13
Health-Care Innovation in Emerging Markets

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Major emerging markets such as India, China, and Brazil, in addition to presenting rising middle-class populations, are now playing a part in driving the transformation of the health-care sector, from R&D and clinical trials to local manufacturing.

However, significant challenges remain, from intellectual property (IP) issues to manufacturing quality and drug pricing and reimbursement. The health-care sector follows the general structure of three clusters of emerging markets:

- The BRICMT group, comprising Brazil, Russia, India, China, Mexico, and Turkey, have shown strong growth, and some are reaching market sizes comparable to those of mature Western countries.
- The "second-tier" markets include a group of Eastern Europe economies, as well as some countries in Southeast Asia and Latin America.
- The third group includes African markets with high populations but smaller market sizes. Although the region has high potential, only a few of its countries, such as South Africa, Egypt, Algeria, and Nigeria, have a pharmaceutical market volume exceeding $1 billion (Booz & Company, 2011).

As a consequence of economic growth and shifting demographics, epidemiology patterns in the higher-income emerging markets are evolving from communicable to chronic illnesses such as diabetes, and cardiovascular and oncological diseases.

However, economic growth is not, by itself, a predictor of innovation success or of the market potential for high-cost innovation products.

Innovation depends on a complex set of factors including government financing for health-care services, the rise of private insurance to supplement often inadequate public funds, patient access to services, and good regulatory systems for manufacturing. In addition, the positive role of the

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private sector, and especially of foreign investment and technology transfer, is directly linked to IP protection (see Figure 13.1).

Since 2005, when all WHO (World Health Organization) member states committed to universal health coverage, progress has been made towards the United Nations Millennium Development Goals (MDGs), but the gap remains large between these and market realities. For instance, nearly half of all HIV-infected patients requiring antiretroviral therapy still were not receiving it by 2011, and an estimated 150 million people suffer great financial harm because they must pay out-of-pocket for health services (WHO, 2013).

In India, with a population of over 1.2 billion, the addressable segment for an oncology therapy with a $10,000 yearly cost would only be 23 million people. By contrast, for an anemia treatment cost of $270 a year, as many as 290 million people could have access and affordability (Booz & Company, 2011).

In response, some markets are moving towards value-driven drug evaluation and pricing. Brazil has created CONITEC (National Commission for Incorporation of Technologies in the Unified Healthcare System),

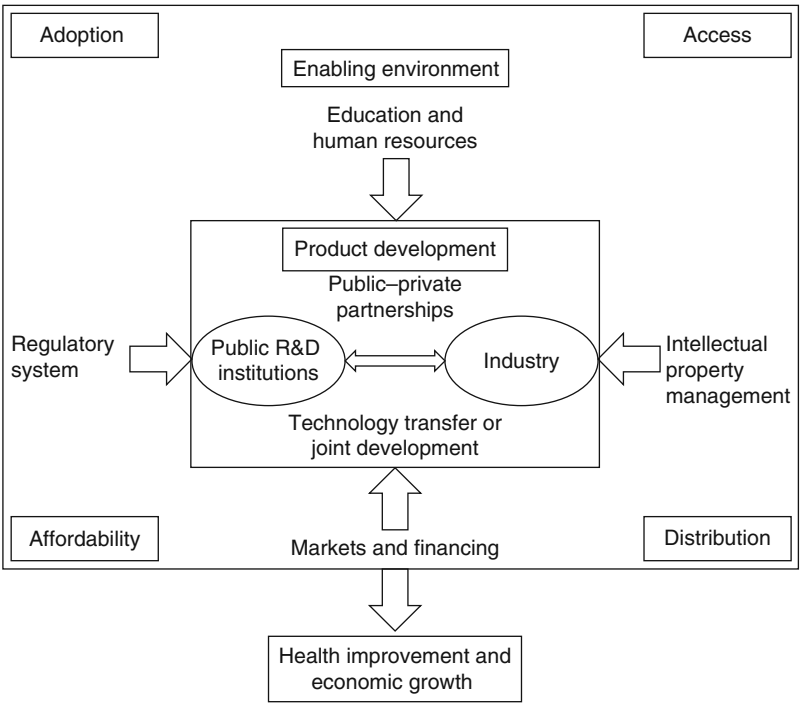

Figure 13.1 Health delivery systems and services
Source: Adapted from Morel et al. (2005).

an economic evaluation agency, and China is collaborating with the British National Institute of Health and Clinical Excellence (NICE) (Booz & Company, 2011). These policies, as well as inadequate IP protection, may have a negative impact on innovation. Since 2009, China has had a National Drug Reimbursement List (CNDRL) and also capped retail prices for its Essential Drug List. This had two unintended consequences: drug shortages, as manufacturers stopped production of some low-profit products, and quality issues in a context of drastic cost reduction. In response, China announced in April 2014 the easing of price caps on 520 low-cost essential drugs (IMS Institute for Healthcare Informatics, 2014).

A key barrier to private-sector-driven innovation remains the inadequacy of IP protection. After the Patent Act of 1970, IP applied only to process manufacturing, not products, which helped make India the world leader in the manufacturing of generic drugs, but blocked market entry for foreign firms. After India joined the World Trade Organization (WTO) in 2005, IP was introduced for pharmaceutical products, but this has been offset in part by some cases of compulsory licensing such as the granting to local firm Natco the rights to manufacture and market Bayer's oncology drug Nexavar (sorafenib) in 2012 (Booz & Company, 2011).

Despite these challenges, emerging markets are expected to represent a growing share of medicines, including biologic products, produced by Western as well as local firms such as Biocon in India. Global spending in medicines is projected to reach over $1 trillion by 2017, and biologic agents will continue to outpace overall growth and reach up to 20 percent of total market value by 2017.

Although China's growth was revised down, following a decrease in GDP prospects, its pharmaceutical market is expected to grow between 14 and 17 percent in the 2013–18 period. Volume-based growth will be driven by government efforts to expand the Essential Drug List, as well as to improve access to services, insurance coverage, and use of private hospitals (IMS Institute for Healthcare Informatics, 2013).

In Brazil, the government has supported health research with its Biotechnology Development Policy and a ten-year, $4 billion development program. An upper-middle-income country, Brazil has a population of about 200 million people, most of whom live in poverty despite a GDP per capita that reached over $11,000 at purchasing power parity (PPP) by 2011. Over 70 percent of the disease burden for the poor is contributed by chronic noncommunicable illnesses such as diabetes, cancer, respiratory and cardiovascular conditions, thereby showing similarity with the disease profile of mature markets. Brazil has a strong R&D capacity, but the private sector contributes only about 20 percent of the total investment. A notable strength is its well-developed vaccine industry, with one of the best national immunization programs among developing countries. The country has over 180 biotech firms, and it received a $2.5 million grant in 2007 to set up

manufacturing capacity for the influenza vaccine (Abuduxike and Aljunid, 2012). Given the diversity of research and market conditions across emerging markets, this chapter will cover in more depth India, China, and Brazil, to show their different approaches to health-care innovation.

India

India now accounts for over 17 percent of the world's population, and is projected to become the most populous country by 2050, with 1.6 billion people. It shows rapid urbanization, with over 30 percent of the population in massive metropolises of more than 10 million such as Delhi, Mumbai, and Kolkata. It is very diverse, with at least six major religions, several officially recognized languages, and 28 states with large differences in income. Despite GDP growth averaging 6.6 percent in 1990–2010, the country has not increased public spending on health care correspondingly, and the literacy rate is only 74 percent.

In addition to chronic diseases such as diabetes and cardiovascular illnesses, India has seen the growth of communicable diseases such as HIV/AIDS. Tuberculosis in India is the number one cause of death, with a rate double that of China, accounting for over one-quarter of all cases worldwide (with a total of 8.8 million). Despite rising per capita income, reaching nearly $3,700 by 2011 at PPP, India is divided between a large share of its population (69 percent) in rural areas with inadequate access to health services, and a growing middle class of about 250 million that can afford Western allopathic medicine (Burns, 2014).

When it comes to balancing the outcomes of patient access, high quality care, and cost efficiency, India therefore faces challenges on all fronts. It rates low on indicators such as infant mortality or life expectancy at birth, it has inadequate regulation of providers and medical product quality, and nearly 70 percent of all health-care costs are borne out of pocket by the population (see Figure 13.2).

National policies

Since 2000, India has increased the government's role in funding health care, engaged in initiatives to develop the biotechnology industry, and supported the rise of private-sector health insurance. Biotechnology was defined by the 1992 Convention on Biological Diversity as any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use (MOITI, 2008).

Following the creation in 1986 of the Department of Biotechnology (DBT), India approved in 2007 an extensive National Biotechnology Development Strategy (NBDS), with several recommendations, including a Small Business Innovation Research Initiative to fund early-stage research, public/private partnership support, a national task force to set up model academic

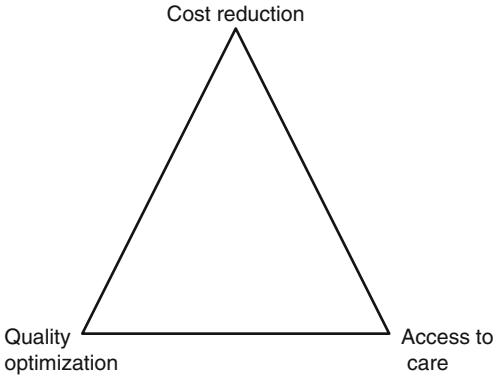

Figure 13.2 The triple aim of health care
Source: Adapted from Lawton (2014).

curricula, the reengineering of university departments to promote interdisciplinary research, and the creation of biotechnology parks. In addition to the well-established technology clusters in Bangalore and Hyderabad, the DBT has set up other clusters near Delhi and in Punjab. It has encouraged international collaborations such as the Stanford–India Biodesign Program, and a substantial allocation from the UK's Wellcome Trust to fund biomedical research over five years (Frew, 2014).

The Indian government is also seeking to extend insurance coverage. Under private and public insurance, only about 25 percent of the population is covered. The newer central and state government schemes aim to increase protection of the poor against catastrophic health events, focusing on surgical procedures and secondary care. The government aims to cover 300 million people in the near future. Further recommendations include the introduction of quality-based purchasing, better utilization management, and expanded autonomy for public hospitals (La Forgia and Nagpal, 2012).

A key step toward private-sector innovation was the entry in 2005 of India into the WTO, whereby it had to comply with the agreement of Trade-Related Aspects of Intellectual Property Rights (TRIPS). Their main elements were:

- Enforcement of product patent protection in all branches of technology, including drugs.
- 20 years of protection, instead of 14 or 7 in the case of the Indian Patent Act.
- No discrimination between imported and domestic products.

However, the promotion of private-sector innovation remains challenging, since India has imposed compulsory licensing in recent cases.

Indian biotechnology industry

Indian biotech holds about a 2 percent share of the global industry, and is expected to grow to about $74 billion by 2020. It comprises about 400 companies and includes leading vaccine manufacturers. India is the largest producer of recombinant hepatitis B vaccine, and is gaining importance as a clinical trial destination (IBEF, 2014).

Along the health-care value chain including payers/insurers, providers, distributors, and suppliers, India has substantial strengths in product development, low manufacturing costs (50–55 percent lower than in the West), and provider quality, shown by some internationally recognized organizations such as the Apollo Hospitals. It still has weaknesses in health infrastructure and insurance coverage.

Diagnostics is a competitive subsegment with double-digit growth, reaching nearly $500 million in revenue by 2010, split between multinationals such as Roche, Abbott, and Siemens, and domestic companies.

The therapeutics sector is led by Biocon, followed by the Serum Institute, Panacea, and Shanta Biotech. The Serum Institute was the first Indian company to be approached by the WHO in 2008 to develop and manufacture the H1N1 flu vaccine (Frew, 2014).

Although firms such as Biocon have a strong portfolio of biologics, R&D as a whole remains limited in India, and product development is dominated by generics. The top five Indian companies still account for only 1 percent of R&D spend by the top five global multinationals, and over 75 percent of innovations carried out in India are incremental (Tyagi et al., 2014).

Indian company strategies

Leading Indian domestic firms are practicing networked innovation, with a combination of organic growth, geographic expansion, and partnerships with multinationals.

Biocon's strategy

Aspiring to US$1 billion in revenues by 2018, and reaching nearly US$500 million in 2014, Biocon has a broad portfolio including small molecules, biosimilars, and contract research services. Founded in 1978 by Kiran Mazumdar-Shaw, it divested in 2007 its historic enzymes business to Novozymes and began to develop lovastatin, a cholesterol-lowering drug whose patent expired in 2001. Following its launch of recombinant insulin Insugen, it moved to biologics in 2006, with the first humanized monoclonal antibody for head-and-neck cancer developed in India.

Between 2005 and 2010, Biocon entered into numerous R&D licenses and other partnerships. In 2014, it launched CANMAB for a type of HER2-positive breast cancer, positioned as "the world's most affordable breast cancer drug."

Biocon's collaboration with Mylan, started in 2009, includes generic insulin analogs and biosimilar monoclonal antibodies. Both companies

share development and capital costs, and have a profit-sharing arrangement in regions where Mylan has exclusive commercialization rights (the US, Canada, Europe, Australia, and New Zealand for insulin, targeting a global market size of $16 billion, and yielding a $20 million upfront fee for Biocon). Other partnerships have included a 2004 alliance with a US antibody technology partner, Vaccinex, and a 2007 agreement with Abraxis Bioscience to outlicense a biosimilar GCSF (granulocyte colony stimulating factor) to North American and European markets.

Biocon's R&D approach focuses on the entire development pathway, from process development to clinical research. Its patent portfolio totals over 900 applications worldwide with over 180 granted patents, covering fermentation, protein purification, drug delivery systems, and biologics. Importantly in the Indian context, the company's manufacturing meets cGMP standards (good manufacturing practices), and Biocon was the first Indian biotech to receive ISO 9001 certification. Beyond its Bangalore site, Biocon has planned a $200 million investment in a Malaysia site. Biocon also leverages its manufacturing with research services; it is India's largest CRO (contract research organization) with over 2,000 scientists, a capital investment of about $130 million, and agreements with 16 of the top 20 pharmaceutical companies worldwide. Its key customers include:

- Bristol-Myers Squibb – largest R&D Big Pharma center in Asia, started in 2009, extended to 2020, for novel molecule research.
- Baxter partnership in 2014 with Biocon subsidiary, Syngene, centered in part on preclinical evaluation in parenteral nutrition and renal therapy.
- Abbott Nutrition's R&D center in India allied with Syngene in 2012 to develop a nutrition products line with emerging market needs.

Biocon's stepwise strategy, moving from small molecule generics to biologics through organic growth, manufacturing optimization, and R&D partnerships, has been rewarded by the marketplace: on the first day of listing for its 2004 IPO (initial public offering), Biocon was only the second Indian company to cross the $1 billion mark, and it continues to lead the Indian industry (Biocon, 2015).

Other Indian biotechs

Besides Biocon, other domestic biotechs have had varying strategies, most often with a focus on vaccines. The Serum Institute was the first Indian firm to be approached by the WHO to manufacture the H1N1 flu vaccine.

Shanta Biotechnics was founded in 1993, and also focused on vaccine manufacturing. It developed international partnerships including, in South Korea, the International Vaccine Institute, and managed an exit strategy, with its 2009 purchase by Sanofi Pasteur at an estimated valuation of €550 million (Frew, 2014).

Panacea Biotec was set up in 1984 and developed collaborations including one with the Netherlands Vaccine Institute. It had an IPO in 1995 and gained its first product patent two years later. However, it encountered quality issues in its manufacturing in 2011, but these were later resolved.

Besides leaders like Biocon, many Big Pharma firms have engaged in partnerships with Indian companies, but these have met with varying success, at least in part because of IP challenges. Representative cases include Gilead's collaboration with Indian generic firms in HIV/AIDS, and Bayer's contrasting experience in oncology.

Gilead partnerships in India

Founded in 1987, Gilead had become the global market leader in HIV treatment, with its first antiretroviral product Viread (tenofovir) or TDF in 2001, followed by Emtriva (emtricitabine) and combination therapies Truvada, Atripla, and Complera by 2011.

Global estimates of HIV patients were more than 34 million that year. By 2000–1, two Indian generic firms launched antiretrovirals (ARVs) at respective prices of $800 and $295 per patient per year, vs an average US cost of $10,000–$15,000, which limited its access to only 2 percent of patients in developing countries. Gilead filed the Viread patent application in India in 1997, but by 2006, while it was still under review by the Indian Patent Office, it faced pre-grant oppositions from generic manufacturers including Cipla and some NGOs.

To increase access to its ARVs, Gilead adopted a new strategy in 2006, by then extending voluntary, nonexclusive licenses to Indian companies to manufacture generic TDF-based ARVs for developing countries. It subsequently partnered with 14 Indian firms, including Mylan, Hetero, Ranbaxy, and Strides Arcolab. The deals allowed them to manufacture ARVs in India and sell them there and to 94 other countries, as well as to codevelop drug combinations. By 2011, 1.8 million patients were receiving Gilead HIV drugs in the developing world, and the price for generic Viread had fallen to 19 cents per day. Given this success, Gilead expanded its agreements with its four partners, and extended them to the Medicines Patent Pool (MPP), and Natco that could itself sublicense to any qualifying Indian firm. Royalties to Gilead were reduced from 5 to 3 percent and generic TDF was also allowed to be sold for chronic hepatitis B. Most importantly, the partners were granted nonexclusive rights to three of Gilead's pipeline HIV medicines.

By contrast, the official policy was negative. In 2009, the Indian Patent Office rejected TDF patents on the grounds that they lacked an inventive step. Gilead then appealed the decision. In the US, the NGO PubPat filed a request for a reexamination of the Viread patents, claiming that the TDF compound was "obvious." Following its review, the US Patent and Trademark Office (USPTO) concluded that the patents were not obvious and reaffirmed their validity (Sachan et al., 2013).

By leveraging innovation in advanced manufacturing by Indian firms, Gilead had created long-term partnerships that balanced incentives for local innovations and global access at low cost.

Bayer and the Nexavar experience in India

Founded in 1863, Bayer has had a long history in India, where it was first set up in 1896. Bayer India was targeting $1.3 million in sales by 2015, from medical care, animal health, and pharmaceuticals, comprising women's health and cardiovascular drugs, as well as specialty medicines.

The USPTO granted a first patent for kidney cancer to Bayer's Nexavar (sorafenib) in 2007, and it was a blockbuster by 2012, with $1.04 billion in global sales. Competitors included Pfizer's Sutent, Novartis's Afinitor, and GSK's Votrient. Although not a cure, Nexavar could prolong a kidney patient's life by four to five years, and could be taken orally. Bayer applied for an Indian patent in 2001, but Nexavar was sold at $5,500 for a month's supply, at a price equivalent to that in the US.

The Indian generic firm Natco had filed for a voluntary license for Nexavar, but was turned down by Bayer. In 2011, Natco then applied for a compulsory license (CL), proposing to sell generic sorafenib at a discount of over 97 percent ($160 per month).

In March 2012, the Indian Controller General granted the first ever CL in India to Natco, committing it to a 7 percent royalty to Bayer. The ruling was based on low availability (mostly in top metropolitan hospital pharmacies), high price, and a lack of "working" of the patent in India. Bayer then filed a petition to block Natco's generic; it had also launched an access program in cooperation with Indian providers, selling Nexavar at 10 percent of the market price. By 2012, Bayer estimated that 73 percent of eligible patients were covered by this program. Nevertheless, the WHO had reacted positively to the ruling, and its potential expansion to other Western drugs in that category remained a threat for foreign manufacturers.

These contrasting strategies by Gilead and Nexavar illustrate the remaining barrier to innovation and technology transfer posed by compulsory licensing, despite the entry of India into the WTO in 2005. Some of these opportunities and challenges also apply to Brazil, within a very different market situation.

Brazil

Brazil's economy is the second largest in the Western Hemisphere and the eighth largest in the world, with a largely urbanized population of about 200 million, a 2013 GDP of $2.3 trillion at PPP, and a growth rate of over 5 percent in the 2000–12 period. This growth, however, slowed in 2013 and was expected to drop further by 2015 (Lima, 2015).

While there have been improvements in living standards, life expectancy at birth was only 73.5 years in 2010, and the under-five child mortality rate was still 16 deaths per 1,000 live births (World Bank, 2013). A major problem remains the disparity in income and access to health services between southern states and the poorer northeast region.

Health system evolution

A major policy event was the creation of the Sistema Unico de Saude (SUS) or Unified Health System in 1996, which sought to embody the principle of a universal right to health established in the Federal Constitution of 1988. The SUS seeks to shift responsibility for its administration to municipal entities, with technical and financial cooperation from the federal government and the states.

The SUS unified disparate subsystems (Social Security, the Ministry of Health, states, and municipalities) and invested heavily in primary care with its flagship program, the Family Health Strategy (FHS). The current system has a decentralized structure, with a tripartite administration by the federal, state, and municipal Ministry of Health secretariats, and with financing at all three levels (see Figure 13.3).

While the Agencia Nacional de Saude Suplementar (ANS) supervises health insurance plans, health providers and pharmaceutical products are the responsibility of the Agencia Nacional de Vigilencia Sanitaria

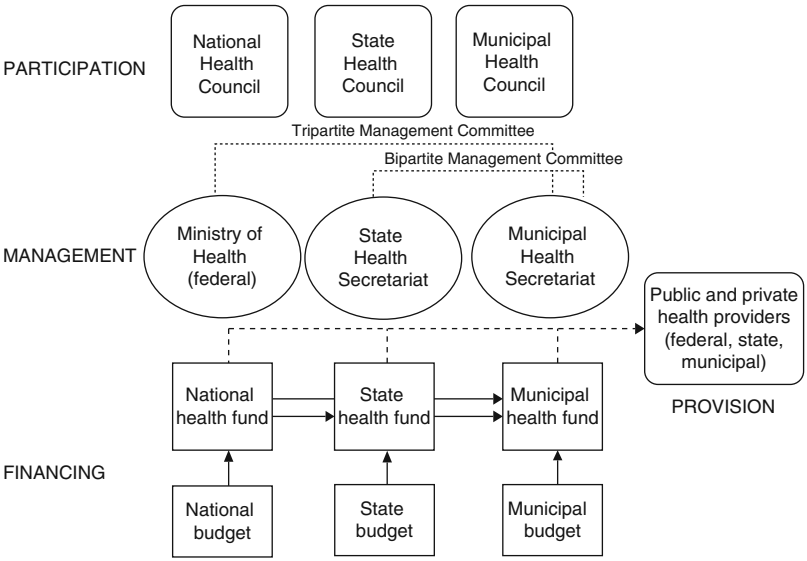

Figure 13.3 The decentralized national health system in Brazil
Source: Adapted from Mori Sarti et al. (2012).

(ANVISA), functioning as the equivalent of the US' FDA (Food and Drug Administration).

Under the SUS, many health indicators such as the under-five child mortality rate improved (from 58 to 16 deaths per 1,000 live births, from 1990 to 2009), but inefficiencies remain in the hospital and insurance sectors. Nearly 70 percent of the population uses the SUS, but private insurance grew by almost 50 percent in 2000–10, to reach nearly 46 million. Of the 9 percent of GDP spent on health in 2011, 47 percent came from the government, but 53 percent was privately funded. The current health system is mixed:

- Publicly funded and provided care (65 percent of medical consultations)
- Publicly funded but privately provided care (10 percent of consultations)
- Privately financed and funded care (25 percent of consultations)

General hospital care is largely supplied by the private sector, under contract with the SUS. Specialist care is concentrated in larger urban centers, and tertiary care is provided mainly by the SUS. The ministries of Health and Education retain about 100 large referral and teaching hospitals (World Bank, 2013).

There are wide differences in the outcomes of this system across therapeutic areas. While the SUS-administered HIV/AIDS program has been very successful, specialist care shows access problems.

A Federal Audit Tribunal found that, due to low access to specialist care and diagnostics, 60 percent of cancer patients were diagnosed at a late stage (3 or 4). There are general delays in accessing treatment, with median wait times in 2010 from 76 to 113 days, depending on the type of treatment. Paradoxically, Brazil purchases advanced medical equipment, but a substantial proportion is allocated to municipalities that do not have the size to utilize it appropriately. The country has over 6,700 hospitals, but over 65 percent have fewer than 50 beds and operate at a very low level of efficiency (45 percent mean bed occupancy rate) (Gragnolati et al., 2012).

This is being alleviated by a consolidation trend: in 2009, Brazilian insurer Amil acquired Medical Health, with a combined coverage of over 6 million members, and it also started to buy hospitals, with a network of 40 throughout Brazil. In 2012, United Health moved to buy Amil for about $4 billion, with further foreign investment in hospitals pending regulatory approval.

National policies – intellectual property

The National Industrial Property Institute (INPI) regulates patent applications. Although Brazil signed the WTO/TRIPS agreement, major obstacles remain:

- Long approval period (backlog of about nine years by the Biotechnology Patent Division)

- Restrictive patentability criteria, with a long list of nonpatentable items including nucleotide and peptide sequences derived from living organisms
- Restricted access to biodiversity, requiring approval to access the genetic heritage (Resende, 2012)

A notable case of Brazil's policy is its contentious compulsory licensing in 2007 of the Merck AIDS drug, efavirenz, to secure supply at a lower cost. The 1997 Brazilian Patent Law requires that foreign products be made in Brazil within three years of receiving a patent. If the foreign company does not comply, Brazil can issue a compulsory license to a local firm. This was done as early as 2001, when the Ministry of Health authorized FarManguinhos to produce nelfinavir, a Pfizer drug licensed to Roche in Brazil. Negotiations ensued, resulting in a 40–65 percent reduction by Roche and Merck for the price of five drugs.

This supported a very effective AIDS program, but alienated foreign firms, several of which threatened to withdraw from Brazil. Several program milestones have occurred from 1986 to the present time:

- 1986: National Program on HIV/AIDS is established (1,537 cases)
- 1991: Ministry of Health (MOH) starts distributing free antiretroviral drugs (18,487 cases)
- MOH launches a large education campaign and begins to reimburse treatment under the SUS (25,186 cases)
- 1996–98: Free drug distribution is established by law in 1996, and mandated for private insurers by 1998 (91,916 cases)
- 2001: Brazil threatens to break patents and negotiates price reductions (139,473 cases)
- 2007–8: Survival rates improve significantly (474,273 total cases since 1980). Brazil invests $10 million in a Mozambique factory for antiretroviral drugs.

Thanks to behavior changes resulting from information campaigns, as well as accessible treatment, mortality peaked in 1994 (12.2 deaths per 100,000 population), then dropped by half by 1998 (Gragnolati et al., 2012).

Brazil's biopharmaceutical industry

Although the Brazilian market is significant, with approximately $40 billion in sales, and a growth of 10.5 percent annually since the mid-2000s, its innovation output is small (only 0.45 percent of the international database of biotech patents). Moreover, only 7 percent of these originate from Brazilian companies, whereas 73 percent come from universities and research centers, 13 percent from foreign firms, and 7 percent from foreign universities.

In addition to patent threats for foreign firms, this may be related to the historical dominance in Brazil of large generic firms such as Ache, Hypermarcas, Eurofarma, or EMS. The biotech sector is more recent, with initial R&D in biofuel, agribusiness, and environmental domains as well as health care. Out of 143 biotechs, 33 percent focus on human health. Most are highly dependent on foreign imports, especially reagents and laboratory equipment; 75 percent are clustered in São Paulo, Minas Gerais, and Rio de Janeiro, with others in the southern states of Rio Grande do Sul and Parana.

Business models are varied, with 66 percent relying on sales of internally developed products, and others adding services, sales of third-party products, and outlicensing of technologies (Resende, 2012). The market is dominated by foreign firms and large local generics companies.

Biotech financing

Capital in Brazil is generated by corporate partnerships, venture capital, and private equity, as well as public funds. Public funding includes CRIATEC, a seed capital fund, the BNDES (National Social and Economic Development Bank), and FINEP, an agency linked to the Ministry of Science, Technology, and Innovation. There has also been significant funding from private nonprofits such as the Gates Foundation (Resende, 2012).

Company strategies: alliances and acquisitions

Acquisitions by foreign firms have been increasing. Sanofi was one of the pioneers in Brazil, first establishing a presence in 1955. Sanofi maintains four manufacturing sites, with a staff of over 5,000. In 2009, it bought Medley, Brazil's third-ranked firm, raising its sales to $1.8 billion. Other acquisitions include Pfizer's purchase that same year of a substantial stake in a generic firm, Laboratorio Teuto Brasileiro. Public–private partnerships are also increasing, and a notable case is the GSK/Fiocruz alliance.

GlaxoSmithKline/Fiocruz partnership

GSK announced in 2009 a major collaboration with Fiocruz, leveraging Brazil's know-how in vaccine manufacturing, and the rising importance of vaccines in the GSK portfolio, accounting for 15 percent of sales. Vaccines complemented therapeutics well, allowing the company to demonstrate value to payers through local manufacturing. In Brazil, SUS purchased 90 percent of vaccines, 50 percent of medical equipment, and 25 percent of pharmaceuticals. GSK's competitors included Novartis and Johnson & Johnson, who also had expansion objectives in emerging markets.

The Fundaçao Oswaldo Cruz (Fiocruz) was set up in 1900 with a mandate to improve public health, and currently operated a large site in Rio de Janeiro and four other scientific hubs. It employed 4,500 people, with an annual budget of $800 million.

Initially supplying active ingredients to Fiocruz's biologics division, Bio-Manguinhos, GSK started in 1985 to share production technology for a polio vaccine. In 1998, a five-year deal allowed for GSK to transfer Hib (haemophilus influenza type B) vaccine technology. Brazil's government purchased the vaccine from GSK at a negotiated price during that time, and by 2009, the country reached comprehensive immunization.

In 2009, GSK and Fiocruz announced a major new public–private partnership for a vaccine against pneumococcal infections, and the joint development of a dengue fever vaccine. GSK agreed to transfer technology for its Synflorix vaccine, including a complex manufacturing sequence of eight processes and over 200 quality control tests. GSK was to sell the vaccine to the Health Ministry over a ten-year period, at an initial price of €11.50 per dose, expected to drop to €5 in later years (vs a European price of €35–40 per dose). It was expected that GSK could sell over $1.5 billion of Synflorix vaccines, as Brazil aimed to vaccinate all newborns.

A second component of the GSK/Fiocruz deal was joint R&D for a vaccine for dengue fever, which infected between 50 and 100 million annually worldwide. GSK and the Brazilian government each pledged $51 million to research and test the vaccine (Daemmrich, 2012).

Domestic Brazilian firms

The industry is polarized between large, diversified generic firms and small biotech innovators with links to universities. Generic manufacturers include EMS, founded in the mid-1950s and reaching revenues of $2.8 billion by 2012, with five divisions: similar, generics, branded drugs, hospital drugs, and over-the-counter (OTC) products.

EMS's competitors include Hypermarcas (consumer goods conglomerate founded in 2001, with 2013 revenues of $1.8 billion, and OTC products including antiseptics like chlorhexidine). Another generic firm with nearly 50 years of history in Brazil, Ache has licensing agreements in 11 countries for its portfolio in areas including hypertension, atherosclerosis, depression, and inflammation. A partnership with Hypermarcas, EMS, and Uniao Quimica aimed to create a biotech joint venture, Bionovis.

In biotechnology itself, many companies have state and university links. Instituto Butantan is affiliated with the São Paulo State Secretary of Health. It was founded in 1901 according to the Pasteur Institute model, focusing research on venomous animals to develop vaccines such as rabies, hepatitis, diphtheria, and tetanus. It has since advanced to molecular biology and immunology, produces monoclonal antibodies, and operates the Hospital Vital Brazil, specializing in the treatment of poisonous animal stings.

International academic links are shown by other biotechs such as FK Biotecnologia, founded in 1999 and focusing on oncology with links with Dana Farber, and the Axis Biotec Group, set up in Rio de Janeiro's Biotechnology Development Park. Through its companies Cellpraxis and

Pharmapraxis, the group focuses on regenerative medicine and cell therapy, and has links with the Federal University of São Paulo (UNIFESP) and the University of South Florida. By contrast with Brazil, a very different innovation model is developing in China.

China

Although technology was a key part of the "four modernizations" program launched in 1978, the real impetus came in China after 2000. The 2006 National Medium and Long-Term Plan for Science and Technology Development aimed by 2010 to derive 60 percent or more of economic growth from technological progress. Between 2000 and 2010, China's R&D expenditure doubled as a share of GDP, to 1.75 percent, and China's world share of researchers was equal to that of the US (20 percent, with 1.4 million scientists).

Following China's entry into the WTO, its applications for international patents more than tripled in 2006–11, representing 9 percent of the world total. Of these, 21 percent were for chemicals and biopharmaceuticals. The 2006 National Plan aimed to increase R&D intensity to 2.5 percent of GDP by 2020, but also to promote "indigenous innovation," decreasing reliance on foreign technology by 30 percent or below existing levels. In the 12th Five Year Plan (2011–15), the emphasis was put on the life sciences, especially drug discovery and infectious diseases.

A key element of China's innovation system is the rising role of enterprises. Government research institutes account for less than 20 percent of R&D spend. Given that producing in China is a key way for foreign firms to access the market, multinationals have set up numerous R&D and production centers (over 350 R&D centers in Shanghai alone by 2010) (Fabre, 2014).

Health system in China

To provide health services to its population of 1.3 billion, China has over 900,000 medical facilities, most of them state-run. Although much progress has been made with basic coverage for 95 percent of the population, problems remain, such as a fragmented infrastructure, underfunding of preventive services, and wide regional variations in access to health care.

Public hospitals have a three-tier structure: tier 1 is made up of small community centers, tier 2 covers regional facilities, and tier 3 includes large provincial hospitals with 500 or more beds. Given the low incidence of private health insurance, part of medical expenses is paid out-of-pocket; this amounted to 36 percent of expenditure in 2010 (Herzlinger and Kindred, 2014). Due to the low reimbursement rate for hospitals, these expect a share of income from drug price mark-ups, since hospital pharmacies dispense a large proportion of drugs. Medicines from foreign and domestic suppliers

are distributed by a fragmented network of wholesalers, and sold mostly by hospitals, with a smaller share sold in retail pharmacies (Yu et al., 2010).

National policy – intellectual property

The governance of the biotech industry includes the National Development and Reform Commission (NDRC), the State Food and Drug Administration, and the ministries of Health and Commerce. NDRC is in charge of strategic planning and regulates drug prices, the Ministry of Commerce regulates the export and import of medical devices and equipment, and the Ministry of Health (MOH) guides reform and monitors clinical trials (Wang et al., 2009).

The Patent Office of the State Intellectual Property Office (SIPO) is responsible for the processing of patent applications. In 2000, China's Patent Law was amended in order to comply with the TRIPS agreement of the WTO. However, there were significant enforcement issues, illustrated by the notable case of Pfizer's Viagra patent (Li et al., 2010).

After Pfizer's launch of Viagra (sildenafil) for erectile dysfunction (ED), it had a rapid global uptake, reaching over $1 billion in sales by 1999. In China, about 74 percent of men aged 60–69 suffered from ED, and by 2004, the market was estimated at $7–12 billion. In July 2000, Pfizer was approved to sell Viagra in China, and it was granted a patent by SIPO in 2001. Before approval, illegally imported Viagra pills and local counterfeits flooded the market.

As early as 1998, Guangzhou Viamen, a local firm, had registered its own drug under a trademark ("Weige") similar to the Viagra name, and it started selling it in 2003. In addition, within a month after Pfizer's patent approval, 12 local firms challenged its validity, arguing that it failed to fulfill a "novelty" requirement of China's Patent Law. Pfizer then filed a court case against SIPO. In 2006, SIPO's ruling was overturned and the patent upheld. However, despite a final appeal regarding the trademark, Pfizer lost that litigation in 2009. The company had invested $500 million in China for four production sites and an R&D center. Independently of the patent issue, due to the dominance of counterfeits and local generics, China only accounted for less than 0.5 percent of Viagra's global sales of $1.3 billion in 2000. The launch of branded competitors in 2003 (Bayer's Levitra and Lilly's Cialis) further eroded Viagra's share, before its China patent was due to expire in 2014.

This episode left a lasting impression on foreign companies, and the Office of the US Trade Representative released in 2005 a Special 301 report, including China on the Priority Watch List due to "serious concerns about [its] compliance with its WTO TRIPS obligations" (Li et al., 2010).

China's biopharmaceutical industry

China includes over 5,000 manufacturers, virtually all of which produce generics. Despite the government's efforts to consolidate it, partly by requiring compliance with GMP standards, the industry remains fragmented, with the top ten companies holding less than 11 percent of the market.

About 70 percent of production is Western-type drugs, with the rest comprising traditional Chinese medicines (TCMs). Most leading players, such as Sinopharm or Shanghai Pharmaceuticals, are state-owned enterprises (SOEs) that are often vertically integrated, owning pharmacy chains. Distribution is fragmented, with over 13,000 distributors, who reap most of the drug price margins (Tao, 2014).

Price controls and reductions have long been practiced in China. In 1996–2007 alone, the government reduced the price of 1,500 drugs 19 times. It also set up an Essential Drug List of over 300 medicines, for which hospital pharmacies could not raise prices. The National Reimbursement Drug List (NDRL) split over 2,000 products into two groups: one of about 500 low-cost drugs, and the rest comprising higher-priced, patented Western drugs (Herzlinger and Kindred, 2014). Within the industry, biotech had started to develop as early as 1984, and counted over 900 firms by the mid-2000s. The main coordinating body is the China Center for Biotechnology Development (NCBD), set up in 1983 under the Ministry of Science and Technology.

While the SOE status of many biotechs has advantages including government relationships, they have grown by increasing volume and prices, and have been largely limited to incremental innovations. However, some remarkable leaders have recently emerged, such as BGI (Beijing Genomics), founded in 1999 and now counting divisions in the Americas and Europe.

Foreign company strategies

In order to gain market access, and despite patent issues, most multinationals have been long established in China. Pfizer has several GMP manufacturing facilities, and set up in 2012 a joint venture with Hisun to market branded generics. Germany's Merck announced in 2011 a $1.5 billion investment for its Asian R&D center in Beijing. Similarly, Novo Nordisk invested an additional $100 million in a China R&D complex that opened in 2012.

Western companies also continue to be very active with Chinese acquisitions. In 2010 alone, Sanofi purchased an OTC distributor for $521 million, Nycomed acquired for $210 million a majority share of a local manufacturer, and Sumitomo paid $96 million for a minority share in a domestic distributor. GSK entered China in 1984 with a joint venture in Tianjin, and has since invested about $500 million in an R&D center and six manufacturing sites, with a research staff of 7,000. Its Chinese portfolio includes hepatitis and respiratory drugs, antibiotics, dermatology, depression, and oncology products (Tao, 2014).

Bayer operates several companies in Greater China (including Hong Kong and Taiwan) and is engaged in several collaborations with the Chinese Academy of Science. It also supports research programs at Tsinghua University and the China European International Business School (CEIBS) in Shanghai.

Domestic company strategies

The industry is dominated by large SOEs with greatly diversified portfolios. Some optimize their innovation through technology transfer from joint ventures. Sinopharm, jointly owned by the China National Pharmaceutical Group and Fosun International, reached revenues in 2013 of $33 billion and has a broad portfolio, ranging from TCMs to devices, reagents, and pharmaceuticals. Its joint ventures include deals with Otsuka, J&J, and BMS. The Harbin group products include antibiotics and OTC brands, with 73 percent of its portfolio devoted to Western medicines, and the rest to TCMs. It is expanding its R&D through investment from banks such as Citic Capital in Hong Kong.

A notable example of an evolving SOE is Shanghai Pharmaceuticals.

Shanghai Pharmaceuticals

Shanghai Pharmaceuticals (SPH) is a vertically integrated conglomerate with a wide range of products, from active ingredients to small molecules and biologics as well as TCMs. It was formed by the merger of several SOEs and had an IPO in Hong Kong in 2011. By that time, its revenue was nearly $9 billion. Major initial investors were Temasek Holdings (Singapore), the Hong Leong Group (Malaysia), the Bank of China, and Pfizer.

Unusually for an SOE, SPH has spent about 4.5 percent of revenues on R&D. It focuses on five therapeutic areas: cardiovascular, metabolism, central nervous system, anti-infectives, and immunology. Its strategy is to prioritize products with high margins, market shares, and entry barriers. SPH also owns China's second-largest distribution network, engages in direct sales with hospitals, and has a network of about 1,700 retail pharmacies. All of the company's manufacturing sites meet or exceed GMP standards.

Before its IPO, SPH set up an agreement with Pfizer for distribution and cooperation on drug approval and commercialization, which could be followed by further R&D collaboration (Herzlinger and Kindred, 2014).

At the other end of the industry spectrum, cutting-edge biotechs have emerged, and one of the most dynamic and internationally recognized is BGI.

BGI's strategy

Founded in 1999, the group has now gained a global footprint, with divisions in the Americas and Europe. It was created as a nongovernmental independent research institute in order to represent China in the Human Genome Project. By 2002, BGI had sequenced the rice genome. The following year, it decoded the SARS virus genome and developed a diagnostic kit. It also set up a genomics collaboration with Zhejiang University. By 2008, it had published the first human genome of an Asian individual.

In addition, BGI is certified as meeting ISO 9001 standards for high-throughput sequencing services. It set up in 2010 BGI Americas in

Cambridge, MA, and BGI Europe in Copenhagen. It has alliances with most of the top global pharmaceutical firms, and has made acquisitions such as California-based Complete Genomics, a supplier of DNA sequencing technology, for $118 million (Specter, 2014).

Conclusion

In conclusion, the analysis of biotechnology innovation in India, Brazil, and China shows a very diverse set of health systems, with different proportions of government regulation and financing, but with general progress toward a goal of basic universal health-care coverage. The industry situations are also varied, with a dominance of SOEs in China, vs long-established generic manufacturers in Brazil and India.

Across these countries and in emerging markets in general, local talent and university resources, linked to foreign investment, are fueling the rapid development of remarkable biotechnology companies such as Biocon and BGI. To reach the optimal potential of their technology, governments in emerging markets will need to address the remaining challenges, from inequities in access to health care, to IP and manufacturing quality issues.

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