Brazilian health biotech—fostering crosstalk between public and private sectors

Rahim Rezaie[1,4], Sarah E Frew[1,4], Stephen M Sammut[2,3], Maya R Maliakkal[1], Abdallah S Daar[1] & Peter A Singer[1]

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** online) to conduct case studies of 19 domestically owned Brazilian health biotech firms (**Table 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.

Authors with president of Silvestre Labs and chairman of Cryopraxis, Rio de Janeiro. From left to right: Sarah Frew, Eduardo Cruz and Rahim Rezaie.

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.

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

[1]McLaughlin-Rotman Centre for Global Health, University Health Network and University of Toronto, MaRS Centre, South Tower, Suite 406, 101 College Street, Toronto, Ontario, M5G 1L7, Canada. [2]Wharton Health Care Systems, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6218, USA. [3]Burrill & Company, 1 Embarcadero Center, # 2700, San Francisco, California 94111, USA. [4]These authors contributed equally to this work. e-mail: peter.singer@utoronto.ca

Table 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 some δ opioid receptors), an anticancer recombinant protein derived from tick saliva showing activity against melanoma.	N/A
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.
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.

(continued)

Table 1 Continued

Company or organization	Products on the market	Products in development	Domestic/international quality certification
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 Paulo)	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 products, 75 hospital-use products and 48 products for animal health.	Mucus adhesive and nanoparticle-based ophthalmic products. More details not available.	ANVISA GMP certification.
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

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.

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 home-grown 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

Eurofarma's new manufacturing facilities in Itapevi, São Paulo.

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 (ref. 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.

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.

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 domain 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 multipeptides 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.

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.

Therapeutics. Many of the private companies in our study have developed, or are developing, innovative therapeutics (**Table 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

Box 1 Case study: Silvestre Laboratories

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 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).

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 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).

Contract services. The Brazilian contract service companies included in this study focus 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 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.

Partnerships for innovation

Because Brazilian health biotech firms lack the necessary R&D capabilities required for the development of complex innovative prod-

Table 2 Financial background for companies interviewed[a]

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)
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)

(continued)

Table 2 Continued

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)
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 Research	1999	Private	N/A	N/A	3 angel investors	Most foreign clientele	N/A	30
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 Bioinformatics	2002	Private	N/A	R$0.15 ($0.08) from each of FINEP and FAPESP, with some funds from CNPq	Votorantim Venture (São Paulo) provided R$0.5 ($0.27)	N/A	N/A	8
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. [d]Cryopraxis Criobiologia is a spin-off of Silvestre Laboratories and has now established its own subsidiary in the United States called CellPraxis USA Inc. (Jupiter, FL, USA). [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.

Technicians inside Cryopraxis, preparing samples for research and storage.

ucts, effective partnerships with Brazilian universities and public institutes are central to the innovation strategy of most companies (**Table 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 **Tables 3** and **4**, domestic collaborations are more common than partnerships between Brazilian firms and foreign entities.

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 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.

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**). 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.

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 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

Table 3 Alliances/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.
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 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.

Box 2 Case study: COINFAR

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.

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.

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

Table 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.
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).

Box 3 Case study: Eurofarma Laboratorios

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.

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.

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 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.

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 non-governmental/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].

Staff at Intrials Clinical Research, São Paulo

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

Box 4 Case study: PeleNova Biotecnologia

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.

Table 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 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.

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 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.

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 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.

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**, 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

Box 5 Recommendations for biotech development in Brazil

- 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.

Staff at Katal Biotecnologica assembling diagnostic kits.

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 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.

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The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturebiotechnology/.

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