GBR 500 (Monoclonal Antibody, VLA-2 Adhesion Molecule Antagonist)	Multiple Sclerosis, Inflammatory Bowel Disorders	Phase I	BE
	GBR 600 (Monoclonal Antibody, Anti-Platelet Against Von Willebrand Factor)	Acute Coronary Syndrome	Phase I	BE
	GRC 17536 (TRPA1 Receptor Antagonist)	Pain, Respiratory Disorders	Phase I	NCE
Lupin Pharmaceuticals (Pune)	LLL 2011	Migrane	Phase III	Plant-based Medicine
	LL 4858	Tuberculosis	Phase II	NCE
	LL 4218	Psoriasis	Phase II	NCE
	LLL 3348	Psoriasis	Phase II	Plant-based Medicine
	Lead Compound	Diabetes	Preclinical	NCE

	2 Lead Compounds	Rheumatoid Arthritis, Diabetes	Preclinical	NCE
Stempeutics (Bangalore)	Stem Cell-based Therapy	Myocardial infarction and individuals with critical limb ischemia (CLI)	Phase II	BE
Zydus Cadila (Ahmedabad)	ZYOG1 (Glucagon-like Peptide-1 Agonist)	Type 2 Diabetes	Phase I	BE
	ZYH1	Dyslipidemia	Phase III	BE
	ZYI1	Anti-inflammatory and pain management	Phase II	NCE
	ZYO1	Anti-obesity	Phase I Completed	NCE
	ZYH7, ZYH2, ZYT1	Dyslipidemia and metabolic disorders, diabetes, dyslipidemia Respectively	Phase I	NCE
	H1N1 Flu Vaccine (VaxiFlu-S)	Swine Flu	On the Market	BE
Orchid Chemicals and Pharmaceuticals Ltd. (Chennai)	BLX-1002 (thiazolidinedione)	Type 2 Diabetes	Phase II Completed	NCE

Ranbaxy (Gurgaon)	RBx 11160 (Arterolane)	Malaria	Phase III	NCE
Torrent Pharmaceuticals (Ahmedabad)	Advanced Glycosylation End-products breaker compound	Treatment of complications related to diabetes (e.g. neuropathy, nephropathy, retinopathy and heart failure).	Phase II	NCE
	T2 Analog	Metabolic Syndrome	Phase I	NCE
	Anti-hypertensive Compound	High blood pressure	Preclincal	NCE

* Abbreviations: NCE = New Chemical Entity, BE = Biotechnological Entity.

Table 5.3 Brazilian companies with innovative vaccines or medicines in development or on the market, and breakdown of these products with respect to the nature of the product, targeted indication(s) and development phase

Company Name	Innovative Pipeline Leads or marketed Products	Targeted Indication(s)	Development Phase	Nature of the product*
Aché Laboratórios Farmacêuticos (São Paulo)	Achéflan	Topical Anti-inflammatory	On the Market	Plant-based Medicine
	ACH 04	Anti-diarrhea	Phase I	Plant-based Medicine
	ACH 05	Cognitive Disorder	Phase III	Plant-based Medicine
	ACH 09	Metabolic Syndrome	Phase III	Plant-based Medicine
	ACH 15	Anti-inflammatory	Phase I	NCE
	ACH 16	Anti-diabetic	Preclinical	NCE
	ACH 17	Erectile Dysfunction	Preclinical	NCE
	ACH 20	Hepatic Steatosis	Preclinical	NCE

	ACH 24	Virtiligo	Phase I	Plant-based Medicine
Pele Nova Biotecnologia (São Paulo)	Protein-based Lead	Rheumatoid Arthritis and Colitis	Phase I	BE
FK Biotec (Porto Alegre)	Whole-cell Autologous Therapeutic Vaccine	Prostate Cancer	Phase III	BE
	Cell-based Cancer Vaccince	Myeloma	Phase I	BE
	Humanized Monoclonal Antibody	Gastrointestinal, Breast and lymphatic cancers	Preclinical	BE
	Small Molecule	Myeloma, Lymphoma and Melanoma	Preclinical	NCE
Recepta BioPharma (São Paulo)	mAb hu3S193 – A Monoclonal Antibody	Ovarian Cancer	Phase II	BE
	3 Monoclonal Antibodies	Cancer	Preclinical	BE
Cristalia (Itapira)	Lodenafil carbonate	Erectile Dysfunction	On the Market	NCE
	Anagesic Peptides (Kappa receptor inhibitor)	Acute and Chronic Neuropathic Pain	Preclinical	BE
	LassBio 753 (Anti-TNF inhibition)	Acute and Chronic Pain	Preclinical	NCE

	Cris 074 (Antiretroviral protease inhibitor)	HIV/AIDS	Preclinical	NCE
	Cris 123 (Adenosin Kinase Inhibitor)	Metabolic Syndrome	Preclinical	NCE
	LassBio 294 (Cardiotonic)	Heart Failure	Preclinical	NCE
	GRP Antagonist Peptide	Cancer treatment	Preclinical	BE
	Lidocaine Analogs	Acute Asthma	Preclinical	NCE

* Abbreviations: NCE = New Chemical Entity, BE = Biotechnological Entity.

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Chapter 6
Biopharmaceutical Innovation After TRIPS

6 Biopharmaceutical Innovation in China, India and Brazil after TRIPS

6.1 Introduction

Over the past two decades China, India and Brazil have made significant strides to develop capabilities in the biotechnology and pharmaceutical sectors. Economic growth and rapid expansion of the overall pharmaceutical markets in these counties have also helped to maintain the momentum towards innovation. Indications of this shift are evident in both government policy and industrial activities. The transition from largely generics-based into innovative activities has been kindled by the adoption of product patent regimes as part of these nations' commitments under the World Trade Organization's Trade-related Aspects of Intellectual Property (WTO-TRIPS) agreement. All three countries have now been signatories to this treaty for at least five years, and in all cases have been aware of its pending enforcement for over 15 years. As such, institution of product patent regimes in these countries represents a key point of technological and business discontinuity for domestic industries, and provides an ideal opportunity to explore how they have responded to this change.

The objective of this paper is to explore how national institutions, public policy and industry globalization interact to shape commitments to new drug and vaccine innovations by indigenous biotechnology and pharmaceutical (henceforth biopharmaceutical) firms in China, India and Brazil. It starts out by the observations made in chapter 5, which analyzed new drug and vaccine development by domestic enterprises. The paper then underscores institutional factors that contribute to limiting private investments in drug and vaccine development.

Discussions in this paper are presented in the following order. First, research design and methodological aspects are reviewed. Second, key background information including: theoretical aspects related to the role of institutions in innovation, and key governmental support policies aimed at advancing science and technology (S&T) innovation in each country are presented. Third, empirical findings related to entrepreneurial involvement in novel drug and vaccine innovations in China, India and Brazil are presented. Fourth, findings related to the latter are discussed in light of several institutional challenges that limit private investment in novel drug and vaccine discovery in the stated countries. Lastly, the implications of this study are explored with respect to relevant literature and national innovation policy. The paper ends with a few concluding remarks.

6.2 Research Design & Methodology

This research uses a qualitative case study design, where a case is defined at two levels. The biopharmaceutical sectors in China, India and Brazil each represent a country-case. Each country case is then informed by a group of 'nested' cases, which represent indigenous enterprises in each country. The primary data-source is semi-structured, face-to-face interviews with key executives of selected enterprises and other key-informants familiar with the sector in each country or involved in related institutions. Secondary data sources include relevant publications and enterprise and government documents and websites. Lastly, this analysis has benefited from cite visits to nearly all companies studied, attendance at a number of relevant conferences in each country and observing general trends in the sector. A detailed list of data sources include the following:

Key informant interviews: This study has been informed by primary data from 99 interviews representing 61 companies and 25 institutions involved in the biopharmaceutical sectors in China, India and Brazil between 2006 and 2009. A breakdown of interviewee categories is shown in **Table 6.1**. Interview data were collected between 2006 and 2009 as part of a series of country-specific case studies. As such, this paper presents a cumulative analysis of all related data.

The first set of studies were published as a series in the *Nature Biotechnology* journal focused on understanding the role of the private sector in health product development and provision [1-3]. Those studies involved an array of companies across the health product development value-chain involved in the development and production of vaccines, diagnostics and therapeutics. A second set of interviews conducted in 2009 aimed more directly at indigenous firms with novel health products in the pipeline, and included interviews with institutional informants.

Innovative Product data: This paper is also informed by findings from the previous chapter, highlighting new vaccine and medicinal innovations in Brazil, China, and India.

Core arguments of this paper are advanced in light of three propositions as follows:

> **Proposition 1:** Introduction of product patent regimes in China, India and Brazil (& TRIPS adoption) has had only a modest impact on indigenous attempts at development of drugs and vaccines based on new chemical or molecular entities (NCMEs)
>
> **Proposition 2:** Barriers to private investments into NCMEs are largely institutional in nature
>
> **Proposition 3:** National policies aimed at changing the overall economic incentive structure would likely have only marginal impacts due to considerable influence from extra-national factors

6.3 Theoretical and Background Information

6.3.1 Innovation Systems Theory

Over the past number of decades, there has been a growing recognition that technological innovation is a by-product of interactive processes involving various institutions, organizations and individuals. Developed most prominently by Freeman [4], Lundvall [5] and Nelson [6], the systems of innovation (SI) framework has denoted a movement away from the traditional '*linear*' model of innovation to one that views innovation as product of a systemic phenomenon. Innovation system has been defined to include: "*all important economic, social, political, organizational, institutional, and other factors that influence the development, diffusion, and use of innovations*" [7]. The notion that innovation can be viewed as a territorial phenomenon, with the most important interactions taking place at the national or regional levels, have contributed to the development of national (NSI) and regional systems of innovation (RSI) frameworks [8, 9]. At the same time, it has been observed that the "*relevance of global forces in innovation is rapidly increasing*", particularly with respect to high-tech sectors [10]. Cooke (2005) asserts that: "*under 'knowledge economy' conditions, globalization evolves from 'Globalization 1' which was orchestrated by multinational corporations and multilateral trade institutions, to 'Globalization 2' which is driven by the quest by multinationals for exploitable knowledge in 'knowledgeable regions' often quite dependent on public research funding resources*" [8]. Cooke goes on to suggest that specific regions with small scale but global reach can exploit *open innovation [11]* as a way to "*overcome inherent knowledge asymmetries and overturn the imbalance in an evolutionary process over time*" [8]. The question is whether such an approach is viable in the context of emerging innovative sectors in transition economies like China, India and Brazil. In this regard, the sectoral systems of innovation (SSI) approach developed by Malerba *et al* [12, 13] may present a good complement. SSI places less emphasis on geographic boundaries and takes greater stock of technological aspects. Malerba defines a sector as "*a set of activities that are unified by some linked product groups for a given or emerging demand and which share some common knowledge*" [12]. He envisions a sectoral framework to focus on three main dimensions, including: a) knowledge and technological domain, b) Actors, inclusive of organizations, individuals and networks, and c) Institutions, including: norms, routines, common habits, established practices, rules, laws and standards. Breschi and Malerba ascribe three characteristics to the sectoral innovation systems approach involving: a) firms as central actors within the innovation system, b) the importance of selection environment vis-à-vis competitive relationships among firms, and c) the notion that the boundaries of the system are determined by technological features[13]. The specific features of technologies are then related to the concept of Technological Regime (TR), which constitutes four fundamental factors including: a) opportunity conditions, b) appropriability conditions, c) cumulativeness of technological knowledge, and d) the nature of relevant knowledge base [14].

6.3.2 Institutions and Innovation

Institutional analysis has gained increasing interest in recent decades as a way to explain differential competitive performance of firms across sectors, countries and time periods.

Firms have been the subject of much research as key players in advancing technological innovation [15, 16], itself linked with national competitiveness [17]. Indeed linkage between institutions, innovation and national competitiveness has bolstered the case for the existence of national innovation systems [5]. Institutions and organizations are considered to be essential dimensions of SI as "*they provide the stability needed for innovative efforts to take place and to be successful*" and they are thought to determine "*the rate and direction of innovation*" [5]. Institutional analysis adds to previous work, by Alfred Chandler and others, which associated firm performance to strategy and organizational structure.

The discourse on the role of institutions in firm performance has taken place notwithstanding the fact that; "*There is no consensus as to what is meant by institutions or by institutional analysis*" [18]. Douglas North states that institutions are "*rules of the game in a society*" [19], which acts as constraints on human interaction. He stipulates that: "*Institutions form the incentive structure of a society and the political and economic institutions, in consequence, are the underlying determinant of economic performance*" [20]. North views institutions as the rules and norms, which determine the type of organizations that will emerge and how those organizations will function and be structured. Others however, have argued that institutions and organizations are inseparable and emerge and co-evolve, or that they represent the behaviours that follow from rules and norms [21]. In an attempt to introduce some coherence to the field, Hollingsworth (2002), has developed a taxonomy of the different levels of institutional analysis. He suggests that institutions are composed of norms, rules, conventions, habits and values, which in turn shape four other levels including; institutional arrangements, institutional sectors, organizational structures as well as outputs and performance [18].

It is generally recognized that the basic rules and norms of a society are enduring and to the extent that they shape institutional factors at other levels, they can impact the speed and scope by which these changes are realized. Carlota Perez emphasizes both institutional as well technical changes as requirements for *system* change. She is credited as arguing that: "*system changes cannot take place except through a combination of profound social and organizational, as well as technical innovations, and this necessarily* *takes a long time*" [22]. Freeman [4] observed that the success of Japanese technological supremacy was not just a function of the scale of research and development (R&D) efforts, but also to other social and institutional adjustments. System change is thought to be required in order to adapt to a new techno-economic paradigm, suggesting that different technologies demand different organizational arrangements [23]. However, institutional inertia, which is a basic feature of institutions often means that societies find it difficult to meet requirements for system change in a timely fashion [24]. This is in part because, "*to restructure its system of innovation generally calls for a major redistribution of power within a society*" [18].

The differential development of competitive and innovative performance in pharmaceuticals across nations reflects the important role that institutions have historically played in this sector. Henderson *et al*, observe that: "*from its inception, the evolution of the pharmaceutical industry has been tightly linked to the structure of national institutions…*(that) *played a critical role in generating isolating mechanisms*" [25]. The same authors go on to declare that: "*In the post-war era, the institutional arrangements surrounding the public support of basic research, intellectual property protection, procedures for testing and approval, and pricing and reimbursement policies have all strongly influenced the process of innovation directly and the economic returns…for undertaking such innovations*"[25]. Below, we delve into some of these factors in light of their relevance to the countries studied.

6.3.3 IP Protection and Innovation

The theoretical rationale underlying patenting is that it creates a temporary monopoly, which incentivizes investment into the discovery and development of new products, processes and technologies. The TRIPS agreement is an attempt at expanding the number of countries where monopoly markets can be established, as well as the classes of products that can be protected. The basic presumption underlying adoption of pharmaceutical patent regimes by WTO members was that it would substantially increase incentives for innovation, including for key neglected tropical diseases [26].

While evidence on the impact of strong IP protection on innovation efforts of firms in all sectors is mixed, [27-33], the relationship is more firmly established in the pharmaceutical sector [34], albeit not in all countries [35]. This, in part, results from the fact that once discovered pharmaceutical products/molecules are relatively easy to copy and reproduce [36]. While the impact of strong IP generally manifests through its promotion of R&D activities, IP protection is not the only driver of R&D expenditure. Present or expected market demand [37, 38] and enhanced market valuation [39] are among other motivations for firms to conduct R&D. Indeed R&D expenditures are not always aimed at generating IP rights and generally include activities related to the development of capabilities to manufacture existing products such as generic drugs.

The precise nature of a country's IP protection regime is often a function of its development goals and overall institutional setup. Policy makers are said to face a trade-off between strengthening IP protection to stimulate foreign direct investment and facilitating knowledge spillovers to domestic firms [39, 40]. However, as knowledge spillovers do not occur automatically [40, 41], permissive IP regimes are often not sufficient by themselves to develop domestic industries. Adoption of strong patent regimes can also have adverse consequences as was seen when Korea's pharmaceutical industry was considerably devalued after the country's introduction of a product patent regime in 1986 [33]. Overall, it has been observed that: "*patents help to determine the direction of technical change and that the adoption of patent laws in countries without such laws may alter existing patterns of comparative advantage across countries*" [30]. In the area of pharmaceuticals the potential benefits and costs of patent protection are stated to include: a) "lower fixed costs of basic and clinical research, which are sunk prior to commercialization, b) higher probability of research success through each phase of the scientific and clinical-trials process, c) lower variable costs of producing drugs if commercialization occurs, and d) Higher profits for either product introduction or licensing" [26].

6.3.4 National Support for Science and Technology Innovation

It has been shown that overall R&D expenditure is associated with knowledge production and industrial innovation at both firm- and country-level. Recognizing this link all three countries studied have expanded their R&D expenditures - at least in absolute dollar terms - (see **Table 6.3** and **Table 6.4**), and aim at enhancing private R&D investments as well. This section highlights key policy initiatives and related expenditures to advance science, technology and innovation in China, India and Brazil. It reveals that; a) most governmental initiatives target all sectors and, b) while growing, dedicated public funds to health product innovation are unlikely to make a significant impact given the high cost of innovation in this area; a point that is particularly salient for India and Brazil.

6.3.4.1 China's Vision for a Bio-economy

China aims at the formation of a 'bio-economy' as part of its vision to become an 'innovation-oriented' country by 2020. As part of this vision, the country has identified eight priority areas for advancement including biotechnology. Overall gross national expenditure on R&D (GERD) rose from 0.57% of GDP in 1996 [42] to 1.7% in 2009, reaching approximately $ 86.6 billion US [43]. Business R&D expenditures (BERD) composed about 73% of this total in 2008. China's adoption of the '*Outline of the Medium- and long-term plan for National Science and Technology Development* (2006-2020)' aims at forming a national innovation system centered on enterprises. It compels the government to: a) increase R&D expenditure to 2.5% of GDP by 2020, b) provide fiscal incentives for enterprise R&D, c) use strategic public procurement to stimulate domestic innovation, d) build national infrastructure for innovation and e) train and recruit talent [44, 45]. While the country's expenditures on basic research grew from 11.7 to 22 billion Yuans from 2004-8 [45], the share of GERD was only 4.6% 2009, holding a decade-long trend [43]. Notwithstanding this observation, China has become the second major publisher of scientific articles globally and enjoys a rapid growth rate in the medical field as well (see **Table 6.4**). Government funds are mostly channeled through five key programs - including: Key technologies R&D Program, the SPARK Program, High-tech Research and Development Program (863 Program), Torch Program and the Key Basic Research Program (973 Program) - that focus on priority areas. In 2008, the central government allocated approximately 29 billion Yuan to S&T programs [45], with most funds flowing to universities and research institutes [44]. The central government's commitment to biotechnology grew from 0.8 million RMB between 1996-2000 to 10 billion RMB for the period 2006-2010 [46]. This coincided with an increase in intramural expenditure on R&D by China's medicinal industry, which grew from 2.8 to 7.9 billion Yuan from 2003-8 [45].

China's nearly two-decade long focus on laying the groundwork for an innovation-based economy has resulted in an impressive array of science, technology and innovation infrastructure, with much more planned for the coming years. Perhaps the largest and most transformative government program in this respect has been the Torch program. As of 2009, the program had stimulated the development of 54 high-tech parks/zones, about 20 of which have a life science component. These parks are designed to serve as innovation clusters, by providing R&D infrastructure and allowing for close interactions between firms, investors and research entities. The Torch program also administers an innovation fund (called *Innofund*), which spent approximately 7 billion RMB between 1999 and 2007, supporting about 12,000 projects within small and medium technology-based companies. This fund's budget for 2008 has been estimated at 1.46 billion Yuan [45].

The state and municipal governments in China often have their own supportive programs for technological entrepreneurship. These efforts include, but are not limited to: preferential tax policies, lower lease rates for facilities and business and technology development services, relocation and cost of living allowances to help recruit talent and science and technology development funds. For instance, Shanghai Pudong S&T Investment Co., Ltd., an initiative of the Shanghai government, has a fund-of-funds with over 700 million RMB, which it invests in other venture capital (VC) funds that invest in tech-based companies. This municipality plans to spend 100 billion RMB (US $14.9 billion) over the next three years in innovative sectors including Bio-pharmaceuticals (http://en.expo2010.cn/a/20101011/000001.htm). Nearly all companies we studied that undertake innovative activities had received financial support from various levels of government.

6.3.4.2 India's Fostering of an Innovation Ecosystem

India's policy goal is to promote the development of an innovation ecosystem with a key focus on encouraging public-private interactions. The country's overall R&D expenditure as a portion of GDP effectively stagnated at 0.7-0.8% from 1996-2007, reaching an estimated $24 US billion at the end of this period (see **Table 6.3**). The private sector increased its share of R&D expenditures from 18% of total in 2003 to 28% in 2007 and was led by the country's pharmaceutical sector, which had an expenditure of Rs. 2826.86 million in 2006 [47]. The Eleventh Five-Year Plan (2007-2012) aims to increase public expenditures on S&T by 220% in nominal terms compared to the previous plan [47]. As shown in **Table 6.4**, the country's global share of R&D expenditures nudged only slightly between 1996 and 2005, while China's rose more than three-fold. Looking at the country's scientific publications reveals a similar trend, with India trailing both China and Brazil by a significant margin. However, India has managed to keep pace with China when it comes to triadic patent applications (See **Table 6.4**), perhaps testifying to the strength of the country's entrepreneurial sector and its outward orientation. It is estimated that the combined budget allocation for the key departments involved in health research increased from $US 2.46 billion in 1990/91, to approximately $US 6.64 billion in 2004/5 in terms of purchasing power parity [48]. The budget for the Department of Biotechnology (DBT), which is the main agency involved in biotech promotion, was equivalent to approximately $US 350 million in 2004/5 in terms of purchasing power parity [49] and is estimated to be Rs. 900 Crores (~$215 US million) for 2009-10 in current dollars (http://dbtindia.nic.in). The DBT supports many initiatives that aim at enhancing human resources in biotech, encouraging public-private collaboration, facilitating technology transfer, promoting and supporting biotech entrepreneurship, forming a centralized biotech regulatory agency, and establishing international collaborations. Approximately 30% of the department's expenditures are targeted at encouraging public-private partnerships with the remaining funds used to support other scientific bodies and enhance basic research (http://dbtindia.nic.in). For 2009-10, only about Rs. 32 Crores are aimed directly at supporting entrepreneurial R&D infrastructure such as technology incubators and biotech parks, a sharp contrast to China's heavy infrastructure focus. Two key initiatives specifically targeted at chemistry-based pharmaceutical R&D by the Department of Science and Technology (DST) include: Drugs and Pharmaceutical Research Program [50] and the Pharmaceutical Research and Development Support Fund (www.dst.gov.in). A host of other government programs[1] encourage innovation and entrepreneurship in all sectors, but most tend to be of a modest scale.

The Indian government has also reduced import duties for biotechnology products and other materials required for drug development and production [51], and has put in place a number of other initiatives to assist R&D companies and export-oriented manufacturers and service providers. The government has publicized a draft of its proposed National Innovation Act that emphasizes increasing R&D expenditures, creation of Special Innovation Zones and enhanced data confidentiality, among other measures.

6.3.4.3 Brazilian Quest to Commercialize Indigenous Knowledge

Brazil spends approximately 1% of its GDP on R&D, with just over 50% coming from public resources. While the country's R&D expenditure and its global share of the same has remained constant in recent years, its global share of scientific publication rose by about 130% (see **Table 6.3** and **Table 6.4**) in the decade leading up to 2005 due to overall economic growth. Business R&D expenditures (BERD) comprising only 23% of national R&D spending in 2003 [52], increased to about 48% in 2006, but continues to lag behind China and most OECD countries [42]. Expenditures by the biopharmaceutical industry are unknown, but likely to be fairly small since the country's biotech sector remains very young [53] and few incumbent pharmaceutical firms invest in R&D. The National Council for Scientific and Technological Development (CNPq), the Ministry of Science and Technology's Financing Agency for Studies and Projects program (FINEP) and the São Paulo State Funding Agency (FAPESP) are major funders of scientific

[1] These include: the Department of Scientific and Industrial Research's Technopreneur Promotion Program (TePP), DST's Technology Development and Demonstration Program (TDDP), the Technology Business Incubator (TBI) program and the Technology Development Board (TDB) as well as the Council for Scientific and Industrial Research's New Millennium Indian Technology Leadership Initiative (NMITLI).

research in the country. In 2009 FAPESP invested R$ 679.5 million in research funding, equivalent to 1.5% of the state's GDP (http://www.inovacaotecnologica.com.br).

The Brazilian Innovation Law enacted in 2005, and a few subsequent statutes, aim at enhancing private-sector commitment to R&D. Modeled on the US Bayh-Dole Act of 1980, this law allows for direct governmental support of innovative activities within private enterprises and for the sharing of IP and other resources between public and private sectors. FINEP is the main national funding agency for innovation and has a number of related programs. First, it administers a set of 14 sectoral and two cross-sectoral funds, including one for health and another for biotechnology. In 2008 its expenditures in all 16 funds reached an estimated US$ 1.4 billion [54]. Second, it runs the Economic Subsidies program, which supports innovative projects within companies by seeking competitive proposals on specific themes. Since 2006, this program has dedicated approximately R$ 300 million for biotech and health-related projects (www.finep.gov.br). Third, FINEP's PRIME (Primeira Empresa Inovadora) program, which was launched in 2009, aims to direct R$ 650 million in grants to approximately 5,000 start-up enterprises over three years (http://www.finep.gov.br). Fourth, the Brazilian government had dedicated over R$ 600 million to ten VC funds that invest in tech-based firms, leading up to 2007 [55]. Lastly, FINEP's INOVAR program aimed at SMEs, dedicated R$ 300 million from 2008-2010 to three types of funds; VC, private equity and seed funds. The Brazilian Development Bank (BNDES) also earmarked about R$ 6 billion between 2008 and 2010 to support innovation-related activities. It has a number of initiatives including FUNTEC, which funds technology institutes, CRIATEC, a R$ 100 million seed fund for small companies as well as other sector-specific programs including in pharmaceuticals. Four federal laws implemented between 1991-2005 allow for fiscal incentives for R&D-performing companies, which amounted to US$ 3.6 billion in 2008, or 37% of business R&D expenditure, but the majority was used by firms in the Information Technology sector [54].

6.4 Study Findings

Study findings are discussed in the context of the three propositions stated above.

6.4.1 Proposition 1: TRIPS Adoption has had Limited Impact on Indigenous Health Product Innovation

Our findings (in Chapter 5) suggest that while the adoption of pharmaceutical product patent regimes in China, India and Brazil has stimulated some domestic efforts to develop innovative health products, these attempts have thus far been modest – as measured by efforts to develop new vaccines and medicines. As reported in the previous chapter, we identified 176 innovative products within 43 indigenous firms across China, India and Brazil. Of these, Indian companies had 87 innovative products (49% of total) while Chinese and Brazilian firms accounted for 63 (36% of total) and 26 (15%) innovative products, respectively.

We suggest that the present level of new vaccine and medicinal innovations indicate that the introduction of pharmaceutical product patents has not stimulated a broad-based movement towards radical innovation by the biopharmaceutical sectors in China, India and Brazil. Given the considerable size and growth rates of the pharmaceutical markets in the countries concerned, one can arguably expect to see a higher level of efforts towards new product innovations. In all three countries, a handful of firms account for the majority of new chemical and molecular entities under development. While this guarded foray into innovation may, in part, be a function of the stage of development of industries [56], and business opportunities presented by other regulatory changes [47, 57], a number of key institutional barriers also play a significant role in shaping the incentive system for drug and vaccine innovation.

6.4.2 Proposition 2: Barriers to Innovation are Largely Institutional in Nature

The implicit assumption underlying strong patent systems is that these create sufficient economic incentives to enable orchestration of adequate resources for innovation. A key point advanced here is that these incentives are highly contingent upon a set of core assumptions, which often do not hold true in the context of biopharmaceutical innovation in developing countries. Arguments in favour of strong patent regimes generally assume that: a) relevant scientific capacity is present and accessible to enterprises, b) the requisite regulatory and financial infrastructure for innovation is adequate, c) there exists a market that is willing and able to absorb higher costs associated with novel health products and d) patents are indeed required for industrial growth and competitiveness. Here we discuss how institutional challenges in the emerging markets studied put in question these core assumptions and indeed serve to weaken patent regimes themselves.

6.4.2.1 Idiosyncratic Patent Regimes in China, India and Brazil

China, India and Brazil have all signed the TRIPS agreement over the past 15 years and began to implement it through national legislation effective in 1997, 2001 and 2005 respectively. Although *external* pressures provided the initial impetus for strengthening IP protection regimes in these countries, the desire to become innovative has added some internal motivation in recent years. The overall evolution of pharmaceutical patent regimes in recent years is a reflection of a complex interplay of internal and external pressures on policy makers, the latter group's desire to balance industrial interests with public-health goals, as well as each country's logistical preparedness for patenting and enforcement. Attempts to balance these issues have led to idiosyncrasies in patent regimes that are believed to detract from related incentives. That said, from the perspective of domestic health entrepreneurs in China, India and Brazil, patent protection is only one of many challenges they face, and arguably not the most pressing one.

Since inception in 1984, China's patent law has undergone three major amendments aimed at strengthening the country's patent regime [58-61]. Challenges related to IP protection in China has primarily related to inherent ambiguities in IP law, in part attributable to the speed with which the legal system was constituted after opening up in late 1970s [59]. They also relate to the nature of the country's enforcement regime, where patent infringement cases are typically handled by municipal courts at the jurisdiction of the accused [62]. Notwithstanding these perceptions, China has witnessed a significant increase in patenting activity by both domestic and foreign applicants, including patenting of medicines [45, 59]. The growing presence of multinational pharmaceutical companies, and a greater involvement of these firms in R&D activities locally, is another indication of growing confidence in China's patent regime for pharmaceuticals.

IP strategy has played a major role in building India's pharmaceutical industry and continues to be the subject of ongoing debate. Introduction of a more permissive patent law in 1970 was instrumental in fostering a generics-based industry that is now ranked 4th globally in terms of volume and 13th in terms of monetary value placing it in a better position to transition to a stronger IPR regime [48, 56, 57, 63, 64]. In 1994, the country signed the TRIPS Agreement and implemented it in 2005. Ever since, a number of provisions in India's present Patent Act have remained the subject of debate and legal consideration. The most controversial feature of India's patent law is the way it attempts to limit the granting of patent rights to truly innovative products. Under section 3(d) of India's Patents Act new uses for existing products or their derivatives are not patentable unless they demonstrate improved efficacy [65]. The Patent Act allows Indian companies to continue to manufacture and export patented pharmaceuticals to least-developed countries that lack manufacturing capabilities, further bolstering India's export strengths [66, 67]. Additionally, patent rights for 'mailbox' applications – submitted prior to 2005 –are only valid after the granting date of the patent, not as of the publication date. This means that Indian companies can continue to market patented products that they had on the market before the patent was granted. Indeed these factors, together with rapid pharmaceutical export growth, likely account for the majority of R&D expenditures by Indian pharmaceutical enterprises, estimated at about 35% annually from 2000 onwards [47]. This observation is consistent with our results suggesting that investments into novel products have been limited, as well as previous findings that pharmaceutical process patenting by Indian enterprises rose significantly in the years leading up to TRIPS Adoption [68].

The Brazilian pharmaceutical patenting regime attempts to balance core requirements of novelty, inventive step and industrial application with issues of access, benefit sharing and public health. Brazil reinstituted pharmaceutical patenting in accordance with the TRIPS agreement starting in 1997. Basso, 1996 observes that: "*The Brazilian law, owing to its laconic wording, leaves room for unending discussions on the goals and legality, scope of application, and operation of such mechanism".* The result has been a gradual involvement of a number of non-legal institutions in patenting of pharmaceutical products, in addition to the country's patent office (INPI). The key organization among these is the country's National Sanitary Surveillance Agency (ANVISA), which received prior consent right over pharmaceutical patents through a subsequent statute passed in 2001. This right allows ANVISA to conduct "*a material analysis based on aspects relevant to public health … so as to avoid an excessive and unduly limitation of the access to the pharmaceutical product object of the patent application"* [69]. A key point of contention between INPI and ANVISA has been disagreement regarding 'new use' patent applications, where the active ingredient itself is not new, but the application concerns modifications in processes, mode of administration or dosage forms. In this sense Brazil and India both aim at stemming the practice of *evergreening*, although evidence from the US-FDA show that 65% of the 1,035 new drugs approved between 1989-2000 involved active ingredients already in marketed products [70]. In addition, the novelty requirement is significantly compromised for biotech-based products that were originally discovered from a natural source. While this category may compose a small fraction of patent applications overall, they likely constitute a significant portion of potential innovations in the biotechnology sector, especially given Brazil's vast biodiversity endowment. Lastly, the occasional use of compulsory licensing by the Brazilian government as a means to realize lower drug prices may discourage multinational firms from developing products in Brazil, particularly in collaboration with indigenous firms [1].

6.4.2.2 Knowledge and Technology Transfer Mechanisms

Access to knowledge, particularly of the proprietary variety, is a key determinant of competitive advantage in biopharmaceuticals. While all three countries have made significant strides in terms of research productivity, as measured by their publication records, they lag in terms of their ability to discover and develop drugs and vaccines based on NCMEs. Inherent inter-linkages between knowledge production and transfer mechanisms, together with the absence of related empirical work, make it difficult to determine the extent to which each of these dimensions independently contribute to reducing innovation opportunities in each country. What we observe however is that, thus far, relatively few NCMEs have been transferred from domestic universities and research institutes to previously established or spin-off firms. Furthermore, the relatively few VC firms that are open to investing in early-stage projects appear unable to find a significant number of desirable innovation opportunities from domestic sources and in some cases are deterred by bureaucratic tech-transfer practices of domestic institutions.

Challenges related to knowledge transfer are rooted in cultural legacies that have historically isolated the public and private sectors from each other. China's cultural revolution followed by the dominance of the state in science and technology, together with the relative novelty of a private-sector in general, have led to isolation of relevant institutions. The institutional segregation extends to government institutes themselves, where "*each research unit tends to be an isolated work unit, and island on its own…the same applies to ministries, other government organizations, and state-owned enterprises*" [71](pg. 22). To the extent that linkages among Chinese universities, research institutes and enterprises exist, they tend to be stimulated by government programs [72]. The Brazilian constitutional declaration that health is the right of every citizen and the obligation of the state has contributed to a precarious role for the private industry [1]. This phenomenon, together with an ideological divide over patenting and the lack of effective IP protection and tech-transfer mechanisms within R&D-conducting Brazilian institutions mean that few domestic inventions turn into marketed products [73]. The overall incentive system in all three is perceived as heavily skewed towards researchers staying in their current positions, hence limiting spin-off prospects, which is a key path for technology transfer in biotech/pharmaceuticals in leading nations.

Lastly, our analysis suggests that, ironically, governmental policies aimed at enhancing knowledge flows may be fostering a more 'closed' innovation system; and hence, adversely affecting longer-term innovative success. While, in recent years, all three countries have taken steps to enhance public-private linkages, related incentive programs are often exclusively limited to indigenous partners. This insular posture creates a tension between the demands of health product innovation – which require a diverse set of knowledge and expertise, often not available domestically – and the incentives created by public policies favoring domestic collaboration. This stance may result from a failure to recognize the crucial role of *asymmetric knowledge capabilities* [8] on innovative capacity, and opportunities to overcome related challenges using global networks. A consequence is that limitations on domestic knowledge-creation and technical capabilities of the public sector, also limit innovative success of the entrepreneurial sector and vice versa. Stated differently, an almost exclusive policy focus on generating and commercializing endogenous knowledge may ultimately detract from the country's indigenous capacity to innovate; by overlooking a much larger pool of exogenous knowledge. Since, governmental inducements have to date played a key role in sparking domestic innovation in health, albeit on a limited scale, constraints related to access to these incentives are likely to have a considerable effect on firms' innovative activities. An added dimension as articulated by an Indian entrepreneur is that: "*public-private partnerships are an indirect way of funding public institutions. If you get a grant, 80-90% of funds go to the university or institute*". Similar concerns prevailed in Brazil as well at least until the institution of the country's new Innovation Law in 2005.

6.4.2.3 Dearth of Innovation Financing

While public support for enterprise innovation has been rising overall, private financing of early-stage projects remain a major challenge for health entrepreneurs in China, India and Brazil. As discussed previously, all three countries studied have public programs to support innovation. However, our findings suggest that few of these programs have had direct benefits for companies that conduct NCME development. The only programs that have reached the firms involved have been initiatives akin to the US Small Business Innovation Research (SBIR) Program, which provide direct government assistance for enterprise R&D. However, these are limited in terms of the number of companies they support and the extent of financing they can offer. Furthermore, venture capital firms, including those in which governments are partial investors, have shown relatively little propensity to invest in high-risk projects. There are a few exceptions such as the BioVeda China Fund (Shanghai) and Morningside Venture (Beijing). The result is that early-stage financing for highly innovative companies is inadequate in all three countries, although China appears less affected due to more substantial contributions from government and indirect subsidies of innovation activities through infrastructure provision activities.

The dearth of private financing is related to a number of factors. First, a limited history of VCs investment and successful exits means that the market as a whole has not been derisked for subsequent investors. While, the VC industry as a whole has been growing substantially in all three countries, few investments are made into innovative biopharmaceutical companies. One reason is that exit opportunities tend to be much more limited in the emerging markets. There is little history of innovative company acquisition by either domestic firms or multinationals or successful initial public offerings. There are also indications that domestic investors tend to undervalue companies that invest substantially in innovative R&D.

Currently two mechanisms serve as the main source of financing for enterprise R&D, in addition to government funds. The first approach is to finance innovation activities from internal revenues. This strategy necessarily limits investments to the ability and willingness of given firms to invest. It also serves to distract firms into revenue-generating activities, which in some cases has led to the eventual abandonment of innovative activities altogether. Furthermore, the impetus to innovate has not been particularly strong among incumbent pharmaceutical enterprises. While path-dependencies contribute to this behaviour, the fast-growing generics market - in part as a result of governmental promotion of generics – has provided ample opportunities for profits over the last decade. The second scheme for financing innovative projects is to rely on partnerships with large firms, most often pharmaceutical multinational corporations (MNCs). This is an emerging trend in China and India, but there is little indication of this type of activity in Brazil.

6.4.2.4 Tension between Radical Innovation and Affordability

Weak market demand for highly innovative and domestically developed health products remains a key barrier to innovation in China, India and Brazil. These countries have traditionally been highly price-sensitive when it comes to medicines, largely due to lagging per capita income levels and the significant costs of innovative health technologies. To lower drug prices, many countries including those mentioned, institute price-control mechanisms, use procurement and reimbursement procedures and/or mandate the use of generics where appropriate. In some cases, such as in China and Brazil, the public sector also produces a considerable amount of medicines and vaccines used in the country. The overall goal of these efforts is to reduce the ultimate retail price for the consumer or to improve government finances. Thus far, the predominant mode of competition for indigenous biopharmaceutical firms in China, India and Brazil has been price-based, and largely sustained by the fast-growing pharmaceutical markets. Going forward, these countries will need to balance access to health products with their desire to become innovators themselves.

Hitherto, innovations that have been most rewarded in the market place have been those that have resulted in price reductions, not product differentiation. For example, Indian firms Shantha Biotechnics and Biocon gained significant market share when their process innovations allowed them to reduce the market price for hepatitis-B vaccine and insulin respectively [2]. Indeed, the notion of *affordable innovation* has gained significant traction in the Indian entrepreneurial sector both as a source of competitive advantage, and as a way to address developing world health needs and perhaps those of industrialized nations. In contrast, a couple of novel gene therapy products developed by Chinese firms have seen relatively little market penetration, in large part due to their high treatment costs. The highly price-sensitive pharmaceutical markets also serve to shrink profit margins significantly, thereby limiting the ability of most indigenous firms to make substantial investments in new innovations. Lastly, there is a common perception among indigenous entrepreneurs that the more affluent domestic consumers often have a bias in favour of imported products.

6.4.3 Proposition 3: Extra-national Influences Limit the Scope for National Policies

The assertion here is that extra-national influences resulting from globalization of the innovation process limit what national policies can achieve independently. Archibugi and Lammarino find that the relevance of globalization has been increasing significantly over the past few decades, particularly in the case of high-tech sectors and especially within the US-EU-Japan triad [10]. In the case of biopharmaceutical innovation, our analysis hints at the rapid dissolution of this historical triad with greater inclusion of emerging markets, chiefly India and China.

While primarily spurred on by pharmaceutical MNCs, indigenous enterprises in these countries are important participants in the globalization phenomenon. The dominance of the global biopharmaceutical industry by a relatively few large MNCs, and their aim to reduce innovation costs, is playing a significant role in shaping domestic industries in emerging markets. These effects are mediated through competitive dynamics, financing of innovative activities by MNCs within domestic enterprises, outsourcing of R&D activities from MNCs to firms in emerging markets, and the fact that MNCs represent the most likely purchasers of pipeline products somewhere along the developmental trajectory. The latter effect arises from the fact that few firms in the emerging markets have the wherewithal to absorb the high costs and financial risks associated with full clinical development of modern medicines. The high cost of pharmaceutical innovation has contributed to a growing outsourcing of discovery and development activities by MNCs, contributing to a fragmentation of the drug development value chain across many countries. The result so far has been the burgeoning of fast-growing contract manufacturing, and R&D services sub-sectors in India and China. These trends demonstrate that globalization trends can provide opportunities for different regions or countries to tap into niche segments within the broader global value chain, and to build on their capabilities over time. However, maximizing *innovative* capabilities demand that national policies be better aligned with sectoral and global dynamics. This is especially so in the context of developing nations with limited resources, as devoted public funds are often insignificant in comparison with R&D budgets of biopharmaceutical MNCs.

Another important factor is the highly dispersed knowledge base for biopharmaceutical innovation at both the knowledge production and utilization levels. This is, of course, not to argue that these capabilities are evenly distributed. Indeed, asymmetric knowledge capabilities [8] themselves a function of institutional heterogeneity [25] play an important role in differential innovative capacity across regions and nations. But to observe that the underlying knowledge and technological domains involved in modern medicines - as well as the networks of actors involved in their discovery and development - have a highly international structure. Organizational aspects of this process often take the form of collaborative networks of firms and/or research groups with the end result of linking disparate expertise at a global, or at least international, level.

In summary, our analysis resonates closely with assertions by Susan Bartholomew, who after studying the national biotechnology innovation systems of the US, the UK, Germany and Japan, concluded that: "*The increasing power of transnational corporations and the growth of international R&D networks provides evidence to suggest that technological advances may be more properly viewed as products of a global technological system…It is no longer sufficient to ask if national differences in technological capabilities will persist in the face of global integration; rather, we must seek to understand how country-specific innovation systems are intertwined within the global system*" [74]. Again, this is not to diminish the role of national institutions in innovation, but rather, to suggest that on their own they do not sufficiently explain the complexities associated with biopharmaceutical innovation in the present day context.

The apparent disconnect is in the administration of recent governmental science, technology and innovation policies, which appear to be primarily informed by the NSI approach. Even for industrialized nations, it has been suggested that in the context of biotechnology, a strict application of the NSI approach may not be relevant [74]. The often stringent and dynamic regulations governing health products means that few, if any, countries can afford to assemble and maintain a state-of-the-art ensemble of expertise required to develop human therapies all on their own in a sustained fashion. This challenge is merely elevated for developing countries with less resources and greater institutional constraints. Using an NSI-based approach to devise national innovation policies is problematic in at least three ways. First, it does not sufficiently account for sector-specific influences, which can extend far beyond national boundaries. Second, it forces nations to focus almost exclusively on *internal* knowledge generation and utilization rather than adopting an *open innovation* stance that is more aligned with the global biopharmaceutical industry structure. Lastly, the NSI-based approach focuses on a set of interventions that generally apply to all sectors regardless of need or suitability. This also results in resource dilution, which can be especially consequential in the context of resource-constrained, developing nations.

6.5 Globalization, Sectoral Systems of Innovation, & Innovation Policy

We propose that the sectoral systems of innovation approach [75] is a more appropriate alternative to inform national innovation policy, particularly in the context of catch-up high-tech sectors of the emerging economies. The SSI is best suited to describe the dynamics of biopharmaceutical innovation for a number of reasons. Firstly, the SSI has a diminished emphasis on geography and devotes greater attention to technologies, product classes and innovating firms. These aspects play a crucial role in shaping the biopharmaceutical industry structure and evolution as alluded to above. Secondly, the SSI considers three important dimensions including: knowledge and technological domain, Actors and networks, and institutions. Our studies suggest that of these elements, only institutions have a predominantly national character. Indeed pharmaceutical regulatory regimes, which represent a key facet of institutional influence on innovation in this sector, are themselves becoming harmonized not only in developed countries but also in the emerging markets, albeit not formally. Regulatory coordination in the emerging markets manifests through modeling of national regulations on the International Conference for Harmonization (ICH) guidelines or those of other key agencies such as the US-FDA or the European EMEA. It is also increasingly common for firms in the emerging markets to conduct their innovative activities in accordance with internationally recognized guidelines from the outset. Thirdly, the SSI recognizes that in some cases even specific individuals can serve a crucial role in building or shaping innovation systems. This can be particularly important in nascent industries. For example, in the relatively new health biotech sub-sector in Brazil, it has been recognized that a few people played a decisive role in 'kick-starting' the country's foray into innovative activities in biotechnology [76]. Lastly, the SSI framework allows for the national, or even regional, components of the broader global sector to be envisioned as "sub-sectors"; nested within a broader global system of innovation. In this respect Malerba has proposed that: "*… within broad sectoral systems, different innovation systems related to different product groups may exist. The choice of the level of aggregation depends on the goal of analysis*" [12]. It is of pragmatic utility to view the global biopharmaceutical sector as being composed of different "sub-sectors", which discover, develop and produce the ‘intermediate’ products/technologies of the sector. Some of these sub-systems may be based in specific countries or regions, due to the presence of specific knowledge base, skill sets or other endowments.

Cook’s conception of *knowledge asymmetries* [8] and Chesbrough’s notion of *open innovation* [11] also provide important insights to this discourse. The notion of *knowledge asymmetries* demands the formation of networks to compensate for deficiencies within individual regions. Present policy objectives in China, India and Brazil seem more informed by the NSI approach and seemingly aim at developing the full ensemble of capabilities required for *independent* innovation in a sector that is highly *interdependent* at the global level. The idea of *open innovation* suggests that greater openness to knowledge flows in and out of firms enhances firm-specific innovative performance. The implication in a globalized sector is that national policies aimed at supporting innovation within enterprises should facilitate, or at least not frustrate, knowledge-flows across borders.

The approach proposed here views the evolving nature of innovation as a global *network* of actors*,* through which most individual firms must realize incremental value. Furthermore, it hints at how specific nations, especially developing ones, can become innovative not by aiming at broad-based and independent innovation from the outset, but by building capacity for *interdependent* innovation within the global value chain. Looking at present day innovation-inspired biopharmaceutical companies in emerging markets, particularly in China and India, suggests that the most important interactions do not necessarily occur at the national level, as is implied by the NSI framework. Rather transformative interactions increasingly appear within a complex global network of firms, and organizations. Indeed, one observes close parallels between the dynamics that increasingly govern biopharmaceutical innovation with those that govern the overall global economy, as presented by Manuel Castells in his book, *The Rise of the Network Society* [77]. Through his classic trilogy on *The Information Age; Economy, Society and Culture*, Castells argues that in the context of the information age, ‘the basic unit of economic organization’ is a *network* of organizations, not individual firms or countries for instance. He states that the “*... dominant functions and processes in the information* *age are increasingly organized around networks. Networks constitute the new social morphology of our societies, and the diffusion of networking logic substantially modifies the operation and outcomes in processes of production, experience, power and culture*" [77] (p500). A basic idea underlying networks is that "*social ties can bind nodes together in such a way as to construct a new entity whose properties can be different from those of its constituent elements*" [78]. If one views a global high-tech sector as a social organization that is based on networks in dynamic flux, then the intrinsic characteristics of those networks, as well as how the different networks relate to each other would be predicted to have important influences over outcomes. This conception has important implications from the perspective of agent(s) whose goal is to contribute to this flux by intervening at appropriate times and junctions to change the trajectory of given outcomes.

6.6 Conclusions

In this study we examine the impact of new pharmaceutical product patent regimes in China, India and Brazil on the development of innovative drugs and vaccines. Using qualitative case studies of biopharmaceutical companies in these markets, interviews with institutional informants and insights gained from publicly available data we tested three propositions. In particular, we conclude that; a) introduction of pharmaceutical product patent regimes has had only a modest impact on entrepreneurial attempts to develop novel drugs and vaccines in all three countries, b) key challenges that diminish patent incentives tend to be institutional in nature and, c) the increasingly globalized nature of health product innovation limits what individual countries can achieve, particularly where resources are more limited.

As a whole, we find that to succeed in biopharmaceutical innovation, nations must adjust scientifically, sectorally and globally all at the same time. In particular, the results suggest that the present national innovation strategies tend to be broad-based and do not sufficiently account for important sector-specific dynamics. All three countries need to strike a better balance between focus on knowledge creation and utilization. China's seemingly low expenditures on basic research, in terms of the portion of dedicated funds, may continue its considerable dependence on foreign technology for years to come. On the other hand, India and Brazil's much heavier devotion to supporting basic research means that the knowledge utilization infrastructure does not receive adequate attention. While both countries seem cognizant of these deficits, and are in some respects starting to respond, new initiatives and government expenditures continue to favour strategies aimed at knowledge creation rather than infrastructure.

Growing fragmentation of the drug development value-chain across many countries has significant policy implications, particularly for latecomer countries. To the extent that they focus on health product innovation, national institutions and government policies in these countries are geared towards achieving independence, in terms of innovative capability, in an increasingly globally interdependent sector. One way this effect manifests is by an overreliance on domestic sources of knowledge and technologies at the expense of a much larger pool of knowledge and technologies from abroad. While existing evidence suggests that interactions between firms and research-conducting entities in a country have been important for technological catch up, the role of these interactions may now be diminished in the context of globalizing knowledge. The other consequence is that national institutions often counter sectoral forces, which in a largely hierarchical and global sector like biopharmaceuticals are indeed formidable. In short, there is an inherent contradiction between the broadly insular institutional contexts in the countries studied and the increasingly global nature of biopharmaceutical innovation. Developing countries, including those studied here, may need to be much more strategic with respect to the specific areas they focus on if they are to maximize likelihood of innovative success. To do this effectively, public policies need to reflect important sector-specific dynamics and as such are best informed by analysis at this level.

There has been significant policy focus, especially in India and Brazil, on enhancing enterprise R&D expenditures. While this can be beneficial in overall economic terms, enhanced enterprise R&D expenditure does not necessarily equate to innovation; a link that is often taken for granted. Provisions in the Chinese and Indian patent regimes that allow them to manufacture patented products for exportation to select countries essentially mean that the reverse-engineering machinery will remain active for years to come. While this has short-term economic benefits and can serve to advance global health, it does diminish the necessity to innovate by participating firms vis-à-vis extending shelf life for their existing business models.

Notwithstanding remaining challenges, China and India in particular will likely achieve some success in biopharmaceutical innovation in the not too-distant future. This is due to their rapidly growing markets, the considerable commitment to innovation by the Chinese government and export strengths of India's pharmaceutical sector that brings in considerable revenues. However, as indicated by the number of technologies in the pipeline of indigenous firms, and given the high attrition rate of pharmaceutical innovation in general, these successes are likely to be modest in the near term.

Further analysis is needed to map each country's relative competitive strength within the global biopharmaceutical value-chain and the adjustments necessary for participation within this system. It is also critically important to better understand the role of pharmaceutical multinationals in shaping the development of biopharmaceutical sectors in the emerging markets and other developing countries. In the context where major drugs and vaccines are increasingly developed in collaboration with foreign firms, domestic or indigenous innovation may lose its meaningless. These trends may have significant implications for how countries reap health and economic benefits from their public investments. Another area that is presently underexplored is the close linkage of health systems and the capacity to innovate on health products. Healthcare reform initiatives, such as the one underway in China, provide a great opportunity to ensure alignment of incentives so as to maximize population health while encouraging innovation in health technology.

6.7 Tables

Table 6.1 Number of Companies and Other Institutional Informants Participating in this Study

Country	# of Companies Interviewed (# of Interviewees)	# of Other Institutions (# of Institutional Informants)	Total # of Interviewees	Year(s) Interviews Conducted
China*	16 (16)	13 (14)	30	2009
India**	26 (30)	7 (9)	39	2005/2006 and 2009
Brazil***	19 (24)	5 (6)	30	2006/2007 and 2009
Totals	61 (70)	25 (29)	100	2005-2009

* This study has also benefited from insights through a previous study by Frew *et al [3]*, in which 22 firms were interviewed in 2006/7, nine of which overlap with the companies studied in 2009. All institutional informant interviews were conducted in 2009.

** Indian Interviews were conducted in two stages. 21 companies were interviewed in 2005/6 for the first phase of this study and published [2]. A second group of 13 companies were interviewed in 2009, eight of which overlapped with the first group. All institutional informants were interviewed in 2009.

*** Brazilian interviews were conducted mostly in 2006/7 with 5 interviews in 2009.

Table 6.2. Gross Domestic Expenditure on R&D (GERD) as a Percentage of GDP and total Expenditures in Billions US Dollars in Purchasing Power Parity, 1996-2007

	OECD Average	China (GERD in $ Billions US PPP)	India (GERD in $ Billions US PPP)	Brazil (GERD in $ Billions US PPP) [2]	United States (GERD in $ Billions US PPP)
1996	2.10	0.57	0.65	-	2.55
2000	2.23	0.90	0.78	1.02	2.74
2002	2.24	1.07 (39.2)	0.75 (12.9)	1.0 (13.0)	2.66 (277.1)
2004	2.21	1.23	0.77	0.90	2.59
2005	2.25	1.33	0.80	0.97	2.62
2006	2.26	1.42	0.80	1.0	2.62
2007	2.3	1.44 (102.4)	0.8 (24.8)	1.1 (20.2)	2.7 (398.1)

Data Sources: OECD Science, Technology and Industry: Outlook 2008 and UNESCO Science Report 2010 entitled "The Current Status of Science Around the World"

Table 6.3. Global Share of Total R&D, Scientific Articles and Triadic Patents for China, India, Brazil and Select Countries

	No. of Published Articles[3] for 2000, 2008	Share of Total World Scientific Articles (%)		Annual Growth Rate of Scientific Articles b/w 1995-2005[1]	Country Publications in Clinical Medicine (in Thousands of Articles) for 2002, 2008[3]	Global Share of R&D Expenditures in 1996 (and 2005) (%)	Business R&D Expenditures for 2002, 2007 (As a % of National R&D Spend)[3]	Share of Triadic Patent Families (%)[2]	
		1995	2005[1]					1995	2005 (Annual Growth, 1997-2004)
European Union	-	34.7	33.1	-	-	27.2 (24.2)	-	-	26.4[4]
United States	224634, 272879	34.2	28.9	0.6%	81.8, 103.8	37.3 (34.6)	65.2, 67.3	-	41.8[4]
Japan	72681, 74618	8.3	7.8	-	21.4, 21.7	15.7 (13.7)	74.1, 77.7	26.8	28.96
China	28916, 104968	1.6	5.9	16.5%	3.8, 13.5	2.2 (7.6)	60.1, 70.4	0.06	0.69 (45%)
India	16650, 36261	1.7	2.1	4.7%	3.3, 7.5	1.4 (1.7)	19.3, 29.6	0.03	0.22 (42%)
Brazil	10521, 26482	0.6	1.4	8%	3.2, 8.8	1.4 (1.4)	45, 44.7	0.04	0.11 (15%)

Data Sources: OECD Science, Technology and Industry: Outlook 2008
[1] Numbers for Scientific Articles for US and India are for 2006. Data obtained from the National Science Foundation website: http://www.nsf.gov/statistics/seind10. (Accessed, June 23, 2010)
[2] Source is the National Science Foundation, http://www.nsf.gov/statistics/seind10. (Accessed, June 23, 2010). Patents filed at the European Patent Office (EPO), the US Patent & Trademark Office (USPTO) and the Japan Patent Office (JPO), which protect the same invention. Data from 1998 onwards are OECD estimates
[3] Source: UNESCO Science Report 2010 entitled "The Current Status of Science Around the World"
[4] These numbers are for 2006. Source: UNESCO Science Report 2010 entitled "The Current Status of Science Around the World"

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Chapter 7
Transition to Innovation

7 Transition to Innovation: Health Biotechnology in China, India, Brazil and South Africa

7.1 Introduction

The innovative health biotechnology sectors in China, India, Brazil and South Africa are the largest in the developing world. Over the past two decades, national policies, domestic economic growth, and global trends have stimulated growth and innovation within domestic biopharmaceutical enterprises in these countries (collectively referred to as emerging economies/markets hereafter). The increased interest in these sectors has also been driven by the considerable growth rates and potential of pharmaceutical markets, which have outpaced those of major industrialized markets (see **Table 7.1**). While Brazilian and South African policy objectives have primarily focused on reducing dependence on imports and lowering the cost of health products for local populations, those of India and China aim to form an innovation ecosystem and vibrant bio-economy, with greater export ambitions. While each country is unique in its underlying health environment, policy choices, health outcomes, and institutional context, in all four countries, biotechnology is a priority area.

The basis of this article is qualitative case study analysis of 20-30 domestic enterprises in each of Brazil, China, India and South Africa [1-4]. The firms chosen were primarily involved in the development and manufacturing of health products including vaccines, therapeutics, and diagnostics. The individual country studies focused on products and services, partnerships, intellectual property portfolios, business models, financial environments and barriers to development for companies in each country. They also proposed recommendations for policymakers and industry, designed to accelerate domestic development and commercialization of health products. This paper therefore draws on insights from face-to-face interviews with representatives of 91 domestic health biotech enterprises in the emerging economies (**See Table 7.2**) and 25 other institutions in China, India, and Brazil including government agencies involved in biopharmaceutical development, venture capital firms, and industry associations. Secondary sources informing our analysis included published articles and websites of companies studied and appropriate government agencies.

While the earlier papers were primarily country-by-country descriptions, this paper analyzes key issues and trends in health biotechnology firms' transition to innovation in these emerging economies. The core research questions we address here are: how do health biotechnologies develop in emerging economies and whether countries have specialized with respect to the type of technologies they focus on? What entrepreneurial strategies and enterprise structures have been commonly used to facilitate the transition into innovative sectors? What are the key barriers deterring health product innovation and what role does the government play in assisting enterprises to overcome these challenges? We address these questions while also highlighting some similarities and differences across China, India, Brazil, and South Africa.

7.2 Technological Upgrading and Industry Specialization

The health biotech sectors of emerging economies are undergoing a major transformation, characterized by increased technological sophistication of product portfolios and R&D activities. Companies in all four countries are developing new capabilities and novel health products but differ in focal points.

7.2.1 Technological Layering and Upgrading for Indigenous Growth

A common strategy for entrepreneurs in emerging economies has been to begin with technologically and financially less demanding products and/or services and to venture into more sophisticated areas as capabilities and revenues improve. Diagnostics and medical devices were common starting points for a number of firms in Brazil and South Africa, respectively, while vaccines represent a major entry point for many firms in India. For instance, Hyderabad-based firms Bharat Biotech and Shantha Biotechnics (now part of Sanofi-Aventis) started out in vaccine manufacturing, and have since expanded their range of activities to include manufacturing of other recombinant products. China's Beijing Wantai, a primarily diagnostics company, together with its parent company is focused on innovative research including efforts to commercialize a novel hepatitis E vaccine. Similarly, Brazil's FK Biotech (Porto Alegre) has expanded its range of activities from manufacturing of monoclonal antibodies for diagnostic kits to development of a cancer vaccine. Starting with local markets, some firms have grown to become global players over time. For example, Vision Biotech (Cape Town, South Africa) claimed to be the second-largest manufacturer of rapid tests for malaria worldwide, and the Serum Institute of India (Pune) is a major global vaccine supplier. Also, a growing number of incumbent pharma companies are developing manufacturing capabilities for recombinant products, with many in India and China already benefiting from related efforts over the past decade.

Historically the main thrust of firms in emerging economies has been to offer non-novel products and services; the efforts described here represent innovation. Reverse-engineering of existing drugs discovered elsewhere has had a considerable learning effect for industries in China, India and Brazil, facilitating the adoption of new technologies and easing the transition into innovative activities. Firms have not only gained experience in health product manufacturing and marketing, but have also developed the necessary technical expertise that allow them to venture into more sophisticated areas. In this respect, the absence of a strong domestic pharmaceutical manufacturing sector in South Africa puts it in a different category than the three other countries studied, resulting in the absence of a skilled knowledge base on which to build.

A key driver of technological upgrading, particularly by Indian firms, has been their interest in export markets, including the major markets of the US and Europe. While domestic populations constitute the main market for most health biotech enterprises studied, there is a growing interest to export products among most medium to large firms. Thus far, export of finished products is notable only in India, where the traditional pharmaceutical sector has increased its foreign sales by over 21% annually between 1996 and 2005 [5] and the country's fast-growing biotech sector, as a whole, garners 56% of its revenues from export of products and services [6]. India's upgrading of manufacturing facilities to meet US-FDA requirements has helped it to increase the export of health products to the US and elsewhere. In contrast, few companies in China, Brazil and South Africa have thus far exported finished medicines to highly regulated markets. In the short-term, most companies seem to prefer a gradual approach where they export health products to other developing nations before targeting the more lucrative markets of the industrialized world.

7.2.2 Industry Specialization by Country

Notwithstanding the fact that health biotech industries in the emerging markets are in a transition period, one can observe patters of specialization by country. The Indian health biotech sector has built on its considerable accomplishments in small-molecule drug manufacturing to become a key vaccine manufacturer. A dozen vaccine companies generate over 50% of the annual revenues for the fast-growing biotech sector as a whole, a market that was estimated at over US$2 billion in 2008 [6]. The entry of Indian, as well as some other developing-country firms, into vaccine production took off in the 1990s as manufacturers in the industrialized countries began to abandon these markets in favor of more lucrative ones elsewhere [7]. It has been suggested that the emergence of Global Alliance for Vaccines and Immunization (GAVI) and the GAVI Fund played a significant role in stimulating the technological expansion of vaccine manufacturers in the developing world, including India and Brazil [7]. Among the largest Indian vaccine producers are Serum Institute of India, Panacea Biotec (New Delhi), Biological E (Hyderabad), Bharat Biotech and Shantha Biotechnics. Some of these firms have become major global suppliers of vaccines to public immunization programs in collaboration with UNICEF, PAHO and the WHO[3]. Recent involvement of four Indian companies - namely, Bharat Biotech, Zydus Cadila (Hyderabad), Panacea Biotech and the Serum Institute - in the race towards a domestically developed vaccine for H1N1 influenza signals the country's growing technological capability in vaccine development. Other key focus areas for India include a growing trend towards production of biogenerics and the discovery and development of novel small-molecule drug candidates. Mumbai-based Piramal Life Sciences and Glenmark Pharmaceuticals are among the leaders in this group, each having over 10 lead drug candidates in development. Other Indian firms are working on developing new drug delivery systems, monoclonal antibodies, diagnostic tests and manufacturing of recombinant medicines[3]. In anticipation of India's adoption of the World Trade Organization's Trade-related Aspects of Intellectual Property Rights (TRIPS) agreement in 2005, the pharmaceutical industry in India spent 13.2 billion rupees on R&D between 2003-2004, accounting for 3.6% of overall revenues [8]. The global competitiveness of India's private industry in both vaccines and therapeutics is, in part, a result of the relative openness of its domestic market and limited involvement of the government sector in health product manufacturing. In China and Brazil (and until recently in South Africa), the prominent role of state-sponsored or public sector institutes in vaccine development and production has diminished the scope for domestic private-sector activity in this area.

Chinese firms seem more focused on developing novel therapeutics in frontier areas and often leverage traditional Chinese medicine (TCM) knowledge and resources. Gene therapies against some cancers, developed by Shenzhen SiBiono (Shenzhen) and Shanghai Sunway (Shanghai), have been on the market for over four years [2]. As of mid-2009, approximately 9,000 patients had been treated for head and neck cancer with SiBiono's innovative gene therapy product, marketed as Gendicine®, approximately 1,200 of which came from outside China. Other innovative projects in the pipeline included a novel drug candidate for cutaneous T-Cell lymphoma by Shenzhen Chipscreen (Shenzhen), an HIV treatment candidate by Fusogen (Tianjin) and products to address lung fibrosis and liver cirrhosis by Shanghai Genomics. There are also significant efforts towards modernization of TCM, involving manufacturing quality control, efficacy tests, and determining active ingredients and their mechanisms of action. While Chinese emphasis on innovative new vaccine development has generally trailed behind India, strong emphasis by the Chinese government in recent years on technological advancement in this area may help to reverse this trend in the coming years. The Chinese vaccine manufacturing sector as a whole is one of the largest in the world, however, with over 30 vaccine manufacturers producing over a billion vaccine doses annually, with a predominance of domestic enterprises [9]. As a sign of recent progress, Sinovac Biotech (Beijing) gained manufacturing approval from the Chinese State Food and Drug Administration (SFDA) for its single-dose H1N1 vaccine in September 2009, preceding the launch of clinical trials by its Indian counterparts mentioned above. Subsequent to this approval, the company received orders from Mexico and Korea, in addition to over 20 million doses from the Chinese central government. In general, the private vaccine market in both China and Brazil remains open to private companies, although foreign firms continue to face some restrictions in China.

The Brazilian health biotech industry is populated by a growing number of technology-based small and medium sized (SME) enterprises as well as generics-based pharmaceutical incumbents, some of whom are transitioning to innovative R&D activities. Overall, the sector remains very young with the vast majority of health biotech enterprises coming into existence in the current decade [10]. A handful of the SMEs we studied had marketed and/or were developing novel technologies. Examples of these firms include Pele Nova Biotechnologia, Recepta Biopharma (both in São Paulo), FK Biotec, and Katal Biotechnologia (Belo Horizonte). Some of these firms have leveraged early success in diagnostics to develop more technologically advanced products [1]. Similarly, large generics firms including Aché Laboratories and Eurofarma (both in São Paulo) are building capabilities in manufacturing large molecules, as part of their foray into biotechnology. However, regardless of size, Brazilian companies tend to shy away from vaccine development and production, particularly those for infectious diseases, primarily due to the dominant role played by the country's public sector in this area. Furthermore, in Brazil, and also in China, the public sector supplies a considerable portion of basic medicines deemed essential for public health. Where public and private domains have significant and overlapping boundaries, it can serve to create tension between the sectors [1], possibly detracting from the country's overall innovative capacity.

The nascent health biotech sector in South Africa relies considerably on the significant research capabilities of the country's universities and research institutes to identify novel technologies and products for commercial development [4]. For example, Elevation Biotech (Johannesburg), which was spun out of the University of Witwatersrand and the National Health Laboratory Service (both in Johannesburg), is developing novel peptides to inhibit HIV entry into cells. This company has received a grant from the International AIDS Vaccine Initiative (IAVI) to develop and test new vaccine antigens. Other innovative firms include iThemba and Arvir (both in Johannesburg), which are developing cost-effective methods to manufacture HIV drugs and Disa Vascular (Cape Town), which is involved in development and manufacturing of coronary artery stents. A few South African firms have also ventured into nutraceuticals including Biomox Pharmaceuticals (Pretoria) and Cape Kingdom (Cape Town). Biovac Institute (Cape Town), a public-private partnership mandated to supply the needs of South Africa's vaccination program, was formed in 2003 after attempts at a purely public system failed to accomplish this goal.

In all four countries, natural resources are increasingly leveraged to identify and develop novel health technologies. Biodiversity resources and traditional medicines serve as a major source for lead compound identification for firms in the emerging markets. For example, Shanghai Ambrosia Pharmaceuticals (Shanghai), uses its novel platform technologies to screen TCMs for lead molecules against cancer and immunological diseases. Brazil's Aché Pharmaceuticals and

Pele Nova have marketed phytotherapeutic-based products used for inflammation and skin lesions respectively, and a number of others are developing other products originating from Brazilian biodiversity [1]. India's Piramal Life Sciences, in collaboration with public universities and research institutes, has developed a large bank of natural products and product extracts as well as a microbial library containing over 40,000 different cultures. Many of the company's lead molecules under study – including some in clinical trials – were sourced from these assets. Avesthagen (Bangalore) uses a multi-disciplinary approach to develop health products, including dietary supplements, drawing extensively on knowledge from Indian medicinal plants.

In summary, specialization patterns are broadly reflective of the institutional environment in each country, local knowledge as embodied in universities and research institutes, access to unique and country-specific resources, the divergent involvement of the public sector in health product manufacturing and provision, and evolving competition between local and global rivals.

7.3 Entrepreneurial Strategies and Enterprise Structures

As late as a decade ago, firms involved in the health area were essentially a population of manufacturers or formulators of generic products. By contrast, today there is a much broader scope of business strategies utilized to generate revenues and invest in future prosperity across the emerging markets. A growing number of firms view product R&D as an important component of their business models. However, the extent of their commitment to R&D and the nature of their involvement vary across countries.

7.3.1 Fragility of the Purely R&D-Based Business Model

The few pure R&D firms in existence today, such as Recepta BioPharma (Brazil), Fusogen Pharmaceuticals Inc. (China), and iThemba Pharmaceuticals (South Africa), tend to be supported substantially from governmental sources. This trend is most pronounced in China, where the government increasingly subsidizes R&D activities within firms both directly by offering financial support and indirectly by expanding access to more cost-effective R&D infrastructure. Indian firms have traditionally had less direct support from government sources, perhaps contributing to the near absence of a pure R&D-based model among firms in this country. A relatively recent trend that is making the pure R&D-based model more viable is the growing interest on the part of large pharmaceutical MNCs to partner with domestic firms, a trend that is currently most noticeable in China. A case in point is Hutchison MediPharma (Shanghai), which is an integrated R&D company whose discovery and development activities are supported, in part, through relationships with Eli Lilly (Indianapolis, IN), Merck KGaA (Whitehouse Station, NJ) and Johnson & Johnson's subsidiary Ortho-McNeil-Janssen Pharmaceuticals (Raritan, NJ). These relationships are motivated, in part, by the desire on the part of multinationals to reduce drug development costs by tapping cheaper scientific labor in the emerging markets. Benefits to domestic firms include; access to financing for innovative projects, technological learning, and reputational advantages of working closely with major global enterprises.

7.3.2 Short-term strategies fueling Long-term Innovation

According to our analysis, challenges associated with securing private funding for a pure R&D-based model have caused most innovation-minded entrepreneurs to adopt an indigenous growth model at or shortly after inception; where R&D activities are financed through internal revenue generation. The result is that these enterprises often undertake two distinct sets of activities: one set aims at generating revenues in the short-term, while the other is focused on innovation for long-term growth. For example, when Mr. Eduardo Cruz, the founding director of Cryopraxis (Rio de Janeiro), wished to start a company in 2000 that would develop stem-cell therapies, his initial strategy was to start a cord blood banking service to help finance R&D activities. A common approach for generating revenues, in all four countries, remains the in-house manufacturing and marketing of products, be they generics, copycat therapeutics, or modifications of existing health products, often targeted at niche markets. A strategy we observe to be very common among firms in China and India is to offer a variety of product development and/or manufacturing services, often to foreign clients. Examples of firms utilizing this model include India's Bharat Biotech and the Chinese firms Shenzhen Chipscreen and Shanghai Genomics. While the dearth of private financing has been a key driver of this trend, investors' preference for early revenue-generation is also a major influence on pushing investees in the direction of revenue-generation from early on in their life cycle. In most industrialized economies, it is well established that financing new product development with current revenues is more expensive and constraining compared to investment-driven financing. However, whether by choice or necessity, health biotech enterprises in the emerging economies have yet to utilize the latter strategy on a considerable scale.

7.3.3 Services for Contract & Risk-Sharing

A trend particularly common in India and China is the emergence of wholly services-based businesses with a focus on providing sophisticated and cost-effective research, development, and manufacturing services. Deals in this regard are generally structured in one of two ways. One strategy is essentially transactional in that services are rendered in return for payments upon completion of specified milestones. The risks and upside of novel drug development are retained entirely by the client in this instance; the contracting firm provides services but does not participate in either the risk or the potential returns from R&D beyond the fees that are charged for particular services. The provision of contract research services is relatively new. Previously, domestic companies only offered manufacturing and clinical research services with limited capability in other aspects of drug discovery and development. Companies adopting the newer model typically serve foreign clients by focusing on discovery and development as well as contract manufacturing for proprietary health products. For example, India's Syngene (Bangalore) set up an R&D facility in 2009, which is dedicated to lead identification and early development of novel drug candidates for Bristol-Myers Squibb (New York). Among the growing group of service providers are: China's Wuxi Pharmatech, Sundia Meditech Company (both in Shanghai) and India's Advinus Therapeutics (Bangalore) and Jubilant Organosys (Noida). All of these firms have enjoyed considerable growth in recent years. The second strategy combines upfront payments with future royalties and/or manufacturing rights. HD Bioscience (Shanghai), Jubilant BioSys (Bangalore) and Suven Life Sciences (Hyderabad) are among a growing list of companies that are increasingly adopting the latter strategy.

7.3.4 Partnership for Growth and Innovation

Health biotech firms studied tend to have a considerable reliance on partnerships with domestic universities and research institutes as well as foreign entities. Firm-university linkages typically serve to fill in gaps in internal R&D capabilities and access facilities/equipment and, to a lesser extent, to the transfer of new technologies to firms. There appears to be a strong correlation between the levels of R&D interest among firms and their linkages with domestic universities and research institutes in all countries studied. For example, R&D-intensive firms such as Recepta Biopharma of Brazil, Shanghai Sunway and Sinovac Biotech of China, and Avesthagen in India have strong collaborations with academic institutions. Similarly, most South African firms, which are often established to commercialize university-originated technologies, maintain close linkages with them post-inception. In contrast, domestic entrepreneurial collaboration, particularly those aimed at product development, appears limited across all countries concerned.

Innovative R&D activities by firms in the emerging markets are also associated with increased international linkages. These partnerships often manifest as co-development arrangements, where novel health products are jointly discovered and/or developed between Indian and Chinese firms and foreign counterparts; usually large multinational corporations (MNCs). For example, in 2007, Shanghai Sunway and Genzyme (Cambridge, MA) agreed to co-develop the latter company's proprietary product Ad2/HIF-1a, which is a gene therapy product targeted for treating peripheral arterial disease. South Africa's leading vaccine provider, the Biovac Institute, has grown through a number of strategic international collaborations [4]. China's Hutchison Medipharma (Shanghai) and India's Jubilant Biosys (Bangalore) and Suven Life Sciences (Hyderabad) are other examples of companies that have significant levels of collaborations with multinational firms. Under this approach, the emerging-markets partner often shares in the risks and in the upside returns from successful commercialization projects. In addition to considerable entrepreneurial collaborations, Indian and Chinese firms also maintain significant linkages with foreign universities. On the other hand, South African firms studied had an almost exclusive focus on interactions with foreign companies, while Brazilian emphasis seemed equally divided between foreign firms and universities/research institutes.

A recent trend manifesting primarily in India and China has been the acquisition of domestic biopharmaceutical firms by foreign entities. Examples of these include purchase of India's Shantha Biotechnics (Hyderabad) and Piramal Healthcare (Mumbai) by Sanofi Aventis (Paris, France) and Abbot Laboratories (Abbott Park, IL), respectively and the takeover of South Africa's Vision Biotech (Cape Town) by Inverness Medical Innovations, Inc. (Waltham, MA).

7.4 Barriers to Innovation – Implications for Public Policy

Our analysis revealed a number of important barriers that hinder entrepreneurial progress in health product innovation in the countries studied. Although most challenges are similar across the countries studied, the underlying reasons for each are often different.

7.4.1 Human Resources

While all four countries have expanding capabilities in science and technology in general and life sciences in particular, access to specially trained personnel in health biotech innovation is often limited. The most common strategies to fill shortage of skilled labor have been to: a) increase science and technology capacity in general through investment in research, b) develop of targeted training programs, and c) recruit highly trained personnel from abroad. As a result of the first strategy, all countries studied have increased their relative contribution to global scientific publications in recent years (**Table 7.1**). In particular, China's publication and citation rates have been rising substantially, making it the fifth largest publisher globally [11]. While this trend speaks to a strengthening of the science and technology base, it is often not sufficient to address the shortage of specially trained personnel. Efforts by the emerging economies to train personnel domestically are not only time-consuming, but face challenges of their own. Many training programs relevant to health biotech in the emerging economies are based in university systems, which have been traditionally isolated from industry. As a result they are not perceived to be effective at detecting and addressing the changing industrial demands.

Nonetheless, some efforts in this regard are underway. For example, India's Department of Biotechnology has a number of programs including sponsorship of post-graduate training in biotechnology and the provision of stipends for post-graduate students to work in the industry for six months. Similarly, Brazil has initiated a program that sponsors researcher salaries for a period of time while they work in industry. South Africa's human resource challenges seem related to the country's inability to sufficiently retain highly trained individuals [4] and the lack of a strong pharmaceutical manufacturing sector to provide a basic skill-set for further industrial development. Lastly, the Chinese, and to a lesser extent Indian, industries have been beneficiaries of returnees, who in many cases have obtained specialized training abroad and have strong scientific and commercial networks. China's post-1978 policies towards overseas study allowed tens of thousands of Chinese students and scholars to go abroad for education and training. However, only an estimated 25% of these students return to China after their training [12]. In response the Chinese government has put in place an ambitious suite of programs and incentives to recruit back highly-trained Chinese professionals and academics from abroad, with mixed results [12]. For instance, Simon and Cao find that these incentives have thus far failed to recruit the most-highly trained and accomplished groups [12]. What is also uncertain is whether those who do return will be sufficiently supported to stay for the long term, and if the skewed compensation scheme in favor of returnees can be maintained without adversely affecting overall employee morale. What is clear is that China's ambitious R&D infrastructure building programs, as part of its overall goal to build an innovative and globally competitive bioeconomy, will continue to create demands for specialized skills in various areas. It remains to be seen whether current initiatives will be sufficient to meet this demand.

7.4.2 Access to R&D Infrastructure

As many companies in the emerging economies have ventured into innovative activities only in recent years, their in-house R&D capabilities and infrastructure are often limited. A common strategy to obtain required services is to partner with researchers within universities or public institutes. This strategy is helpful to a degree but a number of factors detract from its effectiveness. These include the historical lack of an entrepreneurial culture within universities and the traditional isolation of the public and private sectors in these countries. Though governments have made some efforts to bridge the public and private sectors, often through funding of collaborative projects, in most cases there is little indication that these efforts have made a very significant impact. An exception to this may be China, where the involvement of government in many state-owned enterprises (SOEs) makes interactions with universities and research institutes easier. In addition, China has embarked on an ambitious infrastructure-building exercise through its Hi-tech Parks Initiative. In the span of less than 20 years the country has built 54 high-tech parks, with an estimated 20 having a life science component. The largest of these is the Zhangjiang Hi-Tech Park in Shanghai. Initiated in 1992, this park occupies an area of 25 square kilometers and is already home to over 4000 enterprises, with approximately 400 being life science companies, institutes and service providers. Other major life science clusters include Zhongguancun Life Science Park in Beijing and bioBay in Suzhou, which is a joint project between China and Singapore. These parks offer a host of benefits and invariably have one or more incubator facilities, which especially cater to small and medium enterprises. While India possesses a few clusters that are similar in some ways - such as Genome Valley in Hyderabad - and Brazil is said to be working on enhancing its industrial R&D infrastructure, the scale and speed of development in China is breathtaking by comparison.

7.4.3 Regulatory Issues

One of the most common challenges facing innovation-inspired firms in the emerging economies is related to clarity and effective enforcement of regulations governing health products. Again, while the outcome often manifests in delays in regulatory approval, the underlying causes often vary across nations. For instance, while a fragmented regulatory regime in India has historically posed serious challenges to the growth of the innovative health biotech sector, lack of practical experience on the part of Brazilian and South African regulators was thought to make product approval challenging in these countries. Other challenges in Brazil and South Africa were primarily related to delays in approval of clinical trials, which was perceived to detract from a major competitive advantage possessed by these countries. In recent years India has been in the process of reforming its biotech regulatory system by trying to institute a centralized regulatory agency called the National Biotechnology Regulatory Authority (NBRA). Long in coming and motivated, in part, by the desire to better regulate genetically-modified crops and other organisms, limitations on NBRA's scope of activities serve to maintain the anachronistic separation of institutions that govern small- versus large-molecule drugs. In this sense, India may have missed a great opportunity to create a truly centralized regulatory agency, which can oversee all heath products and optimize resultant synergies. China's regulatory regime has also had significant setbacks in recent years due to corruption scandals involving some high-ranking officials at the country's SFDA. However, the agency has rebounded from these challenges and has recently made progress in a number of areas. For example, in early 2009 the SFDA instituted its Green Channel initiative, which is an expedited approval process, allowing regulators to waive requirements for Chinese trials for innovative new drugs, new combinations, and those targeted at unmet medical diseases in the country. Furthermore, it has undertaken a variety of initiatives aimed at addressing product quality issues in the country's vast and complex pharmaceutical sector.

7.4.4 Intellectual Property Protection

While firms in all four countries are increasingly cognizant of patenting, issues related to the efficiency of processing patent applications and effective enforcement of property rights continue to create uncertainty. In all of the countries studied except South Africa, a new pharmaceutical product patent regime was formally adopted between 1993 and 2005. While these countries are still adjusting to the new intellectual property (IP) regime, they also struggle to minimize negative impacts it might have for both public health and domestic industries. These attempts have resulted in country-specific peculiarities in patent legislation that serve to diminish associated incentives and have led to a few high-profile court cases, particularly in Brazil and India, where patents rights have either been denied or not enforced as expected. Among the most controversial elements built into patent legislation are provisions related to compulsory-licensing and those that aim to curtail the practice commonly referred to as 'ever-greening', which allows companies to collect monopoly rents by patenting minor changes to a given drug whose patent-life is about to expire. For instance, in September 2009, the Indian patent office rejected an application by Gilead Biosciences (Foster City, USA) for the anti-AIDS drug tenofovir, in part based on arguments that the application lacked sufficient inventiveness. Brazil had earlier declined patent rights for the same product, declaring it of interest to public health in that country. Under the new Indian patent act, new uses for existing products are not patentable unless they demonstrate improved efficacy [7]. It is not yet clear how this will impact on domestic companies, many of which are mainly concerned with improving existing technologies such as combination vaccines and new drug-delivery systems. Concerns regarding China's patent regime stem primarily from the nature of its decentralized enforcement regime. Patent infringement cases are generally handled by municipal courts at the jurisdiction of the accused, introducing potential conflicts of interest into the process [13]. Amendments to China's patent legislation, which took effect in October 2009, are aimed at enhancing the quality of patents, improving enforcement and better alignment of China's approach with other major markets.

7.4.5 Innovation Financing

Among the countries studied, China has the largest pool of public money dedicated to its science and technology programs. It administers most of these funds through three key programs: the

High-Tech Research Development Program (known as the 863 Program), the Torch Program, and the National Key Basic Research Program (known as the 973 Program). The Torch Program is perhaps of most direct significance to the industry as the other two primarily focus on basic research. This program has an array of initiatives designed to support development of new technology industries. Since its inception in 1988, it has facilitated the building of 54 National High-tech Parks, which are designed to integrate R&D, manufacturing and enterprise incubation. The Torch program also administers a 7 billion RMB (USD 1.02 Billion) innovation fund (Innofund), which funded 11,980 firms from 1999-2007, with approximately 20% of funds devoted to biotechnology.

India's Department of Biotechnology (DBT) is the lead government agency that promotes biotechnology and pharmaceutical innovation in the country. DBT targets approximately one third of its annual budget – estimated at approximately Rs. 900 Crores (~USD 201 M) for 2008/9 – to promoting public-private collaborations. Among its key programs supporting industrial R&D is the Small Business Innovation Research Initiative (SBIRI), which in 2009 provided funding for 48 projects within enterprises (www.dbtindia.nic.in). The DBT's other key foci are in skill development and regulatory reform. The overall contribution from other agencies, particularly with respect to support of R&D within enterprises has been more modest thus far.

In Brazil, the Studies and Projects Funding (FINEP) Program of the Ministry of Science and Technology is the key program that supports enterprise R&D. Through a series of initiatives, including sector-specific funds and investments in venture capital funds, FINEP aims to advance innovation within the industrial sector. One of its latest initiatives is the Prime Program (Primeira Empresa Inovadora), which aims at supporting approximately 5,000 technology-based startup companies, between 2009-2011), through an offering of R$ 120,000 (~$68,000 US) in grants to each enterprise over the first year, followed by interest-free loans for qualifying applicant during the subsequent year (www.finep.gov.br).

The 2001 National Biotechnology Strategy in South Africa was the key policy instrument that highlighted the need to capture the commercial opportunities offered by biotechnology. The strategy led to the establishment of Biotechnology Regional Innovation Centers (BRICs), the main government initiatives in biotech development. The South African government had earmarked 450 million Rands ($58 million) from 2004-2007 for related initiatives [4].

Overall, the more recent and targeted government policies attempt to increase entrepreneurial commitment to innovative R&D by direct subsidization of these efforts and indirectly by investing VC firms and offering support for access to R&D infrastructure. Based on our data, the majority of companies that undertake radical innovation projects with the objective to develop novel products have been beneficiaries of direct government assistance. In most cases, companies appear to undertake radical innovations only when government assistance reduces investment risks to a tolerable level, or when they can secure private capital for those projects. Indirect support mechanisms have varied from building R&D infrastructure in China, increasing entrepreneurial access to public-sector R&D resources in Brazil, support of technology-focused venture capital funds most notably in China and Brazil and the creation of Biotechnology Regional Innovation Centers in South Africa. While limited in most cases, governmental incentives have served to spur some innovative activities within enterprises.

While private financing, especially from institutional investors, has been gradually improving, few invest in highly innovative projects. Venture capital (VC) firms that invest in innovative companies include BioVeda China Fund (Shanghai), APIDC Ventureast Biotechnology Venture Fund (Hyderabad, India), DFJ-FIR Capital (Belo Horizonte, Brazil) and BioVentures (Cape Town, South Africa). Limitations on financial exits for investors are thought to be a key contributor to the shortage of VC investments in innovative companies. The BOVESPA-MAIS (São Paulo) branch of the Brazilian stock exchange and the recently launched Shenzhen Stock Exchange aim at improving this situation in the their respective countries. Recent interest in company acquisition by multinational corporations in China and India may provide yet another avenue for investors to divest. At the same time, companies eye international stock exchanges as well, where they can achieve a more favorable valuation.

7.5 Concluding Remarks

Our research shows that emerging market firms are making attempts to join the rank of innovating companies in the industrialized world. In fact, our work suggests that, in this globalizing world, the trajectories of developed and emerging economy firms are becoming increasingly intertwined. For health biotech sectors in the emerging markets, particularly those of China and India, the transition to innovation also means greater global integration. Thus far, company activities in the emerging economies have tended to coalesce around particular themes and issues: medical devices and infectious diseases in South Africa; vaccines and small molecules in India; genetic and stem cell therapies and traditional medicines in China; and diagnostics and biodiversity-linked therapeutics in Brazil. Going forward, almost none of the firms we studied plan on developing novel therapeutics for global consumption fully on their own. Therefore, at least in the short-term, promising leads in development within firms in the emerging markets will likely find a home within the pipelines of major global players. This trend may ultimately re-shape the focus of these sectors in the coming years. While the nation-state continues to play an essential role in building innovative capacity in health biotech, the ultimate outcome of each country's collective efforts is likely to be shaped just as much or more by global factors.

The national pattern of initiatives aimed at fostering innovative health biotech sectors appears to be shaped as much by governmental policies as by the special circumstances that constitute the innovation environment in each country. While all of the countries studied have housed strong universities and research institutes for decades, to kindle innovative activities within the private sector has required more focused government policies. Early indications are that policies with the most obvious impact on spurring innovative activities within the private sector have been those that offer direct and indirect financial support for these enterprises. Indeed it is of note that the mere adoption of a product patent regime in pharmaceuticals by China in 1993 (even prior to its adoption of the TRIPS agreement and its enforcement in 2001), by Brazil in 1997, and the expectation of the pending TRIPS enforcement in India in 2005 were not sufficient, on their own, to spur significant entrepreneurial investment into radical health innovations. Rather, entrepreneurial commitment to innovation, as a trend, became noticeable concomitant with increased government support for innovation within the entrepreneurial sector. Thus far, governments in China, India, Brazil and South Africa have played a crucial catalytic role in spurring health product innovation in the private sector, albeit on a limited scale. It remains to be seen whether these efforts will be of sufficient scale and duration to help galvanize private investments necessary for a successful transition to innovative sectors.

While the countries studied vary in certain respects, our analysis shows that they are also affected by similar forces and often respond in similar ways. It is possible to see similarities in the way entrepreneurs attempt to fund their innovative activities, their preference for collaboration with international firms, their strategies to monetize their IP and their overall orientation towards a global market from the outset. Experience with health technologies in the emerging markets indicates that broad-based interventions (such as the introduction of product patent regimes or macroeconomic adjustments) though often necessary, are unlikely to be sufficient in kick-starting innovative activities. This observation may be especially pertinent in the context of the emerging high-tech sectors housed within 'catch-up' economies. It is exceedingly important to realize that success in health biotech innovation is about the hard work of adapting scientifically, nationally and globally all at the same time. The implication is that countries that can best understand this complexity and situate their own strengths vis-à-vis the broader global value-chain will be most likely to reap the resultant benefits.

7.6 Tables

Table 7.1 Population size, GDP, and Pharmaceutical Market Parameters for China, India, Brazil, South Africa a few Developed Nations

Country	Population Size, 2008 (Millions)	GDP for 2008 in Constant 2000 Prices, $ billions)	Pharmaceutical Market Size, $ US billions, 2008 (Projected Size in 2013)	Pharmaceutical CAGR, 2004-2008 (Forecast CAGR for 2008-2013)
China	1330	2562	20.7 (50.4)	21.10% (19.5%)
India	1148	835	9.6 (16.4)	10.30% (11.3%)
Brazil	191	819	11.2 (16.8)	10.40% (8.4%)
South Africa	44	184	1.5 (1.9)	5.90% (4.9%)
Japan	127	5263	65.3 (67)	2.40% (0.5%)
Germany	82	2095	36.2 (37.4)	2.90% (0.7%)
Canada	34	878	24.2 (27.2)	6.60% (2.4%)
United States	304	11701	273.9 (335.6)	3.70% (4.2%)

Source: DataMonitor 2008, Country-specific Pharmaceutical Industry Profile Reports. CAGR stands for Cumulative Annual Growth Rate.

Table 7.2 Emerging Economy Health Biotech Firms Included for this Analysis

China	India	Brazil	South Africa
Amoytop Biotech	Avestha Gengraine Technologies	Aché Laboratórios Farmacêuticos	African Clinical Research Organization (ACRO)
Beijing Haiyan Pharmaceutical*	Advinus Therapeutics*	BioCancer	Altis Biologics
Beijing Wantai Biological Pharmacy Enterprise	Bharat Biotech International	Biolab Sanus Farmacêutica	AngioDesign
Bio-Bridge Science	Bhat Bio-Tech India	BioGene	Arvir Technologies
CapitalBio Corporation	Bharat Serums andVaccines	BIOMM Technology	Aspen Pharmacare
FusoGen Pharmaceuticals	BigTec Laboratories*	COINFAR	Bioclones
GeneScience Pharmaceuticals	Biocon	Cryopraxis Criobiologia	Biomox
Hutchison MediPharma*	Biological E	Eurofarma Laboratórios	Biovac Institute
HD Biosciences	Dr. Reddy's Laboratories	FK Biotecnologia	Cape Kingdom
Kanghong Pharmaceutical Group*	GangaGen Biotechnologies	Hebron Farmacêutica	Disa Vascular
Shanghai Ambrosia Pharmaceutical*	Indian Immunologicals	Intrials Clinical Research	Elevation Biotech
Shanghai Fudan-Yueda Bio-Tech	Jubilant BioSys*	Katal Biotecnológica	Gknowmix
Shanghai Genomics	LifeCare Innovations	Labtest Diagnóstica	Kapa Biotech
Shanghai Genon Bio-Engineering	Lupin Pharma	Nortec Química	National Bioproducts Institute
Shanghai Huaguan Biochip	Piramal Life Sciences	Pele Nova Biotecnologia	Synexa Life Sciences
Shanghai Sunway Biotech.	Panacea Biotec	Recepta Biopharma	Veritrial Clinical Trials
Shanghai United Cell Biotech	Reliance Life Sciences	Scylla Bioinformatics	Vision Biotech
Shenzhen Beike Biotechnologies	Serum Institute of India	Silvestre Laboratories	
Shenzhen Chipscreen Biosciences.	Shantha Biotechnics	União Química	
Shenzhen Tiandakang Gene Engineering*	Strand Life Sciences		
SiBiono GeneTech	Suven Life Sciences*		
Simcere Pharmaceutical Group*	Transgene Biotek		
SinoCells Biotech	Wockhardt		
SinoGenoMax	Clinigene		
Sinovac Biotech	SIRO Clinpharm		
Starvax International	Syngene		
Tianjin SinoBiotech			
WuXi PharmaTech			
Zenson Sci & Tec. Co.			

* These companies were not part of our initial studies series of studied published in NBT from 2006-2009.

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Chapter 8
Implications for Global Health

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8 Global health or global wealth?

8.1 Introduction

Health enterprises in the emerging economies, particularly in China, India and Brazil, have made significant contributions to local and global health needs through low-cost manufacturing of health products. Moreover, a key policy objective for these countries is to foster a strong and innovative health biotech/pharmaceutical sector. The health biotech companies in this sector are innovating close to the 'coalface' of global health problems, making appropriateness, translation, uptake and affordability of the resulting solutions more likely. Even so, the shift from imitation to innovation in these countries—a trend largely stimulated by the adoption of the World Trade Organization's (WTO; Geneva) Trade-Related Aspects of Intellectual Property Systems (TRIPS)—is raising questions about the future market trajectory of the sector.

A basic question is whether this movement toward innovative products would mean movement away from poorer market segments, both at home and abroad. Stated differently, as enterprises in the emerging markets take on more costly innovative projects, would they be compelled to choose between global health and global wealth? Alternatively, is it possible for health entrepreneurs in the emerging economies, as their firms become more sophisticated technologically and financially, to address the needs of the poor while simultaneously taking advantage of more lucrative markets?

Here we argue that the objectives of global health and global wealth can be achieved simultaneously, provided targeted support mechanisms are in place to enable product development for the poorest market segments, for which a purely entrepreneurial model may not be suitable.

8.2 Accessing global markets: implications for global health

Through service-provision arrangements with multinational pharmaceutical companies (MNCs), more and more enterprises in the developing world, such as China's Wuxi PharmaTec (Shanghai) and India's Advinus Therapeutics and Jubilant Organosys (both in Bangalore), are integrating themselves into the global product development value-chain. Furthermore, there is a growing trend toward collaborative development of innovative health products. For example, China's Hutchison Medipharma (Shanghai) and Shenzhen Sunway (Shenzhen) work with several global pharmaceutical MNCs to develop health technologies. The concern from a global health perspective is that these trends may, over time, shift the focus of domestic health biotech sectors in emerging economies toward the needs of more lucrative global markets and reflect the priorities of pharmaceutical MNCs.

This argument presumes, however, that the focus of the MNCs is static and will remain targeted on developed world markets. In fact, growth in pharmaceutical markets in emerging economies has begun to outstrip that of developed markets. DataMonitor has reported average annual growth rates of approximately 10% for Brazil and India and 21% for China between 2004 and 2008 with similar growth forecasts until 2013. Therefore, pharmaceutical MNCs and large biotech companies have significantly increased their focus on the markets of emerging economies.

The needs of developed and developing countries in terms of health products overlap in significant ways. Some health conditions, such as infectious diseases and, in particular, neglected tropical diseases, are disproportionately or almost exclusively affecting the developing world. Other health conditions, such as noncommunicable chronic diseases (NCDs), exist in both the developed and developing countries and have become the main source of disability and mortality worldwide. Indeed, in some instances, they are becoming growing epidemics in the emerging economies [1]. Therefore, the contributions of health enterprises based in the emerging economies to NCDs are by themselves highly relevant to global health.

Tapping global markets for products and services strengthens domestic firms by enhancing their technological, financial and marketing resources. A closer look at the pipeline of innovative products in Indian firms, such as Wockhardt, Piramal Life Sciences (both in Mumbai), Dr.

Reddy's Laboratories (Hyderabad) and Biocon (Bangalore) reveals their considerable relevance to domestic populations. As such, efforts that strengthen domestic industries can ultimately advance global health by enhancing the ability of domestic enterprises to address locally relevant diseases in a more innovative manner.

Therefore, the confluence of factors associated with global integration and targeting of global markets by firms in the emerging economies, together with the changing mindset and practice on the part of large pharmaceutical MNCs, hold the potential to temper any broad-based movement away from most local and global health needs by the former group of firms. These trends also enhance innovative capacity of domestic industries.

8.3 Entrepreneurial model: a critical vehicle for global health

Traditionally, the primary preoccupation of health entrepreneurs in emerging economies was copying and manufacturing existing products discovered and developed elsewhere. Over the past decade, many firms in these markets have extended this activity by adapting health technologies to developing world contexts and have leveraged process innovations and reduced labor costs to offer quality products at prices that are more affordable. For example, process innovations by India's Biocon (Bangalore) and Shantha Biotechnics (Hyderabad) helped reduce the cost of insulin and hepatitis B vaccine in the Indian market by >40% and >95%, respectively. However, the incremental nature of these innovations means that the firms involved incur substantially less cost than if they were to discover and develop the original products independently; something that will increasingly be required in the post-TRIPS period. Although there will continue to be considerable scope for incremental and business model innovations, these cannot, by themselves, address neglected disease areas for which no effective prevention, diagnosis or treatments are available. The latter challenges demand radical innovations where new solutions are explored with respect to unmet medical needs—a strategy that entails considerable financial risks and demands access to advanced technologies and know-how.

Notwithstanding cost advantages in the emerging economies, a purely entrepreneurial model, left on its own, is unlikely to address disease areas with relatively low monetary market potential. Thus far, health enterprises in developing countries have served to effectively shrink the proportion of populations without access to many health products, but they cannot eliminate the access gap on their own. We propose that limited but selective and well targeted interventions by domestic governments and the global health community can allow firms in emerging economies to expand their target market to include more of the poorest market segments, both at home and abroad.

8.4 Supporting the entrepreneurial model

Previous efforts to advance global health have included the formation of a variety of public-private-partnerships (PPPs) [2], advance market commitments (AMCs) [3-4], priority review vouchers [5] and patent pools to share intellectual property [6]. Several key organizations serve to inform and enable these and other initiatives. For example, BioVentures for Global Health (San Francisco, CA) engages biopharmaceutical companies in global health, in part by highlighting market opportunities with a global health impact. The Results for Development Institute's (R4D; Washington, DC) Center for Global Health R&D Policy Assessment (http://www.healthresearchpolicy.org) provides independent reviews of proposed solutions that aim to accelerate global health R&D. These initiatives have been supported from public and philanthropic sources as well as the private sector in pursuit of global health goals. However, these mechanisms have, to date, been primarily (though not exclusively) used by multinationals and biotech companies based in wealthy countries, although they can also be adapted to better meet the needs of emerging economy firms. For example, the Drugs for Neglected Diseases Initiative (DNDi; Geneva) produced a new anti-malarial ASMQ (a combination drug including artesunate and mefloquine) with the Oswaldo Cruz Foundation (Rio de Janeiro, Brazil), and the Program for Appropriate Technology in Health (PATH) developed a meningitis vaccine with the Serum Institute of India (Pune, India).

We believe that tapping into the fast-growing capabilities of health enterprises in the emerging economies is an effective way to complement these current initiatives. At a time when the innovative capacity of emerging-economy firms is growing rapidly, access to technologies relevant to global health is getting easier. Patent pools, such as that initiated by GlaxoSmithKline (GSK; London) [6], demonstrate an increased willingness by major patent holders to share intellectual property rights for the true diseases of poverty. Indeed, GSK has recently announced that it will also publish its research results related to a group of over 13,000 promising compounds against malaria [7]. Another key initiative, which serves to increase access to knowledge is the global access strategy used by the Bill & Melinda Gates Foundation (Seattle, WA) and Grand Challenges Canada (http://www.grandchallenges.ca). Combining the innovative capacities of firms in the emerging economies with increased access to knowledge and technologies required for more radical innovations will accelerate development of health products targeted at diseases of the poor.

Below, we briefly discuss three more mechanisms that could provide support to health biotech companies in emerging economies [8-11] in their pursuit of global health objectives.

8.4.1 Orphan drug–like legislation in emerging economies

In the US, orphan drug legislation [12] provides a host of incentives for products targeted at markets with low purchasing power because of their low prevalence, generally fewer than 200,000 people. This concept has been proposed as a model for domestic governments in emerging economies to apply to diseases of the poor [13], where low market potential stems not from low disease prevalence but from the reduced purchasing power of affected populations.

An approach based on the orphan drug model would focus resources toward diseases of the poor by offering support for upstream R&D activities and reduce investment risks for entrepreneurs through mechanisms such as extended periods of market exclusivity and expedited regulatory approval. Furthermore, to account for specific national contexts, it could include further measures that address issues such as eventual procurement and delivery of related products to target populations.

8.4.2 Global Health Accelerator

The Global Health Accelerator (GHA) [14] aims to tap the innovative capacity of emerging economy companies to advance development of products directed against diseases of the poor. For example, in the field of neglected tropical diseases, a total of 78 companies in the four emerging economies we studied have marketed 69 drugs, diagnostics and vaccines, with 54 more in the pipeline. Although these companies are often successful at addressing local diseases, they do not, however, have the financial or human resources to focus on distant markets.

The GHA platform is envisaged as providing to health entrepreneurs in the emerging economies a suite of services that include international market and regulatory assessment, identification of commercialization partners and distribution channels, and facilitation of access to financing. In addition, it would include a global health prize to recognize excellent examples of Southern innovation against diseases of the poor.

8.4.3 Global health funds targeted to emerging economies

The PATH-assisted Program for the Advancement of Commercial Technology–Child and Reproductive Health (PACT-CRH) has transferred a number of health technologies to Indian companies and provided over US$7 million in loans to 11 enterprises. In July, the Wellcome Trust (London, UK) also partnered with India's Department of Biotechnology (New Delhi) to launch the 'R&D for Affordable Healthcare' initiative, a £45 ($71.5) million program to support technology transfer and development by public and private sectors in India (http://www.wellcome.ac.uk/News/Media-office/Press-releases/2010/WTX060350.htm). In another initiative, Charles A. Gardner of the Global Forum for Health Research has proposed the provision of direct grants to innovating SMEs in developing countries, motivated by 28 years of his experience with the US Small Business Innovation Research (SBIR) program (http://healthresearchpolicy.org/sites/healthresearchpolicy.org/files/IDCR%20SBIR.pdf). Elsewhere, David Stevens and colleagues at the R4D Institute have put forward a 'Local Currency Guaranteed Development Bond SME Loan Program' (http://www.resultsfordevelopment.org).

In the United States and other developed countries, venture capital (VC) has had a critical role in the development of biotech industries. There is now also a fund based in New York—the Acumen Fund—that takes a VC-like approach to funding global health challenges. In addition, VC funds that invest in health technologies have sprung up in the emerging countries themselves. These include the Andhra Pradesh Industrial Development Corporation's Ventureast Biotechnology Venture Fund (Hyderabad, India), Bioveda China Fund (Shanghai, China) and Bioventures (Cape Town, South Africa). Although such funds sometimes struggle to balance social benefits while realizing financial return on investments, there is the potential to learn from these experiences to promote global health.

8.5 Conclusions

There is not an inevitable trade-off between global health and global wealth. Both goals can be pursued in parallel. But this will require concerted action on the part of the global health community, including governments in emerging economies and international donors, to optimize the potential to global health goals of innovative emerging economy firms. The window of opportunity for action will not remain open for long. The global health community needs to better tailor existing measures (PPPs, AMCs, patent pools and priority review vouchers) to involve and support emerging-economy companies. New entrepreneurial support mechanisms, such as orphan drug-like legislation in emerging economies, the Global Health Accelerator and new funds, could add the growing capabilities of these firms to the repertoire of assets available for global health. Doing so will enable the global health community to seize this window of opportunity and ensure that innovative capacity is tapped not only in the industrialized countries but also in the emerging economies, so that the health needs of the poor can be more fully addressed.

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Chapter 9
Conclusions

9 Concluding Chapter

9.1 Background

This work is contextualized in Chapter 2 within the biopharmaceutical sector globally and the evolution of this sector in the countries studied. The stated chapter also reviews the literature on technological innovation, the innovation systems framework and why innovation matters in the first place. It highlights that the process of technological advancement is cumulative, with the implication that present technologies of a society influence significantly its future technological trajectory. This observation, together with the knowledge that technological innovation is a key factor in enhancing economic productivity, and ultimately of social prosperity, provides an economic rationale for emerging markets to build on their innovative capabilities. Enhancing domestic access to affordable health technologies only adds to this motivation. However, how countries, especially developing ones, can become innovative in a complex high-tech sector, such as biopharmaceuticals, is not as clear. In recent decades we have learned that innovation is a byproduct of an interactive process involving a variety of actors and institutions, which collectively form an innovation system. At the same time, we also see that our present understanding of technological innovation is largely based on experiences of industrialized nations, with their application to developing-world contexts much less clear.

The sections that follow highlight key contributions of this work to the literature with respect to the extent and nature of biopharmaceutical innovation in the emerging markets, and how the systems of innovation perspective may be best utilized in such contexts.

9.2 Overall Contributions

Each of the chapters/manuscripts in this work contributes to addressing the overall research question related to the role of indigenous enterprises in health technology innovation in China, India, and Brazil and how it is impacted on by the institutional context in which firms reside. For this purpose, I aimed to examine the following key areas:

1. Current innovative capabilities and entrepreneurial innovation strategies in China, India and Brazil
2. Entrepreneurial barriers and incentives for innovation
3. The role of government policy in innovation within domestic enterprises and how the innovation environment can be improved
4. Implications of study findings for addressing global health issues

The following summarize the response to each of the above dimensions.

9.2.1 Innovative Capabilities and Entrepreneurial Innovation Strategies

Innovative capabilities of indigenous enterprises in China, India, and Brazil were assessed in two phases. The first approach involved, a set of country-specific case studies, which focused on approximately 20 enterprises in each country. These included the Brazil case study presented in Chapter 4, as well as those of China and India provided in Appendices C and D, and my subsequent analysis of innovative companies in China and India. These studies focused on, among other factors, capabilities of enterprises across the health product development value-chain and the strategies that firms used to advance their innovation objectives. These studies collectively reveal that the enterprise sectors in the stated countries have responded to the new pharmaceutical patent regimes by building some capacity to develop new health technologies, although to various degrees across different countries. As discussed in Chapter 7, these attempts manifest in building capabilities in new areas as well as upgrading of existing capabilities. The second approach to analyzing innovation within the enterprise sector in each country was to examine the extent and nature of new vaccine and medicinal innovations. This study, presented in Chapter 5, reveals that in all three countries companies are involved in a variety of innovative efforts ranging from traditional herbal medicines to chemistry-based small molecules, and leading edge biotechnologies such as genetic and cell-based therapies – while the degree of focus on each of these areas differs across countries. At the same time, the study identified only 43 firms across the three countries (a relatively small portion of total) that were involved in significant innovative activities related to vaccine or medicinal development. This observation implies that there is scope for much greater involvement in innovation at a sectoral level in all three countries studied.

Overall, this research reveals a striking similarity across the emerging markets with respect to entrepreneurial innovation strategies. These commonalities include how innovation-inspired health entrepreneurs attempt to fund their innovative activities, their preference for collaboration with international firms, their strategies to monetize their IP and their overall orientation towards a global market from the outset. Collectively, the stated strategies seem to constitute adaptation strategies for indigenous firms to their specific contexts.

9.2.2 Entrepreneurial Barriers and Incentives for Innovation

Chapters 4, 6, 7, and Appendices C and D pay considerable attention to entrepreneurial barriers to innovation across China, India and Brazil. In general, challenges facing health entrepreneurs in these countries appear to overlap to a considerable degree, although the underlying reasons are often different across countries. The most common challenges highlighted across the three countries included; innovation financing, access to specially-trained human resources and affordable R&D infrastructure, regulatory issues, IP protection, and importation of required supplies.

The incentives related to innovative activities broadly relate to the potential market size, and related State initiatives. The latter aspect is discussed below.

9.2.3 Globalization, the Nation State, and Innovation Policy

9.2.3.1 Industry Globalization

In the context of biopharmaceutical innovation in the countries studied, if one starts analyzing the innovation system from the firms' perspective, as I have done, one is quickly drawn into the global/international dimension of this endeavor. This happens not only because of the fairly common entrepreneurial assertion that 'biotech innovation is not a national but a global/international phenomenon', but also through observing interactions of firms with external entities and their desire to work with leading firms and address global markets. In the context of the biopharmaceutical innovation, the reality is increasingly not just reflective of national dimensions, but is the sum of a milieu of national, international, and sectoral dynamics, with growing integration of emerging markets into the global system, particularly for India and China. The growing maturity and global nature of the underlying knowledge, the high costs of innovation in biopharmaceuticals, expanding technical capabilities in the emerging markets, and enhanced IP protection in the countries studied are all drivers of this trend. These factors appear to work together in accelerating the fragmentation of the drug development value chain – with a dispersion of activities across different firms and countries. Furthermore, the often stringent and dynamic regulations governing health products means that few, if any, countries can afford to assemble and maintain a state-of-the-art ensemble of expertise required to develop human therapies all on their own. In this respect I agree with Mytelka that:

> "… Without a firm grasp on the changing nature of competition in globalized industries, it is no longer possible to assess the dynamics of local innovation systems or develop appropriate policies to stimulate and support them … In building the system-wide capabilities required to access information and use new knowledge most effectively for innovation … managing the interface between the global and the local will be critical" [1].

I would extend Mytelka's observation to suggest that when it comes to biopharmaceutical innovation it is not only competition among firms that matters, but also increasingly cooperation among them.

9.2.3.2 Role of the State

This work (as discussed most directly in Chapter 6) suggests that national institutions and industry globalization interact to shape the overall entrepreneurial commitment to health technology innovation by the entrepreneurial sector. It argues that: a) economic incentives created by new pharmaceutical patent regimes and TRIPS adoption have not been sufficient to stimulate large-scale private investment into innovative health technologies, b) key institutional barriers – such as patent regime peculiarities in each country, inefficient tech-transfer mechanisms, shortage of innovation financing, and the inherent tension between innovation and affordability – contribute to explaining the relatively modest entrepreneurial involvement in innovation thus far, and c) extra-national factors play an increasingly important role in shaping industry evolution and entrepreneurial innovation strategies in the countries studied, but are largely not reflected in national policy. It is increasingly clear that national aspects and institutions, on their own, do not sufficiently explain the complexities associated with biopharmaceutical innovation in the present day context. Also, that there is an inherent disconnect between the broadly insular national science, technology and innovation policies in the countries studied and the increasingly global nature of biopharmaceutical innovation.

In the context of the countries studied, industry globalization has not, in my view, diminished the role of the state in biopharmaceutical innovation so much as it has changed it. Industry integration at a global level, while posing certain challenges, creates new opportunities for policy intervention at the same time. A key question is how can these opportunities be identified and taken advantage of?

To the extent that government policies have made recent attempts to advance innovation, they generally imitate those elements that are believed to have been effective in advancing innovation in other jurisdictions. These include: fostering a venture capital industry, instituting R&D tax incentives for the enterprise sector, encouraging public-private partnerships, and offering direct financing to companies for innovative projects. These efforts have played a catalytic role in sparking innovative activities by the enterprise sector, albeit on a limited scale thus far. Below, I suggest that the historically broad-based policies aimed at overall economic gains and science and technology development, were insufficient in stimulating development of innovative biopharmaceutical sectors in the emerging markets, and propose that a more sector-specific focus may be more appropriate in such contexts.

9.2.3.3 NSI-type Policies and Consequences

While it is often not made explicit, the general policy approach to advancing innovation in biopharmaceutical sectors seems broadly in line with the national systems of innovation (NSI) framework. However, the use of NSI approach to inform innovation policy, at least in the biopharmaceuticals area, has a number of potentially adverse implications. First, The NSI perspective implies that all elements of an innovation system ought to be present within the nation itself. As alluded to earlier, in the context of biopharmaceutical innovation this may neither be possible nor desirable, especially from the perspective of developing countries. In the context of these countries improving their knowledge base, R&D capabilities, and training of the labor-force often loom large and could rationally be thought of as a pre-requisite for almost everything else. The tendency has been to perpetually prioritize knowledge *creation* over most other ‘downstream’ elements that are more related to knowledge transfer and *utilization*. In practical terms these observations mean that the vast majority of government expenditures in the emerging markets have flown to building and strengthening their scientific and R&D systems within the public sector. In other words, with respect to innovation it appears that government policies have a general tendency to target supply-side issues aiming to improve research outputs, with relatively little attention to the demand-side in terms of what I refer to as *knowledge utilization infrastructure*. This tendency may to some extent be informed by an inherent bias in the innovation systems literature, which deals “…mainly with generation and only to a limited extent with the diffusion of innovations. … In order to understand how successful innovation systems are in generating economic growth, one would have to include the demand side as well, including entrepreneurial activity and business formation” [2]. Over the past few decades, governmental attention to knowledge creation has helped all three countries studied to raise their scientific publication rates significantly. At the same time knowledge utilization infrastructure – such as improved tech-transfer mechanisms, shared and affordable R&D facilities, training of specialized human resources, and more effective regulatory and IP systems – remain largely inadequate. Only China has made considerable strides towards improving some of these elements, particularly with respect to improving entrepreneurial access to affordable R&D infrastructure. Second, the demand to put in place all components of the innovation system, and the inability of most countries – perhaps with the exception of China – to undertake related tasks simultaneously leads to the sequential development of various components of the system over an extended period of time. This means that the innovation system as a whole remains largely dysfunctional, or at the very least inefficient, until all essential components have been put in place and are functioning optimally, with requisite interconnections. This is by nature a very long-term, costly and uncertain endeavor that may neither be affordable, nor appropriate for many countries. Third, the NSI approach leads to an almost exclusive focus on *internal*, as in within country, knowledge generation and utilization, rather than adopting an *open innovation* posture, which allows actors within a country to capitalize on knowledge generated elsewhere, and to market their own knowledge abroad. This ability to tap into knowledge and capabilities abroad is most crucial in the context of globally integrated industries, and more broadly in the context of the knowledge economy. Fourth, the NSI-based approach focuses on a set of interventions that generally apply to all sectors and promotes resource dilution, which may be particularly damaging in the context of resource-constrained economies. The most common policy approaches to encourage R&D and promote innovation involve fiscal incentives. While these are generally believed to be beneficial in terms of encouraging R&D activities, their impact is diluted by the mere fact that they tend to target all/most sectors. The resource dilution effect manifests at the sectoral level as well. For example, individual financial grants that often support public-private partnerships, or are offered to companies directly, tend to be fairly small and distributed among a wide variety of projects in many subject areas. This may mean that even when promising projects receive funds, these may not be sufficient for advancement to a stage where it can galvanize private investment. In the absence of much greater governmental expenditures the resource dilution effect can only be averted by focusing on fewer areas – however politically untenable this option may be.

9.2.3.4 Sectoral Systems of Innovation (SSI) and Innovation Policy

I believe that it is generally more accurate, and indeed more constructive, to view the biopharmaceutical innovation system at a broad level as a *global* or at least a *multinational* system of innovation, with components within nation states. This is not to suggest that a given nation cannot in principle 'internalize' all necessary elements, but that the costs of development and maintenance of such an all-encompassing system would in all likelihood not justify the benefits to be had. Yet, this approach, as if almost by default, seems to be the *modus operandi* in the countries studied. I must say that China's ambitious and sustained government efforts, and the resurgent interest and presence in this market by large multinational pharmaceutical firms, may result in the semblance of such a system in the foreseeable future. However, at current expenditure levels, a productive "indigenous" innovation system for health technologies may yet take some time to develop.

There is broad consensus that the same institutions produce differential effects in different sectors. Nations must learn to deal with complexities of treating different sectors and sub-sectors differently as can be justified based on their inherent characteristics. This is in part because relatively small deficiencies within an innovation system can have disproportionately large effects on firms' ability to innovate. A classic example was the costly and time-consuming processes involved in the importation of biotechnological research materials into China, India and Brazil. Such relatively small, but important sector-specific nuances are often overlooked when innovation policies do not consider sectoral idiosyncrasies.

However, I must also point out an inherent contradiction in the way that the SSI framework is currently utilized. While, in principle this framework is not delimited by national boundaries, in practice it is very common for authors to refer to those parts of a particular sector housed within a nation as that country's sectoral system of innovation. To illustrate by just one example, Marques and Oliveira [3] refer to Brazil's aeronautics industry as an example of a sectoral system of innovation, notwithstanding the facts that it is essentially composed of one major firm, Embraer (Rio de Janeiro), which in 1990s had an import content of approximately 95% with very few Brazilian suppliers. It is clear that policy intervention in such a context would necessarily need to account for the international aspects of this sector. The reason the distinction is important is that in the context of medicinal innovations a similar situation can be seen in some countries, but national policies tend to underestimate the importance of elements external to the country.

In summary, the use of the NSI approach as a tool to inform policy creates a tendency for policies to overlook important sectoral dynamics and globalization effects, and seems to sets up an all-or-nothing situation in terms of the ability of specific nations to reap value from innovation in biopharmaceuticals. In other words, a given country is deemed innovative only if it has the full ensemble of elements and interconnections required to independently discover and commercialize new technologies. Another direct result is an overemphasis on *national* institutions as the predominant factors that determine innovative success. While I appreciate that some institutions play a key role in biopharmaceutical innovation, I do not subscribe to the notion that "significant changes in the traditional institutions and the habits and practices of economic agents in developing countries" [4] are required if they are to become innovative. A look at Korea, Taiwan and Singapore reveals that a focused approach to technological development and tapping into the global innovation and production systems is a viable strategy for nations to transition from technology users to producers.

9.2.4 Implications for Global Health

Chapter 5 shows that, with respect to development of novel technologies, indigenous firms in the countries studied were primarily focused on diseases that have global markets (for instance diabetes or a variety of cancers), and to a lesser extent on new drugs for diseases that disproportionately affect the poor (e.g. cholera, malaria and diarrheal diseases). However, at the same time, I found that the Indian and Chinese firms collectively exhibited a tendency to address the subset of global diseases that are most relevant locally. While this finding is based on limited data at this juncture, and assuming it holds true over time and on a broader scale, it adds another pillar to the rationale in support of indigenous efforts towards technological innovation in the developing world themselves.

The findings of Chapter 5 align well with arguments made in Chapter 8, where the potential role of emerging market firms are explored with respect to addressing global health issues. In the latter chapter we suggest that, from the perspective of developing novel therapies, emerging market firms may not be able to address diseases of poverty on their own, and should be supported in this regard. Collectively, the data and arguments presented in Chapters 5 and 8 of this dissertation, point to a new approach to addressing global health, by tapping into the innovative capabilities of health enterprises in the emerging markets. Presently, most efforts aimed at developing vaccines and therapeutics for neglected diseases are based in countries in the Northern hemisphere. While necessary, these efforts will arguably be insufficient to address existing and emerging needs of poor populations in the developing world in a sustainable fashion.

9.3 Conclusion

The institution of pharmaceutical patenting regimes, together with other supportive policies introduced in recent years, have clearly sparked entrepreneurial efforts in China, India and Brazil towards the development of proprietary health technologies. This occurrence is a significant departure from past practice for these countries, which for decades have relied on imitation of health technologies developed elsewhere. Notwithstanding this general momentum towards innovation, the pace of progress in this regard has arguably been modest relative to the considerable size and growth rates of pharmaceutical markets in the countries studied. This research relates this performance to the prevailing institutional challenges that are themselves rooted in an under-appreciation of important factors that impact on biopharmaceutical innovation. These factors are inclusive of those intrinsic to the technological field(s), those related to industry globalization, as well as their interaction with the national context. In other words success in biopharmaceutical innovation requires simultaneous adjustments in scientific, national and sectoral dimensions of this endeavor. Given the considerable costs and complexities associated with present day biopharmaceutical innovations, developing nations in particular need to be much more strategic on the specific areas they focus on – both in terms of the choice of sector(s) and their involvement within chosen areas – if they are to maximize likelihood of innovative success and economic benefits. To do this effectively, public policies need to reflect important sector-specific dynamics, and as such are best informed by analysis at this level.

9.4 Limitations of this Study

This is a qualitative, multiple-case study and as such subject to the natural limitations inherent in these methodologies. Some of the associated limitations are alluded to within chapters of this thesis. Overall, as the primary data source informing this work has been interview data with industry informants, the conclusions may reflect their views and perceptions more closely. There is a natural and inherent subjectivity in the materials presented, although I have tried to ensure that assertions made are the result of careful synthesis of information from a variety of sources to minimize this. Furthermore, although the study discusses vaccines, drugs and diagnostics, these are not equally covered in all stages of this research. Greater focus on vaccines and medicines is due to the fact that innovations in these areas generally involve greater technological complexities and resource requirements – making them more challenging to develop. Lastly, not all firms that undertake innovations in health products will have been included in this study, and neither are health technologies being developed exclusively within public universities and research institutes. As such results here should not be taken to reflect the sum of all innovation efforts for the countries concerned.

9.5 Future Directions

This work has been an exercise in multidisciplinary research. While it has given me an overall impression of the health technology innovation process in general, it has also raised many questions that remain essential for a fuller understanding of this complex process. Below, I list a few of the key areas that are worth exploring further.

9.5.1 Fragmented Value-chain: Find your Niche

If we accept the idea that the drug development value chain is increasingly fragmented and global in nature, then further analysis to map each country's relative comparative strengths within this value-chain, and the adjustments necessary for participation within this system will be beneficial. Access to extensive biodiversity resources in Brazil, presence of a large and pharmaceutically naïve patient population in India, and traditional Chinese medicines in China are examples of factors often touted as offering advantages that can be leveraged for health technology innovation. The remaining question is how can these countries leverage these and other advantages to position themselves optimally within the global drug development value-chain. Will they be primarily generators of proprietary IP or developers of IP generated elsewhere?

Furthermore, in the context where major drugs and vaccines are increasingly developed in collaboration with foreign firms, domestic or indigenous innovation may lose its meaning. In such a context, it is not clear how individual countries can reap economic benefits from their public investments.

9.5.2 Universities and Research Institutes: what's on offer?

One question worth exploring is whether there is a dearth of commercializable ideas/technologies in domestic universities and research institutes or if there is a failure in technology transfer from these institutions to companies. My sense is that many people, policymakers included, assume that domestic universities and research institutes in the countries concerned possess considerable amounts of knowledge that could be commercialized. This is in part justified based on the growing scientific publication records out of these institutions in recent years. From this perspective, the suggestion/assumption is that there is a breakdown in the tech-transfer mechanisms from universities/research institutes to companies. This failure is, in part, attributed to weak absorptive capacity of indigenous companies for new technologies and knowledge. At the same time, there is anecdotal evidence that the relatively few venture capital firms that are open to investing in new health technologies in the emerging markets experience considerable difficulties in finding desirable technologies to invest in. I have also noticed that in some cases venture capitalists find the university system to be too bureaucratic and cumbersome to work with. The result is that they may prefer not to engage with them in the first place. Having said all this, these are initial impressions based on anecdotal evidence. It would be desirable to conduct empirical analysis focused on technologies that may presently be stagnant within indigenous universities and research institutes. Such findings may help galvanize more private investments and strengthen the rationale for improved technology transfer mechanisms.

9.5.3 Technology Transfer: Beyond borders

If we accept the basic notion that the biopharmaceutical sector, and related innovations in particular, as well as the basic knowledge that they draw from have a considerable global dimension, then we could ask whether it makes sense to limit the notion of technology transfer to the national level. This is not to suggest that attempts in this regard are not made. Indeed, there is a growing trend towards promoting international scientific collaborations with the objectives to facilitate learning, transferring knowledge and technologies across borders, and sharing costs of large-scale projects. However, these are often limited in scope. To adjust to the new realities of globalized high-tech industries and adopt an open innovation mindset would seem to demand that tech-transfer operate on an international level.

9.5.4 Biopharmaceutical Knowledge: Just how tacit?

There is much in the literature that discusses the various features of knowledge, including how tacit it may be. This term refers to whether the necessary knowledge can easily be codified or not. Generally knowledge is not codified if it is difficult to do so, or if it is too expensive relative to potential benefits that may come from codifying it. The notion that some elements of knowledge is tacit, hence not easily transferable, has been used, in part, to explain differential concentration of innovative and industrial activities across various geographic regions. I am not disputing the notion in principle, but – having some previous knowledge and practical experience in the biotechnology field – I have often wondered the extent to which the underlying knowledge in this field can be considered tacit. One of the strengths of the life and physical sciences areas is that scientists are fairly competent and disciplined at codifying their ideas and findings. A central assumption underlying scientific experimentation and publications is that another scientist should be able to replicate the experiment and arrive at similar results, following the instructions as described. I would venture to say that this is generally not very difficult and in most cases the tacit elements, if they exist, are not significant enough to prevent this process. Therefore, I think there is value in establishing to what extent the knowledge underlying biopharmaceutical innovation is indeed tacit. Should we conclude that the tacit component is relatively insignificant in this respect, this would seem to suggest different catch-up strategies, perhaps with lesser emphasis on indigenous basic research and greater attempts at knowledge 'importation'.

9.5.5 Healthcare System; Innovation Friendly?

Another area that is presently underexplored is the potential impact of healthcare systems in China, India and Brazil for innovation in health products. Development of health technologies in the industrialized world relies substantially on the healthcare infrastructure and resources to test and validate technologies. As such, the level of preparedness and openness of the healthcare systems to companies that undertake innovative activities in the emerging markets is likely to be a key determinant of innovative success for many firms. In addition, healthcare systems are also primary users and often distributors of a considerable portion of health products in the emerging markets. As such, they play a key role in mediating between patients and technology developers, and often have a significant role in procurement of related products.

9.5.6 Regulatory Systems: Shall we dance?

A distinguishing feature of biopharmaceutical sector is that most of its activities are highly regulated. The main role of regulators is to ensure that health products meet safety standards and are efficacious for indicated condition(s). The evolving nature of the underlying science and continuous emergence of novel technologies means that regulatory systems must constantly adapt to new realities. This is no easy task. The result is that almost all regulatory systems in the developing world, including in the countries studied, are not fully prepared to deal with new health technologies. This is, in part, related to the fact that they do not have sufficient experience since their domestic industries have not historically been involved in developing new technologies. However, this sets up a situation where regulators can only receive and maintain the necessary expertise if they deal with approval of new technologies. On the other hand, regulatory unpreparedness acts as a major hindrance to development of an innovative industry in the first place, delaying the learning process for regulators.

If I can be so idealistic as to assume that the sole purpose of national regulatory systems are to ensure safe and efficacious products (unfortunately politics has much to do with it too), then surely a more harmonized international system (or ideally unified regulatory systems) would seem a much more effective approach. Harmonization is already taking place in the industrialized world primarily through the International Conference for Harmonization (ICH) guidelines, with Europe, the US, Japan, Canada and Australia as observers of these guidelines. However, there is minimal harmonization and standardization of regulations elsewhere, contributing to increased development costs for health products. It would be worthwhile to explore whether and how a more harmonized system – at least across the emerging markets themselves – might impact on domestic innovation in these markets.

9.5.7 Foreign Firms; Friends or Foes?

For emerging markets venturing into the innovation landscape, it is critically important to understand the role of pharmaceutical multinationals in shaping innovative activities of indigenous enterprises. Large pharmaceutical multinational corporations (MNCs) are growing their presence in the emerging markets, particularly India and China. In a radical departure from past practice, MNCs are also starting to conduct significant levels of R&D activities in the countries mentioned, and are securing services of domestic firms to this end. Over the past 5-8 years, this trend has led to the emergence of a fast-growing R&D services industry in China and India, which may also be of benefit to domestic industry for similar purposes in the near future. My studies also reveal a growing trend towards collaborative drug development between indigenous and foreign enterprises in these countries. At the same time competitive dynamics sometimes translates to tense relationships between foreign firms, as a group, and domestic enterprises. At this point, it is not clear what the net impact of MNCs might be for innovation within indigenous health enterprises in the emerging markets.

9.6 References

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